

MEETING ABSTRACTS

Partnering With Patients:
The Cornerstone of Cancer
Care and Research

**59th
Annual Meeting of the
American Society of Clinical Oncology**

June 2-6, 2023

2023 Annual Meeting Abstracts

(a supplement to *Journal of Clinical Oncology*)

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Letter From the Editors

The *2023 ASCO Annual Meeting Abstracts* (a supplement to *Journal of Clinical Oncology*) is an enduring record of the more than 2,900 abstracts selected by the ASCO Scientific Program Committee for presentation as part of the ASCO Annual Meeting.

Abstracts can be accessed online through the ASCO Meeting Experience (asco.org/abstracts). Online abstracts include the full list of abstract authors and their disclosure information. To download a PDF of the full abstract supplement and/or the presented abstracts by track, visit conferences.asco.org/am/abstracts-posters.

Publication-only abstracts are included in the online supplement to the June 1 issue of *Journal of Clinical Oncology* at JCO.org and are also available online at asco.org/abstracts.

All abstracts carry *Journal of Clinical Oncology* citations, for example:

J Clin Oncol 41:16s, 2023 (suppl; abstr 500).

We are excited to promote and increase awareness of *JCO Meeting Abstracts* publication through social media,

specifically to increase awareness of less publicized, yet important research. We continue to partner with JCO to curate abstract collections for publication on JCO.org and promote collections via Twitter. For the *2023 ASCO Annual Meeting* the collections will reflect the presidential theme of partnering with patients through cancer care and research and will include de-escalation of therapy, patient reported outcomes, personalized cancer medicine, and improving patient health equity in addition to highlighting our merit awardees. Follow us on Twitter @JCO_ASCO, @ASCO, #ASCO23!

Should you have any questions or comments about this publication, we encourage you to provide feedback by contacting us at abstracts@asco.org.

Sincerely,

Pamela L. Kunz, MD
ASCO Meeting Abstracts Editor,
Journal of Clinical Oncology

Ryan D. Gentzler, MD, MS
ASCO Meeting Abstracts Associate Editor,
Journal of Clinical Oncology

ASCO Abstracts Policy

Public Release of Abstracts

The 2023 ASCO Annual Meeting Regular Abstracts were publicly released by ASCO at 5:00 PM EDT on Thursday, May 25, 2023. Abstracts are publicly available online at asco.org/abstracts. Late-Breaking Abstracts, which include all Plenary Abstracts, will be publicly released according to the following schedule:

- Late-Breaking Abstracts presented in a scientific presentation on Friday, June 2, will be publicly released Friday, June 2, at 8:00 AM EDT.
- Late-Breaking Abstracts presented in a scientific presentation on Saturday, June 3, will be publicly released Saturday, June 3, at 8:00 AM EDT.
- Late-Breaking Abstracts presented in a scientific presentation on Sunday, June 4, will be publicly released Sunday, June 4, at 8:00 AM EDT.
- Late-Breaking Abstracts presented in a scientific presentation on Monday, June 5, will be publicly released Monday, June 5, at 8:00 AM EDT.
- Late-Breaking Abstracts presented in a scientific presentation on Tuesday, June 6, will be publicly released Tuesday, June 6, at 8:00 AM EDT.

In the unlikely event that ASCO publicly releases an abstract in advance of the scheduled time, the release will be publicly announced on <https://conferences.asco.org/am/abstract-policies-embargoes-exceptions>.

Conflict of Interest Disclosure

All financial relationships reported by contributors to this activity are provided to learners prior to the start of the activity. During planning and development of the activity, relevant financial relationships were mitigated for all contributors. Relationships are considered self-held and compensated unless otherwise noted (I = Immediate family member; Inst = My Institution). Disclosures are submitted per the ASCO Policy for Relationships with Companies.

LBA1**Plenary Session**

INDIGO: A global, randomized, double-blinded, phase 3 study of vorasidenib versus placebo in patients with residual or recurrent grade 2 glioma with an IDH1/2 mutation. *First Author: Ingo K. Mellinghoff, Memorial Sloan Kettering Cancer Center, New York, NY*

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2023, issue of the *Journal of Clinical Oncology*.

LBA2**Plenary Session**

PROSPECT: A randomized phase III trial of neoadjuvant chemoradiation versus neoadjuvant FOLFOX chemotherapy with selective use of chemoradiation, followed by total mesorectal excision (TME) for treatment of locally advanced rectal cancer (LARC) (Alliance N1048). *First Author: Deborah Schrag, Memorial Sloan Kettering Cancer Center, New York, NY*

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2023, issue of the *Journal of Clinical Oncology*.

LBA3**Plenary Session**

Overall survival analysis from the ADAURA trial of adjuvant osimertinib in patients with resected EGFR-mutated (EGFRm) stage IB–IIIA non-small cell lung cancer (NSCLC). *First Author: Roy S. Herbst, Medical Oncology, Yale School of Medicine and Yale Cancer Center, New Haven, CT*

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2023, issue of the *Journal of Clinical Oncology*.

LBA4**Plenary Session**

SWOG S1826, a randomized study of nivolumab(N)-AVD versus brentuximab vedotin(BV)-AVD in advanced stage (AS) classic Hodgkin lymphoma (HL). *First Author: Alex Francisco Herrera, City of Hope National Medical Center, Duarte, CA*

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2023, issue of the *Journal of Clinical Oncology*.

LBA100

Clinical Science Symposium

KEYNOTE-671: Randomized, double-blind, phase 3 study of pembrolizumab or placebo plus platinum-based chemotherapy followed by resection and pembrolizumab or placebo for early stage NSCLC. *First Author: Heather A. Wakelee, Department of Medicine, Division of Oncology, Stanford University, Stanford Cancer Institute, Stanford, CA*

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2023, issue of the *Journal of Clinical Oncology*.

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Clinical Science Symposium

The impact of response-directed surgery and adjuvant therapy on long-term survival after neoadjuvant ipilimumab plus nivolumab in stage III melanoma: Three-year data of PRADO and OpACIN-neo. *First Author: Irene L.M. Reijers, Netherlands Cancer Institute, Amsterdam, Netherlands*

Background: Neoadjuvant ipilimumab (IPI) + nivolumab (NIVO) has been shown to induce high pathologic response rates associated with an excellent relapse-free survival (RFS) in high-risk stage III melanoma. While OpACIN-neo tested different neoadjuvant IPI + NIVO regimens followed by therapeutic lymph node dissection (TLND) without adjuvant systemic therapy (ST), PRADO tested a personalized approach. In patients (pts) achieving a major pathologic response (MPR; $\leq 10\%$ viable tumor), TLND and adjuvant ST were omitted, and pts with pathologic non-response (pNR; $>50\%$ viable tumor) were treated with adjuvant ST (BRAF/MEKi or anti-PD1) $\pm$ radiotherapy after TLND. Here, we address 1) whether omitting TLND in MPR pts had an adverse effect on long-term survival and 2) whether adding adjuvant ST in pNR pts had a favorable effect on survival. **Methods:** The 3-year (3y) RFS and distant metastasis-free survival (DMFS) of pts with MPR and pNR from PRADO and OpACIN-neo were analyzed, comparing MPR pts with TLND versus without TLND and pNR pts with adjuvant ST versus without adjuvant ST. Survival rates were calculated and compared with Kaplan-Meier and log-rank methods. Associations between baseline characteristics and RFS or DMFS were examined by Cox regression analysis. **Results:** Median follow-up was 37.9 months in PRADO (cutoff Jan 8, 2023) and 46.8 months in OpACIN-neo (cutoff Feb 14, 2022). For MPR pts, TLND omission did not affect survival, with a 3y RFS of 93% versus 96% ($p=0.47$) and 3y DMFS 98% versus 98% ($p=0.92$) for pts without TLND ($n=59$) versus with TLND ($n=53$), respectively. In pNR pts, an indication for a RFS and DMFS benefit was seen favoring pts with adjuvant ST ($n=17$: $n=10$ BRAF/MEKi and $n=7$ anti-PD1) over pts without adjuvant ST ($n=23$), with 3y RFS rates being 64% versus 35% ($p=0.10$) and 3y DMFS rates 70% versus 52% ($p=0.24$). Baseline clinical characteristics did not differ between PRADO and OpACIN-neo pts or were not associated with RFS and DMFS. **Conclusions:** Omitting TLND in MPR pts after neoadjuvant IPI + NIVO seems not to affect RFS/DMFS. Given the high survival rates, adjuvant ST is unlikely to give further benefit in these pts. In pts with pNR, addition of adjuvant ST with ongoing anti-PD1 or switch to BRAF/MEKi appears to improve RFS and DMFS. Clinical trial information: NCT02977052. Research Sponsor: BMS.

3y rates	Personalized	Non-personalized	p-value
MPR pts (n=112)	No TLND (n=59)	TLND (n=53)	
RFS	93%	96%	0.47
DMFS	98%	98%	0.92
pNR pts (n=40)	Adjuvant ST (n=17)	No adjuvant ST (n=23)	
RFS	64%	35%	0.10
DMFS	70%	52%	0.24

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Clinical Science Symposium

Biomarkers predicting response to 5 immunotherapy arms in the neoadjuvant I-SPY2 trial for early-stage breast cancer (BC): Evaluation of immune subtyping in the response predictive subtypes (RPS). *First Author: Denise M. Wolf, University of California San Francisco, San Francisco, CA*

Background: Previously, we showed that in our first PD1-inhibitor (PD1-inh) arm of I-SPY2, pCR associates with high STAT1/chemokine/dendritic signatures in TN and with high B-cell/low mast cell in HR+. From these results, we defined a research-grade Immune classifier incorporated into the RPS (PMID: 35623341), a schema designed to increase pCR if used to prioritize treatment. A clinical-grade version of the Immune (ImPrint) and other RPS biomarkers are now used in I-SPY2.2. Here we evaluate immune markers in 5 Immune-Oncology (IO) therapy arms (2 PD1-inh, 2 PD1-inh combinations, and 1 PDL1-inh combination). **Methods:** 343 patients with HER2-negative BC with information on pCR and mRNA in 5 IO arms ($n=60-72$ pts) plus controls (Ctr: 343) were considered. 32 continuous markers including 30 immune (7 checkpoint genes, 14 immune cell, 3 T/B-cell prognostic, 1 TGFB and 5 tumor-immune) and ESR1/PGR and proliferation signatures, were assessed for association with pCR using logistic regression. p-values were adjusted using the Benjamini-Hochberg method (BH $p<0.05$). Correlations to multiplex immunofluorescence (mIF) data from our initial arm (immune cell and spatial proximity markers) were calculated. Performance of ImPrint, developed with Agendia Inc, was characterized overall and within HR subsets. **Results:** A larger number of the research-grade immune markers predict response to IO in HR+ than in TN, with the most for HR+ in combination-IO arms (27/32 biomarkers). Tumor-immune signatures dominated by chemokines/cytokines were most consistently associated with pCR across IO arms and across receptor status. Moreover, we found that these markers correlate to mIF spatial proximity measures reflecting high spatial co-localization of PD1+ immune and PDL1+ tumor cells, in TN especially ($r=0.59$; $p=0.003$). The ImPrint classifier was evaluated in the IO arms. In HR+, 28% were ImPrint+, and pCR rates were 76% in ImPrint+ vs. 16% in ImPrint-. In TN, 46% were ImPrint+, and pCR rates were 75% in ImPrint+ and 37% in ImPrint-. Overall (HR+ and TN, in all IO arms), pCR rates were 75% in ImPrint+ and 23% in ImPrint-. Performance varied by arm, with the highest pCR rates for HR+/ImPrint+ $>90\%$; and for TN/ImPrint+ $>81\%$. In contrast, pCR rates in the control arm were 34% for ImPrint+ (HR+:33%; TN: 34%) and 13% for ImPrint- (HR+: 21%; TN:8%). **Conclusions:** Tumor-immune signaling signatures predict response for IO drug class in both TN and HR+HER2-. The ImPrint single-sample classifier predicts response to a variety of IO regimens in both subsets and may inform prioritization of IO vs other treatments and best balance likely benefit vs risk of serious immune-related adverse events. Clinical trial information: NCT01042379. Research Sponsor: QLHC.

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Clinical Science Symposium

Friendly-user score assessing gut dysbiosis and resistance to immune checkpoint inhibitors (ICI). *First Author: Lisa Derosa, Gustave Roussy Cancer Campus, Villejuif, France*

Background: Accumulating evidence pointed to the impact of the intestinal microbiota on ICI outcomes across various cancers. Although specific gut microbial species have been associated with beneficial responses (*i.e. Akkermansia muciniphila* (Akk)), no consensus exists on a gut fingerprint predicting immunoresistance to clinical routine use. **Methods:** NCT04567446 provided whole genome sequencing (WGS) of longitudinal fecal samples from patients (pts) with advanced non-small cell lung cancer (NSCLC) during ICI (alone or with chemotherapy) in France and Canada. Topological Pearson networks clustered into species interacting groups (SIG) correlating with overall survival (OS; $OS<12=NR$; $OS>12=R$). Forty harmful (SIG1) and thirty-four beneficial (SIG2) WGS species were associated with NR and R to ICI. A monodimensional score (TOPOSCORE) based on SIG1/SIG2 ratio combined with Akk relative abundance was calculated and compared to machine-learning (ML) algorithms. Multivariate Cox analysis (MVA) adjusted for established risk factors (ATB, gender, age, ECOG, PD-L1, LIPI score). Intraindividual dynamics of the TOPOSCORE was evaluated in pts with at least two fecal samples. Three independent cohorts of NSCLC and genitourinary (GU) cancers pts validated the data. **Results:** In $n=245$ and $n=148$ NSCLC pts, we could classify pts into dysbiotic (SIG1+,33%) and eubiotic (SIG2+, 67%), using the TOPOSCORE. Pts falling within the SIG2+ exhibited a significantly prolonged OS than pts falling into SIG1+ (HR: (95% CI), 0.50 (0.36-0.71), $p<0.0001$). TOPOSCORE also predicted OS in 277 ICI-treated NSCLC and GU pts and compared to the state-of-the-art ML algorithms, held the highest percentage of correct predictions (63%). At MVA, TOPOSCORE was independently associated with OS (HR: 0.56 (0.39-0.81), $p=0.002$). Analyzing the intraindividual dynamics of the TOPOSCORE ($n=67$), we found that 74% of SIG2+ and 68% of SIG1+ individuals remained in their initial classification during ICI treatment. We finally scaled the calculation of the TOPOSCORE down to 24WGS (instead 75WGS) and set up a qPCR-based friendly-user test capable of accurately identifying the fecal presence of the bacteria of interest within 48 hrs. We confirmed ($n=323$) that OS was superior in those pts harboring a 24-bacteria-qPCR-based TOPOSCORE falling within the SIG2+ category (HR: 0.65 (0.48 to 0.87), $p=0.0005$). **Conclusions:** TOPOSCORE represents a robust biomarker predicting and following the dynamic of the immunoresistance to ICI across cancers on an individual basis. By converting the WGS TOPOSCORE to a qPCR-based test with a rapid turnaround time, it will be possible to adopt this score in routine clinical practice to improve pts stratification and ICI success rates guiding the selection of dysbiotic pts amenable to microbiota-centered interventions and eubiotic fecal microbiota transplantation donors. Clinical trial information: NCT04567446. Research Sponsor: None.

LBA104

Clinical Science Symposium

Effect of CBM588 in combination with cabozantinib plus nivolumab for patients (pts) with metastatic renal cell carcinoma (mRCC): A randomized clinical trial. *First Author: Hedyeh Ebrahimi, City of Hope Comprehensive Cancer Center, Duarte, CA*

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2023, issue of the *Journal of Clinical Oncology*.

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Clinical Science Symposium

Fecal microbiota transplantation combined with anti-PD-1 inhibitor for unresectable or metastatic solid cancers refractory to anti-PD-1 inhibitor. *First Author: Sook Ryun Park, Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea*

Background: The gut microbiome is emerging as a key regulator of the immune system during immunotherapy. However, the effect of modulating the gut microbiome in patients (pts) with cancer refractory to immunotherapy remains largely unknown. We aimed to evaluate whether the fecal microbiota transplantation (FMT) could help overcome resistance in pts with advanced solid cancer refractory to anti-PD-(L)1 inhibitors and identify specific commensal bacteria that contribute to the efficacy of FMT (NCT04264975). **Methods:** This is a prospective, single-arm clinical trial of FMT plus anti-PD-(L)1 inhibitor in pts with advanced solid cancer refractory to anti-PD-(L)1 inhibitors. The key eligibility criteria for donors included ongoing durable complete or partial response ≥ 6 months with anti-PD-(L)1 monotherapy for advanced solid tumors. FMT was performed using colonoscopy, followed by continuation or reintroduction of anti-PD-(L)1 inhibitor until unacceptable toxicity or disease progression. Repeated FMT from the same or different donors was allowed. **Results:** From Jan. 2019 to Aug. 2020, 13 pts with metastatic gastric cancer (GC) (n=4), esophageal squamous cell carcinoma (ESCC) (n=5), and hepatocellular carcinoma (HCC) (n=4) were enrolled; male (77%), median age=60 yrs (range, 38-76), and median line of prior systemic therapy=3 (range, 2-5). All had confirmed disease progression on nivolumab monotherapy with primary (46.2%) or secondary resistance (53.8%), and underwent FMT with continued nivolumab. There were six FMT donors (HCC [n=4], GC [n=1], ESCC [n=1], who had maintained (CR; n=4) or (PR; n=2) with nivolumab or pembrolizumab monotherapy. Of the 13 recipients, five showed SD and one achieved PR after FMT with a disease control rate of 46.2% (6/13) and an objective response rate of 7.7% (1/13). Recipient #7 (R7), who had metastatic HCC with primary resistance to nivolumab, initially showed PD to the 1st FMT from donor #1, but achieved PR after the 2nd FMT from donor #5. Clinical response was accompanied by an increase in levels of cytotoxic T cells in the blood and tumor microenvironment, immune cytokines, and the relative abundance of a new species derived from donor #5 showing 97% whole genome nucleotide sequence similarity with *Prevotella* sp. Marseille-P4119. We isolated this species from feces of R7 and preclinical experiments showed that treatment with this species activated human CD4+ and CD8+ T cells with increased IFN- γ secretion, and suppressed tumor growth in a syngeneic mouse model by enhancing tumor infiltration of cytotoxic T cells. Moreover, the combination treatment with anti-PD-1 and this species reduced the tumor volume more than with anti-PD-1 alone. **Conclusions:** FMT containing the effective microbiota could overcome resistance to anti-PD-1 inhibitor by modulating the tumor microenvironment in advanced solid cancer pts. Clinical trial information: NCT04264975. Research Sponsor: grants from National Cancer Centre, Korea (NCC-1911267); a grant (2018-0608) from the Asan Institute for Life Sciences, Asan Medical Center, Korea.

LBA106

Clinical Science Symposium

First phase 3 results from CARTITUDE-4: Cilta-cel versus standard of care (PVd or DPd) in lenalidomide-refractory multiple myeloma. *First Author: Binod Dhakal, Medical College of Wisconsin, Milwaukee, WI*

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2023, issue of the *Journal of Clinical Oncology*.

LBA107

Clinical Science Symposium

Primary overall survival analysis of the phase 3 randomized ZUMA-7 study of axicabtagene ciloleucel versus standard-of-care therapy in relapsed/refractory large B-cell lymphoma. *First Author: Jason Westin, University of Texas MD Anderson Cancer Center, Houston, TX*

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2023, issue of the *Journal of Clinical Oncology*.

LBA500

Oral Abstract Session

Phase III NATALEE trial of ribociclib + endocrine therapy as adjuvant treatment in patients with HR+/HER2- early breast cancer. *First Author: Dennis J. Slamon, David Geffen School of Medicine at University of California Los Angeles, Los Angeles, CA*

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2023, issue of the *Journal of Clinical Oncology*.

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Oral Abstract Session

Efficacy and safety results by age in monarchE: Adjuvant abemaciclib combined with endocrine therapy (ET) in patients with HR+, HER2-, node-positive, high-risk early breast cancer (EBC). *First Author: Erika P. Hamilton, Sarah Cannon Research Institute, Tennessee Oncology, Nashville, TN*

Background: Adjuvant abemaciclib (a CDK4 & 6 inhibitor) combined with ET demonstrated a sustained benefit in invasive disease-free survival (IDFS) and a tolerable safety profile in patients (pts) with HR+, HER2-, node-positive, high-risk EBC. Almost half of the newly diagnosed breast cancers occur in women older than 65 years. Older pts often have a higher incidence of comorbidities and increased risk for toxicities. Here, we report efficacy and safety by age subgroups in monarchE to help guide management of older pts receiving adjuvant abemaciclib. **Methods:** Pts were randomized (1:1) to receive ET for up to 10 years +/- abemaciclib for 2 years (study treatment period). Efficacy in IDFS and distant relapse-free survival (DRFS) was assessed in the intent-to-treat population by the pre-specified age groups of <65 and ≥65 years, with hazard ratios (HR) estimated using unstratified Cox proportional hazard model within each subgroup. Safety was evaluated among older pts (≥65 years) in two subgroups; 65-74 and ≥75 years. **Results:** In monarchE (NCT03155997), 4787 pts (84.9%) were aged <65 years and 850 pts (15.1%) were ≥65 years. At median follow-up of 42 months, a numerically favorable IDFS effect was observed in both the <65 (270 vs 414 events; HR = 0.646, 95% CI: 0.554, 0.753) and ≥65 (66 vs 85 events; HR = 0.767, 95% CI: 0.556, 1.059) groups for abemaciclib + ET vs ET alone. Similar findings were observed in DRFS. Older pts (≥65 years) had ~5% higher incidence of grade ≥3 adverse events (AEs) than younger pts, mainly diarrhea and fatigue. Neutropenia was not increased among older pts and similarly, venous thromboembolic events occurred at similar rates (≥65 years, 3.0%; <65 years, 2.5%). Serious AEs (SAEs) and treatment discontinuations due to AEs were more common in older pts. Older pts required more dose reductions to manage AEs. **Conclusions:** In pts with high-risk EBC, adjuvant abemaciclib + ET showed treatment benefit across age subgroups with a manageable safety profile. Older pts did have higher rates of AEs and discontinuations, especially those older than 75 years, suggesting that more frequent surveillance with early intervention may be key to the management of these pts. Clinical trial information: NCT03155997. Research Sponsor: Eli Lilly and Company.

	Abemaciclib + ET			ET alone		
	<65 (n=2361)	65-74 (n=354)	≥75 (n=76)	<65 (n=2390)	65-74 (n=333)	≥75 (n=77)
%						
≥1 AE, any grade	98	99	99	89	90	88
Grade ≥3	49	52	67	16	20	27
Diarrhea*	84	79	78	8	14	12
	7	11	18	0.2	0.3	0
Neutropenia	47	41	41	6	2	1
	20	19	20	0.9	0.9	0
Fatigue	40	44	58	18	17	22
	2	5	11	0.1	0.6	0
≥1 SAE	14	21	26	9	12	17
Discontinuations of all treatment due to AEs	5	14	18	0.8	2	6
Dose reductions of abemaciclib due to AEs	42	56	55	NA	NA	NA

*Diarrhea grade 2 for abemaciclib + ET: <65, 31%; 65-74, 31%; ≥75, 25%.

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Oral Abstract Session

Detection of circulating tumor DNA following neoadjuvant chemotherapy and surgery to anticipate early relapse in ER positive and HER2 negative breast cancer: Analysis from the PENELOPE-B trial. *First Author: Nicholas C. Turner, The Institute of Cancer Research, Royal Cancer Hospital, London, United Kingdom*

Background: The PENELOPE-B phase III trial investigated the addition of one year of palbociclib to endocrine therapy (ET), in patients with hormone receptor positive HER2 negative breast cancer with residual invasive disease after neoadjuvant chemotherapy. Prior research has demonstrated that detection of circulating tumor DNA (ctDNA) in the adjuvant setting is associated with a high risk of disease relapse. We assessed the potential of ctDNA analysis to predict future clinical relapse for patients enrolled in the PENELOPE-B trial. **Methods:** Patients who were endocrine naïve at the time of study entry were selected for ctDNA analysis. Plasma samples were collected at baseline (after completion of neoadjuvant chemotherapy and surgery), prior to cycle 7 (approximately 6 months into ET +/- palbociclib), end of treatment (EOT), and progressive disease. A tumor sample was subjected to exome sequencing, and up to 50 tumor somatic mutations were tracked in plasma using error-corrected sequencing combined with a proprietary algorithm for ctDNA detection (RaDaR assay). Detection of ctDNA was associated with invasive disease-free survival (IDFS) and distant metastasis-free survival using Cox proportional hazard models. **Results:** Of 1250 patients enrolled in PENELOPE-B, 129 were endocrine naïve at trial entry, and 78 had a baseline ctDNA sample analyzed. The ctDNA analysis group was representative of the overall endocrine naïve group, with median follow-up of 42.9 months. Seven patients had baseline ctDNA detected, with detection strongly associated with iDFS (HR 8.8, 95% CI 3.3-23.4, p < 0.0001). Detection of ctDNA at cycle 7 (4 patients) was also strongly associated with iDFS (HR 25.5, 95% CI 6.5-99.6, p < 0.0001). Of the 7 patients with baseline ctDNA detection, 2 had undetectable ctDNA at cycle 7 and remained progression free at 30 months, although one later relapsed; the 3 patients with detectable ctDNA at cycle 7 all relapsed within 25 months. Of the 12 patients with a distant relapse within 24 months, only 4 had ctDNA detected at baseline and 3 first at cycle 7/EOT. Of the 8 patients with distant relapse after 24 months, 2 had ctDNA detected at baseline and none first at cycle 7/EOT. **Conclusions:** Detection of ctDNA following neoadjuvant chemotherapy, and surgery, is associated with a very high risk of early relapse suggesting limited efficacy of adjuvant ET. Clinical imaging and studies of experimental therapy are warranted in this patient population. Testing ctDNA after recent neoadjuvant chemotherapy in luminal-A like breast cancer has relatively low 'sensitivity' for predicting future relapse, in particular for later relapses, in part suggesting that response to neoadjuvant chemotherapy may reduce ctDNA detection. Clinical trial information: NCT01864746. Research Sponsor: Pfizer.

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Oral Abstract Session

Effects of ovarian ablation or suppression on breast cancer recurrence and survival: Patient-level meta-analysis of 14,993 pre-menopausal women in 25 randomized trials. *First Author: Richard G. Gray, University of Oxford, Oxford, United Kingdom*

Background: Suppressing ovarian function of women with breast cancer may improve outcome by preventing estrogenic stimulation of any residual cancer, particularly for pre-menopausal women with estrogen receptor (ER)-positive tumors. We report a collaborative meta-analysis of individual participant data from randomized trials of ovarian ablation or suppression. **Methods:** Data were sought from randomized trials that compared ovarian ablation or suppression versus not. Primary analyses included only pre-menopausal women aged < 55 with ER-positive or unknown tumors, stratified into those who received no chemotherapy, or remained premenopausal following chemotherapy, and those whose menopausal status following chemotherapy was not ascertained. Standard log-rank methods estimated ER-weighted annual event rate ratios (RR). **Results:** Individual patient data were provided for 25 of 27 relevant trials, comprising 14,993 (98.7%) of 15,195 women randomized. Overall, fewer breast cancer recurrences were seen with ovarian ablation/suppression than control (RR = 0.82, 95%CI 0.77-0.88; p < 0.0001). Recurrence reductions were significantly (p = 0.0003) larger among women (n = 7,213) known to be premenopausal prior to ovarian suppression (RR = 0.70, 0.63-0.78; p = 0.0003) than among those (n = 7,786) whose menopausal status was uncertain after chemotherapy (RR = 0.91, 0.83-0.99; p = 0.03). For known premenopausal women, 15-year risk of recurrence was improved by 12.1% (28.9% vs 41.0%; p < 0.0001). 15-year breast cancer and all-cause mortality were improved by 8.0% (20.9% vs 28.9%; RR = 0.69, 0.60-0.80; p < 0.0001) and 7.2% (26.0% vs 33.1%; RR = 0.73, 0.64-0.82; p < 0.0001), respectively, with no increase in deaths without recurrence (RR = 0.88, 0.67-1.14; p = 0.33). Recurrence reductions were significantly (p = 0.003) larger among premenopausal women aged under 45 (RR = 0.63, 0.55-0.72; p < 0.0001) than among those aged 45-54 (RR = 0.84, 0.70-1.00; p = 0.045), but did not differ significantly by other recorded patient or tumor characteristics. **Conclusions:** For pre-menopausal women aged under 45, ovarian ablation or suppression substantially reduces the 15-year risk of recurrence and death from breast cancer without increasing mortality from other causes. Research Sponsor: Cancer Research UK medical charity; NDPH, University of Oxford.

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Oral Abstract Session

Evaluation of PAM50 intrinsic subtypes and risk of recurrence (ROR) scores in premenopausal women with early-stage HR+ breast cancer: A secondary analysis of the SOFT trial. *First Author: Lauren Claire Brown, Peter MacCallum Cancer Centre, Melbourne, Australia*

Background: The landmark Suppression of Ovarian Function Trial (SOFT) in premenopausal breast cancer patients revealed that the addition of ovarian function suppression (OFS) to adjuvant endocrine therapy with either tamoxifen (T+OFS) or exemestane (E+OFS) reduces the risk of recurrence compared with adjuvant tamoxifen alone. There are no biomarkers to aid decision-making about intensification of endocrine therapy with OFS. The purpose of this study is to assess the prognostic and predictive ability of PAM50 intrinsic subtypes and ROR scores in premenopausal women with HR+/HER2- breast cancer in the SOFT trial. **Methods:** Gene expression analyses were performed via the NanoString Breast Cancer 360 assay on RNA isolated from FFPE tumor samples from the SOFT trial that were HR+/HER2- (n=1245/3047). PAM50 subtype and ROR score were determined centrally by NanoString Technologies (Seattle, WA, USA), blinded to clinical characteristics, treatment and outcome. Median follow-up was 12 years. Primary endpoint in this study was distant recurrence-free interval (DRFI). Secondary endpoints were breast cancer-free interval (BCFI) and disease-free survival (DFS). Kaplan-Meier analysis and Cox proportional hazards regression models, stratified by prior chemotherapy and lymph node status, were used to evaluate the predictive performance of PAM50 intrinsic subtypes and ROR categories (low vs intermediate vs high), and secondarily ROR score as a continuous variable. We also investigated differences between very young (<40yrs) vs young (>40yrs) women. **Results:** Tumor samples from 1084/1245 (87%) patients successfully completed PAM50 testing and are included in this analysis. Patient characteristics in this cohort were similar to the entire SOFT trial population. Intrinsic subtype and ROR category distribution is described below. Subtype distribution significantly differed between very young vs young premenopausal women, with fewer luminal A and more luminal B and non-luminal tumors seen in the very young (p<0.001). The ROR score distribution also differed significantly: in node-negative patients there were significantly more ROR-high scores amongst very young compared to young women (36% vs 14%, p<0.001). **Conclusion:** Breast cancer diagnosed in very young women has aggressive disease biology. Prognostic and predictive analyses of both intrinsic subtypes and the ROR score are ongoing and will be presented at the meeting. Clinical trial information: NCT00066690. Research Sponsor: Breast Cancer Foundation New Zealand, National Breast Cancer Foundation of Australia, Breast Cancer Research Foundation, NHMRC and the Royal Australasian College of Physicians, Fundación SEOM.

	Very young (<40 yr)	Young (≥40 yr)	Overall
N patients	309	775	1084
Intrinsic subtype			
Luminal A	53%	75%	69%
Luminal B	38%	22%	26%
Basal / HER2-E	5% / 3%	3% / 1%	3% / 2%
ROR (Low/Int/High)			
pN0	37% / 27% / 36%	64% / 22% / 14%	59% / 23% / 19%
pN+	2% / 18% / 80%	7% / 27% / 66%	5% / 23% / 72%

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Oral Abstract Session

3-year invasive disease-free survival (iDFS) of the strategy-based, randomized phase II PHERGain trial evaluating chemotherapy (CT) de-escalation in human epidermal growth factor receptor 2-positive (HER2[+]) early breast cancer (EBC). *First Author: Javier Cortes, International Breast Cancer Center (IBCC), Pangaea Oncology, Quiron Group, Barcelona, Spain, Medica Scientia Innovation Research (MEDSIR), Barcelona, Spain, Universidad Europea de Madrid, Faculty of Biomedical and Health Sciences, Department of Medicine, Madrid, Spain*

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2023, issue of the *Journal of Clinical Oncology*.

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Oral Abstract Session

Association of tumor-infiltrating lymphocytes (TILs) with clinicopathologic characteristics and prognosis in young women with HR+/HER2- breast cancer (BC). *First Author: Megan E Tesch, Dana-Farber Cancer Institute, Boston, MA*

Background: Increased TILs are associated with better prognosis in triple-negative BC, including in patients (pts) age < 40. However, the role of TILs remains unclear in HR+/HER2- BC and little data exist in young pts, in whom immune microenvironment could be altered by age-related host/tumor differences. We assessed the extent and composition of immune infiltration in HR+ tumors of young women and correlated with clinicopathologic features and survival outcomes. **Methods:** From a prospective cohort study of women with BC diagnosed age ≤40, we identified those with stage I-III HR+/HER2- BC and available pre-treatment (tx) tumor tissue. Multiplexed immunofluorescence was used to quantify cytotoxic T (CD8+), T helper (Th, CD3+CD8-), T regulatory (Tregs, FOXP3+CD3+) and exhausted T (PD1+CD8+) cells in stroma and tumor. Univariate analyses tested associations between clinicopathologic variables and immune markers by high or low expression, divided based on median. High vs. low TILs were evaluated in Cox regression analyses for invasive breast cancer-free survival (iBCFS), distant disease-free survival (DDFS) and overall survival (OS). **Results:** In 390 pts, median age was 37 years (21-40), most had grade 2 (51%), T1 (65%), N0 (63%) tumors and 67% received adjuvant chemotherapy. Black pts (n = 17) had higher expression of stromal CD8+ (P=.010), FOXP3+CD3+ (P=.027) and PD1+CD8+ TILs (P=.043); intratumoral TILs did not differ by race. Older age (36-40) was associated with high expression of CD8+ (P=.033) and PD1+CD8+ TILs (P=.031) within stroma and CD3+CD8- TILs within tumor (P=.046). Grade 3 tumors had higher stromal and intratumoral expression of CD3+CD8- (P=.002; P<.001) and FOXP3+CD3+ TILs (P=.020; P<.001). No differences in TILs were seen according to recency of pregnancy, BRCA1/2 status or T/N stage. Over a median follow up of 8 years, 85 iBCFS events, 64 DDFS events and 37 deaths occurred. High stromal expression of CD3+CD8- TILs was associated with better iBCFS (HR 0.49, P=.002) and DDFS (HR 0.57, P=.046), which remained significant when adjusted for T/N stage, grade and chemotherapy (iBCFS HR 0.41, P<.001; DDFS HR 0.45, P=.008). High stromal expression of CD3+CD8- and FOXP3+CD3+ TILs was associated with better OS (HR 0.47, P=.038) and iBCFS (HR 0.58, P=.018), respectively, on adjusted analyses only. High intratumoral expression of CD3+CD8- and FOXP3+CD3+ TILs was associated with better iBCFS (HR 0.59, P=.025; HR 0.63, P=.043) after adjustment only. **Conclusions:** The distribution of TIL subtypes in young women's HR+ BC varied according to race, age and grade. High stromal and intratumoral expression of Th and Tregs was associated with improved BC outcomes. Characterization of immune cell subsets could help refine the prognostic value of TILs in HR+ BC, particularly in young pts who may benefit from individualized escalated/de-escalated tx strategies. Research Sponsor: Breast Cancer Research Foundation, Susan G. Komen.

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Oral Abstract Session

Differential impact of proliferation signature on efficacy of neoadjuvant chemoimmunotherapy in sTIL-high and sTIL-low triple-negative breast cancer (TNBC): Biomarker analysis of the NeoPACT trial. *First Author: Shane R Stecklein, University of Kansas Medical Center, Kansas City, KS*

Background: TNBCs with enrichment of stromal tumor-infiltrating lymphocytes (sTILs) and/or immune gene expression are more sensitive to neoadjuvant systemic therapy (NAST) and exhibit higher rates of pathologic complete response (pCR). Other biomarkers, including proliferation, are also prognostic in TNBC patients treated with NAST. We aim to investigate the impact of proliferation gene expression on efficacy of NAST in sTIL-high and sTIL-low TNBC. **Methods:** 110 TNBC patients treated with neoadjuvant chemoimmunotherapy (Carboplatin+Docetaxel+Pembrolizumab) on the phase II NeoPACT trial (NCT03639948) with available whole exome RNA sequencing were included. sTILs were scored in 5% increments by H&E. Tumors were defined as sTIL-high (≥ 20% sTILs) or sTIL-low (< 20% sTILs). The *ImmSig* Proliferation Signature score (ProlifSig) was computed from RNA sequencing data and samples were classified as ProlifSig-high (≥ median) or ProlifSig-low (< median). ProlifSig was tested for prediction of pCR in sTIL-high and sTIL-low groups. Logistic regression was used to examine the independent prognostic utility of sTILs and ProlifSig on pCR. **Results:** 63/110 (57%) patients achieved a pCR. 56/110 (51%) patients were classified as sTIL-high, and 54/110 (49%) classified as sTIL-low. sTILs and ProlifSig as continuous variables were each predictive of pCR (OR = 1.022, 95%CI = 1.009-1.035, P= 0.001 for sTILs; OR = 2.682, 95%CI = 1.23-5.85, P= 0.01 for ProlifSig). In the sTIL-high group, ProlifSig was not associated with pCR either as a continuous score (AUC = 0.56) or when assessed as high/low categories (pCR 78% vs. 67% in ProlifSig-high and ProlifSig-low groups, respectively; OR = 1.79, 95%CI = 0.54-5.89, P= 0.34). In contrast, in the sTIL-low group, ProlifSig was significantly associated with pCR both as continuous score (AUC = 0.74) and when assessed as high/low categories (pCR 57% vs. 29% in ProlifSig-high and ProlifSig-low groups, respectively; OR = 3.18, 95%CI = 1.03-9.86, P= 0.045). On multivariate analysis, sTILs and ProlifSig were independent predictors of pCR (OR = 1.02, 95%CI = 1.01-1.03, P= 0.004 for sTILs; OR = 3.13, 95%CI = 1.44-6.83, P= 0.004 for ProlifSig). **Conclusions:** In TNBC patients treated with chemoimmunotherapy sTILs and ProlifSig provide complimentary information for prediction of pCR. ProlifSig is positively associated with pCR in sTIL-low tumors but not in sTIL-high tumors. We hypothesize that the therapeutic response in sTIL-high tumors is dominated by lymphocyte-dependent cytotoxic mechanisms, while in sTIL-low tumors, the response may be dominated by proliferation-dependent responses. ProlifSig could identify a subgroup of immune low TNBCs that can achieve substantial rates of pCR with neoadjuvant chemoimmunotherapy. Research Sponsor: University of Kansas Clinical and Translational Science Institute, Team Michelle, ACS-IRG.

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Oral Abstract Session

Do tumor infiltrating lymphocytes (TILs) predict benefits from trastuzumab therapy for HER2 positive breast cancer? Meta-analysis of individual patient data from 4097 women in 5 trials. *First Author: Robert Kerrin Hills, University of Oxford, Oxford, United Kingdom*

Background: High TIL counts are associated with a lower risk of breast cancer recurrence, especially in women with ER negative, HER2 negative tumors and, possibly, greater benefit from trastuzumab in women with HER2 positive cancer: the FinHER trial reported a differential effect of trastuzumab based upon TIL status. We performed a meta-analysis of randomized trials of trastuzumab in early breast cancer to attempt to validate this finding. **Methods:** TILs were quantified in 4097 women in 5 randomized controlled trials (NSABP B-31, FinHER, HERA, Intergroup N9831, PACS-04). All trials contributed to the Early Breast Cancer Trialists' Collaborative Group individual patient data meta-analysis of trastuzumab for women with HER2 positive tumors which found a significant benefit for trastuzumab therapy. TILs were assessed using established International Guidelines, with HERA using digital TIL-scores. The primary outcome was time to first recurrence. Cox regression analyses, adjusted for trial, treatment allocation, and nodal status, were used to quantify the prognostic value of TILs; and standard stratified logrank tests were used to assess the differential effect of trastuzumab therapy. **Results:** The median percentage TILs was 13% (Interquartile Range 5-30), with fewer than 10% of patients exhibiting TILs >50%. The prognostic value of TILs was confirmed, with patients with higher TILs being at lower risk for recurrence (adjusted hazard ratio per 10% increase in TILs 0.87 (95% CI 0.84-0.90), $p < .0001$) with similar effects in both treatment groups. Outcomes improved steadily with increasing TILs, and unadjusted 10-year recurrence rates fell from 30% in women with TILs <10% to 15% in those with TILs 70% or greater. Consequently, analyses of the predictive effect of TILs were stratified into 5 groups (0-9, 10-19, 20-39, 40-59, 60+). Overall, there was a highly significant benefit of trastuzumab on recurrence (HR 0.62 (0.54-0.70) $p < .0001$), but there was no evidence of any interaction between TILs and the proportional reduction in recurrence ($p = 0.8$ for heterogeneity and trend). **Conclusions:** While higher TILs are associated with lower recurrence rates, there was no indication that the proportional reduction in recurrence with trastuzumab varied by TILs, although the number of patients with high levels was limited. Owing to a lower underlying recurrence rate, absolute benefits from trastuzumab were lower, but still substantial, in women with high TIL tumors. Clinical trial information: NCT00045032, ISRCTN76560285, NCT00005970, NCT00004067, NCT00054587. Research Sponsor: Cancer Research UK.

TILs percentage	HR for trastuzumab	95% CI
0-9 (n=1224)	0.60	0.49 to 0.75
10-19 (n=1049)	0.58	0.46 to 0.74
20-39 (n=1000)	0.69	0.53 to 0.89
40-59 (n=474)	0.67	0.45 to 1.00
60+ (n=350)	0.51	0.30 to 0.87
Stratified total (n=4097)	0.62	0.54 to 0.70

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Rapid Abstract Session

Prognosis and trends in chemotherapy use for patients with stage IA triple-negative breast cancer (TNBC): A population-based study. *First Author: Paolo Tarantino, Dana-Farber Cancer Institute, Boston, MA*

Background: Outcomes for patients with stage IA TNBC in the modern era remain poorly characterized, and the benefit and utilization of adjuvant chemotherapy (chemo) in this setting remains controversial. **Methods:** We analyzed data from women diagnosed with pathological stage IA TNBC in the Surveillance, Epidemiology, and End Results (SEER) database during 2010 to 2019. We evaluated the associations of adjuvant chemo with breast-cancer specific survival (BCSS) stratified by tumor size, using multivariate cox models adjusted for tumor size (overall cohort only), age at diagnosis, race, tumor grade, histology, radiation, marital status, income, and rurality. Frequency of chemo use over time was examined by tumor size. Multivariate logistic regression assessed variables associated with chemo administration. **Results:** In total, we examined data from 8,601 women with stage IA TNBC. Median age at diagnosis was 62 years. Most patients had high-grade tumors (70.1%), ductal histology (92.8%), and received adjuvant chemo (61.6%). Median follow up was 48 months (IQR: 20 – 83). The use of chemo significantly increased during 2010-2019 for both T1b tumors (p for trend = 0.001) and T1c tumors (p for trend < 0.001), with 52.5% and 63% of the patients with T1b and T1c TNBCs receiving chemo in 2010, respectively, compared with 60.5% and 71.1% in 2019. No significant differences were observed in the use of chemo for T1mic (p for trend = 0.567) and T1a (p for trend = 0.637) tumors, with low utilization seen in both cohorts (9.5% overall in T1mic, 22.5% overall in T1a). Variables associated with chemo use included younger age, white race, married status, higher income, more recent diagnosis, higher tumor grade, ductal histology, and larger tumor size (all $p < 0.02$). Overall, 5-year BCSS was high across T groups (> 90%; Table). Receiving chemo (vs. none/unknown) was associated with an improved 5-year BCSS (adjusted HR for BCSS = 0.70, $p = 0.006$). For T1c tumors specifically, adjuvant chemo (vs. none/unknown) was also associated with BCSS (adjusted HR 0.64, $p = 0.002$). The small number of BCSS events precluded comparisons for other tumor size subgroups. Table shows sample sizes and 5-year BCSS rate by chemo receipt for each T group. **Conclusions:** In a large population-based cohort of patients with stage IA TNBC, we observed excellent 5-year BCSS outcomes, supporting the good prognosis of this patient population. The use of adjuvant chemo increased over time for T1b and T1c TNBCs, and was associated with improved BCSS for T1c tumors, although evaluation of benefit is limited by the inherent treatment bias in registry data. Research Sponsor: None.

5-year BCSS by tumor size for patients with stage IA TNBC.					
	T1mi,NO (n = 232)	T1a,NO (n = 960)	T1b,NO (n = 2175)	T1c,NO (n = 5234)	Stage IA overall (n = 8601)
Chemo = Yes	100%	98.05%	96.56%	94.51%	95.16%
Chemo = No/Unknown	99.38%	97.7%	95.76%	91.18%	94.35%
Adjusted p-value	-	-	-	0.002	0.006

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Rapid Abstract Session

Assessment of risk of overall and late distant recurrence by Breast Cancer Index in postmenopausal women with early-stage, HR+ breast cancer in the TEAM trial. *First Author: John MS Bartlett, Cancer Research UK Scotland Centre, University of Edinburgh, Edinburgh, United Kingdom*

Background: Individual risk assessment of distant recurrence (DR) is particularly relevant for early-stage HR+ breast cancer patients, as they face a prolonged risk of recurrence even after adjuvant endocrine therapy. Previously, we have shown that the Breast Cancer Index (BCI) and BCIN+ risk groups are significantly prognostic for risk of overall (0-10y) and late (5-10y) distant recurrence in NO and N1 breast cancer patients, respectively, enrolled in the Tamoxifen and Exemestane Adjuvant Multinational (TEAM) trial. Here, the prognostic performance of BCI and BCIN+ as a continuous risk score for overall and late distant recurrence was evaluated in the TEAM trial. **Methods:** BCI testing was performed blinded to clinical outcome with BCI/BCIN+ risk scores calculated as previously described. Cox proportional hazard models adjusted for age, tumor size, grade and treatments were used to estimate hazard ratios (HRs) and the associated 95% confidence intervals (CIs) for BCI/BCIN+ continuous risk scores. The 10y risk of overall and late DR were estimated as a function of risk scores from the Cox models using Breslow estimates. **Results:** Continuous risk curves for overall and late DR were obtained in patients who did not receive adjuvant chemotherapy and those who remained DR-free at 5 years regardless of chemotherapy, respectively, to reflect the two key time points for breast cancer treatment decision-making. In NO patients not treated with chemotherapy (N = 1197), BCI was significantly prognostic for overall DR with a HR of 1.39 (95% CI 1.25-1.54; $p < 0.001$), while BCIN+ was significantly prognostic in N1 patients who did not receive chemotherapy (N = 1319) with a HR of 4.29 (95% CI 2.93-6.28; $p < 0.001$). Among patients who remained DR-free at 5 years, in the NO subset (N = 1285), BCI was significantly prognostic for late DR with a HR of 1.23 (95% CI 1.07-1.42; $p < 0.001$), while BCIN+ remained to be significantly prognostic in the N1 subset (N = 1762) with a HR of 2.78 (95% CI 1.75-4.43; $p < 0.001$). Similar results were observed in the HER2- subset for both overall and late DR. Continuous risk curves for BCI and BCIN+ for overall and late DR showed an increasing risk of DR with higher BCI/BCIN+ scores. **Conclusions:** Results from this largest BCI study to date further support the use of BCI to provide individualized risk estimates for both overall and late DR in women with HR+ breast cancer to aid in personalized decision-making for adjuvant therapy. Research Sponsor: Hologic.

			N	HR (95% CI)	P value
Overall DR (0-10y)	All Pts	NO	1197	1.39 (1.25-1.54)	< 0.001
		N1	1319	4.29 (2.93-6.28)	< 0.001
	HER2-	NO	978	1.52 (1.34-1.73)	< 0.001
Late DR (5-10y)	All Pts	N1	1132	4.04 (2.66-6.13)	< 0.001
		NO	1285	1.23 (1.07-1.42)	< 0.001
	HER2-	N1	1762	2.78 (1.75-4.43)	< 0.001
		NO	1063	1.31 (1.11-1.53)	< 0.001
		N1	1503	2.87 (1.17-4.81)	< 0.001

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Rapid Abstract Session

Racial/ethnic differences in 21-gene recurrence score and survival among estrogen receptor-positive breast cancer patients. *First Author: Jasmin Gill, University at Buffalo, The State University of New York, Buffalo, NY*

Background: Despite studies on racial/ethnic disparities in breast cancer patients, there is limited literature evaluating association of racial/ethnic differences with 21-gene recurrence score (RS) and survival differences stratified by RS risk categories. We performed an observational cohort study to evaluate such disparities in context of RS. **Methods:** The National Cancer Database (NCDB) was queried for patients with ER-positive, pT1-3N0-1aM0 breast cancer who received surgery followed by adjuvant endocrine therapy with available RS from 2006 to 2018. Racial/ethnic groups were stratified by non-Hispanic White (NHW), Hispanic White (HW), Black, and Asian/Pacific Islander (API). Our primary endpoint was overall survival (OS). Logistic multivariable analysis (MVA) was built upon baseline patient and tumor characteristics to evaluate variables associated with RS > 25. Cox MVA was used to evaluate OS. Interaction term analysis was used to identify heterogeneous association of racial/ethnic groups and RS; if significant, subgroup analyses compared magnitude of racial/ethnic differences stratified by RS. To address immortal time bias, Cox MVA analyses were repeated after excluding patients with post-diagnosis survival < 6 months. P values were two-sided. Bonferroni correction was used for multiple comparisons (NHW vs HW women, NHW vs Black women, and NHW vs API women) with p values less than 0.017 being statistically significant. **Results:** A total of 140,133 women (median [interquartile range (IQR)] age, 60 [52-67] years) were included for analysis. 115,651 (82.5%), 8,213 (5.9%), 10,814 (7.7%), and 5,455 (3.9%) were NHW, Hispanic, Black, and API women respectively. Median (IQR) follow up was 66.2 mo. (48.0-89.8). Logistic MVA showed compared to NHW women, Black women were associated with higher RS (26 or higher vs < 26: adjusted odds ratio [aOR] 1.19, 95% confidence interval [CI] 1.12-1.26, $p < 0.001$), while HW (aOR 0.93, 95% CI 0.86-1.00, $p = 0.04$) and API (aOR 1.03, 95% CI 0.95-1.13, $p = 0.45$) were not. Cox MVA showed compared to NHW, Black women were associated with worse OS (adjusted hazards ratio [aHR] 1.10, 95% CI 1.02-1.19, $p = 0.012$) while HW (aHR 0.85, 95% CI 0.77-0.94, $p = 0.001$) and API (aHR 0.66, 95% CI 0.56-0.77, $p < 0.001$) were not. There was significant interaction between race/ethnicity and RS (interaction $p = 0.006$). Subgroup analysis found similarities in those with RS < 26, while only API women were associated with improved OS among those with RS ≥ 26 . After excluding those with post-diagnosis survival < 6 mo., our findings remained comparable. **Conclusions:** To our knowledge, this is the largest nationwide oncology database study to suggest that Black women are associated with higher RS, while HW and API are not. It also suggests that Black women are associated with worse OS among those with RS < 26, while API are associated with improved OS regardless of RS compared to NHW women. Research Sponsor: U.S. National Institutes of Health.

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Rapid Abstract Session

A randomized controlled trial of a mobile app and tailored messages to improve outcomes among women with breast cancer receiving adjuvant endocrine therapy. First Author: Ilana Graetz, Emory University, Rollins School of Public Health, Atlanta, GA

Background: Adjuvant endocrine therapy (AET) use among women with early-stage, hormone receptor-positive breast cancer reduces the risk of cancer recurrence, but adverse symptoms contribute to lower adherence. We evaluated the effectiveness of an app that integrates patient-reported outcomes with electronic health records and tailored messages. **Methods:** Women with early-stage breast cancer initiating AET (November 2018-June 2021) were randomized into three arms: (1) an “App” group that received instructions and access to the study app and weekly text reminders to use it; (2) an “App+Feedback (AF)” group received additional weekly tailored messages about managing symptoms, adherence, and communication; or (3) a “Usual Care (UC)” group without access to the app. The intervention lasted 6-months and participants completed surveys at enrollment, 6-, and 12-months. Increasing/severe symptoms and missed doses triggered alerts that prompted follow-ups from the oncology team. Outcomes included AET adherence, captured using an electronically monitored pillbox and self-reported adherence, symptom burden (FACT-ES), mental and physical health quality of life (SF-12), self-efficacy for managing symptoms (PROMIS 1.0), and 6-month count of emergency department visits/urgent care/hospitalizations [higher cost encounters] and office visits. **Results:** Overall, 300 women were randomized (102 UC, 96 App, and 102 AF). Median age was 60 years (range: 31–83), 34% identified as Black, 21% had incomes below 200% of the federal poverty level, and 20% had a high school degree or less education. Retention at 12-months was 88% (N=264). Mean app logins were 14.4 among intervention participants, which resulted in 4.2 mean alerts, with 58.0% having at least one alert during the 6-month intervention. AET adherence over 12-months measured using the pillbox was similar across groups: 76% for UC, 73% for App, and 71% for AF ($p=0.57$). At 12-months, AF participants had fewer higher cost care encounters over the previous 6 months (0.30, 95%CI: 0.15 to 0.45, $p=0.01$) compared to UC (0.71, 95%CI: 0.44 to 0.97) but not for App only vs. UC (0.46, 95% CI: 0.25 to 0.66, $p=0.15$). Mean mental health scores were 2.0 points better (95% CI: 0.21 to 3.84) at 6-months for AF (43.0) compared to UC (41.0). There were no statistically significant differences by group in self-reported adherence, symptom burden, physical health, self-efficacy for managing symptoms, and office visits at 6- or 12-months. **Conclusions:** While the intervention did not improve AET adherence, the app combined with tailored messages resulted in better self-reported mental health during the intervention and fewer higher cost care encounters at 12-months without increasing office visits. Symptom monitoring apps with tailored messages may be scalable and effective strategies for improving outcomes for patients with breast cancer. Clinical trial information: NCT03592771. Research Sponsor: U.S. National Institutes of Health.

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Poster Discussion Session

ECOG-ACRIN E2197: Comparison of HER2 gene expression by RT-PCR across all HER2 immunohistochemistry groups with recurrence analysis. First Author: Nhu Thuy Can, Genomic Health Inc, an Exact Sciences Corporation (Redwood City, CA), Redwood City, CA

Background: Accurate assessment of HER2-low [immunohistochemical (IHC) score of 1+ or 2+ and in-situ hybridization negative] breast cancer is clinically relevant following DESTINY-Breast04. In hormone receptor positive breast cancers, Oncotype DX assay Recurrence Score results are widely used to guide adjuvant chemotherapy selection, and standardized quantitative HER2 mRNA reference-normalized expression levels by RT-PCR are included in patient reports. Previously, a high degree of concordance between central IHC and quantitative HER2 by RT-PCR was demonstrated in E2197. Here, we compare quantitative HER2 gene expression using Oncotype DX assay within all IHC subgroups and risk of recurrence in E2197. **Methods:** Data analyzed were from a case-control sample from E2197 (no adjuvant anti-HER2 therapy) of 755 patients. Central IHC for HER2 used duplicate 1.0 mm microarrays (HercepTest, Dako) and scored per 2007 ASCO/CAP guidelines. Based on quantitative reference-normalized RT-PCR measures of HER2 expression, cases were assigned: positive ≥ 11.5 units, equivocal ≥ 10.7 to < 11.5 units, and negative < 10.7 units (1 unit increase represents ~2-fold increase in RNA). Spearman's rank correlation was used to measure strength of association between the 2 methods. Cox proportional hazards regression was used to evaluate the association between quantitative HER2 expression and recurrence (defined as invasive breast cancer in local, regional, or distant sites). Analyses were weighted to account for study design. **Results:** 48% were IHC 0, 11% were IHC 1+, 23% were IHC 2+, and 18% were IHC 3+. 85% were HER2 negative, 3% equivocal, and 11% positive by RT-PCR. While there was moderately strong correlation between HER2 IHC and HER2 gene expression by RT-PCR [Spearman's rho: 0.63 (95% CI: 0.59, 0.67); $p<0.001$], there were wide and overlapping ranges of HER2 gene expression across all IHC categories with almost identical medians and inter-quartile ranges for HER2 IHC 1+ and 2+ ($n=248$; see table). An exploratory analysis showed 86% of IHC 0, 97% of IHC 1+, and 99% of IHC 2+ had HER2 > 8 units. After controlling for baseline clinicopathologic features (age, hormone receptor status, grade, size, and nodal status), continuous quantitative HER2 expression was associated with time to recurrence in HER2 IHC 0 to 2+ [HR 1.17 per 1-unit increase in HER2 (95% CI 1.01, 1.35; $p=0.036$)]. **Conclusions:** There was a wide range of quantitative HER2 gene expression using Oncotype DX assay across all IHC categories; continuous HER2 expression is independently associated with recurrence. Quantitative HER2 expression may be useful for identification of HER2-low breast cancer. Further studies are needed. Research Sponsor: None.

	Overall	HER2 IHC			
		0	1+	2+	3+
HER2 RT-PCR					
Median	9.7 (8.9, 10.3)	9.1 (8.4, 9.8)	9.7 (9.3, 10.2)	9.8 (9.3, 10.3)	12.3 (10.6, 13.2)
(25 th , 75 th percentile)					
Min, Max	5.8, 15.1	5.8, 14.9	7.9, 13.5	7.7, 11.4	9.1, 15.1

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Correlation of HER2 low status in I-SPY2 with molecular subtype, response, and survival. First Author: Hope S. Rugo, University of California Comprehensive Cancer Center, San Francisco, CA

Background: HER2low, defined as immunohistochemical (IHC) 1+ or 2+ without HER2 gene amplification, predicted improved progression free and overall survival with trastuzumab deruxtecan (TDXd) compared to chemotherapy in patients (pts) with metastatic breast cancer in Destiny Breast04. Controversy exists regarding the correlation of HER2low with molecular subtypes and outcome. We evaluated these associations in the neoadjuvant I-SPY2 trial. **Methods:** We investigated HER2 IHC class in pts with clinically HER2-negative breast cancer (BC) enrolled in the first 10 arms of I-SPY2. To explore the biology of HER2low, we used Fisher's exact test to assess association of IHC class (0 vs 1+ or 2+) with Response Predictive Subtypes-5 (RPS-5; based on immune, DNA repair damage (DRD), HER2, and luminal markers; PMID: 35623341), SET index [endocrine responsiveness], and Mammaprint high1 (MP1) vs high2 (MP2). Association with pathologic complete response (pCR) was assessed using Fisher's exact test, and association with distant recurrence free survival (DRFS) was assessed using Cox Proportional Hazards modeling. **Results:** Of 742 HER2negative pts enrolled in the first 10 arms of I-SPY2, local HER2 IHC is available for 585; 299 hormone receptor + (HR+) and 286 triple negative (TN). 63% of pts are HER2low, with HER2low status more frequent in HR+ (71%) compared to TN BC (55%; OR = 1.97; $p = 0.00011$). There was no clear relationship between HER2low IHC and RPS-5 subtypes or endocrine sensitivity measured by the SET index. There was no significant association of HER2low with pCR overall or within treatment arms ($p > 0.05$); this was true for TN and HR+ subsets. 562 pts with HER2negative disease have distant recurrence free survival (DRFS) data with a median follow-up of 4.23 yrs. Pts with pCR had excellent outcome (5yr DRFS $> 94\%$), with no impact from HER2low vs 0 status. For pts with nonpCR, after adjusting for HR+ status, the DRFS hazard ratio for HER2low vs 0 status is not significant [0.68(0.46-1.02)]. Within HR+, HER2low is found in $> 70\%$ for both SET low and high. HR+/MP1 pts (with generally low pCR rates) are significantly more likely to be HER2low (75%; (172/219)) compared to HR+/MP2 (61%; (49/80)) (OR: 1.79; Fisher $p = 0.044$). Importantly, 70% of HER2-Immune-DRD- (78% HR+ and 56% TN), a subtype with low response to all I-SPY2-tested agents, are HER2low. **Conclusions:** In I-SPY2 which enrolls patients with MP high risk BC, HER2low by IHC was frequent and higher in HR+ than TN disease. There was no clear association with molecular markers, pCR or DRFS. The frequency of HER2low in the immune-DRD- subtype raises the potential for exploring T-DXd in this high risk, low-response setting. Clinical trial information: NCT01042379. Research Sponsor: U.S. National Institutes of Health; Quantum Leap Healthcare Collaborative.

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Poster Discussion Session

AI-based HER2-low IHC scoring in breast cancer across multiple sites, clones, and scanners. First Author: Patrick Frey, Mindpeak GmbH, Hamburg, Germany

Background: Assessment of immunohistochemical (IHC) HER2 expression plays a pivotal role in breast cancer diagnostics. In the era of HER2-low and HER2-targeted antibody drug conjugates, accurate discrimination of defined HER2 IHC scores is essential. At the same time, HER2 IHC scoring suffers from poor interobserver concordance. Artificial intelligence (AI) may optimize this scoring in regard to standardization, accuracy and efficiency, but previous approaches fail to show the required consistency across samples from different sites, clones and scanning hardware. **Methods:** We have investigated the use of an AI-based HER2 IHC quantifier software to support pathologists in standardized HER2 IHC assessment in breast cancer. Validation specimens were derived from four institutions and five scanners. Using the “region of interest” (ROI) software version (part I), pathologists choose the ROI to be assessed within the whole slide image (WSI). In contrast, the fully automatic version (part II) analyzes the complete WSI. Part I: Three pathologists selected one ROI per slide from a cohort of $n = 150$ specimens. They scored HER2 expression in these ROIs (path-only) according to ASCO/CAP 2018 guidelines (each pathologist $n = 50$). After a 2-week washout period, the same pathologists were presented with the same ROIs and corresponding AI-suggested results (AI-only), and then decided on final HER2 scores (AI-assisted). Scoring times were recorded. Part II: Fully automatic AI accuracy without human intervention was analyzed using the WSI cohort of part I and an additional cohort of $n = 94$ WSIs. For both parts, IHC scores were compared to the clinical workflow derived ground truth defined as the manually assessed HER2 IHC score. **Results:** Part I: In discriminating HER2-neg from HER2-low/pos cases, AI-assisted and AI-only ROI scoring showed agreement rates of 91.3% and 86.7%, respectively, with path-only decisions across all institutions and scanners. In discriminating the four HER2 scores (0, 1+, 2+, 3+) individually, interrater-agreement of AI-assisted vs. path-only ROI HER2 scoring was 78.7%, exceeding literature rates of $< 70\%$, with the mean scoring time per ROI being 29 sec vs. 50 sec, respectively; interrater-agreement of AI-only vs. AI-assisted was 85.3%. Part II: In discriminating HER2-neg from HER2-low/pos cases, fully automatic AI WSI scoring showed 89.1%/86.2% agreement for both cohorts, respectively. **Conclusions:** Across challenging validation data from four institutions and five scanners, scoring with the support of an AI HER2 IHC quantifier software showed very high agreement when discriminating HER2-neg from HER2-low/pos cases and high accuracy for general HER2 scoring. When using AI-assistance, scoring time was reduced by almost 50%. Altogether, these results demonstrate the potential of AI solutions to increase consistency and efficiency of HER2 scoring and ultimately to improve patient outcome. Research Sponsor: None.

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Poster Discussion Session

Outcomes according to treatment received for small node-negative HER2+ breast tumors in the Surveillance, Epidemiology, and End Results (SEER) database, 2010-2019. *First Author: Adrienne Gropper Waks, Dana-Farber Cancer Institute, Boston, MA*

Background: The magnitude of systemic therapy (tx) benefit for small, node-negative HER2+ breast tumors is unknown, with uncertainty about how benefit varies across stage I tumor sizes. We analyzed treatment patterns and outcomes for patients (pts) with stage IA (pT1N0) HER2+ breast cancer in the national SEER database. **Methods:** Pts with one lifetime diagnosis of pT1N0 HER2+ breast cancer between 2010-2019 were included. Receipt of chemotherapy (chemo) was categorized as yes vs no/unknown; receipt of endocrine tx is not available in SEER. All systemic tx was administered in the adjuvant setting. The primary outcome variable was breast cancer-specific survival (BCSS; recurrence events are not available in SEER), which was compared between treatment groups using a multivariate Cox model adjusted for age at diagnosis (dx), race, tumor grade/histology/size, hormone receptor (HR) status, radiation, marital status, income, rurality. Chemo use predictors were evaluated by multivariable logistic regression. **Results:** We identified 12,861 pts with pT1N0 HER2+ breast cancer; 9,513 (74%) HR-positive and 3,348 (26%) HR-. Median age at dx was 59 yrs. Median follow-up was 46 months. In the overall cohort, BCSS at 3, 5, and 7 yrs was: 99.3% (with chemo) vs 99.1% (without chemo); 98.6% (with chemo) vs 97.4% (without chemo); and 97.5% (with chemo) vs 96.4% (without chemo), respectively. Adjusted hazard ratio (HzR) for BCSS events in the chemo vs no chemo group of the overall cohort was 0.63 (p=0.004). BCSS events by tumor size and HR status are shown; p values are not shown where event rates were too low to run an adjusted model. Chemo use increased significantly between 2010-2019 within each tumor size category (all p for trend < 0.04), except for T1a HR+/HER2+ and T1mi HR-/HER2+. Pts were less likely to receive chemo if they were older, Hispanic (vs non-Hispanic White), separated/divorced/widowed (vs single), or had lower median household income (vs > \$75K). Pts were more likely to receive chemo if they had larger tumor size, HR- tumor, higher tumor grade, were married (vs single), or had later yr of dx. **Conclusions:** Receipt of chemo was associated with higher BCSS in the overall stage IA cohort and among pts with HR+/HER2+ stage IA tumors. Tumors ≤ 1cm had excellent outcomes with or without chemo. Sociodemographic factors including income, race, and marital status impacted chemo receipt. Research Sponsor: None.

5 yr BCSS for stage IA HER2+ breast cancer.					
HR+/HER2+	Overall N=9513	pT1mi N=503	pT1a N=1477	pT1b N=2439	pT1c N=5094
Chemo: yes	99.0%	100%	99.8%	99.3%	98.7%
Chemo: no/unk	97.5%	99.1%	98.9%	97.6%	95.9%
Adjusted HzR / p-value	0.60/0.009	-	-	0.67/0.421	0.60/0.02
HR-/HER2+	Overall N=3348	pT1mi N=492	pT1a N=729	pT1b N=712	pT1c N=1415
Chemo: yes	97.6%	100%	98.4%	98.9%	96.7%
Chemo: no/unk	97.3%	99.6%	98.3%	98.6%	92.1%
Adjusted HzR / p-value	0.70/0.19	-	-	-	0.61/0.137

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Oral paclitaxel, carboplatin, and dostarlimab (OPE/Cb/D) without and with trastuzumab in early-stage, high-risk breast cancer: Results from the neoadjuvant I-SPY 2 TRIAL. *First Author: Kay T Yeung, University of California, San Diego, La Jolla, CA*

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2023, issue of the *Journal of Clinical Oncology*.

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Gene expression signatures, stromal tumor infiltrating lymphocytes (sTILs), and change in tumor cellularity to predict pathological complete response (pCR) after 12 week de-escalated neoadjuvant endocrine therapy (ET) vs paclitaxel + dual HER2 blockade in the WSG-TP-II trial. *First Author: Monika Karla Graeser, West German Study Group, Moenchengladbach, Germany*

Background: There are limited data on predictive biomarkers for de-escalated ET or chemotherapy with dual anti-HER2 blockade in HR+/HER2+ early breast cancer (BC). In this translational pre-planned project of the WSG-TP-II phase II-trial (NCT03272477), we aimed to identify associations of gene expression signatures and sTILs with pCR. **Methods:** Patients with cT1c-cT4c, cN0-3 centrally confirmed HR+/HER2+ BC were randomized to 12 weeks of standard ET (n = 100) or paclitaxel (Pac; n = 107). All patients received trastuzumab + pertuzumab (T+P) q3w as neoadjuvant and adjuvant treatment. Gene expression signatures were analyzed using NanoString BC360 panel in baseline biopsies (T+P+ET: n = 72; T+P+Pac: n = 78). sTILs were analyzed in 93 (T+P+ET) and 97 patients (T+P+Pac) at baseline and in 65 (T+P+ET) and 57 patients (T+P+Pac) at week 3. Impacts of standardized BC360 gene expression signatures and sTILs on pCR (ypT0/is ypN0; primary endpoint) expressed in odds ratios (OR) were estimated by logistic regression analysis. **Results:** pCR rate in patients with BC360 analysis was 39.3% (T+P+ET: 23.6%; T+P+Pac: 53.9%). Overall, ERBB2 (OR 2.37; 95%CI 1.55, 3.62) and cytotoxic cells signature (OR 1.42; 95%CI 1.02, 1.99) were favorable for pCR, while apoptosis (OR 0.64; 95%CI 0.44, 0.92), estrogen receptor 1 (OR 0.60; 95%CI 0.42, 0.85), estrogen receptor signaling (OR 0.64; 95%CI 0.45, 0.91), and progesterone receptor (OR 0.67; 95%CI 0.47, 0.94) signatures were unfavorable. Analyzing by treatment arm, a similar pattern was observed in the T+P+Pac arm (ERBB2: OR 2.01; apoptosis: OR 0.59; estrogen- and progesterone-related signatures: OR 0.41-0.58), but not in the T+P+ET arm where only ERBB2 was prognostic for pCR (OR 7.24; 95%CI 2.12, 24.05). Baseline ≥30% sTIL levels (vs < 30% sTILs; n = 16 vs n = 174) were associated with pCR (OR 5.16; 95%CI 1.60, 16.66); significance was not achieved in either trial arm. Compared to < 30% sTILs (n = 90), low tumor cellularity at week 3 precluding sTILs analysis (< 500 invasive tumor cells, n = 22), but not ≥30% sTILs (n = 10), was prognostic for pCR in all patients (OR 9.47; 95%CI 2.94, 30.50) and in individual trial arms (OR 6.00-11.79). **Conclusions:** This hypothesis-generating translational results suggest that gene expression signatures (particularly ERBB2), baseline sTILs, and low tumor cellularity at week 3 predict pCR after ET + double HER2 blockade. Future neoadjuvant trials are needed to prospectively test the use of baseline gene expression and sTILs analysis, and early on-treatment cellularity measurement to select patients with HR+/HER2+ tumors for de-escalated endocrine-therapy-based approaches. Clinical trial information: NCT03272477. Research Sponsor: Roche Pharma AG.

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Poster Discussion Session

MammaPrint Index as a predictive biomarker for neoadjuvant chemotherapy response and outcome in patients with HR+HER2- breast cancer in NBRST. *First Author: Peter D. Beitsch, Dallas Surgical Group, Dallas, TX*

Background: Hormone receptor positive (HR+), HER2- early stage breast cancer (ESBC) is a heterogeneous disease that has shown lower response to neoadjuvant chemotherapy (NCT) compared with other clinicopathologic subtypes. Genomic profiling may help inform neoadjuvant treatment decisions for ESBC by predicting likelihood of pathological complete response (pCR) or chemosensitivity. The 70-gene MammaPrint (MP) test classifies ESBC patients as having a Low or High Risk of distant metastasis. In the I-SPY2 trial, further stratification of MP High Risk into High 1 (H1) or High 2 (H2) improved prediction of chemosensitivity, with significantly higher pCR rates in H2 vs. H1 tumors, particularly in response to immune therapy. Here we evaluate the utility of H1/H2 risk as a biomarker for chemosensitivity and 5 year distant-metastasis free survival (DMFS) in NCT treated patients from the Neoadjuvant Breast Registry Symphony Trial (NBRST). **Methods:** NBRST (NCT01479101) is an observational prospective study that included 1069 patients with ESBC who received neoadjuvant therapy. Patients with HR+HER2-, MP High Risk tumors who received NCT were included in this analysis (n = 327). Patients were further stratified into H1 (score ≤ 0, > -0.57) or H2 (score ≤ -0.57) groups. Differences in pCR between MP High Risk subcategories were assessed by two-sided proportional z-test. Differences in DMFS was evaluated by Kaplan Meier analysis and log-rank test. **Results:** MP classified 198 (61%) patients with H1 tumors and 129 (39%) patients with H2 tumors. Age, tumor stage, and lymph node status were comparable between both groups. However, there was a higher proportion of Grade 3 tumors in the H2 group. A significantly higher percentage of pCR was achieved in H2 tumors (30/129; 23%) vs. H1 tumors (12/198; 6.1%) (p < 0.001). Median follow-up was 5.3 years. The 5-year DMFS (% [95% CI]) was significantly worse for patients with H2 tumors (64.8 [55.9 – 75.1]), with most events occurring early (< 3 years), compared with H1 tumors (77.1 [70.4 – 84.3]; p = 0.012). Patients with H1 tumors that achieved pCR had improved 5-year DMFS (81.8 [61.9 – 100]) compared to H1 tumors that did not achieve pCR (76.8 [69.9 – 84.4]; p = 0.009). Patients with H2 tumors that had a pCR demonstrated significantly better 5-year DMFS (80.7 [65.3 – 99.8]) than patients with residual disease (60.2 [50.1 – 72.4]; p = 0.009). **Conclusions:** These data suggest MammaPrint predicts pCR in HR+HER2- BC patients, with H2 risk tumors exhibiting higher chemosensitivity than H1 tumors. Patients with either H1 or H2 tumors that achieved pCR had similar outcomes, which were significantly improved compared to those with residual disease. Notably, the worst outcomes were observed among patients with H2 risk and residual disease; it should be investigated whether addition of immune therapy to standard NCT would enhance the pCR rates in this patient population. Clinical trial information: NCT01479101. Research Sponsor: Agendia Inc.

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Poster Discussion Session

Primary efficacy analyses of NeoRHEA, neoadjuvant biomarker research study of palbociclib combined with endocrine therapy in estrogen receptor positive/HER2 negative breast cancer. *First Author: Elisa Agostinetto, Université Libre de Bruxelles (ULB), Hôpital Universitaire de Bruxelles (HUB), Institut Jules Bordet, Academic Trials Promoting Team (ATPT), Brussels, Belgium*

Background: CDK4/6 inhibitors (CDK4/6i) and endocrine therapy (ET) are standard of care in the treatment of estrogen receptor (ER) positive, HER2-negative (ER+/HER2-) advanced breast cancer (BC). We tested palbociclib + ET as neoadjuvant therapy to identify baseline biomarkers of no response. **Methods:** NeoRHEA (NCT03065621) was a phase II, single arm trial evaluating 4 months of neoadjuvant palbociclib and ET in pre- or post-menopausal women with ER+/HER2- early BC. The primary objective was to identify biomarkers of no response by locally-assessed ultrasound (US) using RNA-seq on baseline (pretreatment) tumor biopsies. No response to treatment was defined as stable or progressive disease (SD or PD) at post-treatment US based on WHO criteria. Secondary endpoints included residual cancer burden (RCB) of 3 and absence of complete cell cycle arrest (CCCA) defined as Ki67 by immunohistochemistry (IHC) $> 2.7\%$ at surgery. We evaluated baseline clinicopathological characteristics, RNA-seq derived PAM50 subtypes and mRNA expression of *ESR1*, *Ki67*, *CCNE1*, *RB1* and *CDK6* single genes according to US response and CCCA. We also performed gene set enrichment analysis (GSEA) for 50 gene sets related to cancer hallmarks according to US response and CCCA. **Results:** 73 of 100 patients enrolled had baseline frozen tumors with enough cellularity and successful RNA-sequencing performed. Among the 73 patients, 70% were post-menopausal, 84% had cT2 and 70% cN0 tumors, 75% had invasive ductal carcinoma and 66% had histological grade 2 tumors. RNA-seq derived PAM50 subtypes were Luminal A, Luminal B, and non-Luminal in 56%, 36% and 8% of patients, respectively. Among the 73 patients, 31 (42%) had absence of US response (28 and 3 patients had stable and progressive disease by US, respectively) and 23 (31%) had RCB 3 tumors. Fifty-three of 73 patients had Ki67 by IHC available at surgery out of whom, 14 (26%) had absence of CCCA. Neither baseline clinicopathological characteristics nor PAM50 subtypes nor expression of *ESR1*, *Ki67*, *CCNE1* and *RB1* were associated with absence of US response or absence of CCCA. Interestingly, we observed higher baseline mRNA expression of *CDK6* in patients with absence of US response ($p = 0.039$) or those with no CCCA ($p = 0.004$). We observed an enrichment in inflammatory / IFN- γ response and proliferation-related, G2M checkpoint gene sets in patients with US response (NES: 2.06, 2.30, 1.47; FDR: 7.04e-9, 5.48e-17, 0.0193 respectively) and an enrichment in early estrogen response gene set in patients with absence of US response (NES: -1.78, FDR: 0.0006). No signaling pathway was enriched in patients without CCCA. **Conclusions:** High pre-treatment mRNA expression of the *CDK6* gene was associated with no US response or absence of CCCA in patients treated with neoadjuvant palbociclib and ET. Independent validation is needed. Clinical trial information: NCT03065621. Research Sponsor: Pfizer; Fondation Contre le Cancer.

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Axillary surgery efficacy for patients with breast cancer receiving neoadjuvant chemotherapy on NSABP B40 and B41. *First Author: Raymond Mailhot Vega, Department of Radiation Oncology, University of Florida College of Medicine, Jacksonville, FL*

Background: Alliance A011202 is evaluating the efficacy of axillary lymph node dissection (ALND) compared to regional nodal irradiation (RNI) for patients with cN1 breast cancer who receive neoadjuvant chemotherapy (NCTX) that becomes ycN0 but remains pN+. In the absence of its publication, level I guidance does not exist regarding the optimal axillary surgery for patients receiving NCTX. We sought to evaluate outcomes across two national contemporary clinical NCTX trials based on axillary and breast response to NCTX, particularly if more aggressive surgery was associated with more favorable outcomes. **Methods:** With IRB approval (IRB201802781), we obtained data from NCTX trials NSABP B40 and B41. B40 enrolled women with HER2- disease, and B41 enrolled those with HER2+ disease. RNI and axillary surgery were selected at physician discretion and not protocolled. Patients received sentinel lymph node biopsy (SLNB), SLNB+ALND (S+ALND), or ALND. We examined outcomes of locoregional recurrence (LRR), distant recurrence (DR), disease free survival (DFS), and overall survival (OS). Univariable and multivariable analyses of B40 and B41 data were performed to evaluate the associations of axillary surgery with the outcomes above, adjusting for age, tumor subtype, mastectomy or not, breast pathologic complete response (pCR), axillary pCR, tumor subtype, regional nodal irradiation, and grade. Kaplan-Meier estimation was used for OS and DFS, with cumulative incidence function for LRR and DR. **Results:** Median follow-up for studies B40 and B41 were 4.5 and 5.1 years, respectively, including 1154 and 504 patients for analysis. A total of 786 (47%) patients were cN+, and of those, 377 had a pCR (48%). 440 (27%), 505 (31%), and 663 (41%) patients had SLNB, S+ALND, and ALND respectively. 855 (52%) and 803 (48%) patients had mastectomy and lumpectomy, respectively. 783 (51%) received RNI. For the 518 ypN+ patients on B40, 7/25 (SLNB), 69/234 (S+ALND), and 107/259 (ALND) experienced an event. DFS at 5 years was 71%, 68%, and 56% for the SLNB, S+ALND, and ALND groups respectively with ypN+ on B40. For the 112 ypN+ patients on B41, 3/6, 15/43, and 27/63 experienced an event. DFS at 5 years was 50%, 64%, and 55% for the SLNB, S+ALND, and ALND groups, respectively, with ypN+ on B41. In multivariable analyses for the combined population of B40 and B41 for LRR, DR, DFS, and OS, SLNB was never associated with a higher chance of relapse or inferior survival ($HR > 1$) compared to S+ALND or ALND. **Conclusions:** Among women prospectively treated on national trials with NCTX and axillary surgery and RNI selected at physician discretion, receipt of SLNB alone was not associated with a higher likelihood of recurrence compared to S+ALND or ALND. Anticipated results of A011202 will provide level I guidance on axillary surgery for patients with cN1 disease converting to cN0 post-NCTX. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology; U.S. National Institutes of Health.

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Poster Discussion Session

A randomized controlled trial comparing primary tumor resection plus systemic therapy with systemic therapy alone in metastatic breast cancer (PRIM-BC): Japan Clinical Oncology Group study JCOG1017. *First Author: Tadahiko Shien, Okayama university hospital, Okayama-Shi, Japan*

Background: The possibility of primary tumor resection (PTR) improving the survival of de-novo Stage IV breast cancer (dn-StIV BC) patients has been evaluated by several prospective studies but remains controversial. We designed this phase 3 trial (JCOG1017) comparing with/without primary dissection after initial systemic therapy based on clinical subtype in dn-StIV BC patients. **Methods:** Dn-StIV BC patients were enrolled in the first registration. All patients received systemic therapies according to clinical subtypes. The patients not showing refractory disease were randomized to systemic therapy alone (arm A) or PTR plus systemic therapy (Arm B). The same systemic therapy was continued after randomization as additional therapy, for as long as possible. The primary endpoint was overall survival (OS). Secondary endpoints included the proportion of patients without progression at metastatic sites after initial systemic therapies for 3 months, local relapse-free survival (LRFS), primary tumor resection-free survival, and incidence of local ulcer/local bleeding and adverse events. The median overall survival time (MST) after initial systemic therapy for patients with dn-StIV BC was 20 months, on average, and a clinically relevant prolongation of the MST of Arm B was considered to be 6.0 months or longer (hazard ratio: 0.77). The required number of events was 359, to obtain a statistical power of 80% with a one-sided significance level of 0.05. Thus, the planned sample size was 410 patients for the second registration, assuming an accrual period of 7 years and a follow-up time of 4 years. **Results:** 570 patients were enrolled between 11/5/2011 and 31/5/2018 in the first registration. Of these, 407 eligible patients were randomized to either Arm A (N = 205) or Arm B (N = 202). The patient characteristics were well balanced between the two arms. The MST of randomized patients was 70 months, with 221 deaths. The difference in OS was not statistically significant (HR 0.857, 90% CI 0.686-1.072, one-sided $p = 0.1283$). MST was 69 months in Arm A and 75 in Arm B. The proportions of patients without progression at metastatic sites in Arms A and B were 81.5% and 67.3%, respectively ($p = 0.0014$). LRFS in Arm B was significantly longer than that in Arm A (median LRFS 20 vs 63 months: HR 0.415, 95% CI 0.327-0.527, $p < 0.0001$). In Arm B, patients with incomplete resection had poorer outcomes than those in whom resection was complete (94 vs. 61 months, HR 1.971 (1.161-3.347) $p = 0.0120$). In the subgroup analysis, PTR improved survival in patients with ER-positive tumors, pre-menopausal status or single-organ metastasis. **Conclusions:** PTR is not recommended for all dn-StIV BC patients but can control local disease and is acceptable in a select population of patients because of the clear improvement in local control. Clinical trial information: UMIN000005586. Research Sponsor: Japan Agency for Medical Research and Development, the National Cancer Research and Development Fund.

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Poster Discussion Session

Long-term oncologic outcomes after omitting axillary surgery in older women with early stage, node-negative breast cancer: A systematic review and meta-analysis. *First Author: Mariam Rana, Harvard T.H. Chan School of Public Health, Boston, MA*

Background: In 2016, Choosing Wisely recommended the omission of routine sentinel lymph node biopsy (SLNB) in early stage, clinically node-negative, hormone receptor-positive, Her2-negative breast cancer in women ≥ 70 years old, although data supporting this was limited. Our study aimed to examine the long-term impact of omitting axillary staging in elderly women undergoing surgery for early stage, clinically node-negative breast cancer. **Methods:** A systematic review and meta-analysis was conducted. Medline (Ovid) and Embase were searched for published papers and abstracts using a systematic search strategy. Randomized and observational studies comparing women aged ≥ 70 years of age with early-stage, clinically node-negative breast cancer undergoing surgery for breast cancer with and without axillary staging, were included. Included studies reported at least one of the following outcomes: axillary recurrence (primary outcome), disease-free survival (DFS), breast cancer-specific survival (BCSS), and overall survival. Risk ratios (RR) were calculated as summary estimates for all outcomes. A weighted pooled mean difference and 95% CI was calculated using a random-effects inverse variance meta-analysis for each outcome. Heterogeneity was calculated using I^2 statistics, and explored using meta-regression. The Newcastle-Ottawa Scale was used to assess the methodological quality of eligible trials, based on the selection of patients, comparability of cohorts, and the methods of outcome assessment. **Results:** Nine studies were eligible for meta-analysis, including data for 48,523 patients. For the primary outcome of axillary recurrence, data for 3,591 patients was meta-analyzed. Axillary staging was found to reduce the risk of axillary recurrence compared to no axillary staging, although this was not statistically significant (RR 0.59, 95% CI: 0.26 to 1.35, $I^2 = 46.6\%$, $p = 0.21$). For overall mortality, data for 14,981 patients was meta-analyzed, and a statistically significant protective effect of axillary staging on overall mortality was demonstrated (RR 0.55, 95% CI: 0.33 to 0.90, $I^2 = 78.1\%$, $p = 0.003$). No significant differences were observed in DFS (RR 1.02, 95% CI: 0.51 to 2.07, $I^2 = 0.0\%$, $p = 0.37$) and BCSS (RR 0.96, 95% CI: 0.57 to 1.62, $I^2 = 0.0\%$, $p = 0.78$). **Conclusions:** Omission of axillary surgery to stage the axilla may be associated with a higher risk of overall mortality in older women with early-stage breast cancer compared to those who undergo axillary surgery. Omission of axillary surgery in this patient population should be carefully tailored to the individual patient, taking into consideration co-morbidity, life expectancy, and formal measures of frailty. Randomized trials are required to further explore the oncologic safety of omitting axillary staging in women aged 70 years or older undergoing breast cancer surgery. Research Sponsor: None.

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Poster Session

Differences of prediction performances by multigene assays in patients with breast cancer with distinct genetic backgrounds. *First Author: Fei Xing, Department of Oncology, Shengjing Hospital of China Medical University, Shenyang, China*

Background: The 21-gene (Oncotype Dx), PAM50 (Prosigna) and Chinese-based 28-gene (RecurIndex) are validated genomic assays that provide prognostic information for distant recurrence risk in patients with hormone receptor (HR)-positive, HER2-negative early breast cancer (EBC). In this study, we aim to compare the differences in prediction performance by different multigene assays and gene expression profiles between the Eastern and the Western. **Methods:** Under the Affymetrix U133 platforms, the differences in gene expressions and risk scores from the Eastern population comprised of GSE20685 (n = 327) and part of GSE45255 (n = 95), and the Western population GSE25066 (n = 508) and the European in GSE45255 (n = 44) were analyzed respectively. Patients were stratified by 21-gene Recurrence Scores (RS) of low (0-10), intermediate (11-25) and high (26-100) and categorized by ROR-S score of PAM50 of low (0-40), intermediate (41-60) and high (61-100). For 28-gene, a recurrence index for distant recurrence (RI-DR) cutoff of 33 was used to classify patients into high- and low-risk groups. Wilcoxon rank test was used to test for continuous variables and the chi-square test was used for categorical variables. **Results:** The Western population has significantly higher RS (85.9 vs. 65.5, $p < 0.001$) and ROR-S (57.4 vs. 53.7, $p = 0.034$) scores than the Eastern population. The distribution of 28-gene risk groups was significantly different between races with a higher proportion of high-risk in the Western (10.5% vs. 6.6%, $p = 0.035$). The low-risk patients in the Eastern stratified by 28-gene assay had significantly higher distant metastasis-free survival (DMFS) rates than high-risk (80% vs. 52%, $p < 0.001$), which compared with Oncotype Dx RS (96% vs. 76%, $p < 0.001$) and PAM50 ROR-S (93% vs. 72%, $p < 0.001$). At the same time, the analysis of gene expressions revealed significantly high expressions of *YWHA*, *SF3B5*, *CKAP5*, and *DDX39A* in the Eastern than that in the Western. However, most genes from 21-gene and ROR-S were more highly expressed in the Western than that in the Eastern. **Conclusions:** 21-gene and PAM50 provide the good performance and show similar patterns in the prognosis of EBC; However, the DMFS rate of the high-risk in the Eastern population determined by 28-gene was much lower than 21-gene and PAM50, which means there are bigger chemo-benefit in the high-risk from 28-gene. In conclusion, 28-gene has better performance in the prognosis of the Eastern population and is a more suitable tool for Eastern breast cancer patients. Research Sponsor: None.

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Poster Session

Differential benefit of capecitabine-based chemotherapy among TNBC subtypes in the context of the CBCSG010 study. *First Author: Junjie Li, Shanghai Cancer Center, Shanghai, China*

Background: Our previous study classified TNBCs into four mRNA subtypes, provided additional insights into TNBC heterogeneity and potential therapeutic options. Then we conducted a phase Ib/Ii subtyping-based and genomic biomarker-guided umbrella trial (FUTURE, NCT03805399), demonstrated the clinical benefit of subtyping-based targeted therapy for refractory metastatic TNBC. Here, we further evaluate the prognosis and predictive value of molecular classification in early TNBC in CBCSG010 trial (NCT01642771), which is a prospective, randomized phase III trial confirmed adding capecitabine to anthracycline-taxane-based adjuvant chemotherapy significantly improved survival in TNBC. **Methods:** Tumor tissues and pathological sections were retrospectively collected. Immunohistochemical (IHC) staining and hematoxylin and eosin (HE) staining were performed on paraffin-embedded sections to conduct TNBC IHC subtype staining. RNA-sequencing were performed to characterize the intrinsic molecular features of TNBC microenvironment. **Results:** 585 patients enrolled in the CBCSG010 trial, 450 patients had pathological sections, among which 207 patients achieved successfully stained sections. PDL1, CD8 and stromal tumor infiltrating lymphocytes (STILs) were chosen for identified TNBC Immune enriched phenotype. Patients with $\geq 20\%$ positive tumor cell proportion score (TPS) of PDL1, $\geq 10\%$ positive cells of CD8, and $\geq 10\%$ positive STILs were significantly associated with better 5y-DFS (disease-free survival). Among Immune enriched TNBC, kaplan-Meier curves showed that DFS rates were 96.4% and 73.7% in the capecitabine and control groups. Transcriptome data was used to picture the immune microenvironment landscape, showed that “immune-hot” patients (immune cells or immune genes enriched) were more likely to benefit from capecitabine treatment. **Conclusions:** TNBC subtypes is significantly associated with DFS, with Immune enriched phenotype achieving the best outcome, and “immune-hot” patients are more likely to benefit from adjuvant capecitabine. Designing future clinical trials adding immunotherapy in adjuvant treatment of TNBC might base on molecular features. Research Sponsor: the National Natural Science Foundation of China (Grant No. 82172576)

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Poster Session

Efficacy of ovarian function suppression of 3-monthly versus monthly GnRH agonist as endocrine therapy for premenopausal breast cancer patients. *First Author: Daniella Audi Blotta, Hospital Beneficência Portuguesa de São Paulo, São Paulo, Brazil*

Background: The combined analysis of the Suppression of Ovarian Function Trial (SOFT) and Tamoxifen and Exemestane Trial (TEXT) trials have shown significant survival benefit of adding ovarian function suppression (OFS) with GnRH agonists (GnRHa) to aromatase inhibitors (AI) versus tamoxifen in high-risk premenopausal patients (pts) with estrogen receptor (ER)-positive breast cancer (BC). In both studies, GnRHa was administered every 4 weeks. However, the efficacy of 3-monthly GnRHa plus AI has not been well studied. We conducted a retrospective study designed to assess the efficacy of OFS with 3-monthly compared with monthly goserelin, associated with AI, in premenopausal pts with ER-positive BC. **Methods:** Medical records of premenopausal pts with ER-positive BC who received OFS with 10.8mg 3-monthly goserelin plus AI or 3.6mg monthly goserelin plus AI, between June/2013 and January/2023 were reviewed. Patient characteristics, such as age, body mass index (BMI) and prior chemotherapy were analyzed. Estradiol (E2) levels were measured by gas chromatography tandem mass spectrometry. Pts with at least one E2 level above 2.72 pg/ml were considered to have ineffective OFS. Analysis of E2 measurements was divided into periods: < 3 , 3 to 6, 6 to 9, 9 to 12, 12 to 18, 18 to 24 and > 24 months. E2 levels greater than 2.72 pg/ml were evaluated at each timepoint. **Results:** A total of 88 pts were included. 27 (30.7%) received monthly goserelin and 61 (69.3%) 3-monthly goserelin. Patient characteristics were well balanced between the groups. Relevant demographic data are shown in table. For E2 analysis, 20 (22.7%) pts had at least one measurement greater than 2.72 pg/ml, 11 (40.7%) in the monthly group and 9 (14.8%) in the 3-monthly group ($p = 0.007$). The percentages of E2 measurements ≥ 2.72 pg/ml, in each time period, were 0%, 40%, 12.5%, 16.7%, 33.3%, 50% and 50% in monthly group versus 8%, 4.2%, 10%, 14.3%, 4.8%, 8.3% and 5.6%, in 3-monthly group, respectively. **Conclusions:** Our study demonstrated that more pts who underwent 3-monthly goserelin had E2 levels below the defined threshold of 2.72 pg/ml compared with monthly goserelin, when associated with AI, with statistical significance. These findings suggest that 3-monthly goserelin may result in better efficacy in OFS when comparing with monthly and provide greater convenience for pts. Research Sponsor: None.

Variable	Monthly Goserelin, n (%)	3-Monthly Goserelin, n (%)	P value
Median age at OFS start, years (IQR)	39 (35-43)	39 (35-44)	$p = 0.839$
Patients younger than 40 years	14 (51.8%)	34 (55.7%)	Not applicable
Median BMI, kg/m ² (IQR)	23 (21-25)	23 (21-26)	$p = 0.693$
High clinical risk by MINDACT criteria	7 (53.8%)	21 (72.4%)	$p = 0.298$
Metastasis at diagnosis	5 (18.5%)	7 (11.5%)	$p = 0.501$
HER2-positive status	1 (3.7%)	12 (19.7%)	$p = 0.058$
Prior chemotherapy	17 (77.3%)	50 (92.6%)	$p = 0.111$

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Poster Session

Assessing the marginal costs of radiation therapy and antiestrogen therapy for post-lumpectomy, early-stage breast cancer across Medicaid and Medicare plans. *First Author: Victoria Wu, Case Western Reserve University School of Medicine, Cleveland, OH*

Background: With recent Level I evidence (FAST FORWARD) supporting radiation therapy (RT) duration as short as one week and Level I evidence (CALGB9343) supporting RT omission in favor of antiestrogen endocrine therapy (ET) alone in select patients, the necessity of both RT and ET, adjuvantly, in early-stage breast cancer (BC) has been questioned. Evidence providing granular details on the role of insurance in the aggregate cost of RT and ET is lacking. This project disaggregates costs by insurance plan to increase transparency of out-of-pocket (OOP) cost estimates. **Methods:** National Comprehensive Cancer Network guidelines were utilized to determine the proper treatments, with FAST FORWARD radiation dose/fractionation (26 Gy in 5 fractions) representing RT. Treatments were identified using Current Procedural Terminology and Healthcare Common Procedure Coding System codes. OOP costs, deductibles, and copay/coinsurance were calculated for Medicaid, Original Medicare, Medigap Plan G, and Medicare Part D Rx. The medicare.gov, medicaid.oh.gov, aarpmedicareplans.com, and cms.gov were used to determine pricing. Price estimates reflect actual costs per insurance plan rather than costs estimated from claims data. All procedures were considered to be performed in an Ohio hospital setting, insurance coverages were based on the zip code 44106, and total expenses were based on all treatments plus a 5-year follow-up (not adjusted for inflation). **Results:** Treatment charges for ET include medical oncology initial consultation, biannual medical oncology follow-up, baseline bone density study, and Anastrozole cost (5-years). Treatment charges for RT include initial consultation, treatment planning, dosimetry calculations, treatment device, simulation and verification, RT delivery, on-treatment visits, and medical physics consultation. Original Medicare beneficiaries face an OOP cost of 20% for Medicare Part B claims with no cost cap for approved procedures after the deductible. Medications are covered under Medicare Part D with copays. This results in a marginal OOP treatment charge (after 5-year follow-up) of \$767.54 for ET alone and \$1,416.78 for ET + RT. Medigap Plan G beneficiaries face a marginal OOP charge of \$1,225 for both ET alone and ET + RT, assuming the \$226 Medicare Plan B deductible is met by the cost of lumpectomy during the year of RT. For Medicaid beneficiaries (assuming all treatments are approved by Medicaid), all expenses are covered without limit, resulting in no OOP expense for either treatment plan. **Conclusions:** Discussions of adding RT to ET for post-lumpectomy early-stage BC often involves considerations of treatment costs. This model (based on actual cost estimates per insurance plan rather than claims data) can help to enhance cost transparency by comparing expenses between Medicare and Medicaid plans. Research Sponsor: None.

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Poster Session

Association between patient-reported outcomes and therapeutic outcomes in patients with breast cancer: A pooled individual-participant data analysis.*First Author: Natansh Modi, Flinders University, Adelaide, SA, Australia*

Background: Patient-reported outcomes (PROs) are captured in validated tools to provide the patients' perspective and voice on their physical, social, emotional, functional, and cognitive abilities. Pre-treatment PROs have shown prognostic importance in other cancer types, however, the prognostic value of PROs in breast cancer has been minimally explored. **Methods:** In a pooled analysis of contemporary clinical trial IPD from patients with breast cancer, cox-proportional hazard analysis and binary logistic regression was used to assess the association between potential predictors with overall survival (OS) and adverse event (grade ≥ 3) outcomes, respectively. PROs were recorded using the EORTC QLQ-C30 version 3.0 questionnaire in the pooled cohort. Statistical significance was set at a threshold of $P < 0.05$ and was determined via the likelihood ratio test. Model fit and linearity of variable associations were assessed via the Akaike information criterion (AIC). All analyses were stratified by age, performance status, treatment arm, and study. The primary assessed outcome was OS, with grade ≥ 3 adverse events assessed as a secondary outcome. A forward inclusion process (starting with the variable of lowest AIC, PRO domains were retained in the model if they decreased the AIC by 2 or more on addition, and remained statistically significant) was used to evaluate the value of multiple PRO domains on prognostic performances. **Results:** Within data available, the EORTC QLQ-C30 version 3.0 questionnaire was used in a pooled cohort of 8,544 patients across 8 clinical trials. In the pooled cohort, the association between PROs and outcomes was best described by a linear association. Patient-reported physical functioning, appetite loss, and pain were significantly associated with OS. On forward-inclusion, only physical functioning remained within the OS prognostic model. Except for patient-reported financial difficulties, all PRO domains were significantly associated with grade ≥ 3 adverse events. On forward-inclusion, physical functioning, pain, and constipation all remained statistically significant. **Conclusions:** Within large high-quality IPD, pre-treatment PROs demonstrated significant prognostic relationships with therapeutic outcomes in patients with breast cancer initiating contemporary anticancer treatments. Patient-reported physical functioning was found to be the most prognostic PRO domain for OS, while patient-reported physical functioning, pain, and constipation were retained in a multivariable model prognostic of grade ≥ 3 adverse events. Research Sponsor: Cancer Council South Australia and NHMRC (APP2008119 & APP2005294).

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Poster Session

A multicenter phase II study of vaccines to prevent recurrence in patients with HER-2-positive breast cancer. *First Author: Hyo S. Han, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL*

Background: Patients (pts) with early stage HER2-positive breast cancer are commonly treated with neoadjuvant HER2-targeted therapy. Pts who have residual invasive disease have a less favorable outcome and increased risk of recurrent disease than pts with a complete pathologic response (pCR). It also has been observed that pts who do not achieve a pCR have low or absent anti-HER-2 CD4 Th1 responses. We hypothesized that correcting anti-HER-2 CD4 Th1 response using vaccines will be safe, induce anti-tumor immunity in HER2-positive breast cancer and reduce the risk of recurrence. We conducted a multi-center, phase 2, randomized study to determine the safety, immunogenicity and recurrence free survival of two HER2 vaccines (multivalent anti-oncogene DNA vaccine (WOKVAC) or HER-2-pulsed dendritic cell vaccine (DC1)). **Methods:** Pts with HER2-positive early breast cancer were eligible if they had residual invasive disease at surgery after receiving neoadjuvant chemotherapy plus HER2-targeted therapy. Patients were randomly assigned in a 1:1 ratio, with stratification according to residual cancer burden (RCB) (1+2 vs 3) to receive adjuvant HER2 vaccination with either DC1 or WOKVAC. For the initial vaccination phase, DC1 was delivered via US guided inguinal lymph node administration, weekly x 6 weeks and WOKVAC was given intradermally on weeks 1, 4, and 7. Booster vaccines were given at months 6, 9 and 12. The primary end point is to evaluate the safety and tolerability of each vaccine and assess immune response rate as measured by ELISPOT. Each treatment arm will be assessed separately. Secondary endpoints include recurrence-free survival. Exploratory analyses include the assessment of prognostic and predictive biomarkers including circulating tumor cells, serum HER2 levels, and other immune correlative biomarkers. Here we are reporting the initial safety results. **Results:** Total of 110 eligible pts (55 WOKVAC vs 55 DC1) were enrolled from 2/2018 to 12/2022 and received at least one dose of treatment and 38 pts pending completion of the booster phase. Most pts had clinical stage I/II/III 56/35 (82%) and 50% had positive node disease at diagnosis. 82% had hormone receptor positive disease. 37/38/8 patients had RCB 1/2/3. For patients without known RCB status, ypTNM was used to randomize (yp stage I/II/III = 13/13/1 pts). The most frequently observed treatment related adverse events (TRAE) were injection site pain/reaction (38%) and chills (34%), fever (25%) and fatigue (40%) for DC1 arm. For WOKVAC, the most common toxicities included injection site reaction (68%) and fatigue (37%). All of these were grade 1 and 2. Nine patients had events including new primary cancer (1), local recurrence (2), metastatic disease recurrence (6). **Conclusions:** Both DC1 and WOKVAC HER2 vaccines were well tolerated without significant toxicities. Updated results will be presented at the meeting including correlatives. Clinical trial information: NCT03384914. Research Sponsor: Department of Defense.

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Poster Session

The impact of the 4R Oncology model on OncotypeDx turnaround time. *First Author: Jenny Wei, Department of Medicine, The Permanente Medical Group, San Francisco, CA*

Background: The OncotypeDx genomic assay has been widely used to predict recurrence in those with early-stage ER positive breast cancer to determine whether adjuvant chemotherapy is beneficial. Receiving OncotypeDx results in a timely manner prior to medical oncology appointment is critical to inform adjuvant therapy decisions. In this quality improvement project, we implemented a care delivery optimization for patients with breast cancer receiving OncotypeDx assays in an integrated healthcare system. The optimization was conducted as part of implementing the 4R Oncology model (Right Info / Right Care / Right Patient / Right Time), a novel care model that aims to optimize patient-centric care planning, team-based delivery and patient self-management. Herein, we assess the impact of implementing this model on improving OncotypeDx turnaround time. **Methods:** We examined two patient groups with newly diagnosed early-stage ER positive breast cancer who attended a multidisciplinary clinic and underwent surgery at a single medical center. The historical control (HC) group received care pre-4R implementation, from January 2019 through June 2020, while the 4R Intervention group received care from July 2020 to December 2021. The OncotypeDx-related care optimization was a team effort of 5 medical specialties that involved establishing an OncotypeDx reflex testing practice, updating workflows, working with a testing company to streamline the process and implementing a method to align result timing with scheduling medical oncology appointments. Bivariate analyses were used to compare the HC and 4R groups on demographic characteristics and OncotypeDx turnaround time. **Results:** Within the 4R group (N = 208), 72 (34.6%) patients received OncotypeDx and 89 (32.5%) patients from the HC cohort (N = 274) received OncotypeDx. The groups were balanced by median age at time of multidisciplinary clinic visit (HC: 59 years vs 4R: 60 years), female gender (HC: 99.6% vs 4R: 99.5%), race, combined race and ethnicity, language spoken, Charlson Comorbidity Index and tumor characteristics. The average turnaround time from surgery date to delivery of OncotypeDx results was significantly reduced in the 4R cohort (19.4 days) compared to that of the HC cohort (23.1 days), a difference of 3.8 days, $p = 0.004$. The availability of OncotypeDx results by the first medical oncology visit after surgery increased from 40% in the HC cohort to 69% in the 4R cohort, $p = 0.0003$, helping optimize the transition to adjuvant therapy for the appropriate population. **Conclusions:** The implementation of the 4R Oncology model within an integrated healthcare system significantly reduced turnaround time for patients with breast cancer awaiting OncotypeDx results, improving patient-centric care and enabling informed discussions at medical oncology visits. The 4R Oncology model is an effective method to optimize delivery of time-sensitive care. Research Sponsor: Genentech (for 4R).

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Poster Session

Does RSCLin provide additional information over classic clinico-pathologic scores (PREDICT 2.1, Influence, CTS-5)? A TEAM Pathology substudy. *First Author: Ana-Alicia Beltran-Bless, The Ottawa Hospital, Ottawa, ON, Canada*

Background: Gene-expression profiling tests (e.g. Oncotype, MammaPrint, Prosignia, Breast Cancer Index and EndoPredict) are widely used in the care of patients with early-stage hormone positive breast cancer (node negative or 1-3 lymph nodes). However, these tests are resource intensive, and few studies have compared their value with either free and widely available clinico-pathologic risk calculators (e.g. PREDICT 2.1, INFLUENCE 2.0, and CTS-5) or tools that combine genomic testing with clinico-pathologic data (e.g. RSCLin). The TEAM pathology substudy population was used to compare these different predicted model scores with outcomes. **Methods:** The TEAM pathology study consists of 3284 postmenopausal hormone positive breast cancer patients treated with either exemestane or tamoxifen followed by exemestane. Accrual was from 2001 to 2006. Genes comprising the multi-parametric Oncotype Dx were used to train signatures to create true assay results. Patient data was then used to calculate recurrence scores through various tools. This included clinico-pathologic models and their respective endpoints PREDICT 2.1 (overall survival at 5 years), INFLUENCE 2.0 (distant metastasis at 5 years), CTS-5 (distant recurrence risk at year 5-10), the purely genomic Oncotype Dx trained results (distant recurrence risk at 9 years), as well as the new clinico-pathologic RSCLin (distant recurrence risk at 10 years). We compared the level of association between these predictive model scores using Spearman correlation coefficients. The prognostic ability of each model was contrasted for each outcome using Harrell's C-statistic. **Results:** Results were available for CTS-5 (3022 patients), INFLUENCE 2.0 (3485 patients), ODX-trained (3825 patients), and RSCLin (3029 patients). Correlation coefficients showed low correlation between Influence ($r = 0.25$) and CTS-5 ($r = 0.17$) with Oncotype-Dx trained results, and high correlation between RSCLin ($r = 0.84$) and Oncotype-Dx trained results. The concordance index was similar (0.65 to 0.68) for all models with distant metastasis-free survival as the outcome. Analysis is ongoing and further results will be available at the time of presentation. **Conclusions:** Other clinico-pathologic tools such as Influence 2.0 and CTS-5 have good prognostic ability when compared to Oncotype Dx-trained results and RSCLin. Research Sponsor: None.

p n	Influence	RS Clin Scores	CTS5
Oncotype Scores	0.25 3485	0.84 3029	0.17 3022
Influence	-	0.56 2913	0.82 2913
RS Clin Scores	-	-	0.53 3022

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Poster Session

Real-world impact of TAILORx on chemotherapy use and SOFT/TEXT on ovarian function suppression uptake in a population based-cohort of women 40 years and under with HR-positive, HER2-negative, axillary lymph node negative breast cancer. *First Author: Malek B. Hannouf, Schulich School of Medicine and Dentistry, Department of Internal Medicine, Western University, London, ON, Canada*

Background: Gene expression profiling (GEP) testing is prognostic for distant recurrence risk in women with hormone receptor positive (HR+), human epidermal growth factor receptor-2 negative (HER2-), axillary lymph node negative (LN-) breast cancer (BC). The TAILORx trial generated prospective evidence demonstrating the 21-gene recurrence score (RS) is also predictive of chemotherapy (CT) benefit. The literature suggests that GEP testing reduces adjuvant CT prescription and is cost-effective. In the same era, the SOFT/TEXT trials demonstrated disease-free survival benefit for the addition of ovarian function suppression (OFS) to endocrine therapy in premenopausal women. Real-world uptake and impact of these advances in the management of HR+, HER2-, LN- BC in young women may be limited due to complex reasons. This retrospective study evaluated GEP and CT use post TAILORx and OFS use post SOFT/TEXT in women 40 years old or younger diagnosed with HR+, HER2-, LN BC from 2011 to 2020 in Alberta, Canada. **Methods:** Clinical variables were retrieved from the Alberta Health Services Cancer Care Breast Data Mart and through review of the electronic medical record. GEP testing and CT use were compared between 3 cohorts of women defined by diagnosis: pre RS funding/pre TAILORx (before April 2014), post RS funding/pre TAILORx (April 2014-May 2018), post TAILORx (June 2018 and beyond). OFS use was compared between 2 cohorts of women defined by diagnosis pre- and post SOFT/TEXT (May 2015). In subgroup analyses, we compared CT use by GEP status and RS category and OFS use by CT status. **Results:** Among the 291 women identified, GEP testing increased by 37% post GEP funding (pre 2% vs. post 39%; $P < .0001$) and by additional 15% post TAILORx (pre 39% vs. post 54%; $P < .0001$) whereas overall CT use declined by 15% post GEP funding (pre 85% vs. post 70%; $P = .01$) and by additional 16% post TAILORx (pre 70% vs. post 54%; $P = .01$). Although not significant, OFS use increased by 8% post SOFT/TEXT (pre 13% vs. post 21%; $P = .08$). In subgroup analyses, post TAILORx was associated with a significant reduction in CT use of 19.5% in non-GEP tested women (pre 85% vs. post 65% $P = .01$) and non-significant increase in CT use of 6% in RS tested women (pre 40% vs. post 46%; $P = .61$) mainly driven by high mid range RS 21-25 and lower high range RS 26-30. There was no significant change in OFS use in non-CT treated women post SOFT/TEXT (Pre 5.3% vs. Post 8%, $P = .68$) whereas OFS use increased by 15% in women treated with CT post SOFT/TEXT (pre 15% vs. post 30%; $P = .01$). **Conclusions:** Public GEP funding and TAILORx led to widespread adoption of GEP and real-world decline in CT use in women 40 years of age or younger diagnosed with HR+, HER2-, LN- BC in Alberta. SOFT/TEXT led to real-world incline in OFS use in those treated with CT but adoption remained suboptimal. Research Sponsor: None.

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Poster Session

Image-only deep learning risk model performance in patients with known germline mutations. *First Author: Faezeh Sodagari, Massachusetts General Hospital, Boston, MA*

Background: Mammograms contain highly predictive biomarkers of future breast cancer risk, which can be identified by deep learning (DL) risk stratification models. DL model performance in discerning risk in patients with known germline mutations has yet to be established. The aim of this study is to assess image-only DL model risk score performance in patients with and without a germline mutation undergoing screening breast MRI. **Methods:** This retrospective, multisite study included the first screening MRI of consecutive females ≥ 30 years from 3/1/2011 to 11/30/2021 at four facilities, with a prior bilateral screening mammogram containing a DL risk score and at least one year of follow-up. A mammography-based DL five-year model was used to assess risk, with an increased-risk threshold of ≥ 2.2 and high-risk of ≥ 5.8 . Patient demographics, germline mutation status, and traditional risk factors were extracted from electronic medical records. Standard screening performance metrics including cancer detection rate (CDR) within one year of MRI were determined. Cancer outcomes were determined via linkage to a regional tumor registry. DL model performance was compared using Pearson's chi-squared tests. **Results:** 4025 patients who underwent screening breast MRI met inclusion criteria. 381 (9.5%) had a known germline mutation. There was no significant difference in age of those with or without a germline mutation (54.9y $\pm$ 10.5 vs 54.8y $\pm$ 8.8, $p = 0.284$) or family history of breast cancer (68.5% vs 65.3%, $p = 0.205$). Patients with a germline mutation were more likely to be White (95.0 vs 91.4%, $p < 0.05$), have non-dense breasts (52.8% vs 35.3%, $p < 0.001$) and less likely to have a personal history of breast cancer (25.7% vs 36.3%, $p < 0.001$). The CDR in those with a germline mutation was higher than those without a mutation (39.4 vs 20.3, $p < 0.05$). The median DL risk score in those with a germline mutation was lower than those without a mutation: 1.9 (IQR: 1.4-2.5) vs 2.3 (IQR: 1.7-3.8), $p < 0.001$. In patients with a germline mutation, the CDR in those with elevated DL scores was higher than those with low DL scores (47.6 vs 34.2, $p = 0.512$: increased-risk threshold; 60.6 vs 37.4, $p = 0.512$: high-risk threshold). A similar trend was seen in those without a germline mutation (26.4 vs 12.8, $p < 0.01$: increased-risk threshold; 27.1 vs 19.0, $p = 0.203$: high-risk threshold). Trends were demonstrated across all comparisons, but significance was only reached in the largest group. **Conclusions:** Compared to patients without germline mutations, those with mutations had higher CDRs on MRI but lower DL risk scores. Patients with higher DL risk scores had higher CDRs in those identified as increased or high-risk by DL model, regardless of germline mutation status. Further study to elucidate mechanisms to explain differential performance of DL models in patients with germline mutations is ongoing. Research Sponsor: MGH, Ralph Schlaeger Fellowship Award.

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Poster Session

Disease-free survival (DFS) as a surrogate for overall survival (OS) in patients (pts) with HR+/HER2- early breast cancer (EBC): A correlation analysis. *First Author: Michael Untch, Interdisciplinary Breast Cancer Center, Helios Klinikum Berlin-Buch, Berlin, Germany*

Background: DFS has been widely adopted as a clinically meaningful primary endpoint in EBC trials in place of OS, which needs extensive follow-up to observe sufficient events and fails to assess survival benefit early. However, a rigorous validation of DFS as a surrogate endpoint for OS is required for each given setting. The objective of this analysis was to evaluate DFS as surrogate for OS in the adjuvant treatment of HR+/HER2- EBC. **Methods:** A systematic literature review (SLR) was conducted using biomedical literature databases (ie, Embase, PubMed, and Medline [from database inception to January 2023]) and key conferences to identify published studies in EBC. The eligibility criteria for the SLR were RCTs that included $\geq 80\%$ of adult pts with HR+/HER2- EBC and assessing different treatment options (ie, cyclin-dependent kinase 4/6 inhibitors [CDK4/6i], endocrine therapies [ET], and chemotherapies [CT]). Studies were considered for correlation analysis if hazard ratios (HRs) were reported for both DFS and OS. The analysis excluded observational studies and trials with immature OS data. Spearman rank correlation (r_s) and weighted linear regression analyses (measured by coefficient of determination [R^2]) were performed to evaluate the correlation between HRs for OS and DFS. Considering heterogeneity, multiple scenario analyses were conducted. Surrogate threshold effect (STE) was also estimated; STE is defined as the maximum value of the HR for DFS that needs to be observed in a trial to ensure the possibility of concluding that a significant effect on OS occurred. Correlation was also assessed using pt-level data from the FACE trial (letrozole vs anastrozole in postmenopausal pts with HR+/HER2- EBC) to validate findings of the trial-level analysis. **Results:** A total of 14 RCTs ($N = 31,668$) were included (CDK4/6, 2; ET, 7; CT, 5). Trial-level analysis showed that r_s between OS and DFS was 0.81 (95% CI, 0.56-0.94), which when weighted by variance was 0.81. Regression analysis showed that 84% of the variability in OS was explained by DFS ($R^2 = 0.84$). A meta-regression model estimated an STE of 0.82 for HR of DFS, which can be leveraged to validate the surrogacy based on the DFS estimated from a future trial. Analysis of pt-level data from the FACE trial demonstrated a correlation between DFS and OS ($r_s = 0.75$). Additionally, correlation coefficients estimated by the Pearson method and iterative imputation were 0.83 and 0.89, respectively. **Conclusions:** Both trial-level and pt-level analyses demonstrate a positive correlation between DFS and OS. These results support the use of DFS as a reliable surrogate endpoint for OS in HR+/HER2- EBC trials to give an early access to innovative therapies. Research Sponsor: Novartis Pharmaceuticals Corporation.

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Poster Session

Effect of astragalus polysaccharides (PG2) treatment of adjuvant chemotherapy-induced fatigue in premenopausal patients with breast cancer. *First Author: Kun Ming Rau, E-Da Cancer Hospital, Kaohsiung, Taiwan*

Background: Fatigue is one of the most common symptoms of breast cancer (BC) patients who are receiving adjuvant chemotherapy. Astragalus Polysaccharides (PG2) had been proved to relieve cancer-related fatigue in advanced BC patients. The aim of this study is to evaluate the efficacy of PG2 as a complementary treatment among stage II/III BC patients with adjuvant chemotherapy of epirubicin-cyclophosphamide(EC) regimen in reduction of chemotherapy-induced toxicity and encouraging compliance with chemotherapy. **Methods:** This double blind, multicenter, phase II trial randomized stage II/III BC patients who would receive adjuvant EC at least 4 cycles to either PG2 500 mg or placebo on day1, 3, 8 every 21 days as the combination. Changes in chemotherapy-related fatigue score (CRFS) was evaluated by the Brief Fatigue Inventory-Taiwanese Form and incidence of Grade 3/4 neutropenia were the primary endpoints. **Results:** A total of 66 eligible patients were enrolled and equally randomized to PG2 and placebo groups, 30 cases in each group completed this trial. In general, there was no significant difference in the mean change of CRFS and fatigue intensity between the groups. But the CRFS and fatigue intensity in premenopausal-PG2 group were less aggravated after 4 cycles of EC than that of postmenopausal-placebo group. Persisted significance difference in CRFSs from cycle 1 day 5 (PG2: 0.6; Placebo: 1.9, $P = 0.023$) to cycle 4 day 15 (PG2: -0.3; Placebo: 0.7, $P = 0.002$). In all population, a lower proportion of patients suffered from grade 3/4 neutropenia from cycle 1 to cycle 4 were observed in the PG2 group compared to the placebo group (78.8% vs. 87.9% in intent-to-treat population). **Conclusions:** PG2 combined with adjuvant EC significantly improved adjuvant EC-induced fatigue in premenopausal BC patients. PG2 assists these patients with maintaining normal daily life and job activities, also less need of family support during chemotherapy. Furthermore, patients treated with PG2 might have better compliance to complete the whole course of adjuvant chemotherapy. Clinical trial information: NCT03314805. Research Sponsor: PhytoHealth Corporation.

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Poster Session

Prognostic impact of adjuvant endocrine therapy for estrogen receptor-positive and HER2-negative T1a/bNOMO breast cancer. *First Author: Yuko Takahashi, Department of Breast and Endocrine Surgery, Okayama University Hospital, Okayama, Japan*

Background: Adjuvant endocrine therapy (ET) is the standard of care for Estrogen Receptor (ER)-positive early-stage breast cancer. However, many patients suffer from adverse events associated with ET. The prognosis of patients with T1a/bNOMO breast cancer with ER-positive and human epidermal growth factor 2 (HER2)-negative is excellent, and it is not clear whether adjuvant ET should be recommended. Here we evaluate the effect of adjuvant ET for ER-positive and HER2-negative T1a/bNOMO breast cancer. **Methods:** This study was a multicenter, retrospective cohort study that evaluated adjuvant ET for patients with ER-positive and HER2-negative T1a/bNOMO breast cancer. Patients who underwent surgery between 2008 and 2012 in 47 institutions of the Japan Clinical Oncology Group (JCOG) breast cancer group were eligible. We analyzed the cumulative incidence of distant metastasis as primary endpoint using the Gray test model and time to event endpoints (distant disease free survival and overall survival) using log-rank test between patients treated with and without adjuvant ET. We also used Gray test model for the analysis of the cumulative incidence of ipsilateral and contralateral breast cancer. Predictive factors were assessed using the Fine-Gray model and the Cox proportional hazards model. **Results:** The median follow-up period was 9.2 years. Of 4758 eligible patients (1202 T1a [25.3%] and 3556 T1b [74.7%] diseases), 3991 (83.9%) received adjuvant ET. The 9-year cumulative incidence of distant metastasis was 1.5% with ET and 2.6% without ET (adjusted subdistribution hazard ratio [sHR], 0.54; 95% CI, 0.32-0.93). In the multivariate analysis, the independent risk factors of distant metastasis were no ET, mastectomy, high grade, and lymphatic invasion. The 9-year overall survival was 97.0% and 94.4% (HR, 0.54; 95% CI, 0.38-0.77). Adjuvant ET reduced the incidence of ipsilateral and contralateral breast cancer (9-year rates; 1.1% vs 6.9%; sHR, 0.17; 95% CI 0.11-0.28, and 1.9% vs 5.2%; sHR, 0.33; 95% CI, 0.22-0.49). **Conclusions:** Adjuvant endocrine therapy significantly reduces distant metastases, however the absolute difference is small for ER-positive and HER2-negative T1a/bNOMO breast cancer. Furthermore, it reduced ipsilateral and contralateral breast cancer as well. Shared decision making regarding the omission of adjuvant endocrine therapy is crucial, especially in patients with low risk of distant metastasis. Research Sponsor: None.

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Poster Session

Pulsed electrical fields in combination with anti-PD1 and survival of mice with TNBC (EMT6) murine breast tumor. *First Author: Ebtesam Nafie, Galvanize Therapeutics INC, Redwood City, CA*

Background: Delivery of pulsed electric field (PEF) energy is used to destabilize cells through multiple biochemical processes. We questioned whether a specific PEF treatment type could synergize with anti-PD1 in an orthotopic Triple Negative Breast Cancer (TNBC) EMT6 mouse model. Our previous studies have demonstrated that PEF treatment induces neo-antigen presentation and triggers an innate and adaptive immune response. Anti-PD1 therapy is ineffective at blocking growth of (TNBC) EMT6 tumors that are orthotopically implanted in mice. We evaluated whether a biphasic monopolar form of PEF could synergize with anti-PD1 when it was administered intraperitoneally or intra-tumorally, and whether there was a change in immune response post treatment. **Methods:** Forty-eight female Balb/c mice were implanted with 200,000 EMT6 cells into the mammary fat pads. Once tumor diameter reached 5 mm they were randomized into 6 groups of 8 animals: 1) Sham/IgG; 2) intra-tumoral (IT) anti-PD-1; 3) intra-peritoneal (IP) anti-PD-1; 4) PEF + anti-PD-1(IP); 5) PEF + anti-PD-1(IT) 6) 2X PEF on day 0 and day 7 + anti-PD-1(IT administered weekly). Sham-PEF mimicked the same procedure but without PEF. Anti-PD1 was administered weekly, IT or IP at 200 µg/mouse and PEF was delivered once on day of randomization. Tumors were measured three times per week, and animal survival was monitored until tumor volume necessitated euthanasia ($\geq 2000\text{mm}^3$). Blood was collected on day 14 for flow cytometric analysis of systemic immune response which included quantifying CD3 positive T cells, B cells and NK cells. **Results:** Anti-PD1 treatment (IT or IP) did not reduce tumor growth, nor did it prolong survival compared to Sham/IgG treated animals. All anti-PD1 alone (IT or IP) as well as Sham treated animals had to be euthanized by day 35. In contrast, PEF combined with anti-PD1 given IT and IP significantly reduced tumor growth by 83% and 70%, respectively, on Day 14 compared to anti-PD-1 only treated animals ($p = 0.03$). Interestingly, EMT6 bearing mice treated with double PEF + IT administered anti-PD1 survived longer compared to mice treated with single PEF + IT administered anti-PD1. On day 65, 71% of double PEF + IT administered anti-PD1 were still alive compared to 12.5% of mice treated with PEF + IT administered anti-PD1 ($p = 0.002$). Flow cytometry analysis on day 14 indicated an increase in circulating adaptive (T- and B-cells) and innate (NK cells) immunocytes in the PEF + anti-PD1 treated animals compared to the control. **Conclusions:** Collectively, these results indicate that some types of PEF ablation synergize with weekly anti-PD1 in stimulating an increase of CD3+ T cells, B cells and NK cells, reducing tumor growth and prolonging survival of tumor bearing mice. These results suggest the synergistic potential of combining Immunotherapy with some forms of PEF, which warrants further study in patients. Research Sponsor: Galvanize Therapeutics.

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Poster Session

HRD signature and HRD genomic landscape of tumors from 896 patients with early-stage breast cancer (BC). *First Author: June Evelyn Jeon, Yale School of Medicine, New Haven, CT*

Background: Pathologic mutations in *BRCA1*, *BRCA2* and *PALB2* lead to impaired homologous recombination repair (HRR). Cells with defects in HRR are dependent on non-homologous DNA end joining for DNA repair through the poly(ADP-ribose) polymerase (PARP) catalytic activity. PARP inhibitors (olaparib, talazoparib) are FDA-approved therapies that are toxic to tumors with HRR deficiency (HRD) and are recommended as adjuvant therapy in high-risk germline *BRCA* (gBRCA) positive BC. Despite the clinical implications of HRD, the prevalence of HRR alterations and HRD signature in early-stage primary BC and its association with hormone receptor (HR) status has not been well characterized. **Methods:** This study used the nationwide (US-based, ~280 US cancer clinics) de-identified Flatiron Health-Foundation Medicine BC clinico-genomic database and included patients (pts) who underwent tissue comprehensive genomic profiling (FoundationOne/FoundationOneCDx) between 2014 and 2022. The analysis included all pts with BC who presented with "early" stage I-III disease, had a primary tissue specimen collected within 3 months of diagnosis, and had a reportable novel scar-based HRD signature (HRDsig). **Results:** A total of 896 primary BC pts with stage I-III met our inclusion criteria. Of these early BC pts 21% (188/896) were HRDsig+ (stage I: 17% (32/188); stage II: 22% (84/376); and stage III: 22% (72/332)). For early BC pts, high rates of HRDsig+ were seen in gBRCA (87% [34/39]), somatic *BRCA* (sBRCA, 78% [14/18]), and gPALB2 (71% [5/7]) mutated tumors, with a lower rate seen with other HRR genes [16% (10/63); *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *sPALB2*, *RAD51B*, *RAD51C*, *RAD51D* and *RAD54L*]. HRDsig+ was also detected in 16% (135/832) of BC without g/s *BRCA* or gPALB2 mutations. BC pts who presented with stage I-III disease have similar prevalence of HRDsig+ when compared to those with stage IV disease (21% [188/896] vs 23% [177/767], $p = 0.31$), with similar trends in HR+ disease (HR+/HER2+: 7% [4/57] vs 9% [4/45], $p = 0.73$; and HR+/HER2-: 17% [78/466] vs 18% [82/463], $p = 0.73$). Conversely, in HR- cohorts, decreased prevalence of HRDsig+ was observed in the stage I-III vs stage IV cohort (HR-/HER2+: 3% [1/38] vs 18% [6/33], $p = 0.04$; HR-/HER2-: 31% [99/321] vs 38% [83/216], $p = 0.08$). **Conclusions:** In this study, HR+/HER2- group was the most common early BC subtype, followed by HR-/HER2-, HR+/HER2+, and HR-/HER2+. This distribution is similar to the SEER study, and closely reflects that of the general population. We observed the expected high rates of HRDsig+ in early-stage BC pts with g/sBRCA or gPALB2 mutations where clinical trial data already support the use of PARP inhibitors for early and advanced disease. Importantly, HRDsig positivity was also seen in 16% of early BC without g/sBRCA or gPALB2, and clinical trials will be needed to determine if these pts could also benefit from HRD directed therapies. Research Sponsor: Foundation Medicine.

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Poster Session

Impact of endocrine therapy adherence on racial disparities in breast cancer survival. *First Author: Kimberley T Lee, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL*

Background: Black women have worse breast cancer outcomes compared to their White counterparts, even for hormone receptor positive (HR+) HER2 negative (HER2-) breast cancer (BC). This tumor type is usually treated with 5-10 years of adjuvant endocrine therapy (ET) to reduce risk of BC recurrence and improve survival. We investigated the impact of adherence to ET on racial differences in survival for HR+ HER2- BC survivors. **Methods:** We conducted a population-based, retrospective cohort study using the Surveillance, Epidemiology, and End Results (SEER)-Medicare database, which links demographic and clinical data with cause of death for persons with cancer and Medicare claims for covered health services. We examined 9,039 women with HR+ HER2- stage I-III BC diagnosed between 2007 and 2016, who received primary breast surgery and initiated ET. Adherence to ET was measured using the medication possession ratio (MPR), which assesses the proportion of time a patient has medication available via filled prescriptions. As in established literature, we defined ET adherence as $\text{MPR} \geq 80\%$. Causal mediation analysis was performed to measure to impact of adherence on survival disparities between Black and White BC survivors. **Results:** Mean age at diagnosis was 72 years, 6.5% were Black, and 20.9% were dual eligible for Medicaid (a surrogate for socioeconomic hardship). Most had stage I or II breast cancer (69.3%) and mastectomy as primary surgery (69.7%). Nineteen percent received chemotherapy and 62.5% received radiation. In univariate analyses, factors associated with ET adherence were Black race (OR 0.62, 95% CI 0.54-0.75), insured by Medicaid (OR 0.72, 95% CI 0.65-0.81), being married (OR 1.14, 95% CI 1.03-1.25), and increased comorbidities (Charlson score ≥ 2) (OR 0.88, 95% CI 0.78-0.99). Age, BC stage, type of surgery, and receipt of chemotherapy or radiation were not associated with ET adherence. In multivariable models adjusting for age, race, marital status, Medicaid eligibility, and Charlson score, Black race and Medicaid eligibility remained inversely associated with ET adherence (OR 0.70, 95% CI 0.59-0.83 and OR 0.77, 95% CI 0.69-0.87 respectively). Among those who were adherent to ET, Black women had 43% higher risk of mortality compared to White women (HR 1.43, 95% CI 1.17-1.76). In mediation analysis, 4.25% of the observed survival disparity between Black and White women can be explained by differences in ET adherence. **Conclusions:** We identified racial disparities in ET adherence and overall survival among women with BC. Adherence to ET accounted for a small percentage of racial disparities in survival. Further research is needed to delineate other factors contributing to ET non-adherence among Black women and to investigate additional factors contributing to known disparities in BC survival. Research Sponsor: Breast Cancer Research Foundation-AACR Career Development Awards to Promote Diversity and Inclusion.

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Poster Session

Real-world outcomes with adjuvant nonsteroidal aromatase inhibitors (NSAIs) vs tamoxifen (TAM) in patients with hormone receptor–positive/human epidermal growth factor receptor 2–negative (HR+/HER2–) early breast cancer (EBC): A US database analysis. *First Author: Stephanie L. Graff, Lifespan Cancer Institute, Providence, RI*

Background: Randomized controlled trial (RCT) meta-analysis data have shown a significantly greater disease-free survival (DFS) benefit with aromatase inhibitors than TAM in patients with HR+/HER2– EBC. Here we compare real-world outcomes in patients with HR+/HER2– EBC who received adjuvant endocrine therapy (ET) with NSAIs or TAM. **Methods:** This was a retrospective analysis of ConcertAI's deidentified electronic medical records data set of patients treated at US academic and community oncology clinics from January 1, 1995 to April 30, 2021. The cohort included patients with stage II–III (if IIIB or IIIC, confirmation was required on residual tumor status) HR+/HER2– EBC who underwent surgery and initiated adjuvant ET (excluding those who switched classes of ET); ovarian function suppression (OFS) was permitted. Menopausal status was determined using age (≥ 50 years) as a proxy for undocumented status. Invasive DFS (IDFS; risk of disease recurrence, death, or second primary tumor), distant DFS (DDFS; risk of distant recurrence, death, or second primary tumor), and overall survival (OS; risk of death) were assessed and defined as the time interval between start of ET and first event. Multivariate Cox regression analyses were performed, adjusting for age, stage, Charlson Comorbidity Index, and prior adjuvant or neoadjuvant chemotherapy for the ET cohort. **Results:** Of the total 3133 patients analyzed, 2507 were included in this analysis (NSAI $\pm$ OFS, $n = 1854$; TAM $\pm$ OFS, $n = 653$). Among these patients, the median (range) age was 59.5 (22.8–86.6) years, 25.4% were premenopausal, and 56.2% had tumor node involvement. The mean (SD) time to ET discontinuation was 46.2 (35.9) months overall and was similar between the NSAI and TAM cohorts. Reasons for ET discontinuation were undocumented or missing from the database for 76.8% of patients. Multivariate Cox regression analyses suggested a significant risk reduction with NSAIs vs TAM, with a 17% reduction in risk of an IDFS event (hazard ratio [HR], 0.83 [95% CI, 0.69–0.98]) and an 18% reduction in risk of a DDFS event (HR, 0.82 [95% CI, 0.69–0.98]). Although there were few events, OS analysis suggested a numerical trend favoring NSAIs over TAM, with a 12% reduction in risk of death (HR, 0.88 [95% CI, 0.69–1.13]). **Conclusions:** This real-world data analysis revealed a reduction in risk of IDFS and DDFS events with adjuvant NSAIs vs TAM in patients with HR+/HER2– EBC. Collectively, RCT and real-world data demonstrate greater benefit with adjuvant NSAIs vs TAM with respect to risk of recurrence in this patient population. Research Sponsor: Novartis Pharmaceuticals Corporation.

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Poster Session

Pathologic complete response after neoadjuvant systemic therapy for breast cancer in BRCA mutation carriers and noncarriers. *First Author: Sara P. Myers, Breast Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Distinct pathological characteristics and mutational signatures in *BRCA*-associated breast cancers may result in differential response to chemotherapy but understanding of treatment response after neoadjuvant chemotherapy (NAC) is limited. We describe a single-institutional experience to compare rates of pathologic complete response (pCR) after NAC in *BRCA* carriers (*gBRCA1/2*) and noncarriers. **Methods:** From 11/2013 to 01/2022, 1426 consecutive women with clinical stage I–III breast cancer were treated with NAC followed by surgery. Baseline disease characteristics were compared between *gBRCA1/2* and noncarriers using two-sample non-parametric tests. Conditional logistic regression was used to evaluate the association between *BRCA* status and pCR (i.e., ypT0/is pN0) adjusting for variables selected using backward elimination. **Results:** 92 (6.5%) and 73 (5.1%) had deleterious mutations in *BRCA1* and *BRCA2*, respectively. Compared to noncarriers, *gBRCA1/2* were younger ($p < 0.001$) with clinical T1 ($p = 0.002$) and triple negative disease (TN) (57% vs 25% noncarriers, $p < 0.001$). Almost all patients received docorubicin/cyclophosphamide/paclitaxel therapy (93%) with *gBRCA1/2* more likely to receive carboplatin ($p < 0.001$). pCR rate was 42% of *gBRCA1*, 21% of *gBRCA2*, and 26% of noncarriers ($p = 0.001$). Among clinically node positive (cN+) patients, nodal pCR was higher in *gBRCA1/2* compared to noncarriers (53/96 (55%) vs 371/856 (43%), $p = 0.012$). This difference was seen in ER+/HER2– (36% *gBRCA1/2* vs 20% noncarriers; $p = 0.027$) and TN subtypes (79% *gBRCA1/2* vs 45% noncarriers; $p < 0.001$). Poorly differentiated tumors ($p < 0.001$), cN+ ($p = 0.010$), lower cT stage ($p = 0.028$), ductal histology ($p < 0.001$), TN and HER2+ receptor status ($p < 0.001$), absence of lymphovascular invasion ($p < 0.001$), carboplatin receipt ($p = 0.041$), and *BRCA1* status ($p = 0.001$) were also associated with pCR on univariate analysis. After adjusting for differentiation and molecular subtype, *BRCA1* status remained independently associated with pCR. **Conclusions:** *gBRCA1* undergoing NAC have higher pCR rates relative to *gBRCA2* and patients with sporadic disease. Across breast cancer subtypes, *gBRCA1/2* more frequently converted to pN0. Defining biological mechanism for these findings would allow customization of treatment based on germline genetics. Research Sponsor: None.

Multivariable model for pathologic complete response.		
Characteristic	Odds ratio (95% CI)	p-value
BRCA status*		
BRCA1	2.40 (1.47, 3.89)	<0.001
BRCA2	1.10 (0.55, 2.06)	0.8
Well/moderately differentiated†	0.30 (0.20, 0.44)	<0.001
Molecular subtypes‡		
TNBC	3.75 (2.53, 5.68)	<0.001
HR+ HER2+	4.77 (3.17, 7.31)	
HR- HER2+	16.3 (10.3, 26.1)	

Abbreviations: CI= confidence interval; IQR= interquartile range; HR= hormone receptor; HER2= human epidermal growth factor 2.
* Relative to noncarrier. † Relative to poorly differentiated. § Relative to HR+ HER2+.

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Poster Session

The worldwide impact of HER2-targeted treatments in women with breast cancer: An epidemiological modeling study. *First Author: David J. Press, Genentech Inc., South San Francisco, CA*

Background: HER2-targeted therapies (trastuzumab, pertuzumab, and T-DM1) have revolutionized the treatment and epidemiological landscape of HER2+ breast cancer, resulting in population-level increases in survival and decreases in disease recurrence. The aim of this epidemiological modeling study was to quantify the estimated global impact of HER2-targeted therapies, by estimating the number of women diagnosed with HER2+ early breast cancer (eBC) who have avoided (or will avoid) metastatic disease recurrence following treatment. **Methods:** We used data and projections from cancer registries, observational studies, clinical trials, and drug sales volumes (ie, utilization) to create annual country-level synthetic cohorts of patients diagnosed with HER2+ eBC, for the years 2004–2033 in 185 countries. The real-world uptake of HER2-targeted treatments and treatment flow was estimated in the main scenario. The impact of chemotherapy alone was estimated in the counterfactual scenario, assuming 100% chemotherapy worldwide. The occurrence of distant recurrences was modeled in both scenarios using weighted transitional probability averages based on invasive disease-free survival curves from clinical trials. **Results:** In total, during the 3-decade study period, we predicted that 11.9 million (M) women would be diagnosed with HER2+ eBC, out of which 7.5M were estimated to be treated with HER2-targeted therapies in a real-world uptake scenario. In the counterfactual scenario with only chemotherapy available, a total of 2.9M women were estimated to experience a metastatic disease recurrence, compared to only 2.1M women in the base scenario of predicted real-world uptake of HER2+ targeted therapies. This corresponds to a reduction of 26% or 768,000 women who may avoid metastatic recurrence since the introduction of HER2-targeted therapies (Table). **Conclusions:** HER2+ targeted therapies have substantially improved breast cancer outcomes and continue to contribute to the reduction in breast cancer recurrence rates. Further research may elucidate treatment-related reductions in costs to society as a result of population-level improvements in disease outcomes for breast cancer survivors. Given the expected rise in the burden of breast cancer globally, therapeutic advances and increased treatment utilization may further accelerate global patient benefit. Research Sponsor: Hoffmann-La Roche.

Estimated number of women globally diagnosed with BC and experiencing distant recurrence, by year and treatment scenario.

	Years of diagnosis/ recurrence			
	2004–2013	2014–2023	2024–2033	2004– 2033
Women diagnosed with BC (in millions)				
Total	15.3	21.0	26.9	63.2
HER2+ eBC	1.9	4.0	5.9	11.9
Treated with any HER2-targeted therapies	0.7	2.3	4.4	7.5
Women experiencing distant disease recurrence (in thousands)				
Counterfactual: Chemotherapy alone	408	886	1,610	2,904
With predicted real-world uptake of HER2+ therapies	380	723	1,033	2,136

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Poster Session

Validation of a novel and rapid reagent free assay to predict outcomes for adjuvant therapy decision making in hormone receptor-positive breast cancer. *First Author: Charles Coombes, Imperial College, London, United Kingdom*

Background: Digistain is a mid-infrared imaging technology that assesses aneuploidy by measuring the nuclear-to-cytoplasmic chemical ratio in the cellular content of tissues to generate the Digistain Index (DI). DI correlates with tumor grade and shows promise for risk stratification. Here we investigated whether DI could predict clinical outcomes in patients with early breast cancer to guide decision making regarding subsequent adjuvant chemotherapy. **Methods:** Infrared spectrometry was performed on existing tissue microarrays to determine the DI of 801 patients with hormone receptor-positive, HER 2-negative primary breast cancer with ≤ 3 positive lymph nodes who had received systemic endocrine therapy only. Multivariate logistic modelling incorporated the DI with pathological features to generate the Digistain Prognostic Score (DPS). Receiver operator characteristics curves were used to assess the ability of DPS to predict 5- and 10-year progression-free survival (PFS), recurrence and overall survival (OS). **Results:** In a Cox-regression analysis, the hazard ratio (HR) of DI to predict OS was 4.49 (95% CI 1.08–18.67; $P = 0.039$) compared with HRs in the range of 1.04–1.81 (all $P < 0.001$) for age, tumor grade, tumor size and lymph node stage. In multivariate modelling analysis, DPS was consistently highly accurate and had negative predictive values for PFS, recurrence, and OS at 5 and 10 years that were similar, if not superior, to existing genomic-based tests. Using the DPS, the HRs for Kaplan-Meier curves for low- vs. high-risk classification were statistically significant ($P < 0.001$) for PFS, recurrence and OS (1.80, 1.83 and 2.49, respectively). **Conclusions:** In patients with early breast cancer, DPS showed high accuracy and predictive performance, and was able to stratify patients into low or high risk. Considering its low cost and ability to provide almost immediate prognostic information, DPS has the potential to offer clinical utility to reduce the use of unnecessary chemotherapy. Research Sponsor: National Institute of Health Research UK.

Influence of hormone therapy timing intake on disease free survival (DFS) for patients with high-risk early breast cancer: Results of the UCBG-UNIRAD phase III randomized trial. *First Author: Sylvie Giacchetti, APHP University Hospital Saint Louis, Senopole, Paris, France*

Background: Circadian rhythms regulate the cellular and molecular processes that determine treatment effects. Scarce data suggest that daily timing could influence endocrine therapy (ET) pharmacology. We prospectively tested this hypothesis within the UNIRAD adjuvant phase III trial (NCT01805271) in patients (pts) with hormone receptors positive (HR+) and human epidermal growth factor receptor 2 negative (HER2-) breast cancer (BC). **Methods:** Between June 2013 and March 2020, 1,278 pts with high-risk HR+/HER2- primary BC were randomly assigned to adjuvant ET combined with EVE or placebo. Pts were stratified according to lymph node involvement, progesterone receptor status, ET (tamoxifen or aromatase inhibitors (AI)), prior neoadjuvant or adjuvant chemotherapy, and duration of ET before randomization. Throughout their participation in the trial, patients were asked to declare prospectively in a daily diary the timing of ET intake within four 6-h slots (06:00 to 11:59 (morning), 12:00 to 17:59 (afternoon), 18:00 to 23:59 (evening), or 24:00 to 05:59 (night)). The prognostic impact of the timing of ET and EVE/placebo on DFS was a prespecified secondary endpoint. **Results:** A total of 855 patients (67%) recorded ET intake daily timings (n = 401 in the EVE arm, n = 454 in the placebo arm). Morning intake was preferred by 465 pts (54%), whilst 344 pts (40%) chose evening intake, and minor proportions took ET in the afternoon (49 patients, 5%) or at night (5 patients, 1%). Pts choosing morning or afternoon intake were significantly older than those preferring evening or night intakes (mean age: morning: 56.4 y.o.; afternoon: 58.4 y.o.; evening: 53.1 y.o.; night: 50.8 y.o.; p < 0.001). Only 10 patients (1.1%) reported changing ET timing during the study. With a median follow-up of 72.5 months, 118 patients relapsed (locally n = 30, metastases n = 84), and 41 patients died. In the whole population, ET intake timing was not associated with DFS (HR 0.77 [95%CI, 0.53-1.12], p = 0.17). ET intake timing effects according to the stratification factors revealed a significant interaction between its prognostic impact and ET agent (tamoxifen versus AI, p for interaction = 0.01). DFS was prolonged in those pts taking tamoxifen in the evening/night rather than in the morning/afternoon (HR = 0.43 [0.22 - 0.85], p = 0.015), while no such effect was found for those on AI (HR = 1.07 [0.68 - 1.7], p = 0.761). Such interaction remained statistically significant at multivariate analysis (HR 0.38, p = 0.003). **Conclusions:** Tamoxifen intake in the evening was associated with an improved DFS in high-risk HR+/HER2- breast cancer pts and could be recommended at no cost in the adjuvant setting. Clinical trial information: NCT01805271. Research Sponsor: French Ministry of Health PHRC; La Ligue contre le Cancer; Novartis.

Additional prognostic value of the BCT score in patients with ER+HER2-breast cancer receiving 21-gene assay-guided adjuvant treatments. *First Author: Sung Gwe Ahn, Gangnam Severance Hospital, Yonsei University, Gangnam-Gu, NA, Korea, Republic of (South)*

Background: In early estrogen receptor (ER)+HER2- breast cancer, a 21-gene expression assay-guided decision-making for adjuvant treatments has been widely utilized as a standard-of-care. The GenesWell BCT is a multigene assay that is designed to predict the risk of distant recurrence (DR) in patients with ER+HER2-breast cancer. This assay consists of nine genes, which are used to generate a risk score that can help guide treatment decisions. We addressed an additional value of the GenesWell Breast Cancer Test (BCT) score using the cohort of ER+HER2-breast cancer patients receiving a 21-gene assay-guided adjuvant treatments, focusing the chemotherapy untreated subset with low 21-gene recurrence score (RS). **Methods:** This multicentre, observational follow-up study was done in 4 academic institutions in South Korea. Patients with ER+HER2- breast cancer who received RS-guided adjuvant treatments were enrolled. A total of 705 patients were included. Of these, the rate of women with node-positive disease was 21.6% (152/705), and the rate of women with younger than 50 years old was 61.4% (433/705). The BCT score was obtained using the specimens which were previously analyzed for RS. The primary endpoint was recurrence-free survival (RFS), and the secondary endpoint was distant recurrence-free survival (DRFS). **Results:** Among the 705 patients, the RS assigned 110 (15.6%) as high risk (≥ 26), whereas the BCT score assigned 239 (33.9%) as high risk (≥ 4). The agreement between two tests was noted in 494 (70.1%); concordances were made in 69 for high and in 425 for low, respectively. At a median follow up of 85 months, 80 had tumor recurrences, 38 had distant recurrences, and the 7-year RFS was 90.0% (95% CI, 87.6%-92.5%). In the 595 patients with low RS, 556 (93.4%) did not receive adjuvant chemotherapy. Within the 556 chemotherapy-untreated patients with low RS, the RFS differed significantly according to the BCT score (p = .014); the 7-year RFS was 92.9% in the BCT-low, while it was 85.7% in the BCT-high. Within the group, the BCT score was demonstrated as an independent prognostic factor for both RFS and DRFS adjustment of tumor size, nodal stage, and histologic grade. In addition, the RFS of the low-BCT score group was superior to that of the high-BCT group in either women younger than 50 years of age with an RS of 21 to 25 or all women with an RS of 21 to 25. **Conclusions:** We found that the BCT score was useful in stratifying the risk of relapse in chemotherapy-untreated patients with a low recurrence score (RS). This indicates that the BCT score could provide additional clinical value in identifying patients with a long-term risk of relapse, particularly in young women with an RS of 21 to 25. Research Sponsor: Gencurix.

Prognostic role of HER2 expression in patients with ER-positive/HER2-negative breast cancer: Results from a population-based cancer registry study. *First Author: Antonino Musolino, Gruppo Oncologico Italiano di Ricerca Clinica (GOIRC), Parma, Italy*

Background: Estrogen Receptor (ER)-positive (+)/Human Epidermal Growth Factor Receptor 2 (HER2)-negative (-) breast cancers (BCs) express variable protein levels of both ER and HER2, which can influence prognosis. **Methods:** We evaluated all invasive ER+/HER2- BCs (n = 3633) that were diagnosed and systematically collected by the Parma Province Cancer Registry, Italy, from 2004 to 2018. Tumors were classified by HER2 (IHC score of 0, 1+ or 2+ with negative FISH) and ER status (ER-low [1-9%], ER-moderate [10-79%] or ER-high [80-100%]). Comparisons of clinicopathologic characteristics and disease outcome were performed. **Results:** BCs with late-stage diagnosis (P = 0.04), high histologic grade (P < 0.0001), or high proliferative rate (P < 0.0001) were more likely HER2 2+/FISH-. The rate of ER-high BCs did not change from 2675 of 2938 (91%) HER2 0 tumors to 508 of 560 (90.7%) HER2 1+, and 124 of 135 (91.9%) HER2 2+/FISH- tumors. Correspondingly, ER-low BCs were not enriched among HER2 0 tumors compared to the other tumors with different HER2 expression (P = 0.6). The 5-year overall survival (OS) for HER2 2+/FISH- BCs was lower than that for HER2 0 or 1+ tumors (P = 0.03). ER-low/moderate tumors were associated with poorer OS in comparison with ER-high BCs (P < 0.0001). HER2 2+/FISH- status was detrimental to OS among patients (pts) with ER-high tumors (P = 0.04), while this finding was not observed among ER-low/moderate BCs (P = 0.21). An interaction between HER2 2+/FISH-expression and ER-high status was found for poorer OS after adjusting for prognostic variables (HR = 1.7; 95% CI: 1.1-2.9). **Conclusions:** The prognostic role of HER2 expression in pts with ER-positive/HER2-negative BCs seems to be restricted to ER-high tumors, while the worse prognosis of tumors with lower ER expression is not associated with HER2 status. These findings may help identify optimal patient inclusion criteria for clinical trials with novel anti-HER2 therapies in ER-positive/HER2-negative disease. Research Sponsor: None.

An analysis of breast cancer index scores predicting benefit of extended endocrine therapy by race. *First Author: Nicholas Siu-Li, University of Hawaii John A. Burns School of Medicine, Honolulu, HI*

Background: Patients with early-stage hormone receptor-positive (HR+) breast cancer have a good prognosis. Prior studies have shown that extending endocrine therapy beyond the first 5 years reduces the risk of late distant recurrence. The Breast Cancer Index (BCI) is a gene expression assay that provides both a prognostic risk of late distant recurrence in addition to a yes/no prediction of benefit from receiving extended endocrine therapy. To date, no studies have examined the relationship between race and BCI score. This study aims to investigate the interaction between race and BCI scores in women with early-stage HR+ breast cancer. **Methods:** We analyzed BCI scores, demographics, and tumor characteristics from 89 women diagnosed with early-stage HR+ breast cancer. Univariate logistic regression analysis was run using race, BCI recurrence risk, hormone status, tumor size, or tumor grade as predictor variables. BCI prediction of benefit was used as the outcome variable. **Results:** Compared to Caucasians, Native Hawaiians had significantly greater odds of having a BCI score predicting benefit from receiving extended endocrine therapy (OR = 7.00, p = 0.04). Additionally, there were significantly greater odds of having a score predicting benefit among those who had a recurrence risk of 5-10% (OR = 3.84, p = 0.04), or $\geq 10\%$ (OR = 9.16, p < 0.001) compared to a recurrence risk < 5%. **Conclusions:** Our findings highlight the utility of characterizing differences in BCI predictive and prognostic scores by race among breast cancer patients with early-stage HR+ tumors. Notably, Native Hawaiian women had 7.0 times increased odds of having a score predicting benefit of extended endocrine therapy compared to Caucasians. This result is salient given the high incidence of breast cancer among Native Hawaiians. Though not statistically significant, our data also demonstrated Filipinos had increased odds of a score predicting benefit as well. Furthermore, our findings show a direct correlation between prognostic risk of late distant recurrence and predictive benefit of extended endocrine therapy with a higher odds ratio associated with higher recurrence risk. Our study shows notable differences in BCI findings when stratifying patients by race. However, our sample size is relatively small, and we lack sufficient data from patients representing other races such as Hispanic and Black. Future studies may expand the sample size and adjust for known breast cancer risk factors. The goal is to identify trends that may improve our usage of the BCI as a tool to effectively guide hormone therapy recommendations in patients with early-stage HR+ breast cancer. Research Sponsor: U.S. National Institutes of Health.

		N	Predictive Benefit (Yes)	OR
BCI Risk (%)	Low (< 5)	41	5	1.00
	Mid (5-10)	23	8	3.84
				(p = 0.04)
	High (≥ 10)	25	14	9.16
				(p < 0.001)
Race	Caucasian	16	2	1.00
	Filipino	14	6	5.25
				(p = 0.07)
	Japanese	31	9	2.86
				(p = 0.22)
	Hawaiian	14	7	7.00
				(p = 0.04)
	Other Asian or Pacific Islander	8	1	1.00
				(p = 1.00)
	Other	6	2	3.50
				(p = 0.28)

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Poster Session

Cardiac safety and efficacy for patients with early-stage breast cancer treated with pegylated liposomal doxorubicin (PLD) or doxorubicin. *First Author: Lichen Tang, Department of Breast Surgery, Fudan University Shanghai Cancer Center; Cancer Institute, Fudan University Shanghai Cancer Center, Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, China*

Background: Anthracyclines play an important role in the treatment of breast cancer (BC) while cardiotoxicity, a serious side effect, limits the clinical application. Pegylated liposomal doxorubicin (PLD) is a new dosage form of doxorubicin encapsulated in liposomes, which can reduce the plasma free level of doxorubicin and drug to normal tissue delivery, thereby reducing cardiotoxicity. The aim of this study was to evaluate the cardiac safety and efficacy of PLD compared with doxorubicin as adjuvant therapy in breast cancer patients. **Methods:** This is an open-label, randomized trial involving patients with operable breast cancer who were at high risk of recurrence after radical surgery (NCT03949634). Patients were randomized (1:1) to receive adjuvant PLD or doxorubicin (A) and cyclophosphamide followed by taxanes ± trastuzumab. The primary endpoint was cardiotoxicity, which was defined as congestive heart failure (CHF) with clinical symptoms, or no symptoms but with an abnormal left ventricular ejection fraction (LVEF). Secondary endpoints included 5-year disease-free survival (DFS) rate, 5-year overall survival (OS) rate and safety. **Results:** Between November 2017 and September 2019, 247 patients were randomized and received study treatment (PLD arm, 131; A arm, 116). The median age was 49 years (range, 26-67) in PLD arm and 48 years (range, 25-70) in A arm. The pathological stages were 18.3% stage I, 58.0% stage II, and 22.1% stage III in PLD arm, while those of A arm were 20.7% stage I, 59.5% stage II, and 19.8% stage III. The median follow-up time was 43.0 months. The incidence of abnormal LVEF was 0 in the PLD arm and 1.7% the A arm (P = 0.220). The incidence of CHF was 0 in the PLD arm and 0.9% the A arm (P = 0.470). Survival data analysis is immature. The exploratory analysis of cardiac-related biomarkers showed that the incidence of high-sensitivity cardiac troponin-T (hs-cTnT) was lower in PLD arm than in A arm (3.8% vs. 30.2%, P < 0.001). Grade 3/4 adverse events (AEs) occurred in 42.7% patients in PLD arm and in 61.2% patients in A arm. The most common grade 3/4 AEs in PLD arm and A arm included neutropenia (34.4% vs. 55.2%), leukopenia (30.5% vs. 39.7%), and hand-foot syndrome (4.6% vs. 0.0%). **Conclusions:** Hs-cTnT elevation may have a role in the AE prediction of anthracycline. PLD usage may present lower incidence of cardiotoxicity than doxorubicin in the adjuvant treatment of patients with early-stage breast cancer. Clinical trial information: NCT03949634. Research Sponsor: CSPC Ouyi Pharmaceutical Co., Ltd.

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Poster Session

Beneficial effect of repeated participation in breast cancer screening upon survival. *First Author: Robert A. Smith, American Cancer Society, Atlanta, GA*

Background: The benefit of mammography screening in reducing population mortality from breast cancer is well established. However, the effect of repeated participation at scheduled screens on case survival is less well documented. **Methods:** In this retrospective analysis of breast cancer survival, we analyzed incidence and survival data on 37,079 women ages 40-69 from nine Swedish counties who had between one and five invitations to mammography screening and were diagnosed with breast cancer between 1992 and 2016. Of these, 4,564 subsequently died of breast cancer. For each breast cancer diagnosed in each county's period of observation, we obtained data on previous screening history, and subsequent death (or not) from breast cancer. Formal comparisons of survival with respect to numbers of screening exams attended prior to a diagnosis of breast cancer were carried out using Cox proportional hazards regression with time-varying covariates, ie, cumulative numbers of screens, yielding hazard ratios and 95% confidence intervals (CI). We corrected for potential self-selection using the method of Duffy et al, which gives a corrected estimate based on the proportion of participants, the uncorrected estimate, and the relative risk of breast cancer death for non-participants compared to an uninvited population. **Results:** Depending on number of invitations, 58-73% (average 65%) participated in all scheduled screens, and 73-96% (average 91%) participated in at least one examination. There was successively better survival among women with increasing numbers of screening exams. For a woman with five previous screening invitations who participated in all five screening exams, the hazard ratio was 0.28 (95% CI 0.25-0.33, p<0.0001), a 72% risk of dying from breast cancer, compared to a woman attending none. Following a conservative adjustment for potential self-selection factors, the hazard ratio was 0.34 (95% CI 0.26-0.43, p<0.0001). **Conclusions:** For those women who develop breast cancer, regular prior participation in mammography screening confers significantly better survival. Most women will not develop breast cancer in their lifetime. These results indicate that for those who do, regular participation in screening considerably improves the probability of surviving it. The distinction between the general, population benefit of mammography screening, and the benefit of regular participation in mammography screening should be clearly articulated in breast cancer screening messaging and decision aids. Research Sponsor: American Cancer Society.

Hazard ratios by number of screens in which the women participated, unadjusted and adjusted for potential self-selection factors.

Number of screens participated in	Hazard ratio (95% CI)	
	Unadjusted	Adjusted
0	1.00 (-)	1.00 (-)
1	0.71 (0.57-0.89)	0.87 (0.67-1.12)
2	0.50 (0.40-0.63)	0.61 (0.45-0.83)
3	0.37 (0.30-0.46)	0.45 (0.34-0.60)
4	0.37 (0.31-0.43)	0.45 (0.35-0.58)
5	0.28 (0.25-0.33)	0.34 (0.26-0.43)

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Poster Session

Influence of adherence to adjuvant endocrine therapy in early breast cancer: Results from a large German real-world claims data analysis. *First Author: Dominik Dannehl, Department of Women's Health, Tuebingen University Hospital, Tuebingen, Baden-Wuerttemberg, Germany*

Background: In hormone-receptor positive (HR+) early breast cancer (EBC) adjuvant endocrine therapy (ET) significantly reduces recurrence and mortality. The most common way to estimate therapy adherence is the use of patient reported outcome measures. Yet, this method is inaccurate due to the social-desirability bias. We therefore aimed to analyze adherence to ET over the first 5 years of treatment by using claims data from a large German health insurance provider (AOK Baden-Wuerttemberg). **Methods:** Female patients diagnosed with HR+ EBC between July 1st 2010 and December 31st 2019 were included into the analysis. Adherence to ET was defined as the ratio of the summed number of pills of filled prescriptions for ET (either aromatase inhibitors or tamoxifen) and the duration of endocrine therapy in days (from the start of the first prescription after completion of surgery and chemotherapy, if applicable). ET administration was observed over 5 years. High/low adherence was defined as a ratio between 0.8 – 1 and 0 – 0.8, respectively. ET duration was divided into yearly intervals and adherence was calculated as above. Continuous high/low adherence was then defined as an adherence between 0.8 – 1 and 0 – 0.8 in each year. Distant recurrence-free survival (DRFS) was calculated from the day of the first diagnosis of EBC until onset of distant metastatic disease. Overall survival (OS) was defined as the period between first diagnosis of EBC until death. **Results:** In total, 20998 patients were included. 17006 patients (81%) were HR+. Regarding overall adherence during the first 5 years, average adherence was 0.81 ± 0.26, with 72% of all HR+ patients showing high adherence to ET. Of 17006 HR+ EBC patients, 8363 (49%) showed a continuous high adherence to ET and 1731 (10%) showed a continuous low adherence to ET over 5 consecutive years. Continuous adherence to endocrine therapy had a significant impact on DRFS (HR: 0.61; 95% CI: 0.52 - 0.71; p < 0.0001) and OS (HR: 0.52; 95% CI: 0.46 - 0.59; p < 0.0001). The 10-year OS rate was 79% / 64% for patients with continuous high / low adherence to endocrine therapy. **Conclusions:** As measured by the number of prescribed pills, adherence during the first 5 years of endocrine therapy was higher than expected by literature. Continuous adherence to ET over 5 years has a significant impact on OS and DRFS. Future research should focus on identifying factors that influence therapy adherence in HR+ EBC patients. Research Sponsor: AOK Baden-Wuerttemberg.

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Poster Session

State-of-the-art management of HER2-negative early breast cancer: Treatment patterns among healthcare professionals and concordance with expert recommendations. *First Author: Marie N. Becker, Clinical Care Options, Reston, VA*

Background: The management of high-risk HER2-negative early-stage breast cancer (EBC) has recently evolved with the addition of newer agents including abemaciclib, olaparib, and pembrolizumab as (neo)adjuvant therapy options for appropriate patients. To aid healthcare professionals (HCPs) in the recommended implementation of these agents, we developed an online treatment decision support tool providing case-specific treatment guidance from 5 breast cancer experts. Here, we report an analysis of cases entered into the tool by HCPs, comparing their planned treatment with expert recommendations. **Methods:** Expert therapy recommendations for 10 case scenarios in high-risk HER2-negative EBC based on 3 pivotal clinical trials (KEYNOTE-522, OlympiA, and monarchE) were obtained in March 2022. Patient and disease characteristics included hormone receptor (HR) status, *BRCA* mutational status, lymph node positivity, presence of residual disease after resection, and additional criteria based on the 3 practice-changing trials. HCPs entered specific patient and disease factors into the tool along with their intended treatment plan and were shown 5 individual expert treatment recommendations for the unique case scenario. **Results:** From June 2022 to January 2023, 547 HCPs entered 982 patient case scenarios into the tool. A comparison of treatment recommendations by experts and HCPs showed divergence for several case scenarios. For patients with high-risk HR-positive/HER2-negative EBC and no *BRCA* mutation, all 5 experts recommended adjuvant abemaciclib plus endocrine therapy. By contrast, 64% of HCPs' therapy choices were discordant with the experts, with 49% choosing chemotherapy followed by endocrine therapy. For patients with triple-negative breast cancer (TNBC) who received neoadjuvant chemotherapy and have no residual disease, all 5 experts recommended observation, whereas 36% of HCPs recommended additional adjuvant therapy. In the setting of *BRCA*-mutated TNBC with residual disease after neoadjuvant pembrolizumab plus chemotherapy, 4 of 5 experts recommended adjuvant pembrolizumab plus olaparib, but just 33% of HCPs chose this combination. One third of HCPs who initially selected treatment options that diverged from expert recommendations or who were uncertain about treatment choice intend to change their therapy selection to align with the experts. **Conclusions:** Analysis of data from this tool suggests differences in clinical practice between experts and HCPs for multiple case scenarios of high-risk EBC, including examples of potential overtreatment. Moreover, our data demonstrate that this decision support tool may lead to better alignment of HCP treatment choices with experts, with the potential to improve clinical management of patients. Research Sponsor: None.

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Poster Session

SEER analysis of 9-year breast cancer specific mortality (BCSM) in patients (pts) with invasive lobular breast cancer (ILC) assessed by the 21-gene Breast Recurrence Score assay. *First Author: Charles E. Geyer, UPMC Hillman Cancer Center, Pittsburgh, PA*

Background: Linking of the results of the 21-gene Breast Recurrence Score (RS) commercial assay to SEER registries provides opportunity to assess real world prognostic performance of the assay in important subgroups of early breast cancer (BC). ILC is less common than invasive ductal carcinoma (IDC) and the performance of the RS assay in ILC is of interest. The relationship between RS results and 5-year BCSM in patients with ILC was reported based on a linkage in 2015 at this meeting in 2017. Here we present a comparison of 9-year BCSM of ILC vs IDC from a linkage update in 2019. These results will be updated further based on a new linkage of RS data to be completed in April 2023. **Methods:** Eligible pts had 0-3 axillary nodes at initial surgery, were hormone receptor positive and HER2-negative with a RS result, had no prior malignancy, and were diagnosed between January 2004 and December 2012. Pts with ICD-0-3 code 8520 were categorized as ILC and those with code 8500 as IDC. 9-year BCSM of both cohorts was estimated using actuarial methods. Multivariable Cox proportional hazards models characterized association between RS results and BCSM. **Results:** Of 89818 pts, 9835 (11.0%) had ILC and 64669 (72.0%) had IDC. Among pts with ILC, median age was 60 years; 12.5% were N1 and 28.4%, 63.7% and 7.9% were grade 1, 2 and 3. Median follow-up was 84 months. Chemotherapy (CT) use and BCSM increased with increasing RS result in both cohorts. After adjusting for age, race, tumor grade, tumor size, nodal status, and histologic subtype, the RS result was independently associated with BCSM ($p < .001$) in both ILC and IDC. **Conclusions:** In this linked SEER analysis of pts with ILC or IDC, the RS results were prognostic for 9-year BCSM, regardless of nodal status. Research Sponsor: U.S. National Institutes of Health; Exact Sciences.

Histologic subtype	RS result	Node-negative			Node-positive		
		N	% CT use	9-y BCSM (95% CI)	N	% CT use	9-y BCSM (95% CI)
IDC	0-15	24265	5.6	1.9% (1.6, 2.1)	3599	21.1	2.8% (2.2, 3.8)
	16-20	13556	17.9	2.5% (2.1, 2.8)	1912	36.8	4.9% (3.7, 6.4)
	21-25	8559	36.7	4.5% (4.0, 5.2)	1051	52.7	8.2% (6.3, 10.6)
	26-100	10544	64.9	8.4% (7.8, 9.1)	1183	73.3	16.0% (13.3, 19.2)
ILC	0-15	3899	6.5	2.6% (2.0, 3.3)	613	22.7	4.9% (2.6, 9.4)
	16-20	2517	17.0	2.6% (1.9, 3.6)	347	37.8	8.1% (5.2, 12.5)
	21-25	1471	34.0	4.8% (3.6, 6.5)	170	44.1	9.8% (5.6, 16.8)
	26-100	724	57.2	8.2% (6.1, 11.0)	94	63.8	16.2% (9.9, 25.8)

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Poster Session

Detection of homologous recombination deficiency (HRD) using a novel genomic and epigenomic liquid biopsy assay in patients with breast cancer. *First Author: Catalin Barbacioru, Guardant Health, Redwood City, CA*

Background: Homologous recombination and repair (HRR) deficiency (HRD) is characterized by genomic instability associated with dysfunction in *BRCA1/2* or other HRR genes. Patients with breast cancer harboring an HRD phenotype with or without HRR mutations have derived clinical benefit from PARPi therapy. We have previously shown that GuardantINFINITY, a novel genomic and epigenomic liquid biopsy assay, can identify HRR SNVs, indels, rearrangements, copy number loss, reversions, and *BRCA1* promoter methylation for patient selection and resistance monitoring, a major challenge for PARPi treatment. Here, we present a method of predicting HRD status by cfDNA using GuardantINFINITY in patients with advanced breast cancer. **Methods:** We developed a probabilistic genomic model to predict HRD status, inferred from genome-wide somatic SNV, indel, and CNV signatures indicative of *BRCA1/2* deficiency, including large-scale state transitions (LST), whole-genome tumor loss of heterozygosity (LOH), telomeric allelic imbalance (TAI). A second probabilistic model, based on targeted measurements of genomic and epigenetic changes was learned from a subset of clinical samples to enhance the genomic model. The model was trained and tested on a cohort of over 12,000 GuardantOMNI and GuardantINFINITY clinical breast cancer samples to assess the sensitivity of accurately detecting deficiency in select HRR-genes (*BRCA1/2*, *PALB2*, *RAD51D*). The aggregated predictive model was validated on an independent cohort of breast cancer samples. **Results:** The model based on genomic and epigenetic signals identified HRR-gene deficiency in a breast cancer cohort with an estimated 95% LoD of 22.5% tumor fraction and an AUC of 0.75 across all tumor fractions, an improvement in sensitivity over when only the genomic model is used (AUC of 0.7, 95% LoD of 28%). Specificity remained high for both models (100%, $n = 83$) in cancer free samples. Application of this model in a cohort of 1,101 patients with unselected breast cancer identified 390 patients with an HRD phenotype, of whom 192 patients had a known HRR-gene mutation. Of the 201 patients with a known pathogenic mutation in an HRR gene, 49 also had co-occurring LoH in the same gene, indicating biallelic loss. **Conclusions:** In this analysis, we demonstrate that a probabilistic model of genomic and methylation predictors can detect HRD status in patients with breast cancer from cfDNA using GuardantINFINITY. Additional analytical and clinical studies to further evaluate this model are ongoing. With HRD prediction, GuardantINFINITY provides a comprehensive minimally-invasive solution for PARPi and DNA damage treatment selection, longitudinal monitoring, and an exploratory platform for investigating epigenetic signals that may underpin resistance. Research Sponsor: Guardant Health.

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Poster Session

Impact of neoadjuvant chemo-immunotherapy on surgical outcomes and time to radiation in triple negative breast cancer. *First Author: Sara P. Myers, Breast Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: The impact of preoperative chemo-immunotherapy on surgical complications and timing of adjuvant therapy is not well understood. We examined the association between neoadjuvant pembrolizumab plus chemotherapy (NAC+P) compared to neoadjuvant chemotherapy alone (NAC) and treatment delays and postoperative complications in triple negative breast cancer (TNBC). The effect of immune-related adverse events (irAEs) on these outcomes was also compared. **Methods:** 143 women with stage II-III TNBC treated with NAC+P based on the KEYNOTE 522 (KN522) regimen from 8/2021-9/2022 were compared to 287 consecutive patients who received NAC prior to 7/2021. Baseline characteristics, time to treatments, and surgical complications were compared between KN522 and non-KN522, and among KN522 with/without irAEs using two-sample non-parametric tests. Linear regression evaluated association of irAEs with time to surgery and radiation. Conditional logistic regression identified factors associated with surgical complications among KN522 patients. **Results:** Age, BMI, race, ASA class, and mastectomy rates were similar among KN522 and non-KN522 patients. Interval from end of neoadjuvant treatment until surgery was one day longer for patients receiving NAC+P (median 32 days (IQR 27, 43) vs. 31 days (26, 37) non-KN522, $p = 0.035$). Time to radiation did not differ ($p = 0.2$). Postoperative complications occurred in 26 (9%) non-KN522 vs 12 (8.4%) of KN522 patients ($p = 0.7$) (Table). 55/144 (38%) of KN522 patients experienced 74 irAE; 42 (76%) required treatment. Pembrolizumab was held in 21 (38%) and discontinued permanently in 17 (31%). One KN522 patient experienced a fatal irAE (pneumonitis). Older age (coeff. 0.38, 95% CI 0.06-0.70, $p = 0.02$) and ASA class 4 (coeff. 53, 95% CI 14-92, $p = 0.009$) were associated with delays to surgery but irAE was not ($p = 0.070$). Neither presence of irAE (coeff. 6.8, 95% CI -0.74-14, $p = 0.081$) or number of irAEs (coeff. 4.1, 95% CI -1.2-9.3, $p = 0.13$) were associated with time to radiation. IrAEs were not associated with surgical complications ($p = 0.5$). **Conclusions:** Postoperative complications or delays to surgery or adjuvant radiation were similar in patients treated with NAC+P compared to NAC. IrAEs were not associated with delays to surgery or adjuvant radiation or postoperative complications. Research Sponsor: None.

Postoperative complications and interventions.

	KN522 n (%); (N = 143)	Non-KN522 n (%); (N = 287)	KN522 n (%); (N = 143)	Non-KN522 n (%); (N = 287)
Complication*				
Cardiac arrest	0	1 (0.4%)	4 (2.8%)	12 (4.2%)
Hematoma	2 (1.4%)	3 (1%)	Antibiotics + bedside procedure Antibiotics + bedside procedure CPR/ACLS	1 (0.7%) 1 (0.3%)
Implant loss	1 (0.7%)	0	0	1 (0.3%)
Skin-flap ischemia	5 (3.5%)	8 (2.8%)	Re-operation	2 (1.4%)
Pneumothorax	0	1 (0.4%)	Local wound care	0
Infection/abscess	4 (2.8%)	13 (4.5%)		2 (0.7%)

*p = value 0.7 *p-value 0.4.

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Poster Session

Trends and outcomes of systemic therapy in hormone receptor-positive early-stage male breast cancer: A propensity score analysis. *First Author: Liuwen Yu, Department of Breast Surgery, Fujian Medical University Union Hospital, Fuzhou, China*

Background: Male breast cancer (MBC) is a rare disease. Research on trends and survival outcomes in systemic treatment for MBC is limited. This study aims to describe trends and survival outcomes of different systemic treatments in hormone receptor-positive (HR+) early MBC and to assess the factors related to treatment selection. **Methods:** We identified stage I-III HR+ invasive MBC patients who have undergone surgery and systemic therapy diagnosed during 2004-2014 from the National Cancer Database (NCDB). Treatment groups include: endocrine therapy (ET), chemotherapy (ET), combination therapy (ET+CT), and None. Using Cochran-Armitage trend tests to describe the temporal trends of different treatments. Performing propensity score models to evaluate overall survival. Conducting a logistic regression to analyze factors associated with ET+CT. **Results:** Among 6217 patients included (median follow-up 50.1months), 1290 (20.7%) patients received no systemic therapy (None), 705 (11.3%) patients only received CT, 2358 (37.9%) patients only received ET, and 1864 (30.0%) patients received ET+CT. From 2004 to 2013, there was a significant increase in the use of ET ($P(\text{trend}) < .001$), which was accompanied by a decrease in CT and no treatment (all $P(\text{trend}) < .001$). And the use of ET+CT showed no significant change. After using overlap weighting (OW) to control confounders, multivariable cox regression analysis showed that ET+CT was associated with improved survival compared with ET (hazard ratio [HR], 0.46; $P < .001$). Sensitivity analyses (including the inverse probability of treatment weighting (IPTW) (HR, 0.49; $P < .001$), IPTW with stabilized weight (HR, 0.49; $P < .001$), propensity score matching (PSM) (HR, 0.51; $P < .001$), PS regression adjustment (HR, 0.47; $P < .001$), and PS stratification (HR 0.44; $P < .001$)) and exploratory subgroup analyses (except for well-differentiated, stage I, and breast conservation + radiotherapy subgroups) indicated similar outcome. Factors associated with receiving ET+CT include younger age, private insurance, Charlson Comorbidity Index was 0, poorer differentiation, higher stage, mastectomy and radiotherapy, estrogen receptor-positive and progesterone receptor-negative, and HER2-positive. **Conclusions:** ET+CT was associated with improved survival compared with ET in HR+ early MBC patients, except for some low-risk subgroups. Research Sponsor: None.

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Poster Session

Decision value of the circulating tumor DNA on the adjuvant anti-Her2 regimens in patients with Her2-positive breast cancer treated with neo-adjuvant therapy. *First Author: Po-Han Lin, National Taiwan University Hospital, Taipei City, Taiwan*

Background: A significant proportion of patients with early-stage Her2-positive breast cancer are treated with neoadjuvant therapy (NAT). Previous studies suggested the presence of circulating tumor DNA (ctDNA(+)) after NAT was a significant predictor for recurrence in early-stage Her2-positive breast cancer. However, it is unknown whether the ctDNA(+) was able to guide adjuvant anti-Her2 regimen for patients with early-stage Her2-positive breast cancer? **Methods:** We enrolled 117 patients who had Her2-positive breast cancer and received NAT. CtDNA was collected before and after NAT as well as detected by Oncomine breast cell-free DNA assay. Adjuvant anti-Her2 regimens were classified as T-DM1 and non-T-DM1. Recurrence-free survival (RFS) was estimated by Kaplan-Meier method and hazard ratio (HR) with 95% confidence interval (CI) was analyzed by Cox proportional hazards regression model. **Results:** Of the 117 patients enrolled, there were 18 patients receiving adjuvant T-DM1 and 99 receiving trastuzumab (N = 70) or trastuzumab plus pertuzumab (N = 29). CtDNA(+) was observed in 79 patients before NAT while 32 patients remained ctDNA(+) after NAT. Multivariate Cox regression model showed that ctDNA(+) after NAT (HR 3.497 95% CI 1.364-8.964, $p = 0.009$) was an independently poor factor that predicted recurrence, after adjustment with clinical and pathologic parameters. Non-pCR was associated with an inferior trend of survival but not a statistically significant factor of recurrence. Patients who received adjuvant T-DM1 had a reduced risk of recurrence (HR 0.118, 95% CI 0.015-0.931, $p = 0.043$) in the multivariate analysis. Further analysis of the prognostic value of adjuvant T-DM1 therapy in context with and without ctDNA, we divided patients into 4 subgroups: ctDNA(-)/non-T-DM1, ctDNA(-)/T-DM1, ctDNA(+)/non-T-DM1 and ctDNA(+)/T-DM1. Our data revealed that patients with ctDNA(+)/T-DM1 had a significantly better RFS than those with ctDNA(+)/non-T-DM1 ($p = 0.019$). The 5-year RFS was similar between patients with ctDNA (+)/T-DM1 and those with ctDNA(-) after NAT. **Conclusions:** The presence of ctDNA in patients with early-stage Her2-positive breast cancer after NAT was independently associated with disease recurrence; however, ctDNA(+) after NAT became inconsiderable when patients were treated with adjuvant T-DM1 therapy, which represented ctDNA(+) as an important factor determining adjuvant anti-Her2 regimen. Research Sponsor: Yonglin Foundation.

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Poster Session

Utility of Ki67 in guiding adjuvant abemaciclib therapy for patients with hormone receptor (HR)-positive, early breast cancer (EBC). *First Author: Rima Patel, Icahn School of Medicine at Mount Sinai, New York, NY*

Background: The monarchE trial found that the addition of adjuvant abemaciclib to endocrine therapy in pts with lymph node (LN)+, HR+ EBC improved invasive disease-free survival in two pt cohorts: (1) ≥ 4 LNs or 1-3 LNs and Grade 3 disease or tumor ≥ 5 centimeters and (2) 1-3 LNs and Ki67 $\geq 20\%$. The FDA approved adjuvant abemaciclib only in pts with HR+, HER2-negative, LN+ EBC with Ki67 $\geq 20\%$. The role of Ki67 as a predictive biomarker in this setting is unclear. ASCO guidelines recommend offering abemaciclib to pts who meet eligibility for either cohort and not restricting inclusion by Ki67. The objectives of this study were to (1) determine the association between Ki67 and the 21-gene recurrence score (RS), an established prognostic and predictive biomarker, using Ki67 cutoff $\geq 20\%$ and (2) compare eligibility for adjuvant abemaciclib by FDA versus ASCO criteria. **Methods:** Women with HR+, HER2-negative EBC with 1-3 LNs, diagnosed between 2018 and 2019, and who had available information on Ki67 and RS in the National Cancer Database were identified. Pts were categorized into Ki67 low ($< 20\%$) or high ($\geq 20\%$) based on cutoff used in the monarchE and stratified by RS of low-intermediate (0-25) or high (26-100). Stratified agreement between Ki67 and RS were assessed using the proportion of agreement and Kappa statistic. McNemar's test was used to compare proportion of pts eligible for abemaciclib by FDA versus ASCO criteria. **Results:** 50,222 eligible women were included. 63.9% ($n = 32,082$) had Ki67 $< 20\%$ and 36.1% ($n = 18,140$) Ki67 $\geq 20\%$. There was fair agreement (Kappa 0.21-0.40) between Ki67 and RS, which was statistically significant (Kappa = 0.272, $p \leq 0.001$). Overall, using the FDA criteria for abemaciclib, 36.1% ($n = 18,140$) of patients would be eligible while based on ASCO criteria, 39.9% ($n = 20,061$) could be offered adjuvant abemaciclib ($p < 0.001$). Among the 20,061 patients eligible for abemaciclib based on ASCO criteria, 57.4% ($n = 11,513$) were eligible due to Ki67 $\geq 20\%$ alone, 9.6% ($n = 1,921$) due to Grade 3 alone, while 33.0% ($n = 6,627$) satisfied both Ki67 $\geq 20\%$ and Grade 3 criteria. There were 33,789 patients who were post-menopausal with RS 0-25 and would be spared chemotherapy, yet 32.1% ($n = 10,856$) would be eligible for adjuvant abemaciclib based on FDA or ASCO criteria. **Conclusions:** There was only fair agreement between Ki67 and RS in patients with 1-3 LNs based on Ki67 cutoff of 20%. Among patients with LN+ EBC, more patients would be offered abemaciclib using ASCO criteria compared to FDA criteria. Most were eligible for abemaciclib based on Ki67 alone, suggesting that Ki67 may provide additional information beyond tumor grade. In postmenopausal women with 1-3 LNs, about 30% may be spared adjuvant chemotherapy based on the RS but still be sufficiently high risk to be considered for adjuvant abemaciclib. Research Sponsor: None.

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Poster Session

Influence of ovarian function suppression on quality of life in breast cancer survivors during adjuvant endocrine therapy. *First Author: Natalija Dedic Plavetic, School of Medicine University of Zagreb, Zagreb, Croatia*

Background: Adding ovarian function suppression to adjuvant endocrine therapy (AET) lowers the disease recurrence rates among premenopausal women with hormone receptor-positive (HR+) early breast cancer (EBC). However, a detrimental effect on endocrine symptoms burden (ESB) is expected. Therefore, this study aimed to investigate differences in Quality of life (QoL) and endocrine symptoms in premenopausal women prescribed AET, with/without gonadotropin-releasing hormone agonist (GnRH). **Methods:** This cross-sectional study included women, with HR+ EBC, premenopausal at diagnosis, treated with AET for more than 3 months, with and without GnRH. The research was conducted with institutional Ethics Committee approval at the University Hospital Centre Zagreb, General Hospital Šibenik, and with online survey. A validated instrument, the Functional Assessment of Cancer Therapy - Endocrine Symptoms (FACT-ES), was used. The collected data were analysed using SPSS v. 29 ($p \leq 0.05$). **Results:** Overall, 314 eligible BC survivors with a median age of 45 years (22-65) and a median duration of AET of 2 years (3 months-12 years) responded to FACT-ES and were included in the analysis. Altogether 45.2% ($n = 142$) of participants were prescribed tamoxifen (TAM), 25.8% ($n = 81$) GnRH+TAM, and 29% ($n = 91$) GnRH+aromatase inhibitor (AI); exemestane (9%), letrozole (13.6%) and anastrozole (6.4%). The total QoL (FACT-ES) score was higher in patients treated with TAM as opposed to patients treated with AI+GnRH ($p = 0.01$). Adding GnRH to TAM did not significantly change QoL when compared to TAM alone or AI+GnRH. In addition, patients on AI+GnRH had lower physical well-being (PWB) score than patients on TAM+GnRH ($p = 0.03$) or TAM alone ($p = 0.05$) and lower endocrine subscale score (ESS-19) than patients on TAM ($p = 0.01$), indicating more endocrine symptoms in premenopausal women treated with AI+GnRH. Among patients treated with AI+GnRH letrozole had lower PWB ($p = 0.03$) and ESS-19 score ($p = 0.01$) than exemestane. **Conclusions:** This study showed that GnRH+AI in premenopausal women with HR+ EBC results in greater ESB and lower QoL compared to patients treated with TAM or GnRH+TAM. Therefore, interventions helping decrease the ESB in patients treated with AI+GnRH should be explored and developed to help patients adhere to and persist in AET. Research Sponsor: None.

	Subscale score - mean (SD)			
	TAM	GnRH+TAM	GnRH+AI	*p-value
PWB	21.15 (6.30)	21.62 (5.21)	19.23 (6.21)	0.02
SWB	21.26 (5.88)	21.32 (5.10)	20.61 (5.64)	0.62
EWB	18.05 (4.23)	18.06 (4.30)	16.91 (5)	0.12
FWB	17.85 (4.60)	18.35 (4.47)	17.09 (4.65)	0.19
ESS-19	54.50 (12.96)	52.43 (11)	49.75 (11.27)	0.01
FACT-ES	132.91 (26.79)	131.78 (24.50)	123.39 (26.37)	0.02

*One-way ANOVA.

Social well-being (SWB), emotional well-being (EWB), functional well-being (FWB).

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Poster Session

Prognosis of squamous cell carcinoma of the breast by biological subtypes and the efficacy of radiotherapy: The Japanese Breast Cancer Registry analysis. *First Author: Mami Ogita, Department of Radiology, The University of Tokyo Hospital, Tokyo, Japan*

Background: Primary squamous cell carcinoma (SCC) of the breast is a rare disease, accounting for about 0.1% of all breast cancers. We aimed to determine the clinical features and prognosis of breast SCC, and the effect of radiotherapy by biological subtypes using the Japanese Breast Cancer Registry. **Methods:** We conducted a matched-pair analysis of 350,977 breast cancer patients with SCC or invasive ductal cancer (IDC) in the Japanese Breast Cancer Registry between 2004 and 2014. Inclusion criteria were female breast cancer patients who underwent surgery with stage I-III diseases, SCC or IDC, and age ≥ 18 . Patients who received preoperative radiotherapy were excluded. We performed 1:1 SCC-IDC exact matching analysis by pre-dominant subtypes in SCC: ER(-) and PgR(-)/HER2(-) or ER(+) and/or PgR(+)/HER2(-). Overall survival (OS), breast cancer-specific survival (BCSS), recurrence-free survival (RFS), and first locoregional or distant metastasis recurrence incidence were compared between IDC and SCC by Kaplan-Meier methods and log-rank test. In-field area recurrence was compared between those who received radiotherapy and those who did not. **Results:** We included 452 SCC and 182,707 IDC patients for the analysis. SCC patients were more likely to present with advanced stage disease compared to those with IDC. Among SCC patients, 59% was ER(-)/PgR(-)/HER2(-), 19% was ER(+)/PgR(+)/HER2(-), 8% was ER(-)/PgR(-)/HER2(+), 2% was ER(+)/PgR(+)/HER2(+), and 12% was data missing. Ten-year OS, BCS, and RFS rates were 70%, 80%, and 66% in SCC, and 88%, 93%, and 81% in IDC, respectively, and SCC carried a significantly worse prognosis than IDC (all $P < 0.001$). For exact-matched analysis, 10-year BCS of ER(-)/PgR(-)/HER2(-) SCC patients was significantly worse than IDC ($P = 0.02$), whereas there were no significant differences between SCC and IDC of ER(+)/PgR(+)/HER2(-) patients in OS, BCS, and RFS. Among patients who received radiotherapy, no difference was found in in-field area recurrence between SCC and IDC in either ER(-)/PgR(-)/HER2(-) or ER(+)/PgR(+)/HER2(-) subtype. **Conclusions:** SCC of the breast was often diagnosed in an advanced stage and had a worse prognosis than IDC. More than half of them were triple-negative subtype. In the triple-negative subtype, SCC was an independent poor prognostic factor. No significant differences in in-field area recurrence after radiotherapy between SCC and IDC suggested that the effect of radiotherapy on local control for SCC was similar to IDC. Research Sponsor: None.

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Poster Session

Survival outcomes of young patients under 40 with breast cancer in Asian countries according to subtype: An international multicenter cohort study.

First Author: Jinyong Kim, Department of hemato-oncology, Seoul National University Hospital, Seoul, South Korea

Background: The incidence of young Asian women with breast cancer has been increasing but these patients are underrepresented in global data. We analyzed the epidemiology and outcomes of the young Asian patients with breast cancer in different subtypes with clinically unmet need. **Methods:** Female patients of age 20 years or older diagnosed with early breast cancer of stage I, II, or III from the prospective cohort of the Asian Breast Cancer Cooperative Group (ABCCG) were analyzed. For comparison, data of patients with early breast cancer from Surveillance, Epidemiology, and End Results Program (SEER) cancer registry was used. The patients were divided into three age groups: young (below 40 years), alleged premenopausal mid-age (40-49 years), and alleged postmenopausal elderly (50 years and older). Multivariable Cox proportional-hazard models for survival were adjusted with age, subtypes consisting of hormone receptor (HR) and human epithelial growth factor receptor 2 (HER2) status, histologic grade, T stage, nodal status, and countries. Patients diagnosed in 2000-2010 were censored at 6 years for comparability with SEER database. **Results:** Total 45,021 patients with breast cancer from Asian countries, 496,332 of SEER Whites and 18,279 from SEER non-Whites were included. The median age at diagnosis was younger in Asians compared to SEER Whites and non-Whites (51, 62, 58 years, respectively). Among subtypes, HR-positive and HER2-negative breast cancer was more frequent among SEER Whites and SEER non-Whites, compared to Asians (75.89%, 73.38% vs. 65.75%, respectively). In the young group, HR-positive and HER2-negative breast cancer was prevalent in Asians and SEER non-Whites, compared to SEER Whites (61.2% and 59.8% vs. 54.7%, respectively). In the elderly group, the proportion of HR-positive breast cancer increased in SEER Whites, while that of triple-negative breast cancer (TNBC) increased in Asians. Elderly group showed the worst survival in all subtypes and in all populations. In Asian population, the mid-age group of the patients with HR-positive and HER2-negative breast cancer showed significantly superior overall survival (OS) than the young group (6 year OS 96.6% vs. 94.4%; hazard ratio 0.62, 95% confidence interval 0.50-0.76; $p < 0.001$). Similarly, young patients in SEER Whites also showed early decline of survival curve compared those in mid-age group (89.1% vs. 94.0%, $p < 0.001$), while young patients of SEER non-Whites showed equivalent prognosis to those in mid-age group (92.4% vs. 95.0%, $p = 0.118$). **Conclusions:** Young Asian breast cancer patients diagnosed with HR-positive and HER2-negative subtypes, but not HER2-positive or TNBC subtypes, are more likely to have worse survival outcomes than those in mid-age. Further studies on young patients with breast cancer are needed for tailored treatments among different subtypes and ethnic groups. Research Sponsor: None.

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Poster Session

Impact of race on Blueprint genomic subtyping in HER2+ breast cancer.

First Author: Sonya A. Reid, Vanderbilt-Ingram Cancer Center, Nashville, TN

Background: Breast cancer (BC) is the leading cause of cancer-related deaths in Black women, who are 41% more likely to die than White women. We've recently reported that Black women have a significantly greater proportion of hormone receptor-positive (HR+) tumors further classified as Basal-Type with Blueprint genomic subtyping, which may contribute to their worse outcomes. Here, we evaluated whether there were differences in tumor genomics among patients with clinically assessed HER2+ (cHER2) tumors between Black and White women. **Methods:** This study includes 204 women with stage I-III cHER2 BC who received Blueprint testing and are participants of the BEST study (SRO1CA204819) at Vanderbilt University Medical Center or FLEX study (NCT03053193). Patients were treated per NCCN guidelines based on immunohistochemistry (IHC)/FISH classification. cHER2 tumors were further classified by Blueprint, an 80-gene molecular subtyping test, as Luminal-Type (gLuminal), HER2-Type (gHER2), or Basal-Type (gBasal). White women within FLEX were matched by age, tumor and node status and included as a reference group. A two-tailed proportional z-test was used to assess Blueprint subtype differences. Limma R package was used for differential gene expression analysis (DGEA) of whole transcriptome data. Significant differentially expressed genes had an adjusted p-value < 0.05 and absolute log2 fold change > 1 . **Results:** Of 102 Black women with cHER2 tumors, 59 had gHER2, 34 had gLuminal and 9 had gBasal tumors, and of 102 White women, 63 had gHER2, 28 had gLuminal and 11 had gBasal tumors. There were no significant differences in the frequency of Blueprint subtypes or in gene expression by race among cHER2 tumors. All gHER2 tumors had upregulated HER2 signaling compared to upregulated estrogen signaling genes in gLuminal tumors, and upregulated genes characteristic of metastasis and triple negative tumors in gBasal tumors. Among patients with available neoadjuvant treatment response data, 57.1% (16/28) gHER2, 33.3% (2/6) gLuminal and 50.0% (3/6) gBasal achieved a pathologic complete response (pCR). **Conclusions:** Unlike HR+HER2- tumors, these data suggest that race may not influence the biology underlying cHER2 tumors. However, there was genomic heterogeneity among cHER2 tumors identified by Blueprint, independent of race. Overall, the rate of Blueprint classification among cHER2 tumors was comparable to NBRST and APHINITY, which demonstrated distinct treatment response and outcome based on Blueprint genomic subtype. In this study, DGEA suggests gHER2 tumors exhibit extensive HER2 signaling and may benefit most from HER2-targeted therapy. Although limited by sample size, rates of pCR to neoadjuvant therapy appear greater in gHER2 than non-HER2 tumors (gLuminal, gBasal). gBasal tumors may harbor more aggressive tumor characteristics, which has important clinical implications for optimizing treatment and improving outcomes in these patients. Research Sponsor: U.S. National Institutes of Health; Agendia.

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Poster Session

Association of human epidermal growth factor receptor 2 expression with 21-gene recurrence score and survival among patients with estrogen receptor-positive breast cancer. First Author: Sung Jun Ma, Roswell Park Comprehensive Cancer Center, Buffalo, NY

Background: Trastuzumab-deruxtecan was recently shown to improve survival for metastatic human epidermal growth factor receptor 2 (HER2)-low breast cancer. HER2-negative breast cancer has been redefined as a group of heterogeneous entities. However, HER2-low status is not considered as a prognostic factor among patients with nonmetastatic breast cancer, and the role of HER2 expression levels in the setting of 21-gene recurrence score (RS) remains unclear. We performed an observational cohort study using a national oncology database to evaluate the association of HER2 expression levels with RS and survival among patients with estrogen receptor (ER)-positive breast cancer. **Methods:** The National Cancer Database was queried for women diagnosed between 2006 and 2018 with ER-positive, pT1-3N0-1aM0 breast cancer who received surgery followed by adjuvant endocrine therapy with or without chemotherapy. HER2 expression levels were stratified by 3 groups: HER2-0 (immunohistochemistry [IHC] 0), HER2-1 (IHC +1), and HER2-2 (IHC +2 and in situ hybridization [ISH] negative). Logistic and Cox multivariable analysis (MVA) were used to identify factors associated with high RS (26 or higher) and overall survival (OS), respectively. Interaction term was analyzed to evaluate any heterogeneous associations in survival outcomes between HER2 levels and RS. Subgroup analysis was performed by repeating Cox MVA stratified by RS. Holm-Bonferroni correction was used to adjust for multiple comparisons, with p value less than 0.05 considered as statistically significant. **Results:** Among 108,973 women, 31,738 (29.1%), 52,839 (48.5%), and 24,396 (22.4%) patients had HER2-0, HER2-1, and HER2-2, respectively. Logistic MVA showed that, compared to HER2-0, HER2-2 was associated with higher RS (adjusted odds ratio [aOR] 1.09, 95% confidence interval 1.04-1.15, $p < 0.001$), but HER2-1 was not (aOR 0.96, 95% CI 0.91-1.00, $p = 0.05$). Cox MVA showed that both HER2-1 (adjusted hazards ratio [aHR] 1.03, 95% CI 0.97-1.10, $p = 0.34$) and HER2-2 (aHR 1.06, 95% CI 0.98-1.14, $p = 0.14$) were not associated with OS. There was an interaction between HER2 expression levels and RS (interaction $p = 0.03$). Among those with RS < 26 , compared to HER2-0, HER2-2 was associated with worse OS (aHR 1.10, 95% CI 1.01-1.20, $p = 0.02$), but HER2-1 was not (aHR 1.04, 95% CI 0.97-1.12, $p = 0.24$). Among those with RS 26 or higher, both HER2-1 (aHR 1.00, 95% CI 0.88-1.13, $p = 0.98$) and HER2-2 (aHR 0.94, 95% CI 0.82-1.09, $p = 0.41$) were not associated with OS. **Conclusions:** To our knowledge, this is the largest study using nationwide oncology database to suggest that, when compared to HER2-0, HER2-2 was associated with higher RS and poor survival among patients with RS < 26 . Further studies would be warranted to evaluate the role of HER2 expression levels for risk stratification to tailor interventions. Research Sponsor: U.S. National Institutes of Health.

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Poster Session

Lipidomic signature from plasma to detect localised breast cancer. First Author: Gillian Lamoury, Royal North Shore Hospital, St. Leonards, NSW, Australia

Background: An effective and accurate blood test to detect localised breast cancer may increase the screening detection rate and improve patient outcomes. We have previously reported a series of lipidomic studies and derived a lipid signature from plasma enriched extracellular vesicles (EVs) that effectively distinguished people with localised breast cancer from cancer-free controls. Here we report on a significant refinement to the test methodology allowing the assessment of the lipid signature directly from plasma samples and its performance, with the aim of advancing the commercial viability of the test as we move towards clinical application. **Methods:** Lipids were extracted from enriched EVs from plasma samples donated by fasted people with localised breast cancer and control samples ($n=793$) and analysed by high resolution accurate mass liquid chromatography-mass spectrometry (LC-MS). Over 400 manually curated lipids were quantified. Following variable selection, a lipid signature capable of distinguishing breast cancer samples from controls was derived. The lipid signature was modelled on each of the cohorts using leave-one-out internal cross-validation. Next, we analysed the lipids in cancer and control ($n=256$) plasma samples corresponding to patients from Cohorts 3 and 4 previously used for EV preparations, and applied the signature derived using EVs on plasma lipidomic data. **Results:** EV samples of people with breast cancer were distinguished from controls with an area under the curve (AUC) of 0.77-0.89 across 4 cohorts. When the lipid signature was assessed directly from plasma the test achieved a comparable AUC of 0.84. Assessing the markers directly from plasma samples would make the test more scalable, higher throughput and easier to perform. **Conclusions:** Our study demonstrated the high performance of a lipid biomarker signature derived from plasma enriched EVs for early detection of localised breast cancer. Our results suggest that the lipidomic signature could potentially be assessed directly from plasma samples instead of EVs reducing the test complexity. Ongoing studies will optimise the plasma lipidomic signature and prospectively compare the test against mammographic and pathological diagnoses. Research Sponsor: BCAL Diagnostics Limited.

Performance of the lipid signature assessed from extracellular vesicles and plasma across patient cohorts.

Cohort	Extracellular vesicles				Plasma
	1 Stage I-IV IDC (n=44) Control (n=44)	2 Stage I-III IDC (n=100) Con- trol (n=101)	3 Stage I-III IDC (n=100) Con- trol (n=101)	4 Stage I-III IDC (n=51) and Stage I-III ILC (n=48) Con- trol (n=100)	3&4 Early IDC, DCIS and ILC (n=199) Control (n=201)
AUC	0.89	0.77	0.88	0.88	0.84

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Poster Session

Correlation of gene signatures of Kaiso and LC3A/B protein expression with distinct tumor ecosystems and to predict response to breast cancer therapy. *First Author: Sandeep K. Singhal, Department of Pathology, School of Medicine and Health Sciences, University of North Dakota, Grand Forks, ND*

Background: The multifunctional transcriptional repressor, Kaiso, is a member of the BTB/POZ (Broad complex, Tramtrak, Bric à Brac/Pox zinc finger) family of zinc finger proteins. Kaiso protein levels in both the nucleus and the cytoplasm have each been shown to be highly sensitive and independent predictors of overall breast cancer survival. Through the use of gene signatures and/or gene modules developed through the analysis of RNA-seq data from breast cancer patients following biomarker stratification by either nuclear Kaiso, cytoplasmic Kaiso, or the Kaiso's functional downstream target LC3A/B, we demonstrate the utility of Kaiso and LC3A/B derived signatures as predictors of treatment outcome. **Methods:** We used a machine Learning approach to assess a cohort of racially diverse 555 BC patients who underwent surgery for their primary BC in Greenville, NC and develop proteomics-based genomics (PbG) signatures. The cross-validated logistic regression model using publicly available gene expression data compiled from neoadjuvant clinical trials (N=996, JCO:30(16):1996-2004). **Results:** Kaiso and LC3A/B derived gene modules show accuracy in predicting pathological complete response (pCR, AUC = 0.728, 95% CI: 0.689-0.764). Moreover, predictive estimates of distant metastasis-free survival utilizing Kaiso and LC3A/B derived gene modules are also significant (overall DMFS, AUC= 0.737, 95% CI: 0.665-0.819) and (DMFS of non-pCR patients AUC= 0.71, 95% CI: 0.633-0.773). We then validate these findings in an independent, racially diverse breast cancer cohort receiving neo-adjuvant treatment (N=443). Gene modules based on Kaiso and LC3A/B were also highly predictive in this independent cohort (total cohort pCR, AUC= 0.775, 95% CI: 0.687-0.838; pCR NHW (N=257), AUC= 0.762, 95% CI: 0.659-0.855; pCR Hispanic (N=125), AUC= 0.725, 95% CI: 0.493-0.873; and pCR NHB (N=42), AUC= 0.681, 95% CI:0.405-0.904). **Conclusions:** Combined analysis by multiplex immunofluorescence and deconvolution of gene expression data show that the protein expression of Kaiso and LC3A/B in tumors are associated with distinct tumor ecosystems where high levels cytoplasmic Kaiso are linked to an immune-suppressed tumor microenvironment. Research Sponsor: U.S. National Institutes of Health.

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Poster Session

Comprehensive profiling of mutational signatures and machine learning and subtypes of homologous recombination deficiency. *First Author: Joonoh Lim, Genome Insight Inc., San Diego, CA*

Background: Recently, genomic features have proven effective at gene-agnostic detection of homologous recombination deficiency (HRD). However, it remains to be explored to what extent we can exploit genome analysis to assess HRD status. Here, we show that a machine learning (ML) classifier based on mutational signatures enables a robust detection and subtyping of HRD and outperforms a current state-of-the-art HRD classifier. **Methods:** We whole-genome-sequenced (WGS) ~700 breast cancers and identified pathogenic variants in HR-related genes (*BRCA1/2*, *PALB2*, *CHEK2*, *RAD51B*, *ATM*, etc.). Mutational signatures of all variant types, single-base substitution (SBS), indel (ID), structural (SV) and copy-number variant (CN), were included as features. Biallelic inactivation in *BRCA1/2* by germline pathogenic variant and somatic loss-of-heterozygosity (LOH) was regarded as true HRD. We trained four different classifiers with *n*-fold cross validation and used averaged scores for prediction. In addition, we performed cluster analysis and subgroup analysis within the predicted HRD cases to unveil the heterogeneity of HRD. **Results:** We identified a total 88 (12%) germline pathogenic variant carriers with somatic LOH, including 29 *BRCA1* (4%), 28 *BRCA2* (4%), 4 *PALB2* (0.6%), and 3 *RAD51B* (0.4%). Among them, 70 (80%) were classified as HRD positives. As expected, most *BRCA1* (28/29) and *BRCA2* (28/28) cases were HRD-positive. All the *PALB2* (4/4) and *RAD51B* (3/3) cases were also classified as HRD-positive, confirming their importance in HR. Inclusion of somatic *RAD51B* biallelic mutants (10; 1.4%) reached a statistical significance for the HRD enrichment (Fisher's; *P* = 0.045). We identified a total 171 (24%) having at least one somatic pathogenic variant with LOH, including 57 *PTEN* (33%), 40 *CDK12* (23%), 17 *RAD51B* (10%), 17 *ARID1A* (10%), and 15 *BRIP1* (9%). 72 of these (42%) were HRD-positive. Our classifier identified 12 (7%) more HRD cases than HRDetect (167 vs. 155; *F1* = 0.99 vs. 0.95) using signature ID6, SV3 (or RS3), LST, and SBS3. Further, it correctly identified *BRCA1* (33/34) and *BRCA2* (27/28) somatic and germline biallelic mutants from each other (*F1* = 0.97), based on RS3, ID6, RS1, and SBS37. Features of *RAD51B* were similar to *BRCA1*, and *PALB2* to *BRCA2*, but our classifier was able to distinguish *PALB2* from *BRCA2* using a combination of CN11, ID11, LOH, CN8, and SBS40 (*F1* = ~1). Total 112 (67%), 48 (29%), and 7 (4%) cases were identified as *BRCA1*-like, *BRCA2*-like, and *BRCA1/2*-like, among which 47 (28%) were monoallelic HR-gene mutants and 27 (16%) were wild types. Our results suggest that mutational signatures can identify ~40% (47/120) more HRD cases than using mutation profile alone. **Conclusions:** We believe that the method developed here, using ML to detect and classify HRD, will benefit from larger WGS data and identify more patients who can benefit from HRD-related therapeutics. Research Sponsor: Genome Insight Inc.

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Poster Session

Association of anthracyclines induced cardiotoxicity (AIC) in patients with early breast cancer (eBC) with germline BRCA1/2 (gBRCA1/2) mutation: BRCAN study. *First Author: Juan José Serrano Domingo, Medical Oncology Department, Ramón y Cajal University Hospital, Madrid, Spain*

Background: BRCA1/2 genes play a critical role in genome stability and DNA repair in human cells, including cardiomyocytes. In animal models, loss of cardiomyocyte-specific BRCA1/2 is associated with DNA damage, apoptosis, cardiac dysfunction, and cardiac mortality following anthracyclines (A) exposure. However, whether these preclinical findings translate to humans still remains unclear. We conducted the BRCAN study to assess the impact of gBRCA1/2 status on AIC in a cohort of patients with eBC. **Methods:** This is a single center retrospective/prospective study including patients diagnosed with HER2-negative eBC treated with A based chemotherapy in the neo/adjuvant setting, known gBRCA1/2 status, left ventricular ejection fraction (LVEF) ≥ 50% at baseline and no previous significant cardiovascular events. During follow-up, we performed myocardial dysfunction blood biomarkers (MDBB), cardiac ultrasound and quality of life questionnaires (QoL). Primary objective was to assess the absolute LVEF change from baseline in BRCA1/2 mutation carriers (gBRCA1/2mut) versus non-carriers (gBRCA1/2wt). Secondary objectives were comparing MDBB and QoL in these groups. **Results:** 137 patients with eBC were included in the study (103 gBRCA1/2wt and 34 gBRCA1/2mut). Patients' characteristics were similar between both groups in terms of age, baseline LVEF, radiotherapy (RT) on left side, total A accumulative dose, time from A exposure, antihypertensive or hypolipidemic agents use and smoking habit. Compared to baseline, LVEF % reduction was -4.7 [-12.0, 0.0] versus -9.5 [-18.0, -5.0] in gBRCA1/2wt and gBRCA1/2mut, respectively (*p*=0.027). To correct for confounding, we fit a regression model for the variables smoking habit, antihypertensive and hypolipidemic agents use. On average, LVEF % reduction in gBRCA1/2mut group was -4.5 [CI 95% -8.6, -0.4, *p*=0.032] compared to gBRCA1/2wt. No differences between MDBB (protein C-reactive, hsTn, NT-ProBNP, D-Dimer, ST-2 or Galectine-3) and QoL (MLHFQ and EQ5-D index) were detected between groups. **Conclusions:** Our data suggest that gBRCA1/2mut patients could represent a high risk population for AIC. A baseline comprehensive cardiovascular risk assessment and a closer follow-up should be recommended in these patients. Further research is needed on order to identify early predictive biomarkers for AIC. Research Sponsor: Instituto Ramón y Cajal de Investigación Sanitaria.

Patient characteristics.			
Characteristic	gBRCA1/2wt	gBRCA1/2mut	p-value
Age*	49.1 (29.3)	43.2 (10.2)	0.126
RT on left side	42 (40.8%)	10 (29.4%)	0.118
Total dose Adriamycin**	237.4 (41.5)	250.8 (35.8)	0.109
Total dose epirubicin**	325 (77.9)	400 (124.9)	0.148
Exposition time (years)*	7.5 (4.6)	8.3 (5.2)	0.203
Initial LVEF (%)*	68.5 (6.7)	68.9 (8.3)	0.380
Antihypertensives	14 (13.6)	1 (2.9)	0.109
Hypolipidemic	25 (24.3)	6 (17.6)	0.569
Smoking habit	17 (17.2)	5 (14.7)	0.824

*Mean (standard deviation); **mg/m².

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Poster Session

ERBB2 mRNA expression to distinguish HER2-low/neg breast cancer prognosis. *First Author: Yueping Liu, Department of Pathology, the Fourth Hospital of Hebei Medical University, Shijiazhuang, Hebei, China*

Background: Antibody-drug conjugates such as Trastuzumab deruxtecan significantly improved progression-free and overall survival for the HER2 low expression (HER2-low) breast cancer (BC) patients, pushing the research field of HER2-low to a new climax. In fact, the traditional immunohistochemistry (IHC) to identify the HER2-low or HER2-negative expression (HER2-neg) has been challenged, and it cannot predict the prognosis of HER2-low/neg patients well. **Methods:** Three pathologists evaluated the HER2 expression status of the subjects via IHC. More than two pathologists judged HER2 0-2 and FISH negative samples were included in this trial. *ERBB2* mRNA level of formalin-fixed, paraffin-embedded BC post-surgery specimens were detected by MammaTyper quantitative real-time polymerase chain reaction (qRT-PCR) kit. The consistency of HER2 immunohistochemistry (IHC) and MammaTyper results were analyzed by interclass correlation coefficients (ICC). Differences in disease-free survival (DFS) were assessed by Kaplan Meier analysis. **Results:** 793 cases were included. The ICC value between IHC and MammaTyper, assessed for HER2-neg vs HER2-low is 0.28. With a median follow up of 2.5 years, there were 36 events in the whole subjects. In the whole subjects, MammaTyper successfully showed that the prognosis of HER2-low was significantly better than HER2-neg (*P* < 0.001, HR = 3.497, 95%CI, 1.807-6.77), but IHC could not distinguished them (*P* = 0.1071, HR = 1.776, 95%CI, 0.9194-3.43). Although the follow-up time is short, HER2-low subjects also showed better prognosis than HER2-neg in TNBC subjects distinguished by MammaTyper (*P* = 0.0271, HR = 2.912, 95%CI, 1.129-7.511), not by IHC (*P* = 0.1032, HR = 2.213, 95%CI, 0.8512-5.756). However, in 291 cases of IHC and MammaTyper detection discordancy group, IHC results showed that the prognosis of HER2-low was worse, which was contrary to the MammaTyper results and the results of the above overall test results, suggesting that IHC could not verily reflect the amount of HER2 expression in some samples, and the prognosis of HER2-low population might be more related to the mRNA expression of HER2. **Conclusions:** Compared with IHC/FISH, MammaTyper qRT-PCR assay may actually reflect the prognosis of HER2-neg/low, which is expected to become a diagnostic beacon for HER2-low target drugs. Research Sponsor: None.

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Poster Session

Do HER2 low tumors have a distinct clinicopathologic phenotype? *First Author: Natália Polidoro, Breast Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Clinicopathologic features of breast cancer subtypes defined by hormone receptor (HR) and HER2 status differ. These analyses classified HER2 IHC <3+ with negative FISH as HER2-. With the recognition of the clinical relevance of HER2 low, there is debate as to whether this is a distinct subtype. We sought to determine if features of HER2 low tumors differ from HER2- and HER2+ after controlling for HR status. **Methods:** Patients undergoing upfront surgery from 1998 to 2010 were identified from a prospectively maintained institutional database. HER2 status was classified by IHC/FISH analysis as HER2-, HER2 low (IHC 1+ or 2+ with negative FISH), and HER2+ (IHC 3+ or FISH +) and stratified by HR status. Univariable (UVA) and multivariable multinomial logistic regression analysis (MVA) were performed to determine associations among variables and subtypes. **Results:** 11,323 tumors from 11,072 patients were included. 5,104 (45%) were HER2 low, 41.2% were HER2- and 13.6% were HER2+. On MVA stratified by HER2 status only, compared to HER2- tumors, HER2 low was associated with LVI (OR 1.2 [95% CI 1.06-1.36]; $p=.003$), multifocality (OR 1.26 [95% CI, 1.12-1.42]; $p<.001$), nodal micrometastasis (OR 1.15 [95% CI, 1.02-1.31]; $p=.024$), and lower rates of <3 positive nodes (OR 0.77 [95% CI, 0.66-0.90], $p=.001$). HER2+ was associated with younger age, high grade, multifocality, extensive intraductal component (EIC), and pN2/3 nodal stage. Clinicopathologic features stratified by HR and HER2 status are shown in the table. On UVA, in both HR+ and HR- tumors, age and multifocality were associated with HER2 low, and LVI, multifocality, and EIC with HER2+ compared to HER2- tumors. On MVA, no variables were independently associated with both HR+ and HR-/HER2 low tumors compared to HER2-. In contrast, HER2+ tumors regardless of HR status were significantly associated with multifocality and EIC. **Conclusions:** HER2 low breast cancer features seem to be driven by HR status and HER2 overexpression. We do not have enough evidence to support the interpretation of HER2 low as a distinct subtype. Research Sponsor: Memorial Sloan Kettering Cancer Center.

Clinicopathologic features by HR/HER2 status.

Characteristic (n %)	HR +					HR -				
	HER2-	HER2 low	p	HER2+	p	HER2-	HER2 low	p	HER2+	p
Median age (IQR)	3,807 58 (48, 68)	4,596 57 (47, 66)	<0.01	1,007 51 (43, 61)	<0.01	862 53 (43, 63)	508 55 (46, 65)	<0.01	543 53 (45, 61)	>0.9
LVI	968 (25)	1,380 (30)	<0.01	440 (44)	<0.01	277 (32)	173 (34)	0.5	238 (44)	<0.01
High grade	1,666 (46)	2,269 (51)	<0.01	815 (83)	<0.01	765 (93)	451 (90)	0.14	506 (94)	0.2
Multifocal	961 (25)	1,334 (29)	<0.01	327 (33)	<0.01	156 (18)	120 (24)	0.01	200 (37)	<0.01
EIC	347 (15)	509 (16)	0.2	171 (24)	<0.01	45 (8.5)	50 (14)	<0.01	104 (30)	<0.01
Nodal disease	2,304 (61)	2,814 (61)		401 (40)		463 (54)	270 (53)		251 (46)	
Mic	126 (3.3)	221 (4.8)	<0.01	34 (3.4)	0.02	15 (1.7)	17 (3.4)	0.06	17 (3.1)	0.04
1-2+	668 (18)	773 (17)	0.4	113 (11)	0.8	130 (15)	74 (15)	0.9	105 (19)	<0.01
≥3+	682 (18)	778 (17)	0.3	455 (45)	<0.01	250 (29)	145 (29)	>0.9	168 (31)	0.09

p values from multinomial UVA.

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Poster Session

Clinical meaning of stromal tumor infiltrating lymphocytes (sTIL) in luminal early breast cancer. *First Author: Esmeralda García-Torralba, Department of Hematology and Medical Oncology, Hospital Universitario Morales Meseguer, Murcia, Spain*

Background: Luminal breast cancer (BC) is associated with lower immune activation. Although stromal tumor infiltrating lymphocytes (sTIL) are a marker of better prognosis and response in hormone receptor (HR) negative tumors, sTIL predictive and prognostic implications are less clear in luminal BC. Further insights on the clinical correlations of immune microenvironment in luminal disease may facilitate therapeutic improvement and prognostic stratification in these patients. **Methods:** Observational and single-center cohort of 345 women with early luminal (HR positive, HER2 negative) BC (2012-2020) treated with chemotherapy. Pre-treatment sTIL were determined in the diagnostic biopsy following validated standard methods. The correlation between sTIL and other tumor characteristics were analyzed (Spearman's Rho and Chi-squared tests). Association of sTIL with pathologic complete response (pCR) in patients treated with neoadjuvant chemotherapy (nCT) was evaluated with logistic regression models. Prognostic value of sTIL for overall (OS) or relapse free interval (RFI) was analyzed by Cox regression models. **Results:** Median age: 50 (range: 24-89); 48.1% premenopausal; 91.3% infiltrating ductal carcinoma; 30.1% grade 3; 87.2% progesterone receptor (PgR)+; 67.5% treated with nCT and 32.8% with adjuvant CT (aCT); 47.6% N0, 32.8% N1, 19.6% N2-3; median ki67: 30% (82.7% >10%). A 29% of patients showed sTIL=0%. Median sTIL infiltration was 5 (Q1-Q3 range [IQR], 0-10), with higher values in premenopausal ($p<0.001$), grade 3 ($p<0.001$), N+ ($p<0.001$) and luminal B tumors (defined as PgR- and/or grade 3 and/or Ki67>15%) ($p<0.001$). Ki67 was significantly correlated with sTIL ($p<0.39$; $p<0.001$). The percentage of sTIL was associated with pCR after nCT (OR: 1.045, 95%CI 1.02-1.07, $p=0.001$). No prognostic impact of sTIL for OS or RFI was found in luminal A tumors. In luminal B cases ($n=286$), any grade of lymphocytic infiltration (defined as sTIL > 0%) was associated with a shorter RFI both in univariate ($p=0.01$) and multivariate Cox models (HR: 4.83, 95%CI 1.28-18.21, $p=0.02$), with a non-significant trend for poorer OS ($p=0.06$). **Conclusions:** In luminal BC, an increased level of sTIL is associated with luminal B subtype characteristics such as higher proliferation, higher tumor grade and nodal involvement. Lymphocytic infiltration has been found to be a predictor of pCR after nCT, but, in contrast with hormone receptor-negative BC, it is also associated with a poorer prognosis for recurrence and a trend towards worse overall survival in luminal B tumors. Research Sponsor: Instituto Salud Carlos III (Spain) (PI21/380); SEOM (Spanish Society of Medical Oncology).

Multivariate Cox model for RFI in luminal B breast cancer.

	Beta	Hazard ratio (HR)	95%CI HR	p
Tumor size (mm)	0.023468	1.0237	1.011-1.037	<0.001
Positive nodes (number)	0.101474	1.1068	1.045-1.172	<0.001
PgR positive	-1.112061	0.3289	0.144-0.751	0.008
Ki67 (percentage)	0.009734	1.0098	0.990-0.992	0.277
sTIL > 0%	1.575154	4.8315	1.282-18.211	0.019

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Poster Session

Outcomes in premenopausal patients with HR+/HER2- breast cancer and lymph node micro-metastasis based on the 21-gene recurrence score. *First Author: Nadeem Bilani, Icahn School of Medicine at Mount Sinai Morningside-West, New York, NY*

Background: Postmenopausal patients with hormone receptor positive, HER2-negative (HR+/HER2-) early breast cancer (EBC) and 21-gene OncotypeDX (ODX) recurrence scores (RS) <26 do not benefit from chemoendocrine therapy (CET) compared to endocrine monotherapy (E). The TAILORx and RxPONDER trials demonstrated this was consistent in node-negative and node-positive disease, respectively. In premenopausal patients, however, guidelines for those with low RS diverge between disease involving 0 (pN0) vs. 1-3 (pN1a-c) lymph nodes. Additionally, treatment decisions are less clear for patients with micro-metastasis (pN1mi), who comprised only about 10% of patients in RxPONDER. This study used the *National Cancer Database* (NCDB) to assess treatment patterns and survival outcomes in premenopausal patients with EBC and lymph node micro-metastasis. **Methods:** A cohort of patients aged <50, diagnosed between 2004-2019 with HR+/HER2- EBC and who underwent ODX testing, was recruited from the NCDB. (A) Firstly, we described demographic and clinical characteristics of a sub-cohort with micro-metastasis using univariate statistics. (B) We confirmed the prognostic value of ODX in this sub-cohort with multivariate Cox regression analysis of overall survival (OS). (C) We explored patterns of practice amongst the total cohort with ODX <26 with chi-squared testing for differences in CET use by nodal status. (D) To elucidate the predictive value of this assay, we performed Kaplan-Meier models comparing OS for those with RS <26 receiving E vs. CET, controlling granularly for nodal status: (i) pN1a-c, (ii) pN1mi, and (iii) pN0. **Results:** Of $n=72,068$ patients aged <50 with HR+/HER2- EBC and ODX data, 6.1% ($n=4,402$) had micro-metastasis. (A) The median age of this subgroup was 45 (IQR 41-47) years. Most tumors were grade II ($n=2,472$, 57.7%) with ductal histology ($n=3,500$, 80.3%). 73.4% of pN1mi cases had RS <26, while 26.6% had RS ≥26. (B) Multivariate Cox regression – adjusting for comorbidity, race and chemotherapy use – confirmed significance in this pN1mi cohort of RS ≥26 prognosticating poorer OS compared to RS 0-15 (HR 4.42, 95% CI 2.35-8.31, $p<0.001$). (C) 29.0% ($n=1,033$) of patients with pN1mi and ODX <26 underwent CET, greater than 15.2% ($n=6,568$) with pN0 and less than 47.3% ($n=2,884$) with pN1a-c staging ($p<0.001$). (D) A benefit in OS ($p=0.017$) was observed in cases with RS <26 and pN1a-c using CET (5-year OS: 99%) vs. E (5-year OS: 97.5%), but not in pN1mi ($p=0.49$) or pN0 ($p=0.57$) disease. **Conclusions:** The management of premenopausal patients with HR+/HER2- EBC, isolated micro-metastasis, and ODX <26 is unclear. Our large registry study found the addition of chemotherapy to endocrine therapy was associated with improved survival in cases with ODX <26 involving 1-3 lymph nodes, but not in node-negative or micro-metastatic disease. Prospective trials are needed to confirm these findings. Research Sponsor: None.

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Poster Session

Phase II randomized window of opportunity trial evaluating cytotoxic and immunomodulatory effects of intratumoral INT230-6 in early stage breast cancer: The INVINCIBLE trial. *First Author: Melanie Spears, Ontario Institute for Cancer Research, Toronto, ON, Canada*

Background: Most breast cancers are considered immunologically cold and are therefore minimally responsive to immunotherapies. Local cytotoxic therapies can induce cell death, expose tumor antigens, provide adjuvants for anti-tumor immune priming, and potentially increase responsiveness to immunotherapies. We conducted a randomized, double blind, Phase 2 presurgical Window-Of-Opportunity trial for intratumoral (IT) INT230-6 (comprising VINblastine (VIN) Cisplatin (VIN)) evaluating clinical and Biological Effects in patients with early-stage operable Breast Cancer (the INVINCIBLE trial NCT04781725). The trial evaluated the immune response within the tumor and microenvironment *in vivo* after IT INT230-6 injections. **Methods:** Women with newly diagnosed and awaiting surgery for early-stage intermediate or high-grade ER+ T1-T2 invasive breast cancers were recruited to the trial. Participating patients were allocated (2:1) to IT injections of INT230-6 vs saline placebo, prior to resection. RNA profiling of the pre-(baseline biopsy) and post-treatment (surgical resection) tumours using the Ion AmpliSeq Transcriptome Human Gene Expression (Thermo Fisher Scientific) and DNA sequencing using a large (500 gene) comprehensive genomic profiling panel (OCAPus,) was performed. **Results:** Significant tumor necrosis was observed in the majority of subjects injected with INT230-6. In the 60 pre-treatment biopsies profiled with OCAPus, the genes most frequently mutated included PIK3CA (38%), TP53 (23%), CDH1 (22%) and TBX3 (17%). Frequent copy number changes were identified in CCND1 (23%), FGFR1 (18%), and CDH1 (17%). Gene expression analysis showed significant differential gene expression between the baseline biopsy and surgical specimens in patients treated with the drug. Pathway analysis identified genes associated with TCR signaling, macrophage markers, IL-18 signaling and B cell receptor signaling were significantly up-regulated in the post treatment samples. **Conclusions:** This is the first study evaluating the potential biologic effects of intratumoral cytotoxicity with INT230-6 and its role as a potential immune priming therapy in traditional immune quiescent ER+ breast cancers. Research Sponsor: INTENSITY.

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Treatment outcomes in patients with discordant recurrence score and RSclin risk predictions. *First Author: Augustin Vannier, University of Chicago, Chicago, IL*

Background: Guidelines recommend the use of genomic assays to aid decision making regarding the use of adjuvant chemotherapy (CT) for hormone receptor-positive, HER2-negative (HR+/HER2-) early breast cancer (EBC). Recently, the RSclin tool, which integrates the 21-gene recurrence score (RS) and clinicopathologic features, was developed to better estimate CT benefit. Here, we studied patients with RSclin/RS discordance to determine if patients (pts) should be treated according to RS or RSclin. **Methods:** This was a retrospective cohort study of pts from the National Cancer Database who were diagnosed with HR+/HER2- node negative EBC from 2010-2020 who underwent RS testing and received adjuvant endocrine therapy with or without CT. Pts were classified as low RS (≤ 26) or high RS (≥ 26) and low ($< 3\%$) versus high ($\geq 3\%$) predicted CT benefit per RSclin. The primary outcome was overall survival (OS) benefit associated with CT administration for pts with discordant RS/RSclin, measured as hazard ratio [HR] for receipt of CT. Hazard ratios were adjusted for age and comorbidity index, and inverse probability of treatment weighting was performed for age, comorbidity index, race, ethnicity, and insurance status. **Results:** 262,748 pts with EBC were included, with a median follow-up of 58 months. Median age was 60 years; 82% were White, 7% Black, 5% Hispanic, and 4% Asian/Pacific Islander. Median tumor size was 1.5 cm, and median RS was 15. The 31,955 cases with concordant high RS/RSclin had an OS benefit with CT (HR: 0.71, 95% CI: 0.67 - 0.75, $p < 0.001$), while the 206,631 cases with concordant low RS/RSclin did not have a survival benefit (HR: 1.00, 95% CI: 0.95 - 1.04, $p = 0.85$, Table). High RS with low RSclin was seen in 435 cases - all with grade 1 tumors, with RS no greater than 28, and tumor size under 1.3cm. No significant CT benefit was seen in this small subset of pts (HR 1.57, 95% CI 0.75 - 3.26, $p = 0.23$). In 23,727 pts with low RS but high RSclin, a CT benefit was seen (HR 0.73, 95% CI 0.67 - 0.78, $p < 0.001$). These pts had high-intermediate RS (median 23, interquartile range 20 - 24) with no other higher risk features. Similar results were seen in older (age > 50) and younger (age ≤ 50) subgroups - although no pts ≤ 50 were in the low RS/high RSclin group. **Conclusions:** RSclin may identify a small number of grade 1 tumors with high RS for which CT is not needed, and may help guide appropriate use of CT for EBC in the sizeable group with intermediate RS. Research Sponsor: U.S. National Institutes of Health.

Group	No CT, n (% of group)	CT, n (% of group)	8 Year OS, no CT (95% CI)	8 Year OS, CT (95% CI)	HR, Receipt of CT (95% CI)	p
High RS / High R5C1N	8592 (26.9%)	23363 (73.1%)	82.0 (80.9 - 83.1)	87.6 (87.3 - 87.8)	0.71 (0.67 - 0.75)	< 0.001
Low RS / High R5C1N	15785 (66.5%)	7942 (33.5%)	90.1 (89.4 - 90.8)	92.9 (92.5 - 93.2)	0.73 (0.67 - 0.78)	< 0.001
High RS / Low R5C1N	273 (62.8%)	162 (37.2%)	93.0 (85.6 - 96.6)	92.1 (88.5 - 94.6)	1.57 (0.75 - 3.26)	0.23
Low RS / Low R5C1N	197327 (95.5%)	9304 (4.5%)	93.3 (93.1 - 93.5)	93.9 (93.6 - 94.2)	1.00 (0.95 - 1.04)	0.85

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Somatic mutations in tumor-adjacent normal breast tissue in young women with high risk family history. *First Author: Mariya Rozenblit, Yale School of Medicine, New Haven, CT*

Background: It's incompletely understood why some women without germline breast cancer predisposing mutations develop early onset breast cancer. Breast cancer in young women is often more aggressive, with high histologic grade, worse prognosis, and higher risk of recurrence. We hypothesize that these women have somatic mutations in the normal breast tissue that contribute to breast cancer tumorigenesis. **Methods:** Whole exome sequencing (WES) data was analyzed from normal tissue adjacent to breast tumor and compared to matched peripheral blood (n=28). All patients were <50yo, had high risk family history as per NCCN guidelines, and had negative Ambry Genetics panel testing. FFPE sections were reviewed by two pathologists to identify normal breast tissue furthest away from tumor. WES was performed on Illumina HS4000 using 100-base pair paired-end reads. Samples were mapped to the human reference genome (vGRCh38). PCR duplicates were marked (Picard), and indel regions were adjusted (GATK). High-quality germline variants (HaplotypeCaller), somatic mutations (Mutect), and indels (IndelGenotyper) were called. Low-quality variants were filtered out. The classification and number of mutations per gene per sample were extracted and analyzed. **Results:** Majority of patients were white (86%), median age 45, with invasive ductal carcinoma (86%), ER+/PR+/HER2- (100%). Median somatic variants per sample were 97 (range: 45-285), all single nucleotide variants, mostly missense mutations, C>T conversions were seen in 45% of mutations. This suggests cytidine deaminase (APOBEC) involvement. All samples had alterations in at least one of the top ten affected genes which include transcription factors in zinc finger family (listed below). Zinc finger proteins play a key role in tumorigenesis, cancer progression and metastasis in a variety of cancers. Upregulation of zinc finger proteins has been associated with worse prognosis in breast cancer. **Conclusions:** We describe novel somatic mutations in zinc finger proteins in normal breast tissue adjacent to tumor that may contribute to early onset breast cancer in patients with high risk family history. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology.

	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034	2035	2036	2037	2038	2039	2040	2041	2042	2043	2044	2045	2046	2047	2048	2049	2050	2051	2052	2053	2054	2055	2056	2057	2058	2059	2060	2061	2062	2063	2064	2065	2066	2067	2068	2069	2070	2071	2072	2073	2074	2075	2076	2077	2078	2079	2080	2081	2082	2083	2084	2085	2086	2087	2088	2089	2090	2091	2092	2093	2094	2095	2096	2097	2098	2099	2100	2101	2102	2103	2104	2105	2106	2107	2108	2109	2110	2111	2112	2113	2114	2115	2116	2117	2118	2119	2120	2121	2122	2123	2124	2125	2126	2127	2128	2129	2130	2131	2132	2133	2134	2135	2136	2137	2138	2139	2140	2141	2142	2143	2144	2145	2146	2147	2148	2149	2150	2151	2152	2153	2154	2155	2156	2157	2158	2159	2160	2161	2162	2163	2164	2165	2166	2167	2168	2169	2170	2171	2172	2173	2174	2175	2176	2177	2178	2179	2180	2181	2182	2183	2184	2185	2186	2187	2188	2189	2190	2191	2192	2193	2194	2195	2196	2197	2198	2199	2200	2201	2202	2203	2204	2205	2206	2207	2208	2209	2210	2211	2212	2213	2214	2215	2216	2217	2218	2219	2220	2221	2222	2223	2224	2225	2226	2227	2228	2229	2230	2231	2232	2233	2234	2235	2236	2237	2238	2239	2240	2241	2242	2243	2244	2245	2246	2247	2248	2249	2250	2251	2252	2253	2254	2255	2256	2257	2258	2259	2260	2261	2262	2263	2264	2265	2266	2267	2268	2269	2270	2271	2272	2273	2274	2275	2276	2277	2278	2279	2280	2281	2282	2283	2284	2285	2286	2287	2288	2289	2290	2291	2292	2293	2294	2295	2296	2297	2298	2299	2300	2301	2302	2303	2304	2305	2306	2307	2308	2309	2310	2311	2312	2313	2314	2315	2316	2317	2318	2319	2320	2321	2322	2323	2324	2325	2326	2327	2328	2329	2330	2331	2332	2333	2334	2335	2336	2337	2338	2339	2340	2341	2342	2343	2344	2345	2346	2347	2348	2349	2350	2351	2352	2353	2354	2355	2356	2357	2358	2359	2360	2361	2362	2363	2364	2365	2366	2367	2368	2369	2370	2371	2372	2373	2374	2375	2376	2377	2378	2379	2380	2381	2382	2383	2384	2385	2386	2387	2388	2389	2390	2391	2392	2393	2394	2395	2396	2397	2398	2399	2400	2401	2402	2403	2404	2405	2406	2407	2408	2409	2410	2411	2412	2413	2414	2415	2416	2417	2418	2419	2420	2421	2422	2423	2424	2425	2426	2427	2428	2429	2430	2431	2432	2433	2434	2435	2436	2437	2438	2439	2440	2441	2442	2443	2444	2445	2446	2447	2448	2449	2450	2451	2452	2453	2454	2455	2456	2457	2458	2459	2460	2461	2462	2463	2464	2465	2466	2467	2468	2469	2470	2471	2472	2473	2474	2475	2476	2477	2478	2479	2480	2481	2482	2483	2484	2485	2486	2487	2488	2489	2490	2491	2492	2493	2494	2495	2496	2497	2498	2499	2500																																																						
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Impact of HER2 low expression in the Oncotype DX RS in patients with operable hormone receptor positive early stage breast cancer. First Author: Laura Sofia Munoz-Arcos, Weill Cornell Medicine, New York, NY

Background: Two thirds of breast carcinomas are human epidermal growth factor receptor 2 (HER2) low. To date, it is still unclear whether hormone receptor (HR) positive HER2 low tumors represent a distinct biological subtype. HER2 low status is not considered an independent predictive factor for benefit from adjuvant chemotherapy in HR positive early breast cancer. We aim to investigate the impact of HER2 low expression on the established predictive biomarker Oncotype DX RS in a cohort of patients with HR positive HER2 negative early breast cancer.

Methods: Retrospective study of patients with stage I-III HR positive HER2 negative breast cancer treated with upfront surgery between 2019-2022 at the Weill Cornell Breast Center and for whom Oncotype DX RS test was available. Patients were grouped to HER2-0 (immunohistochemistry (IHC) score of 0) or HER2 low (IHC score of 1+ or, 2+ with non-amplified *in situ* hybridization) expression. Clinicopathological characteristics and Oncotype DX RS were compared across the different categories of HER2 expression. **Results:** Of 509 patients included, 37% and 63% were grouped as HER2-0 and HER2 low, respectively. Median age at diagnosis was 61 years [IQR 50-69]. Sixty-eight percent of patients were postmenopausal. Stage I, II and III corresponded to 76%, 23% and 1% of patients, respectively. Seven percent of patients had nodal involvement. Ductal carcinoma was the most common histological type (75%) followed by lobular carcinoma (17%). Most tumors had low-intermediate histological grade (81%) with a median Ki-67 of 10% [IQR 5-15]. No significant difference was observed in clinicopathological characteristics between the HER2-0 and HER2 low groups. The overall median Oncotype DX RS was 16 [IQR 11-21]. The median Oncotype DX RS based on a HER2 expression of 0, 1+ and 2+ was 15, 17 and 17, respectively. There was no statistically significant difference between the Oncotype DX RS score and HER2 expression, when comparing HER2-0 to HER2 low ($p = 0.578$), HER2-0 to HER2-1+ ($p = 0.775$) and HER2-0 to HER2-2+ ($p = 0.157$). In the pre-menopausal and lobular carcinoma subgroups, the median Oncotype DX RS was 15 [IQR 9-21] and 17 [IQR 12-22], respectively; and there was no statistically significant difference between the Oncotype DX RS score and HER2 expression ($p > 0.05$). Post-surgery, 87%, 66% and 13% of patients received endocrine therapy, chemotherapy and radiation therapy, respectively. Median follow up time was 16 months [IQR 8-34]. Disease recurrence was documented in 9 (2%) patients. **Conclusions:** In this study, we found no differences in the Oncotype DX RS and the prognostic pathological features between the HER2-0 and HER2 low groups which is in line with previous retrospective studies. Survival analysis was limited by the median follow up. Further studies on the understanding of the biology of HER2-low and its clinical implications in early breast cancer are needed. Research Sponsor: None.

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Exploring HER2-low disease: Does it impact breast cancer survival? *First Author:* Assumpció López-Paradís, Medical Oncology Department, Catalan Institute of Oncology (ICO)-Badalona, B-ARGO (Badalona Applied Research Group in Oncology) and IGTP (Health Research Institute Germans Trias i Pujol), Universitat Autònoma de Barcelona, 08916, Badalona, Spain, Barcelona, Barcelona, Spain

Background: HER2-low has emerged as a potential new entity in breast cancer (BC). Data of this subset is still limited and prognostic results are controversial, suggesting HER2-low does not represent a distinct biological subtype. HER2-low account for up to 50% of BC, representing a potential therapeutic target with encouraging results in the metastatic setting. Hence, we pretend to analyze clinical characteristics of this subset to elucidate commented points. **Methods:** Confirmed HER2-negative BC patients (p) diagnosed between 2006-2017 were retrospectively reviewed in a single center study, in ICO-Badalona. HER2-positive and *in situ* carcinomas were excluded, and p were classified as HER2-low and HER2-O. The prevalence of HER2-low versus HER2-O among p, originally scored as HER2-negative, was measured. Demographics and clinicopathological characteristics were examined and compared via medical charts/ electronic health records. We aim to describe HER2-O/HER2-low populations, and explore its prognostic impact, using Kaplan-Meier and Cox regression models. **Results:** From 1451 infiltrating HER2-negative BC p, 87% were hormone receptor (HR)-positive vs 13% triple negative (TNBC). Overall, 43% were HER2-O and 57% HER2-low (61% IHC 1+ and 39% IHC 2+). Comparing HER2-O vs HER2-low, the latest showed significant higher proportion of ER-positive (80% vs 91.7%, $p = < 0.001$) and PR-positive (69.3% vs 79.1%, $p = < 0.001$) cases, but there were no differences between HER2-low 1+ vs 2+. HER2-O exhibited higher proportion of TNBC p (20% vs 8.3%, $p = 0.001$), grade III tumors (28.8% vs 23.5%, $p = 0.036$) and higher Ki67 median value (26.47% vs 23.88%, $p = 0.041$). No significant differences were observed in median age at diagnosis, menopausal status, clinical stage, clinical nodal status, histological subtype, time to recurrence, time to local recurrence and overall survival (OS). HER2-low presented longer time to distant recurrence (TDR) compared to HER2-O (67.8 vs 54.1 months, $p = 0.015$) and better BC-related OS (19.2 vs 16.3 years, $p = 0.033$). However, in the multivariate analysis, considering HER2, ER, PR, histological grade and nodal status, PR showed the strongest association with longer TDR (HR: 0.69; 95%CI 0.54-0.89, $p = 0.004$); and positive nodal status was the strongest factor related to worse BC-related OS (HR: 2.97; CI 2.10-4.21, $p = 0.000$). No statistical differences in TDR and BC-related OS were observed between HER2 1+ vs 2+ populations. **Conclusions:** HER2-low was significantly associated to HR-positive disease whereas TNBC, histological grade III and higher Ki67% were more represented in HER2-O group. Although HER2-O was related to worse TDR and BC-related OS, these findings could be explained by the presence of an enriched population in worse prognostic features, as suggested by multivariate analysis. New therapies for HER2-O disease are an unmet medical need. Research Sponsor: None.

Extracellular vesicle-derived non-coding RNAs to predict outcome in patients with triple-negative breast cancer (TNBC) with residual disease (RD).
First Author: Shane R Stecklein, University of Kansas Medical Center, Kansas City, KS

Background: TNBC patients with RD after neoadjuvant systemic therapy (NAST) have high risk of recurrence. Biomarkers to risk-stratify patients with RD could individualize adjuvant therapy and inform adjuvant therapy trials. We aim to investigate the impact of circulating extracellular vesicle (EV)-derived non-coding RNAs (exo-ncRNAs) on outcomes in TNBC patients with RD. **Methods:** The study population included 79 TNBC patients with RD post-NAST and available end-of-treatment plasma samples enrolled in an IRB-approved multisite prospective registry. EVs and their associated exo-ncRNAs were isolated by membrane affinity spin columns (Qiagen exoRNeasy). Exo-ncRNA was subjected to next-generation sequencing (Qiagen QIAseq miRNA library kit). $N=47$ served as a discovery cohort and $N=32$ served as validation cohort. With inclusion of transcripts expressed in $\geq 80\%$ of samples, there were 1,123 normalized reads/sample. Hazard ratios and C-statistics for event-free survival (EFS) were computed for each exo-ncRNA. We report exo-ncRNAs that were significantly associated with EFS in both the discovery and validation cohorts. **Results:** Patient and tumor characteristics were balanced in discovery and validation cohorts. Three exo-ncRNAs were associated with increased recurrence risk in both the discovery dataset (*miR-200a-3p*, HR=1.39, 95%CI 1.01-1.89, $P=0.04$, C-stat=0.55; *miR-203a-3p*, HR=1.77, 95%CI 1.15-2.73, $P=0.01$, C-stat=0.59; and *miR-7845-5p*, HR=1.53, 95%CI 1.15-2.05, $P=0.004$, C-stat=0.62) and the validation dataset (*miR-200a-3p*, HR=1.83, 95%CI 1.24-2.72, $P=0.003$, C-stat=0.76; *miR-203a-3p*, HR=1.78, 95%CI 1.10-2.87, $P=0.02$, C-stat=0.67; and *miR-7845-5p*, HR=2.06, 95%CI 1.06-4.01, $P=0.03$, C-stat=0.52). Using the miRNA Target Prediction Database (miRDB), we identified 1,088, 1,352, and 387 predicted targets for *miR-200a-3p*, *miR-203a-3p*, and *miR-7845-5p*, respectively. Amongst 2,827 prediction events there were 2,526 unique target mRNAs. 2,235 mRNAs were targets for one candidate miRNAs, 281 mRNAs were predicted targets for two candidate miRNAs, and 10 mRNAs were predicted as targets for all three candidate miRNAs. **Conclusions:** The expression of *miR-200a-3p*, *miR-203a-3p*, and *miR-7845-5p* in plasma-derived EVs in TNBC patients with RD after NAST is associated with increased risk of recurrence. We identified ten mRNAs that are predicted targets of all three of these miRNAs. If validated in additional cohorts these exo-ncRNAs could be used in a liquid-biopsy assay to identify high-risk patients with RD who could benefit from adjuvant treatment intensification. Research Sponsor: Kansas Institute for Precision Medicine COBRE.

mRNA	miR-200a-3p Target Score (%)	miR-203a-3p Target Score (%)	miR-7845-5p Target Score (%)	Composite Target Score (%)
E2F3	97	92	62	84
USP8	65	86	86	79
YTHDF2	84	76	67	76
SEMA5A	51	99	68	73
RNF38	78	74	65	72
HGF	83	66	61	70
STRN	78	72	55	68
SYNCRIP	63	69	69	67
RALGPS1	78	64	57	66
LRRC28	68	55	59	61

Assessment of the differential profile of breast intratumoral bacteria in treatment responders and nonresponders.
First Author: Amedra Basgaran, BioCortex Ltd, London, United Kingdom

Background: Despite improvements in breast cancer therapy, many patients do not respond to treatment: the response rate varies between 31 and 80% [Walks et al., 2019]. The tumor microenvironment contains a microbiome which is both cancer type-specific and different to surrounding normal tissue [Nejman et al., 2020]. It plays an important role in tumour microenvironment crosstalk with tumor cells and has been implicated in disease pathogenesis, being recognised in the latest hallmarks of cancer [Hanahan et Weinberg, 2011]. It has also successfully predicted treatment response [Chen et al., 2022; Hermida et al., 2022]. Here, we use conventional microbiome analysis alongside our proprietary mechanistically-powered technology platform to compare the intratumoral bacteria between responders and non-responders. We hypothesise that there are significant differences between those groups regarding composition and mechanistic function of the bacteria. **Methods:** The tumor microbiome can be deduced from existing sequencing data of tumor biopsy samples. Using 34 tumor DNA samples from 5 breast cancer studies, we compared the intratumoral bacterial profiles of responders to non-responders of various treatments. We performed microbiome analysis in R, including alpha diversity, compositional abundance profiles, and PERMANOVA (permutational analysis of variance). Additionally, BioCortex CarbonMirror version dated 2023-02-14 was used to infer mechanistic links between bacterial species and the up- and downregulation of genes implicated in the hallmarks of cancer. **Results:** The results show significant differences in diversity and compositional profile between responders and non-responders: Non-responders have significantly higher alpha diversity ($p<0.05$) and a higher proportion of Proteobacteria. PERMANOVA analysis revealed that while responders are more likely to have commensal bacteria, non-responder tumour microbiomes are more likely to harbor pathogenic species such as *Mycoplasmopsis fermentans*. Mechanistic analysis showed that for all responders the tumor microbiome is consistently promoting tumor suppressor genes and downregulating proto-oncogenes. In non-responders, however, the tumor microbiome is upregulating and downregulating both with unclear consistency. **Conclusions:** Our results show microbiome differences between responders and non-responders which were mechanistically implicated in tumor pathogenesis. Further analysis divided by the hallmarks of cancer is required to fully understand the non-responder microbiome links. The reported findings could make the tumor microbiome a useful biomarker aiding patient stratification for both prognosis and treatment choice. They also highlight a potentially meaningful mechanistic link between tumour microenvironment and treatment response that could be leveraged as a novel therapeutic avenue. Research Sponsor: BioCortex Ltd.

Differential genomic and transcriptomic analysis of invasive lobular and ductal carcinomas.
First Author: Jason A Mouabbi, University of Texas MD Anderson Cancer Center, Houston, TX

Background: Invasive lobular carcinoma (ILC) is more aggressive than hormone receptor (HR)-positive invasive ductal carcinoma (IDC). However, in practice, ILC and IDC are often treated in a similar fashion with endocrine therapy and chemotherapy. Identifying novel biomarkers, genetic alterations, transcriptomic features, and tumor microenvironment (TME) variations could initiate the development of personalized treatment plans for patients with ILC. **Methods:** We collected ILC and luminal (non-basal/non-HER2) IDC samples from four datasets (TCGA, METABRIC, RATHER PMC4700448, and UQCCR PMC31263747) and performed differential expression and gene set enrichment analyses, revealing novel genomic, transcriptomic, and TME differences. Using methods from Bagaev et al., we quantified the activity of 29 functional gene expression signatures with single sample gene set enrichment analysis before clustering the samples into five TME subtypes; statistical significance was measured with the Mann-Whitney U test. Differential expression analysis of RNA-Seq data was completed using DESeq2. Further, we analyzed the frequency of specific biomarkers to identify potential therapeutic options. Mutations and biomarker enrichment were assessed using the chi-squared test. **Results:** We analyzed 1,735 samples (1,442 luminal IDCs and 293 ILCs). *CDH1* mutations were more prevalent in ILC samples (56%) compared to IDC samples (6%). Of the 44% of ILC samples with wild-type *CDH1*, 90% had low *CDH1* expression. Inference models showed differences in transcription factors expression between ILC and IDC. ILC had significantly higher expression of *TFAP2B*, *SOC2*, *NOSTRIN*, *THBS4*, *SCUBE2*, and *GDF9* and lower expression of *CDC44*, *PSMG1*, *LMOD1*, and *SLC7A5* (adj $p < 0.0001$ for all genes). Analysis of the TME showed that 44% of ILC samples were immune enriched with high *PDL1*, *CTLA4*, and *LAG3* expression. In comparison, approximately 30% of ILC samples contained enhanced vascularization and expressed high *VEGFA*, *PDGFRA*, and *PDGFRB*. Finally, compared to luminal IDC, ILC tend to have a statistically significant higher TROP2 expression, similar to that seen in basal subtype. **Conclusions:** ILC and IDC expressed distinct genomic alterations, gene expression, transcriptomic features, TMEs, and biomarkers. These differences can be used as a blueprint to tailor ILC phenotype-specific interventional clinical trials. Research Sponsor: None.

Characteristics associated with spatially resolved immune landscapes in triple-negative breast cancer in the FinXX trial and Mayo Clinic cohort.
First Author: Saranya Chumsri, Mayo Clinic, Jacksonville, FL

Background: Several studies have established the crucial role of preexisting immune response measured by tumor-infiltrating lymphocytes (TILs) in triple-negative breast cancer (TNBC). Emerging studies showed that not only the number of TILs but also the location of TILs is as critical. There are 3 distinct immune landscapes described based on the locations of TILs, namely immune enriched (IN), immune excluded (IE), and immune desert (ID), which are associated with outcomes in TNBC treated with immune-checkpoint inhibitors. Here we evaluated characteristics associated with each immune landscape. **Methods:** NanoString IO360, Digital Spatial Profiling (DSP), and CosMx, a spatial multi-omics single-cell imaging platform, were used. DSP was used to quantify 39 immune-related proteins in stromal and tumor-enriched segments from 44 TNBC samples from the FinXX trial (NCT00114816) and 276 samples from the Mayo Clinic (MC) TNBC cohort (Leon-Ferre BCRT 2018). CosMx was performed in 75 samples from the MC TNBC cohort. First, tumors with TIL quantified by H&E $\leq 30\%$ were classified as ID. The rest of the tumors were categorized according to the intratumoral CD8 protein expression by DSP, with IE having intratumoral CD8 in the lower median and IN having intratumoral CD8 in the upper median. Differential expression listed as log fold change (FC) was estimated from the linear mixed model with significance defined as two-sided $p < 0.05$. **Results:** Using DSP in the FinXX trial, intratumoral and stromal higher HLA-DR (FC 1.68, $p=0.001$), B2M (FC 0.8, $p=0.005$), CD4 (FC 0.74, $p=0.01$), and CD40 (FC 1.56, $p=0.001$) were associated with IN compared to ID. When comparing IE and IN, higher intratumoral CD11c (FC 0.97, $p=0.01$) and stromal CD4 (FC 0.89, $p=0.047$), CD20 (FC 0.85, $p=0.016$), CD40 (FC 0.95, $p=0.045$), and CD27 (FC 0.84, $p=0.024$) were associated with IN. Similar findings were observed in the MC cohort. Moreover, intratumoral NY-ESO-1 expression (FC 0.55, $p=0.03$) was associated with IN. Using GSEA with IO360 in the FinXX trial, PI3K-Akt signaling was associated with ID compared to IN ($p=0.01$). We further evaluated the differential gene expression in a spatially resolved manner using CosMx with single-cell sequencing in the MC cohort. Expressions of MHC class I and class II in tumor cells, including HLA-A, HLA-B, HLA-C, HLA-DRA, HLA-DRB1, HLA-DPA1, and HLA-E, were associated with IN compared to ID and IE. **Conclusions:** Using an in-depth analysis with spatially defined context, we identified characteristics associated with distinct immune landscapes in TNBC. Our study highlights the potential future implications of intratumoral MHC expression, CD40, and PI3K-AKT as biomarkers and therapeutic targets. Clinical trial information: NCT00114816. Research Sponsor: Breast Cancer Research Foundation.

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Poster Session

The somatic mutation profile of breast cancer in Uganda. *First Author: Manoj Menon, Fred Hutchinson Cancer Center, Seattle, WA*

Background: Breast cancer, the most common cancer in sub-Saharan Africa (SSA), is characterized by poor survival compared with resource-rich regions. A variety of factors are responsible for this disparity and include late stage at presentation, limited diagnostic and therapeutic options, and potentially biologically more aggressive disease. The application of next generation sequencing to cancer specimens in resource-rich regions has identified new molecular mechanisms. However, such molecular testing has generally not been applied to tumors from SSA where the aggressive nature and younger age of women with breast cancer argues for the potential for novel pathogenic mechanisms. Here, we describe the somatic mutation profile of breast cancer in Uganda. **Methods:** We enrolled 100 consecutive women with a new diagnosis of invasive breast cancer at the Uganda Cancer Institute (UCI) in Kampala - the primary cancer center of Uganda and neighboring countries. Histopathologic classification was performed at the UCI and reevaluated in a blinded fashion at the Fred Hutchinson Cancer Center (Seattle, WA). Demographic and clinical data were obtained. A biopsy specimen of the tumor tissue was obtained, snap frozen, processed using standard protocols to obtain DNA, and sequenced using the clinically-validated UW-OncoPlex assay, identifying all classes of variants and mutations. **Results:** We analyzed data from 100 women with a histologically-confirmed diagnosis of breast cancer between the ages of 35 and 65 - the vast majority of whom presented with either stage 3 or stage 4 (92%). All 100 tumor specimens were successfully sequenced, with 96 (96%) demonstrating somatic mutations. The most commonly altered gene was TP53, with mutations in 65% of patients, with identified variant classes including truncations (18), missense (19), and copy loss (33). *PIK3CA* mutations were identified in 36% of patients, while copy gain or amplification were identified in *MYC* (50%), *CCND1* (31%), *FGFR1* (26%), *EGFR* (9%), and *ERBB2* (24%). Nearly half of the women had either a mutation in *BRCA1* (24%) or *BRCA2* (24%); 6 (6%) of the tumors expressed mutations in both *BRCA1* and *BRCA2*. **Conclusions:** We identified a diverse landscape of somatic mutations - the prevalence of *BRCA1*, *BRCA2*, and *PIK3CA* mutations are considerably higher than in other documented populations. A better understanding of the mutational profile can provide biological insights, inform prognosis, and serve as a predictive biomarker. As mutations in *BRCA1/2* and *PIK3CA* can potentially be treated with targeted therapies (e.g. PARP inhibitor, PI3K inhibitor), such data can inform policymakers, allow for inclusion of these therapeutics in the formulary and in the WHO Model List of Essential Medicines, and reduce health disparities. Notably, all cases were successfully sequenced, with 96% of cases demonstrated somatic mutations, even without employing specific enrichment strategies commonly used in high-income countries. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology; GSK Open Africa Lab.

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Poster Session

10-year mastectomy trends among breast cancer phenotypes: A national cohort study. *First Author: Matthew Lewis Pierotti, Fox Chase Cancer Center, Philadelphia, PA*

Background: Breast cancer tumor phenotype has prognostic value with triple negative (TN) cancers having higher rates of distant metastases early. While tumor phenotypes are prognostic, published data demonstrates that the choice of local therapy does not affect this predisposition or affect survival. This study was performed to determine whether mastectomy is being performed more frequently for TN or HER2+ phenotypes, relative to hormone receptor positive (HR+) phenotypes despite the lack of benefit this should provide. **Methods:** Data from the National Cancer Database (NCDB) was analyzed from 2010 through 2019 to assess mastectomy trends and associations with patient and tumor characteristics. Women with invasive breast cancer were included. Women with Stage IV disease were excluded. Patients were categorized as mastectomy or breast conservation surgery. Patient and tumor characteristics were compared across groups using chi-square and Wilcoxon rank sum tests, and a multivariable logistic regression model was fit to assess the association between mastectomy and tumor phenotype controlling for patient and tumor characteristics. **Results:** 543,590 patients were evaluated. 173,380 (31.9%) patients underwent mastectomy, and 370,210 (68.1%) patients underwent breast conservation surgery. Mean age at diagnosis was 56. There were 425,174 HR+, 64,960 HER2+, and 53,456 TN tumors. The proportion of patients undergoing mastectomy peaked in 2013 at 36.14% before declining. Compared to HR+, HER2+ patients were more likely to undergo mastectomy, OR 1.39 $p < 0.0001$ (95% CI 1.35 - 1.43); however, there was no significant difference in mastectomy between HR+ patients and TN patients. Compared to whites, black patients were less likely to undergo mastectomy, OR 0.71 $p < 0.0001$ (95% CI 0.69 - 0.74), and individuals of Hispanic ethnicity less likely to undergo mastectomy, OR 0.92 $p < 0.0001$ (95% CI 0.89 - 0.95). Compared to private insurance, Medicare had a greater association with mastectomy, OR 1.2 $p < 0.0001$ (95% CI 1.18 - 1.23). There was no significant difference between other forms of insurance (Medicaid, other government insurance, no insurance) and private insurance. Education and income were not associated with different frequencies of mastectomy. Patients with higher comorbidity scores were more likely to undergo mastectomy. **Conclusions:** Mastectomy rates have been declining since 2013 at CoC centers. While TN breast cancer is not associated with increased mastectomy percent, mastectomy continues to be performed more frequently for HER2+ positive phenotype when adjusting for tumor and patient characteristics. These data suggest a need for education about HER2 positive phenotype due to a possible lack of understanding about the why such tumors pose a risk, and the role of local therapy in treating them. Research Sponsor: Fox Chase Cancer Center.

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Poster Session

Phase II study on feasibility of sentinel lymph node biopsy for ycNO patients treated with primary chemotherapy in cT1-3N1M0 breast cancer (SHARE study). *First Author: Rikiya Nakamura, Department of Breast Surgery, Chiba Cancer Center, Chiba, Japan*

Background: Sentinel lymph node biopsy (SLNB)-guided axillary management is still debated for clinically node-positive breast cancer (BC) patients treated with neoadjuvant chemotherapy (NAC). Several phase II studies demonstrated high false-negative rates (FNR) in ycNO BC, but precise diagnostic imaging for nodal involvement may reduce FNR. To explore ideal imaging and lymphatic mapping, the Japanese Society for Sentinel Node Navigation Surgery conducted a prospective non-randomized phase 2 study (SHARE study, UMIN000030558). **Methods:** Clinical T1-3N1M0 BC was eligible under multimodal imaging of breast ultrasound, CT and/or MR mammography. Nodal metastasis was histologically confirmed. Standard regimen for NAC was performed by physician's choice. In case of ycNO BC, SLNB was planned and lymphatic mapping depended on each institutional practice. The primary endpoint is FNR of SLNB and secondary endpoints are the identification rate and outcome of ycNO BC patients at 2 years after surgery. Moreover, in cases of pNO(sn), pNO(i+)(sn) and pN1mi(sn), SLNB followed by lymph node sampling had been allowed instead of axillary lymph node dissection. Based on an estimated FNR of 5%, 224 patients were needed to give 80% power to reject the null hypothesis that the threshold of FNR is 15% with a one-sided type I error rate of 5%. **Results:** Between February 2018 and May 2021, 185 patients from 19 institutes were registered. After 27 ineligible cases of protocol deviation, non-ycNO or withdrawal of SLNB were excluded, 158 ycNO cases underwent SLNB and sentinel lymph nodes were detected in 153 cases. Among them, the median age was 52 years old. Clinical stage was IIA in 40 cases, IIB in 105 and IIIA in 8. Luminal subtype classified by ER, PR and HER2 expression was found in 60 cases, HER2 in 34, Luminal-HER2 in 35 and triple-negative in 24. Finally, 61 cases had positive nodes, which included 7 false-negative cases. FNR was 11.5% (90% confidence interval, 5.5% and 20.5%). The identification rate was 96.8% and the accuracy rate was 95.4%. Before NAC, multimodal imaging was performed in 148 cases (96.7%) and 1 nodal metastasis was detected in 62 cases (40.5%). When multimodal imaging, 1 nodal metastasis, multiple tracers, multiple sentinel lymph nodes were considered for subset analysis, the FNR was 12.1%, 9.1%, 11.1%, and 10.6%, respectively. If isolated tumor cells in lymph nodes had been defined as pathologically negative even after NAC, the FNR was 7.1%. **Conclusions:** Multimodal imaging could not improve FNR in ycNO BC. However, SLNB-guided axillary management should be considered when one positive-node is clinically converted to ycNO after NAC. We will report the outcome of ycNO BC cases next year. Clinical trial information: UMIN000030558. Research Sponsor: The Japanese Society for Sentinel Node Navigation Surgery.

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Poster Session

Racial/ethnic and socioeconomic differences in breast cancer surgery performed and delayed surgical treatment: Mediating impact on mortality. *First Author: Ayrtton Bangolo, Palisades Medical Center, North Bergen, NJ*

Background: Breast cancer is the most common malignancy affecting women of all racial and ethnic backgrounds in the United States (US). Although Socioeconomic status (SES), race/ethnicity, and surgical type/delays are associated with breast cancer mortality outcomes, studies on these associations have been contrasting. This study examined the racial/ethnic and SES differences in surgical treatment types and delays. Also, we quantified the extent to which these differences explained the racial/ethnic disparities in breast cancer mortality. **Methods:** We studied 290,066 women 40+ years old diagnosed with breast cancer between 2010 and 2017 identified from the Surveillance, Epidemiology, and End Results database. We performed logistic regression models to examine the association of SES and race/ethnicity with surgical treatment type and delays. We performed mediation analysis models to quantify the extent to which mortality differences were mediated by treatment, sociodemographic, and clinicopathologic factors. The study subjects were de-identified, and there was no patient contact; thus, the study was exempted from an Institutional Review Board's (IRB) approval. A p-value less than 0.05 indicated significant associations for the descriptive statistics, logistic and Cox proportional hazard regressions, and mediation analysis. We used Stata 17 to perform the analyses. **Results:** Non-Hispanic (NH) Black [Odds ratio (OR) = 1.16, 95% CI: 1.13-1.19] and Hispanic women [OR = 1.27, 95% CI: 1.24-1.31] were significantly more likely to undergo mastectomy compared to NH White women. Similarly, NH Black and Hispanic women had higher odds of delayed surgical treatment than NH Whites. Patients in the highest SES quintile, compared to those in lowest the lowest, were less likely to experience breast cancer-specific mortality (BCSM). Variations in treatment, SES, and clinicopathological factors significantly explained 70% of the excess BCSM among NH Blacks compared to their NH White counterparts. **Conclusions:** In conclusion, health disparity continues to be a major societal concern in the US. It affects people of all ages, socioeconomic classes, and ethnic/racial backgrounds. The findings of this study showed that racial and ethnic minorities, the majority of whom have a lower socioeconomic position, are significantly disadvantaged regarding the evaluation, quality, cost, and duration of medical care. Future studies can assess the multifactorial effects of socio-demographic factors like SES, access to health care assessment, and educational background amidst other variables as a multidimensional predictor of treatment delay and overall survival of breast cancer and other health issues among minoritized populations. Research Sponsor: None.

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Poster Session

Disease outcomes by race in patients with high-risk triple negative breast cancer with residual disease after neoadjuvant chemotherapy: A post-hoc analysis of the EA1131 randomized clinical trial. *First Author: Olga Kantor, Brigham and Women's Hospital, Boston, MA*

Background: Black women with breast cancer have the highest breast cancer mortality (BCM) rates of any racial and ethnic group. The higher burden of triple negative breast cancer (TNBC) in Black women contributes to disparities in BCM, but the extent to which disparate outcomes exist in patients with similar tumor biology is uncertain. The objective of this study was to examine racial differences in disease outcomes and BCM between Black and White patients in a clinical trial population of high-risk TNBC with residual disease after neoadjuvant chemotherapy (NAC). **Methods:** From 2015-2021, the ECOG-ACRIN EA1131 clinical trial randomized 415 clinical stage II-III TNBC patients with residual disease after NAC to either adjuvant capecitabine or platinum. For this analysis, 366 patients with known self-reported Black or White race and follow-up data were included. The aim of this unplanned exploratory analysis was to examine locoregional recurrence (LRR), distant recurrence (DR), and BCM by race using Kaplan-Meier curves for unadjusted estimates and Cox modeling for adjusted analyses. **Results:** Racial distribution of the analysis population included 66 (18.0%) Black and 300 (82.0%) White patients. 239 (65.3%) patients presented with clinical stage II and 127 (34.7%) with stage III disease. All patients had residual pathological disease after NAC: 86 (23.5%) stage I, 176 (48.1%) stage II, and 102 (27.9%) stage III (n=2 unknown). Median age was 49 years in Black and 54 years in White patients, $p=0.003$. Disease presentation, response to chemotherapy, and treatment arm were similar by race. Median follow up was 20 months. 2-year estimated LRR occurred in 31.6% of Black and 18.6% of White patients although this was not statistically significant ($p=0.387$), and 2-year estimated DR and BCM were similar by race. Estimated 2-year outcomes are outlined. Models adjusted for race, age, stage, grade, treatment arm, and locoregional therapy did not identify race as an independent predictor of LRR, DR, or BCM. Higher pathologic stage was the only consistent independent predictor of recurrent disease or BCM (stage III with HR 6.14 for LRR; HR 5.16 for DR; HR 6.84 for BCM; all $p<0.001$). **Conclusions:** In this population of high-risk patients with residual TNBC after NAC with similar tumor biology treated on a clinical trial, there was a trend towards increased LRR in Black patients and similar DR and BCM between Black and White patients at 2 years of follow-up. This suggests that differences in BCM in other breast cancer populations may be at least partially driven by differences in tumor biology. Clinical trial information: NCT02445391. Research Sponsor: None.

Kaplan-meier estimates of 2-year LRR, DR, and BCM by race.

Estimated 2-year Outcome	Black	White	P-value
Isolated LRR	14.3%	4.3%	0.719
Any LRR	31.6%	18.6%	0.387
Any DR	42.2%	42.9%	0.873
BCM	23.8%	30.1%	0.274

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Poster Session

A phase II randomized clinical trial to assess toxicity and quality of life of patients with breast cancer with hypofractionated versus conventional fractionation radiotherapy with regional nodal irradiation. *First Author: Gabriel Oliveira Bernardes Gil, Rede Mater Dei, Nova Lima, Brazil*

Background: The primary aim was comparing acute toxicity between conventional fractionated radiation therapy (CF-RT) and hypofractionated radiation therapy (HF-RT) for patients undergoing breast-conserving surgery or mastectomy with breast or chest wall and regional nodal irradiation (RNI). The secondary endpoints were acute and subacute toxicity, cosmesis, quality of life, and lymphedema features. **Methods:** Unblinded randomized trial with total of 86 patients treated with CF-RT ($n = 33$; 50 Gy/25 fractions $\pm$ sequential boost [10 Gy/5 fractions]) versus HF-RT ($n = 53$; 40 Gy/15 fractions $\pm$ concomitant boost [8 Gy/15 fractions]). Toxic effects and cosmesis evaluation used the Common Terminology Criteria for Adverse Events version 4.03 (CTCAE) and the Harvard/NSABP/RTOG scale. Patients-reported QoL was determined using European Organization for Research and Treatment of Cancer quality of life questionnaire (EORTC QLQ-C30) and the breast cancer-specific supplementary questionnaire (QLQ-BR23). Lymphedema determination compared volume differences between the affected and contralateral arms using the Casley-Smith volume formula. **Results:** Grade 2 and grade 3 skin rash dermatitis were lower with HF-RT than with CF-RT (28% vs. 52%, 0% vs. 6%; $p = 0.022$, respectively). HF-RT vs. CF-RT had lower rate of grade 2 hyperpigmentation (23% vs. 55%; $p = 0.005$). No differences in overall rates of any physician-assessed grade 2 or higher and grade 3 or higher acute toxicity between HF-RT vs. CF-RT were registered. There was no statistical difference between the CF-RT and the HF-RT regarding cosmesis, lymphedema rate (13% vs. 12% HF-RT vs. CF-RT; $p = 1.000$, respectively), and functional and symptom scales during irradiation and after six months of treatment. **Conclusions:** HF-RT showed lower rates of acute toxicity, with no changes in quality-of-life outcomes. Clinical trial information: NCT04015531. Research Sponsor: None.

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Poster Session

Association of minimizing the false negative rate of axillary staging surgery in patients with cN1 breast cancer after neoadjuvant chemotherapy with surgical overtreatment. *First Author: Alison Laws, Dana-Farber Brigham Cancer Center, Boston, MA*

Background: Efforts to minimize the false negative rate (FNR) of axillary staging in cN1 breast cancer patients (pts) treated with neoadjuvant chemotherapy (NAC) have received much attention since the publication of ACOSOG Z1071. We first adopted sentinel node biopsy (SNB) with a requirement of retrieving ≥ 3 nodes, and later transitioned to targeted axillary dissection (TAD) with a requirement of retrieving the biopsy-proven clipped node (CN) and ≥ 3 nodes overall. Group consensus was to perform axillary lymph node dissection (ALND) if these technical requirements were not met. This study evaluates likelihood of surgical overtreatment with ALND due to technical failures of SNB or TAD in cN1 pts who converted to ypN0 status, and reports oncologic outcomes with each approach. **Methods:** Among 598 cN1 breast cancer pts treated with NAC from 2017-2022 in our prospective institutional database, we included 191 (31.9%) with attempted SNB or TAD and ypN0 status. We used descriptive statistics and chi-squared tests to compare technical complications of SNB vs. TAD resulting in requirement for ALND per group consensus despite ypN0 status. Kaplan Meier methods were used to determine oncologic outcomes in those treated with SNB or TAD alone. **Results:** Planned axillary surgery was SNB in 77 (40.3%) pts and TAD in 114 (59.7%). The CN was not visualized for seed localization in 14 pts (12.2% of planned TAD) and the seed was not found to be within the CN intra-operatively in 20 pts (20.0% of those with seed placed). Technical failures resulting in requirement of ALND per group consensus criteria occurred in 14 (18.2%) pts with planned SNB and 17 (14.9%) with planned TAD. Among planned TAD pts, the rate of not retrieving the CN did not change over time ($p=0.52$). Median follow-up in those treated with SNB alone ($n=79$) was 3.5 years with 1 (1.3%) axillary recurrence as well as 2 local and 2 distant recurrences and 1 non-breast cancer death. 3-yr recurrence-free survival was 90.4% (95%CI: 79.5-95.7%). Median follow-up in those with TAD alone ($n=92$) was 1.8 years with no recurrences or deaths. **Conclusions:** This study contributes to a growing body of literature supporting the oncologic safety of omitting ALND in cN1 ypN0 pts treated with NAC, irrespective of the axillary staging approach. Technical limitations in identifying ≥ 3 nodes or localizing and retrieving CNs resulted in overtreatment with ALND in a significant proportion ($\geq 15\%$) of ypN0 pts, without significant differences between SNB vs. TAD approaches. These data support consideration of re-evaluating NCCN guidelines recommending retrieval of ≥ 3 nodes and localization of the CN to minimize risk of overtreatment. Research Sponsor: None.

	Planned SNB (n=77)	Planned TAD (n=114)	p-value
Failed mapping	5 (6.5%)	3 (2.6%)	0.19
<3 nodes	9 (11.7%)	6 (5.3%)	0.11
CN not confirmed to be retrieved	—	8 (7.0%)	—
TOTAL	14 (18.2%)	17 (14.9%)	0.55

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Poster Session

Invasive disease free survival and brain metastasis rates in patients treated with neoadjuvant chemotherapy with trastuzumab and pertuzumab. *First Author: Sonya Chew, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Patients (pts) with human epidermal growth factor receptor 2 (HER2) positive (+) early breast cancer (EBC) receiving neoadjuvant systemic therapy (NAST) have poorer outcomes if they have residual disease (RD) after surgery. HER2 negative (-) RD has been reported in 1/3 of pts after NAST. The KATHERINE trial suggests that pts with HER2- RD (8%) have better invasive disease-free survival (IDFS) with adjuvant (adj) trastuzumab emtansine (T-DM1) versus trastuzumab (H) alone. However, only 18% of the pts enrolled in the trial received NAST with trastuzumab and pertuzumab (HP). We aimed to analyze IDFS and brain metastasis (BM) rates in pts with HER2+ EBC in a modern population homogeneously treated with NAST. We also report the incidence of pts with HER2- RD and their outcomes. **Methods:** Clinicopathologic data for pts with HER2+ EBC who received NAST between 1 Jan 2019 and 31 Jan 2022 were reviewed. External assessment of HER2 status before NAST was allowed. HER2 status of the surgical specimens with RD were assessed internally at our center. IDFS was defined as the time from surgery until first occurrence of invasive cancer recurrence, distant recurrence, or death from any cause. **Results:** The total cohort was 594 pts. 456 (77%) and 138 (23%) received anthracycline-taxane and taxane based chemotherapy, respectively during NAST. 587 (99%) received HP and 7 (1%) received H alone. NAST was completed by 566 (95%) of pts. pCR (ypT0/isN0) was achieved in 325 (55%) and RD was seen in 269 (45%) pts. In 269 pts with RD, 46 (17%) did not have HER2 retesting and were excluded from the final analysis. In the remaining 223 pts, 143 (64%) were HER2+ and 80 (36%) were HER2-. In the 143 pts with HER2+ RD, adj TDM1, HP, H alone and no HER2 directed therapy were received by 120 (84%), 16 (11%), 1 (1%) and 6 (4%) of pts, respectively. In the 80 pts with HER2- RD, adj TDM1, HP, H alone and no HER2 directed therapy were received by 44 (55%), 27 (34%), 3 (4%) and 6 (7%) of pts, respectively. With a median follow up of 24 months, 7 pts developed BM at initial recurrence, 3/325 (0.9%) with pCR and 4/143 (2.8%) with HER2+ RD. None of the pts who developed BM had HER2- RD. IDFS events occurred in 22/594 (3%) pts. RD pts had a higher likelihood of having an IDFS event, 14/269 (5%) in RD and 8/325 (2%) in pCR ($p = 0.04$). In the evaluable 223 pts with RD there was no difference in IDFS between 10/143 (7%) pts with HER2+ RD or 4/80 (5%) with HER2- RD ($p = 0.10$). **Conclusions:** At a single center, in pts who predominantly received HP with chemotherapy as NAST, pts with RD had higher IDFS events than those with pCR. In those with RD, 36% lost HER2+ status; IDFS events appeared similar in those with HER2+ RD versus those with HER2- RD. The HER2 loss rate is higher than reported in KATHERINE possibly due to majority of pts receiving dual HP as NAST. The BM events seen in those with RD and pCR highlights the need for more effective therapy in NAST and adj setting to minimize BM risk. Research Sponsor: None.

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Poster Session

Effect of tumor microenvironment on chemotherapy response of patients with triple-negative breast cancer receiving neoadjuvant chemotherapy. *First Author: Jae-Joon Kim, Pusan National University Yangsan Hospital, Yangsan-Si, South Korea*

Background: Triple-negative breast cancer (TNBC) is a breast cancer subtype that has poor prognosis and exhibits a unique tumor microenvironment, including the corresponding immunological environment. Analysis of the tumor microbiome has indicated a relationship between the tumor microenvironment and treatment response. Therefore, we attempted to reveal the role of the tumor microbiome in patients with TNBC that were receiving neoadjuvant chemotherapy. **Methods:** We collected TNBC patient RNA-seq samples from the Gene Expression Omnibus (GEO; n of pathological complete response [pCR] = 38, n of residual disease [RD] = 50) and extracted microbiome count data using Kraken2 and Bracken. Differential and relative abundance were estimated with linear discriminant analysis effect size (LEfSe). We calculated the immune cell fraction with CIBERSORTx and conducted survival analysis using the Cancer Genome Atlas patient data (n = 115). Correlations between the microbiome and immune cell compositions were analyzed and a prediction model was constructed to estimate drug response using random forest (RF) and support vector machine (SVM). **Results:** Among the drug response group, the beta diversity varied considerably; consequently, 20 genera and 24 species were observed to express a significant differential and relative abundance using LEfSe analysis. The drug response prediction model accuracy exhibited 76.47 and 88.24 percent in RF and SVM, respectively; specifically, *Pandoraea pulmonicola* and *Brucella melitensis* were found to be important features in determining drug response. In correlation analysis, *Geosporobacter ferrireducens*, *Streptococcus sanguinis*, and resting natural killer cells were the most correlated factors in the pCR group, whereas *Nitrosospora briensis*, *Plantactinospora* sp. BC1, and regulatory T cells (Tregs) were key features in the RD group. Further, M2 macrophages and *Brucella* showed significant differences in survival between the pCR and RD groups (p < 0.05). **Conclusions:** Our study demonstrated that the microbiome analysis of tumor tissue can predict chemotherapy response of patients with TNBC receiving neoadjuvant chemotherapy. Further, the immunological tumor microenvironment may be impacted by the tumor microbiome, thereby affecting the corresponding survival and treatment response. Research Sponsor: Medical Research Center program (2018R1A5A2023879) from National Research Foundation of Korea, and the Korea Health Technology R&D Project through the Korea Health Industry Development Institute; Ministry of Health & Welfare, Republic of Korea (HI22C1377); Research institute for Convergence of biomedical science and technology (30-2020-000), Pusan National University Yangsan Hospital Institutional Funding.

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Poster Session

Use of machine learning to predict pathological complete response using multi-modal data from I-SPY2 clinical trials. *First Author: Fahad Shabbir Ahmed, Algorismus, LLC, Detroit, MI*

Background: The objective of the current analysis of the I-SPY 2 data from multiple breast cancer clinical trials for stages II and III cancers was to look at the possibility of developing a machine learning algorithm to predict pathological complete response using multimodal data. **Methods:** Imaging, clinical and biomarkers data form the I-SPY 2 trial was used in this analysis. Four different experiments were designed for to assess different data pre-processing and machine learning methods mainly deep neural networks (DNN) and random forest (RF) classifiers. Experiment 1 and 3 use DNNs while Experiment 2 and 4 used RFs; more over the first two experiments used data that was continuous in nature from the point of view of pre-performed imaging analysis while in later two experiments we had binarized all the variables using a median cutoff for high vs low values. The variables used were treatment recieved, HER2/neu receptor status, hormone receptor status, age, ethnicity, gynecological history, MRI feature data. All models were evaluated using robust testing methods that included sensitivity, specificity, positive predictive values (PPV), negative predictive values (NPV), accuracies (training and test sets), area-under the receiver-operator curve and F1-Score. **Results:** From a total of 985 patients with clinical data we used 384 that had multi-feature MRI data. Time series data for the initial scan (T0) and a scan 3 weeks later (T1). The final comparative analysis showed the best model among the 4 experiment the best performing algorithms for this analysis was random forests using median cutoffs with a best F1-score (0.43), specificity (86.4%), PPV (47.8%), accuracies (train sets, 100%; test sets, 75%), and AUROCs (0.78, 0.56-0.73). **Conclusions:** The use of machine learning to predict pathological complete response using multi-modal data shows good potential as a digital biomarker. However, these results need further validation before a clinical tool is available for the clinicians. Research Sponsor: None.

Experiment	Sensitivity	Specificity	PPV	NPV	Train set accuracy	Test Set accuracy	AUROC (95%CI)	F1-Score
1. Continous data (DNN)	28.57	71.59	24.24	75.90	93.66	61.21	0.55 (0.44-0.62)	0.26
2. Continous data (RF)	32.14	88.64	47.34	80.41	100.0	75	0.78 (0.56-0.73)	0.38
3. Hi/Low median cutoff data (DNN)	100	0.00	24.13	-	31.72	24.14	0.60 (0.13-0.28)	0.39
4. Hi/Low median cutoff data (RF)	39.29	86.36	47.82	81.72	100.0	75	0.78 (0.56-0.73)	0.43

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Poster Session

Neoadjuvant giredestrant + palbociclib (P) vs. anastrozole (A) + P in postmenopausal women with estrogen receptor-positive, HER2-negative, untreated early breast cancer (ER+, HER2- eBC): Patient (pt)-reported outcomes (PROs) in the randomized, open-label, international phase II coopERA BC study. *First Author: Yeon Hee Park, Samsung Medical Center, Seoul, South Korea*

Background: Endocrine therapies (ETs) are the therapeutic mainstay for ER+ BC but persistent adverse events (AEs; eg joint pain, especially with aromatase inhibitors) negatively impact quality of life, and resistance impacts efficacy. Giredestrant, a highly potent, nonsteroidal, oral selective ER antagonist and degrader (PO SERD), may help address these issues. coopERA BC (NCT04436744) evaluated giredestrant in eBC and met its primary endpoint, demonstrating a greater reduction of Ki67 with giredestrant vs. A after 2 weeks. Giredestrant was well tolerated as a single agent and with P. We report exploratory PRO analyses. **Methods:** Pts with cT1c-cT4a-c (≥ 1.5 cm within cT1c) ER+, HER2- untreated eBC and baseline Ki67 score $\geq 5\%$ were randomized 1:1 to 30 mg PO daily (QD) giredestrant or 1 mg PO QD A on days (D)1–14 of a window-of-opportunity phase. A 16-week neoadjuvant phase added 125 mg PO QD P on D1–21 of four 28-D cycles. Presence/frequency/severity/interference of relevant symptomatic AEs were assessed at Cycles 1–4 via NCI PRO-CTCAE library items; overall burden due to AEs, via FACT-G item GP5. **Results:** PRO completion rates were > 80% at all time points. PRO-CTCAE postbaseline frequency scores were comparable between arms and mostly 0/1 (never/rare; reported for: Diarrhea > 80% of pts; hot flash > 60%; joint pain > 65%; nausea > 90%; vomiting > 90%). No rash was reported by > 90% of pts; fatigue at 0/1 severity (none/mild) by > 75% and at 0/1 interference (none at all/a little bit) by 80%. Hot flash frequency scores of 2–4 (occasionally/frequently/almost constantly) were reported by 30% of pts in the giredestrant + P arm and 37% in the A + P arm; joint pain frequency scores of 2–4, by 25% and 35%. Worst postbaseline scores of 3–4 are shown in the table. FACT-G GP5 showed greater proportions of “improved/no change” responses in the giredestrant + P than the A + P arm at Cycles 2–4 (Cycle 2 75%; Cycle 3 71%; Cycle 4 68% vs. 62%; 66%; 53%), and smaller proportions of “worsened” responses (25%; 29%; 32% vs. 38%; 34%; 47%). **Conclusions:** This is the first analysis to our knowledge of PROs with a PO SERD in eBC; it showed that most pts reported minimal symptomatic AEs at frequency and severity levels that were generally numerically lower in the giredestrant + P than the A + P arm (particularly joint pain). Furthermore, there were numeric trends towards greater stability and improvement and less worsening of treatment burden in the giredestrant + P arm. Studies to further assess giredestrant’s clinical benefit are ongoing in the adjuvant setting. Clinical trial information: NCT04436744. Research Sponsor: F. Hoffmann-La Roche Ltd.

n/N pts (%)	Giredestrant + P	A + P
Frequency		
Diarrhea	0/108	3/103 (3)
Hot flash	18/106 (17)	12/101 (12)
Joint pain	8/108 (7)	17/103 (17)
Nausea	1/107 (1)	0/103
Vomiting	0/107	0/103
Fatigue severity	2/107 (2)	7/101 (7)

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Poster Session

Taxane combined with lobaplatin or anthracycline for neoadjuvant treatment of triple-negative breast cancer: A single-center, randomized, controlled, phase-II clinical study. *First Author: Cheng Wang, Southwest Hospital, Army Medical University, Chongqing, China*

Background: Previously, we showed that addition of lobaplatin (L) to taxane combined with anthracycline could improve the pathologic complete response (pCR) rate and lengthen survival significantly if employed as neoadjuvant therapy in patients with triple-negative breast cancer (TNBC). We evaluated the efficacy and safety of neoadjuvant chemotherapy of taxane (T) combined with lobaplatin (L) or anthracycline (E) for patients with TNBC. **Methods:** Ninety-five patients with TNBC (stage I–III) who had not undergone any type of treatment were divided randomly into two groups: TL (docetaxel at 75 mg/m² and lobaplatin at 30 mg/m², D1, one cycle = 21 days, a total of six cycles) or TE (docetaxel at 75 mg/m² and epirubicin at 80 mg/m², D1, one cycle = 21 days, a total of 6 weeks or epirubicin at 80 mg/m² and cyclophosphamide at 600 mg/m², sequential docetaxel at 75 mg/m², D1, one cycle = 21 days, a total of eight cycles). Efficacy was evaluated every two cycles. The final surgical procedure was completed after fulfillment of neoadjuvant chemotherapy. The primary endpoint was the total pathologic complete response (tpCR) rate. The secondary endpoints were the objective response rate (ORR), safety, event-free survival (EFS), and overall survival (OS). The exploratory endpoint was biomarker analysis. **Results:** From June 2019 to November 2022, 97 patients were screened. Finally, 95 patients were enrolled. The median age of the study cohort was 49 years. Nine patients (9.5%) had stage-I disease, 61 patients (64.2%) had stage II, and 25 patients (26.3%) had stage III. Sixty-five patients (68.4%) had Ki67 $\geq 40\%$ and 30 patients (31.6%) had Ki67 < 40%. Seventy patients (73.7%) were cytokeratin (CK)5/6+ and 25 patients (26.3%) were CK5/6-. Of 95 patients, 47 were in the TL group and 48 in the TE group. The tpCR rate in the TL group was 46.8% (22/47), which was significantly higher than that in the TE group (22.9% (11/48); odds ratio (OR) = 2.960, 95% confidence interval (CI) = 1.223–7.164, P = 0.016). The ORR in the TL group was 95.7% (45/47), which was significantly higher than that in the TE group (75.0% (36/48); OR = 27.500, 95% CI = 1.576–35.683, P = 0.011). The prevalence of grade III/IV neutropenia in the TE group was 41.0% (9/22), which was significantly higher than that in the TL group (7.7% (2/26); OR = 8.308, 95% CI = 1.557–44.320, P = 0.013). There was no significant difference in the prevalence of other adverse reactions between the two groups. **Conclusions:** In the neoadjuvant treatment of TNBC, the TL regimen had a higher tpCR rate and ORR than those of the TE regimen, and was safer. Clinical trial information: ChiCTR1900023776. Research Sponsor: None.

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Poster Session

Use of PLR and NLR to evaluate the efficacy and prognosis of neoadjuvant chemotherapy with lobaplatin in triple-negative breast cancer. *First Author: Cheng Wang, Southwest Hospital, Army Medical University, Chongqing, China*

Background: Previously, we showed that addition of lobaplatin (L) to taxane (T) combined with anthracycline (E) could improve the pathological complete response (pCR) rate of neoadjuvant therapy for triple-negative breast cancer (TNBC) and lengthen long-term survival significantly, but the therapeutic markers of this regimen are not known. We investigated if the platelet/lymphocyte ratio (PLR) and neutrophil/lymphocyte ratio (NLR) could be used to predict the efficacy of the TEL regimen. **Methods:** Eighty-three patients with TNBC (stage I–III) who received TEL (docetaxel (T) at 75 mg/m², epirubicin (E) at 80 mg/m², and lobaplatin (L) at 30 mg/m²) from January 2014 to August 2019 were recruited. They received four cycles before surgery and two cycles after surgery. Patients were divided into four groups according to the mean values of the PLR (145.71) and NLR (2.74): high PLR (PLR+), low PLR (PLR−), high NLR (NLR+), and low NLR (NLR−). Differences in the total pathological complete response (tpCR) rate, event-free survival (EFS), and overall survival (OS) were analyzed in different groups of patients using the TEL protocol. **Results:** The tpCR rate in the PLR+ group was 49.0% (25/51), which was significantly higher than that in the PLR− group (25.0% (8/32); odds ratio (OR) = 2.885, 95% confidence interval (CI) = 1.093–7.612, P = 0.032). The tpCR rate in the NLR+ group was 49.1% (26/53), which was significantly higher than that in the NLR− group (23.3% (7/30); OR = 3.164, 95% CI = 1.161–8.626, P = 0.024). The tpCR rate of the PLR+ group was 53.7% (22/41), which was significantly higher than that of the PLR+/NLR+ group (26.1% (11/42), with a high proportion of any index (OR = 3.263, 95% CI = 1.298–8.204, P = 0.012). The median duration of follow-up was 69 months. EFS and OS in the NLR+ group were significantly longer than those in the NLR− group (hazard ratio (HR) = 5.946, 95% CI = 1.526–23.169, P = 0.010 for EFS; HR = 7.803, 95% CI = 1.565–38.907, P = 0.012 for OS). Five-year EFS was 95.1% for the PLR+ group, 91.0% for the PLR+/NLR+ group, 76.0% for the PLR+/NLR− group, and 59.1% for the PLR−/NLR+ group. Compared with the PLR+/NLR+ group, patients in the PLR−/NLR− group had the longest EFS (P = 0.002). **Conclusions:** PLR and NLR could be used to predict the efficacy of neoadjuvant therapy with taxane, anthracycline, and lobaplatin regimen in TNBC, and the low-proportion group had a higher tpCR rate and a better long-term prognosis. Clinical trial information: ChiCTR-TRC-14005019. Research Sponsor: None.

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Poster Session

Neoadjuvant therapy of HER2 directed conventional dendritic cell (DC1) intratumoral (IT) therapy plus weekly paclitaxel, trastuzumab, and pertuzumab in patients with HER-2 positive breast cancer: NATASHA trial. *First Author: Hyo S. Han, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL*

Background: Early stage HER2 positive breast cancer (BC) patients (pts) are commonly treated with neoadjuvant HER2-targeted therapy. Optimizing neoadjuvant therapy by improving efficacy while reducing toxicity is a critical unmet need. IT DC1 therapy combined with an IgG1 antibody mediating ADCC drives strong anti-HER-2 CD4 Th1 responses and complete tumor regression in preclinical models. We initiated a phase I/II neoadjuvant study to explore the efficacy and immune stimulation effects of an initial 6 weeks of immunotherapy phase (IP) using IT DC1 vaccine plus trastuzumab (H) and pertuzumab (P) (as source of IgG1) followed by 12 weeks of paclitaxel (T) and HP. **Methods:** Early stage HER2+ BC pts with tumor ≥ 1 cm were eligible. Treatment included IT DC1 weekly x6 followed by paclitaxel 80 mg/m² IV weekly x 12. Trastuzumab IV every (q) 3 weeks (8 mg/kg loading dose, then 6 mg/m²) and pertuzumab IV q 3 weeks (840 mg loading dose, then 420 mg) x 6 cycles starting from day 1. Two dose levels (DL) of IT DC1 (DL1 = 50 million and DL2 = 100 million cells) were evaluated including 6 pts in each DL. Once the optimal DL is determined based on toxicities, additional 22 patients will be enrolled in expansion phase 2 trial. The primary end point of the phase 1 is the safety, immune responses (measured by ELISPOT). MRI breast was performed at the baseline, post-immunotherapy and post-chemotherapy. Here we are reporting the safety and immune correlates in phase 1 study. **Results:** Twelve pts were enrolled between 10/2021 and 10/2022. Median age was 57 (range 34–74). Nine pts had hormone receptor positive disease with clinical stage I/II/III (5/5/2) and 4 pts had node positive disease. All pts completed IP and 10 patients completed THP chemotherapy as of 2/1/2023. Radiologic response per MRI breast on pre and post-IP showed 6 partial response, 3 complete response and 3 stable disease. Nine pts underwent surgery and 6 out of 9 pts had pCR (RCB 0). The most frequently observed toxicities were chills (50%), diarrhea (42%), nausea (42%), fatigue (42%), and headache (42%). ELISPOT demonstrated a significant decrease of HER2-specific T cell response following 6 weeks of DC1 IT injections in DL2 compared to DL1. **Conclusions:** The addition of IT DC1/HP to neoadjuvant chemotherapy was well tolerated with manageable toxicities. The 100 million DC1 led to a significant decrease in peripherally circulating anti-HER2 T cell response at week 6 following IP and improved radiologic tumor responses which correlates with a higher likelihood of pCR. Data from another IT DC1 trial suggests decreased circulating HER2 responsive T cells are due to increased trafficking of reactive T cells out of circulation into the tumor possibly leading to an enhanced anti-tumor effect. Updated results including correlative biomarkers will be presented at the meeting. Clinical trial information: NCT05325632. Research Sponsor: Moffitt Cancer Center Breast Research Funding.

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Poster Session

Association between pCR, TILs, and Ki-67 at baseline and after 2 weeks in patients with triple-negative breast cancer (TNBC) treated with atezolizumab and chemotherapy +/- a preceding atezolizumab monotherapy window: A translational analysis of the neoMono trial. *First Author: Ramona Erber, Institute of Pathology, Universitätsklinikum Erlangen, Friedrich-Alexander-Universität Erlangen-Nürnberg, Comprehensive Cancer Center Erlangen-EMN (CCC ER-EMN), Erlangen, Germany*

Background: neoMono randomized patients (pts) with triple negative breast cancer (TNBC) to receive (Arm A) or not to receive (Arm B) 2-week Atezolizumab monotherapy prior to neoadjuvant 24-week Atezolizumab + chemotherapy. In prespecified interim analysis, no difference regarding pathological complete response (pCR) was observed among all pts. However, in regard to pCR rates, pts with PD-L1 positive TNBC seem to benefit from addition of the monotherapy window. Here we analyze the association between central TILs and Ki-67 at baseline (BL) / after 2 weeks (2w) and pCR. **Methods:** Ki-67 expression (% positive tumor cells) was analyzed using immunohistochemistry. Analysis of stromal TILs was performed according to the International TILs Working Group. Differences from BL at the 2w time point were denoted as Ki-67-diff and TIL-diff, respectively. Associations between pCR and BL/2w measurements were analyzed using logistic regression. Akaike information criterion (AIC) was used to evaluate goodness-of-fit between models. Since the a priori chosen biomarker thresholds (< 30% [Ki-67] and < 60% [TILs]) resulted in very low subgroup sizes, k-means clustering analysis was performed and association of the cluster labels with pCR was then investigated. **Results:** The analysis included 50 (Arm A) and 51 (Arm B) pts. The threshold of Ki-67 (< 30%) was reached in 98% (BL) and 92% (2w), that of TILs (< 60%) in 11% (BL) and 18% (2w), respectively. PD-L1 (BL) was < 1 in 26%. In separate logistic regression models (including BL and change), both BL-Ki-67 and BL-TILs were significantly though moderately associated with pCR. A combined model using both biomarkers yielded the best AIC. BL-Ki-67 and BL-TILs, as well as TIL-diff were highly significantly though again moderately associated with pCR. Cluster analysis I (using BL-Ki-67, Ki-67-diff, and PD-L1) yielded cluster 1 (medium BL-Ki-67 and subsequent increase) with a pCR rate of 50% compared to 77% in cluster 2 (high BL-Ki-67 and decreasing Ki-67). Similarly, cluster analysis II (using BL-TILs, TILs-diff and PD-L1) yielded cluster 3 (low BL-TILs/non-essential TILs change) with a low pCR rate of 55% compared to 84.4% and 85.7% for clusters 4 (low BL-TILs/substantial increase) and 5 (high BL-TILs/non-essential change), respectively. In a combined regression model of all clusters above, clusters 2 and 4 had the highest pCR probability. **Conclusions:** Our results demonstrate that while BL-Ki-67 and BL-TILs are highly informative of pCR probability, Ki-67-diff and even more so TIL-diff added further significant information. Analysis of the full neoMono dataset will allow us to investigate this association further and to potentially develop a predictive algorithm regarding pCR based on baseline and dynamic biomarkers. Research Sponsor: Roche Pharma AG.

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Poster Session

Artificial intelligence (AI) –based machine learning models (ML) for predicting pathological complete response (pCR) in patients with hormone receptor (HoR) –positive/HER2-negative early breast cancer (EBC) undergoing neoadjuvant chemotherapy (NCT): A retrospective cohort study. *First Author: Luca Mastrantonio, Medical Oncology, Comprehensive Cancer Center, Fondazione Policlinico Universitario Agostino Gemelli-IRCCS, Università Cattolica del Sacro Cuore, Roma, Italy*

Background: The rates of pCR after NCT in HoR positive/HER2 negative EBC are low. Thus, clinicians need validated, unbiased, and reliable tools to better predict pCR at individual patients' level. In this regard, AI can generate ML algorithms with these features, using clinical and pathological characteristics. **Methods:** Medical records were retrospectively retrieved for patients with EBC receiving NCT followed by surgery. Missing data were imputed using chained random forests. pCR was defined as absence of residual invasive cancer on pathological evaluation of the breast specimen and lymph nodes (ypT0/isN0). Differences between pCR and non-pCR patients were assessed using t test or chi-squared test. Eight ML models (c5.0, k-nearest neighbour, random forest [RF], neural network, support vector machine [linear/radial], boosted trees and boosted logistic regression) were trained and tuned. A stratified ten-fold cross-validation was used to prevent overfitting. Models performance was evaluated using the area under the receiver operating characteristics curve (AUC). Features importance was assessed. Disease-free survival (DFS) was evaluated using the Kaplan-Meier method and hazard ratios (HRs) using Cox regression. **Results:** 572 patients were included: 332 (58%) were pre-menopausal and median age was 49.0 (IQR 43–57); 330 (58%) were T2 and 273 (48%) were N1; 437 (76%) had a ductal adenocarcinoma and 308 (54%) were grade 3. Median estrogen and progesterone receptor (ER/PgR) expression was 90 (IQR 80–90) and 57.5 (IQR 5–90); median Ki67 was 35 (IQR 25–55) and 230 (40%) patients were HER2 zero. 565 (99%) patients received a combination of anthracyclines and taxanes; 434 (76%) received sequential and 137 (24%) concomitant CT. pCR was achieved in 87 patients (15%, 95% CI 12–18). Ten variables were included in the model: menopausal status, age, histology, grade, clinical T and N stage, ER/PgR status, Ki67 and HER2 status (zero/low). Among the evaluated models, the RF algorithm had the best performance: the AUC was 0.77 (95% CI 0.71–0.83) and sensitivity and specificity were 0.86 (95% CI 0.82–0.88) and 0.56 (95% CI 0.46–0.66). Variables with the highest importance were Ki67, ER/PgR status, age and nodal status. 511 patients were evaluable for survival: patients with pCR had a significant longer DFS compared to those who did not achieve pCR (HR 0.30; 95% CI 0.14–0.65, p = 0.002). Patients whose pCR was predicted by the model had longer DFS compared to those who pCR was not predicted (HR 0.56, 95% CI 0.21–0.87, p = 0.01). **Conclusions:** The RF-ML algorithm combining clinical and pathological characteristics has the potential to predict pCR in HoR positive/HER2 negative patients undergoing NCT, thus supporting clinicians to individualize treatment for EBC. Research Sponsor: None.

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Poster Session

Association between genomic alterations and response of triple-negative breast cancers (TNBC) to talimogene laherparepvec (TVEC) in combination with neoadjuvant chemotherapy (NACT). *First Author: Hatem Hussein Soliman, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL*

Background: TVEC is an engineered oncolytic virus (OVs) approved for the treatment of melanoma. We published a phase 1/2 trial combining TVEC with NACT in early stage TNBC demonstrating increased pathologic complete response (pCR) compared to expected rates with NACT. RNAseq was performed on 37 pretreatment samples from enrolled patients to identify potential predictive genomic alterations. **Methods:** Transcriptomic RNA sequencing analysis was performed on macrodissected tumor tissue through the Moffitt Molecular Genomics core using Illumina Truseq RNA exome kits. Read adapters were detected using BBMerge (v37.88) and removed with cutadapt (v1.8.1). For gene expression analysis, processed raw reads were aligned to human genome HG19 using STAR (v2.5.3a). Gene expression was evaluated as read count at gene level with HTSeq (v0.6.1) and Gencode gene model v19. Gene expression data were normalized and differential expression between experimental groups were evaluated using DESeq2 (v1.38.2). Ensembl was used for SNP data search. **Results:** Tumor mutation burden was not significantly different between pCR and non-pCR samples (median 227 vs 222 mut/MB, $p = .11$). Top 5 upregulated non-immunoglobulin genes associated with pCR in baseline samples were MYBL1, DNAH8, NR2E1, FGFR2, and SLC12A1 ($FDR < 1\%$). A single nucleotide polymorphism (SNP) of the EIF2A gene (c.C290G, p.T97S) was the top variant associated with response present in 21/37 samples (non-pCR = 17/21 vs. pCR = 4/21, $FDR = < 1\%$). This exon 4 coding region SNP is present in 17% of Black, 35% of White, and 46% of Asian individuals but its biologic or clinical significance is unknown. Lower EIF2A pathway activation was associated with inferior response to therapy. Additional data will be presented at the meeting. **Conclusions:** Genomic alterations including a EIF2A SNP were correlated with response to OV plus NAC in TNBC. EIF2A is an important mediator of cellular responses to OV and may play a role in susceptibility to oncolysis. Additional investigation and validation of these variations in experimental models of OV susceptibility may provide predictive biomarkers for TNBC patients treated with OV plus NAC therapy. Clinical trial information: NCT02779855. Research Sponsor: Amgen.

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Poster Session

Association of HER2/CEP17 ratio with pCR after HER2-directed neoadjuvant treatments in the phase III NeoALTTO trial. *First Author: Christian F. Singer, Klinische Abteilung für Allgemeine Gynäkologie und Gynäkologische Onkologie, Comprehensive Cancer Center - Universitätsklinik für Frauenheilkunde Medizinische Universität Wien / AKH, Wien, Vienna, Austria*

Background: HER2-directed therapies are approved for the treatment of patients with HER2-positive invasive breast cancer as defined by HER2 protein overexpression, or HER2 gene amplification based on HER2/chromosome enumeration probe (CEP17) ratio ≥ 2.2 . Above this accepted HER2 status determination, however, it is still unknown whether the efficacy of HER2-directed therapy in early breast cancer increases with increasing HER2/CEP17 ratios. Therefore, the purpose of the presented work is to evaluate whether quantitative assessment of the HER2/CEP17 ratio predicts pathological complete response (pCR) and event-free survival (EFS) of patients treated with neo-adjuvant HER2-based regimen in the prospective phase III NeoALTTO trial. **Methods:** 455 women with HER2-positive early breast cancer, who had received neo-adjuvant trastuzumab and/or lapatinib for 6 weeks and then together with 12 cycles of weekly paclitaxel were included in this analysis. The HER2/CEP17 ratio in the primary tumor samples was correlated with pCR and survival outcome. **Results:** The Median HER2/CEP17 ratio in NeoALTTO was 5.1 (range: 1.1 – 100.0), and ratios were not associated with age, hormone receptor status, or any of the other clinicopathological variables analyzed. The log HER2/CEP17 ratio significantly predicted for pCR in both uni-variate (OR: 1.83; 95% CI: 1.11 - 3.01, $p = 0.0176$) and multivariate analysis (OR: 1.79; 95% CI: 1.07 - 2.99, $p = 0.0257$). Higher HER2/CEP17 ratios were, however, not associated with improved EFS (adjusted HR = 0.79; $p = 0.3537$). A pCR prediction model which included HER2/CEP17 ratio, treatment arm, and hormone receptor status improved the predictive strength of treatment arm alone from a ROC AUC value of 0.60 to 0.69. **Conclusions:** In patients treated with HER2-based neoadjuvant therapy, quantitative analysis of the readily available pre-treatment HER2/CEP17 ratio by FISH is predictive of pCR but not EFS. Research Sponsor: The NeoALTTO trial received financial support from GlaxoSmithKline (until January 2015) and Novartis Pharma AG (as of January 2015).

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Poster Session

Longitudinal MRI-based fusion novel model to predict pathological complete response in breast cancer treated with neoadjuvant chemotherapy: A multi-center, retrospective study. *First Author: Kun Wang, Department of Breast Cancer, Cancer Center, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, Guangzhou, China*

Background: Accurate identification of pCR to neoadjuvant chemotherapy (NAC) is important for determining appropriate surgery strategy and guiding the resection extent in breast cancer. However, a non-invasive tool to predict pCR accurately is lacking. Our study aims to develop ensemble learning models using longitudinal multiparametric MRI to predict pCR for each molecular subtype of breast cancer. **Methods:** In this study, all patients underwent pre-NAC and post-NAC MRI examinations, and we collected multiparametric MRI sequences. Post-operation pathologic results were used to determine the pathologic complete response (pCR). We extracted 14676 radiomics and 4096 deep learning features and calculated a set of additional delta-value features. Then in the primary cohort ($n = 409$), inter-class correlation coefficient test, U-test, Boruta and the least absolute shrinkage and selection operator (LASSO) regression were used to select the most optimal feature set for each subtype of breast cancer. Finally, 20, 15 and 13 features were selected to construct the models based on 5 specific algorithms with cross-validation method for predicting pCR in HR+/HER2-, HER2+ and TNBC subtypes. The ensemble learning strategy was used to integrate the single-modality models outputs and improve the prediction performance. The diagnostic performances of models were evaluated in the three external cohorts with larger sample size of patients ($n = 343, 170$ and 340 , respectively). **Results:** A total of 1262 patients with breast cancer from four centers were enrolled in this study, and pCR rates were 10.6% (52/491), 54.3% (323/595) and 37.5% (66/176) in HR+/HER2-, HER2+ and TNBC subtype. After model development, the Multi-Layer Perception (MLP) neural network yields the best diagnostic performances in all subtypes and feature sets. In the three subtypes, the stacking model integrating pre-, post- and delta- models yielded the highest AUCs of 0.959, 0.974 and 0.958 in the primary cohort, and AUCs of 0.882-0.908, 0.896-0.929 and 0.837-0.901 in the three external validation cohorts, respectively. In all subtypes, the stacking model had accuracies of 85.0%-88.9%, sensitivities of 80.0%-86.3%, and specificities of 87.4%-91.5% in the external validation cohorts. **Conclusions:** Our study established a novel tool to predict the responses of breast cancer to NAC and achieve excellent performance. The models could help to determine post-NAC surgery strategy for patients with breast cancer. Research Sponsor: National Science Foundation of China (82171898).

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Poster Session

Circulating tumor DNA (ctDNA) monitoring in patients with breast cancer receiving neoadjuvant palbociclib and endocrine therapy: A secondary analysis of the NeoRHEA phase 2 study. *First Author: Alexandra Stanciu, Institut Jules Bordet, Bruxelles, Belgium*

Background: Personalized circulating tumor DNA (ctDNA) assays are being evaluated in early breast cancer (BC). We investigated the value of ctDNA monitoring in the NeoRHEA study. **Methods:** NeoRhea (NCT03065621) is a single arm phase 2 study in which patients with estrogen receptor (ER)+/HER2- early breast cancer were treated with neoadjuvant palbociclib + endocrine therapy (ET) for 4 months. Plasma samples were collected at four timepoints: pre-treatment (BL), after the first treatment cycle (C1D28), before surgery (Surgery) and one month post Surgery (End of Study). ctDNA detection was evaluated using the personalized RaDaR assay. Whole-exome sequencing (WES) was performed on BL tumor biopsies followed by a personalized assay development using tumor, plasma and normal DNA in order to track up to 48-patient specific somatic variants in plasma cell-free DNA (cfDNA) using next generation sequencing. Associations between ctDNA detection and BL clinical-pathological characteristics, cell cycle arrest (CCA) defined as Ki67 $\leq 2.7\%$ at surgery, residual cancer burden (RCB) rate and breast cancer free survival (BCFS) were investigated. **Results:** Of 100 patients enrolled, 78 patients and 302 plasma samples were successfully profiled by the RaDaR assay. The number of variants targeted by the assay ranged between 7-48 (median = 25). The median estimated variant allele fraction for ctDNA positive samples was 0.02% (range 0.0009%-0.91%). A total of 42/76 patients were ctDNA positive at BL, 4/76 at C1D28, 4/75 at Surgery and 0/75 at End of Study. Out of 78 patients, 68% were postmenopausal, 78 % had cT2 and 69% cN0 tumors, 20% had multifocal/multicentric tumors, 18% had histological grade 3 tumors, 76% had CCA (Ki67 not available in 20 patients) and 34% RCB 3 at surgery. ctDNA detection at BL was higher in histological grade 3 tumors ($p = 0.03$), lower in multifocal/multicentric tumors ($p = 0.01$), higher in RCB III tumors, ($p = 0.01$) but was not associated with CCA. With a median follow-up of 3.8 years (range 1-5 years), 4 patients developed distant and one patient locoregional recurrences. ctDNA detection after one month of treatment (logrank $p = 0.02$), but not at baseline ($p = 0.59$) nor at surgery ($p = 0.67$) was associated with worse BCFS. **Conclusions:** Detection of ctDNA in early-stage breast cancer is challenging. Our data suggests association of ctDNA detection with some pathological and clinical variables. Independent validation is needed. Clinical trial information: NCT03065621. Research Sponsor: Pfizer; INIVATA; Les Amis de l'Institut J. Bordet; F.N.R.S.

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Poster Session

Neoadjuvant tislelizumab plus nab-paclitaxel and carboplatin followed by adjuvant tislelizumab in patients with early triple-negative breast cancer. *First Author: Zefei Jiang, Department of Breast Oncology, The Fifth Medical Center of Chinese PLA General Hospital, Beijing, China*

Background: Triple-negative breast cancer (TNBC) is the subtype with the least favorable outcomes. However, TNBC is associated with higher immune cell abundance than other subtypes, making it a good candidate for immunotherapy. Neoadjuvant chemotherapy is the preferred treatment approach for early TNBC. Emerging evidence shows that additional immune checkpoint inhibitors (ICI) in neoadjuvant therapy significantly increases pathological complete response (pCR) and event-free survival in early TNBC. Treatment regimens of paclitaxel and carboplatin (TP) is class I recommendation for TNBC neoadjuvant therapy, the application of ICI with TP regimens is worth exploring. **Methods:** In this multicenter, open-label, phase II study, patients with untreated, histologically confirmed TNBC in stage II-III (per AJCC 8th edition) were enrolled. Patients received six cycles of neoadjuvant therapy with tislelizumab at 200 mg once every 3 weeks plus nab-paclitaxel (125 mg/m² on days 1 and 8) and carboplatin (at a dose based on an area under the concentration 2 on days 1 and 8) every 3 weeks. Patients who either completed or discontinued the neoadjuvant treatment would undergo definitive surgery. After surgery, the patients received adjuvant tislelizumab every 3 weeks for up to 12 cycles. The primary endpoint was the rate of pCR (ypT0/Tis ypN0). The secondary endpoints included 1-, 2-, 3-year event free survival rates and overall survival rates. Based on the Simon's Two-Stage design, if > 13 of 32 patients achieved pCR, the enrollment would proceed to full accrual of 62 patients as planned. If > 29 of 62 patients achieved pCR, we would deem the study to have met the primary endpoint. **Results:** From Mar 2021 to Jan 2022, 32 patients were enrolled; 18 of them achieved pCR, and therefore the study proceeded to complete the enrollment of 62 patients. At the data cut-off of Oct 13, 2022, 62 patients were enrolled, among which 50 patients received neoadjuvant treatment and underwent definitive surgery. The median age was 50 years. 36 (72.0%) patients had stage II breast cancer at diagnosis. 31 of the 50 patients achieved pCR (ypT0/Tis ypN0), and the pCR rate was 62.0% (95% CI, 47.2-75.4). Patients with immune cell PD-L1 expression ≥ 10% had numerically higher pCR rate (81.8% vs 53.6%) than those with PD-L1 expression < 10%. All 50 (100%) patients reported any grade of neoadjuvant treatment-related adverse events (TRAEs). Grade ≥ 3 TRAEs occurred in 27 (54%) patients. The rate of immune-related adverse events (irAEs) was 34% (17/50), with the common occurring (10%) irAE of hypothyroidism (n = 8, 16%). 2 (4.9%) patients experienced grade ≥ 3 irAEs. Severe adverse events were reported in 5 (10%) patients. **Conclusions:** The study has met its primary endpoint. Tislelizumab plus nab-paclitaxel and carboplatin achieved a higher pCR and was generally well tolerated in the neoadjuvant treatment of early TNBC. Clinical trial information: ChiCTR2100041675. Research Sponsor: This study was supported by BeiGene (Beijing) Co., Ltd.

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Poster Session

NeolRX trial: Immunologic induction with peri-lymphatic cytokines to enhance pembrolizumab (pembro) response in stage II/III triple-negative breast cancer (TNBC). *First Author: David B. Page, Providence Cancer Institute, Portland, OR*

Background: The addition of pembro to neoadjuvant chemotherapy (NACT) improves pathological complete response (pCR) rate and recurrence-free survival in stage II/III TNBC, albeit with substantial chemotherapy-attributed toxicity. We hypothesize that locoregional cytokine therapy could be combined with pembro to optimize immune response and clinical outcome. In a phase Ib early-stage breast cancer trial, we previously demonstrated that peri-lymphatic cytokine injection (IRX-2 regimen, comprised of physiologic doses of IL-2, IFN γ , and other cytokines derived from activated donor lymphocytes, given with low-dose cyclophosphamide) is well tolerated and associated with increased intratumoral lymphocytes, T-cell activation, and PD-L1 expression. Here, we report preliminary outcomes of neolRX, a phase II trial evaluating induction IRX-2 + pembro preceding NACT + pembro. **Methods:** Subjects with stage II/III TNBC were randomized to receive induction pembrolizumab (all subjects: 200mg IV) +/- peri-areolar IRX-2 (IRX-2 arm: 1 ml SQ x2 daily for 10 days + cyclophosphamide 300 mg/m² IV x 1) preceding initiation of NACT + pembro. The primary endpoint was pCR rate following NACT + pembro (n = 15 subjects/arm planned); secondary endpoints were safety and tolerability. We explored post-induction/pre-NACT radiographic (ultrasound) and histologic outcomes (TILs, tumor regression) as a biomarker strategy to predict pCR. **Results:** The trial terminated after n = 12 subjects due to withdrawal of drug support for IRX-2. The IRX-2 arm achieved 83% pCR (n = 5/6, CI 36-100%) compared to 33% pCR with pembro alone (n = 2/6, CI 4-78%). The regimen was well-tolerated with minimal IRX-2-attributed toxicities (67% grade I skin bruise). Toxicities during NACT + pembro were similar to Keynote-522. 67% (n = 4/6) of IRX-2 subjects experienced week 3 radiographic regression, with evidence of brisk lymphocyte infiltration on week 3 biopsy, and with 100% pCR rate (n = 4/4) following NACT + pembro. n = 2/6 subjects receiving pembro+IRX-2 experienced pCR on week 3 biopsy, versus n = 0/3 evaluable in control arm. **Conclusions:** Induction IRX-2 + pembro is well tolerated and is associated with encouraging outcomes, supporting further study of peri-lymphatic induction cytokine therapy in stage II/III TNBC. Post-induction radiographic and histologic outcomes may identify patients with immune-responsive tumors, for whom NACT de-escalation may be a promising therapeutic approach to mitigate toxicity. Clinical trial information: NCT04373031. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc.; Brooklyn Immunotherapeutics.

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Poster Session

Neoadjuvant single-dose trilaciclib prior to combination chemotherapy in patients with early triple-negative breast cancer: Safety, efficacy, and immune correlate data from a phase 2 study. *First Author: Jeremy Meyer Force, Department of Medicine, Duke University, Durham, NC*

Background: Trilaciclib, an intravenous CDK4/6 inhibitor, induces transient G1 cell cycle arrest. In preclinical studies, trilaciclib demonstrated immune-modulating effects by enhancing T-cell activation, favorably altering the tumor microenvironment (TME), and improving long-term immune surveillance. Preliminary data from this phase 2, single-arm, open-label study of neoadjuvant trilaciclib in triple-negative breast cancer (TNBC; NCT05112536) showed that single-dose trilaciclib increased CD8+ T-cell/Treg ratios within the TME. Here, we combine immune analysis with clinical outcomes to identify correlates of treatment response. **Methods:** Patients (pts) with early-stage TNBC received single-dose trilaciclib followed by trilaciclib + dose-dense anthracycline/cyclophosphamide and taxane (AC/T). Per investigator discretion, pts received pembrolizumab (pembro) 400 mg Q6W from cycle 1 and/or carboplatin (carbo) AUC 1.5 QW from cycle 5. Tumor biopsies and blood samples were collected prior to treatment, 7 days post single-dose trilaciclib, and during surgery, with an additional blood sample at cycle 2. PD-L1 status was assessed per Ventana SP142 assay (positive immune cell score ≥ 1%). The primary objective is to evaluate the immune-based mechanism of action of single-dose trilaciclib. **Results:** As of January 3, 2023, 18/24 pts had completed treatment and/or had definitive surgery; 1 pt with neuroendocrine features discontinued due to disease progression. Median age was 57 years. At diagnosis, 79% of pts had stage II tumors (88% with ductal carcinoma; 38% with PD-L1+ tumors). 18 pts received pembro + carbo, 3 pts pembro only, and 3 pts carbo only. Common treatment-related adverse events (TRAEs) were fatigue (79%), nausea, (67%), alopecia (67%), and neutropenia events (63%); 42% of pts had grade 3/4 neutropenia events. 4 serious TRAEs occurred in 2 (8%) pts: pembro-related colitis and hypertransaminasemia, trilaciclib/paclitaxel-related urosepsis, and AC-related febrile neutropenia. Response data were available for 15 pts; pathological complete response (pCR) was observed in 7 (47%) pts, with pCR rates of 86% vs 13% for pts with PD-L1+ vs PD-L1- tumors, respectively. Immune analysis of the TME post trilaciclib monotherapy demonstrated several pCR-related features, such as increased stromal tumor-infiltrating lymphocytes and granzyme B+ cells. Correlative blood analysis revealed increased circulating baseline CD8+ T cells in pts achieving pCR. **Conclusions:** Safety and tolerability data are encouraging for trilaciclib in combination with AC/T ± pembrolizumab ± carboplatin in the neoadjuvant setting for early-stage TNBC. Preliminary efficacy data align with standard neoadjuvant chemotherapy regimens. Final pCR data from all pts and immune correlates from tumor and blood samples will be presented. Clinical trial information: NCT05112536. Research Sponsor: G1 Therapeutics, Inc.

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Poster Session

Moderate physical exercise and immune system modulation in patients with breast cancer treated with neoadjuvant chemotherapy. *First Author: Ornella Garrone, Medical Oncology Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy*

Background: The link between physical activity (PA) and immune system is known. However, are not clearly understood which mechanisms are activated by PA. We investigated the effect of moderate PA (MPA), on a panel of circulating cytokines during neoadjuvant chemotherapy (CT) in patients (pts) with breast cancer. **Methods:** Pts received sequential epirubicin and cyclophosphamide for 4 cycles followed by weekly paclitaxel ± trastuzumab. MPA consisted of Nordic or fit walking, 3 workouts/week, 1 hour each, in the 9 weeks before Surgery (S). Blood samples were collected in pts underwent MPA (TR) and in a group of pts who declined MPA (UN) at baseline (T0), at day 1 of week 6 of paclitaxel (starting MPA) (T1) and before S (T2). At each time point the level of 22 cytokines (IL1b, IL2, IL4, IL5, IL6, IL7, IL8, IL10, IL12, IL13, IL15, IL17a, IL18, IL21, CCL2, CCL4, CXCL10, CCL22, IFN γ , TGF β , TNF α , VEGF) was measured using Simple Plex Ella. Sample size was calculated using effect size method considering a Cohen's d of 0.65 as observed for a candidate cytokine (IL-6) between two groups. Considering a desired statistical power of 0.8 and a probability level of 0.05 a minimum of 78 patients were required. The difference among the median value of cytokines was analysed using non parametric Mann Whitney U test. Comparisons between time points in the same group were analysed with Wilcoxon signed-rank test. **Results:** Accrual is completed. 61 pts were TR and 20 UN. Main patients' characteristics are listed. At T0 IL4, IL17, IL18 and VEGF level was significantly higher in UN respect to TR pts. At T1 IL4, IL17 and IL18 level remained significantly higher in UN pts. At T2, UN pts showed significantly higher value of IL4, IL6, IL7, IL8, IL17, IL18 VEGF and TGF β . IL21 was significantly higher in TR pts. Longitudinal analysis between T0 and T1 in TR and UN pts showed significantly lower level of CCL22 and significantly higher level of IL7, IL13 and CXCL10 in TR pts and significantly higher level of IL8 in UN pts. Longitudinal analysis between T1 and T2 showed significantly higher level of IL21, CXCL10, CCL22, TNF α and significantly lower level of IFN γ , IL6, IL8, CCL2, TGF β in TR pts and significantly lower level of CXCL10 in UN pts. **Conclusions:** TR and UN pts differed modestly at baseline including acceptance of MPA. The longitudinal analysis T0-T1 showed that CT induced more evident changes in TR than in UN pts. Longitudinal analysis T1-T2 demonstrated major changes in Th1 and Th2 cytokines only in TR pts. Overall, CT induced weak changes in UN and greater changes in TR pts strengthened by the addition of MPA. These observations suggest a more efficient immune system in TR pts and a possible additional benefit derived from MPA. Research Sponsor: GONO Foundation; ARCO Foundation.

Patients Characteristics	TR (61)	UN (20)
Median age, yrs (range)	53 (34 – 76)	56 (43 – 75)
HR +/-	41/20	14/6
Her2 +/-	27/34	5/15
T3	11	6
Median BMI (range)	24.5 (17.3 – 38.0)	24.6 (17.5 – 44.1)

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Poster Session

Prospective evaluation of pathologic response with neoadjuvant chemo-immunotherapy in metaplastic breast cancer. *First Author: Nour Abuha-dra, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Metaplastic breast cancer (MpBC) is a rare aggressive histologic type of breast cancer that is often resistant to standard chemotherapy with pathologic complete response (pCR) rates ranging between 2-23%. PDL1 expression has been reported in up to 95% of primary MpBCs suggesting that response rates may be improved with addition of immune checkpoint blockade (ICB). Here we evaluate pCR rates (ypT0/is ypN0) in stage I-III MpBCs receiving neoadjuvant chemo-immunotherapy (NAT). **Methods:** The Memorial Sloan Kettering Cancer Center Rare Breast Cancer Program (CARE-4-RARE) is a new clinical and translational program dedicated to the study of rare breast cancers. Since the start of the program, 15 patients (pts) with early-stage MpBC have completed treatment with the neo-adjuvant KEYNOTE-522 regimen. Wilcoxon rank-sum and Fisher's exact tests were used to compare characteristics according to pCR status. All statistical tests used a significance level of 5%. **Results:** Median age at diagnosis was 50 (range, 43-60). All pts were female, 13% self-identified as Asians, 33% as Black and 53% as White. All tumors were poorly differentiated and of triple-negative phenotype, median tumor size was 3.2cm, 80% had stage II disease and 20% were clinically node positive. Metaplastic subtypes included 5 matrix-producing (33%), 3 spindle (20%), 4 squamous (27%), 3 mixed (20%). Of the 15 pts, 4 (27%) achieved a pCR, which suggest the possibility of a higher than expected pCR rate in MpBC with the addition of ICB to chemotherapy. We did not observe a significant difference in clinico-pathological features between pCR vs. non-pCR groups. We observed numerical differences in pCR between MpBC subtypes though the p-value was not significant due to limited sample size. Of these 4 pts, 2 had matrix-producing and 2 had mixed subtypes. Two pts with pCR only received Cb+P+Pem. Three pts (20%) experienced PD (squamous n = 2, spindle n = 1) necessitating discontinuation of NAT and expediting surgery. **Conclusions:** This is the first prospective study to evaluate neoadjuvant ICB in MpBC. These data suggest the possibility of a higher than expected pCR rate in MpBC with the addition of ICB to chemotherapy (27%). This work suggests that neoadjuvant ICB should be considered in MpBC with close monitoring. Notably, 50% of reported pCR in this cohort were in pts who only received Cb+P+Pem. In spite of improved pCR rates, 20% of pts progressed during NAT highlighting the need for better treatment strategies in this treatment-refractory subset of MpBC and close monitoring to allow resection before progression to inoperability. The dichotomy in responses to ICB (super-responsive vs. super-refractory) may suggest the presence of unique biomarkers for immune response in MpBC. By the 2023 ASCO Annual Meeting a total of 26 pts will have completed NAT; we will report updated outcomes along with correlative immune biomarkers (sTIL, PDL1, TMB). Research Sponsor: None.

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Poster Session

Association of biophysics-based biomarker with tumor volumetric response in breast cancer treated with immunotherapy. *First Author: Daniel Cook, SimBioSys, Inc., Chicago, IL*

Background: The treatment landscape of triple negative breast cancer (TNBC) has rapidly changed in recent years, with immuno-oncology (IO) therapies, such as immune checkpoint inhibitors, leading to improvement in patient outcomes. However, the number of patients who benefit is less than 15%, and the therapy itself can prompt severe immune-related adverse events. Breast cancer tumor volume measurements derived from magnetic resonance imaging (MRI) have proven to be a strong predictor of outcome (survival) in patients who either achieve pathological complete response (pCR) or have residual cancer burden (RCB) (ACRIN6657/CALGB150007 I-SPY1). Using an integrative computational approach, we developed both the *TumorIO* biomarker and the *TumorIO Score* to predict response to IO therapy in breast cancer patients. Here, we assess the volumetric response in IO-treated patients and its relationship with the *TumorIO Score*. **Methods:** We assessed the relationship between breast tumor volumetric response to IO therapy and the *TumorIO Score*, a previously developed metric that relates probability of IO responsiveness to spatially-resolved tumor biology. We grouped patients into *TumorIO Score* high vs. low populations, and compared final volumes assessed by MRI and percent response to therapy between groups. **Results:** We analyzed the volumetric response of IO-treated patients from the I-SPY2 trial and from an independent cohort (total n = 67). Over 96% of the IO-treated patients in the I-SPY2 trial (n = 55) had a greater than 90% volumetric response, while in the independent cohort (n = 12) only 50% of patients had greater than 90% volumetric response. Across both cohorts, 95.8% of patients with a high *TumorIO Score* achieved > 90% reduction in tumor volume. Additionally, we identified three patients in our cohort that appeared not to respond to IO therapy, who were later classified as progressor, pseudo-progressor, and non-responder patients. The *TumorIO* biomarker was able to differentiate these three patients, as it associates a unique distinctive biological phenomenon with either response or lack of response. **Conclusions:** The *TumorIO Score* provides a novel technology to address several challenges in neoadjuvant IO therapy, namely: predicting which patients are likely to have pCR in response to IO therapy, as well as identifying patients likely to have a substantial volumetric response to IO. Additionally, this method may facilitate sub-categorizing patients likely to show radiological pseudo-progression prior to IO administration, although a larger cohort is needed to validate these findings. Research Sponsor: SimBioSys, Inc.

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Poster Session

A prospective, phase II, neoadjuvant clinical study based on chemotherapy sensitivity in hormone receptor-positive, HER2-negative breast cancer: FINEST study. *First Author: Li Chen, Fudan University Shanghai Cancer Center, Shanghai, China*

Background: Neoadjuvant therapy for hormone receptor positive/HER2-negative breast cancer presents challenges in patient selection and treatment modalities. Chemotherapy and endocrine therapy are neoadjuvant options for this type of breast cancer. Neoadjuvant endocrine therapy (NET) has a similar response rate to chemotherapy. However, patient selection is a key factor. We designed this study to further optimize the selection of target population and treatment strategy. **Methods:** For breast cancer patients eligible for inclusion, patients were allocated to 2 cycles of chemotherapy using nab-paclitaxel with carboplatin. For patients with better efficacy ($\geq 40\%$ regression after 2 cycles), the original regimen was continued to complete 6 cycles (group A). For patients who had poor efficacy ($< 40\%$ regression after 2 cycles), patients were randomly assigned (1:3:1) to group B, C, D. Group B continued to use the same chemotherapy. Group C were received palidiciclib, letrozole and adebrelmab plus goserelin if patient was premenopausal. Group D were directly received surgery. Primary endpoints were pathologic complete response (pCR) rate and objective response rate (ORR). As the trial progresses, according to Bayesian model, the posterior distribution of pCR rates of group C would be updated. To explore the genomic feature, a genetic panel which includes 484 genes that are targets of approved and experimental therapies and frequently mutated genes in breast cancer was used. **Results:** From Nov 16, 2020 to Jun 10, 2022, 121 patients were enrolled. 76 patients with better efficacy were continued to complete 6 cycles (group A). And 45 patients were randomly assigned to groups C (27 patients), B (9 patients) and D (9 patients). The primary objective was not met. The total pCR rate was 4.1% (5/121) with all pCR patients are in group A. No significant differences were observed in pCR between group B, C and D. ORR was 81.8% in total cohort with 100% in group A, 20% in group B, 81.5% in group C and 0% in group D, respectively. Decreases in Ki-67 were similar across arms. According to the Bayesian model, there is no probability of success of phase 3 study. Therefore, the study was closed. Our analysis illustrated the most prevalent mutations were PIK3CA (41%), followed by TP53 (28%) and GATA3 (17%). We found that AKAP3, ASXL1, INSR, RET or TBX3 mutations were related to the limited treatment benefit of chemotherapy. Mutations in MAP3K1 were likely to be associated with the worse outcome in Group C. **Conclusions:** Neoadjuvant chemotherapy and neoadjuvant endocrine therapy are not mutually exclusive. The overall treatment strategy did not improve the efficacy, but there is still a possibility that some people can get an improvement from the strategy adjustment. Precision analysis may yield the characteristics of patients who would benefit from this shift in treatment strategy. Clinical trial information: NCT04215003. Research Sponsor: Jiangsu Hengrui Pharmaceuticals Co. Ltd. China.

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Poster Session

Whole-genome sequencing based assessment of HER2 focal amplification for precision oncology of breast cancers. *First Author: Ryul Kim, Genome Insight Inc., San Diego, CA*

Background: Focal oncogene amplification confers a growth advantage to tumor cells and drives cancer evolution. Herein, we aimed to explore focally amplified HER2 in breast carcinomas. **Methods:** We performed whole genome sequencing (WGS) and whole-transcriptome sequencing (WTS) in 787 breast cancer samples. HER2 focal amplification was defined as having a segment length less than 3Mbp and ≥ 4 higher copy number than the surrounding region. **Results:** Most of the patients were premenopausal women (n = 574, 72.9%) with a median age of 37 (range 21-76) years. We identified 57 (58.8%) and 27 (5.0%) samples with HER2 focal amplification in HER2-positive (n = 97) and even HER2-negative (n = 536) by immunohistochemistry (IHC) and in-situ hybridization (ISH) according to ASCO guideline for breast cancer, respectively. Regardless of HER2-positivity, HER2 focal amplification was significantly associated with higher HER2 RNA expression. Among 28 patients who received six cycles of docetaxel/carboplatin/trastuzumab/pertuzumab neoadjuvant therapy followed by curative surgery, 21 patients had HER2 focal amplification and 14 (66.7%) achieved pathologic complete remission (pCR). Intriguingly, all patients without HER2 focal amplification (n = 7) failed to achieve pCR. HER2 focal amplification showed enrichment of TP53 mutations (OR 0.245, q < 0.001), but was mutually exclusive with GATA3 mutations (OR 2.82, q = 0.055). The mutational spectrums suggested that the activity in APOBEC family of cytidine deaminases were responsible for the somatic single-nucleotide variants of breast cancer with HER2 focal amplification. Compared to samples without HER2 focal amplification, samples with HER2 focal amplification were less likely to have defective homologous recombination DNA repair pathway. HER focal amplifications were closely associated with various types of structural variations. Translocation partners of HER2 were widespread across the entire genome with notable exceptions on chromosome 2, and most of them were close to super-enhancers implying enhancer hijacking as one of mechanisms of HER2 overexpression. Breast cancers with or without HER2 focal amplification showed distinct RNA expression patterns. Notably, activity of genes involved in doxorubicin-resistance and AKT1 signaling were significantly associated with HER2 focal amplification. **Conclusions:** Our analysis demonstrates that WGS enables better classification of the HER2 amplification status in breast cancer than IHC with ISH, suggesting WGS as a sensitive tool for screening breast cancers for anti-HER2-targeted therapies. Research Sponsor: None.

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Poster Session

Social determinants of health and utilization of neoadjuvant chemotherapy in patients with triple negative breast cancer (TNBC) in the community oncology setting. *First Author: Michael A. Danso, US Oncology Network/Virginia Oncology Associates, Norfolk and Virginia Beach, VA*

Background: TNBC has a higher incidence in African American women compared to European American, often presents at a younger age or more advanced stage, and is associated with worse outcomes. The use of multi-agent neoadjuvant chemotherapy (NC) improves event-free survival and overall survival in patients with early-stage TNBC and is considered standard of care. Race and other social determinants of health (SDOH) have been shown to affect outcomes in patients with TNBC. Differences in use of NC associated with SDOH may be a contributing factor to inferior outcomes. The aim of this study is to determine if SDOH measures affect utilization of NC in patients with early-stage TNBC. **Methods:** This retrospective observational cross-sectional study examined patient profiles, treatment patterns and SDOH indicators among patients newly diagnosed with early-stage breast cancer in The US Oncology Network. Using iKnowMed EHR data, patients diagnosed with TNBC between 03/31/2017 and 09/30/2021 with stages II-IIIb disease or tumor size ≥ 2 cm (T2 or higher) were included. The initial TNBC diagnosis date was used as the index date for each patient and records were assessed from 6 months pre- to 6 months post-diagnosis for NC initiation, baseline characteristics, and social determinants, including Area Deprivation Index (ADI), a validated measure of socioeconomic status. **Results:** 3321 patients with TNBC were identified, with a mean age of 58 years; 59% were White, 15% Black, 3% Asian, and 23% other/unknown; and 2139 (64%) received NC. Patients who received NC relative to those who did not were younger (mean 55.9 vs 61.8; $p=0.001$), had higher BMIs (70% with BMI >25 vs ≤ 25 , $p=0.045$), and had commercial or Medicaid insurance (67.5% with commercial insurance or Medicaid vs. 52.5% with Medicare; $p=0.001$). Regional differences were observed, with proportionally fewer patients receiving neoadjuvant chemotherapy in the south US census regions and more in the west. There was no difference in NC use in Black vs White patients (66% vs 64%). No significant differences in receipt of NC were found for race, ethnicity, or ADI. **Conclusions:** In the community oncology setting, we did not observe inequities in the use of NC based on social determinants analyzed in this study, such as race, ethnicity, and ADI. Poorer outcomes observed in Black patients with TNBC may not be a result of underutilization of NC. Research Sponsor: None.

LBA612

Poster Session

Oral paclitaxel and dostarlimab with or without trastuzumab in early-stage, high-risk breast cancer: Results from the neoadjuvant ISPY 2 TRIAL. *First Author: Rebecca Arielle Shatsky, University of California San Diego Medical Center, La Jolla, CA*

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2023, issue of the *Journal of Clinical Oncology*.

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Poster Session

Use of PROMIS to capture patient reported outcomes over time for patients on I-SPY2. *First Author: Saya Jacob, University of California San Francisco, San Francisco, CA*

Background: Patient reported outcomes (PROs) capture direct feedback from patients in clinical trials. The NIH Patient-Reported Outcomes Measurement Information System (PROMIS) is an open source and validated PRO platform. Data on PROMIS score trajectories over time for breast cancer patients undergoing neoadjuvant chemotherapy (NAC) are limited. **Methods:** We administered paper surveys to patients enrolled on the I-SPY2 trial, a multicenter, randomized phase 2 trial comparing novel agents to standard NAC in high-risk breast cancer. PRO domains included PROMIS Physical Function, Anxiety, Depression, Applied Cognition and Fatigue. Surveys were administered at baseline (post-consent), C1D1, inter-regimen (~12 wks into NAC), pre-surgery and at 1, 6, 12, and 24 months post-surgery. Responses were scored using the HealthMeasures Scoring Service to generate a standardized T score, with a score of 50 representing the general US population mean. Higher Anxiety, Depression and Fatigue scores represent worse symptoms; higher Physical Function and Applied Cognition scores represent better symptoms. We calculated average scores by time-point and compared changes from baseline to various grouped time points using a paired t-test. **Results:** From 1/2012 to 7/2020, 1631 patients enrolled in I-SPY 2 with 959 completing the baseline survey. 62% had at least two "on-treatment" surveys, and 52% had at least one follow-up time-point. Average baseline PROMIS scores for Physical Function, Anxiety, Depression, Applied Cognition and Fatigue were 46.7, 55.1, 47.2, 53.3 and 46.0 respectively. Between baseline and the latest on-treatment time point we observed improvement in Anxiety (-5.2) and worsening in Physical Function, Applied Cognition and Fatigue (-5.4, -6.9 and +8.2 respectively). Between baseline and the latest post-surgery time point, we saw improved Anxiety (-5.9) and worsened Physical Function, Applied Cognition and Fatigue (-5.9, -3.6 and +4.3). Depression changed minimally. **Conclusions:** Using PROMIS, patients on I-SPY2 experienced worse Physical Function, Applied Cognition and Fatigue but improved Anxiety during and after treatment compared to baseline. While changes in Applied Cognition and Fatigue recovered partially after treatment, Physical Function scores did not, suggesting potential for longer term impact on quality of life. Clinical trial information: NCT01042379. Research Sponsor: U.S. National Institutes of Health; Quantum Leap Healthcare Collaborative.

	Baseline	Cycle 1	Inter-regimen	Pre-surgery	1 Mo FU	6 Mo FU	12 Mo FU	24 Mo FU
Completed surveys for those with baseline survey	959	788	625	499	418	249	214	99
	Physical Function	Anxiety	Depression	Applied Cognition	Fatigue			
Change from baseline to latest on-treatment timepoint	15.4 P<0.0001	15.2 P<0.0001	10.2 p=0.71	16.9 P<0.0001	18.2 P<0.0001			
Change from baseline to latest post-surgery time point	15.9 P<0.0001	15.9 P<0.0001	10.1 p=0.87	13.6 P<0.0001	14.3 P<0.0001			

↑=improved; ↓=worsened.

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Poster Session

The proliferation biomarker SPAG5 expression in HER2 low and HER2 overexpression early breast cancer (BC) predicting tumour response to neoadjuvant chemotherapy (NACT) with and without trastuzumab. *First Author: Tarek Mohamed Ahmed Abdel-Fatah, Nottingham Univ City Hosp NHS Trust, Nottingham, United Kingdom*

Background: HER2 low is defined by HER2 immunohistochemistry (IHC) score 1+ or 2+ with negative fluorescent in situ hybridization (FISH-). In metastatic BC the HER2 directing antibody drug conjugates (ADCs) had shown significant efficacy; however, its curative role in early BC has not defined yet. Here we aimed to study the clinical and molecular features of HER Low in 3850 cases of early BC and its response to NACT; Anthracycline/Taxane with/without Trastuzumab to optimize its clinical utility. **Methods:** Paired sections from pre and post NACT samples of 1250 early BCs (NACT cohort) were profiled for HER2 and SPAG5 using IHC and FISH. A novel triple coloured SPAG5 HER2 Ch17 probe was used as well HER2 Ch17 probe. ASCO guidelines were followed. Pre therapy samples of 400 BC were profiled for 450 customised genes using the Nano String nCounter platform. Moreover, 2600 cases of early BC who received adjuvant non-HER2 targeted therapies (ADJ cohort) were studied. The primary end point was pathological complete response (pCR). The Secondary endpoints were relapse free survival and biomarkers changes. **Results:** HER2 low was expressed in 31% (800/2600) of ADJ and 39% (490/1250) of NACT cohorts whereas HER2 overexpression (+) (HER2 IHC+3 or IHC+2/FISH+) was detected in 21% (540/2600) and 32% (401/1250) of ADJ and NACT cohorts; respectively. Compared to those with HER2 IHC 0 expression, HER2 low was associated with more aggressive features: ER-, PR-, Ki67+, SPAG5+, high grade, and p53 mutation and enriched in ERBB2 and its related genes EGFR, ERBB4, GRB7, SPAG5 and FGFR4; $p < 0.0001$. After NACT, HER2 low had the lowest pCR rate (16%; 57/348) compared to HER2 IHC+3 (54%; 120/223), HER2 IHC+2/FISH+ (23%; 14/60) and HER2 IHC 0 (25% (66/264); $p < 0.0001$. Compared to either HER2+ or HER2 IHC 0 cases; HER2 low had higher risk of 5 relapse [(HR (95% CI) = 2.04 (3.05-1.36); $p = 0.001$) and (HR (95% CI) = 1.45 (1.001-2.09); $p = 0.05$); respectively] after NACT. SPAG5 overexpression (+) determined the response for NACT. None of HER2 IHC +2 with negative SPAG5 (-) expression (0/170) either with FISH+ (0/112) or FISH- (0/58) achieved pCR whereas 47% (31/66) of those of HER IHC+2 with SPAG5+ achieved pCR after NACT ($p < 0.0001$). Similarly 73% (78/107) of HER2 IHC+3 with SPAG5+ achieved pCR after NACT+ Trastuzumab compared to 11% (10/95) of those with SPAG5-; $p < 0.0001$. Changes of HER2 expression after NACT was common (50%); 31% (106/348) of the resituate HER2 low tumours were HER2 IHC 0 and 7% were HER2+. Meanwhile 28% (17/60) of HER2 IHC+2/FISH+, 7% (15/223) of HER2 IHC+3 and 14% of HER2 IHC 0 changed into HER2 low. **Conclusions:** HER2 low is common in early BC and is associated with resistance to the anthracycline/Taxane NACT. Significant change of HER2 expression in the residual tumour is common after NACT. SPAG5 expression could help to optimize the use of NACT and ADCs in early BC. Research Sponsor: UK NIHR Invention for Innovation and Nottingham University Hospital Charity.

TPS615

Poster Session

LESS: Single-arm study to de-escalate adjuvant endocrine therapy duration in post-menopausal women with HR+ HER2- early-stage breast cancer at very low risk of metastasis. *First Author: Elise Deluche, Centre Hospitalier Universitaire, Limoges, France*

Background: Adjuvant Endocrine Therapy (ET) is the cornerstone treatment of localized hormone-receptor positive (HR+) breast cancer, with demonstrated benefits on overall survival (30-40% relative decrease in mortality) but also on the risk of local and contralateral relapse (43-50% relative decrease). While the relative benefit of 5 years of ET is identical for small tumors as compared to larger ones, the absolute benefit is much lower, and the risk-benefit ratio becomes questionable given the frequent and impactful side effects of ET which are associated with non-adherence. If recent trials tested longer durations as compared to 5 years for high-risk cancers, older trials have tested shorter durations. Five years appeared at that time as the gold standard because of optimal benefit-risk ratios of tamoxifen among rather high-risk patients. However, shorter treatments of 2-3 years were already associated with substantial benefits and may be enough for very low risk patients. The purpose of this study is to demonstrate that adjuvant ET limited to 2 years of aromatase inhibitor (AI) in postmenopausal women at very low risk of recurrence as determined with a MammaPrint and Blueprint Ultra Low Risk Luminal test result can ensure very high survival without metastatic relapse and allows a reduction of side effects and a better quality of life. **Methods:** LESS (NCT05297617) is a prospective, national, multicenter, single-arm, interventional, non-threshold crossing phase II study evaluating a therapeutic de-escalation that limits adjuvant ET to 2 years of AI. Approximately 696 post-menopausal patients with an invasive unilateral, HR+, HER2-negative, without indication of adjuvant chemoT and genomically-assessed MammaPrint/Blueprint UltraLow risk Luminal A breast cancer tumors, will be enrolled. LESS will include two sub cohorts: the majority of patients with Grade 2, pT1c-2, pN0/N1mic tumors, and up to 80 patients ≥ 65 years with Grade 1, pT1, pN0 and Ki67 <10% tumors. The primary endpoint is distant metastasis free survival (DMFS) defined as the time from date of registration to date of first event of distant recurrence, death, or second primary non-breast invasive cancer. Secondary endpoints include the assessment of quality of life parameters and psychological aspects related to this de-escalation. The null hypothesis (H0) that, in the study population after 2 years of adjuvant AI, DMFS at 5 years is lower or equal to 94.5% will be tested against the alternative - that it is above 94.5%. For an expected DMFS of 96.7% under the alternative hypothesis, a total of 37 DMFS events are required in order to provide approximately 85% power at a one-sided significance level of 0.05 to reject H0 using a logrank test. The 1st patient was included in October 2022, initiating the 2-year inclusion period and 10 years FU per patient. Clinical trial information: NCT05297617. Research Sponsor: Agendia.

TPS617

Poster Session

Phase III study to evaluate the efficacy and safety of GLSI-100 (GP2 + GM-CSF) in breast cancer patients with residual disease or high-risk PCR after both neoadjuvant and postoperative adjuvant anti-HER2 therapy: Flamingo-01. *First Author: Snehal Patel, Greenwich LifeSciences, Stafford, TX*

Background: GP2 is a biologic nine amino acid peptide of the HER2/neu protein delivered in combination with Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF) that stimulates an immune response targeting HER2/neu expressing cancers, the combination known as GLSI-100. In a prospective, randomized, single-blinded, placebo-controlled, multicenter Phase IIb study, no recurrences were observed in the HER2+ population after 5 years of follow-up, if the patient was treated with GLSI-100, survived, and was followed for more than 6 months ($p = 0.0338$). Immunotherapy elicited a potent response measured by skin tests and immunological assays. Of the 146 patients that have been treated with GLSI-100 over 4 clinical trials, GLSI-100 was well-tolerated and no serious adverse events observed were considered related to the immunotherapy. **Methods:** This Phase III trial is a prospective, randomized, double-blinded, multi-center study. After 1 year of trastuzumab-based therapy, 6 intradermal injections of GLSI-100 or placebo will be administered over the first 6 months and 5 subsequent boosters will be administered over the next 2.5 years for a total of 11 injections over 3 years. The participant duration of the trial will be 3 years treatment plus 1 additional year follow-up for a total of 4 years following the first year of treatment with trastuzumab-based therapy. Patients will be stratified based on residual disease status at surgery, hormone receptor status and region. Approximately 498 patients will be enrolled. To detect a hazard ratio of 0.3 in invasive breast cancer free survival (IBCFs), 28 events will be required. An interim analysis for superiority and futility will be conducted when at least 14 events have occurred. This sample size provides 80% power if the annual rate of events in placebo patients is 2.4% or greater. Up to 100 non-HLA-A*02 subjects will be enrolled in an open-label arm. The patient population is defined by these key eligibility criteria: HER2/neu positive and HLA-A*02; residual disease or High risk pCR (Stage III at presentation) post neo-adjuvant therapy; exclude stage IV; completed at least 90% of planned trastuzumab-based therapy. Trial objectives were to determine if GP2 therapy increases IBCFs, to assess the safety profile of GP2 and to monitor immunologic responses to treatment and assess relationship to efficacy and safety. The study has been initiated at a number of sites in the US. The study is also expected to be opened in Spain, Germany, and France. Clinical trial information: NCT05232916. Research Sponsor: Greenwich LifeSciences.

TPS616

Poster Session

lidERA Breast Cancer (BC): Phase III adjuvant study of giredestrant vs. physician's choice of endocrine therapy (PCET) in patients (pts) with estrogen receptor-positive, HER2-negative early BC (ER+, HER2- eBC). *First Author: Charles Geyer, NSABP Foundation and UPMC Hillman Cancer Center, Pittsburgh, PA*

Background: Despite best management with standard ETs, $\leq 20\%$ of pts with ER+, HER2- eBC develop resistance (due to *ESR1* mutations that can drive estrogen-independent transcription and proliferation) and have high recurrence rates. New treatments are needed to reduce recurrence risk and improve survival, tolerability, quality of life, and adherence. Giredestrant, a highly potent, nonsteroidal oral selective ER antagonist and degrader, achieves robust ER occupancy and is active against ER-sensitive or *ESR1*-mutated tumors. It is more potent *in vitro* and achieves higher ER occupancy *in vivo* than fulvestrant. Early-phase studies showed that 30 mg daily as a single agent has promising clinical and pharmacodynamic activity and is well tolerated for ER+, HER2- BC. **Methods:** lidERA BC (NCT04961996) is a Phase III, global, randomized, open-label, multicenter study evaluating adjuvant giredestrant vs. PCET in ER+, HER2- eBC. Pts are randomized 1:1 to oral 30 mg daily giredestrant or PCET (tamoxifen, anastrozole, letrozole, or exemestane; per prescribing information). Stratification factors: Risk (medium vs. high, based on anatomic [tumor size, nodal status] and biologic features [grade, Ki67, gene signatures if available]); geographic region (US/Canada/Western Europe vs. Asia-Pacific vs. rest of the world); prior chemotherapy (no vs. yes); menopausal status (pre-/peri- vs. postmenopausal). Pts will be treated for ≥ 5 years. Continuing PCET > 5 years is per investigator discretion and local standard of care. Eligibility: Female/male; medium/high-risk stage I-III ER+, HER2- eBC; prior curative surgery; completion of (neo)adjuvant chemotherapy (if given) and/or surgery < 12 months before enrollment; no prior ET (≤ 12 weeks of [neo]adjuvant ET allowed). For men and pre-/perimenopausal women, an LHRH agonist will be given per local prescribing information (mandatory for the giredestrant arm). Primary endpoint: Invasive disease-free survival (IDFS, excluding second non-primary BC). Secondary endpoints: Overall survival; IDFS (STEEP definition, including second non-primary BC); disease-free survival; distant recurrence-free survival; locoregional recurrence-free interval; safety; pharmacokinetics; pt-reported outcomes. This study also aims to improve health equity in research and expand clinical trial access. It will use/develop digital healthcare solutions, enabling better understanding of pts' needs and adherence to ET. The primary endpoint analysis will use a stratified log-rank test at an overall 0.05 significance level (two-sided). Interim and futility analyses are planned; an independent data monitoring committee will be in place. 2950/4100 pts have been recruited globally. Clinical trial information: NCT04961996. Research Sponsor: F. Hoffmann-La Roche Ltd.

TPS618

Poster Session

Prospective single-arm study of endocrine therapies with ovarian function suppression in premenopausal patients with node-positive early breast cancer with low genomic risk (INTERSTELLAR trial, KBCSG-25). *First Author: Sung Gwe Ahn, Gangnam Severance Hospital, Yonsei University, Gangnam-Gu, NA, Korea, Republic of (South)*

Background: It is unclear whether the clinical benefit of cytotoxic adjuvant chemotherapy (CT) could be replaced by ovarian-function suppression (OFS) in premenopausal, estrogen receptor (ER)+HER2- breast cancer patients who have high clinical risk score and low genomic risk assessed by multigene assays. The TAILORx trial included a subgroup of premenopausal women with high clinical risk scores and midrange RS scores and found that CT, in addition to endocrine treatment (ET), offered clear benefits in terms of invasive disease-free survival (IDFS) and distant-recurrence-free survival (DRFS) compared to ET alone. However, a majority of the patients did not receive OFS, and the use of OFS as an alternative to chemotherapy in this population is still an area of ongoing research and debate. In addition, in premenopausal women of the RxPonder trial, which enrolled node-positive disease, it is noted that the addition of OFS to ET for at least 12 months improved IDFS numerically in the ET-alone arm, although this improvement did not reach statistical significance. We hypothesized that a favorable DRFS could be achieved by OFS plus ET without CT in premenopausal, pN1, ER+HER2- breast cancer with low genomic risk identified by an NGS-based multigene assay, the OncoFREE. **Methods:** The INTERSTELLAR trial is a prospective, multicenter, single-arm, non-inferiority clinical study. Premenopausal women aged ≤ 50 years with pT1-2 ER+HER2- breast cancer and 1-3 lymph node metastasis will be enrolled. They will be tested with OncoFREE, an NGS-based breast cancer prognosis multigene assay developed and available in South Korea, where a higher portion of the patients is premenopausal. Patients with low genomic risk (Decision Index ≤ 20) are administered OFS plus tamoxifen or an aromatase inhibitor for five years. We hypothesize that the 5-year DRFS of the single arm treated with OFS plus ET would be not inferior to 96.1%, which is observed in the chemo-ET arm from the premenopausal subgroup of the RxPonder trial. The one-sided test with a non-inferiority margin of 3% and statistical power of 80% at a significance level of 0.05 resulted in a sample size of 380 patients with low genomic risk. Considering a 70% designation to low genomic risk by OncoFREE and a 10% drop-out rate, 604 patients will be enrolled from 15 tertiary care hospitals in South Korea. The primary endpoint will be tested in the 380 patients with low genomic risk. The patients with high genomic risk will receive CT followed by ET and will be followed for survival analysis as a secondary end-point. The trial has not enrolled its first patient yet at the time of submission. Clinical trial information: NCT05333328. Research Sponsor: None.

TPS619

Poster Session

ASCENT-05/OptimICE-RD (AFT-65): Phase 3, randomized, open-label study of adjuvant sacituzumab govitecan (SG) + pembrolizumab (pembro) vs pembro ± capecitabine (cape) in patients (pts) with triple-negative breast cancer (TNBC) and residual disease after neoadjuvant therapy (NAT) and surgery. First Author: Sara M. Tolaney, Dana-Farber Cancer Institute, Boston, MA

Background: TNBC has an aggressive disease course with poor prognosis for pts with residual disease (RD) after NAT. In Ph 3 KEYNOTE-522, pts treated with poly-chemotherapy + the immune checkpoint inhibitor (ICI) pembro for ~1 year only had a 3-year event-free survival of 85% (Schmid P, et al. *NEJM*. 2022). SG is a Trop-2-directed antibody-drug conjugate approved for pretreated metastatic TNBC (mTNBC). In Ph 3 ASCENT, SG significantly improved both progression-free survival and overall survival (OS) compared with standard chemotherapy (CT) in pts with mTNBC who received ≥2 lines of therapy, with a manageable safety profile (Bardia A, et al. *NEJM*. 2021). Preclinical data suggest that SG also potentiates the activity of ICIs. The ASCENT-05 study will assess the value of adding SG to a pembro-based adjuvant therapy in pts with RD after NAT. **Methods:** ASCENT-05/OptimICE-RD (AFT-65, NCT05633654) is an open-label, global, multicenter, randomized, phase 3 study that evaluates efficacy and safety of SG + pembro versus pembro ± cape (per treating physician discretion) in pts with TNBC and RD in the post-NAT setting. Key eligibility criteria include pts ≥18 years with a history of cT1, cN1-2 or cT2-4, cN0-2 TNBC with RD in the breast or lymph node(s) after NAT and surgery. TNBC diagnosis per local assessment is based on estrogen receptor and progesterone receptor <10%, and HER2-negative per ASCO/CAP. Other inclusion criteria are receipt of ≥6 cycles of neoadjuvant anthracycline- and/or taxane-based CT ± PD-(L)1 inhibitor ± radiotherapy postoperatively as clinically indicated, and adequate organ function with ECOG performance status 0-1. Key exclusion criteria include metastatic disease, prior ipsilateral/contralateral invasive breast cancer, prior treatment directed to another stimulatory/co-inhibitory T-cell receptor, HER2-directed agents or TOPO-1 inhibitors, evidence of recurrent or distant metastatic disease after preoperative therapy and surgery, germline *BRCA* mutations, myocardial infarctions ≤6 months of enrollment or history of serious ventricular arrhythmia or LVEF <50%, and active serious infections requiring treatment. Pts will be randomized 1:1 to receive SG (10 mg/kg IV on d1 and d8, every 21d for 8 cycles) + pembro (200 mg IV on d1 every 21d for 8 cycles). Cape (1000 mg/m² twice daily, orally on d1-14, every 21d for 8 cycles) may be added to pembro in the control arm. The primary endpoint is invasive disease-free survival. Key secondary endpoints include OS, distant disease-free survival, incidence of treatment-emergent adverse events and clinical laboratory abnormalities, and time to worsening of quality of life based on FACT-B TOI scores. ASCENT-05 will enroll ~1500 pts and is currently open for recruitment. Clinical trial information: NCT05633654. Research Sponsor: Gilead Sciences, Inc.

TPS621

Poster Session

FLEX, a real-world evidence full transcriptome study of 30,000 patients with early-stage breast cancer. First Author: Eric Allen Brown, Comprehensive Breast Care, Troy, MI

Background: Clinical trials have been an invaluable tool in providing improvements in the discovery, treatment, and quality of life for various diseases and disorders including breast cancer, which impacts millions of people each year. Historically, patient trial populations have not been racially diverse due to several factors such as bias, healthcare distrust, access, and eligibility criteria. However, current efforts are focused on improving diversity and inclusion to promote efficacy and health equity across all races/ethnicities. The ongoing, multi-center FLEX trial (NCT03053193), which pairs clinical data and full transcriptome expression data, seeks to enroll 30,000 patients to accelerate real world research. Due to the size of the database, it is also expected to capture patients typically underrepresented in clinical trials. **Methods:** FLEX is the first of its kind, prospective, observational trial that enrolls patients who are ≥18 years old with histologically proven stage I-III breast cancer with up to 3 positive lymph nodes. Patient eligibility for study enrollment include standard of care MammaPrint testing with or without Blueprint and consent to clinically annotated full transcriptome data collection. The study infrastructure facilitates the generation of hypotheses for targeted sub-studies. The FLEX network fosters collaboration with 114 sites, including one site in Greece and Israel, encouraging participating investigators to initiate sub-studies that can address research questions that are important for breast cancer management. All proposed sub-studies are vetted and approved by Research and Scientific Review Committees. Since launching in April 2017, 12,569 patients have been enrolled including those who have been historically underrepresented in trials (African American n=1025; Latin n=341; Asian n=156). Forty-two investigator initiated sub-studies have been approved and are in progress, with 40 abstracts accepted in national and international congresses. Five ongoing sub-studies within FLEX address differences in underlying biology and treatment response/management among African American, Latina, and Asian American patients with early-stage breast cancer. These studies provide a broader understanding of how differential gene expression patterns unique to racial/ethnic groups can impact treatment outcomes. With the large FLEX database, enrollment and sub-studies are extended to other racial/ethnic groups that are underrepresented in clinical trials, but not limited to specific groups. Overall, the FLEX study strives to use full transcriptome data to improve precision medicine in early-stage breast cancer. Clinical trial information: NCT03053193. Research Sponsor: Agendia Inc.

TPS620

Poster Session

A phase II single-arm, open-label trial of T-DM1 (ado-trastuzumab emtansine) and neratinib for HER2-positive breast cancer with molecular residual disease (KAN-HER2 MRD). First Author: Mitchell Elliott, Division of Medical Oncology & Hematology, Department of Medicine, Princess Margaret Cancer Centre and University of Toronto, Toronto, ON, Canada

Background: HER2-positive breast cancer is a biologically and clinically aggressive subtype that has historically been associated with poor outcomes, but for which there are now multiple effective targeted therapies. Patients who have residual disease following standard neoadjuvant therapy have an elevated risk of metastatic recurrence. In addition, the detection of circulating tumor DNA (ctDNA) in the adjuvant period is strongly associated with relapse and can further stratify patients with residual disease. The ctDNA-based detection of molecular residual disease (MRD) is an emerging strategy to identify patients for treatment intensification, and may enable the development of novel curative treatment strategies for "recurrence interception". Preclinical and clinical evidence support the investigation of neratinib, an irreversible inhibitor of the HER2 tyrosine kinase, in combination with standard T-DM1 in the adjuvant setting for patients with HER2-positive breast cancer and evidence of MRD. **Methods:** KAN-HER2 MRD is a multicentre, investigator-initiated, open label, single arm phase II trial to evaluate the addition of neratinib to standard T-DM1 in patients with detected MRD. Participants with HER2-positive breast cancer and residual disease following neoadjuvant therapy are pre-screened (Part A) for MRD using a tumor-informed assay (NeoGenomics RaDaR). Those with ctDNA detected following 2-6 cycles of adjuvant T-DM1 will proceed to the interventional phase (Part B) where neratinib is added to standard T-DM1 at the previously-determined recommended phase 2 combination dose of 160 mg/day, in continuous cycles. The primary endpoint is the rate of ctDNA clearance at 12 weeks after treatment initiation (ctDNAw12); the study is designed with a 2-stage approach and has sufficient power to detect a clearance rate of 40%. Secondary endpoints include MRD rates and their clinical correlates, invasive disease free survival (IDFS), and safety. Bio-specimens including diagnostic biopsies, residual disease, and peripheral blood are being collected from all participants for additional correlative studies. Enrolment in Part A was initiated at the first trial site (Princess Margaret Cancer Centre) in December 2022. KAN-HER2 represents the first reported MRD-directed interception trial for HER2-positive breast cancer. Clinical trial information: NCT05388149. Research Sponsor: Ontario Institute for Cancer Research (OICR) Clinical Acceleration Team Award; Princess Margaret Cancer Foundation; Knight therapeutics, NeoGenomics.

TPS622

Poster Session

MRD assay to evaluate recurrence and response via a tumor-informed assessment: MARIA-Breast observational trial. First Author: Edward D. Esplin, Invitae, San Francisco, CA

Background: The recognition that cancers release nucleic acids into the peripheral circulation of the patient has enabled a new paradigm for disease detection and surveillance. Detectable ctDNA in patients with solid tumors has been associated with disease prognosis pre-treatment, assessing response to therapy in the form of minimal residual disease (MRD), and monitoring for recurrence after curative intent treatment. Utilizing patient-specific genomic mutation profiling of an individual's cancer from a tissue sample, in conjunction with the patient's germline DNA, to create a personalized sequencing panel to then systematically analyze for a subset of these genetic mutations from ctDNA in blood is a strategy that has high sensitivity in detection of MRD. Studies have shown that pretreatment levels of ctDNA using this approach are a potential early indicator of disease recurrence after surgery, that ctDNA clearance may be an early predictor of favorable outcomes and have been shown to correlate with pathologic complete response (Forde et al. *N Engl J Med*. 2022, PMID: 35403841), and that this approach has high sensitivity in its ability to detect recurrence for patients in advance of the current standard of care (Abbosh et al. *Cancer Res* (2020) 80 (16_Supplement): CT023). **Methods:** This is a multi-site, prospective, observational trial in the United States of 200 patients with early stage breast cancer undergoing curative intent treatment, who have FFPE tissue available from resection sufficient for a patient-specific bespoke MRD assay who are willing to provide serial whole blood specimens for ctDNA analysis. Participants are asked to provide study specimens prior to initial treatment intervention, after curative intent surgical resection, during adjuvant therapy (as applicable) and pre-recurrence follow-up. ctDNA will be analyzed with an NGS-based, tumor-informed MRD assay that identifies somatic mutations from DNA obtained from the patient's tumor tissue, subtracts germline variants via NGS-based analysis of the patients germline DNA, and detects a selected set of between 18-50 tumor-specific ctDNA in their blood. All primary tumor specimens will undergo full exome sequencing using the Personalized Cancer Monitoring (PCM) assay. Impact of results of this CLIA-approved MRD assay on clinical decision making will be captured. The primary objective is to assess the ability of MRD to predict post-treatment recurrence. Further objectives are to correlate MRD status with pathologic complete response, determine the lead time to detection of recurrence compared to standard of care, and the association of MRD status with overall survival. Active enrollment started in March, 2022. Clinical trial information: NCT05219734. Research Sponsor: Invitae.

TPS623

Poster Session

NRG-BR007: A phase III trial evaluating de-escalation of breast radiation (DEBRA) following breast-conserving surgery (BCS) of stage 1, HR+, HER2-, RS ≤18 breast cancer. *First Author: Julia R. White, University of Kansas Medical Center Comprehensive Cancer Center (KUMC CCC), Kansas City, KS*

Background: Approximately 50% of newly diagnosed invasive breast cancers are stage 1, with the majority being ER/PR-positive, HER2-negative. Genomic assays such as the Oncotype DX have identified patients (pts) with reduced risk of distant metastasis and without benefit from chemotherapy added to endocrine therapy, freeing them from excess toxicity. Genomic assays are also recognized as prognostic for in-breast recurrence (IBR) after BCS and could similarly allow de-escalation of adjuvant radiotherapy (RT). Reducing overtreatment is of interest to pts, providers, and payers. **Methods:** We hypothesize that BCS alone is non-inferior to BCS plus RT for in-breast recurrence and breast preservation in women intending endocrine therapy (ET) for stage 1 invasive breast cancer (ER &/or PR positive, HER2-negative with an Oncotype DX Recurrence Score [RS] of ≤18). Stratification is by age (<60; ≥60), tumor size (≤1 cm; >1-2cm), and RS (<11, 11-18). Pts are randomized post-BCS to Arm 1 with breast RT using standard methods (hypo- or conventional-fractionated whole breast RT with/without boost, or APBI) with ≥5 yrs of ET (tamoxifen or AI) or Arm 2 with ≥5 yrs of ET (tamoxifen or AI) alone. The specific regimen of ET in both arms is at the treating physician's discretion. Eligible pts are stage 1: pT1 (≤2 cm), pN0, age ≥50 to <70 yrs, s/p BCS with negative margins (no ink on tumor), s/p axillary nodal staging (SNB or ALND), ER &/or PR positive (ASCO/CAP), HER2-negative (ASCO/CAP), and Oncotype DX RS of ≤18 (diagnostic core biopsy or resected specimen). Primary endpoint is in-breast recurrence (invasive breast cancer or DCIS). Secondary endpoints are breast conservation rate, invasive in-breast recurrence, relapse-free interval, distant disease-free survival, overall survival, patient-reported breast pain, patient-reported worry about recurrence, and adherence to ET. We assume a clinically acceptable difference in IBR of 4% at 10 yrs to judge omission of RT as non-inferior (10-yr event-free survival for RT group is 95.6% vs 91.6% for the omission of RT group). BR007 is powered to detect non-inferiority with 80% power and a one-sided $\alpha=0.025$, assuming that there would be a ramp-up in accrual in the first two years (leveling off in Yrs 3-5); 1,670 pts (835 per arm) are required for randomization. Conservative loss to follow-up is 1% per yr. Some of the T1a pts screened may have Oncotype DX scores >18, making them ineligible for the study. In the accrual process, 1,714 pts will be required to register to ensure that our final randomized cohort is 1,670 pts. Current accrual (02-08-2023) is 370 screened and 323 randomized (~87% of predicted accrual). Clinical trial information: NCT04852887. Research Sponsor: U.S. National Institutes of Health.

TPS625

Poster Session

SMALL: Open surgery versus minimally invasive vacuum-assisted excision for small screen-detected breast cancer—A UK phase III randomised multicentre trial. *First Author: Stuart McIntosh, Queen's University Belfast, Belfast, United Kingdom*

Background: Mammographic screening programmes reduce breast cancer mortality but detect many small tumours with favourable biology which may not progress. These are treated with surgery and adjuvant therapies, but associated morbidities mean there is a need to reduce overtreatment. Minimally invasive treatments such as vacuum-assisted excision (VAE) have been described but there is no prospective randomised evidence to support their routine use. SMALL (ISRCTN 12240119) is designed to establish the feasibility of using VAE to treat small tumours detected within the UK NHS Breast Screening Programme (BSP). **Methods:** Phase III multicentre randomised trial comparing surgery with VAE for screen-detected good prognosis cancers. Eligibility criteria are age ≥47 years, unifocal grade 1 tumours (maximum diameter 15mm), strongly ER/PR+ve and HER2-ve, with negative axillary staging. Patients are randomised 2:1 to VAE or surgery, with no axillary surgery in the VAE arm. Excision is assessed radiologically, and if incomplete, patients undergo surgery. Adjuvant radiotherapy and endocrine therapy are mandated in the VAE arm. Co-primary end-points are 1) Non-inferiority comparison of the requirement for a second procedure. 2) Single arm analysis of local recurrence (LR) at 5 years after VAE. Recruitment of 800 patients will permit demonstration of 10% non-inferiority of VAE for requirement of a second procedure, ensuring sufficient patients for single arm analysis of LR rates, where expected LR free survival is 99% at 5 years, with an undesirable survival probability after VAE of 97%. Secondary outcome measures include time to ipsilateral recurrence, overall survival, complications, quality of life and health economic analysis. A QuinteT Recruitment Intervention (QRI) is integrated throughout SMALL to optimise recruitment and informed consent. Recruitment challenges are identified by analysing recruiter/patient interviews, audio-recordings of trial discussions, and by review of screening, eligibility and recruitment data and study documentation. Solutions are developed collaboratively, including recruiter feedback and recruitment tips documents. Results: At 10th February 2023, 231 patients had been recruited from 32 centres, (~45% of eligible patients), with per site recruitment of 0.4-0.5 patients/month. Based on preliminary QRI findings, a recruitment tips document has been circulated (on discussing SMALL, providing balanced information on treatment options and explaining randomisation), with individual recruiter feedback underway and wider feedback planned shortly. Conclusion: SMALL has excellent recruitment to date, confirming feasibility and acceptability, and is expected to have a global impact on treatment of screen-detected breast cancer. Clinical trial information: ISRCTN12240119. Research Sponsor: National Institute for Health Research Health Technology Assessment Programme (UK).

TPS624

Poster Session

Selective avoidance of sentinel lymph node biopsy after neoadjuvant chemotherapy in patients with HER-2 positive/triple negative breast cancer: Prospective, multi-center, single-arm study (ASLAN). *First Author: Jai Min Ryu, Division of Breast Surgery, Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea*

Background: According to advanced neoadjuvant chemotherapy (NACT), which dual HER2 blockade in HER2+ BC and adding carboplatin or immunotherapy in triple-negative breast cancer (TNBC) increased pathologic complete response (ypCR) rates up to 68% and 80%. Because ypCR patients showed better survival, the indications for NACT have expanded to early BC and the expected ypCR rate has increased. Therefore, it may be reasonable to consider omitting surgery in cases with excellent responses to NACT. Several recent retrospective studies and pilot prospective studies have reported axillary pathologic complete response (ApCR) is highly correlated with breast pathologic complete response (BpCR) in HER2+ or TNBC after NACT. The current report describes the design of omission of sentinel lymph node biopsy (SLNB) after NACT in HER2+ or TNBC patients with excellent response. Similarly, EUBREAST-01 (NCT04101851) study is ongoing omission of sentinel lymph node biopsy (SLNB) after NACT in HER2+/TNBC with radiologic complete remission and a BpCR. **Methods:** The ASLAN trial is a prospective, multicenter, single-arm, clinical study. Five tertiary care hospitals in South Korea are participating. Inclusion criteria: women aged 20-69; cT1-3N0-1M0; HER2+ or TNBC (defined by ER-negative (< 10% positive cells in IHC) and PgR-negative (< 10% positive cells in IHC)); expected complete remission at physical examination and radiological expected Tumor size ≤ 2cm or non-mass enhancement ≤ 4cm at breast MRI after standard NACT; planned breast conserving surgery (BCS) with whole-breast irradiation; ECOG performance status 0-1. Exclusion criteria: SLNB before NACT; previous axillary surgery; bilateral BC. Patients who are eligible proceed BCS. After BCS, patients who showed BpCR are enrolled with omission of SLNB. Patients with no BpCR proceed with routine axillary surgery. The assumption for acceptable 5-year RFS ≥84% is based on previous study findings. The calculated total case number for per-protocol analysis is N=178. Primary endpoint: 5-year recurrence free survival. Secondary endpoint: local recurrence free survival, breast cancer specific survival, overall survival, ipsilateral axillary recurrence interval, distant metastasis free survival, contralateral breast free survival, re-operation rate according to breast biopsy after NACT, adverse event, and quality of life. The first patient was enrolled on September 2021. Among 147 patients who screened, 106 patients have been enrolled in January 2022. We plan to complete the target accrual by December 2025. Clinical trial information: NCT04993625. Research Sponsor: NRF 2021R1A2C94010.

TPS626

Poster Session

MELODY (Methods for Localization of Different Types of Breast Lesions): A prospective non-interventional multicenter cohort study to evaluate different imaging-guided methods for localization of malignant breast lesions (EUBREAST-4/iBRA-NET). *First Author: Maggie Banyas-Paluchowski, University Hospital Schleswig-Holstein Campus Lübeck, Lübeck, Germany*

Background: In the last decades, the proportion of breast cancer patients receiving breast-conserving surgery has increased, reaching 70-80% in developed countries. In case of non-palpable lesions, surgical excision requires some form of breast localization. While wire-guided localization has long been considered gold standard, it carries several limitations, including logistical difficulties, the potential for displacement and patient discomfort, and re-excision rates reaching 21%. Other techniques (radioactive seed or radio-occlude lesion localization, intraoperative ultrasound, magnetic, radiofrequency and radar localization) have been developed with the aim of overcoming these disadvantages. However, comparative data on the rates of successful lesion removal, negative margins and re-operations are limited. In the majority of studies, the patient's perspective with regard to discomfort and pain level has not been evaluated. The aim of MELODY is to evaluate different imaging-guided localization methods with regard to oncological safety, patient-reported outcomes, and surgeon and radiologist satisfaction. **Methods:** The EUBREAST and the iBRA-NET have initiated the MELODY study to assess breast localization techniques and devices from several perspectives (NCT05559411, <http://melody.eubreast.com>). MELODY is a prospective intergroup cohort study which enrolls female and male pts. requiring breast-conserving surgery and imaging-guided localization for invasive breast cancer or DCIS. Multiple or bilateral lesions and neoadjuvant chemotherapy are allowed. Primary outcomes are: 1) Intended target lesion and/or marker removal, independent of margin status on final histopathology, and 2) Negative resection margin rates at first surgery. Secondary outcomes are, among others: rates of second surgery and secondary mastectomy, Resection Ratio (defined as actual resection volume divided by the calculated optimum specimen volume), duration of surgery, marker dislocation rates, rates of marker placement or localization failure, comparison of patient-reported outcomes, rates of "lost markers" and diagnostician/radiologist's and surgeon's satisfaction as well as the health economic evaluation of the different techniques. Target accrual: 7,416 patients. Enrollment started in January 2023. The study will be conducted in 20 countries and is supported by the Oncoplastic Breast Consortium (OPBC), AWOgyn, AGO-B and SENATURK. Clinical trial information: NCT05559411. Research Sponsor: Endomag, Merit Medical, Sirius Pintuition and Hologic.

TPS627

Poster Session

Omission of breast surgery for predicted pCR patients with MRI and vacuum-assisted biopsy in breast cancer after neoadjuvant chemotherapy: A multicenter, single-arm, non-inferiority trial (OPTIMIST trial). *First Author: Ji-Jung Jung, Department of Surgery, Seoul National University College of Medicine, Seoul, South Korea*

Background: Advances in chemotherapeutic and targeted agents have increased pathologic complete response (pCR) rates after neoadjuvant systemic therapy (NST). The role of surgery is essential to remove cancer when residual tumor is present, but it may be limited to pathologic confirmation in those with a pCR. As an alternative, pCR can be accurately evaluated with vacuum-assisted biopsy (VAB) in patients suggested to have a pCR on imaging. We aim to show a non-inferiority of omitting breast surgery in patients evaluated to have a pCR on image-guided VAB. **Methods:** The OPTIMIST trial is a prospective, multicenter, single-arm, non-inferiority clinical study. Sixteen tertiary care hospitals in South Korea are participating. Women diagnosed with invasive ductal carcinoma, a clip marker placed in the tumor, and who had completed NST with exceptional response are screened for eligibility. Inclusion criteria: women aged 19-75; cT1-2N0-2M0; triple-negative, HER2+, or low estrogen receptor (<10%); post-NST MRI size ≤ 1 cm and lesion-to-background signal enhancement ratio ≤ 1.6 . Exclusion criteria: malignant calcification > 2 cm; multifocal, bilateral, or inflammatory breast cancer; other malignancy within five years; BRCA1/2 mutation carrier. Under ultrasound or stereotactic guidance, VAB is performed targeting the clip marker to obtain a minimum of 6 cores using 7-10 G needles. When pCR is confirmed, breast surgery is omitted. cNO patients with post-NST MRI tumor size ≤ 0.5 cm and no suspicious lymph nodes, axillary lymph node surgery could also be omitted. Patients with residual tumor or atypical cells proceed with routine surgery. All patients are required to receive whole breast irradiation with tumor bed boost. According to previous studies, the 5-year disease-free survival (DFS) for patients with a pCR after NST was assumed to be 88%. The one-sided test with a non-inferiority margin of 4% and statistical power of 80% at a significance level of 0.05 resulted in a sample size of 384 patients to forego breast surgery. An expected 20% residual tumor on VAB and a 10% dropout resulted in a total of 533 subjects. Primary endpoint: 5-year DFS. Secondary endpoint: 5-year ipsilateral breast tumor recurrence-free survival, 5-year overall survival, 5-year invasive DFS, residual axillary lymph node rate, quality of life scores, symptoms (VAS), and medical cost. An interim analysis is planned at 50% enrollment with a median follow-up period of 1 year. The data safety monitoring board will determine the continuation of the study considering the 1-year DFS. The first patient was enrolled on September 22, 2022, and 12 patients have been enrolled as of February 14, 2023. We plan to complete the target accrual by December 2025. Clinical trial information: NCT05505357. Research Sponsor: National Cancer Center of Korea.

TPS629

Poster Session

Phase 1 dose-escalation, dose-expansion trial of intratumoral HER2- and HER3-primed dendritic cells injections for the treatment of early-stage TNBC and HR low positive breast cancer: DecipHER trial. *First Author: Ricardo L Costa, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL*

Background: Patients with breast cancers (BCs) harboring low expression of hormone receptors (HRs) and human epidermal growth factor receptor-2 (HER2) have poor outcomes. Results from the KEYNOTE-522 trial showed that activation of the immune system using a PD1/PD-L1-targeted approach improves outcomes of patients with these high-risk tumors. Antigen-presenting cells (eg, dendritic cells [DCs]) are pivotal for robust cytotoxic responses due to broader activation of the adaptive immune system (ie, CD4⁺ and CD8⁺ Th1) against tumor-associated antigens (ie, HER2 or HER3) expressed by high-risk BCs. **Methods:** DecipHER is a dose-escalation, dose-expansion phase 1 trial designed to assess the safety and the preliminary efficacy of autologous, HER2- and HER3-primed DCs in combination with KEYNOTE 522 regimen in 30 patients. Patients with clinical stage cT1cN1/2 or cT2-4cN0-2, HR 20, HER2-negative BCs are eligible. Patients with inflammatory BC cancer and uncontrolled immune mediated diseases are excluded. After collection through apheresis, autologous DCs will be primed *ex vivo* against 6 HER2 and 8 HER3 immunogenic peptides. Participants will receive alternating ultrasound-guided intratumoral HER2 and HER3 DC injections administered twice a week for 8 doses in total starting 2 weeks prior to neoadjuvant therapy with KEYNOTE 522 regimen. The dose-escalation phase of the study has 3 planned cohorts (10-20, 30-50, 80-100 million DCs) and follows a 3+3 design (maximum n=18). The 12 additional patients enrolled will be treated at the maximum tolerated dose (MTD) in the dose-expansion cohort. The MTD will be defined as the highest dose level at which < 2 of 6 patients experience dose-limiting toxicities (grade ≥ 3 non-hematologic, ; grade ≥ 3 hematologic toxicity thought to be at least possibly related to DCs ; any grade 4 nausea, vomiting, or diarrhea [or grade 3 if duration > 3 days]) during the 5 weeks following treatment initiation with DCs. Secondary endpoints include the absolute risk of adverse events, clinical and pathological responses, and recurrence free survival. Tumor tissue, blood and stool samples will be collected for correlative analyses. The study is open at H. Lee Moffitt Cancer Center. Clinical trial information: NCT05504707. Research Sponsor: Shula's Foundation.

TPS628

Poster Session

Tailored axillary surgery (TAS) in patients with clinically node-positive breast cancer in the upfront surgery setting: A prospective, single-arm, multicenter trial. *First Author: Kaori Terata, Department of Breast and Endocrine Surgery, Akita University Hospital, Akita, Japan*

Background: Axillary lymph node dissection (ALND), which can induce lymphedema, has been omitted in clinically node-negative(cNO) patients with positive sentinel lymph nodes (SLNs) if they meet the eligibility criteria of ACOSOG Z0011. Furthermore, the omission of ALND has been attempted through targeted axillary dissection (TAD) in patients whose cN+ status converts to ycNO after neoadjuvant chemotherapy. However, ALND remains the standard of care in patients with cN+ who undergo upfront surgery. The aims of this trial are to establish a surgical method of tailored axillary surgery (TAS), which combines TAD and SLN biopsy among patients with cN+ who undergo upfront surgery, and to determine the appropriate criteria for a Phase III TAS trial. **Methods:** We have planned a single-arm Phase II trial to confirm the feasibility and assess patient eligibility for TAS. A total of 300 patients will be enrolled from 33 study sites in Japan. The eligibility criteria are as follows: 1) histologically-proven invasive breast cancer, 2) upfront surgery is planned, 3) pathologically-diagnosed metastatic lymph node (cytology or core needle biopsy), 4) 1-3 LN metastases in level I by imaging, 5) cT1-3, and 6) females aged ≥ 18 and ≤ 74 years on the enrollment date. TAS involves removing marking lymph nodes by TAD (clip, wire, or tattoo) and SLNB, and ALND up to Level II are performed after TAS. These LNs are defined as non-TAS LNs. The primary endpoint is the non-TAS LNs positive rate. Clinicopathological factors (the number of suspected metastases by imaging, the number of metastases in LNs resected by TAS, tumor size, and invasive ductal/lobular carcinoma) are analyzed to predict the non-TAS LN metastasis rate (e.g., $< 10\%$). By using these clinicopathological factors, we determine the eligibility of TAS to omit ALND safely. The secondary endpoints are TAS LNs identification rate, labeled LNs identification rate, marked lymph node resection rate, arm edema incidence rate, and QOL (FACT-B, QuickDASH). After this feasibility study, we will conduct a phase III trial that omits ALND using TAS to investigate the regional recurrence rate. Research Sponsor: Okayama University.

TPS630

Poster Session

DIRECT2: A randomized phase III trial with a fasting mimicking diet program to improve chemotherapy in patients with hormone receptor positive, HER2-negative breast cancer—A Dutch Breast Cancer Research Group study (BOOG). *First Author: Nadia de Gruil, Leiden University Medical Center, Leiden, Netherlands*

Background: Preclinical research has shown that fasting and/or a fasting mimicking diet (FMD) in addition to chemotherapy can enhance cancer treatment effectivity and reduce side-effects. The previous DIRECT1 phase 2 study (de Groot S, Nat. Commun. 2020) indicated that FMD could increase effectivity of neoadjuvant chemotherapy in patients with HER2-negative breast cancer. **Methods:** DIRECT2 is a multicenter, randomized, open label phase 3 study that investigates whether FMD compared to a regular diet during neoadjuvant chemotherapy can improve the pathological and/or radiological response rate in patients with hormone receptor positive (HR+), HER2-negative, stage II/III breast cancer. Secondary endpoints include quality of life, cognition, toxicity $\geq$ grade 3 and the immunomodulating effect of FMD. The FMD consists of a low-caloric diet of 600kcal/day starting 3 days prior to, and on the day of chemotherapy administration every 4 weeks, for a total of 5 FMD cycles during neoadjuvant chemotherapy (4 times dose dense Adriamycin plus cyclophosphamide followed by 12 times weekly paclitaxel). Patients will be supported and monitored by a centralized dietician during each FMD cycle. An additional MRI will be conducted after 4ddAC to evaluate efficacy mid-way through chemotherapy. Furthermore, an optional tumor biopsy will be done to determine the immunomodulatory effects of the FMD which will be determined using cutting-edge RNA sequencing and multispectral imaging techniques. Pathological response will be graded on the surgical specimen according to Miller & Payne 4/5, indicating a 90-100% tumor cell loss. Radiological response will be determined by MRI (RECIST1.1). In total 240 patients are needed to detect an increase from 20% to 37.5% in pathological response rate in the FMD arm allowing for 15% dropout, using a two-sided Z test with pooled variance and 5% significance level with a power of 80%. Randomization will be performed in Castor EDC with variable block sizes and stratified by clinical stage (stadium II versus III) and BMI (< 25 kg/m² versus ≥ 25 kg/m²). Inclusion criteria are HR+, HER2- breast cancer stage II-III, BMI > 18.5 kg/m², WHO status 0-2, without a history of malignancy in the past 5 years, invasive or ipsilateral non-invasive breast cancer. Patients will be excluded in case of pregnancy, lactation or metabolic disease that affects gluconeogenesis and adaptability to FMD. The trial is supported by grants from the Dutch Cancer Society and WCRF. The study is open since February 2023 for inclusion for 4 years and plans to recruit 240 patients in total in 20 participating hospitals in the Netherlands. Clinical trial information: NCT05503108. Research Sponsor: Dutch Cancer Society; World Cancer Research Fund (WCRF).

TPS631

Poster Session

Metformin with neoadjuvant chemotherapy in localized triple negative and HER2neu-positive breast cancer: A prospective phase 2 open label randomized controlled trial (McBETH). *First Author: Mouna Bidaraguppe B M, New Delhi, India*

Background: Repurposing of drugs in cancer is an attractive strategy and metformin has long been an agent with promising yet unproven activity in breast cancer. Despite some recent studies showing inadequate efficacy in adjuvant setting, there is a lack of well powered studies in neo-adjuvant setting in localised breast cancer. Few past studies suggest that metformin may have anticancer effects in the subsets of Her2 neu positive as well as Triple negative breast cancer (TNBC). We initiated this study to investigate if metformin in combination with standard neo-adjuvant chemotherapy is effective in improving pathological complete response rates in these subsets among localised breast cancers. **Methods:** This is an investigator initiated randomised, open label, parallel-group superiority trial. All non diabetic localised chemo-naïve breast cancer patients aged ≥ 18 years planned for neo-adjuvant chemotherapy will be randomly allocated (stratified by HER 2 positive and TNBC) to receive standard neo-adjuvant chemotherapy with or without metformin (850mg twice daily) till the day of surgery. The patients will be followed up until the surgery. The primary objective of this study is to compare the pathological complete response rates (ypT0ypN0) in each arm. The secondary objectives are to compare pathological complete response rates in predefined subsets of HER2 positive and triple negative breast cancer, clinical response rates in each arm, patient reported outcomes in each arm (ESAS-r Scale), breast conservation surgery rates in each arm, incidence and severity of adverse events in both arms. Trial statistical design: Planned accrual is total 242 patients including 10% drop out rate. It is a superiority design with an absolute improvement of 11% in pathological complete response from a baseline of 33% in the standard arm. Conduct to date: study activation: May 2022. Enrolment: 116 subjects. Clinical trial information: REF/2022/05/054208. Research Sponsor: None.

TPS633

Poster Session

A randomized phase 2 non-inferiority trial of (Z)-endoxifen and exemestane + goserelin as neoadjuvant treatment for premenopausal women with ER+/HER2- breast cancer (EVANGELINE). *First Author: Matthew P. Goetz, Mayo Clinic, Rochester, MN*

Background: Ovarian function suppression (OFS) when combined with tamoxifen or an aromatase inhibitor is the standard of care for premenopausal estrogen receptor positive (ER+) human epidermal growth factor receptor 2 negative (HER2-) breast cancer (BC) based on SOFT (Francis 2022) and TEXT (Pagani 2022) clinical trials and confirmed in a meta-analysis (EBCTCG 2022). However, estrogen deprivation in premenopausal women is associated with significant morbidity and up to 40% of premenopausal women with ER+/HER2- BC are intolerant of OFS. For these women, tamoxifen monotherapy is the only FDA approved option. Therefore, there is substantial room to improve endocrine therapy for premenopausal women with ER+/HER2- BC. (Z)-endoxifen is one of the most active anti-estrogen tamoxifen metabolites, with preclinical data demonstrating superiority to tamoxifen and letrozole in aromatase expressing xenograft models and evidence for antitumor activity in early phase clinical trials in patients with prior progression on endocrine therapy including tamoxifen. In addition to its ability to potentially block ER α , (Z)-endoxifen at clinically achievable concentrations inhibits protein kinase C beta 1 (PKC β 1), resulting in downstream AKT inhibition and apoptosis. It is hypothesized that (Z)-endoxifen, when delivered as monotherapy at doses that dually target both ER α and PKC β 1, will potentially inhibit BC proliferation while obviating the need for OFS in premenopausal women. If successful, this innovative approach could spare women with endocrine sensitive BC from the side effects of OFS. **Methods:** To further study (Z)-endoxifen in premenopausal women, a multicenter study in the United States, with possible expansion to other countries was designed (EVANGELINE; NCT05607004). This is a Phase 2, open-label, randomized, neoadjuvant study in premenopausal women with Stage IIA or IIB ER+/HER2- BC. Subjects are randomized 1:1 to either exemestane plus goserelin or (Z)-endoxifen. The primary objective is to determine whether the endocrine sensitive disease (ESD) rate (defined as Ki-67 $\leq 10\%$ after 4 weeks of neoadjuvant therapy) with (Z)-endoxifen is non-inferior to exemestane plus goserelin. Subjects will be enrolled with the intent of surgical treatment in the involved breast(s) after completing 6 months of neoadjuvant treatment. Safety, tolerability, response rates and surgical outcomes will be assessed. Disease progression will be monitored throughout study participation. Paired tumor biopsies and blood sampling will allow for a robust biomarker evaluation. Prior to initiating the Treatment Cohort (162 subjects), up to 12 subjects will be enrolled in a pharmacokinetic (PK) Run-in Cohort to identify the optimal dose for the Treatment Cohort. Enrolment in the PK Run-in cohort began in February 2023. Clinical trial information: NCT05607004. Research Sponsor: Atossa Therapeutics, Inc.; U.S. National Institutes of Health.

TPS632

Poster Session

ORACLE-RIPA study: A phase II, randomized, open-label, parallel-group study comparing the immune modulation effect of neoadjuvant ribociclib, palbociclib, and abemaciclib in early ER+/HER2- breast cancer. *First Author: I-Chun Chen, National Taiwan University Hospital, Taipei, Taiwan*

Background: CDK4/6 inhibitors (CDK4/6i), ribociclib, palbociclib, and abemaciclib, provide similar progression-free survival (PFS) benefits when combined with endocrine therapy in ER+/HER2- metastatic breast cancer (MBC) patients. However, not all CDK4/6i have demonstrated overall-survival (OS) benefits in their respective phase III trials. Both, ribociclib and abemaciclib, have shown significant OS benefits in ER+/HER2- MBC patients, but palbociclib has not. Because of similar benefits of the 3 CDK4/6i on PFS, the OS benefit is likely not a result of differences in their synergistic efficacy of a CDK4/6i with endocrine therapy. CDK4 inhibition on cancer cells can also result in upregulation of MHC-I and MHC-II expression on cell surface and Rb-dependent interferon-gamma secretion. CDK6 inhibition might inhibit T cell and NK cell proliferation causing a negative effect on the tumor microenvironment. CDK6 inhibition can also reduce regulatory T cell numbers and increase cytokine production to enhance cytotoxic T cell function. Thus, we hypothesize that the differential impact of the 3 CDK4/6i on OS might be resulting from different immunomodulation effects. To investigate the functional alterations of the CDK4/6i on the BC microenvironment, the neoadjuvant treatment setting is best to compare the immune modulation effects of CDK4/6i from pre-treatment and post-treatment tumor tissues. **Methods:** This phase II multicenter, randomized, open-label, parallel-group study evaluates the immunomodulation effects of the 3 different CDK4/6i (ribociclib, palbociclib, or abemaciclib) combined with letrozole in neoadjuvant early ER+/HER2- breast cancer patients. A total of 20 patients will be enrolled into each treatment arm. The major inclusion criteria are female patients aged ≥ 20 years old, having a histologically and/or cytologically confirmed diagnosis of ER+ ($> 10\%$) and/or PR+, HER2 negative (IHC 0+/1+, or IHC 2+ plus FISH negative) breast cancer, stage II/III, and adequate organ function. The treatment will be 12 weeks of letrozole plus a CDK4/6i. Premenopausal patients will receive GnRH agonist. Breast tumor biopsy, blood and stool samples will be collected prospectively at the time prior to treatment initiation, at 2 weeks after treatment, and at surgery. A description summary will be utilized to compare the results between the 3 CDK4/6i. The trial results will address questions about differences or similarities of the 3 CDK4/6i within the same study. The study is currently enrolling at 3 medical centers in Taiwan. Clinical trial information: Pending formal number assignment. Research Sponsor: Novartis; National Taiwan University Hospital.

TPS634

Poster Session

Neoadjuvant HER2-targeted therapy $\pm$ immunotherapy with pembrolizumab (neoHIP): An open label randomized phase II trial. *First Author: Heather L. McArthur, University of Texas Southwestern Medical Center, Dallas, TX*

Background: Immune checkpoint inhibition (ICI) is synergistic with HER2-directed therapy in pre-clinical models. Clinically, pembrolizumab (K)-mediated ICI plus HER2-directed therapy with trastuzumab (H) was safe and demonstrated modest activity in H-resistant HER2-positive (HER2+) metastatic breast cancer. Because ICI may confer more robust activity when administered earlier in the course of disease, H and K administered in the curative-intent, treatment-naïve setting may allow for de-escalation of cytotoxics; confer life-long, tumor-specific immunity; and ultimately, improve cure rates. Moreover, the synergy of H and K with paclitaxel (T) may overcome the need for dual HER2-blockade with H plus pertuzumab (P). In this randomized, multicenter, phase II, open-label trial the efficacy and safety of neoadjuvant THP vs THP-K vs TH-K are explored. **Methods:** Patients (pts) ≥ 18 y with previously untreated, stage II-III, HER2+ breast cancer are being randomized and stratified by clinical nodal status (positive vs. negative) and hormone receptor status (positive vs. negative). In arm A, pts received T at 80mg/m² weekly for 12 weeks, H at 8mg/Kg (loading dose) and then 6mg/Kg every 3 weeks x 3 doses, P at 840 mg (loading dose) and then 420mg/Kg every 3 weeks x 3 doses (THP). In arm B, pts received THP plus K at 200mg every 3 weeks x 4 doses (THP-K). In arm C, pts received TH-K. After enrollment of 22 pts to arm C, a prespecified interim efficacy analysis was conducted, and enrollment to this arm was subsequently terminated. Enrollment to the other arms continues with 32/58 pts enrolled to arm A and 33/58 pts enrolled to arm B as of 2/14/2023. Definitive surgery is 3-6 weeks after the last dose. After surgery, pts are treated per the treating physician's discretion per local clinical standard. The primary end point is pathologic complete response (pCR) rate in the breast and axilla (ypT0/Tis ypN0). Secondary end points include pCR rate by ypT0ypN0 and ypT0/Tis, residual cancer burden index, event free survival, breast conserving surgery rate, safety and overall survival. Exploratory correlative studies will characterize potential immune biomarkers predictive of efficacy and/or toxicity. Clinical trial information: NCT03747120. Research Sponsor: Merck; BCRF.

TPS635

Poster Session

A single-arm phase 2 study of peri-operative immune checkpoint inhibition and cryoablation in women with hormone receptor-negative, HER2-negative, early-stage/resectable breast cancer. *First Author: Heather L. McArthur, University of Texas Southwestern Medical Center, Dallas, TX*

Background: Local tumor destruction with cryoablation (cryo) induces inflammation and releases antigens that can activate tumor-specific immune responses. Pre-clinically, cryo with immune checkpoint inhibition (ICI) augmented tumor-specific immune responses and prevented recurrence. Clinically, we established that peri-operative (peri-op) cryo with ICI [ipilimumab (ipi) +/- nivolumab (nivo)] was safe in patients (pts) with operable, early stage breast cancer (ESBC) and generated robust intra-tumoral and systemic immune responses. In this phase 2 study, we evaluate the disease specific impact of peri-op ICI in women with residual triple negative breast cancer (TNBC) after neoadjuvant chemotherapy (NAC), a subset at high risk of early relapse. **Methods:** Eligible women are ≥ 18 y, with ER $< 10\%$, PR $< 10\%$, HER2 negative (per ASCO/CAP definition), ≥ 1.0 cm, residual operable disease after taxane-based NAC. As of 2/14/21, 16/80 pts have been enrolled and treated with ipi/nivo/cryo followed by breast surgery and adjuvant nivo. Pts undergo percutaneous, image-guided cryo with concurrent research core biopsy 7-10 days prior to surgery and received ipi (1mg/kg IV) with nivo (240mg IV) 1 to 5 days prior to cryo. After surgery, pts received 3 additional doses of nivo at 240mg IV Q2 weeks. To reflect the US FDA approval of curative-intent pembrolizumab (pembro) in 2021, the protocol was recently amended to allow standard-of-care pembro as an alternative ICI option. Adjuvant capecitabine or olaparib is recommended for all patients per local standard-of-care. Patients will be stratified by NAC platinum administration, NAC anthracycline administration, and clinical nodal status (positive versus negative). The primary endpoint is 3-year Event Free Survival (EFS). Secondary endpoints include Invasive Disease-Free Survival (IDFS), Distant Disease-Free Survival (DDFS), overall survival (OS) and safety. Exploratory correlative studies will be performed on tumor and serum to characterize the immunologic impact of the intervention and to explore predictors of efficacy and toxicity. Clinical trial information: NCT03546686. Research Sponsor: Komen; ASCO; Bristol-Myers Squibb, BTG International Ltd.

TPS636

Poster Session

A phase II study of concurrent WOKVAC vaccination with neoadjuvant chemotherapy and HER2-targeted monoclonal antibody therapy. *First Author: William R Gwin, University of Washington, Cancer Vaccine Institute, Seattle, WA*

Background: HER2+ breast cancer (BCa) is an aggressive breast cancer subtype. The treatment of Stage I-III HER2+ BCa with neoadjuvant chemotherapy and HER2 monoclonal antibodies (trastuzumab and pertuzumab) induces a pathologic complete response in 43-67% of patients. Residual HER2+ disease (i.e. residual cancer burden) after neoadjuvant therapy is associated with a significantly higher risk of recurrence. Evidence supports that HER2 immunity is progressively lost in HER2 oncogenesis and that restoration of HER2 specific CD4+ Th1 immunity is associated with a lower risk of recurrence. Trastuzumab can partially restore HER2 specific immunity, but only in a minority of patients. We have demonstrated that HER2 specific vaccination can augment HER2 specific immunity. While taxane chemotherapy can deplete immunosuppressive cells (MDSCs) 13 – 17 days after treatment creating an optimal time for vaccination. The WOKVAC vaccine is a plasmid vaccine encoding Th1 selective epitopes from HER2 and two other high-risk cancer antigens IGFBP-2 and IGF-1R. The Phase I trial of this vaccine reported that it is safe and all doses induced antigen specific Type I immune responses. We hypothesize that addition of WOKVAC to neoadjuvant chemo/HER2 targeted therapy will induce a significant increase in the number of patients with Th1 CD4+ and CD8+ T cells after neoadjuvant vaccine/chemo/HER2 therapy. **Methods:** Trial Design: Phase II single arm trial of WOKVAC vaccination with concurrent neoadjuvant taxane based chemotherapy, trastuzumab, and pertuzumab in patients with Stage I-III HER2+ (HR+/-) breast cancer. Enrolled patients will receive WOKVAC vaccine 150mcg on day 13 of cycles 1-3. WOKVAC vaccination may be given with either TCHP or THP. A maximum of 16 patients will be enrolled in this study. Objectives: The primary objective is to evaluate whether concurrent WOKVAC vaccine with chemotherapy and HER2 antibody therapy can significantly increase T-bet+ CD4+ and CD8+ TIL. Secondary objectives are to determine: (1) whether concurrent WOKVAC with neoadjuvant chemo/HER2 therapy is safe, (2) if the magnitude of vaccine induced antigen specific Th1 immunity after neoadjuvant therapy is associated with pathologic response. Statistical Methods: (1) In order to detect a 30% increase in the number of patients with Tbet+ CD4+ and CD8+ TIL in the enrolled patients with 80% power and a one-side alpha of 0.05, our enrollment goal for this study will be 16 patients. (2) Safety will be assessed per CTCAE v5.0. Benchmarks for safety needed to advance this trial concept to a Phase III study will be a grade 3 toxicity rate of $\leq 13\%$ and a grade 4 toxicity rate of $\leq 7\%$. (3) The induction of Th1 immunity will be compared against the presence or absence of a complete pathologic response to determine if there is a significant correlation using Pearson r correlation analysis. Targeted Accrual: The study will accrue up to 16 patients. Clinical trial information: NCT04329065. Research Sponsor: Department of Defense.

LBA637

Rapid Abstract Session

Nine-weeks versus one-year trastuzumab for early-stage HER2+ breast cancer: 10-year update of the Short-HER phase III randomized trial. *First Author: Pier Franco Conte, Department of Surgery, Oncology and Gastroenterology, University of Padua, and Veneto Institute of Oncology IOV-IRCCS, Padua, Italy*

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2023, issue of the *Journal of Clinical Oncology*.

LBA1000

Oral Abstract Session

Primary outcome analysis of the phase 3 SONIA trial (BOOG 2017-03) on selecting the optimal position of cyclin-dependent kinases 4 and 6 (CDK4/6) inhibitors for patients with hormone receptor-positive (HR+), HER2-negative (HER2-) advanced breast cancer (ABC). *First Author: Gabe S. Sonke, The Netherlands Cancer Institute, Amsterdam, Netherlands*

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2023, issue of the *Journal of Clinical Oncology*.

1001

Oral Abstract Session

Second-line endocrine therapy (ET) with or without palbociclib (P) maintenance in patients (pts) with hormone receptor-positive (HR+/+)human epidermal growth factor receptor 2-negative (HER2-) advanced breast cancer (ABC): PALMIRA trial. *First Author: Antonio Llombart-Cussac, Hospital Arnau de Vilanova, Universidad Católica de Valencia, Medica Scientia Innovation Research (MEDSIR), Barcelona, Valencia, Spain*

Background: Cyclin-dependent kinases 4 and 6 inhibitors (CDK4/6i) in combination with ET has become a standard first-line treatment for pts with endocrine-sensitive, HR+/+/HER2- ABC. The optimal treatment after progression on a CDK4/6i remains unknown. This study aims to determine if P maintenance with an alternative ET improves the antitumor activity of second-line treatment in this patient population. **Methods:** A total of 198 pts with HR+/+/HER2- ABC who had disease progression to first-line P plus ET (aromatase inhibitor or fulvestrant) were included. Pts were eligible if they had clinical benefit to the first-line treatment defined as response or stable disease ≥ 24 weeks, or who had progressed on a P-based regimen in the adjuvant setting with disease progression after at least 12 months of treatment but no more than 12 months following P treatment completion. Pts were randomly assigned (2:1 ratio) to receive P plus second-line ET (letrozole or fulvestrant, based on prior ET) or second-line ET alone. Stratification factors were prior ET and the presence of visceral involvement. Primary endpoint was investigator-assessed progression-free survival (PFS) determined by RECIST v.1.1. Secondary endpoints included overall response rate (ORR), clinical benefit rate (CBR), overall survival, and safety. The 2-sided log-rank test ($\alpha = 0.05$) had an 80% power to detect a hazard ratio ≤ 0.59 in favor of P maintenance. **Results:** Between April 2019 and October 2022, 136 and 62 pts were randomized to receive P+ET and ET, respectively. Pts characteristics were well balanced. Median age was 59 years (range: 33-85), 61.1% were ECOG 0, 61.1% had visceral disease, and 89.9% received aromatase inhibitor + P as first-line treatment for metastatic disease. At median follow-up of 8.7 months and 155 PFS events, median investigator-assessed PFS was 4.2 months (95% CI 3.5–5.8) in the P+ET vs. 3.6 months (95% CI 2.7–4.2) in the ET arm (hazard ratio 0.8, 95% CI 0.6–1.1, $p=0.206$). This result was consistent across all stratification subgroups. 6-month PFS rate was 40.9% and 28.6% for P+ET and ET, respectively. Among 138 pts with measurable disease, no significant differences were observed in ORR (6.4% vs. 2.3%) or CBR (33.0% vs. 29.5%) for P+ET and ET, respectively. Grade 3-4 adverse events were higher in pts treated with P+ET (45.2% vs. 8.3%) and no new safety signals were identified. No treatment-related deaths were reported. **Conclusions:** For HR+/+/HER2- ABC pts, maintaining P with a second-line ET beyond progression on prior P-based therapy did not significantly improve PFS compared with second-line ET alone. Planned biomarker analysis may help identify which pts are more likely to benefit from this therapeutic approach. Clinical trial information: NCT03809988. Research Sponsor: Pfizer.

1002

Oral Abstract Session

Dynamics and type of ESR1 mutations under aromatase inhibitor or fulvestrant combined with palbociclib after randomization in the PADA-1 trial. *First Author: Luc Cabel, Curie Institute, Saint-Cloud, France*

Background: In PADA-1, ER+ HER2- metastatic breast cancer patients who displayed a rising ESR1 mutation in blood (bESR1mut) during a first-line therapy with aromatase inhibitor (AI) and palbociclib were randomized between keeping the same treatment or switching to fulvestrant (FUL) and palbociclib (PAL) (Bidard, Lancet Oncol 2022). In this analysis, we investigated the kinetics of bESR1mut after randomization, under AI+PAL or FUL+PAL. **Methods:** Patients who had a rising bESR1mut detected and no synchronous disease progression underwent further serial ctDNA analyses at randomization and then every 2 months until disease progression. ctDNA analysis at randomization, i.e. before any change in endocrine therapy, was intended to study the impact of sampling fluctuations – since rising bESR1mut levels were often close to the limit of detection of the assay. bESR1mut detection was performed with droplet digital PCR (Jeannot, Oncogene 2020), while left over samples were subjected to next-generation sequencing, which allowed for bESR1mut typing and clonality assessment (Callens, Anal Chem 2022). **Results:** 172 patients were randomized in PADA-1 after having a rising bESR1mut and no synchronous disease progression. In these patients, bESR1mut had a median mutant allelic frequency of 0.8 % (range 0.1-25.8%) and a median copy number of 14 copies/ml of plasma (4-1033) on the “rising” sample, with no imbalance between randomization arms. Among them, N=75 (46.6%) had no bESR1mut detected at the repeat blood sample at randomization. Of note, these patients had a lower level of bESR1mut at “rising” compared to those who remained bESR1mut+ at randomization ($p=0.01$). After treatment start, patients who were switched to FUL+PAL experienced a higher rate of bESR1mut clearance at 2 months, compared to those remaining on AI (70.9% vs 32.8%, $p<0.001$). bESR1mut clearance at 2 months was associated with longer PFS (HR=0.36 95%CI=[0.25;0.52], $p<0.001$). The length of bESR1mut clearance was also longer in patients randomized to FUL (median: 7.3 mo 95%CI=[3.7;11.2] vs 1.9 mo 95%CI=[1.8;2.3]; $p<0.001$). At clinical disease progression, N=62 (83%) and N=49 (73%) patients tested positive for bESR1mut in the AI and FUL arms, respectively. Mutation typing in 95 patients with available material revealed that the Y537S mutation was the most prevalent (N=36, 37.9%), while N=25 (26.3%) and N=18 (69.2%) had polyclonal bESR1mut at time of rising bESR1mut and progression, respectively. The mutation type including Y537S- and the presence of polyclonal bESR1mut at time of rising bESR1mut did not influence patients' survival and hazard ratio between arms. **Conclusions:** bESR1mut ctDNA kinetics support the clinical benefit observed in the FUL+PAL arm over the AI+PAL arm. ESR1 mutation type and clonality did not impact the benefit of the treatment switch. Clinical trial information: NCT03079011. Research Sponsor: Pfizer; INCA PRT-K (Grant nb PRT-K19-110).

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Oral Abstract Session

Final overall survival (OS) analysis from the phase 3 TROPICS-02 study of sacituzumab govitecan (SG) in patients (pts) with hormone receptor-positive/HER2-negative (HR+/HER2-) metastatic breast cancer (mBC). *First Author: Sara M. Tolaney, Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA*

Background: Treatment of HR+/HER2- mBC includes sequential endocrine therapy (ET) combined with targeted agents followed by sequential single-agent chemotherapy (CT), which is associated with poor outcomes and quality of life. SG is a Trop-2-directed antibody-drug conjugate approved in multiple countries for pts with metastatic triple-negative breast cancer who received ≥ 1 prior systemic therapy and in the US for pts with pretreated HR+/HER2- mBC. In the phase 3 TROPICS-02 study, SG demonstrated a statistically significant OS benefit versus treatment of physician's choice (TPC) in pts with pretreated, ET-resistant HR+/HER2- mBC at the 2nd planned interim OS analysis with 390 events (median, 14.4 vs 11.2 mo; HR, 0.79 [95% CI, 0.65-0.96]; $P=0.02$; Rugo HS, et al. ESMO 2022. LBA76); this is considered the final analysis per the protocol. Here, we report the results of an exploratory analysis of OS from TROPICS-02 with a longer median follow-up (12.75 mo). **Methods:** Eligible pts with HR+/HER2- mBC who received prior taxane, ET, CDK4/6 inhibitor, and 2-4 prior lines of CT were randomly assigned 1:1 to receive SG (10 mg/kg IV d1 and 8, every 21 d) or TPC until disease progression or unacceptable toxicity. The primary endpoint was progression-free survival by blinded independent central review per RECIST v1.1. Key secondary endpoints included OS and safety. In an exploratory analysis, we evaluated OS by HER2 immunohistochemistry (IHC). **Results:** In total, 543 pts (median prior CT for mBC, 3; visceral metastases, 95%) were randomized to receive SG ($n=272$) or TPC ($n=271$). At data cutoff (Dec 1, 2022), 437 OS events had occurred (median follow-up, 12.75 mo), with 47 (8.7%) new deaths in the SG versus TPC groups (22 [8.1%] vs 25 [9.2%]) since the 2nd planned interim analysis. With this extended follow-up, SG continues to demonstrate improved OS versus TPC (median, 14.5 vs 11.2 mo; HR, 0.79 [95% CI, 0.65-0.95]; nominal $P=0.01$). The OS rates (95% CI) for SG versus TPC were 60.9% (54.8-66.4) and 47.1% (41.0-53.0) at 12 months, 39.2% (33.4-45.0) and 31.7% (26.2-37.4) at 18 months, and 25.6% (20.4-31.1) and 21.1% (16.3-26.3) at 24 months. Overall, 92% of pts were evaluable for HER2 status by IHC (HER2 IHC0, $n=217$; HER2-low, $n=283$). SG demonstrated improved OS versus TPC in the HER2 IHC0 (median, 13.6 vs 10.8 mo; HR, 0.86 [95% CI, 0.63-1.13]) and HER2-low (median, 15.4 vs 11.5 mo, HR, 0.74 [95% CI, 0.57-0.97]) groups. Updated safety will be reported at the time of presentation. **Conclusions:** The final OS analysis of the TROPICS-02 study confirms the clinically meaningful OS benefit of SG over single-agent CT in pts with pretreated, endocrine-resistant HR+/HER2-mBC. This improvement was independent of HER2-low status. This analysis reinforces SG as an effective and safe treatment for this pt population with limited treatment options. Clinical trial information: NCT03901339. Research Sponsor: Gilead Sciences, Inc.

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Oral Abstract Session

A phase 2 study of HER3-DXd in patients (pts) with metastatic breast cancer (MBC). *First Author: Erika P. Hamilton, Sarah Cannon Research Institute, Tennessee Oncology, PLLC, Nashville, TN*

Background: HER3-DXd is an antibody drug conjugate (ADC) comprised of a fully human anti-HER3 IgG1 monoclonal antibody (patritumab), attached to a topoisomerase 1 inhibitor via a tetrapeptide-based cleavable linker that has shown promising efficacy in pts with HER3-expressing MBC (Krop, 2022). This 3-part Phase 2 study examines efficacy of HER3-DXd across MBC subsets and defines the pt population likely to derive greater benefit (NCT04699630). **Methods:** Part A is reported here (Data cutoff 6Sep2022). Pts had HER2 negative MBC with measurable disease per RECIST v1.1, 0-2 prior chemo and prior endocrine therapy (ET) + CDK4/6 inhibitor for hormone receptor (HR)+ BC, or 1-3 prior chemo for triple negative BC (TNBC). Prior treatment (tx) with anti-HER3 agents and ADCs with exatecan derivatives were prohibited. Pts provided pre-tx tissue to evaluate the association of biomarker expression with progression free survival at 6 months (PFS_{6months}). Primary endpoints for Part A are objective response rate (ORR) and PFS_{6months}. Secondary endpoints are safety/tolerability, duration of response (DOR), and clinical benefit rate (CBR) (CR, PR or SD $\geq$ 180 days). **Results:** 60 pts were treated in Part A: median age 57.5 y, 98.3% female; median 5 prior lines of therapy (range 1-15). 32% had TNBC. 48% were HR+. 48% had liver and 32% had lung metastases. HER3 membrane expression was evaluated by overall % membrane positivity at 10X. 47/60 (78%) pts provided evaluable samples at baseline. Among evaluable pts, 64% (30/47) had HER3 expression $\geq$ 75%, 28% (13/47) had 25-74% expression and 8% (4/47) had <25% expression. The median tx duration was 5.2 mos and 21 pts remained on tx at data cut-off. All pts experienced a tx emergent adverse event and 93% of pts experienced a tx related AE (TRAE) with Gr $\geq$ 3 TRAE in 19 pts (32%). The most common ($\geq$ 25%) any grade TRAEs were nausea (50%), fatigue (45%), diarrhea (37%), vomiting (32%), alopecia and anemia (30% each). 7 pts (12%) experienced a serious AE (SAE), including 4 pts (7%) with a related SAE (interstitial lung disease, nausea/vomiting, pneumonitis, thrombocytopenia). 15% of pts experienced a dose reduction and 23% experienced a dose interruption due to an AE. 3 pts died while on tx, 2 unrelated to tx 1 cause unknown. ORR was 35% (95% CIs 23.1, 48.1) for all pts, and the CBR was 48% (95% CIs 35.2, 61.6). Pts with $\geq$ 75% HER3 expression had an ORR of 33% and CBR of 50%, pts with HER3 25-74% expression had an ORR of 46% and CBR of 54%. There were 4 pts with HER3 <25% expression, limiting efficacy assessment. The median DOR was 10.0 mos (95% CIs 5.5, NA). The PFS_{6months} was 60% for all pts, 50% for pts with HER3 $\geq$ 75%, and 70% for pts with HER3 25-74%. **Conclusions:** HER3-DXd had an acceptable safety profile, and the data further confirm the clinical activity in MBC in heavy pre-tx MBC across the broad range of HER3 expression levels. Parts B and Z are ongoing and data from this report support the potential entry of HER3-DXd into the therapeutic paradigm in MBC. Clinical trial information: NCT04699630. Research Sponsor: Sarah Cannon Development Innovations; Daiichi Sankyo.

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Oral Abstract Session

An age-specific pooled analysis of trastuzumab deruxtecan (T-DXd) in patients (pts) with HER2-positive (HER2+) metastatic breast cancer (mBC) from DESTINY-Breast01, -02, and -03. *First Author: Ian E. Krop, Yale Cancer Center, New Haven, CT*

Background: T-DXd is approved for use in pts with HER2+ unresectable or mBC after a prior anti-HER2-based regimen in the metastatic or (neo)adjuvant setting, based on the randomized phase 3 DESTINY-Breast03 study (Cortes et al. *N Engl J Med* 2022). Older pts with HER2+ mBC tend to have worse efficacy and safety outcomes, regardless of treatment (Evans et al. *Cancer Res* 2021). Outcomes of older pts treated with T-DXd have not been thoroughly examined. Here we report age-specific (<65 vs $\geq$ 65 years) efficacy and pooled safety analyses of T-DXd from DESTINY-Breast01, DESTINY-Breast02, and DESTINY-Breast03. **Methods:** DESTINY-Breast01 (data cutoff [DCO], March 26, 2021) and DESTINY-Breast02 (DCO, June 30, 2022) enrolled pts whose disease progressed on trastuzumab emtansine (T-DM1); DESTINY-Breast02 compared T-DXd to chemotherapy of physician's choice. DESTINY-Breast03 (DCO, July 25, 2022) included pts previously treated with trastuzumab and taxane; pts received either T-DXd or T-DM1. **Results:** At baseline, there were 44 (23.9%), 85 (20.9%), and 49 (18.8%) pts $\geq$ 65 years of age who received T-DXd in DESTINY-Breast01, DESTINY-Breast02, and DESTINY-Breast03, respectively. At DCO, median pooled treatment duration with T-DXd was 13.1 mo (range, 0.7-44.0) for pts <65 and 12.4 mo (range, 0.7-45.1) for pts $\geq$ 65. Key efficacy data are shown in the Table. Any-grade treatment-emergent adverse events (TEAEs), grade $\geq$ 3 TEAEs, and serious AEs were observed in 99.6%, 53.6%, and 24.3% of pts <65 and 100%, 65.5%, and 32.2% of pts $\geq$ 65, respectively. There were 125 (18.7%) and 45 (25.4%) TEAEs associated with T-DXd discontinuation in pts aged <65 and $\geq$ 65, respectively. Any-grade adjudicated drug-related interstitial lung disease/pneumonitis occurred in 11.8% of pts <65 and 17.5% of pts $\geq$ 65; grade 5 events occurred in 0.9% and 0.6% of pts <65 and $\geq$ 65, respectively. Additional efficacy and safety data will be presented. **Conclusions:** Results from this pooled analysis further demonstrate that T-DXd has a favorable benefit-risk profile in pts $\geq$ 65 years, with slightly increased toxicity, as expected. Clinical trial information: NCT03248492, NCT03523585, NCT03529110. Research Sponsor: Daiichi Sankyo Inc. and AstraZeneca.

	DESTINY-Breast01		DESTINY-Breast01		DESTINY-Breast03	
	<65 (n=140)	$\geq$ 65 (n=44)	<65 (n=321)	$\geq$ 65 (n=85)	<65 (n=212)	$\geq$ 65 (n=49)
Median overall survival, mo (95% CI)	28.1 (23.3-36.1)	30.9 (21.9-NE)	NR (35.5-NE)	30.2 (22.3-39.2)	NR (40.5-NE)	NR (26.3-NE)
Median progression-free survival, mo (95% CI)	18.1 (13.8-NE)	19.4 (12.4-NE)	17.9 (14.1-20.8)	16.8 (12.7-NE)	30.4 (22.4-NE)	25.1 (14.1-37.3)
Confirmed objective response rate by blinded independent central review, % (95% CI)	62.1 (53.6-70.2)	61.4 (45.5-76.4)	70.7 (65.4-75.6)	65.9 (54.8-75.8)	78.8 (72.6-84.1)	77.6 (63.4-88.2)
Disease control rate, n (%)	136 (97.1)	43 (97.7)	296 (92.2)	82 (96.5)	205 (96.7)	47 (95.9)

NE, not estimable; NR, not reached.

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Oral Abstract Session

Dynamic HER2-low status among patients with triple negative breast cancer (TNBC): The impact of repeat biopsies. *First Author: Yael Bar, Massachusetts General Hospital, Boston, MA*

Background: Trastuzumab deruxtecan (T-DXd) is FDA-approved for HER2-low, but not HER2-0 metastatic triple negative (TNBC) and hormone positive breast cancer. Therefore, identifying HER2-low status is of great clinical importance. Prior studies have shown HER2-low status in TNBC is dynamic, but the correlation between the number of successive biopsies (Bxs) conducted and the likelihood of a HER2-low result is unknown. **Methods:** Patients (pts) were identified from an institutional database including all pts with TNBC treated in a single large academic center between 2017-2022. Only pts with TNBC at diagnosis were included. Bxs without known HER2 status were excluded. Pathological, clinical, and demographic data were extracted. HER2-low was defined as HER2 IHC 1+, or 2+ with non-amplified ISH. The type of Bx was categorized as core Bx, surgical Bx, or metastatic Bx based on the timing and method of Bx acquisition. For the early-metastatic matched analysis, the core Bx was considered the early Bx, unless the core Bx was missing and then the surgical bx was used instead. For cases with several metastatic Bxs the first metastatic Bx was used. **Results:** 529 consecutive pts with TNBC at diagnosis were included. The proportion of pts with HER2-low result increased as the number of successive Bxs increased (60%, 74%, 83%, 87% and 100% when 1 (192 pts), 2 (235 pts), 3 (52 pts), 4 (38 pts), and 5-9 (12 pts) Bxs were conducted, respectively). In women without a prior HER2-low result, about one third converted to HER2-low with each successive additional biopsy (e.g. 322/529 at 1st biopsy, 44/131 on 2nd biopsy, 8/25 at 3rd biopsy, 3/8 at 4th biopsy). HER2 status distribution did not significantly vary between the different types of Bx (58%, 63%, and 54% of pts had a HER2-low result in their core, surgical or metastatic Bx, respectively; p=0.2). Among 246 women with matched core-surgical biopsies, one quarter changed their HER2 status (55% from low to 0, 44% from 0 to low, and 1% from low to 3+). Core-surgical HER2 status conversion rates did not differ between women who had neoadjuvant therapy with residual disease and women who had surgery as their primary intervention. Among women with both matched early-metastatic (70 pts) or two matched metastatic Bxs (39 pts), nearly half (44%) converted their HER2 status (68%, 26% and 6% or 35%, 59% and 6% were converted from low to 0, 0 to low and low to 3+ in the matched early-metastatic or the two matched metastatic Bxs, respectively). **Conclusions:** Our findings show that HER2 status is dynamic in pts with TNBC and support the idea that HER2-low is a spectrum, not a specific entity. We further report the novel finding that for pts with TNBC without a prior HER2-low result, repeat Bxs at progression can increase the chance of obtaining a HER2-low result and provide clinically impactful information. Whether the dynamic HER2 result represents underlying biology or analytic variation remains to be determined. Research Sponsor: None.

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Oral Abstract Session

Randomized trial of fixed dose capecitabine compared to standard dose capecitabine in metastatic breast cancer: The X-7/7 trial. *First Author: Qamar J. Khan, University of Kansas Cancer Center, Westwood, KS*

Background: In metastatic breast cancer (MBC), oral capecitabine prescribed at the FDA approved dose of 1250 mg/m² twice daily, 14 days on followed by 7 days off, is associated with poor tolerance and high discontinuation rates. Mathematical models suggest a fixed dose, dose dense (7 days on, 7 days off) schedule may be optimal for capecitabine efficacy. We conducted a randomized trial to compare the efficacy and tolerability of fixed-dose capecitabine, 1500 mg twice daily, 7 days on, 7 days off (FD) to the FDA approved dose and schedule (SD). **Methods:** Females with MBC and any prior lines of endocrine therapy or chemotherapy were included. HER-2 positive patients were allowed with concurrent trastuzumab. Patients were stratified by line of chemotherapy (first or subsequent), measurable disease, and ER status, and randomized 1:1 to either FD or SD. The primary endpoint was 3-month progression free survival (PFS). Additional endpoints included PFS and overall survival (OS). Capecitabine related toxicities were solicited and graded at each visit. **Results:** Between October 2015 and April 2021, 153 patients were enrolled (N=80 FD, N=73 SD). 78% were hormone receptor positive/HER-2 negative, 11% each were HER-2 positive and triple negative. The 3-month PFS was 76% in the FD arm and 76% in the SD arm (HR=1.01; 95% CI, 0.52 to 1.94; p=0.99). Landmark analysis of PFS at 12, 24 and 36 months is reported. Non-proportional hazards were detected, so restricted mean survival time (RMST) was used to report estimates of effect. PFS (restricted mean) at 36 months was 13.9 months in the FD arm versus 14.6 months in the SD arm (hazard ratio for progression or death, 1.31; 95% CI, 0.56 to 1.15; p=0.24). OS (restricted mean) at 36 months was 21.2 months in the FD arm versus 19.6 months in the SD arm (hazard ratio for death, 0.80; 95% CI, 0.55 to 1.81; p=0.27). Toxicity related treatment discontinuation occurred in 21 patients (28.8%) in the SD arm compared to 6 patients (7.5%) in the FD arm (p<0.0006). Grade 2-4 toxicities (Table) occurred more frequently in patients receiving SD capecitabine (49.3%) as compared to FD capecitabine (25.0%) (p=0.0018). **Conclusions:** Fixed dose capecitabine (1500 mg twice daily) on a 7/7 schedule has less toxicity and similar survival when compared to standard BSA-based dosing on a 14/7 schedule in MBC. Clinical trial information: NCT02595320. Research Sponsor: The University of Kansas Cancer Center and the IIT Steering CommitteeNational Institute of General Medical Sciences (P20 GM130423); The University of Kansas Cancer CCGS from the NCI (P30 CA168524).

Time	Progression free survival by time; adverse events.		P-value (HR; 95% CI)
	FD, N=80	SD, N=73	
	(%)		
12-month	39	50	0.23 (1.31; 0.84-2.02)
24-month	25	23	0.77 (1.06; 0.73-1.53)
36-month	11	0	0.24 (0.81; 0.56-1.15)
Adverse Event			
Diarrhea			
Any Grade	16 (20)	45 (61.6)	0.0039
Grade 2-4	2 (2.5)	15 (20.5)	0.0008
Hand Foot Syndrome			
Any Grade	22 (27.5)	39 (53.4)	0.0033
Grade 2-4	3 (3.8)	11 (15.1)	0.0019
Mucositis			
Any Grade	3 (3.75)	20 (27.4)	0.0001
Grade 2-4	0	4 (5.48)	<0.0001
Neutropenia			
Any Grade	30 (37.5)	31 (42.5)	0.67
Grade 2-4	17 (21.25)	20 (27.4)	0.68

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Oral Abstract Session

CANKADO PRO-React eHealth support in patients with HR+ HER2- metastatic breast cancer receiving palbociclib and endocrine therapy and the affect on time to deterioration of quality of life: Primary outcome analysis of the multicenter randomized PreCycle trial. *First Author: Nadia Harbeck, Breast Center, Department of Obstetrics and Gynecology and CCC Munich, LMU University Hospital, Munich, Germany*

Background: The multicenter, randomized phase IV Intergroup PreCycle trial (NCT03220178) evaluated the impact of CANKADO-based ePRO assessment on quality of life (QoL) in HR+/HER2- locally advanced or metastatic breast cancer (MBC) patients (pts) treated with palbociclib (P) and an aromatase inhibitor or P+fulvestrant. CANKADO PRO-React, an EU-registered medical device, is an autonomous application reacting to changes in pt self-reported QoL. **Methods:** Between 2017 and 2021, 499 pts (median age 59y) from 71 centers were randomized (2:1, stratified by therapy line) between an active (A; CANKADO PRO-React) or an inactive arm (B; inform; limited CANKADO functionality). 412 pts (271 A; 141 B) were available for analysis of the primary endpoint, i.e. time to deterioration (TTD) of QoL (10-point drop on FACT-G), using an Aalen-Johansen estimator for cumulative incidence function of TTD DQoL with 95% pointwise confidence intervals (CI). Secondary endpoints included PFS, OS, and DQoL (QoL deterioration). **Results:** In all pts (ITT-ePRO), a significantly decreased risk (HR 0.6982) for the CANKADO active arm A with 95% CI [0.5059, 0.9635] regarding DQoL was observed (p=0.03). In 1stL pts (n=295), the decreased risk for arm A was 0.7162 (0.4839, 1.06; p=0.09), in 2ndL pts (n=117) 0.6614 (0.3744, 1.168; p=0.2). Absolute pt numbers declined in later visits; until about visit 30, FACT- G completion rates were 80% and higher; mean total scores were similar between arms; the change from baseline showed a linear decline and a nearly constant offset in favor of arm A, particularly in 1st L. No significant differences in clinical outcome were observed between arms: Median PFS (ITT population) was 21.4 (95% CI 19.4-23.7) (A) and 18.7 (15.1-23.5) months (B); median OS was not reached (A) and 42.6 months (B). **Conclusions:** PreCycle is the first multicenter randomized eHealth trial demonstrating a significant benefit of an interactive autonomous patient empowerment application on QoL in MBC pts receiving oral tumor therapy. Clinical trial information: NCT03220178. Research Sponsor: Pfizer.

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Clinical Science Symposium

Association of tumor infiltrating lymphocyte quantity with survival in patients (pts) with metastatic breast cancer (MBC) receiving microtubule-targeting agents: Post hoc analysis CALGB 40502 (Alliance). *First Author: Daniel G. Stover, Ohio State University Comprehensive Cancer Center, Columbus, OH*

Background: Stromal tumor infiltrating lymphocyte (sTIL) quantity is prognostic in primary breast cancer, yet MBC is characterized by lower sTILs. No study has definitively evaluated the association of sTIL quantity with survival outcome in the metastatic (met) setting without checkpoint blockade. CALGB (Alliance) 40502 was a randomized phase 3 trial of 799 MBC pts receiving first-line chemotherapy, comparing paclitaxel, nab-paclitaxel or ixabepilone with or without bevacizumab. We hypothesized that sTILs quantity is associated with outcome in MBC. **Methods:** 582 submitted hematoxylin and eosin slide images from 443 unique pts were evaluable for sTILs in accordance with International TILs Working Group methods. Analysis of sTILs was based on most recent available tissue, with 161/443 (36.3%) having recurrent/met tissue. Using prespecified thresholds of <5% (low) vs ≥5% (high) for sTIL distribution in the met setting, associations between sTILs low/high or as a continuous variable were evaluated with baseline characteristics and outcome. The primary objective was to evaluate the association of sTILs with progression-free survival (PFS) and overall survival (OS), with chemotherapy arm as a covariate. **Results:** High sTILs were more frequent among pts with hormone receptor (HR)-negative disease (64% HRneg vs 34% HRpos, p<0.001), with no significant association with treatment arm, age, menopausal status, race/ethnicity, or body mass index (BMI). Among all evaluable slides, mean sTILs were higher for primary tumors than met (mean 13.3% primary vs 8.4% met, p=3e-4). Among non-lymph node met sites, sTILs ranged from 1.3% (bone) to 9.5% (lung). Among 100 unique pts with paired primary and met slides, the primary had significantly greater mean sTILs (10.5% vs 7.7%, p=0.008). For the primary objective, Cox proportional hazard model of sTILs low vs high was significantly associated with worse PFS (HR 1.34; 95% CI 1.1-1.63, p=0.004) and OS (HR 1.32; 95% CI 1.07-1.63, p=0.009) when controlling for treatment arm. When controlling for both treatment arm and HR status, association of sTILs low vs high demonstrated similar trends but did not reach statistical significance for PFS (HR 1.2; 95% CI 0.97-1.47, p=0.09) or OS (HR 1.14; 95% CI 0.91-1.43, p=0.2). There was no significant interaction between sTILs and chemotherapy arm (all p-interaction >0.05). **Conclusions:** Immune activation measured by sTILs is significantly lower in met tumors than primary breast cancer and varies by met site. In this trial, sTILs were associated with progression-free and overall survival in chemotherapy-treated MBC, with a trend toward independent value adjusted for other prognostic features. Clinical trial information: NCT00785291. Research Sponsor: U.S. National Institutes of Health; Alliance Foundation Trials; BMS, Celgene.

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Clinical Science Symposium

Characterization of the immune microenvironment in matched primary and metastatic breast cancer lesions from the AURORA study: BIG 14-01. *First Author: Florentine Hilbers, Department of Molecular Pathology, Netherlands Cancer Institute, Amsterdam, Netherlands*

Background: Immunotherapy benefit in patients with metastatic breast cancer (MBC) is limited to patients with triple negative breast cancer and PD-L1 expression in the tumor sample. Multi-omics characterization of the anti-cancer immune response in MBC could provide novel insights into the mechanisms behind immune response failure. **Methods:** The AURORA program (NCT02102165) enrolled patients with MBC who received at most one line of treatment in the metastatic setting. RNA sequencing was performed on primary and metastatic lesions. Stromal tumor infiltrating lymphocytes (sTIL) were scored in line with the International Immuno-Oncology Biomarker Working Group for Breast Cancer recommendations. T cell and B cell receptor (TCR and BCR) analysis was performed with MiXCR. Deconvolution of bulk RNA sequencing data was performed using xCell. ImmuneScore-normalized Relative Abundance metastasis/primary Ratios (RAR) of immune cell types were calculated. All comparisons between primary and metastatic lesions were performed on matched samples. Wilcoxon signed-rank tests were used. **Results:** As expected, sTILs decreased from primary to metastatic lesion. However, 9% of metastatic lesions still had ≥20% sTILs. Matched RNA expression data was available for 204 patients. Relative abundance of macrophages (RAR 3.3, p<0.001) and Th1 cells (RAR 1.5, p<0.001) was increased in the metastases, while Treg cells (RAR 0.12, p<0.001), CD8+ T cells (RAR 0.32, p<0.001) and B cells (RAR 0.32, p<0.001) decreased the strongest. Metastases with ≥20% sTILs had higher Treg cells (p<0.001) and B cells (p<0.001) compared to metastases with low sTILs, which had more Th1 cells (p<0.001), mast cells (p<0.001) and NKT cells (p<0.001). De novo metastatic and synchronous primary samples had more BCR (p<0.001) and TCR (p<0.001) clones in common as compared to non-de novo metastatic cancers. **Conclusions:** sTIL percentage decreased from primary tumor to metastatic lesion. Metastatic lesions with many sTILs (≥20%) were enriched for immune response suppressing regulatory T cells. Research Sponsor: Breast Cancer Research Foundation (BCRF), Fondation Cancer (Luxembourg), NIF Foundation, Barrie and Dena Webb, Candriam, Fondation Futur 21, Sogerim, Think Pink Belgium (SMART Fund), Cognizant Foundation, Fund Friends of BIG, and many individual donors; Pfizer grant for non-drug research and Eurofins Foundation; National Lottery (Belgium).

		matched samples	Primary mean sTIL % (IQR)	Metastatic mean sTIL % (IQR)	p-value	Metastatic samples with ≥20% sTILs
Total		716	13 (1-10)	6 (1-1)	<0.001	9%
Subtype	ER+, HER2-	491	11 (1-10)	5 (1-1)	<0.001	6%
	ER+, HER2+	66	12 (1-5)	8 (1-5)	0.39	15%
	ER-, HER2+	31	16 (1-13)	11 (1-5)	0.27	19%
	ER-, HER2-	128	23 (1-40)	10 (1-5)	<0.001	15%
Metastasis	Liver	313	13 (1-10)	2 (1-1)	<0.001	3%
	Lymph node	169	15 (1-15)	12 (1-10)	0.04	19%
	Skin	58	12 (1-7)	4 (1-1)	0.002	3%
	Lung	38	12 (1-10)	20 (1-35)	0.19	32%

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Clinical Science Symposium

RNA expression levels from peripheral immune cells, a minimally invasive liquid biopsy source to predict response to therapy, survival and immune-related adverse events in patients with triple negative breast cancer enrolled in the GeparNuevo trial. *First Author: Hanna Huebner, Department of Gynaecology and Obstetrics, University Hospital Erlangen, Friedrich-Alexander-Universität Erlangen-Nürnberg, Comprehensive Cancer Center Erlangen-EMN (CCC ER-EMN), Erlangen, Germany*

Background: The impact of immune checkpoint therapy on the tumor microenvironment including tumor-infiltrating immune cells is well described. However, little is known about the circulating immune repertoire and its association with treatment outcome. Hence, we set out to investigate the RNA phenotype of peripheral immune cells before and during treatment of patients enrolled in the GeparNuevo trial (Loibl S et al. Annals Oncol 2022). **Methods:** The GeparNuevo trial investigated the outcome after neoadjuvant nabP-EC-chemotherapy in combination with the anti-PD-L1 immune checkpoint inhibitor durvalumab versus placebo in patients with non-metastatic triple negative breast cancer. Blood was collected before therapy (baseline), after window, before epirubicin/cyclophosphamide and at end of treatment. RNA from circulating leucocytes of 117 patients was extracted and analyzed using a custom NanoString nCounter CodeSet. Expression of 290 immune-related genes was quantified. The association of RNA expression and signatures with outcome parameters like pathologic complete response (pCR), distant disease-free survival (DDFS), invasive disease-free survival (iDFS), overall survival (OS), and immune-related adverse events (irAEs) were investigated. **Results:** Immune cell type scores representing macrophages and neutrophils significantly increased during treatment, while B cell, T and Th1 cell scores decreased (p < 0.0001, respectively) regardless of treatment arm. Multivariate logistic respectively multivariate Cox regression analysis revealed a significant association of each baseline *DPP4* and *MYC* gene expression with pCR, DDFS, iDFS, and OS in patients. *CDK2*, *F5* and *HLA-DR* mRNA expressions were associated with the presence of irAEs. The signature score for *TNFR2* non-canonical *NF-κB* pathway, which is known for its protective capacity, was inversely associated with irAEs in the durvalumab arm (OR = 0.454, 95% CI 0.231-0.892, p = 0.0220). Multiple immune-related signatures at baseline were associated with tumor mutational burden. **Conclusions:** Our study indicates the importance of the peripheral immune phenotype for treatment response and survival. This association between RNA expression levels of circulating immune cells and outcome seems to be not only relevant for patients receiving immune checkpoint therapy, but also for those under standard chemotherapy alone. Clinical trial information: NCT02685059. Research Sponsor: This study was funded by Walter Schulz Stiftung and the clinical trial was funded by AstraZeneca and Celgene; Walter Schulz Stiftung; AstraZeneca, Celgene.

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Clinical Science Symposium

BRACELET-1 (PrE0113): Inducing an inflammatory phenotype in metastatic HR+/HER2- breast cancer with the oncolytic reovirus pelareorep in combination with paclitaxel and avelumab. *First Author: Amy Sanders Clark, University of Pennsylvania, Philadelphia, PA*

Background: In preclinical studies, the oncolytic reovirus pelareorep promoted an inflammatory tumor microenvironment (TME) by promoting greater infiltration of tumor infiltrating lymphocytes and upregulating PD-1/PD-L1 expression, potentially increasing the efficacy of immune checkpoint blockade. The addition of pelareorep to paclitaxel (PTX) was associated with improved survival (10.4 vs. 17.4 mos., HR = 0.65, $p = 0.1$) in a prior trial, with the greatest benefit in patients (pts) with hormone receptor-positive (HR+)/human epidermal growth factor receptor 2-negative (HER2-) disease ($N = 57$; 10.8 vs. 21.0 mos., HR 0.60, $p = 0.1$). **Methods:** This is a randomized phase 2 study in pts with HR+/HER2- metastatic breast cancer. Patients must have progressed on at least one hormone therapy with a CDK4/6 inhibitor. After a safety run-in for Cohort 3, patients were randomized 1:1:1 to PTX-alone (Cohort 1), PTX + pelareorep (Cohort 2), or PTX + pelareorep + avelumab (Cohort 3). The primary endpoint was overall response rate (ORR) at week 16 according to RECIST v1.1 without formal comparison across groups. Toxicity, progression-free survival (PFS) and overall survival were secondary endpoints. Blood samples were collected at cycle 1-day 1 (C1D1), C2D1 and C4D1, and T-cell receptor sequencing was performed. **Results:** Forty-eight pts were enrolled between June 2020 and June 2022. Median age was 55.5 yrs, range 37-74. Forty pts (83%) had visceral disease. Six pts (12%) previously received everolimus, and 3 alpelisib. Thirteen pts (27%) received prior taxanes in the neo/adjuvant setting. Three pts who withdrew consent prior to starting therapy and 2 pts who discontinued treatment after week 1 were considered non-responders and were censored for PFS. The most common pelareorep-associated toxicities were fever, chills, and flu-like infusion reactions, which were occasionally severe enough to require hospitalization in 5 (15%) pts despite acetaminophen prophylaxis. Nine pts (33%) discontinued pelareorep and 6 (35%) discontinued avelumab due to toxicity. Pelareorep increased T-cell repertoire turnover, with identification and expansion of new and pre-existing T-cell clones by C2D1. **Conclusions:** The addition of pelareorep to PTX is an active regimen with a high 6-month PFS rate worthy of further study. One third of patients discontinued either pelareorep or avelumab due to toxicity, highlighting the need for attentive supportive care. Survival data is maturing. Clinical trial information: NCT04215146. Research Sponsor: Oncolytics.

	Cohort 1 (n = 15)	Cohort 2 (n = 16)	Cohort 3 (n = 17)
ORR at 16 wks	3 (20%)	5 (31.3%)	3 (17.6%)
Disease Control at 16 wks (CR+PR+SD)	7 (46.7%)	10 (62.5%)	12 (70.6%)
Median PFS	6.4 months (95% CI: 2.0,-)	9.6 months (95% CI: 6.5,-)	7.5 months (95% CI: 3.8,-)
6-month PFS rate	62.5% (95% CI: 27.6, 84.2)	92.9% (95% CI: 59.1, 99.0)	73.2% (95% CI: 42.0, 89.4)

LBA1013

Rapid Abstract Session

TORCHLIGHT: A randomized, double-blind, phase III trial of toripalimab versus placebo, in combination with nab-paclitaxel (nab-P) for patients with metastatic or recurrent triple-negative breast cancer (TNBC). *First Author: Zefei Jiang, Department of oncology, the Fifth Medical Center of Chinese PLA General Hospital, Beijing, China*

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2023, issue of the *Journal of Clinical Oncology*.

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Poster Discussion Session

Efficacy of tucatinib+trastuzumab+capecitabine (TTC) after trastuzumab-deruxtecan (T-DXd) exposure in Her2-positive metastatic breast cancer: A French multicentre retrospective study. *First Author: Jean-Sebastien Frenel, Institut de Cancerologie de l'Ouest, Saint-Herblain, France*

Background: Recent guidelines have positioned T-DXd as a preferred treatment in the second line setting for HER2+ metastatic breast cancer (MBC). TTC is the preferred treatment in third line, however little is known on the efficacy of this combination after T-DXd exposure. **Methods:** We conducted a retrospective study in 12 French comprehensive cancer centers. All patients with HER2+ MBC treated with TTC after prior exposure to T-DXd were included. The primary end point was progression-free survival (PFS) in the whole population. Secondary end-points included overall survival (OS), PFS in subgroups and objective response rate. **Results:** Between 08/2020 and 12/2022, 101 patients were included. Median age was 56.4 y.o. (range 30.8 - 84.8). Median number of prior line of treatment for metastatic disease at TTC start was 4 (2 - 15). 82% and 95% of patients had received previous pertuzumab and T-DM1 respectively. The median duration of previous exposure to T-DXd was 8.9 months (1.4 - 31.4) and 82/101 (81%) patients had progressed under T-DXd while 19 had stopped T-DXd for toxicity or other reasons. TTC regimen was given as a 3rd line or 4th line for metastatic disease in 37/101 (37%) and beyond for the remaining patients. TTC was the immediate subsequent therapy to T-DXd for 86/101 pts (85%). With a median follow-up of 8.5 m (95%CI [7.7; 9.4]), 68/101pts (67%) have stopped TTC for progressive disease. Median PFS was 4.7 m (95%CI [3.8; 5.6]) and median OS not reached (95%CI [10.6; NA]) in the whole population. Patients treated with TTC as the immediate subsequent therapy to T-DXd, had a median PFS of 5.0 m (95%CI [4.0; 6.0]) and a median OS not reached (95%CI [11.9; NA]). Best response to TTC, evaluated by investigators in the 87/101 RECIST evaluable patients, was progressive disease, stable disease, partial response and complete response in 34%, 34%, 30% and 2% of patients respectively. At TTC initiation, 39 (39%) of patients had known brain metastases. Out of the 62 patients without known brain metastases at the initiation of TTC, 2 had brain metastases documented as a site of progression during TTC. **Conclusions:** In this large retrospective cohort, TTC shows significant efficacy for patients with HER2+ MBC previously exposed to T-DXd. Data and subgroup analyses will be updated for the meeting. Research Sponsor: None.

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Poster Discussion Session

Pertuzumab retreatment in patients with HER2-positive locally advanced/metastatic breast cancer: Overall survival results of a phase III randomized trial (JBCRG-M05: PRECIOUS). *First Author: Yutaka Yamamoto, Kumamoto University Hospital, Kumamoto, Japan*

Background: We previously reported that pertuzumab (P) retreatment in combination with trastuzumab (T) + chemotherapy based on physician's choice (C) (PTC) significantly improved investigator-assessed progression-free survival (PFS) compared with T + C (TC) in patients with HER2-positive locally advanced/metastatic breast cancer (LA/MBC) previously treated with P-containing regimens in the phase III PRECIOUS study. Here we report updated OS at the median follow-up of 27.4 mo. **Methods:** Patients previously treated with P-containing regimens as 1st/2nd-line treatment for LA/MBC were randomly assigned 1:1 to two groups, PTC group and TC group, stratified by estrogen receptor (ER) status, previous treatment duration of P, number of previous chemotherapy regimens, and presence or absence of visceral metastasis. The primary endpoint was investigator-assessed PFS. The key secondary endpoints included OS, independent reviewer assessed PFS and safety. Superiority of PTC to TC will be tested using a log-rank test and a one-sided P-value of less than 0.05 will be considered an indicator of superiority. The distribution of OS will be estimated using the Kaplan-Meier method. In addition, the hazard ratio and one-sided 95% CI of the therapeutic effect between the groups will be calculated using the Cox proportional hazard model. **Results:** Of the 219pts enrolled, 217 (108 PTC, 109 TC) were included in the intent-to-treat analysis. At the data cutoff (Dec 31, 2021), OS and PFS events were 138 (63.6%) and 190 (87.6%), respectively. Updated median OS was significantly longer in the PTC group (median OS 36.2 vs. 26.5 mo.; HR = 0.73 [one side 95%CI upper limit, 0.97]; log-rank test $p = 0.0323$). In a prespecified subgroup analysis for OS including ER, visceral metastases, number of previous chemotherapy regimen was broadly constant without disease-free interval. Updated median investigator-assessed PFS (5.5 vs. 4.2 mo.; HR = 0.81 [one side 95%CI upper limit, 1.03]; stratified log-rank test $p = 0.019$) were also significantly better in the PTC group. Median PFS by independent review did not show the difference between two groups (4.4 vs. 4.4 mo.; HR = 1.03 [one side 95%CI upper limit, 1.36]; log-rank test $p = 0.561$). The serious adverse event rate did not differ between the groups (19.0% vs. 23.1%). There were no new safety signals in the two groups. **Conclusions:** Retreatment of P in combination with TC demonstrated significantly improved OS compared to TC. HER2 dual blockade with PT can contribute to improve survival in patients previously treated with P-containing regimens as 1st/2nd-line treatment for LA/MBC. Clinical trial information: NCT02514681. Research Sponsor: Chugai Pharmaceutical.

1016 Poster Discussion Session

The association of centromere amplification and response to trastuzumab in HER2+ metastatic breast cancer. *First Author: Charlotte Andrieu, National Institute for Cellular Biotechnology, School of Biotechnology, Dublin City University, Dublin, Ireland*

Background: Chromosomal instability and copy number aberration (CNA) burden can be associated with patients' survival in some cancers. Centromeres, chromosomal regions crucial for genomic stability, can be found altered by CNA in tumours but remain largely unexplored due to sequencing technologies. Using whole-genome sequencing (WGS) data from cases of long term, never relapsed HER2+ metastatic breast cancer (MBC) patients, also referred as exceptional responders (ExRs), we aim to better characterise the CNA profiles and underlying long-term survival of this "exceptional" cohort and investigate the centromeric and pericentromeric association with prognosis and treatment response. **Methods:** Two hundred and forty-three HER2+ MBC patients were enrolled in the HER2 Patients Project Database from St Vincent University Hospital, Dublin, Ireland. Eighty-five HER2+ MBC patients were identified as exceptional survivors (ExS) with an OS > 60 months (range 60-248 months), of which 28 never-relapsed and responded exceptionally (ExR) to trastuzumab. Patients with an OS < 60 months (N=158, range 0.2-59 months) were identified as non responders (NR). WGS was performed on 13 ExR tumours (primary or metastases) and matching control at a mean depth of 60X and 30X, respectively. Control-FREEC and CNVkit were used to characterise the CNA profiles and estimate the CNA burden. Samples from 10 NR patients were used for comparison with the ExR. **Results:** WGS analysis revealed that ExR samples are more impacted by gain rather than loss of copy overall, with a median fraction altered by gain of 0.24. No significant difference was observed between the ExR and NR in terms of CNA burden. However, a large fragment on chromosome 9 was amplified in 92% of ExR (12/13) which corresponded to the centromere (chr9q11) and a large heterochromatic block (chr9q12). A higher copy number status of this centromeric region was detected in the ExR, with a gain of at least 1 additional copy compared to the NR tumoral samples (P<0.001). The dichotomisation into high versus low copy number of the centromeric region of chromosome 9 was also observed in centromeres of chromosome 17 (P=0.009) and chromosome 19 (P<0.001). No case of polysomy was detected in our cohort and genes located near the centromeres, such as ERBB2 (amplified in both ExR and NR), were independent of the centromeres copy-number status. **Conclusions:** The identification of the genomic aberrations of these metastatic patients, treated with trastuzumab who never relapsed, increases our understanding of the mechanisms involved in MBC progression. Our results suggest that the centromere co-amplification of chr9q11-q12, chr17p11.1-q11.1 and chr19p11-q11 stratifies patients according to their OS. CNA status of the centromeric regions of chromosomes 9, 17 and 19 may therefore represent a novel prognostic predictor to trastuzumab response and new outcomes for patients. Research Sponsor: Cancer Clinical Research Trust (CCRT) Ireland.

1018 Poster Discussion Session

First-line systemic treatment with palbociclib in women aged ≥70 years presenting with hormone receptor-positive advanced breast cancer: Results from the PALOMAGE program. *First Author: Elisabeth Carola, GHPSO, Senlis, France*

Background: Endocrine therapy (ET) combined with a CDK4/6 inhibitor is standard of care for hormone receptors-positive (HR+) advanced breast cancer (ABC). In France, 33% of BC are diagnosed in women aged 70 and older, contrasting with their constant underrepresentation in clinical trials. PALOMAGE, a prospective, observational, longitudinal real-life program, assessed the feasibility of ET combined with palbociclib (PAL), specifically in women aged ≥70 years with HR+ HER2- ABC. **Methods:** Depending on prior treatment for ABC and time of relapse, women were enrolled in two cohorts: ET-sensitive disease (no prior systemic treatment for ABC and no relapse within 1 year after adjuvant ET, cohort A) or ET-resistant disease (relapse on adjuvant ET or < 1 year after completion, or prior treatment for ABC, cohort B). Data collected at baseline and then every 3 months included: sociodemographic, clinical, biological, disease- and treatment-related, response, quality of life (QoL; EORTC QLQ-C30 and ELD14), geriatric (G8 and Geriatric-COre DatasEt (G-CODE)) and safety. Results of feasibility in cohort B (rate of PAL discontinuation at 6 months 28.8%) were reported at SABCS 2021. Here, we report results in cohort A, based on the rate of PAL discontinuation at 18 months for any reason as the primary endpoint. Secondary endpoints included time-to-treatment failure (TTF), progression-free survival (PFS), QoL, and safety. **Results:** For this analysis, 362 patients (from 130 sites) with sufficient data were considered: median age was 78 years (range: 70-94), ECOG was ≥2 in 19.2%, and visceral metastases was present in 39.8%. PAL starting dose was 125 mg, 100 mg, and 75 mg in 80.0%, 14.4%, and 5.6% of patients, respectively, and combined with an aromatase inhibitor in 93.6% or fulvestrant in 6.4%. Baseline scores showed G8 ≤14, ADL ≤5 and IADL ≤3 in 68.2%, 15.5% and 29.4% of patients, respectively. Among the 362 patients, 327 were evaluable for the primary endpoint. With a median follow-up of 20.7 months (95% CI: 18.8-22.0), the 18-month discontinuation rate for PAL was 41.9% (95% CI: 36.6%-47.2%), due to disease progression (20.8%), toxicity (7.7%), patient's choice (6.7%), death (4.6%), or other reason (2.1%). Median TTF and PFS were 22.7 months (95% CI: 19.1-26.0) and 28.1 months (95% CI: 25.6-not reached), respectively. Safety profile showed (360 patients evaluable) 54.4% all grade neutropenia (1.1% febrile neutropenia). Impact of geriatric status on effectiveness and safety will be presented, together with the evolution of QoL. **Conclusions:** In a large real-life population of older women with G8 impaired in two thirds and with ET-sensitive ABC, discontinuation rate of PAL at 18 months was 41.9%, with a median PFS of 28.1 months, consistent with PALOMA2 results. Optimized ET combined with PAL is feasible in unselected older women with HR+ ET-sensitive ABC. Research Sponsor: PFIZER.

1017 Poster Discussion Session

LEONARDA-1: Phase III randomized study of lerociclib plus fulvestrant in patients with HR+, HER2- locally advanced or metastatic breast cancer that has progressed on prior endocrine therapy. *First Author: Binghe Xu, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China*

Background: Lerociclib (GB491), a novel oral CDK4/6 inhibitor with continuously daily dosing, which has demonstrated anti-tumor response and a differentiated safety & tolerability profile in previous clinical trials. The LEONARDA-1 study assessed the efficacy of lerociclib and fulvestrant in endocrine-resistant advanced BC. **Methods:** This is a randomized, double-blind, placebo-controlled phase III study assessing lerociclib in combination with fulvestrant in pre/perimenopausal or postmenopausal, HR+, HER2- locally advanced or metastatic BC patients (pts) who had relapsed or progressed on prior endocrine therapy (ET). Eligible patients were allowed one prior line of chemotherapy for metastatic disease. Pre-/peri-menopausal pts also received goserelin. Pts were randomized 1:1 to receive lerociclib (150mg po bid, d1-28, q4w) or placebo (P) plus fulvestrant (F). The primary endpoint was investigator-assessed progression-free survival (PFS) based on RECIST v1.1. Secondary endpoints included PFS (assessed by BICR), overall survival (OS), response assessment, safety and tolerability, pharmacokinetic (PK) profile. **Results:** By December 2nd 2022 as data cut-off date, 275 pts were randomized, 137 to receive lerociclib + F and 138 to P + F. Median follow-up time was 7.36 months (range, 0.03-11.93+) for lerociclib + F vs 7.33 months (range, 0.03-11.27) for P + F. Baseline characteristics were well balanced (The median age was 54 years and 53.5 years, 41.6% and 44.9% were Pre-/peri-menopausal, 64.2% and 62.3% had visceral disease, 24.8% and 26.1% were primary resistant to prior ET, 28.5% and 29.0% received one line of chemotherapy for metastatic disease, respectively). At the time of cut-off date, 125 PFS events were observed with a median PFS of 11.07 months for lerociclib + F and 5.49 months for P + F (HR: 0.458; 95% CI: 0.317, 0.661, P<0.001 by log-rank test). In patients with measurable disease (n=240, 87.3%), the ORR was significantly higher in lerociclib + F 26.9% (2.5% complete response [CR]) vs 9.9% (0% CR) for P + F. Consistent benefit from lerociclib was seen in pre-/peri-menopausal and postmenopausal subjects. The most common adverse events (AEs) for lerociclib + F versus P + F were neutropenia (90.5% vs. 4.3%), leucopenia (86.9% vs. 6.5%), anemia (34.3% vs. 10.1%), thrombocytopenia (19.7% vs. 3.6%), and diarrhea (19.7% vs. 3.6%). Grade 3 or 4 neutropenia was reported in 46.7% pts on lerociclib + F (G3: 41.6%, G4: 5.1%) vs 0% pts on P + F. There was no case of ≥Grade3 diarrhea reported. The discontinuation rate due to AEs was 0.7% on lerociclib + F and 0% on P + F. Serious AEs were reported for 5.8% and 8.0%, respectively. **Conclusions:** Lerociclib at 150mg twice daily plus fulvestrant significantly improved PFS and ORR and demonstrated a favorable tolerable safety profile in pts with HR+ / HER2- endocrine-resistant advanced BC. Clinical trial information: NCT05054751. Research Sponsor: Genor Biopharmaceutical Ltd.

1019 Poster Discussion Session

Clinico-molecular characteristics associated with outcomes in breast cancer patients treated with CDK4/6 inhibitors: Results from the AURORA Molecular Screening Initiative. *First Author: Elisa Agostinetto, Institut Jules Bordet and Université Libre de Bruxelles (U.L.B.), Brussels, Belgium*

Background: CDK4/6 inhibitor (CDK4/6i) plus endocrine therapy (ET) is the recommended first line standard of care for patients with estrogen receptor positive (ER+), HER2-negative (HER2-) advanced breast cancer (ABC). However, not all patients derive the same benefit from this treatment. We aimed to identify factors associated with outcome in patients treated with CDK4/6i in a real-world setting. **Methods:** AURORA (NCT02102165) is an international program aimed at studying ABC by performing multi-omics profiling on paired primary tumors and metastases. Here we present exploratory results from AURORA patients treated with first line CDK4/6i + ET. DNA from primary and/or metastatic lesions and germline DNA was sequenced for 411 cancer-related genes. Endocrine resistance was defined according to the 5th ABC international consensus guidelines at the start of the first line. Local histology assessment of the primary tumor was used. Progression-free survival (PFS) was calculated from the start of CDK4/6i treatment until disease progression or death (whichever occurred first). **Results:** We analyzed 339 patients treated with CDK4/6i + ET in the first line. PFS differed significantly among the endocrine resistance subgroups (p<0.001). Both TP53 and acquired ESR1 mutations were associated with shorter PFS (hazard ratio [HR] 1.59 [95% CI 1.43-6.73], p=0.004 and 3.10 [95% CI 1.16-2.18], p=0.004 respectively). In a multi-variable analysis, acquired ESR1 mutations were significantly associated with worse PFS independently of endocrine resistance status (HR 2.42 [95% CI 1.01-5.79], p=0.048). Mutations in PIK3CA were not associated with outcome (HR 0.84 [95% CI 0.63-1.13], p=0.25). No PFS difference was observed between lobular and ductal tumors (HR 1.07 [95% CI 0.66-1.75], p=0.61). **Conclusions:** Endocrine resistance status and TP53 and acquired ESR1 mutations were associated with shorter PFS. Factors associated with poor outcome may be used to select patients to test alternative treatment strategies in clinical trials. Clinical trial information: NCT02102165. Research Sponsor: AURORA was funded by Breast Cancer Research Foundation (BCRF) as the main funder; Fondation Cancer (Luxembourg), Fondation contre le Cancer (Belgium), NIF Foundation, Barrie and Dena Webb, Candriam, Fondation Futur 21, Sogerim, Think Pink Belgium (SMART Fund), Cognizant Foundation, Eurofins Foundation, Fund Friends of BIG, managed by the King Baudouin Foundation; Pfizer grant for non-drug research; National Lottery (Belgium).

Subgroup	n (%)	PFS events	Median PFS months (95% CI)
All	339 (100)	194	19.5 (15.9-21.6)
Primary resistant	26 (8)	20	6.6 (3.6-NE)
Secondary resistant	124 (37)	79	14.6 (12.3-19.3)
Endocrine sensitive	93 (27)	48	26.3 (18.6-39.0)
Endocrine Naive	96 (28)	47	27.3 (21.0-40.0)
PIK3CA mutated	137 (40)	73	20.4 (15.6-30.9)
TP53 mutated	79 (23)	54	14.0 (10.8-19.4)
acquired ESR1 mutated*	11 (11)	8	11.7 (3.8-NE)
Lobular	51 (15)	33	19.6 (14.7-26.5)

*Paired samples only (n=96).

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Poster Discussion Session

Trastuzumab deruxtecan (T-DXd) vs treatment of physician's choice (TPC) in patients (pts) with HER2-low, hormone receptor-positive (HR+) unresectable and/or metastatic breast cancer (mBC): Exploratory biomarker analysis of DESTINY-Breast04. *First Author: Shanu Modi, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: DESTINY-Breast04 (NCT03734029) showed improved progression-free survival (PFS) and overall survival for T-DXd vs TPC in pts with HER2-low (IHC 1+ or 2+/ISH-negative) mBC. We present exploratory biomarker analysis in pts with HER2-low, HR+ mBC. **Methods:** Biopsy specimens collected from 326 pts after prior treatment were analyzed using RNA-sequencing and intrinsic subtypes estimated by PAM50 gene expression. *ESR1* and *PIK3CA* mutations and known gene alterations associated with resistance to CDK4/6 inhibitors (CDK4/6i) were assessed in baseline (BL) circulating tumor DNA (ctDNA) samples from 414 pts by Guardant OMNI. Association with objective response rate (ORR) and PFS was evaluated. **Results:** Frequencies of BL intrinsic subtypes in the T-DXd and TPC arms were 41.3% and 46.6% for Luminal A, 48.0% and 37.9% for Luminal B, and 9.0% and 11.7% for HER2 enriched, respectively. According to ctDNA results in the T-DXd and TPC arms, respectively, *ESR1* mutations were observed in 51.3% and 54.0% of pts, *PIK3CA* mutations in 36.1% and 41.6% of pts, and at least one CDK4/6i resistance marker (pts with prior CDK4/6i) was detected in 71.5% and 70.2% of pts. Improved T-DXd efficacy was seen regardless of intrinsic subtype (Luminal A, Luminal B, HER2-enriched), *ESR1* mutation, *PIK3CA* mutation, or CDK4/6i resistance markers (Table). **Conclusions:** Greater clinical benefit was consistently observed with T-DXd vs TPC independent of intrinsic subtype, *ESR1* mutation, *PIK3CA* mutation, or known CDK4/6i resistance marker status. Clinical trial information: NCT03734029. Research Sponsor: This study was funded and designed by Daiichi Sankyo, Inc., and AstraZeneca.

Efficacy in biomarker subgroups.

Subgroup	N T-DXd TPC	T-DXd ORR, % (95% CI)	TPC ORR, % (95% CI)	T-DXd PFS, mo (95% CI)	TPC PFS, mo (95% CI)	PFS Hazard Ratio (95%CI)
Luminal A	92	55.4 (44.7-65.8)	18.8 (8.9-32.6)	13.0 (10.1-16.4)	7.8 (5.4-12.4)	0.57 (0.36-0.89)
Luminal B	107	52.3 (42.5-62.1)	23.1 (11.1-39.3)	8.7 (6.9-11.1)	4.8 (2.7-8.3)	0.60 (0.40-0.92)
HER2 enriched	20	65.0 (40.8-84.6)	8.3 (0.2-38.5)	11.0 (6.6-NA)	2.7 (1.4-5.9)	0.15 (0.05-0.40)
<i>ESR1</i> mutant	142	54.2 (45.7-62.6)	16.2 (8.7-26.6)	9.8 (8.2-12.0)	6.9 (4.3-10.7)	0.67 (0.47-0.97)
<i>ESR1</i> wild-type	135	51.1 (42.4-59.8)	17.5 (9.1-29.1)	10.0 (8.3-12.6)	5.3 (4.0-7.8)	0.43 (0.29-0.62)
<i>PIK3CA</i> mutant	100	53.0 (42.8-63.1)	22.8 (12.7-35.8)	9.7 (7.5-12.3)	6.2 (5.3-7.8)	0.60 (0.40-0.91)
<i>PIK3CA</i> wild-type	57	52.5 (44.9-60.1)	12.5 (6.2-21.8)	10.0 (8.5-12.2)	4.8 (2.9-8.3)	0.50 (0.35-0.70)
CDK4/6i resistance marker ^a positive	153	48.4 (40.2-56.6)	11.0 (4.9-20.5)	9.5 (6.9-10.3)	5.3 (2.9-7.1)	0.56 (0.39-0.80)
CDK4/6i resistance marker negative	73	52.5 (39.3-65.4)	22.6 (9.6-41.1)	12.3 (8.4-23.7)	8.4 (5.4-12.8)	0.57 (0.33-1.01)

^aIncluded only pts with prior CDK4/6i and ≥1 gene alteration (*CCND1*, *CCNE1*, *CDK6*, *FGFR1/2* amplification; *RB1*, *PTEN*, *RAS*, *AKT1*, *ERBB2*, *FAT1* mutation).

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Poster Discussion Session

Sequential use of antibody-drug conjugate after antibody-drug conjugate for patients with metastatic breast cancer: ADC after ADC (A3) study. *First Author: Rachel Occhiogrosso Abelman, Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA*

Background: Optimizing sequential use of Antibody Drug Conjugates (ADCs) is an area of unmet need and of rising clinical importance. With the recent approvals of sacituzumab govitecan (SG) for HR+/HER2- and triple negative metastatic breast cancer (MBC) as well as trastuzumab deruxtecan (T-DXd) for HER2-low MBC, many patients are now candidates for multiple ADCs. However, given potential cross-resistance based on antibody target vs payload (Coates et al, Cancer Discov. 2021), optimal sequencing remains uncertain. We evaluated the safety and efficacy of ADC after ADC for patients with HER2 negative MBC. **Methods:** We included all patients at an academic institution treated with more than one ADC for MBC. Each line of ADC beyond the first was evaluated for presence of the same "antibody target" or "payload" compared to prior ADC. Clinicopathological information was gathered by chart review. We defined "cross-resistance" as progressive disease (PD) at time of first restaging on second ADC. Progression-free survival (PFS) was evaluated as time from start of treatment to disease progression or death from any cause. All PFS estimation was done using the KM method. All pairwise comparisons across ADC were done using a Wilcoxon Rank Sum test to allow for divergences from normality in progression times. Significance was declared as a type I error less than 0.05. **Results:** A total of 193 patients with MBC were treated with ADCs between August 2014-February 2023. Among these, 32 patients were identified as having received more than one ADC (HR+/HER2- = 13, TNBC = 19, HER2 low = 22). Median age at time of second ADC was 57.1 years (range 31.3-88.6) and patients had received a median of 4 lines (range 2-12) of prior treatment before initiation of second ADC. The median PFS on the first ADC used (ADC1) was significantly longer at 7.55 months (95% CI 3.22-10.25) compared to a median of 2.53 months on the second ADC (ADC2) (95% CI 1.38-4.14) (p=0.006). PFS for ADC2 with antibody target change was 3.25 months (95% CI 1.38 months, n/a) compared to 2.30 months with no target change (95% CI 1.38 months, n/a) (p=0.16). At time of first imaging, cross-resistance was present in 17 cases (53.1%), absent in 12 (37.5%), and not evaluable in 3 cases. When the second ADC contained the same antibody target as the first, cross-resistance was present in 9/13 cases (69.2%), compared to 8/16 cases (50.0%) when the second ADC targeted a different tumor antigen. Similarly, differences were noted based on payload switch vs not. **Conclusions:** This study highlights a subset that had cross-resistance to ADC after ADC, while others had durable responses on latter lines of therapy, particularly if a different antibody target was utilized. Further research is needed to validate these findings and discern mechanisms of clinical resistance to guide optimal sequencing of ADC-based treatment options. Research Sponsor: U.S. National Institutes of Health.

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Poster Discussion Session

HER2-low status discordance between primary and recurrent/metastatic breast cancer in a large-scale cohort. *First Author: Mingxi Lin, Fudan University Shanghai Cancer Center, Shanghai, China*

Background: Trastuzumab deruxtecan (T-DXd) was recently approved to treat unresectable/metastatic HER2-low breast cancer. However, patients whose primary tumor is HER2-0 but recurrent/metastatic lesion is HER2-low will lose therapeutic opportunities for T-DXd if a rebiopsy is not performed. In this study, with the largest sample size to date, we aimed to investigate the prevalence of HER2 status conversion. Moreover, it remains debated whether HER2-0 and HER2-low tumors have different prognoses, probably because previous studies did not assess HER2 status entirely based on recurrent/metastatic lesions. Our study aimed to fill this gap. **Methods:** We included 1299 patients with available HER2 status on both primary tumors and recurrent/metastatic lesions at Fudan University Shanghai Cancer Center and West China Hospital. **Results:** A total of 370 (28.5%) patients experienced HER2 status conversion throughout disease recurrence. 144 (31.7%) HER2-0 tumors converted to HER2-low. Inter-metastases heterogeneity of HER2 status was also observed. Compared to HER2-low tumors, HER2-0 tumors showed a higher TP53 mutation rate in the ER-positive subgroup, and a lower PIK3CA mutation rate in the ER-negative subgroup. Patients with tumors converting from HER2-0 to HER2-low had a longer overall survival (HR = 0.59, adjusted P = 0.033) than those with consistent HER2-0 status in the ER-negative subgroup. By combining four risk factors (ER status, Ki67 index, biopsy site, and disease-free interval), we established the first prediction tool to estimate the probability of HER2 status conversion from HER2-0 to HER2-low/positive. **Conclusions:** HER2 status was unstable during the disease course. Our prediction tool could help to screen out patients with a high probability of HER2 status conversion. Our results support that HER2-0 and HER2-low recurrent/metastatic tumors have different genomic features and prognoses. Research Sponsor: FUSCC.

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Poster Discussion Session

Cyclin E cytoplasmic isoform to predict outcome and benefit to capecitabine treatment in patients with HR+/HER2- metastatic breast cancer from the GEICAM/2013-02 PEARL study. *First Author: Angel Guerrero, Instituto Valenciano de Oncología, GEICAM Spanish Breast Cancer Group, Valencia, Spain*

Background: Cytoplasmic cyclin E protein expression, serving as a surrogate for the low molecular weight cyclin E isoform (LMW-E), is a biomarker associated with aggressive breast cancer and predicts resistance to aromatase inhibitors in luminal breast cancer. We investigated the prognostic and predictive value of cytoplasmic and nuclear isoforms of cyclin E in HR+/HER2- metastatic breast cancer (MBC) patients receiving palbociclib CDK4/6 inhibitor and endocrine therapy (PALBO+ET) versus capecitabine (CAPE) in the GEICAM/2013-02 PEARL trial (NCT02028507). **Methods:** Expression of Cytoplasmic and Nuclear isoforms of cyclin E were assessed by immunohistochemistry (IHC). An H-score based on the proportion and intensity of stained cells was explored using median value to categorize in Low / High expression the Nuclear and Cytoplasmic scores (N and C, respectively). In addition, N and C were independently assigned according to staining intensity (1 = no staining, 2 = weak, 3 = intermediate and 4 = strong staining) and then, combined in 4 phenotypes (Ph): Ph1 (N-/C-); Ph2 (N+/C-); Ph3 (N+/C+); and Ph4 (N-/C+), where negative=1-2, and positive=3-4. Cox regression models' analysis were assessed to predict outcome and benefit to treatment, in terms of PFS and OS. Multivariate models were adjusted for confounders: age, site of disease, sites of metastasis, prior chemotherapy for MBC and treatment. Interaction analysis with treatment arm were performed. **Results:** Cyclin E protein was obtained from 344 tumors, with 73% being primary tumors and 27% metastatic. High expression of the Nuclear isoform was independently associated with significantly worse OS (median OS [mOS]=34.23 months [m] for low expression vs 25.72m for high expression; adjusted HR=1.48; p-value=0.016). Phenotype analysis supported this finding, with Ph3 (N+/C+) and Ph4 (N-/C+) demonstrating the worst (mOS=19.55m) and best (mOS=37.19m) outcomes, respectively (using Ph1 as reference, Ph3 HR=2.92; p-value=0.0013). The interaction between the treatment arm and Cytoplasmic cyclin E expression was significant (p=0.0052). Patients with high expression of the Cytoplasmic isoform had significantly better PFS with CAPE (mPFS=14.8m) than with PALBO + ET (mPFS=5.73m) (HR=1.9, p-value=0.0418). Ph4 (N-/C+) had also significantly better PFS for CAPE (mPFS=22.67m) than for PALBO + ET (mPFS=8.51m) (HR=2.94; p-value=0.036). **Conclusions:** This study confirms Cyclin E as a poor prognostic marker associated with worse overall survival in luminal MBC patients. Low molecular weight Cyclin E, detected as Cytoplasmic Cyclin E, identifies luminal MBC that benefit more from CAPE than from PALBO + ET. The low molecular weight Cyclin E isoform appears to be a promising predictive biomarker for the benefit of CAPE and resistance to PALBO + ET treatments in this population. Clinical trial information: NCT02028507. Research Sponsor: AstraZeneca, Pfizer, SEOM.

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Poster Discussion Session

Early prediction of endocrine responsiveness in ER+/HER2 negative MBC: Pilot study with 18F-fluoroestradiol (18F-FES) CT/PET. *First Author: Alessandra Grennari, Università del Piemonte Orientale - Dipartimento di Medicina Traslazionale - DIMET, Novara, Italy*

Background: Estrogen receptors (ER) are considered predictive biomarkers to identify ER+ MBC patients who would likely benefit from endocrine therapies (ET). However, 30 to 40% of ER+ MBC patients fail to achieve a durable response. 18F-FES PET/CT has been shown to represent a valuable and accurate diagnostic tool to determine ER status at the level of metastatic sites and can be proposed as a valid alternative to biopsy of metastatic lesions. In this trial, we evaluated 18F-FES PET/CT as a predictive tool for endocrine responsiveness in ER+ MBC. **Methods:** ET-FES is an international, multi-center, academic clinical trial, conducted within the JTC-2011 ERA-NET TRANSCAN programme. Patients with ER+/HER2- MBC and first evidence of relapse were eligible for the study. All patients underwent a baseline 18F-FES PET/CT in addition to conventional staging procedures. Tumors were classified as endocrine sensitive if overall Standardized Uptake Value (SUV) ≥ 2 ; SUVmax was measured in the 3 largest lesions to quantify ER expression and a cutoff value of 2 was used to dichotomize results (endocrine sensitive vs resistant). In the ET-FES trial, patients with SUV ≥ 2 received single agent ET until PD; patients with SUV < 2 were randomized to receive single agent ET or chemotherapy (CT). The predictive role of 18F-FES PET/CT results was assessed for PFS and OS by univariate and multivariate analyses. **Results:** Overall, 147 patients (142 for ITT analysis) were enrolled from 04/2015 to 12/2020; 113 presented with 18F-FES SUV ≥ 2 and received ET; 29 pts, with SUV < 2 were randomly assigned to ET or first line chemotherapy (CT), following local clinical practice. After a median follow up of 4.6 years, 51 deaths had occurred (54.2%). Median PFS was 18.0 months (95%CI 11.2- 22.9) in the overall population and in 18F-FES SUV ≥ 2 versus 12.4 months (95%CI 3.1 – NR) in patients with SUV < 2 treated with ET and 23.0 months (95%CI 7.7 – 30.0) if treated with CT. Median OS was not reached in the overall patient population and in patients with SUV ≥ 2 , treated with single agent ET. Median OS was 28.1 months (95%CI 14.2 – NR) in patients with SUV < 2 treated with ET versus 52.8 months (95%CI 16.1 – NR) if treated with CT. The Kaplan–Meier estimate of OS at 48 months was 64.4% (SE +/-5%) in all patients and 66% in 18F-FES SUV ≥ 2 ; at 60 months was 54.4% (SE +/-6%) and 57% (SE +/-5%), respectively. Among the 113 pts with SUV ≥ 2 treated with ET, the Kaplan–Meier estimate of OS at 60 months was 73.0% if treated with aromatase inhibitors versus 35% in case of fulvestrant or tamoxifen ($p < 0.0005$). **Conclusions:** ET-FES is the first prospective trial to assess the efficacy of ET alone in patients selected for endocrine responsiveness on the basis of whole body molecular ER imaging by 18F-FES PET/CT. These results suggest that the efficacy of ET may be maximized by using the appropriate assessment of endocrine responsiveness at the different metastatic sites. Clinical trial information: EUDRACT 2013-000-287-29. Research Sponsor: ERANET TRANSCAN JTC - AIRC (Italian Foundation for Cancer Research).

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Poster Session

Clinical features, genomic landscapes, and survival outcomes of HER2-low breast cancer. *First Author: Jin Juan, Department of Breast and Urological Medical Oncology, Fudan University Shanghai Cancer Center, Shanghai, China*

Background: Novel human epidermal growth factor receptor 2 (HER2)-directed antibody–drug conjugates prompt the identification of the HER2-low subtype. To investigate whether HER2-low breast cancer can be defined as a distinct biological subtype, our study conducted a comprehensive analysis on the clinical and molecular features among patients with different HER2 statuses. **Methods:** Clinical and genomic data of 579 metastatic breast cancer patients were reviewed from our next-generation sequencing (NGS) database. Genomic data of breast tumor samples was generated by targeted NGS using a cancer-related gene panel. The cohort included 220 HER2-zero, 194 HER2-low and 165 HER2-positive patients according to the HER2 status from the most recent pathological results. **Results:** First, the clinicopathological characteristics of HER2-low patients were associated with hormone receptor (HR) status. Less lymph node invasion and higher bone metastasis in HER2-low patients were probably because of the higher percentage of HR-positive tumors in HER2-low patients than HER2-zero and HER2-positive patients (63.19%, 42.02% and 28.00%, respectively, $p < 0.0001$). Second, HER2 status shifting from primary to recurrent breast cancer was common, with 38.1% and 48.4% of HER2-zero primary tumors converting to HER2-low tumors when they metastasized in the whole population and the HR-positive subgroup, respectively. Third, HER2-low patients had more brain and lung metastases and cases of de novo stage IV breast cancer than HER2-zero patients in the HR-positive subgroup. Fourth, germline *BRCA2* mutations were observed only in HER2-low patients (11/139, 7.91%) and HER2-low tumors had more somatic *PIK3CA* mutations than HER2-zero tumors in the HR-negative subgroup. Fifth, HER2-low patients had a longer median overall survival (mOS) and median disease-free survival (mDFS) than HER2-zero patients (mOS: 49.1 vs. 30.3 months, log rank $P = 0.0005$; mDFS: 28.17 vs. 20.27 months, log rank $P = 0.036$), but difference was not evident when paired by HR status. Finally, three molecular subtypes based on genomic alterations in HER2-low breast cancer were identified, and Cluster 2, which enriched in *TP53* mutations, was significantly associated with worse outcomes, which provided novel insights into heterogeneity in HER2-low breast cancer. **Conclusions:** The clinical and molecular significance of HER2-low status was influenced by HR expression, and HER2-low tumors had distinct features in subtype analyses based on HR status. Our elaboration of molecular subtypes in HER2-low tumors encourages clinicians to consider the heterogeneity in HER2-low breast cancer. Research Sponsor: National Natural Science Foundation of China (ID: 81903084).

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Poster Discussion Session

Prostate-specific membrane antigen (PSMA) expression in patients with metastatic triple negative breast cancer: Initial results of the PRISMA study. *First Author: Guilherme Nader Marta, Academic Trials Promoting Team, Institut Jules Bordet and l'Université Libre de Bruxelles (U.L.B), Brussels, Belgium*

Background: Radioligand therapy (RLT) targeting prostate-specific membrane antigen (PSMA) prolongs survival of patients (pts) with prostate cancer. Preliminary immunohistochemistry (IHC)-based studies suggest that PSMA is highly expressed in triple negative breast cancer (TNBC). The PRISMA study aims to assess PSMA expression in pts with metastatic TNBC (mTNBC) via positron-emission tomography/computed tomography (PET/CT) to evaluate the feasibility of PSMA-targeted RLT for TNBC. **Methods:** PRISMA is a prospective, single-center study that enrolled pts with progressive mTNBC and measurable disease on ^{18}F -FDG PET/CT to undergo ^{68}Ga -PSMA-11 PET/CT. TNBC definition (ASCO/CAP) was based on the IHC of the primary breast cancer (BC) or metastasis. Target lesions (TL) were defined as metastatic lesions ≥ 1.5 cm with significant uptake in ^{18}F -FDG-PET/CT. The same TL regions were propagated to the ^{68}Ga -PSMA-PET/CT. ^{68}Ga -PSMA-11 maximum standard uptake value (SUV_{max}) was measured for each TL. PSMA patterns A and B were defined according to presence of a majority (pattern A) or a minority (pattern B) of positive TL on ^{68}Ga -PSMA (ie. uptake greater than that of normal liver parenchyma). Mann-Whitney U test was used to assess differences in median SUV_{max} (mSUV_{max}) between subgroups. **Results:** Ten pts with progressive mTNBC were enrolled. One pt was excluded due to lack of TL on ^{18}F -FDG-PET/CT. Median age was 48 years (range 36-68), median number of TL per patient was 8 (5-18). Five pts had a TNBC IHC since the initial BC diagnosis, while 4 had a switch to TNBC (4 with initial estrogen receptor [ER]-positive and 1 with HER2-positive BC). All evaluable pts had inter- and intra-organ heterogeneity in PSMA uptake in TL and 2 pts had some mismatch with FDG-positive and PSMA-negative TL. mSUV_{max} was 2.99 (range 1.7-6.3) in the overall population and was higher in pts with pattern A (5.1 vs 2.6 in patterns A and B, respectively, $p = 0.03$). mSUV_{max} was numerically higher in younger pts (5.0 vs 2.6 in pts < 50 y and ≥ 50 y, $p = 0.28$), PD-L1-positive (5.0 vs 2.7 in PD-L1-positive and -negative, $p = 0.14$), de novo metastatic disease (5.0 vs 2.9 in de novo and recurrent BC, $p = 0.38$) and those with ER-negative primary breast tumor (3.4 vs 3.0 in ER-negative and ER-positive primary BC, $p = 0.9$). **Conclusions:** A significant PSMA uptake was observed in a proportion of pts with mTNBC. Inclusion of additional pts and translational analyses will allow the identification of PSMA expression determinants. PSMA-targeted RLT may be considered as an innovative therapeutic strategy to be explored in selected pts with mTNBC. Research Sponsor: Association Jules Bordet.

Pts ID	Stage at diagnosis	Treatment lines	PD-L1	PSMA pattern	mSUVmax (range)
1	IV	1	Pos	A	5.0 (1.7-16.0)
2	I	2	Neg	B	2.7 (1.8-5.3)
3	II	2	Neg	B	1.7 (0.7-3.9)
4	II	2	Neg	B	2.2 (2.0-5.0)
5	IV	5	Pos	A	6.3 (1.9-9.6)
7	III	1	Neg	A	3.0 (1.2-7.2)
8	IV	1	Neg	A	2.6 (1.5-4.7)
9	III	4	Pos	B	5.2 (2.5-7.6)
10	II	3	Pos	B	4.1 (1.0-7.6)

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Poster Session

Concordance between liquid and tissue biopsy in participants with newly diagnosed recurrent breast cancer. *First Author: Ana Elisa Lohmann, University of Western Ontario, London, ON, Canada*

Background: Tissue biopsy is recommended to confirm breast cancer (BC) recurrence. Liquid biopsy (including circulating tumour cells (CTCs) and circulating tumour DNA (ctDNA)) is a non-invasive approach for detecting cancer that may provide information to identify treatment choices and replace invasive biopsies. This ongoing study aims to assess the concordance between tissue and liquid biopsy testing in subjects presenting with suspicion of distant recurrence from BC. **Methods:** Patients with suspected metastatic BC were enrolled; tumour characteristics and treatment were recorded. Blood samples were collected within 30 days before tissue biopsy, or within 7-28 days after tissue biopsy and before any systemic or radiation treatment. Samples were shipped to EPIC Sciences and processed within 96 hours; after plasma isolation, nucleated cells were plated; slides and plasma were banked. CTCs were identified using Epic Sciences digital imaging and machine learning algorithms. Single-cell isolation for genomic ctDNA analysis was performed. Cell free DNA was analyzed using a validated NGS panel to detect ctDNA alterations. The presence of metastases was classified as suspicious, highly suspicious, definitely metastatic BC or other by the treating oncologist based on the patient's clinical presentation and biopsy pathology results. Epic Sciences classified samples into similar categories based on CTC and ctDNA assay results. These classifications were performed independently. Sensitivity of the Epic Sciences methodology to detect metastatic BC (as determined by the treating oncologist), and its false positive rate were calculated. **Results:** 100 patients were enrolled from June 2020 to October 2022; shipping delays precluded EPIC assays in six patients; 94 patients were analyzed. Of 83 cases deemed suspicious, highly suspicious, or definitely metastatic BC by the treating oncologist, 61 were also deemed so by Epic Sciences (sensitivity of 73.5%, 95% confidence interval, CI 63.1% - 81.9%). Of 66 cases assigned as suspicious, highly suspicious, or definitely metastatic BC by the Epic Sciences, 4 had new primary cancers (3 lung cancer, 1 hepatocarcinoma), for a false positive rate of 6.1% (95% CI 1.9% - 15.0%). One additional case was classified as un-specified adenocarcinoma (possibly breast) by the treating oncologist; resolution awaits further follow-up. **Conclusions:** Preliminary results show that 73.5% of distant BC recurrences were correctly identified by liquid biopsy. A small number of false positive results occurred in patients with other new primary cancers. Additional analyses with CTC characterization are ongoing. Research Sponsor: Epic Sciences; London Health Science Foundation; Grants.

Treating Oncologist	Epic Sciences		
	Suspicious, highly suspicious or definitely metastatic BC		
	Suspicious, highly suspicious or definitely metastatic BC	Other*	Total
	61	22	83
	5	6	11
	66	28	94

*Other cancer diagnosis, other benign condition and non-diagnostic.

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Poster Session

Effect of homologous recombination deficient (HRD) breast cancers on a distinct immune marker phenotype by comprehensive genomic and immune profiling (CGIP). *First Author: Heidi Chwan Ko, Labcorp Oncology, Durham, NC*

Background: Preclinical evidence suggests that breast cancer with features of genomic instability may upregulate the host antitumor immune response by producing neoantigens through DNA damage and increasing interferon production through the stimulator of interferon genes (STING) pathway. In this study, we evaluated the association between features of genomic instability and immune response in a real-world breast cancer population. **Methods:** We analyzed retrospective comprehensive genomic and immune profiling (CGIP) results from 529 breast tumors tested in the real-world clinical setting. We defined the HRD phenotype as tumor with any single nucleotide variants (SNV), indels, copy number variations (CNV) or fusions in the following genes: ARID1A, ATM, ATRX, BAP1, BARD1, BLM, BRCA1/2, BRIP1, CHEK1/2, FANCA, MRE11A, NBN, PALB2, RAD50 and RAD51. Otherwise, they were considered HR-proficient (HRP). PD-L1 expression (CPS positive ≥ 10) and TMB (high ≥ 10 Mut/Mb) were determined using IHC and DNA sequencing, respectively. mRNA expression signatures of tumor inflammation (TIGS, strong/moderate/weak), cell proliferation (CP, high/moderate/poor) and cancer testis antigen burden (CTAB, high/low) were determined by RNA-sequencing from a 395-gene panel. We used over-representation and proportion analysis using chi-squared test to determine association of HRD to immune correlates. **Results:** Among 529 cases, the median patient age was 63.2 years (25.5-93.5). The majority of patients were female (519, 98%), and the most common tumor histology was invasive ductal carcinoma (287, 54%). A total of 405 (77%) and 124 (23%) of patients had HRD and HRP phenotypes, respectively. A greater proportion of HRD tumors (16%) had higher TMB compared to HRP (5.6%, $p=0.003$). HRP tumors showed a relatively low CP index, whereas HRD tumors were associated with a moderate CP index score ($p=0.007$). HRD phenotype was associated with a significantly higher proportion of weakly inflamed tumors, as represented by lower TIGS scores ($p=0.007$). No significant difference in PD-L1 or CTAB was found between HRD and HRP phenotypes. **Conclusions:** Breast tumors with mutations in the HR genes demonstrated greater TMB and moderate cellular proliferation index of both tumor and immune cells, which suggest susceptibility to immune checkpoint inhibitors. Interestingly, this cohort lacked elevated markers of immune infiltration (TIGS), indicating a mechanism of potential tumor immune evasion. These results suggest that CGIP may allow for more informed treatment decisions in HRD breast cancers. Furthermore, assessment of HR status and immunotherapy susceptibility may support clinical trial selections for therapies targeting the complex interplay of genomic and immune components of breast cancer (e.g., a combination of PARP inhibitor and immunotherapy). Research Sponsor: Labcorp.

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Poster Session

Metastatic patterns and outcomes by HER2 and hormone receptor (HR) status in patients (pts) with metastatic breast cancer (mBC). *First Author: Qianyu Yuan, Flatiron Health, New York, NY*

Background: HER2-low status in mBC is predictive of benefit to trastuzumab deruxetan, but whether it is biologically distinct from HER2-neg disease is unclear. To better understand the prognostic significance of HER2-low status, we assessed patterns of metastases and real world overall survival (rWOS) by HER2 and HR status. **Methods:** Pts with mBC diagnosis from 1/1/2011 to 5/31/2022 were selected from the nationwide de-identified Flatiron Health electronic health record (EHR)-derived database. HER2 and HR status was derived from human abstraction (IHC 0-1+/2+/3+, FISH pos/neg, ER/PR) and machine learning-extraction (to classify IHC 0/1+). HER2 and HR tests prior and up to 60 days after metastatic diagnosis date (met Dx date) were included, results closest to met Dx date were used. Sites of metastasis (SOM) were grouped into mutually exclusive groups: brain, non-visceral (bone, skin, lymph node) and visceral (liver, lung, etc). Metastatic patterns stratified by HR/HER2 status were compared using chi-square tests. The association between HER2 status and rWOS, stratified by HR status, was evaluated using Cox models adjusted for age, race/ethnicity, practice, SOM, SES, and stage. rWOS stratified by HR/HER2 status and SOM were estimated via KM analysis. **Results:** Among 22,932 pts with mBC, HER2-low prevalence was 49%. HER2-low mBC was more likely to be HR+ than HER2-neg or HER2+ (84%, vs 70% and 65%; $p<0.01$). Pts with HER2-low and HER2-neg mBC had similar SOM overall, distinct from HER2+. For example, among HR+ pts, HER2-low and HER2-neg pts were less likely than HER2+ pts to have brain (4% and 4% vs 10%; $p<0.01$) or visceral metastases (51%, 50% vs 58%; $p<0.01$) but more likely to have non-visceral metastases (45% and 46% vs 32%; $p<0.01$). Compared to HER2-low pts, HER2-neg pts had similar rWOS if HR+ (hazard ratio 1.02, 95% CI 0.98-1.08) and slightly worse if HR-neg (hazard ratio 1.18, 95% CI 1.03-1.21). rWOS varied by HR/HER2 status and SOM. **Conclusions:** Our findings indicate that HER2-low mBC has biologic similarities to HER2-neg mBC. While slight differences were observed between HER2-neg and HER2-low pts in the HR-neg subgroup, overall rWOS differences were associated more strongly with HER2+ status, HR+ status, and metastatic pattern, indicating that HER2-low status may be more informative as a predictive rather than a prognostic biomarker. Research Sponsor: Flatiron Health.

rWOS in months, median (95% CI), stratified by HR/HER2 status and SOM.

	HR+/HER2-low N = 9,376	HR+/HER2-neg N = 5,094	HR+/HER2+ N = 2,847	HR-neg/HER2-low N = 1,873	HR-neg/HER2-neg N = 2,153	HR-neg/HER2+ N = 1,570
Brain	17.8 (14.2 - 20.2)	15.9 (13.0 - 24.0)	28.4 (24.9 - 34.2)	8.3 (7.1 - 10.7)	8.3 (6.4 - 9.8)	17.2 (13.4 - 26.5)
Visceral	34.6 (33.3 - 36.5)	33.6 (31.9 - 36.3)	46.1 (42.0 - 50.2)	12.8 (12.2 - 14.1)	11.5 (10.6 - 12.8)	37.2 (33.6 - 41.4)
Non-visceral	47.3 (45.7 - 49.7)	47.2 (43.7 - 49.2)	61.0 (56.0 - 66.2)	21.0 (18.3 - 24.0)	19.6 (18.1 - 23.3)	54.9 (49.0 - 72.9)

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Poster Session

Comparison of immune microenvironment between primary and metastatic breast tumors. *First Author: Heidi Chwan Ko, Labcorp Oncology, Durham, NC*

Background: Immune evasion is one of the mechanisms by which cancer cells gain the ability to metastasize from the primary tumor to distant sites. In triple-negative breast cancer (TNBC), metastatic tumors are shown to be more immunologically silent than primary tumors. As a result, there are varying degrees of responses to immunotherapy between early-stage and metastatic tumors. Positive clinical responses to immune checkpoint inhibitors (ICIs) are seen in patients with early-stage TNBC regardless of PD-L1 expression. In this study, we investigated the differences in the immune signatures of primary and metastatic breast cancer in a real-world patient population. **Methods:** We analyzed retrospective comprehensive genomic and immune profiling (CGIP) results from 529 breast tumors tested in the real-world clinical setting. Tumor specimens were classified as primary breast (PB), any lymph nodes (LN; regional and non-regional) or metastatic visceral (MV) sites. LN samples were chosen as positive controls due to expected elevated inflammatory signaling. PD-L1 (CPS positive ≥ 10) and TMB (high ≥ 10 Mut/Mb) were determined using IHC and DNA sequencing, respectively. mRNA expression signatures of tumor inflammation (TIGS, strong/moderate/weak) and expression of LAG3, TIGIT and TIM3 were determined by RNA-sequencing from a 395-gene panel. LAG3, TIGIT and TIM3 were selected due to emerging clinical trials in solid tumors. We used over-representation and proportion analysis using chi-squared test to determine the association of specimen sites to various genomic and immune correlates. **Results:** Among 529 cases, the median patient age was 63.2 years (25.5-93.5). The majority of patients were female (519, 98%), and the most common tumor histology was invasive ductal carcinoma (287, 54%). A total of 224 (42%), 72 (14%), and 232 (44%) of patients had specimens from PB, LN, MV, respectively, while 1 (0.19%) patient had an unknown source. Samples of PB harbored greater degree of immune infiltration, demonstrating higher TIGS score than MV ($p=0.014$). Primary lesions also demonstrated a greater proportion of PD-L1 positive than metastatic lesions (44% vs 21%, $p<0.001$) and higher expressions of immune checkpoints such as TIGIT ($p<0.001$), LAG3 ($p=0.037$) and TIM3 ($p<0.001$). **Conclusions:** We found that non-lymph node breast cancer metastases harbor a less active immune response than primary breast lesions, showing a lower degree of immune cell infiltration and decreased expression of immune checkpoint markers. These findings support the notion that the immune microenvironment of breast cancer metastases is immunosuppressive and may exhibit a tempered response to ICIs. Therefore, combination treatments of ICIs with chemotherapy, targeted therapies or cancer vaccines may be promising therapeutic approaches to enhance the immune responses and potentially overcome resistance to ICIs in metastatic breast cancer. Research Sponsor: Labcorp.

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Poster Session

Gene expression profiling of paired primary breast cancers and brain metastases to identify brain metastases-specific biological changes. *First Author: Gaia Griguolo, Department of Surgery, Oncology and Gastroenterology, University of Padua, and Division of Medical Oncology 2, Veneto Institute of Oncology IOV-IRCCS, Padova, Italy*

Background: Despite the clinical impact of breast cancer (BC) brain metastases (BM), their biological complexity still remains poorly understood. We here evaluate the genomic profile of paired primary and metastatic samples to characterize biological changes acquired by BC during metastatization to the brain. **Methods:** The expression of 758 BC-related genes was evaluated using the BC360 Panel (nCounter platform) in matched primary BC and their associated BM. Intrinsic molecular subtyping was determined using the PAM50 subtype predictor (Parker et al. JCO 2009). Hormone receptor (HR) and HER2 status were evaluated on the BCBM. A False Discovery Rate (FDR) corrected paired two-class SAM was used to identify changes in single genes expression between paired BC and BM samples. **Results:** Twenty-one matched primary BC and BM samples were analyzed. BC subtype evaluated on the BMs was distributed as follows: 24% (N=5) HR-/HER2-, 24% (N=5) HR+/HER2- and 52% (N=11) HER2+. A considerable shift in PAM50 subtype was observed between primary BC and paired BM. While subtype concordance was high for HER2-enriched (HER2-E) tumors (100%), all Luminal A (LumA) primary BCs switched to either HER2-E (75%) or Luminal B (LumB, 25%) on the BM sample, as did 45% of Basal-like BCs (Basal to HER2-E). A clinical switch from HER2- primary BC to HER2+ BM (defined by IHC and ISH) was observed in only one pair (5%). Consistently, HER2-E ($p<0.001$) and LumB ($p=0.001$) PAM50 signatures were significantly more expressed, while the LumA ($p<0.001$) and Normal-like ($p=0.001$) signatures were significantly less expressed in BMs as compared to paired primary BCs (FDR-corrected Wilcoxon paired signed rank test). No significant change was observed in the expression of the Basal-like signature ($p=0.562$). Among the 758 evaluated genes, 60 and 318 genes, respectively, were significantly up- and downregulated in BMs as compared to primary BC (FDR $<5\%$). Upregulated genes were enriched, among others, in genes involved in survival and migration (e.g. FGFR4), cell proliferation (e.g. CCNB1, CDK1) and HER2-amplicon (e.g. ERBB2, GRB7). Down-regulated genes were enriched in genes involved in immune response (e.g. CD8A, CCL5, PDCD1LG2, TNF), angiogenesis (e.g. PDGFRB) and response to hormonal stimuli (e.g. ESR1, BCL2). **Conclusions:** Gene-expression profiling of matched primary BCs and BMs shows recurrent gene expression modifications in metastatic samples which might have potential therapeutic implications (e.g. acquisition of HER2-E subtyping and increase in ERBB2 mRNA levels). Research Sponsor: University of Padova - STARS Grant; AIRC.

Primary Breast cancer	Brain Metastasis			
	Basal-like	HER2-enriched	Luminal A	Luminal B
Basal-like	6 (55%)	5 (45%)	0	0
HER2-enriched	0	6 (100%)	0	0
Luminal A	0	3 (75%)	0	1 (25%)
Luminal B	0	0	0	0

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Poster Session

UGT1A1 *28/*28 genotype and risk of toxicity and disease progression in breast cancer patients treated with sacituzumab govitecan-hziy. *First Author: Megan Wong, City of Hope Comprehensive Cancer Center, Duarte, CA*

Background: In metastatic and locally recurrent breast cancer the antibody drug conjugate, sacituzumab govitecan-hziy (SG), is approved as a second-line therapy in triple negative disease and a third-line therapy and beyond for ER+, endocrine resistant disease. UGT1A1 metabolizes the SN-38 payload of SG, and polymorphisms of the gene can lead to decreased enzyme activity and increased toxicity. We sought to determine if patients who were homozygous for the UGT1A1*28 allele (polymorphism (*28/*28)) experienced increased toxicity and a lower rate of disease progression when treated with SG. **Methods:** To evaluate the association of the *28/*28 genotype with the competing endpoints of Discontinuations for Disease Progression, Toxicity, and Futility, this pilot study undertook a single-center, retrospective chart review of breast cancer patients who received SG at City of Hope. Eligible subjects included breast cancer patients who received at least one dose of SG, had a known UGT1A1 status, and were followed for toxicity and disease progression. Data collection and analysis included reasons for discontinuing SG, onset of adverse effects, UGT1A1 status, age, gender, race and ethnicity, prior lines of therapy, and tumor receptor status. **Results:** Between July 2020 and September 2022, 67 women and 1 man underwent UGT1A1 testing prior to initiation of SG; the median age was 57.8 years, 75.0% had triple negative disease, and SG was given as a median third line of therapy. Seventeen (25%) patients were homozygous for *28 and 24 (35.3%) were heterozygous. Notably relating race and genotype, all 7 self-reported Black subjects were either carriers or homozygous for *28; there were no Black wildtype subjects. Most subjects were followed until Discontinuation for Disease Progression (55.9%), Toxicity (8.8%), or Futility (5.9%). Alternatively, 4.4% of subjects were lost to follow-up and 1 subject halted treatment due to cancer remission. The remaining 23.5% of subjects still took SG by the close of study in November 2022. On competing risk analysis comparing the wildtype group, *28/*28's association with increased Discontinuation for Toxicity, was confirmed with a Hazards Ratio of 5.52 (95% confidence interval [CI] 1.15-26.49, p = 0.03). In contrast, Discontinuation for Disease Progression was unassociated to *28/*28 status in comparison to the wildtype group with a Hazards Ratio of 0.80 (95% CI 0.39-1.65, p = 0.54). **Conclusions:** Despite the relatively small sample size, 25% of patients had the *28/*28 genotype. We confirmed that *28/*28 is associated with a higher risk for discontinuation of SG for toxicity without an association to disease progression based on mutation status. Early UGT1A1 testing as standard practice may identify patients at risk for excess toxicity, who may undergo early dose reductions to prevent discontinuation of this important advanced breast cancer treatment. Research Sponsor: City of Hope Comprehensive Cancer Center.

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Poster Session

Comprehensive characterization of androgen receptor expression in breast cancer. *First Author: Priya Jayachandran, Division of Medical Oncology, USC Norris Comprehensive Cancer Center, Keck School of Medicine, Los Angeles, CA*

Background: The androgen receptor (AR) is a hormone-regulated transcription factor that plays an important role in breast cancer (BC) pathogenesis. While estrogen receptor inhibitors are well-studied in BC, the role of AR on prognosis and therapy is less well-known. Here we aim to characterize the clinicopathologic and molecular features of AR expression in BC. **Methods:** 27,169 BC samples were tested by NGS (592, NextSeq; WES, NovaSeq), WTS (NovaSeq) (Caris Life Sciences, Phoenix, AZ). Microsatellite-instability (MSI) was tested by IHC and NGS. Tumor mutational burden (TMB) totaled somatic mutations per tumor (high ≥ 10 mut/Mb). Tumors with AR-high(H) and AR-low(L) expression were classified by top and bottom quartile, respectively. Real world overall survival (OS) and treatment-associated survival was obtained from insurance claims and calculated from tissue collection or treatment start to last contact using Kaplan-Meier estimates. Statistical significance was determined by chi-square and Mann-Whitney U test with p-values adjusted for multiple comparisons (q<0.05). **Results:** Median AR expression was higher in lobular compared to ductal carcinoma (2.2-fold) and in HR+/HER2- compared to TNBC (13.9-fold). Compared to AR-L, AR-H BC had higher frequency of *PIK3CA* (50.6% vs 12.7%), *CDH1* (20% vs 2.2%), *ESR1* (12.8% vs 1.4%), *MAP3K1* (9.4% vs 1.4%), *GATA3* (11.2% vs 2.7%), *AKT1* (5.7% vs 1.4%), *NF1* (8.6% vs 3.6%), *ARID1A* (6.9 vs 3.6%), *SPEN* (2.8% vs 1.5%), and *PTEN* (7.9% vs 6.2%) mutations and TMB high (9.5% vs 7.7%), but lower frequency of dMMR/MSI-H (0.6% vs 1.7%) and PD-L1 (18.7% vs 45.3%) positivity (all p<0.05). AR-H tumors also showed enrichment of the *IL2-STAT5* pathway (NES: 1.33, FDR: 0.24). Further, AR-H BC had higher expression of immune checkpoint genes (*CD274*, *PDCD1LG2*, *LAG3*, *HAVCR2*, *FOXP3*, FC: 1.1-1.4, all p<0.05) and T cell inflamed scores (32.5% vs 26.2%, p<0.05). AR-H BC had increased immune cell infiltration of B cells (6% vs 4%), M2 Mφ (5% vs 2%), and NK cells (3% vs 2%), but decreased infiltration of M1 Mφ (2% vs 3%) (all p<0.05). AR-H BC had upregulation of M2 Mφ related genes (*ARG1*, *IL10*, *CCL17*, *CXCR1*, FC: 1.2-1.8, all p<0.05) and downregulation of M1 Mφ related genes (*CCL2*, *CCL5*, *CXCL9*, *CXCL10*, FC: 1-1.5, all p<0.05). AR-H BC was associated with improved OS compared to AR-L BC (mOS: 1843 vs 1096 days; HR 0.6, 95% CI 0.5-0.7, p<0.00001), and with doxorubicin (2294 vs 2054 days; HR 0.7, 95% CI 0.5-0.9, p<0.001), paclitaxel (2239 vs 1967 days; HR 0.7, 95% CI 0.5-0.9, p<0.001) and trastuzumab (inf vs 2351 days; HR 0.6, 95% CI 0.4-0.9, p<0.01) treatment. **Conclusions:** Our data suggest a strong association between AR expression and increased mutations in several cancer related genes, immune checkpoint markers, the *IL2-STAT5* pathway, differential immune cell infiltration, and improved overall survival. Research Sponsor: None.

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Poster Session

Negative estrogen receptor expression assessed by 18F-FES PET in metastatic breast cancer with ER-positive primary tumor. *First Author: Biyun Wang, Department of Breast Cancer and Urological Medical Oncology, Fudan University Shanghai Cancer Center, Shanghai, China*

Background: The 18F-fluoroestradiol positron emission tomography/computed tomography (18F-FES PET/CT) technique provides a convenient method to evaluate the overall estrogen receptor (ER) expression in metastatic breast cancer (MBC) patients. There are long debates on the characteristics and treatment strategy of patients with positive primary ER lesion but negative ER expression in metastatic disease. 18F-FES PET offers an opportunity to answer this question. **Methods:** This study enrolled MBC patients with ER-positive primary tumor who received 18F-FES PET/CT in our center. Descriptive statistics were used in clinicopathologic characteristics and compared with Chi square test or t test. Progression-free survival (PFS) was estimated by Kaplan-Meier method and compared by log-rank test. **Results:** 16.46% (52/314) patients with an ER-positive primary tumor had negative ER expression assessed by 18F-FES for MBC prior to receiving first-line systemic therapy. The rate of ER-negativity tested by 18F-FES was negatively co-related with levels of ER expression in early stage, with a positive to negative conversion in 2 of 3 (46.3%) ER-low (ie, ER 1%-9%) tumors, 7 of 10 (70.0%) ER-moderate (ie, ER 10%-49%) tumors, 16 of 114 (14.0%) ER-high (ie, ER 50%-95%) tumors, and 1 of 8 (12.5%) ER-very high (ie, ER > 95%) tumors (p < 0.001). Chemotherapy (83.33%, 40/48) was the most common treatment strategy afterward, among which capecitabine monotherapy (64.29%, 27/42) was a dominant alternative. PFS was significantly prolonged with capecitabine alone versus other chemotherapy (median PFS: 13.14 vs 6.21 months, p = 0.035). **Conclusions:** 18F-FES could identify negative conversion of ER in MBC which occurred frequently. Patients with lower ER expression in the primary lesion were more likely to have negative ER expression in the metastasis. In real-world clinical practice, chemotherapy was the primary choice by most physicians and capecitabine monotherapy had shown good efficacy. Research Sponsor: None.

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Poster Session

Metastatic breast cancer (MBC) with ultra-high tumor mutational burden (UHTMB): A comprehensive genomic profiling (CGP) study. *First Author: Kristina Fanucci, Lifespan Health System, Providence, RI*

Background: Pts with MBC whose tumors feature high TMB (≥ 10 mutations/Mb) are eligible for on label immune checkpoint inhibitor (ICI) treatment. This study evaluated the genomic landscape of MBC with "Ultra high" TMB, defined at > 20 mutations/Mb. **Methods:** 2049 MBC underwent hybrid capture-based CGP to evaluate all classes of genomic alterations (GA), TMB, microsatellite instability (MSI) and trinucleotide mutational signatures. HER2 IHC results were available in a subset of pts. PD-L1 expression on immunocytes was determined by IHC (Ventana SP142). **Results:** 45/2049 (2.2%) of MBC were UHTMB. 45 (100%) pts had metastatic disease. 38 (84%) had documented Stage IV disease and 7 documented axillary LN metastases at the time of sequencing. Local breast tumor was used for CGP in 19 (42.2%) MBC and metastatic site biopsy was used in 26 (57.8%). When compared with 2004 non-UHTMB pts with UHTMB were older (mean 64.6 yrs vs 58.2 yrs p < .0001), more often had lobular histology (40.0% vs 14.5% p < .0001) and ER+ disease (86.6% vs 70.0%). Of the 35 UHTMB cases with HER2 IHC data available, 11 (31.4%) were HER2 IHC negative (0+), 21 (60.0%) were HER2-low status (9 1+ and 12 2+/ISH negative) and 3 (8.6%) were HER2 IHC positive (3+), 1/3 HER2 IHC2+ cases and 2/45 (4.4%) of all UHTMB cases were positive for HER2 copy number gain on CGP. UHTMB cases had more driver GA/tumor (mean 9.8 vs 5.7 p < .0001) and were less often TNBC (13.3% vs 27.0% p = .041) compared to non-UHTMB high cancers. Mutation signature analysis revealed APOBEC was predominant in UHTMB samples (82.5%); MMR signature was also observed in 10% of cases. MSI high status was significantly more frequent in UHTMB high cases (11.6% vs 0.4% p < .0001). GA more frequently identified in UHTMB cases included *CDH1* (45.5% vs 14.3% p < .0001), *PIK3CA* (81.8% vs 37.9% p < .0001), *CDKN2A* (11.4% vs 3.2% p = .017), *ARID1A* (25.0% vs 5.0% p < .0001) and *NF1* (20.5% vs 5.9% p = .0014). PD-L1 (*CD274*) gene amplification (2.3% vs 1.3%) or protein expression by the Ventana SP142 assay (57.14% vs 51.10%) were not significantly different among groups. **Conclusions:** UHTMB MBC is a rare, yet clinically important subset of clinically advanced breast cancer driven by APOBEC mutagenesis, with high incidence of ER+ lobular histology and frequent alterations in *CDH1* and *PIK3CA*. In addition to potential benefit from ICI based treatment, UHTMB MBC present with a high frequency of HER2-low status which may impact therapy decisions for this rare disease. Research Sponsor: Foundation Medicine.

	Cases with 10-20 Mut/Mb (120)	Cases with TMB < 20 Mut/Mb (2004)	Cases with TMB >20 Mut/Mb (45)	P Value (TMB < 20 vs >20)
Mean Age	60.3	58.2	64.6	0.000
ER+ Status by IHC	69.10%	68.22%	86.60%	0.013
HER2+ Amplification by CGP	14.17%	8.87%	6.81%	NS
Frequency of ILC Status	31.77%	14.50%	40.00%	< .0001
TNBC Status	20.83%	27.05%	13.30%	0.041
CDH1	27.10%	14.32%	45.50%	< .0001
PIK3CA	55.10%	37.86%	81.80%	< .0001
MSI High Frequency	1.81%	0.40%	11.60%	< .0001
Mean TMB	12.500	3.5	32.4	< .0001

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Poster Session

Association of C-MYC, MYC target gene, and unfolded protein response (UPR) expression with clinical benefit from the oral aurora kinase A (AURKA) inhibitor, alisertib (A), in combination with paclitaxel (P) compared with P alone in patients (Pts) with HER2-negative metastatic breast cancer (MBC). First Author: Sara A. Byron, Integrated Cancer Genomics Division, Translational Genomics Research Institute, Phoenix, AZ

Background: AURKA is a key regulator of the mitotic spindle, G2/M transition and epithelial-mesenchymal transition. AURKA is amplified and/or overexpressed in breast cancer and is associated with therapy resistance and worse survival. A randomized phase II trial in hormone receptor (HR)-positive, HER2-negative and triple negative (TN) MBC pts showed that addition of A to weekly P significantly improved progression-free survival (PFS) compared with P alone (O'Shaughnessy J et al. *JAMA Network Open*, 2021). Pts' primary or metastatic disease tissues were analyzed for biomarkers associated with clinical benefit from A. **Methods:** Retrospective analysis of tumor whole exome and whole transcriptome sequencing of formalin-fixed paraffin embedded pre-treatment tissues from 96 pts (77 HR+, 19 TN) was performed. Clinical benefit from A+P or P was defined as having PFS of at least 6 mos and lack of benefit as PFS less than 6 mos. Enrichment for cancer gene mutations was assessed using Fisher's exact test. Transcriptome data were evaluated for differential expression with DeSeq2 and gene set enrichment analysis (GSEA) and compared to cancer hallmark gene sets. Molecular features were compared between A+P responders and non-responders, P responders and non-responders, and A+P and P responders. P-values <0.05 were considered significant. **Results:** *PIK3CA*, *TP53*, and *CDH1* were altered in 41%, 39%, and 13% of tumors, respectively, and these and other known cancer genes were not associated with A+P benefit. Alterations in *AKT1*, *PIK3CA*, *ERBB2*, *CDH1*, *TP53*, and *KMT2C/KMT2D*, as well as amplifications of *CCND1*, *MYB*, and *MDM2*, did not preclude benefit from A+P. RNA expression of AURKA, or its upstream regulator, FOXM1, was not significantly different based on treatment group or benefit from A+P or P. Increased C-MYC RNA expression (p=0.008), and enrichment for MYC targets and UPR by GSEA were enriched in pts with lack of benefit from P compared to those with benefit from P (p<0.05), but not in pts with lack of benefit from A+P. Wnt/Beta-catenin signaling was enriched in pts with lack of benefit from P compared to those with benefit from P (p=0.03), and with lack of benefit from A+P compared to those with benefit from A+P (p=0.086). Benefit from A+P was associated with enrichment for MYC targets and UPR compared with benefit from P (p=0.024), suggesting activity of A+P, but not P, with high MYC activation and UPR. **Conclusions:** A added to P improved PFS in HR+ HER2- and TN MBC pts compared with P alone. Pts whose breast cancers had increased C-MYC expression, high MYC activation and increased UPR on RNA expression derived greater clinical benefit from A+P than from P alone. Clinical trial information: NCT02187991. Research Sponsor: Takeda Pharmaceuticals.

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Poster Session

Genomic characterization of the GATA3 mutational landscape in breast cancer. First Author: Jason A Mouabbi, University of Texas MD Anderson Cancer Center, Houston, TX

Background: GATA3 expression is broadly used as a biomarker for diagnosing cancer of breast origin and its expression is strongly associated with estrogen receptor (ER)-positive luminal phenotype. Although *GATA3* mutations are observed in 12-18% of breast cancers (BC), they are poorly characterized. Recently, the pharmacological inhibition of MDM2 has been shown to significantly impair tumor growth in *GATA3*-deficient models in vitro, in vivo, and patient-derived xenograft harboring *GATA3* somatic mutations. Therefore, given the potential targetability of *GATA3*-mutated BC cells, it is important to better understand and characterize the mutational landscape of *GATA3* to help guide future prospective clinical studies. **Methods:** We accessed a cohort of BC samples profiled genomically and transcriptomically from two open-source datasets: TCGA (n=961) and METABRIC (n=1866). We used the chi-squared test to analyze the frequency of *GATA3* mutations across PAM50 subtypes (Basal, HER2, Luminal A, Luminal B, Normal-like) and histological BC subtypes (invasive ductal carcinoma [IDC] and invasive lobular carcinoma [ILC]). Mutations affecting other genes in the *GATA3*-mutated samples and the *GATA3* wild-type (WT) samples were compared using the chi-squared test. We analyzed the mutational landscape of the *GATA3* gene and correlated different sites of mutations with *GATA3* expression, MDM2 amplification, other co-occurring mutations, and clinical behavior. *GATA3* expression levels were compared using the Mann-Whitney test. **Results:** Of the analyzed 2,827 BC samples, *GATA3* mutations were unevenly distributed in the five PAM50 subtypes, as Luminal A and B subtypes had the highest frequency (16% and 17%, respectively) and the basal subtype had no observed *GATA3* mutations (p<0.0001). Further analysis showed that *GATA3* mutations were more common in luminal IDC than ILC (17% vs 8.7%; p<0.0001). While mutations in *C9orf72*, *AKT1*, *TBX3* and *ARID1A* were more frequently co-occurring with *GATA3* mutations, mutations in *TP53*, *CDH1* and *PIK3CA* were mutually exclusive with *GATA3* mutations (adjusted p<0.0001 for all genes). Analysis of the *GATA3* mutational landscape identified two types of mutations in *GATA3*: a group of truncating mutations occurring at the end of the *GATA3* gene (after the 307 position including the splice site at 308) and a group occurring before the 307 position. The first group was associated with increased *GATA3* expression, MDM2 amplification, and was mutually exclusive with *TP53* mutations. The second group had little to no effect on *GATA3* expression and behaved similarly to *GATA3* WT. **Conclusions:** A subtype of *GATA3* mutations are mutually exclusive with *TP53* mutations and are associated with increased MDM2 amplification, making them an ideal target for clinical trials involving MDM2 inhibitors. Research Sponsor: None.

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Poster Session

Multi-factor dynamic analysis of ctDNA and CTC to aid the diagnostic prognosis of patients with metastatic breast cancer (MBC). First Author: Qiang Zhang, Northwestern University, Department of Medicine, Division of Hematology/Oncology, CTC Core Facility, Lurie Cancer Center, Chicago, IL

Background: The monitoring of circulating tumor DNA (ctDNA) and circulating tumor cell (CTC) in patients with MBC predicts treatment resistance and prognosis. We previously reported that *ESR1* alterations in ctDNA were associated with tumor tissue characteristics and CTCs which may help to elucidate disease prognosis in MBC (2019 ASCO#1036, 2022 ASCO#1057). Furthermore, ctDNA can be used to evaluate tumor heterogeneity in MBC (2020 ASCO#1028). Here, we report a multi-factor analysis in ctDNA and CTC which may help to elucidate disease prognosis in MBC. **Methods:** This study included 391 MBC patients who received systemic treatment before 2022 under an IRB-approved clinical trial at NU Lurie Cancer Center. Whole blood samples (7.5ml/each) were collected from all patients at three time points including before treatment, three months, and six months after treatment for CTC enumeration using the CELLTRACKS system (Menarini). The corresponding ctDNA was analyzed by Guardant360 NGS evaluating 74-gene mutations. The maximum follow-up period was 380 months from first diagnosis. Causal Inference with Ensemble Learning was used for statistical analyses. **Results:** Of the 391 patients ctDNA analysis, TP53 mutations were found in 160 patients (TP53^{Mut}, 40.92%), CDH1 mutations were found in 21 patients (CDH1^{Mut}, 5.37%), Myc mutations were found in 53 patients (Myc^{Mut}, 13.55%), and BRAF mutations were found in 35 patients (BRAF^{Mut}, 8.95%) inclusive of all timepoints. The corresponding ctDNA mutations were not detected in 231 patients for TP53 (TP53^{WT}, 59.08%), in 370 patients for CDH1 (CDH1^{WT}, 94.63%), in 338 patients for Myc (Myc^{WT}, 86.45%), or in 356 patients for BRAF (BRAF^{WT}, 91.05%). There was shorter median overall survival (mOS) in the ctDNA mutated groups compared to the non-mutated groups: 88 months TP53^{Mut} vs 184 months TP53^{WT}, HR 1.91, P = 0.0002; 133 months CDH1^{WT} vs 81 months CDH1^{Mut}, HR 2.03, P = 0.02; 76 months Myc^{Mut} vs 179 months Myc^{WT}, HR 3.24, P < 0.0001, and 77 months BRAF^{Mut} vs 146 months BRAF^{WT}, HR 2.45, P = 0.007. Furthermore, ≥5 CTCs were found in 32.42% patients. These patients had a shorter mOS compared to patients with no CTC detected at any time point (70.1 months vs 131 months; P < 0.001; HR 2.97). CTC-clusters were 50 times more likely to predict metastasis than single CTCs. We also found that greater than 5 CTC-clusters, clusters with 1-5, and no CTC-clusters were found in 12.55%, 11.25%, and 76.19% patients, respectively. Larger CTC-clusters had shorter mOS at 63 months, 121 months, and 163 months, respectively (P < 0.0001). **Conclusions:** In this study, we identified multiple liquid biopsy factors including ctDNA and CTC-clusters at various time points, and found that these are associated with prognosis. The synergy of multiple ctDNA mutations and CTC-clusters during treatment may expand the predictive role of liquid biopsy for the monitoring of disease progression in patients MBC. Research Sponsor: This study was supported in part by grants from the Lynn Sage Breast Cancer Research OncoSET Program, Robert H Lurie Cancer Center, Northwestern University.

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Poster Session

Preclinical and early clinical data of ZN-1041, a best-in-class BBB penetrable HER2 inhibitor to treat breast cancer with CNS metastases. First Author: Fei Ma, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences, Beijing, China

Background: HER2+ breast cancer brain metastases (BCBM) is an aggressive malignancy with high prevalence and limited treatment options. ZN-1041 is a best-in-class HER2 inhibitor designed to be delivered across the blood-brain barrier (BBB) with high selectivity and broader safety margin to treat HER2+ BCBM. **Methods:** Brain penetration of ZN-1041 and other approved HER2 tyrosine kinase inhibitors (TKI) were evaluated. Anti-tumor activity of ZN-1041 alone or in combination were evaluated in xenograft models. ZN-A-1041-101 (NCT04487236) is an on-going phase 1, multicenter, open-label study. The study comprises first-in-human dose escalation of ZN-1041 monotherapy (phase 1a) in HER2+ solid tumor patients (pts) with or without BM, dose escalation (phase 1b) and expansion (phase 1c) of ZN-1041 in combination with capecitabine and trastuzumab in pts with HER2+ BCBM (including active BM). The primary objective was safety and tolerability. The secondary objective includes pharmacokinetics and anti-tumor response including ORR per RECIST 1.1 and intracranial ORR (iORR) per RANO-BM. **Results:** Unlike currently approved HER2 TKIs which are strong human efflux transporter P-gp and BCRP substrates, ZN-1041 is not a substrate of either and has high BBB permeability, therefore predicted to have good BBB penetration. ZN-1041 alone demonstrated dose-dependent and significant anti-tumor activity when compared to tucatinib in BM model. ZN-1041 could synergize with capecitabine and trastuzumab to demonstrate significantly improved intracranial efficacy in BM models, while maintaining good tolerability. In total, 21 HER2+ mBC pts were enrolled to complete phase 1a and 1b. No dose-limiting toxicities or treatment-related SAE were observed across all dose levels. PK exposure was increased with dose escalation and K_{puu,CSF} of ZN-1041 was 4.9. In ZN-1041 monotherapy, the overall ORR and iORR were 50% in TKI naïve, unequivocal HER2+ pts. The longest treatment duration was 15 months. As of data cutoff (Dec 02, 2022), totally 35 TKI naïve, HER2+ BCBM pts with median 2L treatments were enrolled for phase 1c and all pts were well tolerated to date. Adverse reactions of grade 3 or higher (≥5%) were hepatic function impairment (8.7%), headache (8.7%), hyperbilirubinemia (5.7%), ALT increased (5.7%), AST increased (5.7%), GGT increased (5.7%) and WBC decreased (5.7%). Among 19 BCBM pts with at least twice tumor assessment, the overall ORR was 78.9% (95% CI: 54.4–93.9) and iORR was 73.7% (95% CI: 48.8–90.9), DCR was 100%. In addition, 6 pts completed first tumor assessment and 5 achieved PR and 1 had SD per RECIST 1.1. **Conclusions:** Encouraging efficacy and tolerability was observed for ZN-1041 monotherapy or combined with capecitabine and trastuzumab in TKI naïve, HER2+ BCBM patients. A Phase 2 pivotal trial for HER2+ BCBM with ZN-1041, capecitabine and trastuzumab combination therapy is planned. Clinical trial information: NCT04487236. Research Sponsor: Suzhou Zanrong Pharma Limited.

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Poster Session

Preclinical and early clinical data of ZN-1041 in combination with trastuzumab deruxtecan to treat breast cancer with or without CNS metastases.
First Author: Carey K. Anders, Duke Cancer Institute, Durham, NC

Background: While treatment options for advanced HER2+ breast cancer have improved, HER2+ breast cancer brain metastases (BCBM) remain a clinical challenge warranting the development of additional, brain permeable HER2-targeted therapies. ZN-1041 is a brain permeable, selective HER2-targeted oral tyrosine kinase inhibitor. Preclinical studies have demonstrated efficacy and safety of ZN-1041 warranting clinical development alone and in combination with approved monoclonal antibodies or antibody drug conjugates for patients (pts) with HER2+ BCBM. **Methods:** Anti-tumor activity of ZN-1041 alone or in combination with trastuzumab emtansine (TDM1), trastuzumab deruxtecan (TDXd), or trastuzumab (H) plus pertuzumab (P) was evaluated in BT474 BM orthotopic xenograft models. ZN-A-1041-101-US (NCT05593094) is an on-going phase 1, multicenter, open-label study. The study comprises dose escalation of ZN-1041 monotherapy (Phase 1a) in pts with HER2+ solid tumors with or without BM, dose escalation (Phase 1b) and expansion (phase 1c) of ZN-1041 in combination with TDM1 (Arm 1), TDXd (Arm 2), or HP as maintenance therapy (Arm 3) in pts with HER2+ mBC with or without BM. The primary objectives were safety, tolerability and recommended phase 2 dose. The secondary objective includes pharmacokinetics (PK) and preliminary efficacy per RECIST 1.1. **Results:** Preclinically, ZN-1041 alone or combined with TDM1, TDXd or HP demonstrated significant improvement in intracranial tumor growth inhibition compared to TDM1, TDXd, or HP alone. As of data cutoff, Phase 1a (n = 7 pts) and Arm 2 of Phase 1b (n = 3 pts) were completed. Among 10 pts enrolled, 8 pts had received prior HER2 TKI. In Phase 1a, ZN-1041 was well tolerated with no dose-limiting toxicities (DLTs) or drug discontinuation due to toxicity up to a dose of 800 mg BID. Adverse reactions were mainly grade 1. The most common treatment related adverse reactions (TRAEs≥15%) were grade 1 nausea (43%) and vomiting (29%), with no ≥ grade 2 diarrhea reported. PK exposure was increased with dose escalation. In Phase 1a, one pt with mBC (without BM) achieved a confirmed partial response (PR) at 400 mg BID dose for > 15 months; one with gastric cancer achieved stable disease at the first dose level of 50mg BID for nearly 1 year. In Phase 1b, pts who had previously progressed on TDXd and/or TKI were enrolled and received ZN-1041 at a dose of 800 mg BID in combination with TDXd. Combination therapy was well tolerated with no DLTs reported. One pt with BCBM who was previously on tucatinib and TDXd had a confirmed PR. **Conclusions:** Safety and tolerability was observed for ZN-1041 with maximum tolerated dose 800 mg BID as monotherapy and combined with TDXd in pts with advanced HER2+ malignancies. Encouraging efficacy was observed in treatment-refractory settings. Additional safety and efficacy data of ZN-1041 in combination with TDM1, TDXd or HP are warranted. Clinical trial information: NCT05593094. Research Sponsor: Suzhou Zanrong Pharma Limited.

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Poster Session

Cardiac function of long-responders to dual anti-HER2 antibodies amongst patients with HER2 positive advanced breast cancer.
First Author: Kelvin K H Bao, Department of Clinical Oncology, Queen Elizabeth Hospital, Hong Kong, Hong Kong

Background: Dual anti-HER2 antibodies pertuzumab (P) and trastuzumab (T) in combination with taxane (D), followed by PT maintenance, is the standard first line treatment for HER2 positive advanced breast cancer (HER2+ ABC). Treatment associated cardiotoxicity necessitates regular cardiac function surveillance, which is a burden particularly for treatment long-responders. Data for cardiac safety of prolonged P+T exposure is scarce. We investigate the real-world impact on cardiac function in long-responders to treatment with dual anti-HER2 antibodies. **Methods:** We identified consecutive patients with HER2+ ABC who received the CLEOPATRA regimen (PT-D) between Jan 2014 and Dec 2020 from an institutional cancer registry. All patients had pre-treatment multiple-gated acquisition (MUGA) scan or echocardiogram, and subsequently at 3-monthly intervals until end of treatment to monitor left ventricular ejection fraction (LVEF). Patients on treatment for ≥36 months were considered long-responders. The Wilcoxon signed-rank test was used to assess any significant difference in LVEF at various landmark time-points in comparison to their pretreatment baseline. **Results:** 101 women with HER2+ ABC were eligible for analysis. Median age at treatment was 62 (IQR, 56.0-69.0). The median duration of treatment was 17.3 months (IQR, 9.0-31.3). 22.8% of patients were long-responders, who received a median of 67 cycles of treatment (IQR, 58-88). Compared to baseline, median LVEF was significantly decreased at 6m (median, 66% vs 69%, p=0.02), however there were no significant differences for any of the subsequent time-points up to 84 m. All of the larger LVEF drop (≥10% from baseline) occurred by the first 24 months, representing 4.7% of the overall measurements. Risk factors present for patients experienced treatment suspension (n=3) included previous exposures to anthracycline and left sided radiotherapy. **Conclusions:** In patients with HER2+ ABC who were long-responders to first-line PT-D, prolonged exposure to dual anti-HER2 antibodies was not associated with significant cardiotoxicity. It is safe to de-escalate the cardiac surveillance for this population. Research Sponsor: None.

Time-points (months)	Number of patients	Baseline LVEF (%) (median, IQR)	Subsequent LVEF (%) (median, IQR)	Wilcoxon signed-rank test
0	101	69 (64.0-72.5)	-	-
6	90	69 (64.8-72.3)	66 (63.0-72.0)	p=0.02
12	64	69 (63.5-72.0)	69 (63.0-73.0)	p=0.27
24	48	69 (65.0-72.8)	69 (63.0-73.0)	p=0.76
36	23	71 (63.5-74.5)	68 (63.0-72.0)	p=0.11
48	13	72 (63.5-74.5)	66 (64.0-72.0)	p=0.08
60	8	72 (63.0-74.0)	69 (63.5-71.5)	p=0.17
72	3	74 (66.0-76.0)	71 (64.0-75.0)	p=0.10
84	3	74 (66.0-76.0)	70 (58.0-73.0)	p=0.10

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Poster Session

Anti-HER2 antibody inetetamab plus camrelizumab and utidelone for pre-treated HER2-positive metastatic breast cancer: Final results from the phase 2 ICU trial.
First Author: Huimin Lv, Department of Breast Disease, Henan Breast Cancer Center. The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, Zhengzhou, China

Background: We previously reported (Yan, ASCO 2022) promising efficacy and acceptable safety of anti-HER2 antibody inetetamab in combination with camrelizumab and utidelone regimen in preliminary 20 HER2-positive metastatic breast cancer (MBC) patients who progressed after at least two lines of HER2-directed therapies with trastuzumab and TKIs. Inetetamab is a novel anti-HER2 antibody. Camrelizumab is an anti-programmed death receptor 1 (PD-1) antibody. Utidelone, a genetically engineered epothilone analogue, has shown promising efficacy in heavily pretreated MBC. Here we report the final ICU study results. **Methods:** In the ICU study (NCT04681287), patients received intravenous camrelizumab (200 mg once every 3 weeks), inetetamab (initial dose of 8 mg/kg, then 6 mg/kg, once every 3 weeks), and utidelone (30 mg/m², days 1-5, every 3 weeks) until disease progression or intolerable toxicity. The primary endpoint was 3-month progression-free survival (PFS) rate according to the Response Evaluation Criteria in Solid Tumors, version 1.1. Secondary endpoints included objective response rate (ORR), PFS and safety. Simon's two-stage design was adopted for this study. All AEs were graded according to the grading criteria in the Common Terminology Criteria for the Evaluation of Adverse Events, 5th edition. **Results:** From Apr 23 2021 to Sept 1 2022, a total of 46 HER2-positive MBC patients were enrolled with median age of 52 (range 43-57). As of Jan 18, 2023, the median follow-up was 11.37 months. There were 12 patients (26.09%) with ER+/PR+, 7 patients (15.22%) with ER+/PR-, one patient (2.17%) with ER-/PR+, 26 patients (56.52%) with ER-/PR-. The median number of previous systemic therapies for advanced disease was three. Previous HER2-targeted therapies included trastuzumab (46 [100%]), TKIs (46 [100%], of which pyrotinib 39 [84.78%] and lapatinib 12 [26.09%]), pertuzumab (13 [28.26%]), and margetuximab (3 [6.52%]), T-DM1 or other HER2-ADC (7 [15.22%]). The 3-month PFS rate in 46 patients was 71.84%. The confirmed ORR was 28% (13/46), include one (2.17%) patient achieved complete response. The median PFS was 5.59 months. The most common treatment-related adverse events (TRAEs) were peripheral neuropathy (40 [86.96%]), capillary proliferation (27 [58.7%]), and alopecia (17 [36.96%]). Grade ≥3 TRAEs included rash (3 [6.52%]), peripheral neuropathy (1 [2.17%]) and AST increase (1 [2.17%]). Moreover, there were no grade 4 or above TRAEs. No related treatment discontinuation or deaths occurred. **Conclusions:** Final efficacy and safety results were consistent with previous ICU study preliminary analyses. The ICU study showed a favorable benefit-risk profile and is an important option for Chinese patients with HER2-positive MBC after at least two lines of HER2-directed therapies with trastuzumab and TKIs. Clinical trial information: NCT04681287. Research Sponsor: China Scientific Research Fund for HER2 Target from China Anti-Cancer Association (No.CORT-239-M14).

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Poster Session

Zanidatamab (zani), a HER2-targeted bispecific antibody, in combination with docetaxel as first-line therapy (1L) for patients (pts) with advanced HER2-positive breast cancer (BC): Updated results from a phase 1b/2 study.
First Author: Xiaojia Wang, Department of Oncology, Zhejiang Cancer Hospital, Hangzhou, China

Background: Despite HER2-targeted agents improving outcomes in HER2-positive (+) BC, some pts develop resistance, relapse, or do not respond to current 1L therapies. Zani, also known as ZW25, is a novel HER2-targeted bispecific antibody that binds to two distinct extracellular domains of HER2. Preliminary results from this phase 1b/2 trial (NCT04276493) showed that zani plus docetaxel had a manageable safety profile and demonstrated promising antitumor activity in pts with advanced HER2+ BC; here we present the updated data following enrollment completion. **Methods:** Cohort 1 of this open-label study is evaluating zani in combination with docetaxel as a 1L therapy in adult females with advanced HER2+ BC who may have received prior neoadjuvant/adjunct therapy. Cohort 1a pts received zani 30 mg/kg intravenously (IV), Cohort 1b pts received zani 1800 mg IV, both with docetaxel 75 mg/m² IV every 3 weeks. The primary endpoints were safety and investigator (INV)-assessed objective response rate (ORR) per RECIST v1.1. Secondary endpoints included INV-assessed duration of response (DoR) and disease control rate (DCR). **Results:** As of Nov 22, 2022, 37 pts (median age 55.0 years [range: 33-80]) were assigned to Cohort 1a (n=10) or 1b (n=27). Median study follow-up was 15.5 months (range: 1.1-29.3); patients received a median of 13 treatment cycles (range 1-37) and 18 (48.6%) pts remained on treatment. Of the 33 efficacy evaluable (EE) pts, confirmed ORR was 90.9% (95% confidence interval [CI]: 75.7, 98.1). Efficacy data are summarized in Table. In total, 36 (97.3%) pts experienced ≥1 treatment-related adverse event (TRAE); 25 (67.6%) pts experienced ≥grade 3 TRAEs. The most common ≥grade 3 TRAEs were decreased neutrophil count, experienced by 18 (48.6%) pts, and decreased white blood cell count, experienced by 7 (18.9%) pts. Serious TRAEs occurred in 6 (16.2%) pts; no TRAEs led to death. **Conclusions:** Zani combined with docetaxel demonstrated promising antitumor activity as 1L therapy for advanced HER2+ BC, with a manageable safety profile. Clinical trial information: NCT04276493. Research Sponsor: BeiGene, Ltd.. This study was sponsored by BeiGene, Ltd. Medical writing support for the development of this abstract, under the direction of the authors, was provided by Emily Finn, MSc, of Ashfield MedComms, an Inizio company, and was funded by BeiGene, Ltd.

Summary of efficacy results (EE analysis set*)			
	Cohort 1a (n=8)	Cohort 1b (n=25)	Total (n=33)
Confirmed best overall response, n (%)			
Complete response	1 (12.5)	1 (4.0)	2 (6.1)
Partial response	7 (87.5)	21 (84.0)	28 (84.8)
Stable disease	0 (0.0)	2 (8.0)	2 (6.1)
Progressive disease	0 (0.0)	1 (4.0)	1 (3.0)
Confirmed ORR, n (%)	8 (100)	22 (88.0)	30 (90.9)
95% CI	63.1, 100	68.8, 97.5	75.7, 98.1
Confirmed DCR, n (%)	8 (100)	24 (96.0)	32 (97.0)
95% CI	63.1, 100	79.6, 99.9	84.2, 99.9
Median DoR, months	12.4	NE	NE
(95% CI)	5.5, NE	12.1, NE	12.1, NE
Confirmed DoR, range†	3.5 [‡] -23.5 [‡]	4.3 [‡] -16.5 [‡]	3.5 [‡] -23.5 [‡]

*Four pts without any postbaseline tumor assessments were excluded from the EE analysis set. Data cut off: November 22, 2022.
†Censored.

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Poster Session

Updated results from a phase 2 study on dalpiciclib and pyrotinib, a dual-oral chemotherapy-free regimen in HER2-positive advanced breast cancer (DAP-HER-01). *First Author: Min Yan, Department of Breast Disease, Henan Breast Cancer Center. The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, Zhengzhou, China*

Background: Cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors have shown synergistic effect with anti-HER2 therapy on hormone receptor (HR)-positive and HER2-positive breast cancer from preclinical models and several clinical studies, while data of this combination in HR-negative and HER2-positive diseases are limited so far. DAP-HER-01 (NCT04293276) was aimed at evaluate the efficacy and safety of the novel dual-oral, chemotherapy-free regimen of CDK4/6 inhibitor dalpiciclib and pan-HER tyrosine kinase inhibitor pyrotinib in HER2-positive advanced breast cancer (ABC) regardless of HR status, and reported to meet the primary endpoints previously (overall ORR 70%), in which HR-negative patients achieved a higher ORR (81.8%, vs 55.6% in HR-positive patients; Min Yan, et al. ESMO 2021, Poster 276P). Here we reported the updated results of this trial. **Methods:** DAP-HER-01 was a single-arm, phase 2 study conducted in HER2-positive ABC patients with no more than one prior systemic treatment at advanced setting. Enrolled patients received dalpiciclib and pyrotinib until progression, unaccepted toxicity, or no further benefit. The primary endpoint was ORR as per RECIST 1.1, and secondary endpoints included progression-free survival (PFS), overall survival and safety. **Results:** Between April 9, 2020, and May 19, 2021, 41 patients were enrolled and received study treatment, and 40 of them were assessable for efficacy. With a median follow-up of 19.2 months, the median progression-free survival (PFS) was 11.0 months (95% CI: 7.3-19.3). Considering HR status, the PFS in HR-negative patients was not matured (estimated median: 16.6 months; 95% CI: 7.3-NA), but still showed a tendency to be longer than that in HR-positive patients (median: 9.1 months; 95% CI: 5.4-11.0). Patients with brain metastases at baseline could also benefit from this treatment (median PFS: 11.0; 95% CI: 5.4-NA). Consistent with the safety data reported before, the most common grade 3 or 4 treatment-related adverse events were leukopenia (68.3%), neutropenia (65.9%) and diarrhea (19.5%). Most adverse events were tolerable, and no study-related death reported. **Conclusions:** Combined with previous reports, our findings suggest dalpiciclib combined with pyrotinib achieved promising efficacy and manageable toxicity in the treatment of HER2-positive ABC, including patients with HR-negative disease or brain metastases. This combination could be considered as a completely oral, chemo-free regimen for patients with HER2-positive ABC and is worthy of further study. Clinical trial information: NCT04293276. Research Sponsor: XINRUI Project of Cancer Supportive Care and Treatment Research.

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Poster Session

Real-world treatment patterns in patients with HER2+ unresectable or metastatic breast cancer: Interim results from HER2 REAL Asia cohort. *First Author: Soo-Chin Lee, National University Hospital, Singapore, Singapore*

Background: HER2 REAL (NCT04857619) is the first multi-country, retrospective study exploring the treatment practices and outcomes in patients (pts) with HER2+ locally advanced, unresectable (u)/metastatic (m) breast cancer (BC) from routine clinical care in the APAC and LATAM. **Methods:** Adult HER2+ u/mBC pts diagnosed since reimbursement or wider access of trastuzumab emtansine (T-DM1) or 01 Jan 2017, whichever was earlier with ≥ 12 months (mo) of follow-up data from index date (u/mBC diagnosis) and treated with ≥ 1 -line of therapy (LOT) were enrolled per medical chart review from 6 countries. Here we present interim descriptive analyses (cut-off 30 June 2022) on demographics, clinical characteristics, and treatment patterns. **Results:** Of the 763 enrolled pts, 370 with median (range) age of 55 (20–81) yrs from Hong Kong, Korea, Singapore, and Taiwan were eligible for interim analyses; 368 (99.5%) were female with 210 (57.1%) postmenopausal. A total of 210 (57.1%) pts with reported data had a median time of 2 (0–18) yrs from initial BC diagnosis to u/mBC relapse. At index date, majority had ductal carcinoma (227/254 [89.4%]), visceral (255/355 [71.8%]), and non-visceral (258/355 [72.3%]) metastases; 80/355 (22.5%) had CNS metastases. Family history of BC was reported by 45/370 (12.2%) pts completing the questionnaire; 209/370 (56.5%) had hormone receptor-positive BC. Treatments reported in the first to fifth line were quite variable. HER2-directed therapy was received by 323/367 (88.0%) in LOT1 (mainly trastuzumab [TRA] and pertuzumab [PTZ]-based) and 298/343 (86.9%) in LOT2 (mainly T-DM1). Median duration of LOT1 and LOT2 were 7.8 (0–130) and 5.0 (0–100) mo, respectively, that decreased to 2.3 (0–30) mo in LOT5. The prime reason for treatment discontinuation was disease progression (LOT1: 294 [80.1%]; LOT2: 273 [79.6%]; LOT3: 187 [68.5%]). Serious adverse effects from treatments were rare (LOT1: 7 [1.9%]; LOT2: 10 [2.9%]; LOT3: 5 [1.8%]). **Conclusions:** The interim analyses show heterogeneous treatment patterns in real-world among pts with HER2+ u/mBC progressing on HER2-directed therapies possibly due to access disparity in these 4 Asian countries. Clinical trial information: NCT04857619. Research Sponsor: AstraZeneca.

Real-world treatment patterns.

LOT ^a , n (%)	Median duration of LOT (range), mo	TRA + PTZ + CT	T-DM1	TRA + CT	Lapatinib + CT	CT alone	HT alone	Anti-HER2 ^b + HT	Anti-HER2 ^b + CT + HT
LOT1 (N=367) (n=361)	7.9 (0–130)	163 (44.4)	17 (4.6)	51 (13.9)	-	54 (14.7)	16 (4.4)	-	63 (17.2)
LOT2 (N=343) (n=314)	5.0 (0–100)	22 (6.4)	155 (45.2)	24 (7.0)	30 (8.7)	45 (13.1)	-	19 (5.5)	21 (6.1)
LOT3 (N=273) (n=221)	4.2 (0–57)	13 (4.8)	40 (14.7)	42 (15.4)	35 (12.8)	89 (32.6)	16 (5.9)	18 (6.6)	-
LOT4 (N=167) (n=145)	2.7 (0–33)	8 (4.8)	-	29 (17.4)	29 (17.4)	85 (50.9)	11 (7.8)	-	-
LOT5 (N=114) (n=99)	2.3 (0–30)	10 (8.8)	7 (6.1)	17 (14.9)	14 (12.3)	55 (48.3)	7 (6.1)	-	-

^aReported in $\geq 4.0\%$ pts. ^bMainly includes TRA, PTZ, and Lapatinib. Abbreviations: CT, chemotherapy; HT, hormone therapy.

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Poster Session

PLEASURABLE: Results and biomarkers analysis from the phase II study of dalpiciclib combined with pyrotinib and endocrine therapy (ET) in women with dual-receptor positive (ER+/HER2+) metastatic breast cancer (MBC). *First Author: Jian Zhang, Phase I Clinical Trial Center, Fudan University Shanghai Cancer Center, Shanghai, China*

Background: In the front-line setting, our previous work demonstrated an impressive median progression-free survival (PFS) of 11.3 months with 66.7% response rate, and concluded a recommended phase 2 dose of pyrotinib 320mg/d, dalpiciclib (SHR6390, a novel CDK4/6i) 125mg/d, and letrozole 2.5mg/d for HR+/HER2+ MBC patients (pts) (Xichun Hu, FRONT ONCOL 2022). Results and biomarkers analysis from phase II dose expansion study are presented. **Methods:** ER+/HER2+ MBC Pts eligible for first- or second-line treatment were enrolled to receive dalpiciclib combined with pyrotinib and ET (letrozole or fulvestrant determined by physician's choice). The primary endpoint was objective response rate (ORR). For biomarkers analysis, ⁶⁸Ga-HER2 affibody, pre-treatment tissue-derived DNA and circulating tumor DNA (ctDNA) were assessed by PET/CT, and next-generation sequencing (NGS), respectively. **Results:** As of January 19, 2023, 48 pts were enrolled. 17 pts (35.4%) were treatment naïve, and 31 pts (64.6%) had received prior trastuzumab. The ORR was 68.1% (32/47) and disease control rate was 100% (47/47). In trastuzumab-naïve and trastuzumab-pretreated patients, ORR was 81.3% (13/16) and 61.3% (19/31), respectively. PFS and OS data were not mature by cut-off date. No new safety signals were observed. The most frequent treatment-related adverse events were neutropenia (95.8%; G3:60.4%, G4:6.3%), leukopenia (91.7%; G3:45.8%), diarrhea (87.5%; G3:2.1%), anemia (79.2%; G3:4.2%), oral mucositis (68.8%; G3:2.1%) and platelet count decreased (41.7%; G3:2.1%, G4:2.1%). The heterogeneity of ⁶⁸Ga-HER2 affibody uptake was observed among patients, both at baseline (N=16, median SUV_{max} 7.5, range, 2.3-34.9) and after 2 cycles of therapy (N=12, median SUV_{max} 4.0, range, 0-14.9). All patients with a decline in ⁶⁸Ga-HER2 affibody uptake (N=8) achieved partial response, while the uptake in non-responders was elevated (N=2). NGS was conducted to detect somatic and germline mutations in baseline tissue (n=10) and ctDNA (n=10) samples. Two patients with BRCA mutation (one had somatic BRCA1/2 mutation and another with germline BRCA2 mutation) had no tumor response. **Conclusions:** The chemotherapy-sparing regimens showed significant anti-tumor activity for ER+/HER2+ MBC pts in the front-line setting. The ⁶⁸Ga-HER2 affibody PET/CT may be a potential predictive biomarker of therapy response. Additional analysis including correlation of biomarkers with long-term outcomes is underway. Clinical trial information: NCT03772353. Research Sponsor: None.

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Poster Session

Pyrotinib plus capecitabine for patients with HER2-positive metastatic breast cancer and brain metastases: 3-year follow-up results from the phase 2 PERMEATE trial. *First Author: Min Yan, Department of Breast Disease, Henan Breast Cancer Center. The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, Zhengzhou, China*

Background: HER2-positive metastatic breast cancer has a high risk of brain metastases, leading to poor survival. Our phase 2 PERMEATE trial (NCT03691051) has shown the promising efficacy of pyrotinib (an irreversible pan-HER receptor tyrosine kinase inhibitor) plus capecitabine in patients with HER2-positive metastatic breast cancer and brain metastases, with an intracranial objective response rate of 74.6% (44/59) and 42.1% (8/19) in patients with radiotherapy-naïve (cohort A) and radiotherapy-treated (cohort B) brain metastases, respectively. Here we updated 3-year follow-up results from this trial. **Methods:** Patients received 21-day cycles of pyrotinib (400 mg orally once daily) and capecitabine (1000 mg/m² orally twice daily on days 1-14) until disease progression or intolerable toxicity. Patients with progression isolated to the brain lesions would be withdrawn from the study, but could resume on the study treatment after local surgery or radiotherapy until the second progression at any site or death, at the discretion of the investigator. Intracranial and extracranial responses were assessed according to the Response Evaluation Criteria In Solid Tumors, version 1.1. Progression-free survival (PFS; time from the initiation of the study treatment to progression at any site or any-cause death), overall survival (OS), and second PFS (PFS2; time from progression isolated to the brain lesions to the second progression at any site) were reported. **Results:** By the data cutoff date on February 8, 2023, the median follow-up duration was 40.5 months (95% CI: 39.0-43.0). Cohort A showed a median PFS of 10.7 months (95% CI: 7.6-14.9) and a median OS of 35.9 months (95% CI: 25.1-not reached). The 1-year and 3-year OS rates were 84.6% (95% CI: 76.0-94.4) and 49.8% (95% CI: 38.0-64.6), respectively. Fifteen patients with progression isolated to the brain lesions in cohort A resumed on the study treatment after local treatment, with a median PFS2 of 10.4 months (95% CI: 6.5-19.7). Cohort B showed a median PFS of 5.6 months (95% CI: 5.4-11.9) and a median OS of 31.4 months (95% CI: 22.0-not reached). The 1-year and 3-year OS rates were 78.9% (95% CI: 64.0-99.6) and 29.1% (95% CI: 13.0-60.4), respectively. **Conclusions:** These findings suggest the long-term survival benefit provided by pyrotinib plus capecitabine in patients with HER2-positive metastatic breast cancer and brain metastases, especially in the radiotherapy-naïve cohort. Clinical trial information: NCT03691051. Research Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

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Poster Session

Artificial intelligence–powered tumor-infiltrating lymphocytes analyzer to reveal distinct immune landscapes in breast cancer by molecular subtype and HER2 score. *First Author: Seunghwan Shin, Oncology, Lunit, Seoul, Korea, Republic of (South)*

Background: Tumor-infiltrating lymphocytes (TIL) reflect an ongoing anti-tumor immune response in the tumor microenvironment (TME) and have been studied as a predictive as well as prognostic biomarker in breast cancer (BC). The immune profile differs depending on BC molecular subtypes, with triple-negative BC (TNBC) and HER2-positive BC more frequently infiltrated by higher numbers of TIL than hormone receptor (HR)-positive tumors. In this study, we analyze TIL and immune phenotype by molecular subtype in BC and explore differences based on HER2 scores using an AI-powered TIL analyzer. **Methods:** A total of 1,973 cases of BC with molecular subtype, HER2 immunohistochemistry (IHC) or in situ hybridization (ISH) results, and TIL analysis from H&E slides from TCGA (n=1021), Samsung Medical Center (SMC, n=663), and KyungHee Medical Center (KHMC, n=289) were included in the analysis. The density of TIL were spatially analyzed from H&E WSI, and the immune phenotype (IP) was analyzed for each 1 mm²-sized patch. Tumor microenvironment (TME) was categorized into three types: inflamed (TIL distributed intratumorally), Immune-excluded (TIL excluded, out of cancer stroma), immune-desert (scant TIL in TME), and the score for each IP was calculated as the percentage of the total patches in WSI. **Results:** TNBC showed the highest TIL density in both cancer epithelium (214.5 ± 299.7/mm²) and stroma (1133.3 ± 1245.9/mm²), and a high percentage of inflamed IP (35.7%), IS (28.4 ± 28.1) than other subtypes (inflamed IP: 17.5%, IS 16.2±20.2, both p<0.001). HER2-positive BCs showed higher sTIL density (904.0 ± 901.7/mm²) compared to HR- positive BC (616.7 ± 794.1/mm²) but were associated with a higher percentage of immune-excluded IP (71.2%) and IES (57.6 ± 24.6). HR-positive BC had a high percentage of immune-desert IP (30.4%). In both HR-positive and negative BCs, higher IES was observed as the HER2 score increased. HER2-positive BC significantly showed a higher proportion of cancer stroma in the cancer region from WSI (Stromal ratio, 0.682 ± 0.149 vs. 0.578 ± 0.176, p<0.001). **Conclusions:** Different TIL densities and IP were seen in BC for each molecular subtype, pointing to a distinct immune landscape. HER2 score was associated with immune-excluded IP despite having higher TIL density, which should be considered for immunotherapy in BC. Research Sponsor: None.

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Poster Session

Real-world patient characteristics and treatment patterns associated with tucatinib therapy in patients with HER2+ metastatic breast cancer. *First Author: Carey K. Anders, Duke University Cancer Institute, Durham, NC*

Background: Tucatinib (TUC) is an oral HER2-targeted therapy approved by the FDA in Apr 2020 for use in combination with trastuzumab and capecitabine (TRA+CAP) for patients with previously treated HER2+ metastatic breast cancer (MBC). In the randomized HER2CLIMB trial, median (95% CI) overall survival (mOS) and progression-free survival (PFS) for patients receiving TUC with TRA+CAP were 21.9 (18.3, 31.0) and 7.8 (7.5, 9.6) months, respectively. Median duration of therapy was 7.3 months. HER2CLIMB used a standard of care comparator arm and included patients with active and stable brain metastasis (BM). HER2CLIMB was conducted prior to approval of fam-trastuzumab deruxtecan (T-DXd) so did not assess the impact of TUC-based therapy following T-DXd. Objective: Describe patient characteristics, treatment patterns, and clinical outcomes for TUC-based treatment in the real-world setting. **Methods:** This retrospective study included patients in the Komodo Health dataset (aggregating data from patient administrative health claims in the United States) diagnosed with MBC between Jan 1, 2017 and Sep 3, 2022 and initiating TUC post- approval in Apr 2020. Patient characteristics were described in the baseline period (≤6 months from TUC initiation). Key outcomes were time to next treatment (TTNT; as a proxy for PFS), time to discontinuation (TTD), and persistence (proportion continuing treatment at each timepoint) in all TUC-treated patients, and in patients receiving TUC immediately following T-DXd. **Results:** Of 16,990 patients identified with HER2+ MBC, 528 received TUC-based treatment. Of these, 57 (11%), 164 (31%), 154 (29%), and 153 (29%) received TUC in first-line (1L), second-line (2L), third-line (3L), and fourth-line or later (4L+), respectively. Median follow-up from TUC initiation was 9 months. Overall, 400 patients (76%) had BM prior to initiating TUC (43 [75%], 138 [84%], 111 [72%], and 108 [71%] in 1L, 2L, 3L, and 4L+, respectively). Median (95% CI) TTNT was 10.7 (9.4, 13.1) months overall and 11.5 (9.6, 14.4) in patients receiving TUC in 2L or 3L. Median (95% CI) TTD was 8.5 (7.2, 9.3) months overall, and 9.1 (7.7, 9.9) in patients receiving TUC in 2L or 3L. TUC persistence in the overall cohort was 46% (91/200) at 12 months and 35% (40/115) at 18 months. Sixty-one patients (12%) received TUC immediately following T-DXd (median 4L; 12 in 2L/3L, 49 in 4L+); of whom 36 (59%) had BM prior to initiating TUC. TTNT and TTD for patients treated with TUC following T-DXd were 7.5 (5, 13.3) and 7.3 (3.2, 9.5) months, respectively. **Conclusions:** In the real-world setting, a higher proportion of patients receiving TUC had BM compared with the HER2CLIMB patient population. TUC-based treatment in the real world is used in multiple lines of therapy and is associated with a similar TTNT and TTD to PFS observed in HER2CLIMB, inclusive of a cohort of patients who received TUC following T-DXd therapy. Research Sponsor: Seagen Inc; Merck.

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Poster Session

Secondary primary malignancy risk by ER, PR, and HER-2 status in post-menopausal women with breast cancer: A population-based analysis. *First Author: Muhammad Hammad Khan, King Edward Medical University, Lahore, Pakistan*

Background: Breast cancer is the most commonly diagnosed cancer and second leading cause of death due to cancer in women in the United States. We aimed to determine site specific incidence of SPMs in post-menopausal women with primary BC using data from the US Surveillance, Epidemiology, and End Results (SEER-17) cancer registries. **Methods:** We retrospectively analyzed post-menopausal women aged 45 or older with a first primary breast cancer diagnosis between 2000 and 2019, excluding those aged 45 or younger or with non-breast cancers as their first malignancy. We defined SPMs as second malignancies occurring at least 6 months after the initial breast cancer diagnosis and calculated standardized incidence ratios (SIRs) and absolute excess risk (AER) using SEER*Stat. Statistical significance was determined using p-values <0.05 and a 95% CI assuming a Poisson distribution of SPM incidence. **Results:** Among 774,965 post-menopausal women ≥45 years old with primary breast cancer, 10.8% developed SPMs, with significantly increased risk compared to the general population (SIR=1.14, 95% CI=1.13-1.15, p<0.05), particularly for solid tumors (SIR=1.16, 95% CI=1.15-1.16, p<0.05) and certain malignancies including salivary gland (SIR=1.77), thyroid (SIR=1.56), endocrine system (SIR=1.56), and hematological malignancies such as ALL, ANLL, and AML (SIR>1.70). Women aged 45-59 and Black women had the highest risk for all malignancies. PR receptor-positive women had higher risk for thyroid SPMs, while PR-negative women had higher risk for SPMs in female genitalia, bones and joints, and hematological malignancies. HER-positive and triple-positive (HER ER PR) women had higher risk for thyroid and hematological SPMs, while triple-negative women had higher risk for ALL, ANLL, and AML. **Conclusions:** This study found that 11% of post-menopausal women with primary BC develop SPMs, with thyroid cancer being the most common. Black and older women (45-59 years) had a higher risk of developing SPMs. Research Sponsor: None.

Site of SPM	ER(-)				PR(-)				HER2(-)			
	N	SIR	95%CI	AER	N	SIR	95%CI	AER	N	SIR	95%CI	AER
All Sites	13,305	1.25#	1.23-1.27	30.5	21,753	1.17#	1.17-1.18	23.4	18,716	1.10#	1.09-1.12	12.9
All Solid Tumors	11,863	1.27#	1.25-1.29	29.13	19,263	1.20#	1.18#-1.22	22.43	16,451	1.11#	1.09-1.12	11.82
All Lymphatic and Hematopoietic Diseases	46	2.08#	1.52-2.77	0.28	1,586	1.03	0.98-1.08	0.34	1,589	1.13#	1.07-1.18	1.32
Thyroid	348	1.41#	1.27-1.57	1.18	587	1.47#	1.35-1.59	1.31	789	1.93#	1.8-2.07	2.81
Other Female Genital Organs	89	2.31#	1.85-2.84	0.58	140	2.11#	1.78-2.49	0.52	120	1.52#	1.26-1.82	0.3
Bones and Joints	21	2.10#	1.3-3.21	0.13	27	1.58#	1.04-2.29	0.07	23	1.39	0.88-2.09	0.05
Salivary Glands	46	2.08#	1.52-2.77	0.28	68	1.78#	1.38-2.25	0.21	57	1.58#	1.2-2.05	0.16
Female Genital System (uterus, ovary, vagina)	1,446	1.19#	1.13-1.25	2.66	2,194	1.07#	1.03-1.12	1.05	1,916	0.99	0.95-1.04	-0.1

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Poster Session

HER2 persistence after treatment with T-DXd in breast and gastrointestinal cancers. *First Author: Joshua Z. Drago, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: T-DXd is a HER2-targeted antibody drug conjugate approved for treatment of advanced HER2-positive breast and gastroesophageal cancers and HER2-low breast cancers. The prevalence of HER2 loss after exposure to T-DXd is unknown and has implications for treatment strategies in refractory patients. **Methods:** We investigated clinically reported HER2 immunohistochemistry (IHC) scoring on post-treatment tissue biopsies from patients who received at least 2 cycles of T-DXd as of 2/2023. IHC was performed using mAB clone 4B5 (Ventana) and scored by ASCO/CAP guidelines on a scale of 0 to 3+. MSK-IMPACT next generation sequencing (NGS) was performed on paired pre- and post-treatment samples when available. Statistics are descriptive. **Results:** A total of 62 patients with breast, gastroesophageal, or colon cancer had available post-treatment biopsies. The majority (n = 51) had breast cancer, including 32 with HER2-positive and 19 with HER2-low disease. Median time on therapy was 30 weeks in HER2-positive and 21 weeks in HER2-low breast cancer. All 32 patients with HER2-positive breast cancer had detectable HER2 expression by IHC on post-treatment biopsies (median IHC score 2+; range 1+ to 3+). Of those with HER2-low breast cancer, 12 (63.1%) patients had detectable IHC after treatment. Of the 7 with IHC scores of zero, 3 also had scores of zero on the most proximal pre-treatment biopsies. Seven patients with gastroesophageal and 3 with colorectal cancer were included, with a median time on therapy of 12 and 9 weeks respectively, of which 1 (9%) exhibited HER2-loss after treatment. Among all patients with HER2-positive cancers, the rate of complete HER2-loss by IHC after exposure to T-DXd was 2.3%. Thirty-two patients had paired genomic analysis, including 25 breast and 7 gastrointestinal cancers. No change was observed in the fraction of genome altered (p = 0.0736, q = .327) or tumor mutational burden (p = 0.139, q = .487) with T-DXd exposure. Changes in *ERBB2* copy number did not show clear directionality, with 15 patients (46.7%) exhibiting *ERBB2* amplification pre-treatment and 12 (37.5%) post-treatment, the sum of 3 temporal gains and 6 losses of *ERBB2* amplification across the threshold of 1.8. **Conclusions:** HER2 remained detectable by IHC in the majority of patients treated with T-DXd in this cohort, especially those with HER2-positive cancers. These findings suggest that resistance to T-DXd may occur via target-independent factors, and that HER2 could still be exploited therapeutically in these populations. Further prospective studies using quantitative assays are needed to confirm these hypotheses. Research Sponsor: U.S. National Institutes of Health.

Tumor Type	N	Median Time on Tx (Wks)	Median HER2 IHC Post-Tx	IHC 0 Post-Tx
				N (%)
HER2-Positive Breast Cancer	32	30	2+ (1-3)	0 (0)
Her2-Low Breast Cancer	19	21	1+ (0-2)	7 (36)*
Gastroesophageal Cancer	7	12	3+ (0-3)	1 (14.2)
Colorectal Cancer	4	9	2+ (2-3)	0 (0)
Total	62	23.5	2+ (0-3)	8 (12.9)

*3 of these 7 patients had IHC scores of 0 pre-treatment.

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Poster Session

Validation of a single-cell sequencing assay for the detection of circulating tumor cells in metastatic breast cancer. *First Author: David Bourdon, Epic Sciences, San Diego, CA*

Background: Blood Biopsy and the evaluation of Circulating Tumor Cells (CTC) has provided valuable clinical information for patients with metastatic breast cancer, specifically where a tissue biopsy is not feasible. A critical problem in the field is that most assays cannot distinguish true CTCs from other types of rare cells. By combining established protein biomarkers associated with circulating epithelial cells with single-cell whole-genome sequencing to assess copy number variations (CNVs, a signature for genomic instability - GI), we differentiate rare cells from true CTCs. Additionally, we can determine the presence or absence of regions that contain gene amplifications (e.g., ERBB2/HER2). Here we report the validation of a clinical blood biopsy CTC assay that can enumerate CTCs, determine if those CTCs have GI and if selected CTCs are expressing HER2 or ER antigens. **Methods:** Relevant cell line controls of epithelial origin and known expression levels of ER or HER2 were spiked into healthy donor whole blood at varying concentrations. The nucleated cells were deposited on microscope glass slides at high density. Immunofluorescence staining of slides was performed to identify the presence and localization of nuclei (via DAPI), pan-CK, HER2, ER, CD45 and CD31. Nucleated cells were classified as CTC candidates if they were pan-cytokeratin⁽⁺⁾ and CD45/CD31⁽⁻⁾, and were further characterized for expression of ER and HER2 protein. Defined CTC candidates were imaged and located by specific coordinates allowing single-CTC isolation for whole genome amplification. Single-cell sequencing data was then analyzed with the Epic CTC DNA copy number analysis pipeline to detect GI and amplification at the ERBB2 locus. **Results:** The limit of detection for CTCs was determined to be 1 CTC in 6 million white blood cells with a linear range of 1- 300 CTC per slide. The sensitivity and specificity for HER2 detection was determined to be 94% and 97%, respectively. ER assay sensitivity and specificity were 91% and 100%, respectively. Overall accuracy was 100% for HER2 and 94% for ER detection. Overall precision across all relevant variables produced %CVs <10% for HER2 and ER. A genome possessed GI if more than 12 large-scale transitions (LSTs) were detected. For detection of 2-fold amplification at the ERBB2 locus, gene amplification was detected with 85% sensitivity and 94% specificity. Tested healthy donor blood samples were absent of detected CTCs and lacked LST/GI or ERBB2 amplification in all (46) isolated WBCs. **Conclusions:** These results reflect the validation of a novel clinical assay combining CTC detection with single-cell GI and amplification of the ERBB2 locus. This assay better discriminates CTC detection with the addition of an assessment of GI. Additionally, along with protein expression measures of ER and HER2, it provides the ability to assess if HER2 expression is driven by ERBB2 amplification. Research Sponsor: Epic Sciences.

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Poster Session

Impact of race and age on intrinsic subtype distribution and treatment decisions in metastatic breast cancer: Preliminary analysis of HARMONY (LCCC1829). *First Author: Joannie M. Ivory, The University of North Carolina at Chapel Hill, Chapel Hill, NC*

Background: Gene expression profiling (GEP) is used to classify breast cancer (BC) into four intrinsic subtypes: Luminal A (LumA), Luminal B (LumB), HER2-Enriched, and Basal-like. Non-LumA subtypes are associated with poorer outcomes. Studies in early BC show that hormone receptor-positive (HR+)/HER2-negative (HER2-) tumors have a higher frequency of non-LumA subtypes in Black and younger (<50) women. Similarly, triple negative BC, which carries the poorest prognosis and is mostly Basal-like, are overrepresented in Black and younger women. These variations in intrinsic subtype contribute to outcomes disparities. The extent to which these racial and age differences in subtypes and mortality occur in metastatic breast cancer (MBC) is unknown. **Methods:** HARMONY (NCT03769415) is a prospective clinical trial in patients with newly diagnosed MBC. Bulk tumor GEP (PAM50 intrinsic subtyping) is performed on primary and metastatic tumors. A primary objective is to determine the extent and treatment implications of molecular discordance (defined *a priori* as treatment differences by intrinsic subtype compared to clinical subtype); other endpoints to be reported later include GEP comparisons between primary and metastatic samples. Here we examine differences in a) intrinsic subtype and b) treatment patterns in MBC by race and age. **Results:** At the time of analysis, the study had accrued 220 participants. Mean age was 58, 24% were Black women. Sixty-five percent had HR+/HER2- MBC, 14% HER2-positive, and 21% triple negative. Unlike in early BC, LumB exceeded LumA (LumA 27%, LumB 35%, HER2-Enriched 12%, Basal-like 25%). Similar to early BC, subtype varied by race and age with more non-LumA subtypes in young and Black women. Discordance between intrinsic and clinical subtype was seen in 24% of Black, 20% of White women, in 29% of younger and 18% of older women. Treatment patterns also differed by race and age, where a higher percentage of younger Black women received first-line chemotherapy compared to younger White women overall (45% vs. 10%, p=0.0025), and in HR+/HER2- disease (33% vs 8.7%, p=>0.05). No difference was seen in older women (24% vs 17%, p=0.44). Median progression free survival was worst in younger Black women compared to all other participants (5.4 vs 19.5 months, p=0.027), which may be driven by clinical subtype. **Conclusions:** Intrinsic subtype of tumors in a metastatic population has a different distribution by race and age than early BC, with more poor-prognosis non-LumA subtypes, and approximately 1 in 5 have discordance between clinical and molecular subtype, which may be therapeutically relevant. Clinical trial information: NCT03769415. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology.

	Total population			
	≤ 50 (59)	> 50 (136)	Black (46)	White (140)
Luminal A	10.2%***	34.6%***	15.2%	28.6%
Luminal B	40.7%	33.1%	39.1%	35%
HER2-Enriched	20.3%*	8.8*	15.2%	12.1%
Basal-like	28.8%	23.5%	30.4%	24.3%

*** p-value <0.001, * p-value <0.05.

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Poster Session

First-in-human phase 1 dose escalation study of the KAT6 inhibitor PF-07248144 in patients with advanced solid tumors. *First Author: David Sommerhalder, NEXT Oncology, San Antonio, TX*

Background: KAT6A and KAT6B regulate gene transcription via acetylation of histone H3K23 and their dysregulation drives lineage-specific gene expression in cancer. We report dose escalation data from the first-in-human phase 1 (Part 1A and 1B; NCT04606446) study of the KAT6-selective inhibitor PF-07248144. **Methods:** Part 1A (monotherapy dose escalation) enrolled patients (pts) with advanced/metastatic ER+/HER2- breast cancer (mBC), CRPC, or NSCLC, resistant/intolerant to standard therapy. Part 1B (PF-07248144 + fulvestrant combination dose escalation) enrolled pts with advanced/metastatic ER+/HER2- mBC with disease progression after ≥1 line of CDK4/6 inhibitor and endocrine therapy (ET). PF-07248144 (1-15 mg in Part 1A) was administered orally once per day (QD) in 28-day cycles following Bayesian design with overdose control. Study objectives: primary - assess PF-07248144 safety and tolerability, including dose limiting toxicities (DLT); secondary - evaluate PF-07248144 pharmacokinetics (PK); and exploratory - evaluate pharmacodynamics (PD; peripheral blood mononuclear cells [PBMC] and tumor H3K23Ac inhibition) and antitumor activity (using RECIST 1.1 by investigator assessment). **Results:** At data cut off (30 Sep 2022), 29 pts were enrolled: 25 in Part 1A (12 mBC, 11 CRPC, 2 NSCLC) and 4 in Part 1B (mBC). Part 1A evaluated 5 dose levels (1-15 mg QD) and Part 1B evaluated 5 mg PF-07248144 QD + 500 mg fulvestrant. Median age across Part 1A and 1B was 67 yrs (range 48-90). A total of 83% (Part 1A) and 75% (Part 1B) of pts with mBC had received > 3 prior lines of systemic anticancer therapy. Three DLTs (Grade 3 [G3] neutropenia) were observed: 2 in Part 1A (8 mg and 2 mg QD) and 1 in Part 1B (5 mg QD). A maximum tolerated dose was not identified; 5 mg QD was identified as the recommended dose for expansion for both monotherapy and fulvestrant combination. Across Parts 1A and 1B, treatment-related AEs (TRAEs; any grade) in ≥20% pts were dysgeusia (72%), anemia (52%), neutropenia (48%), thrombocytopenia (31%), diarrhea (31%), white blood cells (WBC) decreased (28%), fatigue (24%), and aspartate aminotransferase increased (21%); the majority of TRAEs were G1-2. TRAEs ≥G3 seen in > 1 pt were neutropenia (6/29; 21%), anemia (5/29; 17%), and WBC decreased (2/29; 7%). PF-07248144 PK was linear between 1 and 15 mg. H3K23Ac inhibition (≥70%) in PBMCs was achieved at steady state at doses of ≥1 mg. Tumor H3K23Ac levels were reduced by > 50% in 4 paired tumor biopsies at exposures associated with preclinical anti-tumor activity. Confirmed and durable partial responses were observed in 1/8 (Part 1A) and 2/4 (Part 1B) response-evaluable pts with ER+/HER2- mBC who progressed on prior ET+CDK4/6 inhibitor treatment. **Conclusions:** PF-07248144 was well tolerated and associated with strong KAT6 inhibition in PBMCs and tumors and confirmed partial responses in pts with heavily treated ER+/HER2- mBC during dose escalation. Clinical trial information: NCT04606446. Research Sponsor: Pfizer.

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Poster Session

Comparative overall survival of patients in trials of CDK4/6 inhibitors in combination with endocrine therapy in advanced breast cancer. *First Author: Coralea Kappel, University of Toronto, Toronto, ON, Canada*

Background: CDK4/6i and endocrine therapy (ET) are an international gold standard therapy in estrogen receptor (ER) positive and HER2-negative advanced breast cancer (aBC). Individual trials of abemaciclib, palbociclib and ribociclib show similar impact on progression-free survival yet differing statistical significance for OS. A robust comparative evaluation of the efficacy, safety, and tolerability of the three drugs is warranted. **Methods:** We searched PubMed, ASCO, ESMO and SABCS proceedings to identify phase 3 randomized clinical trials reporting OS of CDK4/6i in combination with ET in ER-positive aBC in first or second line. A network meta-analysis using WinBUGS was performed to evaluate comparative efficacy, based on the ET partner, in the absence of direct comparisons. Trial level data on common and serious adverse events (AE) were extracted for each drug. The odds ratio (OR) for each AE was calculated comparing each CDK4/6i to the respective endocrine therapy backbone (aromatase inhibitor (AI) or fulvestrant) alone. **Results:** Seven studies comprising 4087 patients met the inclusion criteria. Median follow up was 70.2 months. Four studies paired a CDK4/6i with an AI or tamoxifen, 3 studies were paired with fulvestrant. There were no statistically significant differences in OS between any of the CDK4/6i with any ET backbone. Compared to palbociclib, ribociclib and abemaciclib showed significantly lower grade 1-2 fatigue/asthenia (ribociclib OR 0.69 [95% CI 0.58, 0.83]; abemaciclib OR 0.6 [95% CI 0.49, 0.74]) and abemaciclib showed significantly lower grade 1-2 alopecia (abemaciclib 0.76 [95% CI 0.6, 0.97]). Compared to palbociclib, ribociclib and abemaciclib showed significantly higher GI toxicity (ribociclib any grade vomiting OR 1.71 [95% CI 1.36, 2.15]; abemaciclib any grade vomiting OR 2.1 [95% CI 1.61, 2.62], any grade diarrhea 13.2 [95% CI 10.31, 16.78]). Treatment discontinuation was highest with abemaciclib. **Conclusions:** In this network meta-analysis, there was no statistically significant difference in OS between CDK4/6i despite differences in individual trials. Real-world data analyses may help to identify if a there is a meaningful inter-drug difference in efficacy. Significant differences between CDK4/6i are observed for safety and tolerability outcomes. Research Sponsor: None.

Differences in OS between the CDK4/6i with any ET or AI backbone.				
AI backbone.				
Control	Palbociclib		Ribociclib	Abemaciclib
Experimental				
Palbociclib	-		0.79 (0.56, 1.14), p = 0.21	0.79 (0.52, 1.19), p = 0.26
Ribociclib	1.26 (0.88, 1.80), p = 0.21		-	0.99 (0.74, 1.33), p = 0.96
Abemaciclib	1.27 (0.84, 1.92), p = 0.26		1.01 (0.70, 1.46), p = 0.96	-
Fulvestrant backbone				
Palbociclib	-		0.90 (0.60, 1.33), p = 0.59	0.93 (0.62, 1.40), p = 0.73
Ribociclib	1.12 (0.75, 1.66), p = 0.59		-	1.04 (0.71, 1.52), p = 0.85
Abemaciclib	1.08 (0.72, 1.61), p = 0.73		0.96 (0.66, 1.42), p = 0.85	-

HR (95% CI), p value.

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Poster Session

Lasofoxifene (LAS) plus abemaciclib (Abema) for treating *ESR1*-mutated ER+/HER2- metastatic breast cancer (mBC) after progression on prior therapies: ELAINE 2 study update. *First Author: Senthil Damodaran, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Endocrine therapy (ET), particularly aromatase inhibitors (AIs), for estrogen receptor (ER)-positive breast cancer can lead to acquired *ESR1* mutations (*mESR1*) driving endocrine resistance and tumor progression. Treatments for mBC with *mESR1* are limited, especially after progression on ET/cyclin-dependent kinase 4 and 6 inhibitor (CDK4/6i) combinations. In ELAINE 2, LAS, a next-generation ET (breast ER antagonist) plus Abema had a median progression-free survival (PFS) of ~13 mos, objective response rate (ORR) of 33%, and 24-wk clinical benefit rate (CBR) of 62% with a favorable safety profile in patients with resistant *mESR1* mBC (Damodaran S, et al. *J Clin Oncol*. 2022;40:16 suppl 1022). Here, we report ELAINE 2 data with longer patient follow up (Jan 31, 2023). **Methods:** In this open-label, phase 2, single-arm study, 29 women with *mESR1*, ER+/HER2- mBC that progressed on prior ET took oral LAS 5 mg/day and Abema 150 mg BID until disease progression/toxicity. The primary endpoint was safety/tolerability; secondary included PFS, CBR, and ORR. Data were summarized descriptively with no formal hypothesis testing. **Results:** Patients (median age 60 yrs) had received a median of 2 prior therapy lines for mBC; all but one had prior CDK4/6i exposure and 14 (48%) had prior chemotherapy for mBC. LAS/Abema was well tolerated with primarily grade 1/2 treatment-emergent adverse events (most commonly diarrhea, nausea, fatigue, and vomiting). One treatment withdrawal occurred due to grade 2 diarrhea. No deaths occurred. LAS dose was not reduced; Abema dose was reduced to 100 mg BID in 6 (21%) patients. Median PFS was 56.0 wks (~13 mos) and CBR 65.5% (95% CI, 47.3–80.1). Median overall survival was not estimable. In 18 patients with measurable lesions, ORR was 55.6% (95% CI, 33.7–75.4), with median time to response of 5.7 mos and median duration of response of 6.4 mos. Seventy-six percent, 56%, and 39% of patients were progression free at 6, 12, and 18 mos, respectively. Three (10%) patients had scan-identified venous thromboembolic events, with one symptomatic pulmonary embolism and one symptomatic deep vein thrombosis. In 26 patients with evaluable baseline and wk 4 ctDNA, *ESR1* mutant allele fraction decreased from baseline to wk 4 in 81% of patients and was not detected in 54%. **Conclusions:** With longer ELAINE 2 follow up, LAS/Abema continues to be well tolerated with clinically meaningful efficacy in women with *mESR1*, ER+/HER2- mBC that had progressed on ET and CDK4/6is. Decreases in *mESR1* ctDNA suggest effective target engagement of LAS. The PFS (median ~13 mos) and ORR (56%) with LAS/Abema are promising and a confirmatory phase 3 study (ELAINE 3) will begin in 2023. If ELAINE 2 results are confirmed, the combination of LAS and Abema would address a critical unmet need, providing a practice changing option for treating *mESR1* breast cancer. Clinical trial information: NCT04432454. Research Sponsor: Sermonix Pharmaceuticals.

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Poster Session

Circulating tumor cells (CTCs) dynamics after CDK4/6i for hormone-receptor positive (HR+) metastatic breast cancer (MBC): A biomarker analysis of the PACE randomized phase II study. *First Author: Lorenzo Gerrata, CRO Aviano National Cancer Institute, IRCCS, Aviano, Italy*

Background: PACE is a multicenter randomized phase II trial investigating palbociclib (P) in combination with fulvestrant (F) after progression on any CDK4/6 inhibitor (CDK4/6i), with or without the PD-L1 inhibitor avelumab (A), in HR+/HER2- MBC. CTCs are rare cells in the blood stream whose detection is associated with worse outcome and treatment resistance. **Methods:** Eligible patients (pts) had HR+/HER2- MBC with prior progression after ≥ 6 months (mo) of AI and CDK4/6i for MBC, or during/within 12 mo in the adjuvant setting, with ≤ 1 prior chemotherapy for MBC. Pts were randomized 1:2:1 to F, F+P, or F+P+A. CTC detection and enumeration were performed utilizing CellSearch (Menarini Silicon Biosystems) at baseline (BL), at time of first tumor assessment (TTA1), and at progression. Results were dichotomized using the standard CTC threshold (≥ 5 CTCs/7.5 ml) into a novel prognostic classification: StageIV_{indolent} and StageIV_{aggressive} (Cristofanilli et al 2019). Concurrent ctDNA Sequencing was performed using Guardant360 (Guardant Health). **Results:** Of the 220 randomized pts, 203 (92%) had sample available for BL CTC enumeration, 155 had detectable CTCs (70.5%), and 99 (48.8%) were StageIV_{aggressive}. *De novo* disease at initial diagnosis was associated with StageIV_{aggressive} (47.5% vs 30.8% StageIV_{indolent}), and distribution of visceral versus non-visceral disease was similar across the two CTCs groups. StageIV_{aggressive} represented 38.3%, 54.8%, and 46.2% of the F, F+P and F+P+A treatment groups, respectively. BL CTCs were prognostic in the overall cohort; median PFS was 5.7mo vs 3.5mo for StageIV_{indolent} vs StageIV_{aggressive} (HR: 1.69, 90%CI 1.27-2.24, P<0.001). Median PFS for the F, F+P and F+P+A arms was 1.9mo, 4.6mo and 5.4mo in StageIV_{aggressive} compared to 8.2mo, 5.3mo and 8.3mo in StageIV_{indolent}. Among patients in the StageIV_{aggressive} subgroup, the F+P and F+P+A arms demonstrated improved outcomes compared to F alone. (F+P vs F HR 0.43, 90% CI 0.25-0.71, and F+P+A vs F HR 0.26, 90% CI 0.14-0.49). No benefit of F+P or F+P+A over F was observed in the StageIV_{indolent} subgroup (F+P vs F HR 1.45, 90% CI 0.87 - 2.40 and F+P+A vs F HR 1.06, 90% CI 0.61 - 1.84, each p(interaction)<0.01). Changes in StageIV CTC characterization (indolent vs aggressive) between BL and TTA1 among the subset of 175/203 pts with both timepoints available are reported. **Conclusions:** Baseline CTC enumeration is prognostic in patients receiving F with or without CDK4/6i. The StageIV_{aggressive} subgroup may derive preferential benefit with combinations of F+P or F+P+A over F alone. Findings should be confirmed in other studies. ctDNA analyses are ongoing. Clinical trial information: NCT03147287. Research Sponsor: Pfizer.

CTC at BL	CTC at TTA1	
	StageIV _{indolent}	StageIV _{aggressive}
StageIV _{indolent} (n=94)	72 (76.6%)	22 (23.4%)
StageIV _{aggressive} (n=81)	31(38.3%)	50 (61.7%)
Overall (n=175)	103 (58.9%)	72 (41.1%)

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Poster Session

Prognostic factors in hormone receptor positive oligometastatic breast cancer. *First Author: Lacaze Jean Louis, Institut Claudius Regaud (ICR), Institut Universitaire du Cancer de Toulouse-Oncopole (IUCT-O), Département d'Oncologie médicale, Toulouse, France*

Background: Some recommend curative treatment for oligometastatic breast cancer (OMBC). To date, no randomized clinical trial has demonstrated the benefits of such a strategy. We present the largest retrospective series of patients treated consecutively for ER and/or PR positive (HR+) OMBC in a single institution. The objective was to describe the clinical and biological characteristics and prognostic factors of HR+ OMBC. **Methods:** We retrospectively reviewed all patients treated consecutively from 2014 to 2018 at our institution for synchronous or metachronous metastatic breast cancer (MBC). HR+ OMBC was defined as MBC with up to five metastases at diagnosis, positive hormone receptor status, and no other inclusion criteria. Clinical and biological characteristics, treatment modalities - intent-to-cure vs palliative - and outcomes were recorded. Progression-free survival (PFS) and overall survival (OS) were calculated. Log rank test and Cox regression models were used for survival analyses including time-dependent variable. **Results:** Of 998 patients treated for MBC within our institution between 2014 and 2018, 11.3% (N=113/998) met inclusion criteria. 62.5% of them had SBR grade I/II HR+ OMBC and 80.5% had HR+/HER2- OMBC. 89.3% patients had only one organ involved. None had more than two; 89.3% patients had 1-3 metastases at diagnosis. Among these 113 patients, 63.7% had bone metastases, 54.9% had bone only metastases, 19.5% had visceral metastases, 17.7% had lymph node metastases, 7.1% had brain metastases, and 3.5% had other metastases. Forty-one patients (36.3%) were treated in a curative intent with systemic treatment plus ablative focal treatment of primary tumor – or local relapse – and all distant metastases. Median follow up was 67.2 months (95%CI=[63.1-75.4]). For the entire series, five-year PFS and OS were respectively 35.2% (95%CI=[25.6-44.6]) and 67.0% (95%CI=[56.7-75.3]) respectively. In univariable analysis, liver metastases was associated with worse OS (HR=3.13, 95%CI=[1.43-6.87], p=0.003). In multivariable analysis, HER2 positive status (HR=0.43, 95%CI=[0.21-0.90], p=0.024), bone only metastases (HR=0.46, 95%CI=[0.27-0.78], p=0.004), and intent-to-cure treatment (HR=0.53, 95%CI=[0.30-0.93], p=0.027) were significantly associated with longer PFS. In multivariate analysis, only intent-to-cure strategy was associated with better OS (HR=0.24, 95%CI=[0.09-0.60], p=0.002). **Conclusions:** This is the largest retrospective series of patients treated consecutively for HR+ OMBC to date. 71.5 % of OMBC and 11.3 % of all MBC are HR+ OMBC. Most had only one invaded organ and 1-3 metastases. Among our cohort, intent-to-cure treatment improve drastically HR+ OMBC PFS and OS. A multimodal intent-to-cure strategy should be routinely discussed for patients with HR+ metastatic breast cancer with one to five metastases at diagnosis. Research Sponsor: None.

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Poster Session

ctDNA mutational profiles in luminal breast cancer with early vs late distant relapse: Geicam/2014-03. *First Author: Angel Guerrero, Fundación Instituto Valenciano de Oncología (FIVO), GEICAM Spanish Breast Cancer Group, Valencia, Spain*

Background: Patients with hormone receptor-positive early breast cancer (BC) can develop resistance to endocrine therapies (ET) and face a continuous risk of relapse, which can occur anywhere from a few months (m) to several decades after surgery. The causes of early vs late relapses are not well understood. Our research examines the presence of oncogenic drivers in circulating tumor DNA (ctDNA) at the time of relapse in patients with luminal BC who have either an early or late distant recurrence. **Methods:** We identified pts included in the GEICAM/2014-03 study (NCT02819882) with: 1) HR-positive BC, 2) metastatic relapse either <36m (early relapse, [early-R]) or >120m (late relapse, [late-R]) from diagnosis, and 3) ctDNA obtained before first line treatment for advanced disease. The AVEIO ctDNA assay was used for identifying genomic aberrations in 77 cancer-related genes. **Results:** Eighty-four pts, 36 in early-R and 48 in late-R groups, were selected. Median time to relapse was 24.97m in early-R vs 151.84m in late-R. Median time from last dose of adjuvant ET to relapse was 0.03m for early-R vs 74.06m for late-R. Median PFS to first line treatment was 7.62m in early-R and 35.15m in late-R. With a median follow-up of 32.08m, median OS after diagnosis of metastatic disease was 27.74m for early-R and not reached for late-R. ctDNA analysis detected at least 1 mutation (mut) in 71/84 (85%) pts (89% in early-R vs 81% in late-R). Early-R pts were enriched in mut in *TP53* (44% vs 19%), *ESR1* (11% vs 4%), *MAPK_ERK* pathway (14% vs 6%), and *ERBB2* copy number alterations (CNA) (25% vs 2%). *PI3K/AKT* pathway alterations had similar frequency in both recurrence groups (38% vs 42%) and they were not associated with OS. Seven *ESR1* mut were detected in 6 pts. In the early-R group there were 5 *ESR1* mut (71% of total *ESR1* mut), median mutant allele frequency (mMAF): 0.64%; while in the late-R, 2 *ESR1* mut (29%), mMAF: 0.4%. *ESR1* mut were associated with worse OS (median OS 48.48m vs 12.84m wild-type vs mutant; p=0.0025). There were 10 pts with *ERBB2* CNA at metastatic relapse: 9 (25%) in the early-R and 1 pts (2%) in the late-R. Seven pts (70%) had HER2-positive. Pts with ctDNA *ERBB2* CNA had worse OS (median OS 48.48m vs 20.52m wild-type vs mutant; p-adj=0.025). **Conclusions:** In luminal breast cancer (BC), early and late distant relapse differ at both the clinical and genomic levels. Early relapse is a highly aggressive form of the disease and is enriched in *TP53* mutations and actionable genetic alterations, such as mutations in the *ESR1* and CNA in *ERBB2*, as detected by ctDNA analysis at the time of metastatic relapse diagnosis. Clinical trial information: NCT02819882. Research Sponsor: AstraZeneca in alliance with Daiichi Sankyo Spain, Roche, Celgene, Pfizer and SEAGEN; AMACMEC Association.

Mutations identified in <i>ESR1</i> .				
ID	Recurrence Group	Adjuvant ET	Mutation	MAF (%)
1	late-R	Tamoxifen	p.Y537S	0.20
2	late-R	AI (Letrozol)	p.Y537N	0.60
3	early-R	AI (Anastrozol)	p.E380Q	0.14
4	early-R	Tamoxifen	p.E380Q	0.17
5	early-R	AI (Letrozol)	p.E380Q	0.89
5	early-R	AI (Letrozol)	p.Y537C	0.64
6	early-R	AI (Exemestane)	p.S463P	1.89

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Poster Session

Interim analyses (IA) of the giredestrant (G), G + abemaciclib (A), and G + ribociclib (R) arms in MORPHEUS Breast Cancer (BC): A phase I/II study of G treatment (tx) combinations in patients (pts) with estrogen receptor-positive, HER2-negative locally advanced/metastatic BC (ER+, HER2– LA/mBC). *First Author: Mafalda Oliveira, Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain*

Background: Limitations of current approved endocrine therapies (ETs), a mainstay tx for ER+ BC, include incomplete ER signaling inhibition. Novel ETs, such as selective estrogen receptor antagonists and degraders (SERDs), may help overcome this. G, a potent, nonsteroidal, oral (PO) SERD, is well tolerated and has shown robust ER occupancy and encouraging antitumor activity as monotherapy and in combination with the cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) palbociclib (P). MORPHEUS BC (NCT04802759) is evaluating the safety and efficacy of G tx combinations in ER+, HER2– LA/mBC. We present results from the 16-week IA of G and G + CDK4/6i (A or R). **Methods:** Eligible pts had disease progression on 1–2 lines of ET (including a CDK4/6i) for LA/mBC. Pts were randomized 1:6 (planned n = 15 per arm) to receive G (30 mg PO QD; control arm), G + A (150 mg PO BID), or sequentially, G + R (600 mg PO QD) until disease progression/unacceptable toxicity. The study was not designed to make explicit power and type I error considerations for a hypothesis test. Primary endpoints were safety and objective response rate; other endpoints included progression-free survival, overall survival, clinical benefit rate, disease control rate (DCR), duration of response, and pharmacokinetics. Genetic alterations were defined using baseline circulating tumor DNA. **Results:** As of Feb 4, 2022, 15 pts were enrolled in the G + A arm; 73% received one prior line of tx in the LA/mBC setting; 27% received prior fulvestrant; 73% had liver metastases at baseline (BL). As of Sept 22, 2022, 11 and 16 (of whom 14 were evaluable) pts were enrolled in the G and G + R arms, respectively; 64%/86% received one prior line of tx in the LA/mBC setting; 73%/36% received prior fulvestrant; 73%/57% had liver metastases at BL. Three pts had a partial response (PR; G + A, n = 1; G + R, n = 2); 19 had stable disease (G, n = 5; G + A, n = 7; G + R, n = 7). DCRs were 36% (G), 40% (G + A), and 50% (G + R). Safety is shown. **Conclusions:** G combined with a CDK4/6i (A or R) was well tolerated, with no unexpected safety signals. Three PRs were seen in this heavily pretreated population of pts with disease progression post-CDK4/6i tx. This study provides the first data supporting the combinability of G with the CDK4/6is A and R, in addition to P as seen in prior studies. G can therefore be combined with all three approved CDK4/6is. Clinical trial information: NCT04802759. Research Sponsor: F. Hoffmann-La Roche Ltd.

	G	G + A	G + R
Tx-related adverse events (TRAEs) Grade 3–4	46% 0	80% 40%	100% 43%
AEs/TRAEs leading to tx discontinuation	0	0	7%
AEs leading to dose modification/interruption	18%	60%	64%
Fatal AEs	0	0	0
Most common TRAEs (≥ 20% of pts)	Fatigue Diarrhea, nausea, abdominal pain, fatigue, neutropenia, vomiting, decreased appetite	Fatigue Diarrhea, nausea, abdominal pain, fatigue, neutropenia, vomiting, decreased appetite	Nausea, fatigue, neutropenia, asthenia, QT interval prolongation

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Poster Session

Outcomes with first-line (1L) ribociclib (RIB) + endocrine therapy (ET) vs physician's choice combination chemotherapy (combo CT) by age in pre/perimenopausal patients (pts) with aggressive HR+/HER2– advanced breast cancer (ABC): A subgroup analysis of the RIGHT Choice trial. *First Author: Nagi S. El Saghir, American University of Beirut Medical Center, Beirut, Lebanon*

Background: The progression-free survival (PFS; primary endpoint) results from the Phase II RIGHT Choice trial demonstrated a statistically significant median PFS (mPFS) benefit of ~1 yr with RIB + ET over combo CT (mPFS, 24.0 vs 12.3 mo; hazard ratio [HR], 0.54; 95% CI, 0.36–0.79; *P* = .0007) in pts with aggressive HR+/HER2– ABC. Younger pts with aggressive ABC have a worse prognosis, which impacts treatment (tx) decisions. Hence, a subgroup analysis of key efficacy endpoints from RIGHT Choice by age (< 40 vs ≥ 40 y) was undertaken. **Methods:** Pre/perimenopausal pts (aged 18–59 y) with HR+/HER2– ABC and no prior systemic therapy for ABC were randomized 1:1 to either RIB with letrozole/anastrozole + goserelin or investigator's choice of combo CT (docetaxel + capecitabine, paclitaxel + gemcitabine, or capecitabine + vinorelbine). Pts in the trial had ABC not amenable to curative therapy and for which combo CT was clinically indicated by physician's judgment (ie, symptomatic visceral metastases, rapid progression of disease or impending visceral compromise, or markedly symptomatic non-visceral disease). **Results:** In total, 70 pts were aged < 40 y and 152 were aged ≥ 40 y. In the combo CT arm, pts aged < 40 y fared worse and had a shorter mPFS, shorter median time to tx failure (mTTF), and higher 3-month tx failure rate (TFR) than pts aged ≥ 40 y. Pts aged < 40 y showed a significant PFS benefit with RIB + ET vs combo CT (mPFS, not reached [NR] vs 10.2 mo; HR, 0.38). This PFS benefit with RIB + ET over combo CT was also observed in pts aged ≥ 40 y (21.2 vs 16.0 mo; HR, 0.71). Regardless of age, the mTTF was longer and the 3-month TFR was lower in the RIB + ET arm than the combo CT arm. The median time to response (mTTR), overall response rate (ORR), and clinical benefit rate (CBR) were similar between the two tx arms in both age groups. **Conclusions:** This analysis demonstrated a clinically meaningful PFS benefit and improved secondary outcomes with 1L RIB + ET over combo CT along with similar treatment responses in both tx arms in pts aged < 40 y as well as in those ≥ 40 y with aggressive HR+/HER2– ABC. This analysis supports RIB + ET as a preferred tx option in this pt population, including younger pts aged < 40 y. Clinical trial information: NCT03839823. Research Sponsor: Novartis Pharmaceuticals Corporation.

Age	Arm	n	mPFS (95% CI), mo	HR (95% CI)	mTTF (95% CI), mo	HR (95% CI)	mTTR* (95% CI), mo	ORR,* %	CBR,* %	3-mo TFR (95% CI), %
< 40 y	RIB + ET	32	NR (10.2-NR)	0.38 (0.18-0.79)	NR (10.2-NR)	0.30 (0.15-0.58)	4.7 (2.8-15.9)	65.6	75.0	9.4 (2.0-25.0)
	CT	38	10.2 (6.7-11.2)		7.0 (5.3-10.2)		2.7 (1.4-4.9)	57.9	65.8	26.3 (13.4-43.1)
≥ 40 y	RIB + ET	80	21.2 (17.1-29.3)	0.71 (0.44-1.15)	18.5 (12.7-24.0)	0.58 (0.38-0.88)	6.3 (4.4-12.9)	65.0	82.5	12.5 (6.2-21.8)
	CT	72	16.0 (8.8-21.7)		11.0 (7.8-15.5)		4.5 (2.8-8.4)	61.1	76.4	19.4 (11.1-30.5)

* Unconfirmed.

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Poster Session

Endocrine therapy resistance (ETR) in hormone receptor-positive, HER2-negative metastatic breast cancer (HR+, HER2– mBC): Prevalence, biomarker characteristics, and outcomes. *First Author: Rinath Jeselsohn, Dana-Farber Cancer Institute, Boston, MA*

Background: ETR to prior adjuvant ET poses challenges to first-line treatment (1L tx) of HR+, HER2– mBC. Understanding patient (pt)/disease heterogeneity is crucial for developing new txs that target specific ETR mechanisms to improve pt outcomes. We investigate ETR, including prevalence, genomic profiles, and survival outcomes in pts with HR+, HER2– mBC treated in the 1L setting. **Methods:** This retrospective two-cohort study of pts initiating 1L systemic tx for mBC (diagnosed after Jan 1, 2015) used data from the Flatiron Health (FH) electronic health record-derived de-identified database (FH cohort), and FH-Foundation Medicine, Inc. (FMI) clinico-genomic database (CGDB cohort; solid biopsy FMI test required). The de-identified data originated from ~280 US cancer clinics (~800 sites of care). Pts with ETR to prior adjuvant ET were defined per ESMO guidelines (table footnote); primary ETR (1ETR) was divided into pts relapsing within 1 year (yr) or 1–2 yrs of adjuvant ET. Genomic profiles were assessed in the CGDB cohort. In both cohorts, real-world (rw) progression-free survival (PFS) and overall survival (OS) were estimated in pts who received 1L tx with fulvestrant (F) + CDK4/6i inhibitor (CDK4/6i). **Results:** In the FH cohort (N = 4052), 16.1% of pts had 1ETR (ET < 1 yr: 7.9%) and 33.9% had secondary ETR (2ETR). In the CGDB cohort (N = 696), *ESR1* mutations (*ESR1* m) were present in 10.8% of 158 pts with 1ETR (ET < 1 yr: 4.2%; 1–2 yrs: 16.1%) and 19.9% of 317 pts with 2ETR. In pts who received 1L F + CDK4/6i, shorter median (m) rwPFS (statistically significant) and OS (not significant) were seen in pts with 1ETR vs. 2ETR, but outcomes were not affected by the presence of *ESR1* m in pts with 2ETR. **Conclusions:** Overall, half of pts with 1L HR+, HER2– mBC have ETR to prior adjuvant ET. Pts with ETR have tumors with heterogeneous genomic profiles and varied survival outcomes. *ESR1* m are infrequent in pts with 1ETR and < 1 yr of adjuvant ET but are more common in 2ETR. In pts treated with 1L F + CDK4/6i, PFS and OS were worse with 1ETR than 2ETR. This study highlights the importance of further understanding the heterogeneity in molecular profiles and outcomes within ETR. Research Sponsor: F. Hoffmann-La Roche Ltd.

	Pts, n	Events, n	mPFS, mo (95% CI)	Pts, n	Events, n	mOS, mo (95% CI)
Survival outcomes in pts with ETR and 1L F + CDK4/6i tx						
FH cohort						
1ETR*	171	124	7.7 (6.2, 9.0)	171	99	20.6 (16.7, 31.2)
1ETR (ET 0–1 yrs)	69	54	7.3 (5.0, 10.3)	69	45	17.0 (13.6, 35.0)
1ETR (ET 1–2 yrs)	102	70	7.7 (6.4, 11.0)	102	54	24.3 (17.6, 33.5)
2ETR† (ET ≥ 2 yrs)	490	325	11.7 (9.8, 13.5)	490	246	32.3 (30.0, 39.1)
CGDB cohort, 2ETR only‡						
<i>ESR1</i> m	22	14	10.6 (5.0, NE)	33	15	30.5 (19.9, 46.5)
<i>ESR1</i> wildtype	55	35	10.0 (4.7, 16.1)	72	30	22.4 (16.7, NE)

* Relapsing during < 2 yrs of adjuvant ET.

† Relapsing during ≥ 2 yrs of adjuvant ET or ≤ 1 yr from last ET.

‡ Risk set adjustment applied in survival analyses to account for delayed entry of pts in the cohort post-index date.

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Poster Session

Efficacy and safety of tenalisib, a PI3K δ/γ and SIK3 inhibitor, in patients with locally advanced or metastatic breast cancer: Updated results from an on-going phase II study. *First Author: Tamta Makharadze, LTD High Technology Hospital Med Center, Batumi, Georgia*

Background: Several studies have shown that the upregulation of the PI3K-AKT-mTOR pathway interacts with the Estrogen Receptor pathway and confers endocrine resistance. Elevated Salt Inducible Kinase-3 (SIK3) expression, which often is overexpressed breast cancer, is shown to contribute to tumorigenesis. Tonalisib (RP6530), a highly selective, PI3Kδ/γ and SIK3 inhibitor, has shown promising efficacy in T-cell lymphoma with a distinct safety profile. Tonalisib's major metabolite, INO385 is a SIK3 inhibitor. Breast cancer cell line studies have demonstrated that tonalisib potentiated the activity of paclitaxel and doxorubicin. The aim of this phase II study was to investigate the efficacy and safety of single-agent tonalisib in patients (pts) with HR+ HER2- locally advanced or metastatic Breast cancer. **Methods:** This randomized, open-label study was designed to evaluate two doses (800 mg BID and 1200 mg BID) of Tonalisib in MBC pts (including TNBC) whose disease had progressed following at least one line of therapy. Tonalisib was administered orally daily for every 28 days cycles until the disease progression. The study would enroll forty pts (20 at each dosage level), with the primary outcome being the proportion of patients who did not have disease progression at the end of six months. Other outcomes were investigator-assessed ORR, PFS, DCR (DCR=CR+PR+SD) and Clinical Benefit Rate (CBR= CR+PR+SD≥24 weeks) as per RECIST v1.1 criteria. **Results:** The trial enrolled 40 pts. Pts had a median of 3 (range 1-7) prior therapies of which, 87% pts had prior endocrine therapy, which included 40% pts treated with an aromatase inhibitor and 30% of pts treated with fulvestrant as their last therapy respectively. Prior chemotherapy in any setting included taxane (60%), and anthracycline (47.5%). The median age was 63.8(31-71) years, 77.5% pts had visceral disease, and 95.0% had 2 or more metastatic lesions. As of 06-Feb-2023, of the 40 pts, 5 pts (12.5%) showed PR and 22 (55%) had SD. The CBR was 57.5% while the DCR was 67.5%. The median duration of response in PR pts and median duration of clinical benefit were 9.36 and 7.46 months respectively. The progression free survival (PFS) was 5.6 months (range: 0.93 to 15.26+ months). Drug related AEs were manageable. The most common AEs (≥10%) of any grade were transaminitis, GGT elevation, and rash. Grade 3/4 events were limited to GGT elevation (12.5%), and transaminitis (12.5%). Discontinuations due to related AEs were infrequent (<5%) and limited to two events (one event each of rash and GGT elevation). **Conclusions:** Based on the data from the ongoing study, tonalisib shows encouraging efficacy as a single agent in pts with relapsed/refractory HR+ HER2- difficult to treat MBC patients. Updated efficacy and tolerability data will be provided at the time of presentation. Clinical trial information: NCT05021900. Research Sponsor: Rhizen Pharmaceuticals AG.

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Poster Session

Efficacy analysis of CDK4/6 inhibitors (CDKi) + endocrine therapy (ET) treatment in hormone receptor-positive/HER2-negative (HR+/HER2-) advanced breast cancer (aBC): Biomarker analysis including chemoendocrine score (CES) by CDKi type in SOLTI-1801_CDK-PREDICT study. *First Author: Pablo Tolosa Ortega, Medical Oncology Department, Hospital 12 de Octubre, Madrid, Spain*

Background: CDKi + ET improved progression-free survival (PFS) and ribociclib also overall survival (OS) in HR+/HER2- aBC first-line setting. Intrinsic subtypes (IS) are prognostic and predict benefit from CDKi + ET (Finn. SABCS 2017, Prat. JCO 2021, Tolosa. SABCS 2022). We previously reported a PAM50-based CES in HR+/HER2-negative early BC (Prat et al. CCR 2016). Here, we evaluated the association of CES with PFS following CDKi therapy in aBC. **Methods:** CDK-PREDICT prospectively evaluated 113 HR+/HER2- aBC patients (pts) treated in the first-line setting with CDKi + ET. RNA from FFPE metastatic tumors was analyzed at the nCounter (Nanostring Technologies) using a 72 custom gene panel including the PAM50 genes. CES was evaluated as a continuous variable, and categorically (CES-E[endocrine-sensitive], CES-I[intermediate] and CES-C[chemo-sensitive]) using the previously reported cut-offs. Multivariable analyses were used to test CES association with PFS. **Results:** The median follow-up for PFS was 18.5 m. PAM50 IS and CES distribution are shown. No statistically significant difference in mPFS by CDKi. CES (as a continuous variable or as group categories) was found significantly associated with mPFS. mPFS for CES-E pts was NR (95% CI: 26.0 - NR), 20.7m for CES-I (95% CI: 14.2 - 31.7m; HR= 1.98, p<0.05) and 11.7m for CES-C (CI 95%: 7.0 - 18.8; HR= 3.72, p<0.05). CES-C was associated with lower PFS compared to CES-I (aHR= 0.55, p=0.10) and CES-E (aHR= 0.29, p<0.05) independent of CDKi, ET, intrinsic subtype (Luminal versus not), endocrine sensitivity, onset metastatic and visceral disease. CES-C was significantly associated with higher expression of, MIA and lower expression of CCND1, CCNE1, FOXA1, MLPH and UBE2T compared with CES-E (p< 0.05). In CES-E pts mPFS for palbociclib was NR (IC95:22.9-NR) compare with 43.8 m for ribociclib (IC95: 12.0-NR); aHR=1.17 p=0.546), in CES-I pts mPFS for palbociclib was 18.9 m (IC95: 5.8-27.3) compare with 31.7 m for ribociclib (IC95: 12.2-NR); aHR=0.50 p=0.294), and in CES-C pts mPFS for palbociclib was 11.6 m (CI95: 2.7-15.7) compare with 10.0 m for ribociclib (CI95: 2.1-NR; aHR=0.48 p=0.102). Abemaciclib not reported due to low numbers (n=16). **Conclusions:** We confirmed independent prognostic value of CES in first-line setting, suggesting a not statistically significant benefit with ribociclib vs palbociclib in CES-I. Research Sponsor: This project has received a research grant from "Instituto de Salud Carlos III (ISCIII), Ministerio de Economía y Competitividad" (Spain) awarded within the National Research Program with reference PI 18/ O1408, co-funded with European Union ERDF funds.

Patient characteristics n (%)	Total (113)	Palbociclib (61)	Ribociclib (36)	Abemaciclib (16)
Intrinsic Subtypes:				
Luminal	101 (89)	56 (92)	35 (97)	10 (63)
Non-Luminal	12 (11)	5 (8)	1 (3)	6 (37)
Chemoendocrine score:				
CES-E	54 (48)	36 (59)	13 (36)	5 (31)
CES-I	37 (33)	17 (28)	13 (36)	7 (44)
CES-C	22 (19)	8 (13)	10 (28)	4 (25)

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Poster Session

Capivasertib (C) and fulvestrant (F) for patients (pts) with aromatase inhibitor (AI)-resistant HR+/HER2- advanced breast cancer (ABC): Characterization and management of common adverse events (AEs) from the phase 3 CAPItello-291 trial. *First Author: Hope S. Rugo, University of California San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, CA*

Background: In the CAPItello-291 trial in eligible pts with AI-resistant HR+/HER2- ABC, the addition of C (a potent, selective pan-AKT inhibitor) to F significantly improved PFS (primary endpoint) compared with placebo (P) in the overall (HR 0.60; 95% CI 0.51–0.71; p<0.001) and AKT pathway-altered population (HR 0.50; 95% CI 0.38–0.65; p<0.001). We report a detailed analysis of AEs. **Methods:** Pts were randomized 1:1 to receive F (500 mg IM on days 1 and 15 of cycle 1, and day 1 of each subsequent 28-day cycle) with either P or C (400 mg BID; 4 days on, 3 days off). Pts with HbA1c <8.0% and diabetes not requiring insulin were eligible. Incidence, management, and time to onset were summarized for common AEs (>10% any grade and >2.0% grade ≥3; CTCAE v5.0). **Results:** Overall, 708 pts were randomized to C+F (n=355) vs P+F (n=353); safety population C+F (n=355) vs P+F (n=350). Baseline risk factors potentially associated with hyperglycemia were a history of diabetes in 34 pts (10%) in the C+F arm vs 20 pts (6%) in the P+F arm (baseline median [range] HbA1c 5.4% [4.0–8.3] vs 5.4% [3.9–7.7]), median weight 65.0 kg (34–150) vs 66.5 kg (37–147) and 54% vs 53% of pts overweight/obese in the C+F vs P+F arms, respectively. Common AEs were diarrhea, rash, and hyperglycemia; maximum AE grade was mostly 1/2 and led to low rates of discontinuation. In the C+F arm, medications for the management of AEs were used in 151/257 pts (59%) with diarrhea (mostly loperamide; n=135), 109/135 pts (81%) with rash (mostly antihistamines; n=75/topical corticosteroids; n=64), and 28/60 pts (47%) with hyperglycemia (mostly metformin; n=18). **Conclusions:** Diarrhea, rash, and hyperglycemia, the most commonly reported AEs associated with AKT pathway inhibition, occur early in treatment with C+F, are generally low grade and manageable, and are associated with low rates of dose modifications/discontinuations. Clinical trial information: NCT04305496. Research Sponsor: AstraZeneca.

		Diarrhea ^a		Rash ^a		Hyperglycemia ^a	
		C+F	P+F	C+F	P+F	C+F	P+F
Any grade; n (%)		257 (72.4)	71 (20.3)	135 (38.0)	25 (7.1)	60 (16.9)	14 (4.0)
Maximum grade; n (%)	1	164 (46.2)	61 (17.4)	57 (16.1)	19 (5.4)	26 (7.3)	8 (2.3)
	2	60 (16.9)	9 (2.6)	35 (9.9)	5 (1.4)	26 (7.3)	5 (1.4)
	3	33 (9.3)	1 (0.3)	43 (12.1)	1 (0.3)	7 (2.0) ^b	1 (0.3)
Median (interquartile range) time to onset, days		8.0 (2.0–22.0)	22.0 (10.0–57.0)	12.0 (10.0–15.0)	48.0 (22.0–108)	15.0 (1.0–51.0)	47.5 (28.0–120.0)
AE leading to dose change; n (%)	Reduction	28 (7.9)	0	16 (4.5)	0	2 (0.6)	0
	Interruption	35 (9.9)	3 (0.9)	42 (11.8)	0	9 (2.5)	3 (0.9)
	Discontinuation	7 (2.0)	0	16 (4.5)	0	1 (0.3)	1 (0.3)

^aGroup terms (preferred terms): diarrhea (diarrhea, frequent bowel movements, gastrointestinal hypermotility); rash (rash, rash macular, maculopapular rash, rash papular, rash pruritic) and hyperglycemia (blood glucose increased, hyperglycemia). ^bOne additional pt (0.3%) had grade 4 hyperglycemia.

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Poster Session

Clinical activity of camizestrant, a next-generation SERD, versus fulvestrant in patients with a detectable ESR1 mutation: Exploratory analysis of the SERENA-2 phase 2 trial. *First Author: Mafalda Oliveira, Medical Oncology Department and Breast Cancer Group, Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain*

Background: Camizestrant, a next-generation oral selective estrogen receptor antagonist and degrader (ngSERD), was compared at two dose levels to fulvestrant 500 mg (F) in post-menopausal women with advanced ER+, HER2→ breast cancer with disease recurrence or progression after ≤1 endocrine therapy in the advanced setting in the Phase 2 randomized SERENA-2 study (NCT04214288). Camizestrant demonstrated statistically significant and clinically meaningful benefit vs F in progression-free survival (PFS) in the overall study population (Oliveira M et al. SABCS 2022 Annual Meeting. Abstract GS3-02.). **Methods:** Baseline circulating tumour DNA was collected at screening and/or Cycle 1 Day 1 and analysed by next-generation sequencing. A post hoc exploratory analysis compared investigator assessed PFS with camizestrant (data from 75 and 150 mg combined) vs F in patients with detectable baseline ESR1 (the gene that encodes ERα) hotspot mutations (ESR1m). Patients were divided into subgroups based on whether 1 or >1 ESR1m variants were detected, the specific ESR1m, and whether mutations were detected in BRCA1/2 or the MAPK pathway. The most prevalent mutations are presented. A Cox proportional hazards model was used to compare PFS. **Results:** 48/147 (32.7%) patients treated with camizestrant and 35/73 (47.9%) treated with F had a detectable ESR1m in at least 1 baseline sample. ESR1m were detected in 6/9 (67%) patients with a BRCA1/2 mutation and 5/26 (19%) with a MAPK pathway alteration; however, the numbers were too small to analyse efficacy in these subgroups. **Conclusions:** Camizestrant showed improved outcome vs F in patients with a detectable ESR1m at baseline and in the subgroups tested. The greatest median PFS improvement was seen in patients where a single ESR1m variant was detected, suggesting that early intervention upon detection of an ESR1m may provide the maximum patient benefit for camizestrant, a hypothesis that is being tested in the SERENA-6 clinical trial (NCT04964934). Clinical trial information: NCT04214288. Research Sponsor: Astra Zeneca.

	Camizestrant n (%)	Camizestrant median PFS, months (90% CI)	F n (%)	F median PFS, months (90% CI)	Camizestrant vs F PFS HR (90% CI)
ESR1m detected	48/147 (33)	8.0 (4.5–12.0)	35/73 (48)	2.2 (1.9–3.8)	0.44 (0.28–0.68) ^a
1 ESR1m variant detected ^b	21 (44)	12.9 (4.5–14.7)	17 (49)	2.2 (1.9–3.3)	0.52 (0.28–0.97) ^c
>1 ESR1m variant detected ^b	27 (56)	4.7 (2–11.1)	18 (51)	2.3 (1.9–3.8)	0.45 (0.25–0.81) ^c
D538G detected ^b	28 (58)	4.5 (2–9.1)	23 (66)	2.2 (1.9–3.8)	0.61 (0.36–1.03) ^c
Y537C/D/N/S detected ^b	33 (69)	9.1 (3.9–12.7)	23 (66)	2.3 (1.9–5.6)	0.46 (0.28–0.76) ^c

^a Stratified Cox proportional hazards model used, adjusting for prior CDK4/6i and lung/liver metastases. ^b % calculated based on the number of patients with ESR1m detected (camizestrant n=48; F n=35). ^c Unadjusted HR presented due to smaller number of events in subcategories.

LBA1068

Poster Session

Palbociclib (P) plus tamoxifen (TAM) ± goserelin in women with hormone receptor-positive (HR+)/HER2-negative (HER2-) advanced breast cancer (ABC): Primary results of NCCH1607/PATHWAY, an Asian international double-blind randomized phase 3 trial. *First Author: Takahiro Kogawa, National Cancer Center Hospital East, Chiba, Japan*

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2023, issue of the *Journal of Clinical Oncology*.

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Poster Session

Exploratory biomarker analysis of acclERA breast cancer (BC): Phase II study of giredestrant vs. physician's choice of endocrine therapy (PCET) for pre-viously treated, estrogen receptor-positive, HER2-negative advanced BC (ER+, HER2- aBC). *First Author: Ann Collier, Genentech, Inc., South San Francisco, CA*

Background: ET is the mainstay treatment of ER+ aBC. Giredestrant is a highly potent, nonsteroidal, oral selective ER antagonist and degrader (PO SERD) that achieves robust ER occupancy. acclERA BC (NCT04576455) is a Phase II, randomized, open-label study that evaluated giredestrant vs. PCET in the second- or third-line ER+, HER2- aBC setting. The study did not reach statistical significance for the primary endpoint of investigator-assessed progression-free survival, although giredestrant demonstrated a more pronounced effect in patients (pts) with *ESR1*-mutated (*ESR1m*) tumors. We present an exploratory biomarker analysis. **Methods:** Pts (N = 303) were post- or pre-/perimenopausal women, and men, with ER+, HER2- aBC who had received 1-2 prior lines of systemic therapy for aBC. Randomization was 1:1 to giredestrant (30 mg PO daily) or PCET (fulvestrant/aromatase inhibitor). Baseline plasma circulating tumor (ct)DNA (n = 232) was evaluated with the FoundationOne Liquid CDx (n = 229) or PredicineCARE (n = 3) assays; *ESR1* and other gene mutations in ctDNA were defined as variants with known or likely impact on protein function. Gene expression and PAM50 molecular subtype were assessed by RNAseq from tumor tissue (n = 184) which, based on collection date relative to aBC, was defined as representing early BC (eBC, n = 67), first line (1L, n = 64), or post-1L (n = 46). ER pathway activity was quantified by expression of a predefined set of 38 ER-induced or -repressed genes. **Results:** The majority of tumors were of the Luminal A (51%) and Luminal B (43%) PAM50 subtypes. Post-1L *ESR1m* tumors (n = 17) were significantly enriched for Luminal B (64%) compared with eBC (39%), 1L (44%), and post-1L tumors with no *ESR1m* detected (*ESR1nmd*; n = 29; 45%) (p < 0.001). Post-1L *ESR1nmd* tumors, but not *ESR1m* tumors, had significantly lower ER pathway activity compared with eBC or 1L tumors (p = 0.0001, 0.001). Within the post-1L subgroup, those with *ESR1m* had a distinct ctDNA mutational profile with more *GATA3* (n = 29) and fewer *CHEK2* mutations (n = 0) than *ESR1nmd* (n = 3 and n = 11, respectively). Tumor ER pathway activity and *ESR1* expression in tumor tissue, as well as pre-treatment ctDNA composite tumor fraction and *ESR1* variant allele frequency, were significantly correlated with best overall response to single-agent ET (partial response vs. progressive disease; p < 0.001, p = 0.022, p = 0.001, and 0.045, respectively). **Conclusions:** These data show that tumor response to single-agent ET is correlated with baseline ctDNA features and with tumor ER pathway activity. Interestingly, ER pathway activity was significantly lower in late-line tumors, except in *ESR1m* tumors. Overall, these results support the continued investigation of improved and personalized treatment options for pts with ER+, HER2- aBC. Clinical trial information: NCT04576455. Research Sponsor: F. Hoffmann-La Roche Ltd.

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Poster Session

Indirect treatment comparison of first-line CDK4/6-inhibitors in post-menopausal patients with HR+/HER2- metastatic breast cancer. *First Author: Joseph J Zhao, Yong Loo Lin School of Medicine, National University of Singapore (NUS), Singapore, Singapore*

Background: In phase III studies, the CDK4/6-inhibitors palbociclib, ribociclib, and abemaciclib all have demonstrated similar clinical efficacy in hormone receptor-positive (HR+)-human epidermal growth factor receptor 2 negative (HER2-) metastatic breast cancer (MBC) with regards to the primary endpoint of progression-free survival (PFS). However, the lack of overall survival (OS) benefit in the PALOMA-2 study is inconsistent with the OS benefit seen with the other two CDK4/6-inhibitors. This study sought to elucidate indirect treatment survival outcomes between CDK4/6-inhibitors in this setting. **Methods:** Phase III randomized controlled trials comparing first-line aromatase inhibitor with or without a CDK4/6-inhibitor in post-menopausal patients with HR+/HER2- MBC. A graphical reconstructive algorithm was utilized to retrieve patient level time-to-event data from reported Kaplan-Meier OS and PFS curves. Survival analyses were conducted with Cox proportional hazards model with a shared-frailty term incorporated to account for inter-study differences. Two-stage indirect treatment comparison model was conducted as a sensitivity analysis. **Results:** Three randomized phase III trials – PALOMA-2, MONALEESA-2 and MONARCH-3 – comprising 1,827 patients were included. Indirect pairwise comparison of all CDK4/6-inhibitor showed no significant PFS differences across one-stage and two-stage models (all p > 0.05). Likewise, indirect treatment comparison between ribociclib vs palbociclib (one-stage: HR=0.903, 95%-CI: 0.746-1.094, p=0.297), abemaciclib vs palbociclib (one-stage: HR=0.843, 95%-CI: 0.690-1.030, p=0.094) and abemaciclib vs ribociclib (one-stage: HR=0.933, 95%-CI: 0.753-1.157, p=0.528) failed to demonstrate a significant OS difference. **Conclusions:** Findings from this indirect treatment comparison suggest no significant PFS or OS differences between CDK4/6-inhibitor agents when combined with an aromatase inhibitor in post-menopausal patients with HR+/HER2- MBC. Research Sponsor: None.

Indirect treatment comparison outcomes.

	Comparison	One-Stage Model		Two-Stage Model	
		HR (95%-CI)	p-value	HR (95%-CI)	p-value
Progression-free survival	abemaciclib vs ribociclib	0.722 (0.520 – 1.002)	0.051	0.921 (0.597 – 1.420)	0.710
	abemaciclib vs palbociclib	0.790 (0.583 – 1.071)	0.129	0.790 (0.514 – 1.216)	0.285
	ribociclib vs palbociclib	1.094 (0.825 – 1.451)	0.531	0.858 (0.594 – 1.239)	0.415
Overall Survival	abemaciclib vs ribociclib	0.933 (0.753 – 1.157)	0.528	0.993 (0.719 – 1.372)	0.966
	abemaciclib vs palbociclib	0.843 (0.690 – 1.030)	0.094	0.815 (0.585 – 1.135)	0.227
	ribociclib vs palbociclib	0.903 (0.746 – 1.094)	0.297	0.821 (0.614 – 1.098)	0.183

HR, hazard ratio; CI, confidence interval.

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Poster Session

Oral elacestrant vs standard-of-care in estrogen receptor-positive, HER2-negative (ER+/HER2-) advanced or metastatic breast cancer (mBC) without detectable *ESR1* mutation (EMERALD): Subgroup analysis by prior duration of CDK4/6i plus endocrine therapy (ET). *First Author: Virginia G. Kaklamani, UT Health San Antonio, San Antonio, TX*

Background: The phase 3 EMERALD trial reported significantly prolonged progression-free survival (PFS) and a manageable safety profile with oral elacestrant (Ela) vs standard of care ET (SoC) in patients (pts) with ER+/HER2- mBC following progression on prior endocrine and CDK4/6i therapy. Duration of prior CDK4/6i was shown to be a potential predictor of efficacy in pts with *ESR1* mutations (*ESR1m*) receiving elacestrant. Median PFS (mPFS) for pts with *ESR1m* receiving <6 mos of prior CDK4/6i was 1.87 mos (Ela) vs 1.87 mos (SoC), compared with 4.14 mos (Ela) vs 1.87 mos (SoC) for pts receiving CDK4/6i ≥6 mos and 8.61 mos (Ela) vs 1.91 mos (SoC) for pts receiving ≥12 mos of prior CDK4/6i. Understanding the clinical activity of Elacestrant in *ESR1* non-detected (*ESR1nd*) ER+/HER2- mBC is still needed. Preclinical ER+ PDX models suggest that elacestrant is equally active in *ESR1* wild-type (*ESR1wt*) and *ESR1m*. In the PDX model ST3932 (*ESR1wt*), derived from a pt treated with palbociclib plus aromatase inhibitor (AI) that was resistant to palbociclib in vivo, elacestrant demonstrated statistically significant single-agent antitumor activity (Patel, 2019). **Methods:** Pts with ER+/HER2- advanced or mBC who previously had 1-2 lines of ET, mandatory CDK4/6i, and ≤1 chemotherapy were randomized, 1:1 to receive oral elacestrant or SoC (investigator's choice of AI or fulvestrant). An ad hoc subgroup analysis was performed on pts with *ESR1nd* by prior duration of CDK4/6i plus ET (<6 mos, ≥6 mos, ≥12 mos) in the advanced or metastatic setting. **Results:** Among the 478 pts enrolled, 250 (n=124, Ela; n=126, SoC) did not have a detectable *ESR1m*. Interestingly, in 41 pts with *ESR1nd* (n=20, Ela; n=21, SoC) that rapidly progressed on prior CDK4/6i plus ET (<6 mos), treatment with elacestrant was associated with prolonged mPFS vs SoC (5.32 mos vs 1.87 mos, respectively) (HR=0.518 [95% CI 0.216-1.165]), compared with a mPFS of 1.91 mos (Ela) vs 1.97 mos (SoC) for pts who were on CDK4/6i for ≥6 mos (HR=0.911 [95% CI 0.640-1.298]) and 2.33 mos (Ela) vs 2.04 mos (SoC) for pts who were on CDK4/6i for ≥12 mos (HR=0.886 [95% CI 0.586 - 1.337]). In these 41 pts, mean time to chemotherapy was 137.7 days for elacestrant vs 75.5 days for SoC. Safety results were consistent with previously reported data. Specific pt characteristic information will be provided in the presentation. **Conclusions:** In this post-hoc analysis, oral elacestrant delayed disease progression and time to subsequent chemotherapy in pts who did not have a detectable *ESR1m* and rapidly progressed within 6 months of CDK4/6i plus ET before study entry. Preclinical data support these findings. While caution needs to be exerted given small numbers, the results highlight the potential role of elacestrant in *ESR1wt* tumors, and more research is warranted. Clinical trial information: NCT03778931. Research Sponsor: Stemline Therapeutics, Inc.

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Poster Session

A multicenter, single-arm, open-label trial of birociclib, a CDK4/6 inhibitor, as a single agent, in patients with refractory HR+/HER2- metastatic breast cancer. *First Author: Jiayu Wang, Department of Medical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China, China*

Background: Birociclib is a new molecular entity and selective inhibitor of cyclin-dependent kinase (CDK) 4 and 6. This phase II study (NCT04539496) was to evaluate the single-agent efficacy and safety of Birociclib in patients with refractory HR+/HER2- metastatic breast cancer (MBC). **Methods:** This phase II study is a multicenter, single-arm, open-label trial in patients with HR+/HER2- MBC who had progressed after prior endocrine therapy and 1-2 prior chemotherapy regimens in the metastatic setting. Birociclib 480 mg was administered orally on a continuous schedule twice daily until disease progression or unacceptable toxicity. The primary endpoint was objective response rate (ORR). The secondary endpoints included disease control rate (DCR), clinical benefit rate (CBR), duration of response (DoR), progression-free survival (PFS), overall survival (OS) and safety. **Results:** 131 patients were enrolled from 29 hospitals in China between 10/2020 and 8/2021, with a median duration of follow-up of 17.74 months. Among them, 84.7% patients had visceral disease, and 61.1% patients had ≥3 metastatic sites. In the metastatic setting, patients had received a median of 3 (range, 1-6) prior systemic therapies including a median of 1 (1-2) chemotherapy regimen and 2 (1-5) endocrine therapy regimens. The investigator-assessed confirmed ORR was 22.9% (95% CI: 16.0-31.1); DCR was 66.4% (95% CI: 57.6-74.4); CBR was 39.7% (95% CI: 31.3-48.6), among which 1 (0.8%) patient was with confirmed complete response (CR) and 29 (22.1%) patients were with confirmed partial response (PR). Median DoR was 13.1 months (95% CI: 9.4-16.6). Median PFS was 7.4 months (95% CI: 5.5-9.2). The OS rates at 12 months and 21 months were 81.8% and 64.6%, respectively. Birociclib demonstrated similar activity in subgroups with visceral disease and liver disease, ORR were 20.7% (95% CI: 13.6-29.5) and 18.5% (95% CI: 9.9-30.0), DCR were 64.9% (95% CI: 55.2-73.7) and 66.6% (95% CI: 51.7-76.9), CBR were 39.6% (95% CI: 30.5-49.4) and 35.4% (95% CI: 23.9-48.2), DoR were 14.8 months (95% CI: 7.6-NA) and 11.2 months (95% CI: 5.5-NA), PFS were 8.2 months (95% CI: 5.5-9.3) and 7.3 months (95% CI: 5.388-9.101), respectively. The most common treatment-emergent adverse events (TEAE) were diarrhea [93.1% (all grades); 18.3% (≥grade 3)], neutropenia [87.0% (all grades); 43.5% (≥grade 3)], and leukocytopenia [86.3% (all grades); 32.8% (≥grade 3)]. Most of AEs were grade 1 or grade 2 and could be alleviated or cured by symptomatic treatment. **Conclusions:** In patients who have limited treatment options with refractory HR+/HER2- metastatic breast cancer, continuous dosing of single-agent Birociclib exhibited promising and sustaining clinical activity with acceptable safety profile, thus it provided an alternative orally administered therapy option. Clinical trial information: NCT04539496. Research Sponsor: Xuanzhu Biopharmaceutical Co., Ltd., Beijing, China.

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Poster Session

Clinical outcomes and correlation with longitudinal circulating tumor (ct) DNA dynamics of a phase I/II study of GSK525762 combined with fulvestrant in patients with hormone receptor-positive/HER2-negative (HR+/HER2-) advanced or metastatic breast cancer. *First Author: David W. Cescon, Princess Margaret Cancer Center, University Health Network and University of Toronto, Toronto, ON, Canada*

Background: Endocrine therapy is the main treatment option for hormone receptor-positive and human epidermal growth factor receptor 2-negative (HR+/HER2-) metastatic breast cancer (mBC). However, many patients experience disease progression due to resistance to endocrine therapy. Molibresib (GSK525762) is a small-molecule inhibitor of bromodomain and extra-terminal (BET) family proteins (BRD2, BRD3, BRD4, and BRDT). Pre-clinical data suggested that the combination of molibresib with endocrine therapy might overcome endocrine resistance. This study aimed to investigate the safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy (objective response rate [ORR]) of molibresib combined with fulvestrant in women with HR+/HER2- mBC. The association between early ctDNA dynamics and clinical outcomes was also assessed. **Methods:** In this phase I/II dose-escalation and expansion study, patients received oral molibresib 60 mg or 80 mg once daily in combination with intramuscular fulvestrant. Patients enrolled had relapsed/refractory, advanced/metastatic HR+/HER2- BC with disease progression on prior treatment with an aromatase inhibitor, with or without a cyclin-dependent kinase 4/6 (CDK4/6) inhibitor. Baseline and week 4 plasma samples were collected and tested using a 74-gene ctDNA panel. Molecular response (MR) was defined as at least 50% reduction of baseline ctDNA level calculated as the average allele frequency of detected single nucleotide variants or indels. **Results:** The study included 123 patients. The 3 most common molibresib-related adverse events (AEs) were nausea (52%), dysgeusia (49%), and fatigue (44%). At molibresib 60 mg, >90% patients experienced treatment-related AEs, with varying incidence of Grade ≥ 3 AEs (17%–71%) amongst subgroups. The ORR was 13% (95% confidence interval [CI], 8–20), not meeting the 25% threshold for proceeding to phase II. Among 82 patients with detected baseline circulating tumor DNA, a strong association was observed between baseline copy number amplification (CNA) presence and poor progression-free survival (PFS) with hazard ratio (HR) of 2.89 (95% CI, 1.73–4.83; $P < 0.0001$). MR was significantly correlated with better PFS (HR=0.38; 95% CI, 0.19–0.75; $P = 0.0037$), which was further improved when MR was refined as no baseline CNA (HR=0.22; 95% CI, 0.09–0.54; $P = 0.0003$). **Conclusions:** Molibresib in combination with fulvestrant did not demonstrate clinically meaningful activity in this study. Copy number adjusted ctDNA MR is a promising early marker for clinical benefit. Clinical trial information: NCT02964507. Research Sponsor: GlaxoSmithKline.

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Poster Session

Impact of pathogenic germline BRCA1/2 and PALB2 mutations and tumor aneuploidy in patients with HR+/HER2- metastatic breast cancer treated with CDK4/6 inhibitors. *First Author: Jesús Fuentes Antrás, Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, Toronto, Canada*

Background: CDK4/6 inhibitors lack established predictors of efficacy in HR+/HER2- mBC. Pathogenic germline BRCA2 variants, somatic homologous recombination deficiency (HRD) and APOBEC signatures conferred worse survival in small series. Broader tumor DNA panels enable the detection of these and other parameters such as aneuploidy and tumor mutational burden. **Methods:** Clinical and molecular data from a single institution cohort of CDK4/6-treated HR+/HER2- mBC pts were analyzed. ECOG PS was 0–1. Clinical variables were collected retrospectively. Primary endpoints were progression-free survival (PFS) and overall survival (OS). Tumor-only sequencing was performed on clinical samples with 161-gene OCAV3, 523-gene TSO500 or 555-gene lab-developed NGS panels. HRD was assessed with the Signature Multivariate Analysis (SigMA) tool using a likelihood-based measure to estimate single base substitution signature 3. Aneuploidy scores were defined as the fraction of covered arms harboring arm-level somatic copy number alterations as determined by ASCETS v1.1. **Results:** 153 pts were available for analysis. Median age was 54 y (29–88). 74% were postmenopausal, 28% *de novo* metastatic and 67% had visceral disease. Palbociclib was used in 80%, ribociclib in 17% and abemaciclib in 3%, mostly as early lines (1L 65%, 2L 22%). Median follow up was 46 mo (7–84) and median time from sample collection to CDK4/6i was 0.6 y (–18.5–+2.6). 76% of samples have been sequenced. The median number of mutations (Mts) was 3 (1–32), most commonly in PIK3CA (37%), GATA3 (26%) and TP53 (20%). ESR1, KRAS and ARID1A, but not RB1 muts were numerically enriched in post-CDK4/6i mets (n=8). TP53 (HR 1.85 CI 1.02–3.33) and GATA3 (HR 0.48, CI 0.28–0.83) muts were associated with PFS. Germline (g) testing was available in 68 (44%) pts, with 21 pts carrying pathogenic variants including 11 BRCA2, 2 BRCA1 and 2 PALB2. Cox regression showed a strong negative impact of gBRCA1/2-PALB2 on PFS (HR 4.0 CI 2.0–7.9) and OS (HR 3.5 CI 1.6–7.7) adjusted for age, visceral disease and prior chemo. In 1L, mPFS/OS was 9.9/28.1 mo for gBRCA1/2-PALB2 carriers, 26.8/NR mo for non-carriers and 23.7/49.2 mo for untested (Cox HR PFS 5.1 CI 2.1–14.0; HR OS 4.0 CI 1.4–11.2). Pts with gATM/CHK2/BRIP1 had a 1L PFS/OS $\geq 15/45$ mo. Among 36 pts assessed for HRD, 22 were HRDlow and 14 HRDhigh with no significant survival association. 3/4 known gBRCA1/2 carriers were HRDhigh and 7/8 gWT HRDlow. In these pts, higher aneuploidy was associated with shorter PFS and OS (Cox HR PFS 2.0 CI 0.9–4.3, $p=0.07$; HR OS 2.6 CI 1.0–7.1; $p=0.05$). **Conclusions:** Pathogenic gBRCA1/2-PALB2 and higher aneuploidy were associated with shorter survival. Profiling of aneuploidy, HRD, TMB and APOBEC in all pts is ongoing including 55 baseline ctDNA samples and 361 samples from the GENIE BPC cohort. Results will account for FDR, left truncation and optimal cutoffs. Research Sponsor: Government of Ontario through the OICR Adaptive Oncology (AO); Princess Margaret Cancer Foundation (PMCF) through the Cancer Genomics Program (CGP) at University Health Network (UHN).

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Poster Session

ESR1 mutational landscape and impact of co-existing resistance variants on clinical outcomes in patients with metastatic breast cancer. *First Author: Arielle J Medford, Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA*

Background: Mutations in estrogen receptor 1 (ESR1) confer resistance to aromatase inhibitors but may retain sensitivity to selective estrogen receptor degraders (SERD). Recently, elacestrant, an oral SERD, was approved for patients with HR+/HER2- ESR1^{mut} metastatic breast cancer (MBC). In this study, we evaluated the genomic landscape of ESR1 alterations from a genomic database and also evaluated the impact of resistance-associated alterations on clinical outcomes. **Methods:** A large de-identified database of mutations detected in plasma cell-free DNA (cfDNA) from patients with HR+/HER2- MBC was assessed for ESR1 mutations and resistance-associated co-alterations. We used the Guardant 360 assay, a 70- to 74-gene targeted next generation sequencing panel and applied a breast cancer subtype classifier based on detected mutations (Bardia A, SABCS 2020). In addition, clinical outcomes were evaluated from a clinically annotated institutional dataset, linking genomic alterations with progression-free survival (PFS) and overall survival (OS) to single-agent SERD therapy for patients with MBC. **Results:** Among 11,456 patients with MBC and detectable cfDNA, 4,694 were classified as likely HR+/HER2-, of which 2,708 (58%) had ESR1 missense mutations, the majority of which occurred in the ligand binding domain (n = 2,690, 99%). Among the latter, alterations included 204 unique mutations, of which 55 were variants of uncertain significance (VUS). Multiple ESR1 mutations were detected in 979 (36%) patients. Among 567 patients classified as HR+/HER2- that underwent serial sampling, 136 (24%) had detectable ESR1 missense mutations that were previously undetectable. Within the ESR1^{mut} population, 1,990 (74%) had co-existing non-synonymous, non-VUS alterations at genes associated with SERD resistance: PIK3CA (n = 1,330; 49%), ARID1A (n = 314; 12%), PTEN (n = 201; 7%), ERBB2 (n = 180; 7%), AKT1 (n = 139; 5%), and NF1 (n = 103; 4%); top amplifications were FGFR1 (n = 522; 19%), EGFR (n = 277; 10%), and MYC (n = 177; 7%). Among a clinically annotated HR+/HER2- subgroup (n = 350), 51 patients received SERD monotherapy, either fulvestrant (n = 9) or oral SERD on clinical trial (n = 42); among 28 patients with cfDNA variants associated with SERD resistance, median PFS and OS were lower compared to the 23 patients without resistance mutations (PFS: 2.4 vs 11.3 mo; HR = 0.44; 95% CI, 0.23–0.81; $p = 0.008$; and OS: 21.1 vs 31.4 mo; HR 0.47; 95% CI, 0.22–0.98; $p = 0.045$). **Conclusions:** ESR1 mutations that qualify patients to receive approved SERD therapy are detectable by plasma-based genotyping and can associate with various genomic co-alterations, including variants that may impact clinical outcomes. Further research is needed to confirm the impact of co-alterations in additional datasets and evaluate the role of SERD-based combination therapy to further improve clinical outcomes of patients with MBC. Research Sponsor: None.

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Poster Session

Comparing the prognostic and predictive utility of serum thymidine kinase 1 and CA 15-3 in patients with hormone receptor positive metastatic breast cancer starting first-line endocrine therapy in SWOG S0226. *First Author: Erin Frances Cobain, University of Michigan, Ann Arbor, MI*

Background: Serum levels of thymidine kinase 1 activity (TKa), a fundamental enzyme in DNA synthesis and cellular proliferation, are prognostic of benefit from endocrine therapy (ET) in patients (pts) with hormone receptor positive (HR+) metastatic breast cancer (MBC) who participated in SWOG S0226, a prospective randomized trial comparing anastrozole vs. anastrozole and fulvestrant given in 4 week cycles. The assay for TKa (DiviTum TKa) was FDA approved in July 2022 for monitoring of postmenopausal HR+ MBC pts. The assay for circulating MUC1, CA 15-3, is routinely utilized in monitoring of pts with MBC. We compared the prognostic and predictive utilities of CA 15-3 and TKa in pts from S0226. **Methods:** TKa was measured in 1725 sera from 432 pts while CA 15-3 was measured in 1298 sera from 326 pts at baseline (BL), cycles 2, 3, 4 and 7. Prespecified cutoff levels of ≥ 250 DuA and ≥ 30 U/mL were considered high for TKa and CA 15-3 respectively. Progression-free survival (PFS) and overall survival (OS) were analyzed by Kaplan-Meier and Cox regression stratified by prior adjuvant tamoxifen use. To examine markers over time, a landmark Cox regression analysis was done starting at initiation of Cycle 4. BL and recent (Cycle 3 if available, otherwise Cycle 2) markers were assessed for simultaneous prediction of subsequent PFS and OS. **Results:** BL TKa was elevated in 190/432 (44%) and CA 15-3 was elevated in 254/326 (78%). Agreement between assays was 53%. Pts with high versus low BL TKa had significantly worse PFS (median 11.6 vs. 17.2 months, HR = 1.68, 95% confidence interval (CI) 1.37–2.06) and OS (median 34 vs. 58 months, HR = 2.16, 95% CI 1.73–2.70) whereas pts with high versus normal BL CA 15-3 had no significant difference in PFS (median 13.6 vs. 16.1 months, HR = 1.23, 95% CI 0.93–1.62) but worse OS (median 45 vs. 66 months, HR = 1.82, 95% CI 1.30–2.53). A multivariable Cox model with both markers shows only TKa as being prognostic for PFS (TKa HR = 1.61, 95% CI 1.28–2.03; CA 15-3 HR = 1.21, 95% CI 0.91–1.59), but both prognostic for OS (TKa HR = 2.09, 95% CI 1.61–2.71; CA 15-3 HR = 1.70, 95% CI 1.22–2.38). In the landmark multivariable analysis, positive TKa at BL was a strong predictor of PFS (HR = 1.65, 95% CI 1.28–2.14), but recent TKa was not (HR = 1.25, 95% CI 0.93–1.68). In contrast, positive CA15-3 at BL was not a predictor of PFS (HR = 0.73, 95% CI 0.46–1.17), but recent CA15-3 was (HR = 1.97, 95% CI 1.26–3.06). **Conclusions:** BL TKa is highly prognostic in pts with HR+ MBC initiating first-line systemic ET, with low BL TKa conferring superior prognosis. In contrast, CA 15-3 is only modestly prognostic at BL, but is prognostic after 3 cycles of treatment. These hypothesis-generating data suggest further study is needed to determine how these biomarkers should be employed in a complementary manner to monitor response to systemic therapy in HR+ MBC. Clinical trial information: NCT00075764. Research Sponsor: U.S. National Institutes of Health; AstraZeneca, Biovia.

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Poster Session

Relation between circulating biomarkers at diagnosis of early luminal-like breast cancer and subsequent risk of distant metastases. *First Author: Yentl Lambrechts, Laboratory of Experimental Oncology (LEO), Department of Oncology, Leuven, Belgium*

Background: Predicting development of distant metastases after treatment of early luminal breast cancer (BC) remains a major challenge. Besides clinical-pathological features of the primary tumor, baseline circulating factors could also play a role as prognostic biomarkers. **Methods:** Patients with newly diagnosed early BC (grade 2/3, ER+, HER2-non- amplified) were selected from our institutional BC registry, with associated blood biobank collecting baseline plasma/serum samples at diagnosis. Circulating biomarkers potentially modulating the metastatic process (chemokines, micro-RNAs (miRNAs), Leukemia Inhibitory Factor (LIF), and osteopontin), and serum-induced functional myeloid interferon (IFN) and nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) signaling-responses, were measured at early BC diagnosis (before any treatment) in patients who subsequently developed distant metastasis within five years after diagnosis and therapy (META group) and in a 1:1 control group of patients, pairwise matched for age, tumor grade, stage, and histological subtype, who remained disease-free for at least seven years (NON-META group). All blood biomarkers were analyzed pair-wisely using the univariable Wilcoxon signed rank test (two-tailed). Multiple testing correction was done by applying a false discovery rate (FDR) of 0.05. In addition, a multivariable logistic regression analysis (MVA) was performed to find blood biomarkers signatures that can predict the development of metastases at first diagnosis of early BC. **Results:** 102 matched patient pairs were included. Univariable paired analysis showed significantly increased baseline expression of LIF ($p=0.012$) and six miRNAs (miR-143-3p: $p=0.015$; miR-197-3p: $p<0.001$; miR-223-3p: $p=0.006$; miR-223-5p: $p=0.045$; miR-338-3p: $p=0.045$; miR-365a-3p: $p=0.025$), and decreased serum-induced myeloid -IFN-responses ($p=0.023$) and ten miRNAs (let-7b-5p: $p=0.006$; miR-106a-5p: $p=0.045$; miR-106b-5p: $p=0.015$; miR-107: $p=0.014$; miR-144-3p: $p=0.015$; miR-15a-5p: $p=0.045$; miR-15b-3p: $p=0.032$; miR-185-5p: $p=0.045$; miR-18a-5p: $p=0.015$; miR-30b-5p: $p=0.045$) in the META group compared to the NON-META group. MVA yielded a seven-biomarker signature, which includes miR-197-3p ($p=0.008$), miR-139-5p ($p<0.001$), LIF ($p=0.007$), miR-106b-5p ($p=0.003$), serum-induced IFN/ISG response ($p=0.006$), miR-652-3p ($p=0.015$), and miR-133b ($p=0.025$) with a C-index of 0.79 (0.70-0.88) to predict distant metastases. After 5-fold internal cross-validation, C-index was 0.63 (0.52-0.74). **Conclusions:** Baseline circulating miRNAs, LIF, and serum-induced IFN-response levels at early luminal BC diagnosis are associated with subsequent distant metastases. Further external validation is required to confirm the prognostic value of these biomarkers. Research Sponsor: Kom op Tegen Kanker.

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Poster Session

A phase I trial of palbociclib (palbo) and bosutinib (bos) with fulvestrant (fulv) in patients (pts) with hormone receptor-positive, HER2-negative (HR+/HER2-) metastatic breast cancer (MBC) refractory to an aromatase inhibitor (AI) and a CDK4/6 inhibitor (CDK4/6i). *First Author: Candace Bavette Mainor, Medstar Georgetown University Hospital-Lombardi Comprehensive Cancer Center, Washington, DC*

Background: Standard therapy for HR+/HER2- MBC includes a CDK 4/6i with endocrine therapy (ET). Eventual resistance results in progression of disease (PD). A potential mechanism of CDK4/6 resistance is through Src activation. Targeting Src and ET suppresses proliferation of ER+ hormone independent breast cancer cells. Therefore, adding bos, a Src inhibitor, to palbo + fulv may overcome this resistance and restore sensitivity to CDK4/6i. **Methods:** This is a single arm, 3+3 dose escalation phase I trial (NCT 03854903) of bos + palbo + fulv for pts with HR+/HER2- MBC who have PD after ≥ 1 AI, ≥ 1 CDK4/6i, and < 3 lines of chemo for MBC. Pts were enrolled in two cohorts, A and B, with two dose levels in cohort B. Fulv was given at standard dose. Cohort A: bos 300mg (D1-5/wk), palbo 75mg D1-21 q28 days, fulv; cohort B1: bos 300mg (D1-5/wk), palbo 100 mg D1-21 q28 days, fulv; cohort B2: bos 500mg (D1-5/wk), palbo 100 mg D1-21 q28 days, fulv. Primary objective was safety and tolerability, including MTD and recommended phase 2 dose (RP2D). Secondary objectives included ORR, and CBR 24 wks. Serum, plasma, and peripheral blood mononuclear cells were collected for Src activation, cell cycle profile arrays, and cytokine array screens. **Results:** 18 evaluable pts were enrolled between 4/2019 – 11/2022. To date, 16pts have completed and 2 pts remain on treatment. All pts had received prior palbo and 15/18 (83%) had received prior fulv. Median number of prior therapies in the metastatic setting was 3.2. The combination in cohort A and B1 was well tolerated. The combination in cohort B2 (bos 500mg D1-5/wk) was toxic which resulted in bos dose reduction in all pts in the B2 cohort. There were no DLTs. The RP2D was bos 300 mg D1-5/wk, palbo 100 mg D1-21 q28 days, and standard dose fulv. No pts came off treatment due to adverse events (AEs). Most common AEs were G1/2 (9 pts) and G3/4 (7 pts) neutropenia (no neutropenic fever); G1 nausea (8 pts); G1/2 (12pts) and G3 (1pt) diarrhea; G1/2 rash (4 pts), and no G5 events. Median PFS was 5.9 months with 95% CI (3, 10.1). CBR at 6 months was 50% (9/18) (95% CI (0.26, 0.74)). The ORR was 6% (0 CR, 1 PR cohort B2), but best response was SD in 11 pts. Correlative studies underway include assessment pre and post treatment of 1) Src levels and activity to confirm that bos is acting on target and 2) RNA sequencing of Src activation and cell cycle profiles and 3) cytokine array screens to test if Bos affects inflammatory markers. **Conclusions:** Bos + palbo + fulv was well tolerated at the RP2D. A robust CBR of 50% was seen despite all patients having prior PD on palbo and 83% on fulv. This is an effective combination for HR+/HER2- MBC which warrants further investigation and may represent a mechanism to overcome resistance to CDK4/6i and provide another oral treatment option. Clinical trial information: NCT03854903. Research Sponsor: Pfizer-Aspire award.

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Poster Session

Alpelisib + endocrine therapy in patients with PIK3CA-mutated, hormone receptor-positive, human epidermal growth factor receptor 2-negative, advanced breast cancer: Analysis of all 3 cohorts of the BYLieve study. *First Author: Stephen Chia, University of British Columbia, Vancouver, BC, Canada*

Background: The phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) gene is mutated in ~40% of patients (pts) with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) advanced breast cancer (ABC). Alpelisib (ALP), an α -selective PI3K inhibitor and de-grader, is indicated in combination with fulvestrant (FUL) for pts with HR+, HER2- ABC following progression on/after endocrine therapy (ET)-based treatments (tx). Primary analyses from the 3 cohorts of the Phase 2, open-label, noncomparative BYLieve study demonstrated the efficacy of ALP + ET in pts with HR+, HER2-, PIK3CA-mutated ABC who progressed on/after other tx, including immediately after a cyclin-dependent kinase 4/6 inhibitor (CDK4/6i). Presented here are efficacy and safety data from the full 3 cohorts of the BYLieve study. **Methods:** Pts in all 3 cohorts completed ≥ 18 mo follow-up plus 1 mo safety follow-up. Efficacy assessments included DoR, BOR, PFS, PFS2, and OS. Safety/tolerability of ALP were also assessed. Median (m) PFS, PFS2, and OS were assessed by Kaplan-Meier methodology per local investigator assessment. **Results:** Cohort A (ALP + FUL) comprised 127 pts whose immediate prior tx was CDK4/6i + aromatase inhibitor (AI); Cohort B (ALP + letrozole) enrolled 126 pts whose immediate prior tx was CDK4/6i + FUL. In Cohort C (ALP + FUL), 126 pts had disease progression on/after AI and received CT or ET as immediate prior tx. Median follow-up for the 3 cohorts was 21.8, 25.3, and 18.5 mo, respectively. mPFS in Cohorts A, B, and C was 8.0 mo (95% CI, 5.6-8.6), 5.6 mo (3.7-7.1), and 5.6 mo (5.4-8.1), respectively; mPFS2 was 15.2 mo (95% CI, 11.4-21.7), 13.0 mo (10.2-13.9), and 13.5 mo (11.5-17.3), respectively. mOS in Cohorts A, B, and C was 27.3 mo (95% CI, 21.3-32.7), 29.0 mo (24.5-34.8), and 20.7 mo (16.9-28.1), respectively. Efficacy of ALP + ET in 2nd and 3rd lines will be presented. In Cohorts A, B, and C, respectively, 29 (22.8%), 19 (15.1%), and 23 (18.3%) pts discontinued tx due to adverse events (AEs). The most common any grade AEs in all 3 cohorts (A; B; C) were diarrhea ($n=82$, 64.6%; $n=86$, 68.3%; $n=68$, 54.0%), hyperglycemia ($n=76$, 59.8%; $n=82$, 65.1%; $n=85$, 67.5%), nausea ($n=59$, 46.5%; $n=69$, 54.8%; $n=51$, 40.5%), rash ($n=40$, 31.5%; $n=39$, 31.0%; $n=51$, 40.5%), and fatigue ($n=39$, 30.7%; $n=39$, 31.0%; $n=44$, 34.9%). Hyperglycemia was the most common grade ≥ 3 AE, observed in 37 (29.1%), 32 (25.4%), and 30 (23.6%) pts in Cohorts A, B, and C, respectively. **Conclusions:** After ≥ 18 mo follow-up, with mature data, ALP + ET demonstrated clinical activity in BYLieve Cohorts A, B, and C. Within the trial, ALP + ET showed median OS between 20.7 mo and 29.0 mo following prior CDK4/6i, chemotherapy, or ET. AEs associated with ALP were well defined and manageable, with no new safety signals observed in any cohort. Clinical trial information: NCT03056755. Research Sponsor: Novartis Pharmaceuticals Corporation.

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Poster Session

Phase 1/2 dose expansion study evaluating first-in-class eIF4A inhibitor zotatifin in patients with ER+ metastatic breast cancer. *First Author: Ezra Rosen, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Zotatifin (eFT226) is a first-in-class, potent and sequence selective inhibitor of RNA helicase eIF4A that promotes a stable mRNA:eIF4A: drug ternary complex at specific polypurine motifs within the 5'-UTR, preventing translation of select transcripts. In preclinical models zotatifin treatment simultaneously down-regulated translation of numerous oncogenes including CDK4, ER α , ERBB2, KRAS, and CCND1. **Methods:** Following a 3+3 dose escalation portion of the protocol (Part 1), Part 2 is a Simon's two-stage design of cohorts of up to 18 patients (pts) with ER+ metastatic breast cancer enrolled at the recommended phase 2 dose of zotatifin (0.07 mg/kg IV two weeks on/one week off) in combination with fulvestrant (ful) (ECBF: Expansion, Combination, Breast, Ful) or in combination with ful and abemaciclib (abema) (ECBF+A: Expansion, Combination, Breast, Ful + Abema). Key eligibility criteria included at least one line of therapy for advanced/metastatic disease, progression on hormone therapy, and in addition, the ECBF cohort required prior CDK 4/6 inhibitor (CDKI). Primary endpoint was objective response rate (ORR) per RECIST v1.1. Additional endpoints included safety, other efficacy analyses, and for Parts 1 and 2, characterization of pharmacodynamic (PD) markers and pharmacokinetics. **Results:** As of a data cut-off of Jan 31, 2023, 18 pts were enrolled in each cohort. Median prior metastatic lines of therapy were 3 and 7 in ECBF+A and ECBF, respectively. In 16 evaluable pts in ECBF+A cohort, there were two confirmed partial responses (PR), two additional PRs awaiting confirmatory scans, and 8 pts with best overall response (OR) of stable disease (SD). All pts with PR/unconfirmed PR received prior CDKI and ful, including one pt with disease progression on combination abema and ful as the last therapy prior to enrollment. In 18 evaluable pts in ECBF, there was one confirmed PR and six SD as best OR. There were no dose-limiting toxicities or grade (Gr) 5 adverse events (AEs) in either cohort. In ECBF+A the most common AEs (all Gr 1/2) were diarrhea (44%) and nausea (31%) and 21% of pts had Gr 3/4 AEs. The most common AEs in ECBF (all Gr 1/2) were nausea (39%) and constipation (27%), and 28% of pts had Gr 3/4 AEs. Blood-based PD markers and ctDNA in Part 1 showed dose-dependent evidence of target engagement and anti-tumor activity. **Conclusions:** In dose expansion cohorts of heavily pre-treated metastatic breast cancer pts, eIF4A inhibitor zotatifin showed evidence of anti-tumor activity in combination with fulvestrant and abemaciclib and had a favorable safety profile consisting of primarily grade 1/2 adverse events. Clinical trial information: NCT04092673. Research Sponsor: eFFECTOR Therapeutics, Inc.

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Poster Session

Real-world (RW) outcomes of patients (pts) with advanced breast cancer (aBC) with and without resistance alterations (alts) detected in cell-free circulating tumor DNA (ctDNA) prior to CDK4/6 inhibitor (CDK4/6i) plus endocrine therapy (ET) treatment. *First Author: Seth Andrew Wander, Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA*

Background: CDK4/6i plus ET is standard of care first-line (1L) therapy for hormone receptor positive (HR+), HER2- aBC. While molecular analyses from trials and pts have identified several mechanisms of resistance to CDK4/6i plus ET, currently, no biomarkers (outside of hormone status) are used for therapy selection. We utilized RW data to assess impact of putative baseline CDK4/6i+ET resistance alts (CDK4/6i+ET-R) on clinical outcomes among pts with aBC treated with CDK4/6i. **Methods:** Pts with aBC were identified via the Guardant INFORM database; those with a ctDNA test within 90 days prior to CDK4/6i start were included in this analysis. Based on previous studies, oncogenic or likely oncogenic alterations (as characterized by OncoKB) in the following genes were considered CDK4/6i+ET-R alts: RB1, PTEN, AKT1, CCNE1, ERBB2, FGFR1, FGFR2, and KRAS. Pts with >1 CDK4/6i+ET-R alt were compared to pts without any CDK4/6i-R alts. Kaplan-Meier plots, log-rank tests (LR) and multivariate Cox proportional hazards models (HR) adjusted (adj) for age, sex, year of ctDNA test and line of therapy were used to assess differences in time to next treatment (TTNT) and overall survival (OS). **Results:** 1075 pts with aBC treated with CDK4/6i (27% receiving 1L treatment) met inclusion criteria, 293 of whom (27%) had >1 alt in a CDK4/6i+ET-R gene. Pts with CDK4/6i+ET-R alts had significantly shorter TTNT (8.7 mos vs 14.2 mos, LR p=0.001; adj HR 1.36, 95%CI 1.11-1.66, adj p=0.003) and OS (28.3 mos vs 60.9 mos, LR p<0.0001; adj HR 2.19, 95%CI 1.69-2.82, adj p<0.0001) compared to those without. This divergence was more pronounced for patients receiving 1L CDK4/6i (TTNT: 10.7 mos vs 24.6 mos, LR p=0.006, adj HR 1.84, 95%CI 1.18-2.87, adj p=0.007; OS: 23.8 mos vs 67.3 mos, LR p<0.0001, adj HR 3.27, 95%CI 1.89-5.62, adj p<0.0001). Individual gene contributions towards less favorable TTNT are shown. **Conclusions:** We demonstrate via RW data that patients with >1 pre-treatment ctDNA alt in a curated list of CDK4/6i+ET-R genes have significantly worse outcomes on CDK4/6i plus ET treatment, a difference more pronounced among patients receiving 1L therapy. This data is among the first successful efforts to validate a clinically useful multi-gene clinical biomarker that has the potential to predict CDK4/6i plus ET resistance. Further exploration of this signature's prognostic and predictive utility for CDK4/6i plus ET use is ongoing to better refine personalized treatment selection in HR+/HER2- aBC. Research Sponsor: None.

Gene	Total N	TTNT multivariate model adj HR (95%CI)	p-value
CCNE1	18	1.82 (0.98-3.38)	0.06
ERBB2	36	1.74 (1.09-2.76)	0.02
RB1	11	1.64 (0.72-3.73)	0.24
KRAS	59	1.63 (1.15-2.29)	0.006
AKT1	39	1.61 (1.01-2.56)	0.05
FGFR1	121	1.10 (0.83-1.47)	0.51
PTEN	52	0.98 (0.61-1.57)	0.92
FGFR2	10	0.76 (0.28-2.11)	0.60

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Poster Session

Discovery of CDK4/6 bifunctional degraders for ER+/HER2- breast cancer. *First Author: Hannah Majeski, San Diego, CA*

Background: CDK4/6 inhibitors (CDK4/6i) such as palbociclib and ribociclib are used to treat ER+/HER2- breast cancer, but patients can develop resistance via many mechanisms, several of which converge on the upregulation of CDK6. This has been shown to limit the effectiveness of CDK4/6i in ER+ breast cancer with up to 20% patients exhibiting innate resistance and up to 70% patients developing acquired resistance after 3 years on therapy (Scheidemann, 2021, doi:10.3390/ijms222212292). **Methods:** To address this limitation, we utilized our PRODEGY platform of Cereblon (CRBN) binders to synthesize CRBN mediated CDK4/6 bifunctional degraders to potentially inhibit tumor growth for treatment of naïve ER+/HER2- breast cancer and CDK4/6i resistant tumors. **Results:** Target degradation by immunoblot analysis of the triple negative breast cancer (TNBC) cell line, MDA-MB-231, treated with our CDK4/6 bifunctional degraders for 6 hours showed up to 85% degradation of CDK4 and CDK6 with DC₅₀s of 1-100nM. CDK4/6 phosphorylates the protein RB which releases the transcription factor E2F, inducing the expression of genes which promote cell cycle progression. Analysis of RB phosphorylation by in-cell western upon 24 hours of CDK4/6 degrader treatment showed phospho-RB IC₅₀s at <30nM. Cell cycle analysis by staining with propidium iodide after 24 hours of treatment with CDK4/6 degraders induced G0/G1 cell cycle arrest at concentrations as low as 10nM. We used a 2D colony formation assay (CFA) as a readout for inhibition of proliferation by cell cycle arrest. Our CDK4/6 degraders showed potent inhibition of cell proliferation with CFA IC₅₀s of <100nM in TNBC cell lines and <25nM in ER+ cell lines, including MCF7, T47D and ZR751 compared to CDK4/6i which ranged from 200nM to 500nM in MCF7 cells. We demonstrated that our CDK4/6 bifunctional degraders were significantly more potent in vitro than the CDK4/6i ribociclib and palbociclib, and the increased activity was due to CRBN mediated target degradation. Our CDK4/6 bifunctional degraders display excellent pharmacokinetic properties in mice with half-lives between 2-10 hours, oral bioavailability between 50-96%. MCF7 xenograft results with our proof-of-concept CDK4/6 degrader showed dose-dependent tumor growth inhibition and greater potency compared to the clinical CDK4/6i ribociclib. We saw tumor regression with our degrader at higher doses which we did not see at any dose of CDK4/6i. **Conclusions:** Our CDK4/6 bifunctional degraders display excellent single agent activity in vitro and in vivo particularly in comparison to clinically approved CDK4/6i, indicating that using a degrader approach to targeting this pathway may be more effective than current inhibitor therapies. Research Sponsor: Biotheryx, Inc.

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Poster Session

Trop-2 mRNA expression and association with clinical outcomes with sacituzumab govitecan (SG) in patients with HR+/HER2- metastatic breast cancer (mBC): Biomarker results from the phase 3 TROPiCS-02 study. *First Author: Aditya Bardia, Medical Oncology, Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA*

Background: SG is a Trop-2-directed antibody-drug conjugate approved in multiple countries for patients with metastatic triple-negative breast cancer who received at least 1 prior systemic therapy and in the US for patients with pretreated HR+/HER2- mBC. In the TROPiCS-02 study, SG significantly improved progression-free survival (PFS; median, 5.5 vs 4.0 mo; HR, 0.66 [95% CI, 0.53-0.83]; P=0.0003) and overall survival (OS; median, 14.4 vs 11.2 mo; HR, 0.79 [95% CI, 0.53-0.83]; P=0.020) over treatment of physician's choice (TPC) in patients with pretreated, endocrine-resistant HR+/HER2- mBC. In TROPiCS-02 post hoc analyses, SG improved OS regardless of Trop-2 expression by immunohistochemistry (IHC; Rugo HS, et al. SABCS 2022), but association using more sensitive assays are lacking. Here, we examine efficacy outcomes for SG versus TPC by Trop-2 gene (*TACSTD2*) mRNA expression and the correlation of *TACSTD2* expression with other genes. **Methods:** Patients with HR+/HER2- mBC who received ≥1 prior taxane, endocrine therapy and a CDK4/6 inhibitor, and 2-4 prior chemotherapy regimens for mBC were randomized 1:1 to SG or TPC. The primary endpoint was PFS by central review per RECIST v1.1. RNA was isolated from archival tumor tissue samples using AllPrep DNA/RNA kits and libraries prepared with TruSeq RNA Exome Prep Kit. Sequencing was via NovaSeq (2x150bp). Gene expression quantitation was performed using Salmon. *TACSTD2* expression was defined as high or low via median cut. **Results:** In the mRNA analytical cohort (N=197), 49% had *TACSTD2* high expression (SG, n=51; TPC, n=46), and 51% had *TACSTD2* low expression (SG, n=47; TPC, n=53). Baseline characteristics were generally consistent between *TACSTD2* expression subsets and the intention-to-treat population. A positive concordance between *TACSTD2* expression and Trop-2 IHC (H-score) was observed (categorical concordance 71%; Cohen's kappa = 0.41). *TACSTD2* expression was similar across HER2 IHC0 and HER2-Low subgroups (log2 transcripts per million [TPM] of 3.36 [IQR, 2.76-4.22] and log2TPM of 3.44 [IQR, 2.59-4.22], respectively). SG showed a numerically higher median PFS (*TACSTD2* high, 7.3 vs 5.6 mo; *TACSTD2* low, 5.6 vs 2.8 mo) versus TPC regardless of *TACSTD2* expression. Similarly, for OS, outcomes favored SG over TPC regardless of *TACSTD2* expression. **Conclusions:** This mRNA-based biomarker analysis demonstrated that SG improves PFS and OS outcomes in patients with pretreated, endocrine-resistant HR+/HER2- mBC regardless of Trop-2 mRNA expression. There was no correlation between Trop-2 mRNA expression and HER2 status. Trop-2 mRNA expression was not predictive of benefit with SG. Additional studies are needed to determine whether Trop-2 mRNA expression has a prognostic role in mBC. Clinical trial information: NCT03901339. Research Sponsor: Gilead Sciences, Inc.

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Poster Session

Targeting squalene epoxidase in breast-to-brain metastasis: A new therapeutic target for brain extravasation and colonization using animal models. *First Author: Pony Yu-Ling Lee, Pharmacology Discovery Services Taiwan, Ltd., partner lab of Eurofins, New Taipei City, Taiwan*

Background: Brain metastasis is the most common malignancy of the central nervous system which causes severe morbidity and mortality in multiple cancer types of patients and represents an unmet medical need. Several critical steps are required for a successful brain metastasis, including local invasion, intravasation, dissemination, extravasation, and colonization. Extensive research has been conducted to elucidate the mechanism of cancer metastasis with limited information toward how cancer cells extravasate and colonize. **Methods:** To understand the underlying molecular mechanisms and applications of molecular targets for brain metastasis therapy, murine models are employed for investigation of brain extravasation and colonization. To investigate the roles of SQLE in breast-to-brain metastasis *in vivo*, we silenced *SQLE* expression directly with lentiviral shRNA in the brain metastatic MDA-MB-231-BR cell line (231-BR/shSQLE) and used 231-BR cells expressing a scramble shRNA (231-BR/shScr) as the control. Brain metastases were induced by intracardiac, orthotopic, or direct intracranial injections of 231-BR/shSQLE or 231-BR/shScr cells into immune deficient mice. The essential roles of SQLE in the specific step(s) of breast-to-brain metastatic process were evaluated by *ex vivo* immunofluorescence analysis of brain slices from the animals. To verify SQLE as an oncogenic factor that can be selected as a potential therapeutic target in suppressing breast-to-brain metastasis, we evaluated the inhibitory effects of NB-598 (a SQLE inhibitor) in both the 231-BR orthotopic and intracardiac mouse models. **Results:** Recently, we identified a novel mechanism by which squalene epoxidase (SQLE), the second rate-limiting enzyme in the cholesterol biosynthesis, plays a critical role in the processes of breast cancer metastasized to the brain, especially in brain extravasation and colonization. Interestingly, the pharmacologic inhibition of SQLE has been widely used against fungal infections, and the next-generation SQLE inhibitors have been recently shown to exert an anticancer effect. Our data demonstrated that SQLE is essential for 231-BR cells to extravasate into the parenchyma as well as the formation of micro and macro-metastases in the brain. Interestingly, we found that astrocytes play a key role in supporting 231-BR-developed brain macro-metastasis. *In vitro* blood-brain barrier (BBB) models further demonstrated the critical roles of SQLE in promoting 231-BR cell invasion and penetration through BBB. Inhibition of SQLE by NB-598 demonstrated anti-tumor proliferation and anti-metastasis. **Conclusions:** Pharmacologic inhibition of SQLE by NB-598 suppressed 231-BR tumor growth at the mammary fat pad and distal metastases to organs, suggesting that targeting SQLE represents a therapeutic opportunity for breast cancer metastases. Research Sponsor: Pharmacology Discovery Services Taiwan, Ltd., New Taipei City, Taiwan; Institute of Biomedical Sciences, Academia Sinica, Taiwan and Institute of Translational Medicine and New Drug Development, China Medical University, Taiwan.

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Poster Session

Influence of chromatin remodeling molecule ARID1A on metastatic heterogeneity in triple negative breast cancer: Binding of YAP. *First Author: Ye Wang, Department of Breast Cancer and Urological Medical Oncology, Fudan University Shanghai Cancer Center, Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, China., Shanghai, Shanghai/China, China*

Background: Heterogeneity is the prominent character of TNBC and one predominant cause of treatment failure. As a key nuclear SWI/SNF protein complex subunit, ARID1A plays a critical role in tumor identity determining by manipulating gene expression. The present study aimed to investigate whether and how ARID1A determined the metastatic heterogeneity of triple-negative breast cancer. **Methods:** This study retrospectively collected and analysed clinical and pathological data from 258 patients diagnosed with triple-negative breast cancer at Fudan University Cancer Hospital from August 2015 to June 2016 to define the prognostic ability of ARID1A. CRISPR/Cas9 or plasmids-mediated ARID1A were used to determine the ARID1A function in regulating the metastatic character in TNBC. Cell morphology, tumor invasion, and metastasis were analyzed in terms of ARID1A status both in vitro and in vivo experiments. The molecular mechanism of ARID1A determining metastasis potential of TNBC was explored by RNA-Seq and nuclear positioning. **Results:** ARID1A low expression was found to have independent prognostic value for poor OS (43.9 vs 53.6 months, $P=0.0001$) and RFS (31.0 vs 45.5 months, $P=0.0029$) in TNBC patients. Both nuclear and cytoplasmic protein analysis and Immunofluorescent localization assay confirm that ARID1A recruits the Hippo pathway effector YAP into nucleus in human triple negative breast cancer cells. Next we designed the YAP truncator plasmid and confirmed by Co-Immunoprecipitation that ARID1A could competitively bind to the WW domain of YAP to form the ARID1A/YAP complex. Furthermore, down-regulation of ARID1A promoted migration and invasion both in human triple negative breast cancer cells and xenograft model through Hippo/YAP signaling axis. **Conclusions:** Our study provides new insights into the previously unrecognized role of ARID1A in TNBC metastasis, which might provide new therapeutic options for patients with TNBC. Research Sponsor: National Science and Technology Major Project [grant number: 2020ZX09201-013].

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Poster Session

Olaparib (O) + ceralasertib (C) in patients (pts) with metastatic triple-negative breast cancer (mTNBC): Translational analysis of the VIOLETTE trial. *First Author: Natalia Lukashchuk, AstraZeneca, Cambridge, United Kingdom*

Background: O is a PARP inhibitor approved in a number of tumor types and for use in pts with germline (g) mutations in *BRCA* (*BRCAm*) HER2-negative metastatic breast cancer. C is an inhibitor of DDR kinase ATR. Analysis of VIOLETTE (NCT03330847) in pts with mTNBC showed no improvement in PFS with a combination of C and O vs. O, whether in the context of pathogenic *BRCAm*, non-*BRCA* HRR pathway mutations (*HRRm*), or homologous recombination repair (*HRR*) wildtype (*HRRwt*) tumors. We report an exploratory translational analysis of predictive genomic biomarkers of response to O $\pm$ C beyond *gBRCAm*. **Methods:** Pts received O (300 mg twice daily) $\pm$ C (160 mg daily; days 1–7; 28-day cycles) as a second- or third-line treatment option. Pts were prospectively stratified into molecular strata based on pathogenic/likely pathogenic alterations in *BRCA1/2* (*BRCAm*; $n=83$) or in ≥ 1 of 13 selected non-*BRCA* HRR genes (*HRRm*; $n=40$) or *HRRwt* ($n=103$) using FoundationOneCDx (F1CDx) sequencing assay of archival tumor sample. Advanced genomic analysis included genome-wide loss of heterozygosity (a marker of *HRR* deficiency [HRD]) with a 16% cut-off to define HRD+ ($\geq 16\%$) vs HRD- ($<16\%$), zygosity, and predicted g/somatic (s) status of *BRCA* and *HRR* alterations based on a validated computational FMI algorithm. Efficacy was evaluated by blinded independent central review of PFS, RECIST response, and best percentage change from baseline in target lesion size. **Results:** Out of evaluable pts for origin of *BRCAm* ($n=42$), 81% ($n=34$) were of germline, and 19% ($n=8$) were of somatic origin. Of pts evaluable for zygosity ($n=48$), most *BRCA* alterations were biallelic (90%; $n=43$), and of pts evaluable for HRD status ($n=47$), most were HRD+ (94%; $n=44$). Of *HRRwt* pts evaluable for HRD status ($n=79$), 57% were HRD+ ($n=45$). Responses by biomarker are shown. Responses in *BRCAm* pts were seen in all subgroups (zygosity, HRD, or g/s origin of mutation), including *sBRCAm* (ORR: $n=3/4$ on O; $n=2/4$ on O+C). Responses were also seen in patients with heterozygous *BRCA* alteration ($n=3/5$) by genomic result and in *BRCAm*/HRD- pts ($n=3/3$) across both arms. Pts with select *HRR* genes (*BARD1*, *RAD51C/D*, *ATM*, *CDK12*) also achieved responses on O or O+C. **Conclusions:** Responses to O were seen in pts with both *gBRCAm* and *sBRCAm*. Beyond *BRCAm*, the efficacy of O was observed in pts with alterations in select *HRR* genes, such as *BARD1* or *RAD51C/D*; further clinical investigation is required. Small sample size and HRD analysis performed on archival tumor samples should be considered limitations. Clinical trial information: NCT03330847. Research Sponsor: AstraZeneca.

Overall response rate in selected biomarker subsets; n/N (%).			
Strata	Subgroup	O	O+C
<i>BRCAm</i>	Predicted <i>sBRCAm</i>	3/4 (75)	2/4 (50)
	Predicted <i>gBRCAm</i>	9/16 (56)	8/18 (44)
	Unknown	7/23 (30)	10/18 (56)
<i>HRRm</i>	<i>BARD1m</i>	2/3 (67)	0/1 (0)
	<i>RAD51C/Dm</i>	1/3 (33)	2/2 (100)
	<i>ATMm</i>	0/3 (0)	1/4 (25)
	<i>CDK12</i> (co-occurring <i>PPP2R2A</i>)	0/1 (0)	1/3 (33)
<i>HRRwt</i>	HRD+	2/22 (9)	4/23 (17)
	HRD-	0/17 (0)	1/17 (6)

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Poster Session

The overall survival analysis of FUTURE-C-PLUS: Combination of famitinib with camrelizumab plus nab-paclitaxel as first-line treatment for advanced, immunomodulatory triple-negative breast cancer—An open-label, single-arm, phase 2 trial. *First Author: Li Chen, Cancer Center, Fudan University, Shanghai, China*

Background: Camrelizumab and nab-paclitaxel demonstrated promising anti-tumour activity in refractory metastatic immunomodulatory triple-negative breast cancer (TNBC) in FUTURE trial. Anti-angiogenic agents have been reported to facilitate immune infiltration. Famitinib is a tyrosine kinase inhibitor targeting VEGFR-2, PDGFR and c-kit. The FUTURE-C-PLUS trial (NCT04129996) which added famitinib to camrelizumab and nab-paclitaxel is a single-arm, phase 2 trial evaluating this novel triplet combinatorial strategy in patients with advanced immunomodulatory TNBC. Study design and the primary endpoint ORR has been reported previously (Zhi-ming Shao, et al. ASCO 2021, Abstract 1007). The final PFS data had been published in Clinical Cancer Research (Clin Cancer Res 2022;28:2807–17). Here, we reported the final overall survival of this trial. **Methods:** Briefly, this study enrolled women aged 18–70 years, with previously untreated, histologically confirmed, unresectable, locally advanced, recurrent or metastatic immunomodulatory TNBC. Immunomodulatory TNBC was defined as CD8 expression on at least 10% of cells using immunohistochemistry analysis. Eligible patients received the triple therapy. **Results:** Forty-eight patients were enrolled and treated between Oct 2019 and Oct 2020. The median follow-up was 33.1 months (range, 31.8–34.4). 39 (81.3%, 95% CI 70.2–92.3) patients had a confirmed objective response which has been reported in ASCO 2021. At this updating data cutoff (Feb 1, 2023), the median progression-free survival was 13.6 months (95% CI, 8.4–18.8). While overall survival was 29.4 months (95% CI, 23.3–35.5). The disease control rate was 95.8% (46/48). The most common treatment-related grade 3 or 4 adverse events were neutropenia (16 [33.3%]), anemia (5 [10.4%]), febrile neutropenia (5 [10.4%]), and thrombocytopenia (4 [8.3%]). No new safety concerns were detected. No treatment-related deaths were reported. **Conclusions:** These data, combined with those from our previous reports, provide further evidence for the triplet combination of famitinib, camrelizumab and nab-paclitaxel as an active therapy in advanced immunomodulatory TNBC. To our knowledge, this is the best overall survival reached in first-line treatment of advanced TNBC. A randomized controlled FUTURE-Super trial is ongoing to further validate these findings. Clinical trial information: NCT04129996. Research Sponsor: Jiangsu Hengrui Pharmaceuticals Co. Ltd. China.

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Poster Session

ARID1A deficiency in triple-negative breast cancer induces adaptive immune resistance and sensitivity to immune checkpoint inhibitors. *First Author: Margaret Chen, Department of Breast Cancer and Urological Medical Oncology, Fudan University Shanghai Cancer Center, Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, 200032, PR China, Shanghai, China*

Background: Adaptive immune resistance (AIR) is pivotal to triple-negative breast cancer (TNBC) progression. Although immune checkpoint inhibitors (ICIs) shed new light on reversing AIR, the treatment effect and predictive markers of immunotherapy remain controversial. The present study focused on epigenetic regulation for TNBC AIR and explored whether this could be clinically targeted. **Methods:** Through screening an epigenetic gene set in TNBC patients from The Cancer Genome Atlas (TCGA), ARID1A was pinpointed as most significantly correlated with AIR. Humanized immune system (HIS) mice were adopted for TNBC transplantation, identifying CD8⁺ T cells as most significantly correlated with TNBC ARID1A. To probe the mechanism underlying TNBC ARID1A deficiency-induced CD8⁺ T cell malfunction and AIR, RNA-seq of both TNBC patients and TNBC cell lines were analyzed and the candidate mediator gene, PD-L1, was identified and verified through western blot, qPCR, IHC, dual luciferase reporter assay and cell co-culture. Chromatin immunoprecipitation and ATAC-seq further demonstrated direct binding of ARID1A to *NPM1* promoter to regulate PD-L1 expression. Finally, HIS mice were treated with ICI and the clinical trial CTR20191353 was retrospectively analyzed. **Results:** Among a series of epigenetic modulators, we first observed that ARID1A, a core subunit of the chromatin remodeling complex SWI/SNF, demonstrated highest correlation with AIR in TNBC patients. This was verified in HIS TNBC mice and a patient cohort from Fudan University Shanghai Cancer Center by higher malignancy observed in ARID1A-deficient TNBC. Both bulk and single-cell RNA-seq in TNBC patients uncovered an immunosuppressive microenvironment induced by TNBC ARID1A deficiency, and CD8⁺ T cells was identified as the immune cell type most significantly correlated with TNBC ARID1A. CD8⁺ T cell malfunction and AIR in ARID1A-deficient TNBC was induced by upregulated PD-L1, but ARID1A did not directly regulate PD-L1 expression. We found that ARID1A bound to the *NPM1* promoter and that ARID1A deficiency increased *NPM1* chromatin accessibility as well as gene expression, further activating PD-L1 transcription. In HIS mice, ICI demonstrated the potential to reverse TNBC ARID1A deficiency-induced AIR manifested by reducing tumor malignancy and activating antitumor immunity. In CTR20191353, a phase 1b clinical trial of pucotenlimab combined with chemotherapy for TNBC, patients with ARID1A deficiency demonstrated significantly better prognosis and the longest progression-free survival was found in ARID1A-low/PD-L1-high group. **Conclusions:** In AIR epigenetics, TNBC ARID1A deficiency induced AIR via the ARID1A/*NPM1*/PD-L1 axis, leading to poor outcome. While ARID1A deficiency provided survival advantage for TNBC cells, it simultaneously left the Achilles' heel which could be targeted with ICI. Research Sponsor: This work was supported by the National Science and Technology Major Project [grant number: 2020ZX09201-013].

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Poster Session

The case for acceleration of prospective multi- stakeholder led community-based research in young Black women with triple negative breast cancer (TNBC). *First Author: Jeanne Regnante, Tigerlily Foundation, Stone Ridge, VA*

Background: Black women face a three- fold increase in TNBC BRCA1 gene mutations. In TNBC, there is a higher rate of recurrence and metastasis to other organs. Lower access to timely care and more advance stage at diagnosis contribute to poorer outcomes. Black women have the lowest survival rate at each stage of TNBC diagnosis compared to other demographic groups. Research Question: Over the past 10 years, what real world community interventions have been published regarding risk for and diagnosis with TNBC in Black or African American women?

Methods: Using the following keywords: TNBC, diversity, health equity, young adults, Black, African American, authors conducted PUBMED and Google Scholar searches for years 2011 to 2022 to summarize publications on community-based interventions with Black or African American women at risk of or diagnosed with TNBC. **Results:** A validated publication assessment revealed 70 publications: 63 retrospective and 7 prospective studies. Prospective studies were categorized using the NASEM cancer continuum of care domains. The number of studies that addressed the domains included: risk=1, screening=1, diagnosis=3, treatment=2, survivorship=1 end of life=0, outcomes=1. No studies reported the following criteria: A co-creation approach with community-based participatory research principles; interventions led by patients and Black women who are at risk for TNBC; multi stakeholder interventions led by community leaders or patient organizations with long-standing trust of diverse populations; addressing and resolving social drivers of health inequities, mental health, palliative care services or implicit bias; or inclusion in clinical studies. **Conclusions:** It is critical to address the disproportionate impact of TNBC in partnership with Black women. To achieve equitable health outcomes, we advise public and private sector leaders to make more funding available to support community-engaged approaches in high prevalence geographic areas. 1) Provide CBPR training and opportunities for diverse investigators and patient- and community-based organizations. 2) Build capacity for social needs assessment and interventions. 3) Employ community-based implementation science focused on all care continuum domains including the gaps between domains. 4) Increase public awareness of health issues in Black women and address resistance, access and eligibility for participation in clinical research. 5) Offer RFPs to transform care through collaboration between researchers, providers, patient and community-based organizations, health departments, and payers; engaging clinical and lay navigators and community health workers; design solutions that address barriers; and development and implementation of policy with a focus on standardization, accountability, and enforceability. Research Sponsor: None.

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Poster Session

Phase Ib study of talimogene laherparepvec (T-VEC) in combination with chemotherapy (CT) or endocrine therapy (ET) in patients with metastatic, unresectable, or locoregionally recurrent HER2-negative breast cancer (BC). *First Author: Laura Ann Huppert, University of California, San Francisco, San Francisco, CA*

Background: Talimogene laherparepvec (TVEC) is a modified oncolytic herpes simplex 1 (HSV1) virus that may enhance tumor immune infiltration and is currently FDA-approved for the treatment of unresectable cutaneous, subcutaneous, and nodal melanoma. Anti-tumor responses have been seen both locally and systemically, and an abscopal systemic effect has been described in distant organ metastases. **Methods:** In this single arm, open label Phase Ib study, patients received intra-tumoral TVEC (first dose 10^6 PFU/mL followed by 10^8 PFU/mL q2-3 weeks; volume based on tumor size up to max 4mL) in combination with CT (gemcitabine/ carboplatin [GC], nab-paclitaxel [Nab-P], or paclitaxel [P]) or ET at the discretion of the treating physician. All patients had at least one 1 cm lesion that was injectable at the bedside. The primary endpoint was safety and tolerability. The secondary endpoint was response by RECIST 1.1. Blood and tissue-based immune correlates including injected and neighboring non-injected lesions were evaluated. **Results:** 19 pts were enrolled on this study (2/5/20 – 1/25/23) and evaluable for toxicity with 1 pt non-evaluable for efficacy due to early discontinuation. Median age was 52.1 years. Nine pts (47%) had HR+/HER2- BC and 10 pts (53%) had TNBC. Injected lesions included intact subcutaneous skin nodules (7), non-fungating breast or chest wall lesions (12), and fungating breast or chest wall lesions (9). Pts had a median of 3 prior lines of systemic therapy in the metastatic setting (range 0-9). 13 pts (74%) had visceral metastases. Pts received TVEC with the following treatment partners: GC (n=8, 42%), Nab-P (n=7, 37%), P (n=2, 11%), ET (n=2, 10%). Median treatment duration was 11.6 weeks (range 1.0-45.0 weeks). Grade 3-4 treatment-related adverse events included neutropenia (n=5, 26%), anemia (n=1, 5%), thrombocytopenia (n=1, 5%), and injection site skin ulceration (n=1, 5%). Three pts (16%) had Grade 1-2 injection site skin ulceration. Response per RECIST 1.1 was evaluated in 16 pts (2 pts had rapid progression prior to first response evaluation): PR (n=2, 13%), SD (n=5, 31%), and PD (n=9, 56%). Disease response at the site of TVEC injection was clinically evaluated in 18 pts, with response rates (RR) as follows: partial response (PR) (n=11, 61%), stable disease (SD) (n=4, 22%), and progressive disease (PD) (n=3, 17%). Mass cytometry (CyTOF) analysis demonstrated a decrease in HLA-DR expression circulating lymphocytes and in TIM3 expression across multiple cell types in responders vs. non-responders; updated correlative analyses will be presented. **Conclusions:** The addition of intra-tumoral TVEC to CT or ET is safe and tolerable in pts with advanced BC. This treatment induces changes in circulating immune responses. Clinical trial information: NCT03554044. Research Sponsor: Amgen.

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Poster Session

Sociodemographic and clinicopathologic factors of triple negative breast cancer at an academic urban safety-net hospital. *First Author: Judy Jiaqi Wang, Boston Medical Center, Boston, MA*

Background: Racial disparities in breast cancer in the United States is a persistent and ongoing problem. Decades of research is derived from large population based data sets and little is published with granular detail of specific, actionable factors to target for interventions. From a large urban safety-net hospital, we evaluate sociodemographic and clinicopathologic factors on survival outcomes of triple negative breast cancer. **Methods:** We conducted a single-institution retrospective study of patients with invasive breast cancer, diagnosed and treated between January 2010 and December 2021 at an academic safety-net hospital where insurance systems allow for access and treatment for all patients. Demographic, tumor and treatment characteristics were obtained. Chi-square and ANOVA were used to examine associated factors among White, Black, and other races. Survival was analyzed using the Kaplan-Meier estimator and log-rank test. Significant risk factors were identified with Cox regression analysis. **Results:** 251 women with invasive triple negative breast cancer were diagnosed and treated during the study period. Median age was 58 years, 68.9% were non-white, and 64.9% were publicly insured or uninsured patients. Median time from diagnosis to treatment initiation was 29 days and follow up period was 1392 days. Having a non-English primary language and living in areas with lower socioeconomic indices are observed in non-White patients (P=0.003, 0.033) and predictive of a higher clinical stage at presentation (P=0.011, 0.021). Black patients were diagnosed at higher histologic grade (Black: 82.4%, White: 79.7%; P=0.003) and White patients were more likely to change facility during the treatment course (White: 32.4%, Black: 16.03%; P=0.005). No significant racial disparities were observed in time to treatment, recurrence rate, and overall survival. Among patients indicated for adjuvant therapies, including chemotherapy, immunotherapy, and radiation, rates of recommendation and completion of therapy did not vary by race. Five year survival did not significantly vary by race when adjusted for demographic and clinicopathologic factors. **Conclusions:** At an academic urban safety-net hospital where access to diagnostic and treatment resources are comparable across patient populations, no racial disparities were seen in treatment, recurrence, and survival outcomes. Further research on racial differences in breast cancer biology and health behaviors may improve understanding of triple negative disease or mitigate later stage diagnosis. Research Sponsor: None.

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Poster Session

Early efficacy evaluation of ORIN1001, a first in class IRE1 alpha inhibitor, in advanced solid tumors. *First Author: Mothaffar F. Rimawi, Lester and Sue Smith Breast Center, Dan L. Duncan Comprehensive Cancer Center, Baylor College of Medicine, Houston, TX*

Background: ORIN1001 is a first-in-class small molecule targeting a novel enzyme with a unique mode of inhibition that selectively blocks the Inositol Requiring Enzyme 1 α (IRE1) RNase and blocks X-Box Binding Protein 1 (XBP1) activation in the endoplasmic reticulum. ORIN1001 is now undergoing Phase 1/2 clinical testing in advanced solid tumors. **Methods:** In a Phase 1 dose escalation trial (3+3 design), ORIN1001 was administered PO daily as a single agent in patients (pts) with advanced solid tumors and in combination with Abiraterone in pts with relapsed, refractory breast cancer. Safety, tolerability, pharmacokinetics, and preliminary efficacy of ORIN1001 was evaluated and a RP2D determined. **Results:** As of Jan, 2023, 30 patients with advanced cancer have received ORIN1001 as a single agent at doses up to 650 mg per day in 21-day continuous cycles and 13 patients with breast cancer have received ORIN1001 at doses up to 400 mg in combination with Abiraterone in 28-day continuous cycles. For single agent, DLTs consisting of thrombocytopenia were observed at 200 mg (2 pts) and 650 mg (2 pts) and, rash was observed at 200 mg (1 pt) and 500 mg (1 pt). For combination treatment, DLTs consisting of thrombocytopenia were observed at 300 mg (1 pt), fatigue/ rash at 400 mg (1 pt), febrile neutropenia/low WBC at 400/500 mg (1 pt at each dose). Common (> 15%) adverse events were predominantly nausea and/or vomiting (Grade 1-2 in severity). ORIN1001 exposure increased in a dose proportional manner with a mean $T_{1/2}$ at steady state of approximately 20 hours. For single agent, best response per RECIST 1.1 was partial response (PR) in 2 of 30 pts. These PRs included a stage IV colon cancer pt exceeding 44 months on treatment at 100 mg, and stage IV ER-/PR-/HER2+ breast cancer pt with 5 months on treatment at 500 mg. Stable disease (SD) was observed in a total of 16 of 30 pts with breast, colorectal, mesothelioma, liver, prostate, kidney or ovarian cancer. For combination therapy with Abiraterone, a PR was observed in one ER-/PR-/HER2- breast cancer pt at 300 mg ORIN1001 and SD was observed in 5 of 13 pts. SD included both triple negative and ER+/HER2- breast cancer pts at 300 or 400 mg with ongoing treatment exceeding 5 months. Of note, in a separate Phase 1 oncology basket trial in China, there were 2 PRs; 1 pt with stage IV NSCLC at 300 mg and 1 pt with metastatic castrate resistant prostate cancer at 100 mg exceeding 9 and 5 months of treatment with ORIN1001 in combination with Abiraterone, respectively. **Conclusions:** Phase 1 clinical evaluation of ORIN1001 has demonstrated tolerability and dose proportional PK. The proposed RP2D is estimated to be 500 mg and 300 mg ORIN1001 for single agent and in combination with Abiraterone, respectively. Early efficacy data with ORIN1001 demonstrate clinical responses (SD and PR) in multiple pts with heavily-pretreated advanced solid tumors as a single agent or in combination with Abiraterone in breast cancer patients. Clinical trial information: NCT03950570. Research Sponsor: Fosun Orinove.

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Poster Session

Olaparib (O) in advanced triple negative breast cancer (aTNBC) patients (pts) with BRCA1/2 promoter methylation: GEICAM/2015-06 study (COMETA-Breast). *First Author: Juan De La Haba, Instituto Maimónides de Investigación Biomédica de Córdoba (IMIBIC)–H. Universitario Reina Sofía, Universidad de Córdoba. GEICAM Spanish Breast Cancer Group, Cordoba, Spain*

Background: Epigenetic silencing by aberrant *BRCA1/2* promoters' methylation (*BRCA*-meth) can be responsible for a dysfunctional *BRCA* protein. *BRCA*-meth occurs in 15-57% of TNBC pts. *BRCA*-meth breast cancer (BC) display pathologic features and genetic profiles like germline *BRCA1/2*-mutated (*gBRCA1/2m*) carriers. O is a PARP inhibitor approved for treating *gBRCAm* HER2-negative advanced BC (aBC) pts. These are the results of a phase II study assessing the O efficacy in aTNBC pts with *BRCA1/2*-meth (NCT03205761). **Methods:** We included aTNBC pretreated pts (≥ 1 line) with centrally confirmed somatic *BRCA1/2*-meth (in most recent lesion(s) available) and no *gBRCA1/2m*. O 300mg b.i.d. was administered. *BRCA1/2* CpG island was considered methylated if value was $\geq 25\%$. Overall response rate (ORR) (complete response [CR] + partial response [PR]) according to RECIST 1.1) was the primary objective. Thirty-one evaluable pts were required based on an optimal 2-stage Simon's design (α error=0.05, 1- β error=80%), estimating an ORR increase of 24%, with a null hypothesis of 30%. Whole exome/transcriptome and 105-genes NGS assays (Tempus xE & xF) were performed on pretreatment tumor and sequential ctDNA of a long-term responder. **Results:** Eleven pts received ≥ 1 cycle of O (ITT population). Median age was 51 years (37-64), and 8 pts were postmenopausal. All MO pts at diagnosis had neo/adjuvant chemotherapy (CT). Median O exposure duration was 8 (1-88) weeks and relative dose-intensity was 97% (76-100), with any dose modifications in 6 pts. ORR was 9% (1 PR/11; 95% CI, 0.2-41). Clinical benefit rate (CR + PR + stable disease of any duration) was 36% (4/11; 95% CI, 11-69). Most pts (n=9) discontinued O due to BC progression. Median PFS was 2 months (95% CI, 1-4), and median OS was 9 months (95% CI, 1-14). One pt with confirmed PR was on O for >20 months. AEs were reported in 3 pts in line with O safety profile. No AE led to O discontinuation and no SAEs were reported. The statistical assumptions for the 1st Simon's model stage were not met ($\geq 4/12$ pts with CR or PR), so the recruitment did not proceed onto the 2nd stage. Preliminary NGS analysis on the long-term responder identified alterations on tumor (TP53, BCL11A, MYC) and on-treatment ctDNA (PMS2). **Conclusions:** In this proof-of-concept study, O did not show clinically nor statistically significant antitumor activity in pretreated aTNBC pts with *BRCA1/2*-meth. Clinical trial information: NCT03205761. Research Sponsor: None.

Methylation, n	
BRCA1	7
BRCA2	2
BRCA1/2	2
Proportion of BRCA1/2 promoter methylation, median (range); %	
BRCA1	37 (15 – 53)
BRCA2	6 (2 – 53)
Time since BC diagnosis to study inclusion, median (range), months	
M0 (n=7)	63 (11; 231)
M1 (n=4)	33 (3; 75)
No. of metastatic sites, n	
1	2
2	3
3	4
4	2
Visceral involvement, n	
Prior therapies for aBC, n *	7
CT	3
CT + BT (biological therapy)	3
CT + BT + endocrine therapy	1

*7 pts had ≥ 3 CT lines.

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Poster Session

Phase II study of pembrolizumab plus mifepristone in patients with advanced HER2-negative breast cancer. *First Author: Nan Chen, University of Chicago, Chicago, IL*

Background: Metastatic breast cancer is incurable, and novel treatment (tx) strategies are needed. Single agent immune checkpoint inhibitor (ICI) tx has limited efficacy; combination approaches may yield better results. Multiple mechanisms of glucocorticoid-induced immunosuppression have been proposed, including the suppression of the cytotoxic Th1 cytokine response via glucocorticoid receptor (GR) activation. We hypothesize that pretreatment with a GR antagonist shifts the cytotoxic immune response toward Th1, thus enhancing response to ICIs. We present the safety and efficacy of the combination of pembrolizumab and mifepristone in advanced HER2-negative breast cancer. **Methods:** This (NCT03225547) was a phase II non-randomized study of pembrolizumab and mifepristone in patients (pts) with advanced HER2-negative breast cancer. Pts with prior ICI tx were excluded. Pts received mifepristone 300mg daily and pembrolizumab 200mg every 3 weeks; mifepristone was started 7 days prior to pembrolizumab. The primary endpoint was objective response rate (ORR). Secondary endpoints included progression-free survival (PFS), overall survival (OS), disease control rate (DCR), and safety and tolerability. **Results:** 18 patients were enrolled from March 2018 – November 2020; 10 patients with TNBC (cohort 1) and 8 patients with HR+ BC (cohort 2). Mean age was 53 yrs (range 33-74) and 33% of patients were self-reported Black. In cohort 1, 50% of patients were tx naive in this advanced setting, and 90% of patients had < 2 prior lines of tx. In cohort 2, 25% of patients had not received prior chemo in the metastatic setting. The overall ORR was 6%. One pt with TNBC had a complete response (CR). She received 36 cycles of tx; tx was discontinued due to mucositis and rash, and she remains in CR at >48 mos from start of tx. No patients in cohort 2 had a partial or complete response. The most common treatment-related adverse events were rash (61%), thyroid abnormality (17%), and pruritis (17%). 45% of patients experienced a grade 3 or 4 adverse event; all except one (hypokalemia) were due to rash. Rash was described as maculopapular dermatitis. The DCR at 18 weeks was 33.3% in the overall population; it was 44.4% in cohort 1 and 16.7% in cohort 2. Overall median PFS was 1.9 months [95% CI 1.8 – 3.6]. Overall median OS was 12.9 months [95% CI 5.8 – 23.0]. **Conclusions:** While this regimen demonstrated efficacy in a small subset of patients, including one pt with long-term CR, given the non-randomized design, we cannot determine if mifepristone enhanced the efficacy of ICI. In addition, a higher than anticipated rate of skin toxicity, possibly related to mifepristone enhancing the activity of ICI, was observed in the study, leading to early closure. While the benefit/risk analysis of this combination does not support further evaluation, additional investigation of alternative chemotherapy-free, immunomodulatory strategies is warranted. Clinical trial information: NCT03225547. Research Sponsor: Corcept Pharmaceuticals, Merck; U.S. National Institutes of Health.

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Poster Session

The impact of social determinants of health (SDOH) on use of germline genetic testing for triple-negative breast cancer (TNBC) in the community oncology setting. *First Author: Robert Lawrence Reid, US Oncology Network/Virginia Cancer Specialists, Herndon, VA*

Background: TNBC presents at an earlier age of onset and at a more advanced stage, and is associated with a worse outcome in African American women. In a subset of patients, TNBC is associated with germline *BRCA1* and/or *BRCA2* mutations. Genetic testing improves breast cancer and other surveillance as well as treatment outcomes. Current NCCN Guidelines recommend germline testing for all patients with any stage TNBC. Previous versions recommended testing in patients aged 60 years or younger. This study aimed to identify factors associated with receiving genetic testing among patients with TNBC in the community oncology setting. **Methods:** This was a retrospective observational cross-sectional study examining patient profiles, demographics, SDOH indicators, and germline genetic testing data. Patients in The US Oncology Network diagnosed with any stage TNBC between 3/31/2017 and 9/30/2021 aged 60 years or younger were identified. Data from the iKnowMed EHR was used for patient identification, baseline characteristics, and social determinants, including area deprivation index (ADI), a validated measure of socioeconomic status (SES) based on address. Mean ADI percentile scores using national and state level benchmarks were calculated as well as stratifications above and below the 80th percentile (where higher scores > 80 are markers of low SES). Evidence of germline genetic testing (yes/no) was compiled from iKM, network genetic databases, and confirmatory chart audits. Only US Oncology Network sites participating in confirmatory audits were included in this analysis. **Results:** Among participating sites, 1318 patients with TNBC were identified with a mean age of 49 years; 58% were White, 22% Black, 3% Asian, and 16% other/unknown; and evidence for germline genetic testing was found for 981 (74.4%). Statistically significant differences in germline testing rates were found for age (48.4 years for tested, 50.7 years for not tested); race (67% for Black patients, 77% for White); US census region (68% in South, 70% in Midwest, 83% in Northeast, and 87% in West); practice size (mean number of physicians: 32.8 per practice for testing group, 29.2 for untested); and for nationally benchmarked ADI score (mean ADI of 42.3: tested and 47.1 for not tested). No significant difference was seen across the spectrum of ethnicity, with 82% testing among Hispanic or Latino patients compared with 74% for non-Hispanic or Latino, $p = 0.074$. No significant differences were observed for clinical variables. **Conclusions:** We report that 75% of patients with TNBC in our community oncology network received genetic testing. However, significantly lower testing rates were observed for patients who were Black, had lower SES, and resided in the South and Midwest geographic regions. Further research should be performed to understand reasons why testing was not done, to address barriers. Research Sponsor: None.

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Poster Session

Efficacy of oral selective estrogen receptor degraders (SERDs) in the treatment of estrogen receptor positive (ER+), HER2-negative metastatic breast cancer (MBC): A stratified analysis of the ESR1 wild type (wt) and mutant (mt) subgroups. *First Author: Joseph J Zhao, Yong Loo Lin School of Medicine, National University of Singapore (NUS), Singapore, Singapore*

Background: Oral SERDs are a novel drug class developed to counteract endocrine resistance due to ESR1 mutations. Several SERDs have emerged from phase 2 and 3 trials, and the FDA has most recently limited approval for Elacestrant to patients with ESR1mt tumours despite PFS benefit in the overall population. Questions remain on whether patients with ESR1wt tumours stand to benefit from SERDs. We conducted an IPD meta-analysis of the trials EMERALD, SERENA2, ACELERA and AMEERA3 to compare survival outcomes of SERDs in the 2nd or 3rd line setting against endocrine therapy (ET), using KMSubtraction to unveil HRs of unreported ESR1wt subgroups from AMEERA3 and EMERALD. Meta-analysis results were stratified by ESR1 status. **Methods:** RCTs investigating the efficacy of novel SERDs versus ET for ER+, HER2- MBC, and which reported the Kaplan Meier (KM) plots of progression free survival (PFS) were selected after a systematic search of Embase and PubMed from inception until January 21, 2023. A graphical reconstructive algorithm was applied to estimate time-to-event outcomes from reported KM plots in all overall and reported subgroup cohorts, deriving IPD. A bipartite matching algorithm, KMSubtraction was used to subtract patients in the reported subgroup from the overall cohort, to derive survival data for unreported ESR1wt subgroups. An IPD meta-analysis was then performed, pooling data by ESR1 mutation. **Results:** A total of 1216 patients were included in this analysis. In the pooled analysis of the overall cohort, PFS benefit was observed with SERDs compared to treatment of physician's choice (TPC) (HR 0.787, 95%CI 0.683-0.908, $p < 0.001$). In the ESR1mt subgroup SERDs demonstrated improved PFS (HR 0.557, 95%CI 0.440-0.705, $p < 0.001$) compared with TPC. In the ESR1wt subgroup, SERDs demonstrated no significant PFS benefit (HR 0.948, 95%CI 0.790-1.137, $p = 0.565$) when compared to TPC. KMSubtraction was implemented on AMEERA3 to reveal survival data in ESR1wt subgroup. Amcenestrant revealed no significant PFS difference in the ESR1wt population (HR 1.197, 95% CI 0.857-1.670, $p = 0.291$) when compared to ET. Additionally, a separate analysis of EMERALD was performed using KMSubtraction to derive survival data of the ESR1wt subgroup comparing Elacestrant vs Fulvestrant. No significant PFS difference was observed between the 2 agents in the ESR1wt population (HR 0.832, 95% CI 0.587-1.178, $p = 0.299$). **Conclusions:** Our results suggest that PFS benefit in the overall population is mainly driven by the ESR1mt subgroup. These findings are in line with the recent FDA approval of Elacestrant for patients with ESR1mt tumours. Research Sponsor: None.

Subgroup	HR (CI)	P value
Overall	0.787 (0.683-0.908)	< 0.001
ESR1mt	0.557 (0.440-0.705)	< 0.001
ESR1wt	0.948 (0.790-1.137)	0.565

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Poster Session

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Poster Session

High dose alkylating chemotherapy for patients with oligometastatic breast cancer harboring homologous recombination deficiency: Results from the randomized phase 3 OLIGO study. *First Author: Annemiek Van Ommen-Nijhof, The Netherlands Cancer Institute, Amsterdam, Netherlands*

Background: Oligometastatic breast cancer (OMBC) is a clinical entity with favorable prognosis compared to MBC in general, but the optimal treatment for individual patients remains unclear. We compared high dose chemotherapy (HDCT) to conventional dose chemotherapy (CDCT) in patients receiving local ablative therapy (LAT) of all disease sites in HER2-negative OMBC that harbors homologous recombination deficiency (HRD). **Methods:** In this open-label phase 3 study, we randomly assigned patients with OMBC after 3 cycles of induction CDCT to either continue with CDCT (up to a maximum total of 8 cycles) or switch to HDCT. OMBC was defined as 1-3 distant metastatic lesions, with or without locoregional disease, all amenable to LAT. Main eligibility criteria included pathologic proof of a distant metastatic lesion, HRD (based on either germline *BRCA1/2* mutation and/or a BRCA-like profile in the tumor), and a favorable response to induction CDCT. The primary endpoint was event-free survival (EFS), defined as time since randomization to recurrence or death. Overall survival (OS), safety and quality of life (QoL) were key secondary endpoints. Following the advice of the independent data monitoring committee, analyses were performed before the prespecified number of events was reached. **Results:** Between November 2012 and May 2022, 36 patients were allocated to HDCT and 39 to CDCT. 52 (69%) tumors were triple negative and 23 (31%) were hormone receptor positive; 39 patients (52%) had a solitary metastasis and 43 (57%) had synchronous OMBC. After a median follow-up of 52 months (interquartile range 28-97), 42 EFS-events had occurred. Median EFS in the HDCT-group was 28 months (95% CI 21 – not reached (NR)) compared to 25 months (95% CI 14 – NR) in the CDCT-group (hazard ratio (HR) 0.78 (95% CI 0.42 – 1.42, $p = 0.411$). Median OS was 67 months (95% CI 37 – NR) in the HDCT-group versus 36 months (95% CI 26 – NR) in the CDCT-group (HR 0.74, 95% CI 0.37 – 1.48, $p = 0.398$). 5-year EFS was 40% and 30%, and 5-year OS was 51% and 49% in the HDCT- and CDCT-group, respectively. 34 (94%) patients in the HDCT-group experienced grade 3 or higher adverse events, compared to 25 (64%) patients in the CDCT-group; no grade 5 adverse events occurred. QoL was comparable between groups at 12 months. **Conclusions:** HDCT does not improve outcome compared to CDCT in patients with OMBC harboring HRD and can therefore not be recommended. Survival in this highly selected group of patients with OMBC, all receiving LAT, compares favorably to survival in the overall MBC population. The optimal systemic therapy for patients with OMBC requires further study. Clinical trial information: NCT01646034. Research Sponsor: Dutch Cancer Society.

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Poster Session

Phase II study of trifluridine/tipiracil (FTD/TPI) in HER2-negative metastatic breast cancers with or without prior exposure to fluoropyrimidines. *First Author: Joline Si Jing Lim, Department of Haematology-Oncology, National University Cancer Institute, Singapore, Singapore*

Background: Fluoropyrimidines are commonly used in the treatment of patients (pts) with metastatic breast cancers (MBC). FTD/TPI is an oral drug combination of trifluridine with tipiracil, a thymidine phosphorylase inhibitor preventing rapid degradation of trifluridine, thus allowing for increased exposure to active agent, and has showed activity in pts with colorectal and gastric cancers despite prior exposure to fluoropyrimidines. We investigate the role of FTD/TPI in MBC pts with (Cohort A) or without (Cohort B) prior exposure to fluoropyrimidines in a single arm phase II study. **Methods:** Pts were treated with FTD/TPI, and enrolled first into a lead-in dose confirmation phase, followed by two parallel cohorts based on prior exposure to fluoropyrimidines. Primary objectives for each cohort included determination of progression-free survivals (PFS), and secondary objectives included determination of objective response rates (ORR), safety and tolerability. **Results:** A total of 74 pts were recruited (42 for Cohort A, 32 for Cohort B), of whom 4 belonged to lead-in phase. Dosing was confirmed at FTD/TPI 35mg/m² days 1-5 and 8-12 of 4-weekly cycles based on lead-in phase with no dose-limiting toxicities observed, and recruitment then proceeded in 2 parallel cohorts. All pts were evaluable for toxicity and survival analyses, and 72 were evaluable for ORR. Median age at enrollment was 62 years (range 32-85), with median of 4 (range 0-14) prior lines therapy in the metastatic setting, and 47% had de novo metastatic disease. Median PFS was 5.7 months (95% CI 3.8 to 8.3) and 9.4 months (95% CI 5.5 to 14.0) respectively in Cohorts A and B. Similar response rates were observed regardless of prior exposure to fluoropyrimidine, with ORR of 19.5% (95% CI 8.8 to 34.9) and 16.1% (95% CI 5.5 to 33.7) in Cohorts A and B, with 6-month clinical benefit rates of 56.1% (95% CI 39.7 to 71.5) and 61.3% (95% CI 42.2 to 78.2) respectively. Safety profile was consistent with known toxicities of FTD/TPI, with most common treatment-related adverse events of neutropenia, fatigue, nausea and anorexia. 64% of pts required dose modifications during study treatment, most commonly due to neutropenia, that could be overcome by dose reduction or prolongation from 4- to 5-weekly cycles. Only 1 pt required discontinuation due to toxicity from therapy. **Conclusions:** FTD/TPI showed promising anti-tumor activity with meaningful clinical benefit even among pts with prior exposure to fluoropyrimidines, and has a reasonable toxicity profile with appropriate dose modification. An oral chemotherapy option with good disease control provides an attractive treatment alternative to pts with MBC where quality of life is paramount, warranting further investigation in randomised studies. Clinical trial information: NCT04280536. Research Sponsor: National Medical Research Council, Singapore; Taiho pharmaceuticals.

Prognostic value of tumor-derived extracellular vesicles and circulating tumor cells in metastatic breast cancer (BC): A focus on inflammatory BC. *First Author: Eleonora Nicolò, Weill Cornell Medicine, New York, NY*

Background: Circulating tumor cells (CTCs) are an independent prognostic factor in metastatic breast cancer (MBC). The prognostic value of CTCs and the optimal cutoff for patients (pts) with inflammatory breast cancer (IBC), one of the most aggressive types of BC, has not been fully established. Recent evidence showed the complementary prognostic value of tumor-derived extracellular vesicles (tdEVs) to CTCs in MBC. The significance of tdEVs in IBC is unexplored. This study aimed to assess the prognostic value of CTCs and tdEVs in metastatic IBC. **Methods:** This study retrospectively analyzed 308 pts with MBC enrolled at Northwestern University (Chicago, IL) before starting a new line of therapy between 2016 and 2021 (NU16B06 trial). Blood samples were processed for CTCs using the CellSearch system. We applied the open source ACCEPT software to archived CellSearch images to enumerate CTCs and tdEVs. TdEVs cutoff levels were <20 (low), 20-79 (intermediate), and ≥80 (high), as previously reported. The association of CTCs and tdEVs with overall survival (OS) was tested in the overall population (OvP) and IBC pts. **Results:** Of the 308 pts, 69 were diagnosed with IBC. 51% of pts received first-line therapy. CTCs enumerated by ACCEPT were strongly correlated with manual count ($r=0.86$) and hence used for this analysis. Median CTC count was 1 [interquartile range (IQR) 0-7] in IBC pts and 3 (IQR 0-14) in non-IBC ($p=0.11$). A significantly lower median tdEVs count was observed in IBC (7; IQR 3-45) than in non-IBC (22; IQR 4-137) pts ($p=0.03$). In IBC, higher CTC and tdEV counts were seen in the triple negative subtype ($p=0.03$) and non-visceral involvement ($p=0.02$), respectively. In the OvP median OS (mOS) was worse among pts with ≥5 CTCs (HR 2.6; $p=0.001$) and with elevated tdEVs (HR 3.3; $p<0.001$). Only tdEVs were independently associated with poorer OS in multivariable analysis. In pts with <5 CTCs there was a stepwise decrement in OS with increased tdEVs count ($p<0.3$); in pts with ≥5 CTCs, elevated tdEVs levels were associated with significantly worse OS ($p=0.03$). IBC pts with ≥5 CTCs had shorter mOS (8 vs 47 months; HR 3.6; $p<0.001$); this association was weaker using ≥1 as CTC cutoff (HR 2.4; $p=0.01$). OS was adversely associated with increasing tdEVs levels (33 vs 23 vs 7 months for low, intermediate, and high subgroups, respectively; HR 3.7; $p=0.001$). Furthermore, elevated tdEVs were associated with shorter mOS in pts with ≥1 ($p=0.055$) and ≥5 CTCs ($p=0.6$). Among pts with <5 CTCs no significant difference emerged among tdEVs subgroups ($p=0.6$). **Conclusions:** This study confirmed the strong prognostic significance of CTCs and tdEVs in MBC, including IBC. Pts with IBC had fewer CTCs and tdEVs compared to non-IBC, probably due to the predominant lymphatic spread of IBC. tdEVs offer the possibility to better define prognosis of IBC pts. Further studies are needed to evaluate their complementarity to CTCs. Research Sponsor: None.

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Poster Session

Preliminary results from a first-in-human study of ESG401, a trophoblast cell-surface antigen 2 (TROP2) antibody drug conjugate (ADC), in patients with locally advanced/metastatic solid tumors. *First Author: Fei Ma, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences, Beijing, China*

Background: ESG401 is an innovative ADC composed of a humanized anti-TROP2 IgG1 monoclonal antibody conjugated to topoisomerase I inhibitor SN-38 via a proprietary stable-cleavable linker with DAR of 8. **Methods:** Patients (pts) aged ≥18 years with locally advanced/metastatic solid tumors refractory to/relapsed from standard treatment with measurable disease (RECIST v1.1) were eligible. ESG401 is administered intravenously by designated dose and regimen until unacceptable toxicity or progressive disease. The Bayesian Optimal Interval (BOIN) design was used to establish the MTD. **Results:** As of Feb 3, 2023, 35 pts with a median age of 53 were treated with ≥1 dose of ESG401 during escalation at doses of 2-20 mg/kg once Q3W (Regimen A), or 12-16 mg/kg D1,8,15 in a 4-week cycle (Regimen B). 80% of pts were ECOG ≤1, 63% of pts were 3L+; median 4 (2-10) prior lines, 94% of pts had visceral metas (11% brain, 63% liver, 60% lung) at baseline. Only one patient treated with 20 mg/kg experienced DLT. The MTD has not reached either regimen. The most common TRAEs were leukopenia (80%), neutropenia (69%), anemia (66%), fatigue (54%), nausea (51%), and vomiting (46%). The most common ≥ Grade 3 TRAEs were leukopenia (29%) and neutropenia (31%). There was no ≥ Grade 3 thrombocytopenia, diarrhea, skin rash, or oral mucositis. No Interstitial Lung Disease (ILD) was observed. Of 33 efficacy evaluable (EE) pts, 12 partial responses (PR) were observed and 4 pts had achieved SD ≥24 wks. The first dose level found PR (16 mg/kg Q3W) and afterward were taken as therapeutically relevant doses (TRD). The ORR and DCR were 36% (4/11) and 64% (7/11) in 11 TRD pts with TNBC, while 62% (8/13) and 77% (10/13) in 13 TRD pts with HR+/HER2-BC. Two pts with brain metas both got an obvious intracranial response (one pt whose intracranial lesion was significantly reduced to too small to measure). Until the cut-off date, 11 (31%) pts remained on treatment. Three pts were treated over 12 mons and the longest on-treatment duration was 12.9 mons. One pt had consistent PR up to 10.8 mons. **Conclusions:** The preliminary data demonstrated that ESG401 is safe and well-tolerated with promising signals of efficacy in heavily pretreated pts. These encouraging findings warrant further clinical evaluation. Clinical trial information: NCT04892342. Research Sponsor: Shanghai Escugen Biotechnology Co., Ltd.

Summary of tumor response per investigator.								
	Regimen A				Regimen B			
	8mg/kg (N=3)	12mg/kg (N=3)	16mg/kg (N=5 ^a)	20mg/kg (N=5)	12mg/kg (N=5)	14mg/kg (N=6)	16mg/kg (N=6)	Total (N=33)
PR ^b , n (%)	0	0	2 (40.0)	2 (40.0)	3 (60.0)	1 (16.7)	4 (66.7)	12 (36.4)
SD, n (%)	1 (33.3)	0	1 (20.0)	1 (20.0)	1 (20.0)	4 (66.7)	1 (16.7)	9 (27.3)
PD, n (%)	2 (66.7)	3 (100)	2 (40.0)	2 (40.0)	1 (20.0)	1 (16.7)	1 (16.7)	12 (36.4)

^a Includes pts who were assigned to 2mg/kg (N=1) and 4mg/kg Q3W (N=1) while eventually intra-pt escalated to 16mg/kg Q3W.
^b Per RECIST 1.1, but including single-point PRs, not confirmed responses.

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Poster Session

Actionability of comprehensive genomic profiling compared to the tissue-based and plasma-based assay in patients with metastatic breast cancer: A real-world study. *First Author: Hiroshi Tada, Department of Breast and Endocrine Surgical Oncology, Graduate School of Medicine, Tohoku University, Sendai, Miyagi, Japan*

Background: Comprehensive genomic profiling (CGP) was officially approved in August 2021 in Japan under the national health insurance system with three CGP tests in June 2019: FoundationOne CDx (F1CDx), OncoGuide NCC Oncopanel (NCC), which are tissue-based assay (TBA), and FoundationOne Liquid CDx (F1LCDx, starting in August 2021) which is plasma-based panel (PBA). The Center for Cancer Genomics and Advanced Therapeutics (C-CAT) has collected genomic and clinical data of 2,617 Japanese breast cancer patients as of October 2022. Here we assess these PBA and TBA to detect pathogenic or driver alterations informative for matched therapy in patients with metastatic breast cancer (mBC). **Methods:** We queried consecutive mBC patient clinical-genomic data through the C-CAT Research-Use Portal from June 2019 to October 2022 were categorized based on PBA or TBA. We used ClinVar to identify if the called somatic alterations were pathogenic or likely pathogenic, and BoostDM (<https://www.intogen.org/boostdm/search>) to identify potential driver mutations of breast cancer. The proposed rate of matched therapy was determined. The incidence rates were compared using the Pearson χ^2 test. **Results:** Of 2,617 pts who underwent the CGP test, 2,259 (86%) received TBA (74% F1CDx and 12% NCC). The proportion of pts with ≥ 1 pathogenic variant with PBA and TBA was not significant (71.5% vs. 72.7%; $p=0.88$), but the proportion of pts with ≥ 1 driver mutation was significantly higher with PBA than TBA (75.4% vs. 69.8%; $p=0.03$). Regarding the proportion of pts who matched therapy or clinical trials presented among the pts for whom data were available, PBA was significantly lower than TBA (27.7% vs. 38.5%, $p < 0.001$). Although data on post-treatment is still being collected, the proportion of tested patients that received matched therapies recommended by molecular tumor boards of each institute was significantly lower for PBA (4.2% vs. 8.3%; $p=0.007$). **Conclusions:** This study is the first analysis of CGP for mBC in Japan using the C-CAT utilization program. Although significant alterations were well-detected in PBA, the proportion of pts who received matched-therapy post-testing was low for PBA. Possible causes include that PBA has fewer companion diagnoses than TBA in Japan and that PBA is more often used in later lines. Research Sponsor: None.

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Poster Session

Association between baseline radiological tumor burden and outcomes in patients with metastatic breast cancer treated with an immune checkpoint inhibitor. *First Author: Lauren Claire Brown, Peter MacCallum Cancer Centre, Melbourne, Australia*

Background: Lower baseline radiological tumor burden is associated with more favorable outcomes for patients with metastatic non-small cell lung cancer and melanoma treated with immunotherapy. However, minimal data is available for metastatic breast cancer patients. This is despite immunotherapy, in combination with chemotherapy, now being standard-of-care for a subset of metastatic breast cancer patients who have triple-negative disease and are PD-L1 positive. **Methods:** We reviewed data of 82 patients with metastatic breast cancer consecutively treated at our institution from August 2015 to October 2021, who received > 1 dose of an immune checkpoint inhibitor (anti-PD-1 or -PD-L1) within the context of a clinical trial. Baseline tumour burden was assessed by a single radiologist and calculated as sum of Response Evaluation Criteria in Solid Tumours 1.1 baseline target lesions (baseline tumour size [BTS]) or as sum of all measurable baseline lesions (total tumour burden [TTB]); the impact of both parameters on treatment outcomes was investigated. Treatment outcomes assessed were clinical benefit rate (complete response, partial response or stable disease for 6 months or more [CBR6]), disease free survival (DFS) and overall survival (OS). Multivariate analysis adjusted for ECOG status, line of treatment (first line vs second line or beyond), and whether immunotherapy was given in combination with chemotherapy or as monotherapy. **Results:** A total of 82 patients were included in the analysis. 43 patients (52%) received combination chemotherapy with immunotherapy, 39 patients (48%) received immune checkpoint inhibitor monotherapy. Median BTS and TTB were 36.5mm (range 0–204mm) and 43mm (range 0–1123mm) respectively. CBR6 was significantly associated with BTS ($p=0.004$) and TTB ($p=0.002$) quartiles, with clinical benefit time progressively increasing with decreasing tumor burden quartiles. Both increasing BTS ($p<0.001$) and TTB ($p<0.001$) across quartiles were significantly associated with shorter OS. There was a numerical, but not statistically significant, association between both parameters as quartiles (BTS, $p=0.25$; TTB, $p=0.07$) and PFS. In the bottom BTS quartile, 32% of patients were progression-free and 95% alive at 12 months, compared with 15% and 40% respectively in the top quartile. Similar results were seen when TTB was used as the baseline measurement: 32% progression-free and 95% alive at 12 months in the bottom quartile compared with 1% and 33% in the top quartile. Multivariate analysis confirmed that both BTS and TTB, considered as continuous variables, are independently associated with OS. **Conclusions:** Lower baseline radiological tumor burden is associated with better outcomes in patients with metastatic breast cancer treated with immune checkpoint inhibitors. Research Sponsor: None.

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Poster Session

Social determinants of health factors and palliative care services use among patients with metastatic breast cancer in Florida. *First Author: Fantine Giap, Department of Radiation Oncology, University of Florida College of Medicine, Gainesville, FL*

Background: ASCO recommends palliative care (PC) as an adjunct to the oncologic standard of care for patients with metastatic cancer. However, current evidence on PC utilization in patients with breast cancer and its relationship with area-level social determinants of health (SDoH) factors is limited. Therefore, we examined the associations between county-level factors and PC utilization among patients with metastatic breast cancer (mBC) in Florida. **Methods:** We extracted patient-level data ($n = 23,539$ patients diagnosed with mBC between 2012 and 2021) from the One-Florida+ Data Trust and linked it to county-level data (67 Florida counties) from the AHRQ-SDoH Database. PC utilization since cancer diagnosis was identified using ICD-9 code V66.7 or ICD-10 code Z51.5. We assessed differences in PC utilization with county-level SDoH factors (e.g., poverty rate, transportation resource, provider supply, racial segregation) using bivariate analysis. Multivariable Poisson regression, including significant factors from bivariate analysis, was used to compare the PC utilization for the SDoH factors. **Results:** Our study population's overall prevalence of PC utilization was 16.1%. PC utilization was higher for patients with mBC residing in counties with a higher proportion of residents living in poverty and with a greater supply of advanced practice providers (APP: NP, PA), general surgeons, and nursing homes. Patients with mBC in counties with higher proportions of residents who identified as immigrants, with limited English proficiency, without personal transportation, and having higher racial segregation had lower PC utilization. In adjusted analysis, the supply of APP (coefficient: 0.12) and nursing homes (coefficient: 0.09) was associated with increased PC utilization. Conversely, racial segregation (White vs. non-White) was associated with decreased PC utilization (coefficient: -0.07). **Conclusions:** PC utilization among patients with mBC was associated with several SDoH at the county level. Notably, low PC utilization was associated with racial residential segregation and fewer APPs and nursing homes. Further research is needed to identify mediators in these relationships to improve PC effectiveness for patients with mBC in Florida. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology.

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Poster Session

Prognostic value of HER2-low status in breast cancer: A systematic review and meta-analysis. *First Author: Chiara Molinelli, Università degli Studi di Genova, Genoa, Italy*

Background: HER2-Low breast cancer (BC) has been recently identified as a new therapeutic target. However, it is unclear if HER2-Low status has an independent impact on prognosis, both in metastatic and early settings. **Methods:** A systematic literature research of PubMed, Cochrane and conference proceedings (ASCO meetings, SABCS and ESMO congress) up to December 8, 2022 was performed to identify studies comparing survival outcomes of patients affected by HER2-Low BC vs. HER2-zero BC. HER2-Low status was defined as immunohistochemistry score 1 + or 2+ without in situ hybridization amplification. Pooled hazard ratios (HRs) for survival endpoints in the metastatic [progression-free survival (PFS), overall survival (OS)] and in the early [disease free-survival (DFS) and OS] settings as well as their 95% confidence intervals (95%CI) were calculated using the random-effect model of Der Simonian and Laird. The above-mentioned endpoints were also assessed according to estrogen receptor (ER) status. **Results:** Among 1,916 identified records, 42 studies including 1,797,377 patients were eligible for this analysis. We show the pooled HRs in the overall population and specific subgroups. In the early setting, HER2-Low status was associated with significant improved DFS (HR 0.86, 95%CI 0.79-0.92, $p<0.001$) and OS (HR 0.84, 95%CI 0.77-0.92, $p<0.001$) when compared to HER2-zero status. Improved OS was observed in subgroup analysis for both ER-positive and ER-negative HER2-Low populations, while DFS improvement was observed only in the ER-positive subgroup. Similarly, in the metastatic setting, patients affected by HER2-Low BC showed better OS when compared to those with HER2-zero BC (HR 0.94, 95%CI 0.89-0.98, $p=0.008$). HER2-Low metastatic BC was associated with significant improvement in OS compared to HER2-zero BC also in ER-positive and ER-negative subgroups. No significant differences were found in terms of PFS. **Conclusions:** Compared with HER2-zero status, HER2-Low status appears to be associated with an increased OS both in the advanced and early settings, regardless of hormone-receptor expression. Research Sponsor: None.

Setting	Population	OS HR (95%CI)	p value	DFS HR (95%CI)	p value	PFS HR (95%CI)	p value
Early	Overall	0.84 (0.77-0.92)	<0.001	0.86 (0.79-0.92)	<0.001		
	ER-positive	0.85 (0.78-0.93)	0.001	0.86 (0.80-0.93)	<0.001		
	ER-negative	0.87 (0.84-0.89)	<0.001	0.90 (0.78-1.04)	0.155		
Metastatic	Overall	0.94 (0.89-0.98)	0.008			0.99 (0.96-1.03)	0.710
	ER-positive	0.92 (0.87-0.98)	0.013			1.13 (0.94-1.35)	0.192
	ER-negative	0.91 (0.87-0.95)	<0.001			0.92 (0.84-1.02)	0.103

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Poster Session

Biomarker analysis of phase II pembrolizumab maintenance treatment after chemotherapy response in patients with HER2-negative inflammatory breast cancer and triple-negative breast cancer. *First Author: Toshiaki Iwase, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Accumulating toxicities make indefinite chemotherapy unfeasible for many patients with metastatic/recurrent HER2-negative inflammatory breast cancer (IBC) or triple-negative breast cancer (TNBC). We conducted a single-arm phase II trial of pembrolizumab monotherapy to determine the efficacy of maintenance immunotherapy in patients with metastatic HER2-negative aggressive breast cancer and to identify biomarkers correlated with disease control. **Methods:** The study enrolled patients who had a complete response, partial response, or stable disease after a minimum of 3 cycles of chemotherapy for metastatic TNBC/IBC regardless of PD-L1 expression between 2015 and 2022. Pembrolizumab was administered at 200 mg every 3 weeks until disease progression, intolerable toxicity, or 2 years of exposure to the drug. The primary endpoint was the 4-month disease control rate (DCR), and the secondary endpoint was progression-free survival (PFS). Correlative studies were performed to determine associations between clinical response, and immune profiling consisting of T-cell clonality, immunophenotyping, and dendritic cell (DC) function with blood collected at baseline and after 2 cycles of pembrolizumab treatment. **Results:** Of 43 treated patients, 11 had metastatic IBC and 32 had TNBC. The median number of prior lines of chemotherapy for metastatic disease was 1. During a median follow-up of 11.4 months, 33 patients had progressive disease and 25 were deceased. The 4-month DCR was 58.1% (95% CI: 43.4%-72.9%) and the median PFS was 4.8 months (95% CI: 3.0-7.1 months). The median PFS of the metastatic IBC group (2.2 months) and TNBC group (4.8 months) did not differ significantly ($p = .12$). Thirty-one patients discontinued treatment due to progressive disease rather than toxicity. Observed toxicities were consistent with the known profile of pembrolizumab. Correlative blood studies showed availability of PD-1 on CD8 T cells decreased on therapy. T-cell exhaustion markers 2B4, CTLA4, and TIM3 decreased in patients who had therapeutic benefit, while LAG3 increased in patients without benefit. During therapy, *ex vivo* cytokine synthesis (IL-6/IL-12/TNF α) by DCs was superior in patients who benefited from therapy and increased from pretreatment samples. High T-cell clonality at baseline predicted response to immunotherapy (10.4 vs 3.6 months, $p = .04$). Additionally, patients exhibiting the greatest clinical benefit also had a significant increase in T-cell clonality over the course of therapy (20% vs 5.9% mean increase, $p = .04$). **Conclusions:** Increased T-cell clonality and DC activity, along with reductions in T-cell exhaustion, were associated with prolonged disease control following pembrolizumab maintenance therapy, achieving acceptable disease control with manageable toxicity. Clinical trial information: NCT02411656. Research Sponsor: Merck.

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Poster Session

Pilot study of a micro-organosphere drug screen platform to lead care in advanced breast cancer (MODEL-ABC). *First Author: David Graham, Xilis, Durham, NC*

Background: ASCO guidelines suggest using single agent chemotherapy for patients with advanced breast cancer (ABC). Single agent chemotherapy provides modest response rates in ABC, causing patients to be exposed to unnecessary toxicity without benefit. Thus, there is an unmet clinical need to develop a clinically applicable assay to guide treatment. We recently reported the use of Micro-Organospheres (MOS), which are gel droplets that encapsulate tumor cells creating miniature avatars of a patient's tumor and are amenable to high throughput dispensing and drug studies. In our current study, we evaluated the feasibility of generating and dosing MOS from ABC samples as a novel drug screen platform that led to the development and enrollment of a precision oncology trial, known as MODEL-ABC. **Methods:** We first performed a proof-of-concept study on 21 samples from patients with ABC and generated MOS. Drug screens were then performed on these MOS across 7 standard of care (SOC) chemotherapies commonly prescribed for ABC. These data resulted in a platform for the MODEL-ABC study that enrolled patients with ABC of any ER, PR, or HER2 subtype who were eligible for single agent chemotherapy to determine the feasibility of using MOS to predict response to therapy. In this study, biopsies from lesions ≥ 2 cm were obtained as part of SOC to generate MOS and perform drug screens. The patient subsequently received single agent chemotherapy per physicians' choice with either carboplatin, capecitabine, paclitaxel, eribulin, liposomal doxorubicin, gemcitabine, or vinorelbine. MOS were treated using the same chemotherapy as the patient along with 1-3 alternative single agent chemotherapies. **Results:** We generated MOS from 19/21 samples (90% success rate) across several breast cancer subtypes. Dose response curves of MOS were successfully generated across the 7 chemotherapies with a mean turnaround time of 21 ± 7 days validating the clinical applicability of MOS and leading to the MODEL-ABC trial. As of February 14, 2023, 4 of 15 patients have enrolled onto MODEL-ABC. All biopsies provided sufficient tissue for MOS generation, and drug screens were performed in 14-28 days across 2-4 chemotherapies. Two patients received capecitabine, one patient received eribulin, and one patient received paclitaxel. Full results of MODEL-ABC including correlation between MOS drug response and patient outcomes will be reported at the meeting. **Conclusions:** Our platform enables efficient establishment of MOS from ABC patient samples and allows for drug dosing studies to be performed in a clinically meaningful timeframe. Our preliminary data suggests it is feasible to obtain biopsies for MOS development and perform drug screens within 14 days. These findings provided the foundation for evaluating this technology as a potential ABC diagnostic tool and warrants further clinical development in ABC. Clinical trial information: NCT04655573. Research Sponsor: Xilis.

1106

Poster Session

Association of pretreatment chest CT abnormalities with trastuzumab deruxtecan-associated pneumonitis. *First Author: Rachel Occhiogrosso Abelman, Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA*

Background: Trastuzumab deruxtecan (T-DXd) is an antibody-drug conjugate approved for HER2+ metastatic breast cancer (MBC) and HER2-low (IHC 1+ or 2+ with FISH-) MBC. Pneumonitis with T-DXd has been observed in 13.6% of patients (pts) on DESTINY-Breast 01 (including 2.2% fatal events) and 12.1% in pts on DESTINY-BREAST 04 (including 0.8% fatal events). There is an unmet need to determine if pts with baseline lung abnormalities are at increased risk for development of pneumonitis from T-DXd. **Methods:** This retrospective cohort study included all pts treated with T-DXd for MBC at an academic institution from 1/2020 to 2/2023 for more than 1 cycle (>21 days). Outcomes were evaluated from treatment initiation until 2/1/2023. Two board-certified radiologists blinded to outcomes reviewed staging chest CTs performed before initiating T-DXd and graded each scan on 16 parenchymal abnormalities, including presence of interstitial lung abnormalities (ILA). Pneumonitis was retrospectively adjudicated by an independent oncologist using chart review and graded according to CTCAE v5.0 and compared to the treating physician's assessment. The difference of proportions was analyzed with the Pearson Chi-Square test. Significance was declared at the 0.05 type I error threshold. **Results:** A total of 68 pts (median age 57.3 years) were included (30 = HER2+, 24 = HR+/HER2 low, 14 = TNBC/HER2 low). By independent assessment, 16 pts (23.5%) had grade 1 pneumonitis and 3 pts (4.4%) grade 2 pneumonitis. Median time from treatment initiation to pneumonitis was 83 days (range 35-266). By treating physician assessment, 5 pts (7.4%) developed grade 1 pneumonitis and 3 pts (4.4%) developed grade 2 pneumonitis. 16 of 68 pts (23.5%) had baseline ILA and 62 pts (91.2%) had at least one other parenchymal abnormality. As assessed by an independent oncologist, of pts with baseline ILA (N = 16), 12.5% developed T-DXd related pneumonitis, compared to 32.7% of pts without pre-existing ILA (N=52), $p=0.16$. There was no statistical difference in T-DXd related pneumonitis assessed by treating physician between pts with baseline ILA (2/16 patients, 12.5%) compared to pts without baseline ILA (7/52 pts, 13.5%), $p=0.68$. **Conclusions:** In this study, presence of baseline ILA was not associated with subsequent pneumonitis from T-DXd. Notably, the rate of independently assessed pneumonitis was higher than treatment-attributed pneumonitis as defined by the treating physician. Further research is needed to validate these findings and define predictors of treatment-associated pneumonitis. Research Sponsor: U.S. National Institutes of Health.

Rate of pretreatment abnormalities on CT chest in pts with MBC prior to treatment with T-DXd.	
Finding	Patients meeting criteria (Total N=68)
Interstitial lung abnormalities	16 (23.5%)
Radiation changes	48 (70.5%)
Bronchial wall thickening	55 (80.1%)
Emphysema	9 (13.2%)
Infectious or inflammatory ground-glass opacities	15 (22.1%)

1108

Poster Session

Demographic and clinical characteristics of patients with metastatic breast cancer and leptomeningeal disease: A single center retrospective cohort study. *First Author: Laura Ann Huppert, University of California, San Francisco, San Francisco, CA*

Background: Patients (pts) with metastatic breast cancer (MBC) and leptomeningeal disease (LMD) have a poor prognosis with limited therapeutic options. It is critical to better understand the risk factors and natural history of this condition, including pts in a modern cohort. **Methods:** In this single center retrospective cohort study, we identified pts with radiographic and/or cytologic evidence of LMD who received care at the University of California San Francisco (UCSF) from 2000-2023. To identify pts, we used the UCSF Pathology Database, the UCSF Radiation Oncology Database, and EMERGE, a searchable copy of the medical record. We conducted chart review to identify demographic and clinical characteristics, treatment history, and overall survival (OS). **Results:** 106 pts with MBC and radiographic and/or cytologic evidence of LMD were identified. All but one pt was female (n=105; 99.1%); most pts were non-Hispanic (n=93, 87.7%) and white (n=74, 69.8%). Median age at the time of MBC diagnosis was 51.9 years; 25 pts (20%) had de novo metastatic disease. Most pts had invasive ductal carcinoma (n=71, 66.9%), with invasive lobular carcinoma making up 21.7% (n=23) of cases. Pts presented with the following BC subtypes: Hormone receptor (HR) positive, HER2 negative (n=50, 47.1%), HR+/HER2+ (n=19, 17.9%), HR-/HER2+ (n=9, 8.5%), and triple negative (TNBC; n=23, 21.7%). Most pts had brain metastasis (n=78, 73.6%) in addition to LMD. Median time from diagnosis of MBC to LMD was 17.6 months (0-101.2 months). Pts received a median of 3.0 lines of therapy prior to the diagnosis of LMD (range 0-11.0) and 1.0 lines after the diagnosis of LMD (range 0-4.0). Many pts received intrathecal (IT) therapy (n=42, 39.6%) and/or whole brain radiation therapy or spinal radiation (n=49, 46.2%). Median OS from the diagnosis of LMD to death was 3.3 months. There was no significant difference in median OS by subtype: HR+/HER2- 3.5 months, HER2+ 4.7 months, and TNBC 2.2 months ($p=0.45$). There was no significant difference in median OS by histology: ductal (3.3 months) vs. lobular (4.7 months) ($p=0.56$). Pts who received IT therapy survived longer than those not treated with IT therapy (4.7 vs. 2.5 months, $p=0.01$). There was no significant difference in median OS among pts diagnosed with LMD between 2000-2015 (2.9 months) vs. 2016-2023 (3.6 months) ($p=0.74$). **Conclusions:** This study represents one of the largest reported case series of pts with MBC and LMD, including a more modern cohort. There appeared to be an over-representation of pts with lobular cancer and those with de novo metastatic disease. Most pts had brain metastases in addition to LMD. Survival was short in all pts, particularly those who did not receive IT therapy. There was no significant difference in median OS in pts diagnosed with LMD from 2000-2015 vs. 2016-2023; this remains an area of unmet clinical need. Research Sponsor: None.

1109

Poster Session

Distribution and outcomes of HER2-low and HER2-zero metastatic breast cancer in Black and younger women. *First Author: Paola Zagami, UNC Lineberger Comprehensive Cancer Center/University of Milan, Chapel Hill, NC*

Background: Black and younger patients with breast cancer (BC) have higher mortality. This racial disparity has been attributed to different BC biology, access to care, and treatment. With the advent of new antibody-drug conjugates (ADC) for metastatic BC (MBC), “HER2-negative” has been subdivided into HER2-low (IHC 1+ or 2+/ISH-negative) and HER2-0 (IHC 0). Little is known about these subcategories among Black and younger women with MBC. **Methods:** Clinical characteristics, treatment, and outcomes of patients diagnosed with HER2-negative MBC between 2011-2022 and with follow-up through a progression-free survival event on first-line therapy (PFS1) were retrieved from the UNC Metastatic Breast Cancer Database; hormone receptor (HR) and HER2 categories were by clinical criteria from the pathology report. Analyses were limited to HER2-negative BC and stratified/controlled by HR status. Fisher's exact tests were used to compare HER2 status across race and age. The Kaplan Meier method and log-rank tests, as well as Cox proportional hazards models estimated PFS1. **Results:** The cohort included 772 MBC patients (56% HER2-low and 44% HER2-0), 22% Black women and 30% < 50 years old at MBC diagnosis. There were no differences in proportion with HER2-low by race or age ($p > 0.5$). Patients with HER2-low had better observed median PFS1 compared to HER2-0, however, most of these differences were non-significant: overall (HR+ 12.2 vs 9.8m, $p = 0.11$, HR- 4.3 vs 3.3m, $p = 0.29$) and within race and age categories (see table). In Cox modeling, Black women had worse PFS1 ($p = 0.03$), that was no longer apparent after adjusting for HR status ($p = 0.1$), there was no difference by age. Patients with HER2-0 had worse PFS1 ($p = 0.0005$), which remained after adjusting for HR status ($p = 0.05$). In a multivariable model comparing HER2-0 to HER2-low, adjusting for race and HR status, PFS1 remained shorter in the HER2-0 group (hazard ratio: 0.84, CI 0.692 – 1.015, $p = 0.07$). Among those treated with uniform first-line therapy, better PFS1 was observed in HER2-low disease. This included 137 HR+ MBC treated with ET + CDK4/6i (mPFS1 14.3 v 10.3m, $p = 0.33$) and 170 HR- MBC treated with chemotherapy (mPFS1 4.0 v 3.1m, $p = 0.22$) with no variation by race or age. **Conclusions:** Within HER2-negative MBC, distribution of HER2-low and HER2-0 cancers does not differ by race and age. The clinical benefit of first-line therapy is strongly driven by HR status regardless of race and age, and is greater in HER2-low cancers although this cohort did not include HER2-directed ADCs. Research Sponsor: None.

Median PFS (in months) and 95% CIs.

	HR-positive			HR-negative		
	HER2-0	HER2-low	p-value	HER2-0	HER2-low	p-value
<50	6.2 (3.4-13.5)	13.5 (7.3-19.2)	0.36	2.9 (2.1-4.22)	4.0 (2.0-6.0)	0.31
≥50	10.3 (7.2-15.3)	12.2 (9.2-14.9)	0.23	3.9 (2.0-4.6)	4.3 (2.6-6.1)	0.65
Black	13.5 (3.4-22.3)	11.2 (6.9-15.4)	0.70	2.9 (1.6-4.5)	3.0 (1.7-5.2)	0.95
Non-Black	9.5 (6.8-12.5)	12.7 (9.4-15.5)	0.04	3.9 (2.6-5.4)	4.3 (2.6-7.5)	0.26

TPS1111

Poster Session

Randomised open-label phase II study of induction standard of care fulvestrant and CDK4/6 inhibition with addition of ipatasertib in metastatic ER+/HER2- breast cancer patients without circulating tumour (ct) DNA suppression (FAIM). *First Author: Alicia Frances Clare Okines, The Royal Marsden NHS Foundation Trust, London, United Kingdom*

Background: The combination of fulvestrant and one of the three approved CDK4/6 inhibitors (i) is the standard of care for patients with ER+/HER2 metastatic breast cancer progressing on first-line endocrine therapy, or relapsing on or within a year of completing adjuvant endocrine therapy. AKT inhibition combined with fulvestrant has recently demonstrated clinically important activity in patients with advanced ER+/HER2- breast cancer progressing on first-line CDK4/6i plus an AI. Monitoring ctDNA dynamics has potential utility as an early response evaluation tool: Lack of suppression of ctDNA at day 15 in patients treated with palbociclib and fulvestrant in the PALOMA-3 trial was predictive for shorter PFS. We designed FAIM to establish whether the addition of the AKT inhibitor, ipatasertib, improves PFS in patients with poor ctDNA suppression during cycle 1 of fulvestrant and CDK4/6i. **Methods:** FAIM is a phase 2 multi-centre, randomised, open-label superiority trial in patients with ER+/HER2- advanced breast cancer, recruiting at centres in the UK. Patients will undergo ctDNA testing at days 1 and 15 of cycle 1 fulvestrant and CDK4/6i inhibitor. Eligible patients must be aged ≥18, have ER+ (≥1% or Allred score 3/8 or greater) and HER2- advanced breast cancer, measurable disease or assessable bone disease (RECIST 1.1), adequate organ function, fasting glucose ≤150mg/dL and HbA1c ≤7.5% and be eligible for NHS treatment with fulvestrant and CDK4/6i. Patients with diabetes requiring insulin, significant cardiac disease, a history of pneumonitis, or prior exposure to CDK4/6i are excluded. The FoundationOne Liquid CDx assay will be used for ctDNA analysis, a pan-cancer, tumour-agnostic liquid biopsy test that uses error-corrected next-generation sequencing. Patients with poor ctDNA suppression at day 15 will be eligible for the randomised (minimisation) study. Up to 483 patients starting fulvestrant and CDK4/6i will enroll for ctDNA screening to allow 174 patients to enter the randomised study. The primary endpoint of the study is to compare PFS in patients randomised to palbociclib/fulvestrant +/- ipatasertib. Secondary endpoints include safety, overall survival and overall response rate in all randomised patients and PFS in the sub-group of patients with alterations in the PIK3CA/AKT1/PTEN pathway. One hundred patients with ctDNA suppression at day 15, and up to 50 patients with no detectable ctDNA at day 1, will form additional control groups for exploratory outcome comparison to patients with poor ctDNA suppression. Enrolment began in December 2022 and is anticipated to continue for 2 years (NCT04920708). Clinical trial information: NCT04920708. Research Sponsor: Roche; Pfizer.

1110

Poster Session

Imbalance in treatment discontinuation without progression between experimental and control arms among randomized trials in advanced breast cancer. *First Author: Faris Tamimi, Division of Medical Oncology & Hematology, Department of Medicine, Princess Margaret Cancer Centre and University of Toronto, Toronto, ON, Canada*

Background: In Randomized Controlled Trials (RCT), treatment discontinuation (TD) can result in censoring. Imbalanced frequency of TD between arms could impact interpretation of results. Here, we quantify TD between the experimental and control arms among RCT supporting registration of drugs for advanced breast cancer. **Methods:** We identified RCT supporting US Food and Drug Administration's approval of drugs for advanced breast cancer between 2013 and 2023. We extracted data for the number of participants with TD for reasons other than disease progression (PD), death, or completion of treatment. Odds ratio (OR) for TD comparing experimental to control arms were determined for each trial. To assess progression-free survival (PFS) translation into an overall survival (OS) benefit, we calculated hazard ratio (HR) for PFS/OS. Then we assessed whether there was quantitative association between the OR for TD and the ratio of HR for PFS/OS. Quantitative significance was defined according to the criteria of Burnand. **Results:** Analysis included 22 RCT comprising 13853 participants and supporting approval for 18 distinct drugs. TD was reported in 2212 (16.0%) participants. Among these participants, the leading causes of TD were withdrawal of consent (27.8%), site termination (20.7%), adverse events (17.2%), and loss of follow-up (10.9%). There was a statistically significant imbalance in the experimental arm in 4 RCT (18%) (Table), which was observed for everolimus, ribociclib (with fulvestrant), apalibisib, and neratinib. The OR for TD showed quantitative, but not statistically significant negative association with the ratio of the HR for PFS/OS (Beta -0.393; $p = 0.18$). **Conclusions:** TD without PD, death, or completion of treatment occurs in a substantial proportion of participants of several RCT supporting approval of drugs for advanced breast cancer. all the statistically significant imbalanced TD in the RCT were in experimental arms. Quantitative association between imbalanced TD and the ratio of HR for PFS/OS suggests imbalanced TD may impact ability to translate improvements in PFS to OS. Results of RCT with imbalance in TD should be interpreted cautiously. Research Sponsor: None.

OR for TD comparing experimental to control arms.

RCT	OR [95% CI]
OlympiAD	0.66 [0.24, 1.79]
ALTERNATIVE	0.72 [0.29, 1.77]
EMBRACE	0.73 [0.47, 1.13]
EMBRACE	0.74 [0.54, 1.02]
CONFIRM	0.76 [0.53, 1.07]
SOPHIA	0.89 [0.54, 1.48]
CLEOPATRA	0.90 [0.59, 1.37]
MONARCH 3	0.90 [0.48, 1.72]
MONARCH 2	0.90 [0.53, 1.54]
MONALEESA-7	0.92 [0.57, 1.49]
PALOMA-3	1.10 [0.53, 2.30]
EMILIA	1.27 [0.98, 1.65]
DESTINY-Breast03	1.33 [0.86, 2.06]
PALOMA-2	1.34 [0.90, 1.99]
ASCENT	1.43 [0.95, 2.16]
NALA	1.45 [1.02, 2.07]
MONALEESA-2	1.55 [0.98, 2.47]
HER2CLIMB	1.60 [0.58, 4.43]
KEYNOTE-355	1.77 [0.70, 4.43]
SOLAR-1	1.93 [1.19, 3.12]
MONALEESA-3	1.94 [1.19, 3.13]
BOLERO-2	4.04 [2.33, 7.00]

*Significant p-value.

TPS1112

Poster Session

Phase IIa study of αDC1 vaccines targeting HER2/HER3 combined with pembrolizumab in patients with asymptomatic brain metastasis from triple negative breast cancer or HER2+ breast cancer. *First Author: Shipra Gandhi, Roswell Park Comprehensive Cancer Center, Buffalo, NY*

Background: Brain metastases develop in up to 50% patients (pts) with metastatic triple negative breast cancer (TNBC) and HER2+ BC, constituting an increasing source of morbidity and mortality. HER3, overexpressed in triple negative and HER2+ brain metastatic breast cancer (BMBC), is a resistance factor to HER2-targeted therapies and a driver of CNS metastasis. Disease progression is associated with loss of anti-HER2 and anti-HER3 immunity. Previously, we have demonstrated that glioma-specific peptide-loaded αDC1 which produce CXCL9, CXCL10, CXCL11, CCL5, the chemokines which attract CXCR3- and CCR5- expressing cytotoxic T-lymphocytes (CTLs) and T-helper 1 (Th1) cells, induce clinical responses and long-term disease stabilization in pts with aggressive recurrent primary brain tumors (Okada et al. JCO 2011. PMID: 21149657). We hypothesized that anti-HER2/3-loaded αDC1 in combination with PD1 blockade will result in strong Th1/CTL response against HER2/3 epitopes (Basu A et al. Cancer Immunol Res. 2022 PMID: 34785506), being effective against brain lesions and systemic disease. **Methods:** This is a phase II single-arm, non-randomized multicenter study (NCT04348747). Eligibility includes pts with triple negative and HER2+ BMBC ≥18 years, ECOG PS ≤1, normal marrow and organ function with asymptomatic untreated brain metastases ≥ 5 mm who will receive αDC1 q3 weeks x 3 along with pembrolizumab every 3 weeks. Thereafter, αDC1 booster doses (if available) would be administered every 3 months until disease progression, intolerable side effects or withdrawal from study, up to 24 months. Baseline and 9-week post-αDC1 peripheral biopsies (non-CNS) are required for six pts. 1 of the planned 21 pts have been enrolled and is undergoing treatment. Primary endpoint is CNS response rate (RR) by RANO-BM criteria. If no CNS response is observed after 12 pts, study will be terminated. If ≥ 1 response observed, then 9 more pts will be enrolled, for a total of 21 pts. If ≥ 3 CR are observed, the proposed therapy will be considered as promising for further evaluation. Secondary endpoints include non-CNS RR per RECIST v1.1, median CNS, non-CNS and overall progression-free survival, overall survival and safety. Exploratory endpoints include changes in intratumoral biomarkers (CTLs, PDL1, chemokines) in pre- and post-treatment peripheral tumor biopsies and immune changes in the blood. Clinical trial information: NCT04348747. Research Sponsor: Department of Defense.

TPS1113

Poster Session

Phase I study of adoptive T cell therapy following HER2-pulsed dendritic cell vaccine and pepinemab/trastuzumab in patients with metastatic HER2-positive breast cancer (MBC). *First Author: Hyo S. Han, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL*

Background: Despite major improvement of overall survival of HER2+ MBC with effective HER2 targeted therapies, many patients experience significant toxicities and develop progressive disease during treatment. Therefore, new and more effective therapeutic options are needed. This novel approach will evaluate whether the combination of three immunotherapies in addition to trastuzumab: dendritic cell (DC) vaccination, anti-SEMA4D blocking antibody (pepinemab) and CD4+ T cell adoptive transfer can lead to improved outcomes for patients with MBC refractory to HER2-targeted agents. BC have been considered as immunologically cold which is attributed to immune evasion and suppression of host effector immune cells homing into tumor bed. Progressive loss of Th1 immunity against HER2 oncovirion correlates with poor prognosis. HER2 peptide pulsed type I dendritic cells (HER2-DC1) re-stored anti-HER2 CD4+ Th1 immune response and improved pathologic complete response (pCR) in HER2+ BC. Antibodies to SEMA4D have been shown to modulate the TME by increasing effector cell infiltration and reducing immunosuppression. In preclinical studies, treatment with anti-SEMA4D and HER2-DC1 in mice bearing established HER2+ tumors improved DC homing, expansion of CD4+ T cells, and complete tumor regression, compared to treatment with anti-SEMA4D or HER2-DC1 alone. Further, subsequent expansion and adoptive transfer of CD4+ T cells induced synergistic anti-tumor activity by activating CD8+ T mediated cytotoxicity. Pepinemab was well-tolerated and showed signs of anti-tumor activity in in immunotherapy-resistant and PD-L1 negative/low non-small cell lung cancer patients when combined with checkpoint inhibitor (avelumab). **Methods:** This open label Phase I study is enrolling up to 28 patients with HER2+ MBC. Patients will be treated with 6 weekly injections of dendritic cell (DC1) vaccines in combination with trastuzumab and pepinemab. We hypothesize these therapies may elicit CD4+ HER2-specific T cell responses. HER2-specific T cells will be expanded ex vivo and subsequently infused to patients following lymphodepletion with cyclophosphamide. Trastuzumab and pepinemab will be given as maintenance in addition to booster DC1 vaccines. Patients (ECOG 0,1) must have had disease progression while on trastuzumab for the treatment of HER2+ MBC and received no more than 3 lines of chemotherapy in the setting of metastatic disease. Dose escalation will consist of 3-6 patients each with increasing amounts of transferred CD4+ T cells, followed by dose expansion of 10 patients at the MTD. The primary objective is safety and tolerability; secondary objectives will include evaluation of T cell immunity and immune subsets, efficacy, PK/PD/ADA of pepinemab, and biomarker assessments. Clinical trial information: NCT05378464. Research Sponsor: Moffitt Cancer Center Breast Cancer Funding; Bankhead and Coley Cancer Research Grant.

TPS1115

Poster Session

HER2CLIMB-05: Phase 3 study of tucatinib or placebo in combination with trastuzumab and pertuzumab as maintenance therapy for HER2+ metastatic breast cancer. *First Author: Erika P. Hamilton, Sarah Cannon Research Institute at Tennessee Oncology, Nashville, TN*

Background: The current first-line (1L) standard of care (SOC) for human epidermal growth factor receptor 2-positive (HER2+) metastatic breast cancer (MBC) is trastuzumab (T) plus pertuzumab (P) and a taxane. Despite advances in 1L SOC, most patients progress during maintenance therapy with T + P. Tucatinib is a tyrosine kinase inhibitor (TKI) approved in combination with T and capecitabine for adults with HER2+ MBC, with and without brain metastases (BM). In HER2CLIMB, the addition of tucatinib significantly prolonged progression-free survival (PFS) and overall survival (OS) in patients with HER2+ MBC and was well tolerated. Adding tucatinib also reduced the risk of disease progression or death in patients with untreated and/or active BM (Murthy et al. 2020, Curigliano et al. 2021). HER2CLIMB-05 investigates whether adding tucatinib to 1L SOC as maintenance therapy will extend PFS while maintaining quality of life (QOL). **Methods:** HER2CLIMB-05 (NCT05132582) is a phase 3, randomized, double-blind study evaluating tucatinib plus T + P as maintenance therapy for HER2+ MBC. Approximately 650 patients will be enrolled. Eligible patients will have advanced HER2+ disease, no progression on 4–8 cycles of prior 1L SOC, Eastern Cooperative Oncology Group Performance Status of 0 or 1, and no or asymptomatic BM. Exclusion criteria include prior treatment with anti-HER2 and/or anti-epidermal growth factor receptor TKI (prior SOC for early BC is permitted) or inability to undergo contrast magnetic resonance imaging of the brain. Patients will be randomized 1:1 to receive either tucatinib or placebo twice daily, with T + P once every 21 days. Patients with hormone receptor-positive disease may receive endocrine therapy. The primary endpoint is investigator-assessed PFS. Secondary endpoints include OS (key endpoint), PFS by Blinded Independent Central Review (BICR), time to deterioration of health-related QOL, central nervous system PFS, safety, and pharmacokinetic (PK) parameters. PFS and OS will be compared using a 2-sided stratified log-rank test between treatment groups. Time-to-event endpoints will be summarized using the Kaplan–Meier method. PK and safety data will be summarized using descriptive statistics. Enrollment is ongoing in the US, Canada, Brazil, APAC and EU countries with additional sites planned. Clinical trial information: NCT05132582. Research Sponsor: Seagen, Inc.

TPS1114

Poster Session

A phase 1, first-in-human, open label, escalation and expansion study of ORM-5029, a highly potent GSPT1 degrader targeting HER2, in patients with HER2-expressing advanced solid tumors. *First Author: Sara A. Hurvitz, Division of Hematology/Oncology, David Geffen School of Medicine at the University of California Los Angeles/Jonsson Comprehensive Cancer Center, Los Angeles, CA*

Background: Targeted protein degradation (TPD) molecules have expanded the therapeutic options through their catalytic mechanism of action (MOA) and ability to degrade “undruggable” proteins. To increase the efficacy versus tolerability window of protein degradation and improve drug delivery, ORM-5029 uses a Dual-Precision TPD (TPD²) approach combining the catalytic mechanism of TPDs with the precision of tumor-targeting therapeutic antibodies. ORM-5029 is a first-in-class human epidermal growth factor receptor 2 (HER2)-targeted antibody-drug conjugate (ADC) comprised of SMOI006, a highly potent GSPT1 degrader, conjugated to pertuzumab, a clinically validated antibody. HER2 is overexpressed in cancers such as breast, ovarian and gastric, and associated with early-onset aggressive disease. ORM-5029 is in development for treatment of HER2-expressing solid tumors. The MOA is mediated by targeted uptake of the ADC, release of the TPD payload, and cell death by GSPT1 degradation. ORM-5029 showed robust *in vitro* and *in vivo* efficacy in multiple HER2-expressing models with comparable activity to trastuzumab deruxtecan and strong activity in trastuzumab emtansine-refractory models. **Methods:** This phase 1 first-in-human study evaluates the safety, tolerability, and efficacy of ORM-5029 administered by intravenous infusion in patients (pts) with HER2-expressing advanced solid tumors (NCT05511844). The escalation, guided by the Bayesian Optimal Interval design, explores cohorts of ORM-5029 to identify the maximum tolerated dose (MTD) and/or expansion dose level (EDL). Each cohort will enroll ≥3 breast cancer pts with at least HER2 1+ (HER2 low) or greater by immunohistochemistry or positive by *in situ* hybridization. Expansion cohort A (HER2+ breast cancer) may enroll in parallel to escalation evaluating doses showing pharmacodynamic activity or efficacy. Up to 10 pts may be enrolled at each dose explored in cohort A. Enrollment into expansion cohort B (up to 21 pts) and cohort C (up to 22 pts) will begin once the EDL has been determined to further assess the safety, tolerability and efficacy of ORM-5029 using a Simon's optimal 2-stage design. Cohort B will enroll pts with HER2+ breast cancer refractory or intolerant to standard treatment after ≥2 HER2 therapies in the metastatic setting. Cohort C will enroll pts with advanced solid tumors that are refractory or intolerable to standard treatment or for which no standard treatment is available, including HER2+ gastric or gastroesophageal junction adenocarcinoma or tumors with HER2 expression, amplification or mutations (e.g., colorectal, bile duct, ovarian, bladder, non-small cell lung). Study enrollment began in October 2022 in the United States. Escalation cohort 1 was completed without DLT; enrollment in cohort 2 began as of December 2022. Clinical trial information: NCT05511844. Research Sponsor: Orum Therapeutics USA, Inc.

TPS1116

Poster Session

UCLA B-13: A phase 1b trial evaluating the safety of ribociclib, tucatinib, and trastuzumab in patients with metastatic, HER2+ breast cancer and a multicenter, randomized, open-label, phase 2 study of preoperative treatment with ribociclib, trastuzumab, tucatinib, with or without fulvestrant versus docetaxel, carboplatin, trastuzumab, and pertuzumab in HR+/HER-, HER2+ breast cancer. *First Author: Nicholas Patrick McAndrew, David Geffen School of Medicine at University of California Los Angeles, Los Angeles, CA*

Background: Overexpression of the HER2 protein is an important prognostic and predictive biomarker in about 20% of breast cancers, and while trastuzumab-based regimens are still considered standard of care in the early and metastatic settings, these regimens require chemotherapy co-administration. Pre-clinical mouse models suggest that a tucatinib/CDK 4/6 inhibitor combination regimen may be equally effective as standard regimens. Thus, finding more effective/tolerable therapies for this disease remains an area of unmet need. This randomized, open label, phase II clinical trial will explore the safety and efficacy of two novel, chemotherapy free combination drug regimens, given neoadjuvantly, in patients with anatomic stage I-III, HER2+ breast cancer. **Methods:** Phase 1b dose escalation trial: To establish the safety profile of the combination of ribociclib and tucatinib, an initial dose-finding phase 1b trial will be performed in patients with metastatic HER2+ breast cancer before moving into the larger phase 2 trial. 3-6 patients will be assigned sequentially to groups of increasing doses of ribociclib (200mg-600 mg) with fixed doses of tucatinib (300mg) and trastuzumab (SOC dosing) for a total of four 28-day cycles. The recommended phase 2 dose will be established when 6 patients have been treated at the highest dose level cohort. As of January 2023, 1 participant has been enrolled in dose level 1. Phase 2 neoadjuvant trial: Following MTD determination and approval from regulatory boards and funding partners, a total of 100 patients will be enrolled in the phase 2 portion of the study. Enrollment will be stratified by hormone receptor status. Patients will be randomized 1:1 (25 in each group) to receive six cycles of one of the following regimens: ribociclib/trastuzumab/tucatinib +/- fulvestrant (28 day cycles) or docetaxel/carboplatin/trastuzumab/pertuzumab (SOC, 21 day cycles), preceded by one run-in cycle of trastuzumab/pertuzumab. To assess for changes in predictive molecular biomarkers, biopsies pre-and-post cycle 1 will be planned in all arms. Early imaging response assessments in the experimental arms will be planned after 2 cycles. Other endpoints include safety, changes in Ki67 expression, RCBi, biomarker analysis, and health-related quality of life. Clinical trial information: NCT05319873. Research Sponsor: Novartis, Seagen Inc.

TPS1117

Poster Session

EPIK-B6: A phase 2, open-label, 2-part, multicenter study of alpelisib in combination with fulvestrant for men and postmenopausal women with PIK3CA mutation HR-positive, HER2-negative, advanced breast cancer, which progressed on/after aromatase inhibitor treatment in Japan. First Author: Hiroji Iwata, Aichi Cancer Center Hospital, Aichi, Japan

Background: The *PIK3CA* oncogene mutation, seen in ~40% of patients with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) advanced breast cancer (aBC), is associated with endocrine treatment resistance and shorter survival. Alpelisib, an α -selective PI3K inhibitor and degrader, was established as standard therapy in combination with fulvestrant for patients with HR+, HER2-, *PIK3CA*-mutated aBC following progression on/after endocrine-based regimen based on the phase 3 SOLAR-1 study. However, alpelisib is not yet approved in Japan. In the SOLAR-1 study, a high percentage of Japanese patients experienced dose reductions/interruptions (78.5% vs 84.4%), and/or discontinuation (56.3% vs 25.0%) of alpelisib in early stages compared with overall population, due to adverse events such as rash and hyperglycemia. Thus, it is difficult to assess the consistency of the benefit of alpelisib + fulvestrant in Japanese patients as compared to overall population due to the short duration of alpelisib exposure and low-dose intensity. The EPIK-B6 study aims to determine the recommended dose (RD) of alpelisib in Japanese patients as well as assess the efficacy and safety of alpelisib + fulvestrant in Japanese men and postmenopausal women with HR+, HER2-, *PIK3CA*-mutated aBC, which progressed while on/after aromatase inhibitor treatment, prior/post CDK 4/6i use. **Methods:** The EPIK-B6 study is designed as a phase 2, open-labelled, 2-part, multicenter study. Part 1 is to determine RD of alpelisib to be used in part 2. Part 2 is designed to assess the efficacy and safety of alpelisib (RD starting on cycle 1 day 1 [C1D1]) + fulvestrant (500 mg on C1D1 and C1D15, and D1 of subsequent cycles) after completion of part 1, in participants with/without prior CDK 4/6i use. Adult Japanese men or postmenopausal women with confirmed HR+, HER2-, *PIK3CA*-mutated aBC and ≥ 1 measurable lesion as per RECIST 1.1 criteria are eligible. Patients previously treated with fulvestrant, any PI3K, mTOR or AKT inhibitors are excluded. Use of prophylactic antihistamine is highly recommended for prevention of rash. The primary endpoint for part 2 is overall response rate based on assessments per RECIST 1.1. Secondary endpoints include progression free survival, overall survival, clinical benefit rate, duration of response, time to response, time to deterioration of ECOG performance status, safety, tolerability, and pharmacokinetics. Part 1 has been completed, and recruitment for part 2 is ongoing until August 2023 approximately. As of December 2022, 9 and 8 patients are enrolled in part 1 and 2, respectively. The study will include approximately 50 participants. Primary Analysis is planned in 2024 after at least 6 months follow-up period. Clinical trial information: NCT04524000. Research Sponsor: Novartis.

TPS1119

Poster Session

evERA Breast Cancer (BC): Phase III study of giredestrant + everolimus vs exemestane + everolimus in patients (pts) with estrogen receptor-positive, HER2-negative locally advanced or metastatic BC (ER+, HER2- LA/mBC). First Author: Erica L. Mayer, Dana-Farber Cancer Institute, Boston, MA

Background: Endocrine therapy (ET) + a cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) is the standard of care in pts with ER+, HER2- mBC in the first-line setting. Fulvestrant $\pm$ a CDK4/6i, and everolimus + exemestane are the current approved second-line regimens. However, therapeutic resistance to some ETs, such as aromatase inhibitors, can arise from *ESR1* mutations (m) driving estrogen-independent transcription and proliferation. Current post-CDK4/6i treatment options are suboptimal. New therapy options are therefore needed to reduce this risk and to improve outcomes, tolerability, quality of life, and adherence to treatment. Giredestrant is a highly potent, nonsteroidal oral selective ER antagonist and degrader (SERD) that achieves robust ER occupancy and is active regardless of *ESR1*-mut status. While Phase I SERD combination data in the post-CDK4/6i setting are encouraging, there are no randomized combination data. Combining giredestrant and everolimus may improve outcomes after CDK4/6is and in pts with *ESR1*m tumors. **Methods:** evERA BC (NCT05306340), a Phase III, global, randomized, open-label, multicenter study will evaluate the efficacy and safety of giredestrant + everolimus vs. exemestane + everolimus in pts with ER+, HER2- LA/mBC who had previous treatment with a CDK4/6i and ET in the LA/mBC or adjuvant setting. Pts will be randomized to either giredestrant (30 mg) + everolimus (10 mg) by mouth (PO) every day (QD), or exemestane (25 mg) + everolimus (10 mg) PO QD. Pts will receive treatment until disease progression or unacceptable toxicity. Pts will use a dexamethasone mouth rinse 4 times QD for 8 weeks concurrently with study treatment. Eligibility: Female/male pts ≥ 18 years with ER+, HER2- LA/mBC and disease progression ≥ 6 months (mo) after initiating ET + CDK4/6i in the LA/mBC setting (and ≥ 4 mo on most recent ET, if ET + CDK4/6i was not the most recent therapy received), or relapsed either while taking or within 12 mo of exposure to combination adjuvant ET (≥ 12 mo) + CDK4/6i (≥ 6 mo), and available blood sample for circulating tumor DNA central testing for *ESR1*m status. Men and pre-/perimenopausal women will receive a LHRH. Co-primary endpoints: Investigator-assessed progression-free survival (per RECIST v1.1) in the intent-to-treat and *ESR1*m populations. Secondary endpoints: Overall survival; objective response rate; duration of response; clinical benefit rate; pt-reported outcomes; safety; pharmacokinetics. Co-primary endpoint analyses will use a two-sided stratified log-rank test at an overall 0.05 significance level. An independent data monitoring committee will be in place for safety. Target enrollment is 320 pts, and this study is currently recruiting. Encore from SABCS 2022 (OT2-01-07). Clinical trial information: NCT05306340. Research Sponsor: F. Hoffmann-La Roche Ltd.

TPS1118

Poster Session

A phase 3 study of gedatolisib plus fulvestrant with and without palbociclib in patients with HR+/ HER2- advanced breast cancer previously treated with a CDK4/6 inhibitor plus a nonsteroidal aromatase inhibitor (VIKTORIA-1). First Author: Sara A. Hurvitz, David Geffen School of Medicine; University of California, Los Angeles; Jonsson Comprehensive Cancer Center, Santa Monica, CA

Background: Patients who receive frontline CDK4/6 inhibitor (CDK4/6i) therapy eventually experience disease progression. Resistance to CDK4/6i is likely a transient adaptive mechanism that may be reversed by inhibition of the PI3K/mTOR pathway. Thus, combination of CDK4/6i and PI3K/mTORi after disease progression on CDK4/6i could restore sensitivity to CDK4/6i and prevent activation of the PI3K/mTOR pathway. This hypothesis was evaluated in a Phase 1b study (Layman SABCS 2021) of gedatolisib (geda), a potent inhibitor of PI3K and mTOR. Subjects with HR+/HER2- ABC with prior CDK4/6i received geda (180 mg IV weekly for 3 weeks, then one week off) with palbociclib (palbo) and fulvestrant (FUL). Median PFS was 12.9 months with 63% overall response rate. Efficacy was observed regardless of *PIK3CA* mutation status (Wesolowski SABCS 2022). Geda was well tolerated, with few discontinuations due to treatment-related adverse events (4%). The most common AE was stomatitis; hyperglycemia of any grade occurred in 26% of patients. This preliminary data, dosing schedule, and study population characteristics form the basis for the Phase 3 trial, VIKTORIA-1 (NCT05501886). **Methods:** This Phase 3 multinational clinical trial will evaluate geda and FUL with or without palbo in patients with HR+/HER2- ABC previously treated with any CDK4/6i in combination with a non-steroidal aromatase inhibitor (AI) therapy. Those without tumor *PIK3CA* mutations will be assigned to Study 1 (n=351) and randomized to Arm A (geda, palbo, and FUL), Arm B (geda and FUL), or Arm C (FUL). Those with *PIK3CA* mutations will be assigned to Study 2 (n=350) and randomized to Arm D (geda, palbo, and FUL), Arm E (alpelisib and FUL), or Arm F (geda and FUL). Key eligibility criteria include adults with confirmed metastatic or locally advanced breast cancer, any menopausal status, radiologically evaluable disease, and prior CDK4/6i treatment in combination with a non-steroidal AI. Prior hormonal therapy, including SERDs, is allowed. Key exclusion criteria include prior treatment with a PI3K, Akt, or mTOR inhibitor, prior treatment with chemotherapy for advanced disease, more than two lines of prior endocrine therapy, bone only disease with no soft tissue components, active CNS metastases, and type 1 diabetes or uncontrolled type 2 diabetes. The primary endpoint is PFS assessed by blinded independent central review per RECIST v1.1. Secondary endpoints included overall survival, safety and tolerability, ORR, duration of response, time to response, CBR, quality of life, and pharmacokinetics. The trial is open for enrollment. Clinical trial information: NCT05501886. Research Sponsor: Celcuity, Inc.

TPS1120

Poster Session

AIPAC-003: A randomized, double-blind, placebo-controlled phase 3 trial testing eftilagimod alpha (soluble LAG-3) in patients with HER2-neg/low metastatic breast cancer receiving paclitaxel, following an open-label dose optimization. First Author: Nuhad K. Ibrahim, University of Texas MD Anderson Cancer Center, Houston, TX

Background: Eftilagimod alpha (efti), a soluble LAG-3 protein, acts as an MHC class II agonist that enhances immunity by mediating antigen presenting cell and CD8 T-cell activation. Data from a randomized, phase 2b trial of efti plus paclitaxel compared to placebo plus paclitaxel in patients (pts) with HR+ HER2- metastatic breast cancer (MBC) (AIPAC; NCT02614833) showed sustained pharmacodynamic activity that was linked to improved overall survival (OS) in the efti arm. AIPAC-003 is a randomized, double-blind, placebo-controlled phase 3 trial testing efti plus paclitaxel in HER2-neg/low MBC pts, including an initial open-label dose optimization lead-in (DOL) component to determine the optimal biological dose (OBD) of efti in this combination. **Methods:** Enrollment for the DOL will begin in March 2023 in max. 66 pts. Primary endpoints (EP) in the DOL include safety and tolerability of 90 mg vs 30 mg efti and defining the OBD of efti in combination with weekly paclitaxel. Determination of the OBD will be based on the totality of safety and tolerability data together with overall response rate (ORR) and pharmacodynamic marker (CD8+ T cells, absolute lymphocyte count) data. In the Phase 3 component approx. 771 pts are randomized to receive either paclitaxel + efti or paclitaxel + placebo in a double-blinded fashion. The primary EP for the proposed Phase 3 is OS. Key secondary EPs include progression free survival and ORR by RECIST 1.1, quality of life and safety. Pts will receive paclitaxel (80 mg/m² I.V. on D1, 8 and 15 in a 4-week cycle), followed by efti or placebo (DOL: 30 or 90 mg efti; Phase 3: OBD of efti or placebo) S.C. on D1 and 15 in a 4-week cycle for up to 12 months. Key inclusion criteria: Pts with either a) HR+ and HER2-neg/low and endocrine therapy-resistant MBC or b) TNBC not eligible for anti-PD-1-based therapy. Pts must have measurable disease, ECOG PS 0-1 and no prior chemo for metastatic disease. Research Sponsor: Immunet S.A.

TPS1121

Poster Session

TACTIVE-U: Phase 1b/2 umbrella study of ARV-471, a proteolysis targeting chimera (PROTAC) estrogen receptor (ER) degrader, combined with other anticancer treatments in ER+ advanced or metastatic breast cancer. *First Author: Rachel M. Layman, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: ARV-471, an oral PROTAC ER degrader, was well tolerated and showed evidence of clinical activity in a phase 1/2 study in heavily pretreated patients with ER+/human epidermal growth factor receptor 2 (HER2)- advanced breast cancer. The CDK4/6 inhibitors abemaciclib and ribociclib are approved in combination with endocrine therapy as first- and second-line treatment for ER+/HER2- advanced or metastatic breast cancer; abemaciclib is also approved as monotherapy and in combination with other agents in additional breast cancer settings. ARV-471 combined with abemaciclib or ribociclib showed evidence of synergistic interactions in ER+ breast cancer cells and greater tumor growth inhibition in a xenograft breast cancer model compared with fulvestrant in combination with these agents. Here we describe the first sub-studies of the open-label, phase 1b/2 TACTIVE-U umbrella study, which evaluate the safety and clinical activity of ARV-471 plus abemaciclib (sub-study A; NCT05548127) and ribociclib (sub-study B; NCT05573555) in patients with ER+/HER2- advanced or metastatic breast cancer. Future combination sub-studies will be included in TACTIVE-U. **Methods:** Patients eligible for sub-studies A and B are aged ≥ 18 years, have histologically or cytologically confirmed ER+/HER2- advanced or metastatic breast cancer not amenable to surgical resection with ≥ 1 measurable lesion by RECIST 1.1, and have received ≤ 2 lines of prior therapy for advanced or metastatic disease and 1 line of any CDK4/6 inhibitor-based regimen in any setting. In sub-studies A and B, patients will receive ARV-471 orally once daily (QD) continuously in a dose escalation/de-escalation approach. In sub-study A, abemaciclib will be given orally twice daily continuously, and in sub-study B, ribociclib will be given orally QD for 21 days followed by 7 days off treatment. For both sub-studies, the primary endpoint of the phase 1b portion is dose-limiting toxicities to determine the recommended phase 2 dose of ARV-471 in combination with abemaciclib or ribociclib. Secondary endpoints of phase 1b are antitumor activity (overall response rate [ORR], clinical benefit rate [CBR], and duration of response [DOR]), progression free survival (PFS), safety (type, frequency, and severity of adverse events and laboratory abnormalities), and plasma concentrations of study drugs. Phase 2 further evaluates the antitumor activity of the combinations; the primary endpoint is ORR and secondary endpoints include antitumor activity (CBR and DOR), PFS, overall survival, safety, plasma concentration of study drugs, and changes in circulating tumor DNA. Clinical trial information: NCT05548127, NCT05573555. Research Sponsor: Arvinas Estrogen Receptor, Inc.

TPS1123

Poster Session

INAVO121: Phase III study of inavolisib (INAVO) + fulvestrant (FUL) vs. alpelisib (ALP) + FUL in patients (pts) with hormone receptor-positive, HER2-negative (HR+, HER2-) PIK3CA-mutated (mut) locally advanced or metastatic breast cancer (LA/mBC). *First Author: Dejan Juric, Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA*

Background: Standard-of-care (SoC) endocrine therapy (ET) for pts with HR+, HER2- LA/mBC was transformed by combinations with cyclin-dependent kinase 4/6 inhibitors (CDK4/6is); a CDK4/6i-based combination is approved in high-risk early BC. However, in most pts, mechanisms of resistance that emerge during or after treatment with a CDK4/6i and ET combination lead to relapse/disease progression. Dysregulating mutations in *PIK3CA*, occurring in ~40% of HR+, HER2- BCs, represent a common mechanism of resistance to CDK4/6is and ET combinations. ALP (a selective PI3K α inhibitor; PI3K α i) + FUL is approved for pts with HR+, HER2-, *PIK3CA*mut LA/mBC, but its widespread implementation in clinical practice has been challenging. As such, there is a significant need to develop PI3K α is with a better therapeutic index. INAVO is a highly potent and selective PI3K α i that also facilitates the degradation of mutated PI3K α isoform. INAVO has demonstrated manageable safety/tolerability, alone and in combination with SoC treatments in HR+, HER2-, *PIK3CA*mut LA/mBC. Moreover, an ongoing Phase I trial showed that INAVO + FUL elicited encouraging preliminary antitumor activity in heavily pretreated pts, including a CDK4/6i-based regimen. **Methods:** INAVO121 (NCT05646862) is a Phase III, randomized, open-label study evaluating INAVO + FUL vs. ALP + FUL in pts with HR+, HER2-, *PIK3CA*mut LA/mBC (confirmed by circulating-tumor DNA or tumor tissue), who progressed during or after a CDK4/6i-based regimen with adequate hematologic and organ function. Up to two prior lines of systemic therapy in LA/mBC, including one line of chemotherapy are allowed. Pts are randomized 1:1 to receive INAVO (9 mg oral daily; PO QD) + FUL (500 mg intramuscularly on Days [D] 1 and 15 of Cycle [C] 1, then D1 of subsequent cycles), or ALP (300 mg PO QD) + FUL. Randomization is stratified by visceral disease (yes vs. no) and prior CDK4/6i therapy (adjuvant vs. metastatic setting). Pts will receive treatment until disease progression or unacceptable toxicity. The primary endpoint is progression-free survival (PFS) by blinded independent central review (BICR). Secondary endpoints include overall survival, BICR-objective response rate, BICR-best overall response, BICR-duration of response, BICR-clinical benefit rate, safety, tolerability, pt-reported outcomes, and pharmacokinetics. The study is open for enrollment, targeting 400 pts at ~200 sites globally. A stratified log-rank test at an overall 0.05 significance level (two-sided) will be used for the primary endpoint analysis. Median PFS will be estimated using Kaplan–Meier methodology. An independent data monitoring committee will be in place for safety and efficacy. Clinical trial information: NCT05646862. Research Sponsor: F. Hoffmann–La Roche Ltd.

TPS1122

Poster Session

VERITAC-2: A global, randomized phase 3 study of ARV-471, a proteolysis targeting chimera (PROTAC) estrogen receptor (ER) degrader, vs fulvestrant in ER+/human epidermal growth factor receptor 2 (HER2)- advanced breast cancer. *First Author: Mario Campone, Institut de Cancérologie de l'Ouest Angers-Nantes, Angers, France*

Background: ARV-471 is an oral PROTAC ER degrader that binds to and degrades wild-type ER and clinically relevant mutants. ARV-471 directly recruits the ubiquitin-proteasome system to degrade ER, whereas selective ER degraders (SERDs) indirectly cause ER degradation. In a first-in-human phase 1/2 study, ARV-471 monotherapy was well tolerated and showed clinical activity in heavily pretreated patients with ER+/HER2- advanced breast cancer. The phase 3 monotherapy dose (200 mg once daily [QD]) was chosen due to comparable efficacy and favorable tolerability relative to 500 mg QD and robust ER degradation in paired tumor biopsies. The randomized phase 3 VERITAC-2 study (NCT05654623) will compare efficacy and safety of ARV-471 vs the SERD fulvestrant in patients with ER+/HER2- advanced breast cancer after prior combination cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor therapy and endocrine therapy (ET). **Methods:** Eligible patients (aged ≥ 18 years) have a confirmed diagnosis of ER+/HER2- locoregional recurrent or metastatic breast cancer not amenable to surgical resection or radiation; 1 prior line of combination CDK4/6 inhibitor therapy and ET; ≤ 1 additional line of ET; most recent ET given for ≥ 6 months before disease progression; and radiological disease progression during or after the last line of therapy. Prior chemotherapy in the locally advanced or metastatic setting and prior fulvestrant are not permitted. Patients (N~560) are randomized 1:1 to receive 200 mg ARV-471 orally QD continuously or fulvestrant intramuscularly on days 1 and 15 in the first 28-day cycle and on day 1 in subsequent cycles; patients are stratified by *ESR1* mutation status and presence of visceral disease. The primary endpoint, progression-free survival, will be assessed by blinded independent central review in the intention-to-treat population and the *ESR1* mutation sub-population. Secondary outcome measures include overall survival, antitumor activity (objective response rate, duration of response, and clinical benefit rate), safety, and quality of life assessments. Clinical trial information: NCT05654623. Research Sponsor: Arvinas Estrogen Receptor, Inc.

TPS1124

Poster Session

CAPTOR-BC: Comprehensive analysis of spatial, temporal and molecular biomarkers predicting response and resistance to first-line treatment with ribociclib + ET in HR+, HER2- advanced breast cancer. *First Author: Peter A. Fasching, Erlangen University Hospital, Department of Gynecology and Obstetrics, Comprehensive Cancer Center Erlangen-EMN, Friedrich-Alexander University Erlangen-Nuremberg, Erlangen, Germany*

Background: The combination of an oral CDK4/6 inhibitor with endocrine therapy (ET) has become the standard first-line therapy for women with advanced HR+/HER2- breast cancer. In this context, the broadest clinical trial data are available for ribociclib, a highly selective CDK4/6 inhibitor, with three phase III trials (MONALEESA-2, -3 and -7) consistently showing a significant overall survival benefit compared to ET monotherapy regardless of treatment line, menopausal status or combination partner. However, *de novo* or acquired resistance to CDK4/6 inhibitors does occur and biomarkers predicting treatment response or providing information on resistance mechanisms are only beginning to be understood. Comprehensive identification and validation of biomarkers before and during ribociclib therapy is needed to better understand mechanisms leading to disease progression, which will be the first step towards developing novel therapies and optimizing treatment sequences. **Methods:** CAPTOR-BC (NCT054552213) is a single-arm, open-label phase IV study evaluating the combination of ribociclib and ET according to SmPC in the first-line treatment of HR+ HER2- advanced breast cancer to identify and validate molecular and non-molecular biomarkers predictive of drug response and resistance. First patient first visit occurred in October 2022 and at least 1000 patients across more than 75 sites in Germany will be enrolled until October 2025. Progression-free survival (PFS) and overall survival (OS) at 12 months are the co-primary endpoints, quality of life (QoL) and toxicity are secondary endpoints. Exploratively, a comprehensive multi-omics biomarker discovery and validation program is integrated into the study. Besides tumor tissue, liquid biopsies profiling circulating tumor (ct)DNA, ctRNA, whole blood RNA, proteins from serum and plasma, and circulating immune cells will be evaluated before, during and after treatment or upon progression to determine correlations with PFS, OS, QoL and adverse events. Clinical trial information: NCT054552213. Research Sponsor: Institut fuer Frauengesundheit GmbH; Novartis.

TPS1125

Poster Session

Ribociclib (RIB) vs. palbociclib (PAL) in patients (pts) with hormone receptor-positive/HER2-negative/HER2-enriched (HR+/HER2-/HER2-E) advanced breast cancer (ABC): A head-to-head phase III study—HARMONIA SOLTI-2101/AFT-58. *First Author: Tomás Pascual, SOLTI Cancer Research Group, Barcelona, Spain. Medical Oncology Department, Hospital Clínic de Barcelona, Barcelona, Spain*

Background: RIB and PAL are CDK4/6 inhibitors with demonstrated efficacy in terms of progression-free survival (PFS) and similar tolerability in pts with HR+/HER2- ABC when combined with endocrine therapy (ET). Only RIB has demonstrated a consistent, statistically significant, and clinically meaningful overall survival (OS) benefit across the MONALEESA (ML) phase III trials, while PALOMA trials failed to achieve similar outcome. Given effective treatments (Tx) may change underlying tumor biology (TB), it is hypothesized that RIB changes TB, enabling a better response to subsequent therapy and thus improving OS. RNA-based intrinsic subtyping reflects differences in TB and has strong prognostic and predictive value in HR+/HER2- ABC. Non-Luminal subtypes, as HER2-E and basal-like (BL), are relatively endocrine-resistant and have poorer prognosis than luminal. Tumors can switch subtypes over time to a more aggressive and less endocrine-responsive biology, which may also be reversed by effective Tx. A retrospective analysis of pooled data from ML 2/3/7 trials showed that HER2-E tumors had surprising benefit from RIB, while BL tumors did not. Pre/clinical data and indirect comparisons suggest that RIB may outperform PAL in HER2-E. Thus, choosing pts with HER2-E tumors as a means of a well defined TB with relative endocrine resistance provides the right setup for HARMONIA study to explore likely differential re-sensitization to endocrine therapy with RIB vs. PAL and ultimately testing which CDK4/6i prepares best for continued response and OS benefit. In addition, HARMONIA explores the value of earlier Tx with chemotherapy (paclitaxel) + anti PD-1 (tislelizumab) in pts with BL tumors to leverage learnings from treating ET-insensitive triple-negative BC. **Methods:** This is an international, multicenter, randomized, open-label, phase III study, using prospective pre-selection based on TB in pts with HR+/HER2- ABC, with HER2-E tumors (main cohort) and with BL tumors (exploratory cohort). HER2-E cohort will randomized pts 1:1 to RIB+ET (letrozole or fulvestrant) or PAL+ET. As per recent protocol amendment, BL cohort pts will be treated with paclitaxel plus tislelizumab, an anti PD-1 monoclonal antibody, pts may be offered to try RIB + ET first, and will remain eligible for paclitaxel + tislelizumab upon progression. Primary endpoint (EP): PFS per RECIST v1.1. Secondary EP: OS, PFS2, clinical benefit rate, duration and time to response, quality of life, and exploratory EP, including subtype switching between primary and metastatic tumor, and after trial Tx. Interim and primary EP analysis will be performed after 224 and 310 PFS events are observed (~80% power using one-sided 5% α). HARMONIA will recruit in Spain (55 sites), Portugal (5), and US (35) within SOLTI & AFT network. Clinical trial information: NCT05207709. Research Sponsor: Novartis Pharma AG.

TPS1127

Poster Session

A phase 1b/2 dose escalation and expansion study of OP-1250 in combination with ribociclib or alpelisib in patients with advanced and/or metastatic estrogen receptor-positive (ER+)/HER2-negative (HER2-) breast cancer. *First Author: Virginia F. Borges, University of Colorado Cancer Center, Aurora, CO*

Background: Therapies targeting the estrogen receptor (ER) are standard of care in the management of ER+/HER2- metastatic breast cancer (MBC) and when administered concurrently with cyclin-dependent kinase (CDK) inhibitors are the most effective first-line therapy. CDK 4/6 inhibitors plus endocrine therapy improve progression-free survival and, for some agents, overall survival for patients with MBC. However, most patients will acquire resistance, highlighting an unmet need for more effective endocrine options in ER+ disease. OP-1250 is a small molecule oral complete estrogen receptor antagonist (CERAN) and selective estrogen receptor degrader (SERD) that binds the ligand binding domain of ER and completely blocks ER-driven transcriptional activity. OP-1250 potentially inactivates both wild-type and mutant forms of ER, the latter of which confers ligand independent activity as a mechanism of resistance to standard of care endocrine therapies. In preclinical studies, OP-1250 in combination with CDK4/6 inhibitors demonstrated synergistic activity in models of both wild-type ER and those with ESR1 (the gene that encodes ER) activating mutations, and in brain metastasis. OP-1250 is orally bioavailable with a favorable pharmacokinetic (PK) profile supportive of once-daily dosing, and a low probability of drug-drug interactions, making it an attractive agent for patients with ER+/HER2- MBC. **Methods:** The study (NCT05508906) is an open-label, multicenter, 2-part study of OP-1250 in combination with either the CDK4/6 inhibitor ribociclib or the PI3K inhibitor alpelisib for patients with MBC. Eligibility includes adults with evaluable (measurable or non-measurable) ER+/HER2- recurrent, locally advanced or MBC confirmed by histology/cytology, ≤ 2 prior hormonal regimens (prior CDK4/6 inhibitors allowed) and ≤ 1 prior line of chemotherapy. Patients in the alpelisib arm must have a PIK3CA mutation. A total of 30 patients will be enrolled in each arm. The dose escalation cohorts will evaluate the safety and PK of varied OP-1250 doses (30mg, 60mg, or 120mg) administered orally (PO) every day (QD) in combination with approved dosages of either ribociclib 600 mg PO QD or alpelisib 300 mg PO QD to identify the recommended phase 2 doses (RP2D). The dose expansion cohorts will assess additional safety and PK parameters and further explore the anti-tumor activity of OP-1250 in combination with ribociclib or alpelisib. Tolerability, safety and PK of OP-1250 in combination with ribociclib or alpelisib constitute the primary endpoints. Overall response rate, clinical benefit rate and duration of response are key secondary endpoints. Enrollment at approximately 20 sites in the United States and Australia is ongoing. Clinical trial information: NCT05508906. Research Sponsor: Olema Oncology; Novartis.

TPS1126

Poster Session

Harnessing olaparib, palbociclib, and endocrine therapy: A phase I/II trial of olaparib, palbociclib and fulvestrant in patients with BRCA mutation-associated, hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer (HOPE). *First Author: Alexandra Torres, University of Pennsylvania-Abramson Cancer Center, Philadelphia, PA*

Background: Hormone receptor-positive (HR+) metastatic breast cancer (MBC) in patients (pts) with germline or somatic *BRCA1* or *BRCA2* (g/s*BRCA1/2*) mutations has dual drivers: hormone receptor signaling and homologous recombination deficiency. The PALOMA-3 trial showed superiority of fulvestrant (F) with palbociclib (P) compared to F alone. The OlympiAD trial showed the poly-ADP ribose polymerase inhibitor (PARPi) olaparib (O) to be superior to chemotherapy in *BRCA1/2*-associated MBC. However, treatment resistance inevitably develops; targeting dual therapeutic drivers concurrently may delay or circumvent resistance. O and P have overlapping hematologic toxicity and the safety of combined O, P and F is unknown. The tolerability of O + P is particularly relevant given the emergence of potentially less myelosuppressive PARPi. **Methods:** HOPE (NCT03685331) is a phase I/II trial to evaluate safety and efficacy of O, P and F in pts with g/s*BRCA1/2*-associated, HR+ MBC. Eligible pts have an ECOG performance status 0-1, measurable/evaluable breast cancer, any/no prior endocrine therapy, and 0-2 lines of chemotherapy prior to MBC diagnosis, or for MBC if no progression during therapy. Prior PARPi and CDK4/6i are permitted on phase I, and are permitted during phase II if there was no progression on them. Treatment (28-day cycles) consists of: O orally twice daily continuously; F 500mg intramuscularly on day 1 of each cycle plus load; and P orally once daily on days 1-21. Phase I begins with a 28-day safety run-in of O and F alone. O and P doses are based on dose level (DL): DL 0 (starting level), O 300mg, P 75mg; DL 1, O 300mg, P 100mg; DL 2, O 300mg, P 125mg; DL-1, O 250mg, P 75mg and DL-2, O 200mg, P 75mg. For phase II, O and P will be dosed at MTD. Pts have tissue collection at baseline and peripheral blood cfDNA analysis at baseline, at progression, and at all scan timepoints (every 3 cycles). Phase I primary endpoint is MTD. A 3+3 dose escalation design is used with a 30% rate of dose limiting toxicity (DLT) deemed acceptable, and 6 patients treated at a dose for it to be declared MTD. A minimum of 2 and a maximum of 18 patients will be enrolled on the phase I. Phase II primary endpoint is PFS using Kaplan-Meier methods and secondary efficacy endpoints are objective response rate and 24-week clinical benefit rate. Phase II will evaluate 54 subjects to provide 80% power to detect an increase in PFS from 7 months with O monotherapy to 10 months. Exploratory objectives include examination of baseline tissue for PARPi predictive biomarkers and measures of tumor immunogenicity as well as serial serum evaluation for reversion mutations. Enrollment is ongoing. Clinical trial information: NCT03685331. Research Sponsor: AstraZeneca, Pfizer; Susan G. Komen Career Catalyst Award.

ABSTRACT
WITHDRAWN

TPS1129

Poster Session

The Amelia-1 study: A phase 1b/2 trial of evexomostat (SDX-7320) plus fulvestrant and alpelisib in patients with advanced breast cancer at risk for alpelisib-induced hyperglycemia. *First Author: Peter Cornelius, Syndevrx Inc., Cambridge, MA*

Background: Alpelisib, a selective PI3K p110 α inhibitor, was approved for breast cancer patients with PIK3CA mutations. An on-target toxicity of alpelisib is hyperglycemia and patients with baseline insulin resistance/elevated HbA1c are at greater risk of developing grade 3/4 hyperglycemia after receiving alpelisib. Restoring insulin sensitivity and reducing systemic insulin levels improved the efficacy of alpelisib in animal models of breast cancer. Evexomostat is a polymer-drug conjugate of a novel small molecule methionine aminopeptidase 2 (MetAP2) inhibitor. In normal mice, it reduced alpelisib-induced hyperglycemia/hyperinsulinemia and in an animal model of breast cancer synergized with alpelisib to regress tumor growth. In a Phase 1 trial, evexomostat improved insulin resistance in patients with elevated baseline insulin, reduced angiogenic factors in patients with elevated baseline levels, increased the insulin-sensitizing adipokine adiponectin and showed anti-metastatic effects in patients with advanced solid tumors. **Methods:** This is a phase 1b/2, open-label, single-arm pilot study (NCT05455619) in postmenopausal women with HR+, HER2- metastatic breast cancer with a PIK3CA mutation who progressed following treatment with endocrine therapy plus a CDK4/6 inhibitor and who are at risk for hyperglycemia (HbA1c between 5.5 and 6.4% inclusive). The primary goal is to determine the safety of evexomostat plus alpelisib and fulvestrant (the "triplet therapy"), including the severity and number of hyperglycemic events, as well as anti-tumor benefit. The starting dose of evexomostat in the triplet therapy is 36 mg/m² (n=6; one dose below the monotherapy MTD of 49 mg/m²). Once the MTD of evexomostat in the triplet therapy has been defined, up to 20 patients will be enrolled at that dose. An additional 20 patients may be enrolled to further characterize the safety and anti-tumor effect of the triplet therapy (up to 52 patients). This trial is open to accrual at multiple sites in the USA. Safety analysis includes the type, frequency, and severity of treatment-emergent adverse events (TEAEs) per NCI CTCAE, v5, and the number and proportion of patients with grade 3 or 4 hyperglycemia during the first 2 cycles of therapy, with an estimate of the exact upper one-sided 97.5% confidence bound. Efficacy analyses include objective response rate (ORR, consisting of complete response (CR) and partial response (PR)). The number of patients without disease progression six months from the start of the triplet therapy will be assessed. The CBR of CRs, PRs plus stable disease $\geq$ 24 weeks from C1D1 will be calculated. Overall survival data will be summarized as available. QoL will be analyzed according to functional scores and recommendations in the EORTC scoring manual. ECOG performance status and change from baseline will be summarized. Clinical trial information: NCT05455619. Research Sponsor: SynDevRx, Inc.

TPS1131

Poster Session

The ARETHA study: A phase 2 randomized control trial of eribulin with evexomostat (SDX-7320) or placebo for patients with metastatic triple-negative breast cancer (TNBC) and metabolic dysfunction. *First Author: Sherry Shen, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: The prognosis for advanced/metastatic TNBC remains poor and novel therapeutic strategies are urgently needed. Insulin resistance and obesity contribute to TNBC progression and are independent predictors of worse survival. Methionine aminopeptidase 2 (MetAP2/p67) is overexpressed in many tumor types including breast. MetAP2 inhibitors exhibit broad anti-tumor activity and attenuate the effects of metabolic dysfunction on tumor growth. Evexomostat (SDX-7320) is a second-generation MetAP2 inhibitor that improved insulin sensitivity, reduced fat mass, and normalized adipokine levels in preclinical models of obesity and reduced tumor growth in TNBC preclinical models. In phase 1 trials, evexomostat monotherapy partially restored insulin sensitivity, reduced adipokines, and showed anti-metastatic effects in patients with advanced solid tumors. The goal of this phase 2 study is to test whether evexomostat prevents worsening of insulin resistance and augments tumor response in patients with metastatic TNBC and metabolic dysfunction in combination with eribulin chemotherapy, a standard of care treatment option after prior anthracycline and taxane exposure. **Methods:** This is a single-center phase 2 randomized control trial of evexomostat, a MetAP2 inhibitor, and eribulin chemotherapy. Key eligibility criteria include metastatic TNBC, measurable disease or $\geq$ 1 predominantly lytic bone lesion, baseline hemoglobin A1c $>$ 5.5% and/or BMI $\geq$ 30 kg/m², and $\leq$ 2 prior lines of therapy in the advanced/metastatic setting. Patients with uncontrolled or insulin-dependent type II diabetes, or who require combination anti-hyperglycemic therapy are excluded. During the safety run-in period, 15 patients will be assigned to receive evexomostat 49 mg/m² Q2 weeks and eribulin 1.4 mg/m² on days 1 & 8 of a 21-day cycle. Upon safety confirmation, an additional 40 patients will be randomized 2:1 to receive evexomostat or placebo with eribulin. The primary endpoint is metabolic efficacy assessed by change in Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) score. Secondary endpoints include objective response rate, progression-free survival, safety and tolerability, patient-reported outcomes, and changes in metabolic markers and body composition. Historically, HOMA-IR scores double during chemotherapy, and this trial will test whether evexomostat attenuates the expected HOMA-IR rise. This trial will have $>$ 90% power to detect a difference between a 1.5-fold change in HOMA-IR in the control arm vs. no change in the evexomostat arm while controlling the Type I error at 5%. As of Feb 2022, 3 patients are enrolled; total accrual of 61 patients is planned with a goal of 55 evaluable patients. Clinical trial information: NCT05570253. Research Sponsor: SynDevRx, Inc.

TPS1130

Poster Session

A phase 2 randomized study of magrolimab combination therapy in adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (mTNBC): ELEVATE-TNBC. *First Author: Natalie Rainey, Cairns and Hinterland Hospital and Health Service, Cairns, QLD, Australia*

Background: Improving outcomes in patients (pts) with TNBC remains a high unmet need. Immune checkpoint inhibitors (ICIs) + chemotherapy (chemo) is approved for newly diagnosed pts with PD-L1+ tumors. Further, single-agent sacituzumab govitecan (SG), a Trop-2-directed antibody-drug conjugate, is approved for pts with mTNBC who received $\geq$ 2 prior systemic therapies ($\geq$ 1 for metastatic disease). However, more options are needed for pts with PD-L1-negative mTNBC and for those with disease progression on chemo $\pm$ ICI. Magrolimab is a monoclonal antibody that blocks CD47, a "don't eat me" signal often overexpressed on TNBC cells. Magrolimab blockade of CD47 induces macrophage-mediated phagocytosis of tumor cells and has shown preclinical activity and promising clinical efficacy in hematologic malignancies. Certain chemos, including taxanes, enhance phagocytic signals on tumor cells, which may lead to synergistic antitumor activity with magrolimab. This study is evaluating the safety, tolerability, and efficacy of magrolimab + nab-paclitaxel/paclitaxel or + SG in mTNBC. **Methods:** This open-label study has 2 cohorts (C) with safety run-in and phase (ph) 2 portions. Eligible pts are $\geq$ 18 y with measurable disease per RECIST 1.1. C1 pts have PD-L1-negative untreated mTNBC. C2 pts have mTNBC and received 1 prior line of therapy in the advanced setting, a taxane in the neoadjuvant/adjuvant or metastatic setting, and, if PD-L1+, an ICI. Exclusion criteria include active central nervous system disease, RBC transfusion dependence, and prior treatment with CD47/SIRP α -targeting agents. C1 assesses nab-paclitaxel/paclitaxel + magrolimab (safety run-in) or $\pm$ magrolimab (ph 2; randomized 1:1). C2 assesses magrolimab + SG (safety run-in and ph 2). In C1 safety run-in, magrolimab is given intravenously (IV) as a 1-mg/kg priming dose on day (D) 1 of cycle 1 to mitigate on-target anemia, followed by 30 mg/kg (cycle 1: D8, 15, 22; cycle 2: D1, 8, 15, 22; cycle 3+: D1, 15) (28-d cycles). In C2 safety run-in, pts receive a 1-mg/kg priming dose on D1, followed by 30 mg/kg (cycle 1: D8, 15; cycle 2: D1, 8, 15) and 60 mg/kg (cycle 3+: D1) (21-d cycles). The recommended ph 2 dose (RP2D) is determined in the safety run-in, with de-escalation if prespecified dose-limiting toxicity (DLT) criteria are met. Once RP2D is determined, the ph 2 cohorts will follow their respective dose schedules. Nab-paclitaxel/paclitaxel and SG are given IV per standard of care. The primary endpoints are incidence of DLTs, adverse events, and abnormal lab results by CTCAE v5.0 (safety run-in); progression-free survival by RECIST 1.1 (ph 2 C1); and confirmed objective response rate by RECIST 1.1 (C2; pooled safety run-in and ph 2). Planned enrollment is $\approx$ 144 pts. Clinical trial information: NCT04958785. Research Sponsor: Gilead Sciences, Inc.

TPS1132

Poster Session

A randomized phase II clinical trial of talazoparib maintenance therapy in patients with triple-negative breast cancer who showed platinum-sensitivity on first- or second-line platinum-based chemotherapy: KCSG BR21-10. *First Author: Joohyuk Sohn, Division of Medical Oncology, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, South Korea*

Background: A potent PARP inhibitor, talazoparib, demonstrated superior clinical activity compared to standard chemotherapy in germline BRCA1/2-mutant advanced breast cancer patients. However, the role of talazoparib treatment in BRCA1/2 wild-type triple-negative breast cancer (TNBC) patients remains undefined, although high incidence of homologous recombination deficiency (HRD) is one of the major characteristics of the TNBC. Previous studies indicated clinical responsiveness to platinum agents is a useful surrogate for HRD that may predict favorable PARP inhibitor response. Here, we present a phase II study to test talazoparib maintenance therapy in germline BRCA1/2 mutation unselected advanced TNBC patients after platinum-based chemotherapy. **Methods:** The KCSG BR21-10 study (NCT04755868) is a randomized double-blind placebo-controlled phase II clinical trial of talazoparib maintenance therapy in metastatic TNBC patients whose tumor showed platinum-sensitivity to first- or second-line platinum-based chemotherapy. The criteria for platinum-sensitivity were set as follows: remaining complete response (CR), partial response (PR), or stable disease (SD) after 6 to 9 tri-weekly doses or 18 to 27 weekly doses of platinum-based chemotherapy. The eligible TNBC patients are enrolled to the trial after completion of platinum-based therapy and 1:1 randomized to receive talazoparib (once daily 1.0 mg) or placebo maintenance therapy. The patient with any germline BRCA1/2 mutation status is eligible, and randomization stratification factors include line of platinum-based chemotherapy, response to platinum-based chemotherapy, and germline BRCA1/2 mutation status. The talazoparib/placebo maintenance treatment is initiated within 8 weeks after the last platinum chemotherapy. At the time of progression of disease, unblinding can be performed and patients in placebo arm may be eligible for crossover to talazoparib single treatment. The primary endpoint is progression-free survival (PFS) after randomization by RECIST 1.1, and the key secondary endpoints are overall survival, PFS2, objective response rate, adverse events by CTCAE 5.0 criteria, and quality of life. We also planned exploratory study to find predictive biomarker by tumor tissue and blood analysis. The median PFS from the randomization is expected to be 3 months in the placebo maintenance arm and we expect that talazoparib maintenance will improve PFS with hazard ratio of 0.65. It is predicted that a total of 206 patients (103 patients in each arm) are required with the α of 0.05 and power of 0.8 (1- β) by two-sided test, considering monthly 3% dropout rate. Currently, 23 of planned 206 patients have been enrolled. Clinical trial information: NCT04755868. Research Sponsor: Pfizer.

TPS1133

Poster Session

Phase I/II study of stereotactic radiosurgery with concurrent olaparib followed by adjuvant durvalumab and physician's choice systemic therapy in patients with breast cancer brain metastases. *First Author: Colette Shen, University of North Carolina at Chapel Hill, Chapel Hill, NC*

Background: Despite progress in the treatment of brain metastasis for HER2+ breast cancer, outcomes for patients with HER2-negative breast cancer brain metastases remain poor. Current standard of care consists of local therapies, including surgery and radiotherapy, followed by systemic therapy. Preclinical studies show inhibitors of poly(ADP-ribose) polymerase (PARP) are effective in combination with radiation therapy as a DNA damage response inhibitor. Triple-negative breast cancer (TNBC) has higher rates of homologous recombination deficiency compared to other breast cancer subtypes, and together with HER2-negative, BRCA-mutated breast cancer would be particularly sensitive to PARP inhibition. PARP inhibition has also demonstrated promising efficacy combined with immunotherapy in patients with germline BRCA-mutant and metastatic TNBC in clinical trials (MEDIOLA, TOPACIO). In addition, immunotherapy with stereotactic radiosurgery (SRS) is associated with favorable intracranial control and survival in patients with brain metastases. We hypothesize that this biologically-driven combination will enhance local control of SRS-treated brain metastases through synergy with PARP inhibition, while controlling micro-metastatic disease in the brain and extracranial sites via potentiation of the immune response. **Methods:** We are conducting a multi-institution, Phase I/II trial of SRS plus olaparib, followed by durvalumab (with physician's choice systemic therapy), for patients with TNBC (any BRCA status) or HER2-negative with BRCA-mutated (germline or somatic) breast cancer brain metastases [NCT04711824]. A total of 41 patients are planned for enrollment at 8 sites. The primary objectives are to evaluate safety and tolerability (Phase I) and determine intracranial disease control at 6 months (Phase II) of this treatment combination. Secondary objectives include determining clinical activity via intracranial and global progression-free survival, overall survival, and intracranial and extracranial response rate. Exploratory objectives will assess potential biomarkers of treatment response, including changes in circulating tumor cells and DNA in blood and cerebrospinal fluid, germline and tumor mutations in DNA repair pathway genes, and PD-L1 expression, as well as quality of life and patient-reported outcomes. A surgical sub-study (n=5) will evaluate olaparib concentration/distribution in resected brain metastases. As of January 2023, cohort 1 of phase I has been completed without dose-limiting toxicity. Clinical trial information: NCT04711824. Research Sponsor: AstraZeneca.

TPS1134

Poster Session

Phase II study of a PARP inhibitor in somatic *BRCA1/2* mutant metastatic breast cancer (MBC). *First Author: Neelima Vidula, Harvard Medical School, Massachusetts General Hospital, Boston, MA*

Background: While PARP inhibitors are approved for germline *BRCA1/2* mutant MBC, and are shown to improve both patient quality of life and progression-free survival (PFS), as a well-tolerated oral targeted therapy, their utility is limited as germline *BRCA1/2* mutations are present in 5-10% of breast cancer. We hypothesize that somatic *BRCA1/2* mutations may also respond to PARP inhibitors. We have demonstrated that somatic *BRCA1/2* mutations can be identified by cell-free DNA and tumor tissue genotyping assays in patients who are not known germline *BRCA1/2* carriers, and some of these are pathogenic. Using a circulating tumor cell culture model developed from a patient with a pathogenic somatic *BRCA1* mutation, we have shown that a PARP inhibitor can induce cell growth inhibition paralleling germline *BRCA1/2* mutant lines. In this trial, we are evaluating the efficacy of a PARP inhibitor in somatic *BRCA1/2* mutant MBC. Our work may help expand the number of patients with MBC who benefit from a PARP inhibitor. **Methods:** In this phase II investigator-initiated clinical trial, 30 patients with MBC harboring somatic *BRCA1/2* mutations identified via a CLIA certified cell-free DNA or tumor tissue genotyping assay are being enrolled at 7 academic centers. Mutations are evaluated for pathogenicity using validated genomic databases such as ClinVar by genetic counselors prior to enrollment. Patients may have metastatic triple-negative or hormone receptor positive (HR+)/HER2- breast cancer progressing on 1 prior therapy, and should not be known germline *BRCA1/2* carriers. Any number of prior therapies are allowed but patients must have adequate baseline performance status and organ function. Patients are treated with talazoparib 1 mg/day (a PARP inhibitor with high potency) until disease progression. Imaging (CT chest abdomen and pelvis as well as bone scan) occurs at baseline and every 3 months for disease assessment. The primary endpoint is progression-free survival (RECIST 1.1). This study has 81% power to demonstrate that talazoparib is associated with "success" (PFS > 12 weeks) in ≥53% patients (4% alpha). Key secondary endpoints include objective response rate and toxicity (NCI CTCAE v 5.0). Correlative studies include collecting cell-free DNA at baseline and monthly to identify the emergence of resistance mutations and impact of *BRCA1/2* reversion mutations and mutant allele fraction on response, and evaluating the Cancer Risk B (CR-B) assay, a novel method that identifies double-strand break repair mutations in circulating blood cells. The study (NCT03990896) is open at Massachusetts General Hospital, MD Anderson, Emory, University of California San Francisco, and Northwestern, and pending activation at Vanderbilt and Cornell, with 11 patients enrolled as of 2/2023. Clinical trial information: NCT03990896. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology; Pfizer ASPIRE Award.

1500

Oral Abstract Session

AI blood signature in common blood tests for detection of gastric cancer in a cohort of 190,000 individuals. *First Author: Tsz Chun Bryan Wong, The Hong Kong University of Science and Technology, Hong Kong SAR, Hong Kong*

Background: Gastric cancer is the fourth leading cause of cancer death worldwide. Lack of symptoms in the early stage of disease leads to delayed presentation and low overall survival rate. Early detection is key, but there is not yet an established test for non-invasive gastric cancer screening. Routine blood test panels, including complete blood count, liver function, renal function and clotting profiles, could be potentially useful in reflecting bodily processes related to cancer. Current literature and territory-wide statistical data analyses from Hong Kong have shown these subtle changes and differences in measured levels of subcomponents between individuals with and without gastric cancer, that are not recognized clinically, form recognizable patterns distinct to gastric cancer. In this study, we hypothesized that gastric cancer signatures could be identified in routine blood data. Deep learning AI algorithms are used to identify the gastric cancer signature. Results from testing and validation of the identified routine blood signature using a Big Clinical Data cohort are reported. **Methods:** This is a territory-wide healthcare database study using data from Hong Kong Hospital Authority data collaboration laboratory. All patients prescribed with medications for dyspepsia and with all blood tests components (CBC, LFT, RFT, clotting function) available in the period between 2004-2015 inclusive were included. In the period, data from 2004 to 09 and 2011 to 14 were used as training cohort and the rest were used as testing cohort. A blood gastric cancer signature was generated using deep learning AI algorithms, and applied to predict gastric cancer in BigData population. **Results:** 193,117 patients were included in the captioned period, in whom 4,790 patients were diagnosed to have gastric cancer. 151,449 (3,815 pts with gastric cancer and 147,634 pts disease free) patients were included in training cohort. In the testing cohort in 2010 and 2015 (975 pts with gastric cancer and 40,693 pts disease-free), the tumor signature yielded a sensitivity of 0.79, specificity of 0.99, positive predictive value of 0.95 and a negative predictive value of 0.99. **Conclusions:** The hypothesis of the presence of a distinctive gastric cancer signature from parameters in routine blood test data is tested and validated in a large population cohort with dyspepsia. The signature has high accuracy and high sensitivity with low false positive and false negative rates. Multicenter prospective testing is being conducted in cohort indicated for OGD in Hong Kong. Research Sponsor: None.

Validation Cohort	N	True positive	False positive	True negative	False negative
2000	238	10	1	226	1
2010	17058	355	9	16612	82
2015	24610	419	28	24044	119

1502

Oral Abstract Session

Childhood leukemia survival in the US-Mexico border: Building sustainable leukemia care using health systems strengthening models. *First Author: Paula Aristizabal, University of California San Diego, San Diego, CA*

Background: Pediatric leukemia outcomes are poor in most low-and middle-income countries (LMIC) and exacerbated by healthcare systems ill-equipped to manage cancer. Effective leukemia management in LMIC involves curating epidemiologic data; providing healthcare workforce specialty training; developing evidence-based treatments and supportive care; safeguarding access to medications and equipment; providing patient and family psychosocial and financial support; partnering with non-governmental organizations, and ensuring treatment adherence. **Methods:** We describe the implementation of a collaborative program to achieve sustainable high-quality care for children with leukemia in a unique border health setting. In 2013, in a partnership between North-American and Mexican institutions, we used the health systems strengthening model developed by the World Health Organization (WHO) *Framework for Action* with domains in Services delivery, Workforce, Information systems, Access to essential medicines, Financing, and Leadership and Governance to implement a sustainable program aimed at improving acute lymphoblastic leukemia (ALL) outcomes at a public, referral hospital in the US-Mexico border region. We evaluated program sustainability indicators, and prospectively assessed clinical features, risk classification, and survival outcomes in children with ALL at Hospital General in Tijuana, Mexico from 2008-2012 (pre-implementation) and from 2013-2017 (post-implementation). **Results:** Our approach led to a fully-staffed leukemia service, sustainable training programs, evidence-based, data-driven projects to improve clinical outcomes, and funding for medications, supplies and personnel through local partnerships. Pre-implementation and post-implementation 5-year overall survival for children with standard-risk and high-risk ALL improved from 52% to 82% ($P = 0.023$) and from 46% to 76% ($P = 0.031$), respectively. All sustainability indicators significantly improved between 2013 and 2017. **Conclusions:** By using a health systems strengthening approach, we improved leukemia care and survival in a public Mexican hospital in the US-Mexico border region. The demonstrated increase in overall survival across a decade after the implementation of our program validates the use of the health systems strengthening models, as they are not only efficacious in improving clinical outcomes, but also serve as financially and organizationally means of building sustainable capacity. Our model serves as an example for future international partnerships aimed at sustainably improving cancer outcomes in LMIC. Future research should evaluate best practices in establishing global health collaborations with particular attention paid towards the individual circumstances that impact healthcare delivery locally in each unique community. Research Sponsor: Rady Children's Hospital San Diego, Patronato Foundation.

1501

Oral Abstract Session

Large-scale observational prospective cohort study of a multi-cancer early detection (MCED) test in symptomatic patients referred for cancer investigation. *First Author: Brian D Nicholson, University of Oxford, Oxford, United Kingdom*

Background: Delays in cancer diagnosis can lead to increased mortality, leading to specialized diagnostic pathways for symptomatic patients when cancer is suspected. Identification of circulating tumour DNA can stratify individuals into those more or less likely to have cancer and predict the cancer origin. This could both expedite cancer diagnosis and reduce harm and inefficient investigation in those who do not have cancer. We evaluated the performance of a next-generation sequencing MCED test (GRAIL, LLC) using cell-free DNA (cfDNA) isolated from whole blood in symptomatic patients referred to cancer diagnostic clinics by their primary care physician. **Methods:** Patients referred for urgent imaging, endoscopy or other diagnostic modalities to investigate symptoms suspicious for cancer were invited to take part. Participants with non-specific symptoms or being tested for lung, gynaecological, upper gastrointestinal (GI) or lower GI cancers gave a blood sample on the day they attended for urgent standard of care investigations. cfDNA was isolated from blood samples and stored until the MCED test was performed in batches, blinded to clinical outcome. The test's predictions (cancer signal detected yes/no; predicted signal origin) were compared with the diagnosis obtained by standard care to establish the positive and negative predictive value (PPV & NPV), sensitivity and specificity across the whole study population, by referral pathway, and by presenting symptom. In addition, sensitivity was analysed by cancer site and stage. **Results:** 6238 participants were recruited over 5 months from the 5 clinical pathways at 44 hospital sites in England and Wales. 5461 individuals had an MCED test result and diagnostic outcome and were evaluable. Mean age was 62.1 years (SD, 13.8), 3609 (66.1%) female, 2533 (46.4%) current or former smokers. 368 (6.7%) evaluable patients had a cancer diagnosed. The MCED test detected a cancer signal in 323 cases, 244 in whom cancer was diagnosed and 79 where it was not, yielding a PPV of 75.5% (95% CI 70.5-80.1%), NPV 97.6% (97.1-98.0%), sensitivity 66.3% (61.2-71.1%), and specificity 98.4% (98.1-98.8%). Sensitivity increased with increasing age and cancer stage, from 24.2% (16.0-34.1%) in Stage I to 95.3% (88.5-98.7%) in Stage IV. Sensitivity 80.4% (66.1-90.6%) and NPV 99.1% (98.2-99.6%) were highest for patients referred with symptoms qualifying for the upper GI pathway. **Conclusions:** This is the first large-scale prospective evaluation of an MCED test in a symptomatic population. These data provide the basis for a prospective, interventional study in patients presenting to primary care with non-specific signs and symptoms with low, but higher than background, probability of being due to cancer. Study data are also being used to enhance the negative predictive value of the current MCED classifier for a symptomatic population. Clinical trial information: ISRCTN10226380. Research Sponsor: GRAIL; UK NIHR.

1503

Oral Abstract Session

Analysis of patient-physician portal secure message content and the associated cost savings in oncology practice. *First Author: Brandon Anderson, San Francisco Medical Center, Kaiser Permanente Northern California, San Francisco, CA*

Background: The consistent utilization of secure messaging ("SM") since the onset of the COVID-19 pandemic has provided cancer patients with unprecedented access to their medical providers, resulting in reduced out-of-pocket costs for patients at the expense of increased workload for oncologists. Herein we analyze oncology SM content and report estimated cost savings from reduced traditional clinic visits. **Methods:** This population-based retrospective cohort study examined the content of patient-initiated SM threads exchanged through the patient portal website or app over a one-year period (6/1/21 to 5/31/22) at 22 Kaiser Permanente Northern California Oncology practices. A trained physician researcher reviewed a random sample of 500 SM threads and categorized them by message content type, acuity, and appropriate level of service. Standard costs were applied using the average of 2021 and 2022 Center for Medicare Services physician fee schedule and US patient average specialty copayment. **Results:** During the study period, 49,230 patients initiated 398,835 unique SM threads to 238 oncology providers. The average number of replies to patients' initial messages was 2.6, with a mode of 1 (maximum 36). Of the SM threads reviewed, only 28.0% required oncologist expertise. Based on thread content, the remaining 72.0% may have been better managed by a nurse (35.4%), medical assistant (29.2%), primary care doctor (6.2%), or a different subspecialty provider (1.2%). Emergency care was required in 2.8% of the total threads reviewed. Significant medical care was provided to patients in 26.0% of the total SM threads which would traditionally require a billable visit (i.e., in-person, telephone, or video). We estimate that these clinical actions may represent 4,299,281.77 of savings in medical care (based on traditional 10-19-minute visits), and 4,562,672.40 in potentially avoided out-of-pocket co-pay costs for patients. **Conclusions:** Increased utilization of remote medical care and specifically SM has recently generated additional workload for oncologists that may have been more appropriately managed by alternative providers. The magnitude of unreimbursed medical care provided via SM and the use of SM by cancer patients for emergent medical situations creates an urgent need for new models to assist with practice management. An alternative architecture for triaging, managing, and billing SM that utilizes artificial intelligence, machine learning algorithms, or medical assistants, nurses, and other providers could help manage the burden experienced by oncologists. Research Sponsor: None.

1504

Oral Abstract Session

Prior authorizations for oral anticancer drugs and delayed prescription fills. *First Author: Michael Anne Kyle, Harvard Medical School (Boston, MA), Boston, MA*

Background: Oral anticancer drugs have proliferated in recent decades. These drugs are increasingly approved based on provisional data via the FDA's accelerated approval pathway and have high prices, motivating payers to closely monitor how they are used. We assessed use of prior authorization (PA) of oral cancer drugs for Medicare Part D beneficiaries and assessed the impact of PA on delays in prescription fills. **Methods:** Using Medicare Part D formulary and claims data from 2010-2019, we described trends in Part D plans' use of PA for oral oncology drugs, identified using the Oncology Care Model drug list (excluding hormonal therapies). We then examined changes in access to imatinib after the introduction of a new PA. We focused on imatinib because it is a highly effective first-in-class drug with a generic entrant in 2016. We compared Part D beneficiaries continuously enrolled in a plan with a policy change (new PA introduced) or a control plan (no change) in the 120 days before and after the policy change or equivalent date (control) and had at least three 30-day imatinib fills in the pre period. This restriction aimed to identify individuals filling regularly and plausibly expected to continue the drug. For each index fill in the post period, we calculated predicted fill (date of previous fill + days supply received). Our outcome variable was the difference (in days) between predicted and observed index fill date, censored at 120 days for post-period observations without an observed fill. We used an event study to model predicted vs. actual time to first fill following a policy change (new PA) relative to the controls (no change), adjusting for patient age, sex, low-income subsidy, average number of days between pre-period fills, year of fill, and plan type (standalone or Medicare Advantage). **Results:** The proportion of oral anticancer drugs requiring a PA increased from 52.8 to 96.3% from 2010 to 2019. For imatinib, PA increased from 65% to 89% from 2010-16, the year generic imatinib entered. PA for generic imatinib was 95% on market entry. In the imatinib event study sample, there were 1,354 index fills for patients. Unadjusted mean delay in index fill was 40 days for new PA and 15 days for controls; median difference was 4 and 3 days, respectively. Discontinuation was comparable: 9.3% (new PA) vs. 9.5% (control). The adjusted difference between predicted and actual fills for new PA was 20.3 days (95% CI 6.5-34.2, $p < 0.004$). **Conclusions:** Use of PA for oral oncology drugs has increased substantially over 10 years. In the setting of high prices and provisional outcomes data, PA may be appropriate. However, PA may delay fills, even for high-value drugs like imatinib. Oral anticancer drug adherence is an NCI priority; further study is warranted to identify opportunities to reduce administrative burden of PA and lessen barriers in access to effective medications. Research Sponsor: U.S. National Institutes of Health.

1506

Oral Abstract Session

Observational prospective study of physical activity in patients with cancer to define an objective performance status (OPS). *First Author: Eva Ruiz-Hispán, University Hospital Fundacion Jimenez Diaz, Madrid, Spain*

Background: Clinical trials in patients with advanced cancer rely on a good selection of candidates based on their functional status. The Eastern Cooperative Oncology Group (ECOG) Performance Status is the most frequently used in adult patients and is based on the subjective impression of the clinician during the interview with the patient. The current use of wearable devices will allow clinicians to assess the functional status of candidates for a clinical trial in a more objective way. We aim to define an "Objective Performance Status" (OPS) by measuring the daily physical activity of patients with metastatic cancer and correlating it with the classical prognostic variables. **Methods:** We prospectively measured daily physical activity with a wearable device in 111 patients with metastatic cancer during the screening period for a phase 1 clinical trial to avoid treatment interference with the functional status. Daily steps/distance and sleeping hours were measured and correlated with overall survival (OS) to define the OPS. **Results:** Full data was available for 70 patients. Median survival was gradually shorter as physical activity decreases (HR 5.76 (95% CI 2.98-11.1) $P < 0.001$). The cut off selected to define the OPS was determined by univariate survival analysis and showed that patients who walk less than 1200 meters per day have 5 times the risk of mortality (poor OPS). Median OS was 3.2 months (95% CI 2.5-5.8) $P < 0.001$ for patients with poor OPS and 11.2 months for patients with good OPS (95% CI 7.2-31.3 $P < 0.001$). **Conclusions:** The objective assessment of performance status (OPS) using a wearable device to monitor the physical activity in patients with cancer is an independent prognostic factor for survival and is an objective predictor of mortality. Research Sponsor: IT department, Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain.

Univariable cox regression models.

Variable	HR	(95%CI)	P-value
Distance (meters) (<1200 vs ≥1200)	5.76	(2.98, 11.1)	<0.001
Steps (<1850 vs ≥1850)	5.28	(2.72, 10.2)	<0.001
Total hours sleep (<7.4 vs ≥ 7.4)	1.15	(0.63, 2.07)	0.644
ECOG (0 vs 1)	2.43	(1.38, 4.27)	0.002
RMH score (0-1 vs 2-3)	1.84	(0.97, 3.46)	0.060

1505

Oral Abstract Session

SCORE: A multisite randomised controlled trial evaluating shared care for colorectal cancer survivors. *First Author: Michael Jefford, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia*

Background: Few studies have considered shared follow up (FU) care (SC) between oncologists and primary care providers (PCPs). SCORE is the first large RCT of SC for survivors of colorectal cancer (CRC). Primary objective: compare SC vs UC on the EORTC QLQ-C30 Global Health Status/Quality of Life (GHQ-QoL) scale to 12 months (mo). Secondary objectives: compare SC vs UC on QoL; patient (pt) perceptions of care; costs and clinical care processes (CEA tests, recurrences). **Methods:** Pts had completed treatment for stage I-III CRC within 3 mo, had a PCP, and no prior cancer. After pt consent, PCPs could opt out. SC replaced 2 routine oncologist visits with PCP visits and included a survivorship care plan, concerns checklist and PCP management guidelines. PCPs were asked to request CEA tests at 3 and 9 mo visits. Assessments were at baseline (BL), 6 and 12 mo FU. Difference (diff) between groups on GHQ-QoL to 12 mo estimated from a mixed model for repeated measures (MMRM). Non-inferiority evaluated by comparing the lower limit of the two-sided 95% confidence interval (CI) for the estimated diff (SC-UC) against a non-inferiority margin (NIM) of -10 points. Per-protocol population (PPP) comprised all randomised pts with ≥ 1 post-BL questionnaire (6 +/- or 12mo) and, for SC, ≥ 1 of the PCP visits. **Results:** 150 pts were randomised to SC (N=74) or UC (N=76); 11 PCPs had declined. Median age 63 years, 39% women, 24% had radiation. Primary site: colon (59%), rectum (32%), overlapping (9%). 138/150 (92%) had BL and ≥ 1 post-BL GHQ-QoL score. 65/74 (88%) of SC pts attended 3- and/or 9-mo PCP visits. The mean (SD) GHQ-QoL scores at baseline / 6 mo / 12 mo were: 69 (18.7) / 69 (21.2) / 72 (20.2) for SC versus 68 (20.0) / 73 (15.1) / 73 (17.2) for UC. The MMRM mean estimate of GHQ-QoL across the 6 mo and 12 mo FU was 69 for SC and 73 for UC, mean diff -4.0 (95% CI: -9.0 to 0.9). The lower limit of the 95% CI did not cross the NIM. For the PPP (N=130/150), mean diff was -5.0 (95% CI: -10.1 to 0.2). No clear evidence of between group differences on other QoL, unmet needs or satisfaction scales (C30, CR29, SUNS, PSQ), accounting for multiplicity. At 12 mo, more patients in SC (40/62, 65%) vs UC (24/58, 41%) felt their PCP was sufficiently knowledgeable (AOPSS). At 12 mo, most popular preferences for FU were: SC for 40/63 (63%) in the SC group; similar preferences for SC 22/62 (35%) and 'Hospital-based care with the doctors that treated the cancer' 22/62 (35%) in UC. CEA completion was 89% at 3 mo and 83% at 9 mo in SC; 63% and 68% in UC. 5 recurrences in SC and 6 in UC arms. Pts in SC on average incurred A\$456 less in health costs vs UC pts. **Conclusions:** SCORE had high PCP participation and pt retention. Compared to UC, pts having SC had non-inferior QoL, and lower costs. Adherence to CEA testing was higher in SC. Pts exposed to SC prefer this model of FU. Clinical trial information: ACTRN12617000004369. Research Sponsor: Victorian Cancer Agency and Cancer Australia.

1507

Oral Abstract Session

A cognitive behavioral digital therapeutic for anxiety and depression in patients with cancer: A decentralized randomized controlled trial. *First Author: Sean R. Zion, Blue Note Therapeutics, San Francisco, CA*

Background: Patients with cancer often experience clinically elevated levels of distress, including anxiety and depression. Psychological interventions, such as Cognitive Behavioral Stress Management (CBSM), have evidenced benefits on distress, quality of life, and long-term health outcomes, however, they are not widely available or easily accessible. Digitizing these interventions may be a means of democratizing access to cancer-focused and empirically-supported mental health care. **Methods:** This double-blind randomized controlled trial (RCT) compared the impact of a 10-module digitized CBSM app [attune] vs. a health education control app [cerena] on anxiety and depression symptoms in patients with cancer (n=449). Patients with non-metastatic (stage I-III) and hematological cancers who were receiving or recently (<6 months) completed systemic treatment and reported a PROMIS-A T-Score ≥60 were recruited to participate in this decentralized clinical trial through a nationwide online advertising campaign. The pre-specified primary outcome was change in anxiety symptoms (PROMIS-A) across conditions over time (week 0, 4, 8, and 12) in the intention-to-treat population analyzed using a linear mixed effects model with repeated measures. Secondary outcomes included change in depression symptoms (PROMIS-D) and global impression of change in anxiety and depression (PGI-C). **Results:** Patients in the study were 80.6% female, 76.5% white, and the mean (SD; range) age was 52.44 (11.46; 25-80) years. Compared to the control, attune participants showed significantly greater reductions in anxiety ($\beta = -0.03$; $p = 0.019$) and depression ($\beta = -0.02$; $p = 0.042$) symptoms over 12-weeks, and at end-of-study (week 12) there was a greater proportion of attune participants in the PROMIS-A ($\chi^2 = 7.13$; $p = 0.004$) and PROMIS-D ($\chi^2 = 3.53$; $p = 0.035$) mild-none symptom severity category. There were also significant group differences in PGI-C, with attune participants more likely to report 'much' or 'very much' improvement in their anxiety ($\chi^2 = 31.76$; $p < 0.001$) and depression symptoms ($\chi^2 = 19.70$; $p < 0.001$). **Conclusions:** Digital therapeutics have the potential to improve access to empirically supported psychological treatments for symptoms of anxiety and depression in patients with cancer. In this decentralized, double-blind RCT, we show that compared with a visually and functionally similar sham app, patients who used attune had significantly greater reductions in anxiety and depression symptoms over time. Moreover, at the end of the study, participants who used attune were significantly more likely to report their anxiety and depression symptoms were 'much' or 'very much' improved, indicating clinically meaningful change. Future work aims to explore implementation strategies to maximize benefit and accessibility of this cancer-specific digital therapeutic. Clinical trial information: NCT05227898. Research Sponsor: Blue Note Therapeutics.

1508

Oral Abstract Session

Remote symptom-monitoring of patients with advanced lung cancer: A Danish national randomized controlled trial—The ProWide study. *First Author: Rasmus Blechingberg Friis, Department of Oncology, Regional Hospital West Jutland, Herning, Denmark*

Background: Symptom-monitoring of patients with lung cancer has previously been shown to improve clinical outcomes. We conducted a national randomized controlled trial to evaluate the effects of remote symptom-monitoring of patients with advanced lung cancer completing induction treatment in a Danish setting. **Methods:** Patients with stage III-IV lung cancer treated with palliative intention, ECOG performance status ≤ 2 , internet access and non-progressive disease after completed induction treatment were eligible. Patients were randomized 1:1 to remote symptom-monitoring (intervention arm) added to standard of care or standard of care alone (control arm). Maintenance therapy was allowed. Patients in the intervention arm weekly completed an electronic questionnaire from home covering 13 common symptoms related to lung cancer. A severity-threshold was applied to each question. When a threshold was exceeded, a notification was sent to a clinical nurse. The nurse was instructed to contact the patient and offer best supportive care. If disease progression was suspected, a computerized tomography (CT) scan was performed. Primary outcome was overall survival. Secondary endpoints included Health-related Quality of Life (HRQoL) measured by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire EORTC QLQ-C30/LC13 and Hospital Anxiety and Depression Scale (HADS) scales. **Results:** Of 494 randomized patients, recruited from 8 departments, 239 were assigned to the intervention and 254 to standard of care (inclusion rate 75%). Weekly compliance to symptom-monitoring during the first year was 82% in the intention-to-monitor population. At a median follow-up of 2.6 years, no significant improvement in overall survival (OS) was found in the intervention arm compared to the control arm (hazard ratio (HR) 0.93, 95% confidence interval (CI); 0.75 to 1.16; $p = 0.54$). Sub-group analyses indicated improved OS for patients treated with carboplatin/vinorelbine (HR 0.65, CI 95%; 0.44-0.96, $p = 0.03$) and for patients treated in a department with prior implementation and use of patient-reported outcomes in clinical decision-making (HR 0.68, CI 95%; 0.46-1.01, $p = 0.054$). For prespecified scales in the HRQoL-analyses, no clinically meaningful effects were found. For physical functioning, mean overall change from baseline was 3.1 points (95% CI 0.1 to 6.2, $p = 0.043$), for pain, -3.9 points (95% CI; -8.4 to 0.7, $p = 0.096$) and for HADS-anxiety, -0.5 points (95% CI; -1.0 to 0.0, $p = 0.070$). **Conclusions:** Remote symptom-monitoring did not significantly improve clinical outcomes for patients with advanced lung cancer in a Danish population. The results indicated benefits for a sub-group of patients not receiving maintenance therapy and that prior organizational experiences may be a prerequisite for improving outcomes of symptom-monitoring. Clinical trial information: NCT03608410. Research Sponsor: Danish Cancer Society; Danish Research Center for Lung Cancer.

1510

Poster Discussion Session

Association between state Medicaid policies and accrual of Black and Hispanic patients to cancer clinical trials. *First Author: Samuel U Takvorian, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA*

Background: The U.S. Medicaid health insurance program may play a key role in mitigating racial and ethnic disparities in cancer clinical trial enrollment, given Medicaid's disproportionate representation of these populations and its coverage of the routine costs of trial participation in some states. We sought to evaluate the effect of Medicaid expansion under the Affordable Care Act (ACA) on changes in the accrual of racial and ethnic minority patients in cancer clinical trials, across all states and specifically those mandating Medicaid coverage of routine trial costs. **Methods:** The study used anonymous enrollment data from Medidata Rave, a large commercial clinical trial data collection platform. We conducted a retrospective difference-in-differences (DID) analysis to examine accrual demographics in states that expanded Medicaid eligibility under the ACA compared with non-expansion states, before and after expansion; and assessed effect modification based on state-mandated Medicaid coverage of routine trial costs. Participants included adults enrolled in interventional cancer clinical trials from 2012-2019, located in U.S. hospital referral regions with $>5\%$ Black or Hispanic population. The primary outcome was participant race/ethnicity, defined dichotomously as Black or Hispanic (vs non-Black, non-Hispanic). We used ordinary least squares regression to model participant race/ethnicity as a function of (1) an indicator for trial enrollment in an expansion state after policy implementation, (2) state fixed effects, and (3) year fixed effects, with standard errors clustered at the state level. To assess effect modification, we stratified the main model across states with and without coverage mandates of routine trial costs. **Results:** The study included 75,700 participants across 1,409 clinical trials and 351 sites. In expansion states, the proportion of participants who identified as Black and/or Hispanic increased from 13.4% before expansion to 13.8% after expansion (0.4 percentage-point [PP] change, 95% CI -0.8 to 1.7). In non-expansion states, this proportion decreased from 17.0% to 15.2% (-1.7 PP change, 95% CI -3.7 to 0.2). These trends yielded a non-significant DID estimate of 2.0 PP (95% CI -1.0 to 5.0). In stratified analyses, Medicaid expansion was associated with a 4.5 PP (95% CI 0.4 to 8.6) increase in the enrollment of Black and/or Hispanic participants in states with coverage mandates, but not in states without coverage mandates (1.1 PP, 95% CI -2.6 to 4.8). **Conclusions:** Medicaid expansion was associated with a significant increase in the proportion of Black and Hispanic oncology trial participants in states that mandated Medicaid coverage of the routine costs of trial participation, but not overall across all states. These findings suggest that Medicaid policies have the potential to advance equitable enrollment in cancer clinical trials. Research Sponsor: None.

1509

Poster Discussion Session

Association of Medicaid expansion with treatment receipt, delays in treatment initiation, and survival among young adult women with breast cancer. *First Author: Xuesong Han, American Cancer Society, Atlanta, GA*

Background: Medicaid expansion under the Affordable Care Act has been shown to increase insurance coverage and early-stage cancer diagnoses for young adults (YAs), the age group with the highest uninsured rate. We examined whether Medicaid expansion was associated with increased receipt of timely, guideline-concordant treatment and survival among YA women newly diagnosed with breast cancer, the most common YA cancer diagnosis. **Methods:** Using the National Cancer Database, we identified 51,675 women aged 18-39 years who were diagnosed with breast cancer in 2011-2018. We applied the difference-in-differences (DD) method to estimate outcome changes pre vs. post Medicaid expansion, in expansion- vs. non-expansion states. Linear probability models estimated associations of Medicaid expansion with receipt of guideline-concordant treatment – including any endocrine therapy among women with ER-positive or PR-positive breast cancer, and any chemotherapy or targeted therapy among women with ER-negative and PR-negative breast cancer – and initiation of guideline-concordant treatment (surgery, chemotherapy, or targeted therapy for stage I-III diagnoses, and systemic therapy for stage IV diagnoses) <60 days after diagnosis. Flexible parametric survival models were used to estimate 2-year overall survival. DD models also adjusted for age, race/ethnicity, rurality, zip code-level income, comorbidity, and diagnosis year, with standard errors clustered at the state level. Analyses were stratified by stage at diagnosis (stage I-III vs. IV). **Results:** Of the subset of women with stage I-III ER-positive or PR-positive breast cancer, the percentage receiving endocrine therapy increased in expansion states (85.20% pre-expansion to 86.46% post-expansion), but decreased in non-expansion states (84.32% to 82.79%), resulting in a net increase of 2.42 percentage points (ppt; 95% CI = 0.56 to 4.28) associated with Medicaid expansion in the adjusted DD model. Among all women with stage I-III breast cancer, the percentage with treatment initiation <60 days after diagnosis decreased less in expansion states (84.10% pre-expansion to 82.36% post-expansion) than in non-expansion states (86.95% to 83.98%), resulting in a net reduction of 1.61 ppt (95% CI = 0.05 to 3.18) in treatment delays associated with Medicaid expansion. Notably, the 2-year overall survival increased in expansion states (96.84% pre-expansion to 96.99% post-expansion), but decreased in non-expansion states (97.24% to 96.30%), resulting in a net survival increase of 1.00 ppt (95% CI = 0.21 to 1.79) associated with Medicaid expansion. **Conclusions:** Among YA women with stage I-III breast cancer, Medicaid expansion was associated with increased receipt of guideline-concordant treatment, reduced delays in treatment initiation, and improved 2-year survival. Research Sponsor: U.S. National Institutes of Health.

1511

Poster Discussion Session

State mandatory paid medical leave policies and survival among adults with cancer in the US. *First Author: Justin Michael Barnes, Department of Radiation Oncology, Washington University School of Medicine in St. Louis, St. Louis, MO*

Background: Cancer treatment is often costly and time intensive. Paid medical leave can help employed patients with cancer more effectively manage side effects and complete recommended cancer treatments without loss of income. Since 2012, several states have introduced mandatory paid medical leave policies. We examined whether mandatory paid medical leave policies were associated with better survival among working age adults with cancer. **Methods:** Adults ages 18 to 64 years diagnosed with cancer 2007-2019 were identified from the Surveillance, Epidemiology, and End Results registry program covering 12 states. The primary outcome was overall survival (OS). The exposure of interest was the presence of state mandatory paid medical leave policies. Difference-in-differences (DID) analyses with additive hazards regression models compared changes in OS from pre- to post- mandatory paid sick leave policy implementation in states with vs. without paid sick leave policies. Models adjusted for year-quarter fixed effects, state fixed effects, state Medicaid expansion status, age, race, sex, marital status, metropolitan residence status, county-level income, cancer site, cancer stage, and insurance status. Clustered standard errors by state were achieved via the cluster bootstrap. The plausibility of the common trends assumption was tested using event study analyses and was satisfied for all analyses. Primary analyses focused on data from 2007-2016, where information on month of diagnosis, county, and insurance coverage status were available (note these variables are not available for 2017-2019), though sensitivity analyses with data through 2019 without these additional variables were conducted. **Results:** A total of 1,491,208 adults with cancer were identified. In adjusted DID analyses, after policy implementation, 1-year OS improved from 85.0% to 86.4% in states with mandatory medical leave policies compared to 85.1% to 85.6% in states without such policies. This translates to a 0.85% improvement in 1-year OS (hazard DID: -0.0007, 95% CI = -0.0016 to -0.0001, $P = .027$). The largest improvement was found among the uninsured population (hazard DID: -0.0038, 95% CI = -0.0076 to -0.0011, $P = .013$). In sensitivity analyses with abbreviated data through 2019, results were similar (DID for 1-year OS: 1.3%; hazard DID: -0.0010, 95% CI = -0.0025, 0.0001, $P = .070$). **Conclusions:** State mandatory paid medical leave was associated with improved survival for working-age adults with newly diagnosed cancer, particularly for those who are uninsured. Policy changes that better support patients through cancer treatment may pay off with improved cancer outcomes. Research Sponsor: None.

1512

Poster Discussion Session

Impact of the oncology care model (OCM) on Medicare payments, utilization, and care delivery: Update through year 5. *First Author: Gabriel A. Brooks, Dartmouth Cancer Center, Lebanon, NH*

Background: OCM was a voluntary episode-based alternative payment model designed to improve the value of care for fee-for-service Medicare beneficiaries receiving systemic therapy for cancer. Participating practices received monthly enhanced oncology services (MEOS) care coordination payments and could receive additional payments (or penalties) if they met quality and total episode spending goals during 6-month episodes. **Methods:** We used a difference-in-differences approach to evaluate OCM impacts on Medicare payments, utilization, and quality measures during 6-month episodes before (July '14-January '16) and after (July '16-June '21) OCM's start. Patient-episodes were attributed to OCM-participating practices ($n = 202$) or propensity-matched comparison practices ($n = 534$). Statistical significance was defined as $p \leq 0.10$ to avoid missing program impacts. **Results:** Total episode payments (TEP) for 6-month OCM episodes increased from 29,120 in the baseline period to 35,467 in the OCM period (+21.8%). In reference to comparison episodes, OCM led to a 499 relative reduction in TEP (90%CI -771, -227, -1.7% relative to baseline.) OCM had no significant impact on TEP for low-risk breast, prostate, and bladder cancers, and OCM led to a relative decrease of 755 (CI -1140, -371) for all other higher risk cancers. Reductions in TEP were largest for high-risk breast cancer, lymphoma, lung cancer and colorectal cancer. The overall OCM impact on TEP was attributable to relative reductions in both Part A payments (-152, [CI -257, -47]) and Part B payments (-276, [CI -459, -92]). There was no OCM impact on Part D payments. While OCM had no impact on Part B chemotherapy payments, OCM reduced Part B non-chemotherapy drug payments by 251 (CI -330, -173; -9.3%). Utilization analyses showed no impact of OCM on ED visits or hospitalizations, but OCM reduced the likelihood of ICU admission by 0.6 percentage points (PP; CI -1.0, -0.1, -5.4%). OCM had no impact on initial chemotherapy regimen selection, but OCM led to greater use of biosimilar cancer therapies and value sensitive changes in the use of antiemetics, bone supportive medications, and WBC growth factors (including greater use of biosimilar WBC growth factors; all $p < 0.10$). OCM reduced hospitalizations in the last 30 days of life by 0.8 PP (CI -1.6, -0.1; -1.5%) with no impact on use of chemotherapy or hospice at the end of life. Despite OCM-related TEP reductions, OCM resulted in net losses to Medicare after accounting for MEOS and performance-based payments. **Conclusions:** OCM led to reductions in TEP with similar or improved quality. Reductions in TEP were greatest for common, high-cost cancer types and were driven primarily by changes in use of supportive care medications. The Medicare Enhancing Oncology Model will build on the experience of OCM to further the goal of improving the quality and value of cancer care for Medicare beneficiaries. Research Sponsor: Centers for Medicare and Medicaid Services.

1514

Poster Discussion Session

Patient- and clinician-directed implementation strategies to improve serious illness communication for high-risk patients with cancer: A cluster-randomized pragmatic trial. *First Author: Samuel U Takvorian, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA*

Background: Early serious illness conversations (SICs) elicit patients' values, goals, and care preferences and have been shown to improve outcomes and reduce end-of-life healthcare utilization for patients with cancer. However, most patients with cancer die without a documented SIC. Given prior evidence that strategies informed by behavioral economics ("nudges") increase SIC rates, our objective was to test the independent and additive effects of clinician- and patient-directed nudges to increase SIC completion. **Methods:** We conducted a 2×2 factorial, cluster-randomized pragmatic trial (NCT04867850) to test the effects of nudges to clinicians, patients, or both, compared to usual care, on SIC completion. Usual care was an active control consisting of clinician-directed text messages sent before routine clinic sessions, identifying patients at high risk of 6-month mortality as predicted by a validated machine-learning prognostic algorithm. The clinician nudge additionally included weekly peer comparisons on clinician-level SIC completion rates. The patient nudge consisted of a patient-facing message sent electronically before an index clinic visit, asking a 3-question survey designed to prime patients for an SIC with their oncology team. Participants included medical/gynecologic oncologists and advanced practice providers (APPs) within a large academic health system and their high-risk patients. We independently randomized oncologist/APP clusters and patients to receive nudges vs. usual care. The primary outcome was a documented SIC in the electronic health record within 6 months of enrollment. Using a Cox proportional hazards model with cluster robust standard errors, we performed a time-to-event analysis and tested for heterogeneity of effect across prespecified subgroups. **Results:** From September 2021 to March 2022, the study accrued 4,450 patients (median age 67, 52.9% female, 17.3% Black, 2.7% Hispanic) seen by 166 clinicians across 4 hospitals and 6 community sites, randomized to clinician nudge ($n=1,179$), patient nudge ($n=997$), both ($n=1,270$), or active control ($n=1,004$). Overall patient-level rates of 6-month SIC completion were: 11.5% (clinician nudge), 11.5% (patient nudge), 14.1% (both), and 11.2% (active control). Compared to the active control, participants in the combination nudge arm were more likely to engage in SICs (hazard ratio [HR] 1.55, 95% confidence interval [CI] 1.00-2.40), whereas those in the clinician (HR 0.95, 95% CI 0.64-1.41) and patient (HR 0.99, 95% CI 0.73-1.33) nudge arms were not. There was no effect heterogeneity across age and race subgroups. **Conclusions:** Clinician- and patient-directed nudges may be synergistic in promoting serious illness communication at scale and equitably in routine cancer care. Effects on end-of-life care among decedents are forthcoming. Clinical trial information: NCT04867850. Research Sponsor: U.S. National Institutes of Health.

1513

Poster Discussion Session

Engagement of Patients with Advanced Cancer (EPAC) randomized clinical trial: Long-term effects on survival and healthcare use. *First Author: Manali I. Patel, Stanford University, Stanford, CA*

Background: The Engagement of Patients with Advanced Cancer (EPAC) randomized Veterans with newly diagnosed stage 3 or 4 cancer or recurrent disease to usual care (control) or usual care with 6-month community health worker (CHW) support (intervention) to engage Veterans in end-of-life (EOL) goals and care preference discussions. At 6- and 15-months follow-up, the intervention tripled goals of care documentation (primary outcome), doubled hospice (secondary outcome), and reduced end-of-life (EOL) acute care use (secondary outcome). This post-hoc analysis after 10 years from study initiation evaluates effects on overall survival (OS) and EOL healthcare use. **Methods:** We abstracted dates of death, emergency department (ED), hospitalization, palliative care (PC), and hospice use within and outside Veterans Affairs (VA) using electronic health record and claims before data cut-off on February 1, 2023 for all EPAC participants. We compared OS using Kaplan Meier and log-rank, risk of death using Cox-proportional hazard models, ED, hospitalization, PC, and hospice use in the last 30 days of life using Logistic Regression, and incidence rate ratios of ED and hospitalizations using Poisson regression. **Results:** Among 213 participants, there were no imbalances in demographic or clinical characteristics. 165 (77.4%) were White, 211 (99%) males, 80 (37.6%) had lung cancer, and 118 (55.3%) had stage 4 disease. Median follow-up was 298 days (range 12-3438). Intervention group participants had greater OS (log rank $p=0.04$), 25% reduction in risk of death, lower acute care use, and greater PC and hospice use than control group participants. **Conclusions:** The CHW-led intervention significantly improved OS and maintained robust effects on EOL healthcare use. The intervention may have had unintended, unmeasured effects on other aspects of care, such as treatment and follow-up adherence, and/or hospice acceptance, which require investigation. Nonetheless, results support integration of community health workers into cancer care to improve clinical outcomes. Clinical trial information: NCT02966509. Research Sponsor: VA Office of Cultural Transformation; U.S. National Institutes of Health.

	Intervention Group	Control Group	Total	Hazard Ratio (HR), Odds Ratio (OR), Incidence Rate Ratio (IRR) (95% Confidence Interval)
Death - no. (%)	88 (83.8)	100 (92.5)	188/213 (88.3)	HR 0.75 (0.56-0.98)
ED Use in last 30 days of life - no. (%)	20 (22.7)	47 (47.0)	67 (35.6)	OR 0.33 (0.18-0.63)
ED Visits in last 30 days of life - mean $\pm$ Standard Deviation (SD)	0.25 $\pm$ 0.48	0.79 $\pm$ 1.02	0.53 $\pm$ 0.86	IRR 0.31 (0.19-0.50)
Hospital Use in last 30 days of life - no. (%)	17 (19.3)	46 (46.0)	63 (33.5)	OR 0.28 (0.15-0.54)
Hospitalizations in last 30 days of life - mean $\pm$ SD	0.22 $\pm$ 0.47	0.71 $\pm$ 0.95	0.48 $\pm$ 0.80	IRR 0.30 (0.18-0.50)
PC - no. (%)	44 (50.0)	35 (35.0)	79 (42.0)	OR 1.86 (1.03-3.33)
Hospice - no. (%)	64 (72.7)	53 (53.0)	117 (62.2)	OR 2.36 (1.28-4.36)
Length of Hospice Stay- mean days $\pm$ SD	100.9 $\pm$ 198.6	43.7 $\pm$ 50.1	113 $\pm$ 155.2	IRR 2.31 (2.20-2.42)

1515

Poster Discussion Session

Identifying clinical trial candidates using AI predictions of treatment change: A pilot implementation study. *First Author: Kenneth L. Kehl, Dana-Farber Cancer Institute, Boston, MA*

Background: Precision oncology clinical trials often struggle to accrue due to the difficulty of identifying patients whose tumors meet complex tumor genomic matching criteria at propitious moments when they need new treatment. We conducted a pilot of deploying an artificial-intelligence (AI) model to find such patients and facilitate clinical trial matching workflows at a large academic cancer center. **Methods:** An AI model was trained to predict initiation of new palliative intent systemic therapy within 30 days of a given imaging report (CT, MRI, bone scan, or PET-CT), using the text of that report and prior reports for each patient. The model architecture and performance were previously published (Kehl et al, JCO-CCI 2021 5:622-630). From April to December 2022, the model was applied prospectively each time patients with solid tumors that had undergone next-generation sequencing underwent an imaging study. Model output was linked to the MatchMiner tool, which matches patients to clinical trials using tumor genomics (Klein et al, NPJ Precis Oncol 2022 6(1):69). The output consisted of lists of patients with tumor genomic matches to specific trials, sorted in order of the likelihood of changing treatment within 30 days. This information was provided to an oncology nurse navigator (ONN) charged with coordinating recruitment to early-phase targeted and immunotherapy trials. For 9 high priority trials, the ONN reviewed records for each patient flagged as likely to change treatment and contacted treating oncologists when patients appeared potentially eligible. The proportions of records leading to oncologist contact, and reasons for oncologist non-contact, were analyzed. **Results:** 2093 patients had tumors with genomic matches to the 9 trials of interest; 492 patients (24%) were deemed "likely" to change treatment by our AI model at least once during the pilot. The treating oncologist for 66 patients (3% of the total; 13% of 492 "likely" patients) was contacted after ONN review for potential eligibility. Reasons for not contacting treating oncologists included cases where they had already decided to continue current treatment (21%); the trial had no slots at the time (14%); or the patient was ineligible on nurse navigator review (12%); or had already been evaluated for the trial (7%), started new treatment (18%), or enrolled in hospice (5%). Of the 66 patients whose oncologists were contacted, 9 patients had a consult regarding early phase trials; 4 consented to participate; and all 4 received protocol treatment. **Conclusions:** Identifying potential precision clinical trial candidates by using AI to find patients likely to change treatment is feasible, but many other factors also impact potential trial enrollment. A prospective study is planned to evaluate the impact of sharing clinical trial information directly with treating oncologists when our model predicts a high probability of treatment change. Research Sponsor: U.S. National Institutes of Health; Doris Duke Charitable Foundation.

1516

Poster Discussion Session

Developing machine learning algorithms incorporating patient reported outcome measures to predict acute care events among patients with cancer. *First Author: Thomas J Roberts, Massachusetts General Hospital Cancer Center, Boston, MA*

Background: Clinical trials have shown that collecting patient-reported outcome measures (PROMs) can improve outcomes among oncology patients. However, there remains uncertainty about how to best collect and use PROMs in routine clinical care. Since 2016 we have collected PROMs for patients receiving cancer treatment within a large health system containing academic and community sites. We sought to examine whether combining PROMs with electronic health record (EHR) data improves the performance of machine learning algorithms predicting patients' risk of 30-day acute care events. **Methods:** The sample included patients with solid tumors receiving curative- or palliative-intent systemic therapy between 9/1/20 and 7/31/22 who completed at least one PROMs survey. PROMs were collected via a 12-item questionnaire based on the Common Terminology Criteria for Adverse Events measurement system. Patients completed questionnaires via the EHR's patient portal or on tablets in waiting rooms. EHR data included 176 variables describing demographics, laboratory values, vital signs, diagnoses, medications, and prior healthcare encounters. A binomial outcome was calculated for each patient encounter to indicate whether the patient had an acute care event (ED visit or hospitalization) in the subsequent 30 days. Data were randomly assigned to training (70%) and test (30%) sets and were used to train and test four models: EHR + PROMs, EHR alone, PROMs alone, and 'PROMs plus,' which included PROMs and minimal EHR data such as age, sex, and site of cancer treatment, which served as an accessible proxy for cancer type. For each model, we compared multiple architectures and selected the best-performing model for comparison. **Results:** Between September 2020 and June 2022, 4,193 patients completed 20,359 PROM surveys during outpatient encounters. There were 2,118 30-day acute care events within the cohort. The area under the receiver operating curves (AUCs) were 0.84 (95% CI 0.81 to 0.86) for the EHR + PROMs model, 0.82 (95% CI 0.80 to 0.84) for the EHR alone model, 0.67 (95% CI 0.65 to 0.69) for the PROMs alone model, and 0.79 (95% CI 0.77 to 0.82) for the PROMs plus model. In the EHR alone and EHR + PROMs models, the most important variables were last albumin, white blood cell count and hemoglobin. In the PROMs plus model, the most important variables were age, treatment site, patient-reported pain, and patient-reported fatigue. **Conclusions:** Incorporating PROMs into machine learning models to predict risk of acute care events can improve model performance. Notably, the model combining PROMs with a small number of easily accessible EHR variables performed nearly as well as models including all EHR data. These models demonstrate the predictive value of PROMs in oncology patients and they lay the foundation for future interventions aiming to reduce acute care events among high-risk patients. Research Sponsor: U.S. National Institutes of Health.

1518

Poster Discussion Session

Towards improvement of oncology care through digital technology: A snapshot of Resilience remote patient monitoring (RPM) system implementation across 19 hospitals in Europe. *First Author: Arlindo R. Ferreira, Resilience and Católica Medical School, Universidade Católica Portuguesa, Paris, France*

Background: In clinical trials, RPM based on patient reported outcomes (PROs) has been shown to reduce symptom burden, increase dose intensity, improve quality of life and overall survival, and is recommended by international guidelines in routine oncology practice during systemic treatment (Di Maio et al., Ann Oncol 2022). Resilience developed a digital RPM system for oncology (CE marked, class IIa medical device) which prompts patients weekly with a notification to complete a survey including common symptoms from the NCI's PRO-CTCAE questionnaire. Severe or worsening symptoms trigger an alert notification to the patient's cancer care team, as well as personalized self-management advice, empowerment and educational material to patients. In this study we report the real-world implementation of Resilience RPM system in France and Belgium. **Methods:** Aggregated system-level metrics were collected covering all participating hospitals between Nov 2021 - Dec 2022. Qualitative and quantitative assessments focused on patient and provider utilization of Resilience RPM system was done. The implementation included a continued interaction between Resilience and hospital personnel for training, coordination and technical support. **Results:** 19 hospitals deployed Resilience in France and Belgium, including two Organization of European Cancer Institutes (OECI)-designated cancer centers and community oncology hospitals. Three integrated RPM with their electronic medical record. Overall, 1262 pts were registered (age range, 20-94), 40% with breast, 20% gastrointestinal and 8% genitourinary cancers. In the last 6 months, the main RPM interface was the mobile app (70%). Patient adherence with weekly RPM surveys was 85%, with a median time from prompt receipt to survey completion of 5h20min. RPM retention for 3 months, regardless of disease status, was 80%. Irrespective of severity, the most commonly reported PROs were performance status decline (94%), pain (89%) and anorexia (82%). The most common severe alert notifications were for nausea (33%), pain (31%) and anorexia (23%). The median time to alert management by the care team was 12h (70% within 24h), with 70% of alerts managed by a nurse navigator follow-up call, 5% by a referral for internal/external appointments, 0.5% with an emergency room referral and 0.4% with a hospitalization referral. 87% (32/38) of providers were satisfied with integrating the solution into their organization and 80% (30/38) felt patients were better managed through use of Resilience RPM. **Conclusions:** Implementation of the Resilience RPM system was feasible across a diverse group of 19 cancer centers in France and Belgium, with high levels of patient and provider participation and engagement. Resilience RPM offers an evidence-based approach to improve the quality and patient-centeredness of cancer care. Research Sponsor: Resilience fundings.

1517

Poster Discussion Session

AI-based radiomic biomarkers to predict PD-(L)1 immune checkpoint inhibitor response within PD-L1 high/low/negative expression categories in stage IV NSCLC. *First Author: George R. Simon, H. Lee Moffitt Cancer Center and Research Institute, Celebration, FL*

Background: Recent efforts exploring the utility of quantitative imaging (radiomic) biomarkers to predict response to immune checkpoint inhibitors (ICI) have shown promise to provide a more accurate and scalable method than biopsy-based PD-L1 IHC and tumor mutation burden. One of the challenges of evaluating ICI biomarkers on retrospective real-world data is the inherent association between a physician's treatment choice and PD-L1 expression status. This work investigates radiomics-based multi-modal biomarkers within patient cohorts receiving first-line therapy (ICI monotherapy, ICI plus chemotherapy, and chemotherapy), and in cohorts of all patients receiving ICI (all-lines) subdivided by PD-L1 expression. **Methods:** Using a large multi-institutional real-world dataset, we analyzed radiomic characteristics of 6,295 primary and metastatic lesions from 1,206 stage IV NSCLC patients treated with PD-(L)1 ICIs from nine institutions across the US and Europe. Patients with unavailable imaging follow-up or with EGFR/ALK oncogenic driver mutations were excluded from analysis, resulting in a total dataset of 791 subjects randomly assigned to training (N = 541) and validation sets (N = 250). Radiomic data was extracted from baseline CT scans capturing tumor heterogeneity, spicularity, and burden in the lung, lymph nodes, and liver. A multi-modal ensemble classifier combining demographic features, PD-L1 TPS, and radiomic data was developed to predict response to ICI therapy per RECIST 1.1 criteria. The model's performance was evaluated in terms of the area under the receiver operating characteristic curve (ROC-AUC) and compared to PD-L1 IHC using the two-tailed DeLong test. **Results:** In first-line cohorts, the model identified responders with an ROC-AUC of 0.83 (0.72-0.94, P = 0.005; N = 80, 81% PD-L1 >= 50%) in ICI monotherapy, 0.65 (0.47-0.83, P = 0.28; N = 78, 71% PD-L1 < 50%) in ICI plus chemotherapy, and 0.38 (0.002-0.76, P = 0.53; N = 37) in chemotherapy. In all-lines cohorts subdivided into PD-L1 high/low/negative expression categories, the model identified responders with an ROC-AUC of 0.72 (0.57-0.87, P = 0.005, N = 102), 0.74 (0.58-0.89, P = 0.003, N = 71), and 0.60 (0.46-0.74, P = 0.16, N = 77), respectively. **Conclusions:** Our study demonstrates that multi-modal models can predict ICI response with high performance. The stronger performance in patients receiving ICI therapy alone indicates the model's predictive, rather than prognostic, power. Furthermore, the model demonstrated good performance in identifying ICI responders within patient sub-cohorts defined by PD-L1 expression status. These insights may be used to inform clinical decision-making, such as escalation or de-escalation of concurrent chemotherapy in stage IV NSCLC patients. In our future work, we will investigate these questions in larger cohorts and prospective studies. Research Sponsor: Onc.AI.

1519

Poster Discussion Session

Expanding veteran treatment access points through Close To Me (CTM) infusion service. *First Author: Jenna L Shields, VA National TeleOncology, VA National Oncology Program Office, Durham, NC*

Background: Diagnosing and treating more than 43,000 Veterans annually, the Veterans Affairs (VA) National Oncology Program (NOP) oversees the largest integrated providers of hematology/oncology services in the US. Within the VA, parenteral therapies are primarily offered at VA Medical Centers (VAMC) in urban areas, often inaccessible to rural patients. Travel distance, parking, time, and caregiver support can prevent patients from adhering to treatment regimens. To resolve these challenges, NOP launched the Close to Me (CTM) infusion service. The service seeks to reduce travel time for patients, improve VA care continuity, and increase access points to patient-centric care by administering treatments utilizing the network of VA Community Based Outpatient Clinics (CBOC). **Methods:** In the CTM CBOC infusion service select medications are compounded at the main VAMC, then transported via a registered nurse to the surrounding CBOCs for administration. Eligible patients must be established with a VA hematologist/oncologist and tolerated 1 cycle of treatment at the VAMC. Patients are assessed via telehealth prior to each treatment at the CBOC. Patient drive miles saved was calculated by subtracting the mileage between the patient's home address and the CBOC from the patient's home address and the VAMC, then multiplied by number of treatment visits at the CBOC. Medication cost avoidance was calculated by subtracting the VA purchase price from the 2023 published Centers for Medicare and Medicaid Services reimbursement rates, then multiplied by number of treatments received at the CBOC. The first CTM CBOC clinics were opened within the Minneapolis VA Health Care System in October 2021, followed by the VA Pittsburgh Healthcare System in June 2022. **Results:** From October 2021 through December 2022, 373 unique patients were treated within CTM CBOC clinics for a total of 532 patient visits. The CTM infusion service resulted in 43,249 patient drive miles saved and 813,352 in medication cost avoidance. No medical emergencies were reported during CTM CBOC treatments. One medication was discarded without use due to damage during shipping. One compounded product was not used due to change in patient status. One patient was non-adherent with treatment appointments on two occasions resulting in an overall 99.6% treatment adherence. **Conclusions:** The CTM infusion service optimizes current VA infrastructure to increase access points to hematology/oncology treatment, reduce travel burden for patients, increase treatment appointment adherence and reduce medication cost expenditures. To facilitate expansion of this successful service, NOP has provided funding and support to 11 additional VAMCs to implement one of the CTM solutions including CBOC, mobile infusion unit or home infusion. A comprehensive implementation toolkit was developed to encourage the independent adoption of this service at appropriate locations across VA. Research Sponsor: National Oncology Program, VA Specialty Care Services.

1520

Poster Discussion Session

Improving cancer care in underserved regions through technology-enabled patient-reported outcomes. *First Author: Kingsley Ndoh, Hurone AI, Inc, Seattle, WA*

Background: The growing cancer burden in Africa is a major public health challenge. There were 8,944 new cases in Rwanda, with over 6,044 deaths reported in 2020. Unfortunately, there are only 13 oncologists in Rwanda for a population of 13 million people. The use of artificial intelligence (AI) tools and digital health in cancer treatment has the potential to mitigate the oncology workforce shortages, support clinical decision-making, and increase access to care. Hurone AI is a Seattle MedTech startup building culturally sensitive AI applications to address the oncologist-patient gaps and improve drug safety in underserved populations. Hurone's premier application, Gukiza, launched at the Rwanda Cancer Center in 2022 to conduct beta testing. Gukiza is a remote patient monitoring system that ensures patients can report side effects or symptoms from their phones and oncology care teams can get real-time treatment insights and provide timely and effective care. **Methods:** Hurone received ethical approval from the Rwanda National Ethical Committee to launch a pilot in September 2022. An initial 45 breast cancer patients aged 20 – 65 who were either newly diagnosed or on active treatment were recruited. Each patient periodically received prompts that asked them about side effects and to score the degree of severity. The questions were adapted from the NCI's adverse events repository. Gukiza analyzed each response and presented a visual analysis of each patient, enabling the cancer care team to send text-based interventions to the patient's phone. Potential emergencies are flagged and sent emergency numbers to call. Through Amazon's cloud analytic tools, Gukiza provides treatment insights to support oncologists' clinical decisions. **Results:** Results are summarized. **Conclusions:** Resource-appropriate digital technologies can be a useful tool in mitigating adverse events during cancer treatment and increasing access to timely care for patients. The data built in such systems can be a useful resource to individualize and improve cancer care and treatment outcomes. Research Sponsor: Amazon Web Services.

User profile	Frequency	
Clinical oncologists	3	
Nurses	4	
Patients	45	
Breast Cancer Types and Stages		
Diagnosis (breast cancer)	Frequency	Percentage
Infiltrative ductal carcinoma	30	75%
Lobular carcinoma	7	18%
Mucinous	3	8%
Inflammatory breast cancer	1	3%
Others	1	3%
Cancer stage	Frequency	Percentage
Stage 1	1	2%
Stage 2	24	53%
Stage 3	19	42%
Stage 4	1	2%
User Engagement	Frequency/Percentages	
Number of prompts	2,825	
Number of patient responses	2,690	
Number of interventions sent	158	
Number of automatic emergency interventions	9	
% of nurse-led interventions	78%	
% of physician-led interventions	22%	

1522

Poster Session

Smoking cessation support and knowledge among newly diagnosed individuals at community cancer centers (ECOG-ACRIN trial EAQ171CD). *First Author: Elyse R. Park, Massachusetts General Hospital, Boston, MA*

Background: ASCO recommends that all individuals diagnosed with cancer who smoke receive tobacco treatment support. Oncology clinicians can use the 5As (Ask, Advise, Assess, Assist (e.g., talk about quitting and recommend medication), and Arrange follow-up) to provide this support. Previous studies that have typically assessed clinician-reported delivery of 5As, so we assessed patient-reported receipt of 5As to 1) assess prevalence of 5As receipt and variations by tumor type (smoking vs non-smoking-related) and 2) associations between 5As receipt and patient knowledge about smoking risks and motivation to quit. **Methods:** We analyzed baseline data of 306 patients enrolled in a randomized trial coordinated by the ECOG-ACRIN NCI Community Oncology Research Program (NCORP) Research Base from 37 sub-affiliate Community and Minority/Underserved practices to ascertain whether 5A receipt differs for individuals with a smoking-related vs non-smoking-related tumor and whether patients' motivation and knowledge of the risks of continued smoking (0 to 10) differs by smoking-related tumor and 5As receipt. Eligibility criteria included a recent cancer diagnosis, English or Spanish-speaking, having smoked a cigarette in the past 30 days, and planning to receive treatment at a participating site. **Results:** 306 patients enrolled between 08/2019 and 12/2022 (70.9% female; 84.9% white non-Hispanic, 8.8% Black; 3% Hispanic; median age = 57 years); 51% had non-smoking-related tumors. Quit motivation was lower for non-smoking-related vs. smoking-related tumors (median= 7 (interquartile range (IQR): 5,9) vs median= 9 (IQR: 5,9) but knowledge of smoking risks (e.g., How much quitting improves chances of getting the full benefit of treatment) were similar (median = 10 (IQR: 8,10) vs 10 (IQR: 9,10)). Rates of Ask and Advise were high and similar for non-smoking-related and smoking-related tumors (Ask =94.7% vs 96.5% and Advise =89.3% vs 91.0%, respectively). However, rates of Assist were lower for non-smoking-related tumors vs. smoking-related tumors (e.g., talked about quitting =70.0% vs 79.2%; recommended cessation medication =63.3% vs. 72.2%) and Arrange follow-up =27.3% vs 37.5%. Quit motivation was lower for those who had not received the 5As (Ask median=7 (IQR 5,9) vs 9 (IQR 5,9); Assist talked about quitting median=7 (IQR: 5,9) vs 9 (IQR: 5,9) or Assist recommended cessation medication (median=6 (IQR: 5,9) vs 9 (IQR: 5,9)). **Conclusions:** Rates of assessing tobacco use and advising cessation at community cancer centers are high for addressing smoking but lower for actual assistance, particularly among patients with non-smoking-related tumors. This underscores the importance of clinicians discussing smoking, highlighting persistent smoking risks and the benefits of cessation, and providing actionable recommendations to reduce smoking risks for all patients. Clinical trial information: NCT03808818. Research Sponsor: U.S. National Institutes of Health.

1521

Poster Session

Multidisciplinary prostate cancer consultation at home: Does the virtual visit platform adversely affect care for elderly patients or impact treatment recommendations? *First Author: Ryan P. Dorin, Hartford Healthcare, Hartford, CT*

Background: Amidst the COVID-19 pandemic, Hartford Healthcare (HHC) implemented a multidisciplinary virtual visit prostate cancer clinic (MDVV) to allow patients to receive cancer consultations at home. This clinic has shown significant logistical advantages for provision of coordinated cancer care. To evaluate concerns regarding usability of the telehealth platform for elderly patients, and the absence of in person physical exam at initial consult, we evaluated the MDVV in terms of patient satisfaction based on age, as well as for differences in treatment recommendations after patients were seen in-person at a pre-treatment follow up visit. **Methods:** Patients with newly diagnosed or progressive prostate cancer were offered a MDVV consultation. Those who assented had sequential virtual consultations with a urologic surgeon, a radiation oncologist, and a medical oncologist, followed by a group conference with all 3 specialists, and were guided through the visit by a nurse navigator. Patients then completed a 7 item satisfaction survey using a 5 point Likert scale evaluating their perception of the efficacy, efficiency, coordination, and overall value of the clinic. Responses were stratified by age group and compared. Chart review determined the impact of subsequent in person office visit on treatment recommendations, and the proportion of patients who underwent staging imaging according to NCCN guidelines. This was compared with a cohort of consecutive patients who completed traditional consults with two high volume prostate cancer surgeons immediately before the pandemic. **Results:** A total of 161 patients with newly diagnosed or progressive prostate cancer received a MDVV consultation from August 2020 – February 2023. Patient age ranged from 47-84 years (9% < 60 yrs, 52% 60-70 yrs, 34% 70-80 yrs, 5% >80 yrs). The median score for patient satisfaction on all 7 domains was 1 (strongly agree), and did not differ between age groups. There were no instances of a change in treatment recommendation after follow up in person office visit. While 100% of the MDVV cohort received multidisciplinary consultation before treatment, only 14/50 traditional cohort patients (28%) ultimately received the same (p<.001). 100% of MDVV patients underwent imaging according to NCCN guidelines, compared with 33/50 (66%) of traditional patients (p<.001). **Conclusions:** A virtual format for a multidisciplinary prostate cancer clinic is a logistically advantageous, effective means of offering in-home consultation to prostate cancer patients, leading to high patient satisfaction, regardless of age. The absence of in-person physical examination at initial consultation did not ultimately impact treatment recommendations. This format also improved access to multidisciplinary consultation and increased adherence to imaging guidelines. Research Sponsor: None.

1523

Poster Session

The impact of the 4R Oncology model of team-based care delivery on timing and sequence of guideline recommended interdependent care in breast and lung cancers. *First Author: Raymond Liu, Department of Medical Oncology, Kaiser Permanente San Francisco Medical Center, San Francisco, CA*

Background: Team-based care improves quality, reduces fragmentation and lowers clinician burnout related to ad hoc care coordination. A key principle of teamwork is managing timing and sequence of interdependent care (Vogel JOP 2016). The 4R Oncology model featured by the NCI ASCO Teams project fosters effective teamwork by facilitating systematic timing / sequence of interdependent care (Trosman JOP 2016). 4R is Right Info / Care / Patient / Time. Using 4R, a large health system created a high-functioning care team and conducted optimizations of interdependent care in breast and lung cancers Oct 2020 - Dec 2021 (Liu JCOOP 2022). Optimizations focused on guideline-based care with suboptimal timing / sequencing in respective cancers. We present results of these optimizations. **Methods:** We compared data from electronic health record on timing and sequence of care between historical control cohorts of patients who received care pre-4R (breast n=270, lung n=173) to the post-optimization 4R cohorts (breast n=208, lung n=139). Patient and tumor characteristics between control and 4R cohorts in both breast and lung cancers were similar. **Results:** Timing and sequence of care for 5 of the 6 breast cancer metrics and all 6 lung cancer metrics was significantly improved between the control and 4R cohorts. Despite significant increase, the rate of timely care for some metrics remained low, such as referrals based on distress screening in breast cancer and palliative care in lung cancer. **Conclusions:** The 4R Oncology model is effective in applying teamwork principles and improving timing and sequence of guideline-based care. Opportunities for further improvement exist to expand the benefit of 4R to a higher number of patients. A learning system being established in our institution will inform iterative care optimizations. Research Sponsor: Genentech, Inc.

Cancer	Metric	NCCN guideline	Control cohort %	4R Cohort %
Breast	Pre-treatment referrals based on distress screening	Breast	23	53*
	Bone density test order for ER+ before endocrine therapy	Breast	58	74*
	Genetic test results available before surgery	Breast	57	61
	ECHO for HER2+ patients within 6 weeks of 1st appt	Survivorship	13	42*
	Oncotype result available before medical oncology appt	Breast	40	69*
	post-surgery			
Lung	Social work contact within 30 days of 1st appt	Distress	75	91*
	Palliative care for stage IV within 6 weeks of 1st appt	NSCL	9	15*
	Formal screening, referral to care for falls, frailty, memory, cognition at 1st appt	Older Adult	0	64*
	Formal screening, referral to dental care at 1st appt	ADA	0	54*
	Formal screening, referral to flu, other vaccines at 1st appt	Infections	0	44*
	PET within 2 weeks from diagnosis	NSCL	54	71*
	NGS results reported within 3 weeks from obtaining tumor tissue	NSCL	47	70*

* Statistically significant vs control, p<0.05. 1st appt, first appointment after diagnosis; NSCL, Non small cell lung; ADA, American Dental Association guideline.

1524

Poster Session

English- and Spanish-preferring patient perspectives on managing acute care needs at two disparate health systems. *First Author: Beverly Kyalwazi, University of Texas Southwestern, Dallas, TX*

Background: Although nearly every participating provider group in Medicare's Oncology Care Model sought to reduce emergency department (ED) use by their patients with cancer, few achieved this. Despite growing spread of specialized oncology urgent care clinics (OUCC) as an ED-alternative to treat commonly anticipated treatment-related symptoms, these clinics are underused. The University of Texas Southwestern (UTSW) and Dallas County Safety-net (Parkland Health) have run OUCCs since 2015. Parkland patients use the ED twice as often as UTSW patients in the first 6 months after cancer diagnosis. Utilizing semi-structured interviews, we investigated oncology patient perspectives on acute care needs and ED decision-making in both systems among English and Spanish-preferring patients. **Methods:** We interviewed 24 UTSW and 16 Parkland oncology patients (5 English-preferring, 11 Spanish-preferring). UTSW is an urban regional academic referral center serving nearly 8 million people with a cancer patient population that is 35% nonwhite and 7% Medicaid or uninsured. Parkland serves patients in Dallas County including a cancer patient population that is 77% nonwhite and 80% with Medicaid or county charity care (uninsured). Translated transcripts were analyzed using iterative thematic analysis and the constant comparative method. We evaluated decision-making, attitudes, beliefs, and barriers to access that influenced decisions to present to the ED across a diverse patient population. **Results:** Patients in both health systems endorsed that they did not receive adequate information about expected side effects from cancer treatment. UTSW patients described direct access (e.g., personal cell phone numbers) to their oncologist, whereas Parkland patients commonly relied on non-clinician family to triage symptoms. Parkland patients reported experiencing barriers to outpatient care (lack of insurance, language barriers, and limited access to outpatient care), and described an acculturation to visiting the ED for acute care needs. When patients called a clinician for triage advice, they were often referred to the ED. Overall, patients were largely unaware of OUCCs and a 24/7 telephone triage line, but were very interested in accessing the OUCC to avoid prolonged wait times and exposure to infectious pathogens in the ED. **Conclusions:** Among ED-visiting patients with cancer, we found notable disparities in rapid informal access to clinicians between oncology patients receiving care through UTSW compared to Parkland. Highlighting the available 24/7 phone line as part of patient counseling on treatment side-effects might mitigate this disparity in access, increase utilization of the OUCCs, and reduce low-acuity ED visits in both health systems. Patient perspectives provide valuable insights on how to better integrate care delivery innovations for this high-risk population. Research Sponsor: Texas Health Resources Clinical Scholars Program, by National Cancer Institute Cancer Center Support Grant (1P30CA142543); Agency for Healthcare Research and Quality (R24HS022418); National Cancer Institute Cancer Center Support Grant (1P30CA142543); Clinician Scientist Development Grant, CSDG-20-023-01-CPHPS, from the American Cancer Society.

1526

Poster Session

Implementation of a multi-cancer early detection (MCED) test using a centralized model within (w/i) a multi-state health system. *First Author: Gautum Agarwal, Mercy Hospital St. Louis, St. Louis, MO*

Background: Cancer is the second leading cause of death globally. Currently, USPSTF recommends screening for only 5 (breast, cervical, colorectal, lung [high-risk], prostate [individualized basis]) cancers, but ~70% of cancer-related deaths are from cancers without recommended screening. Galleri (GRAIL, LLC, Menlo Park, CA), an MCED test, that uses a cell-free DNA-based targeted methylation assay and machine learning classifiers to detect a shared cancer signal and predict the cancer signal origin is available for use as a complement to existing screening tests. We present a model of centralized MCED test implementation w/i a multi-state health system. **Methods:** From 11/2021-7/2022, clinical and operational leadership w/i the Mercy Health System (headquartered in St. Louis, MO), including 44 acute and specialty hospitals with over 4000 integrated providers and 44000 coworkers in 5 states (MO, KS, AR, OK, IL), created an MCED test implementation plan for their health system. **Results:** A model with centralized navigation was developed such that patients (pts) and providers contacted a singular team (MCED team) w/i the Mercy Precision Medicine Division using telemedicine to order an MCED test and navigate processes. In the 2 months prior to and after launch (7/12/2022), 12 medical education sessions were held for various groups w/i the health system, including the centralized MCED team, leaders of subspecialty departments, and all primary care providers, to inform on the MCED test implementation plan. In this model, access to MCED testing commences in 2 ways: (1) pts register through an online form or (2) providers w/i the health system submit a referral to the MCED team through the electronic medical record system. Pts are then contacted by a nurse practitioner on the MCED team for pretest counseling w/i 2 business days. If the pt is still interested after counseling, an MCED test is ordered. Pts go to 1 of 11 Mercy labs to have their blood drawn for MCED testing. "Cancer signal detected (CSD)" test results are given to a specialized navigator who helps schedule diagnostic testing and initial appointments with specialists and coordinates follow-up care and treatment (tx) w/i the health system. Early analytics show that from launch to 1/31/2023, there were 3777 total referrals (2931 pt, 846 provider) that led to 925 MCED test orders, of which 6 had a CSD result. Median time from a CSD test result to pt notification was 22.8 hours, to initial diagnostic evaluation was 3.1 days, and to a cancer diagnosis was 8.7 days. Median time from cancer diagnosis to initiation of tx or first postdiagnosis specialist visit was 33 days. **Conclusions:** This model allowed for efficient time to diagnosis and tx or triage of eligible-risk pts using an MCED test and is an example of how a healthcare system can incorporate and scale the implementation of the MCED test into clinical practice. Research Sponsor: None.

1525

Poster Session

Assessing mail-in cryopreservation for fertility preservation. *First Author: Andre R Belarmino, UCLA Health, Los Angeles, CA*

Background: Over 90% of oncologists agree that sperm banking should be offered to all men at risk of subfertility associated with cancer treatment, but fewer than 50% bring up the topic. Barriers cited include lack of time for the discussion, perceived high cost, and lack of convenient facilities. The advent of mail-in semen analysis (SA) testing and cryopreservation may improve access to this service via lower patient cost, decreased required oncologist logistical support, and home rather than local lab collection. That said, average sperm recovery rate after sample thaw is ~50% with immediate banking, and sperm recovery rate after delayed cryopreservation with a mail-in approach remains unknown. **Methods:** This is a prospective preliminary study assessing freeze-thaw total motile count at 3 time points of cryopreservation: upon receipt of sample, at 24 hours, and at 48 hours post collection. We collected 39 fresh semen samples from 13 healthy adult volunteers. Samples were diluted with 5mL of Fellow Health preservation solution and analyzed (World Health Organization guidelines V5). Samples were divided into 3 aliquots: Aliquot #1, T0 was immediately frozen with equal part cryoprotectant. Aliquot #2, T24 and aliquot #3, T48 were left at room temperature for 24 and 48 hrs respectively, analyzed, and then frozen. Aliquots were then thawed on a heat block at 37C for 10 minutes and analyzed. **Results:** Baseline SA values were: volume 3.3ml +/- 1.3, concentration 138.3 +/-57.4 x 10⁶, motility 49% +/-6%; Total Motile Count (TMC) 213 +/- 110 million. TMC was the primary endpoint as measured by baseline semen volume, concentration, and motility at 3 time points (T0, T24, T48). The average loss from freeze/thaw in TMC at T0 was 45%, at T24 was 55% relative to T24 pre-freeze, and at T48 was 59% relative to T48 pre-freeze (p = 0.013). On average, samples with starting TMC between 50-100 million had enough motile sperm for six intrauterine insemination (IUI) cycles when frozen and thawed at T0, two at T24, and two at T48. Samples with starting TMC between 100-200 million had enough motile sperm for 16 IUI cycles when frozen and thawed at T0, eight at T24, and four at T48. Samples with starting TMC > 200 million had enough motile sperm for 42 IUI cycles when frozen and thawed at T0, 21 at T24, and nine at T48. All samples had ample viable cells (> 50,000) at all three time points for in vitro fertilization (IVF). **Conclusions:** Mail-in cryopreservation using our improved methodology may increase access to this service for oncological patients while still facilitating reasonable assisted reproductive technology care relative to in-person cryopreservation. Research Sponsor: Fellow Health.

1527

Poster Session

Differential responses to systemic therapy among patients who are financially fragile and receiving Medicaid: Results from ePRO and biometric monitoring study. *First Author: Scott David Ramsey, Fred Hutchinson Cancer Center, Seattle, WA*

Background: Cancer patients with Medicaid insurance have a 50% higher risk of unplanned ED admissions during systemic chemotherapy compared to commercially insured cancer patients. In a prospective study of an ePRO app and smartwatch to remotely monitor patients receiving anti-cancer therapy, we compared symptoms and biometric data among financially fragile (able vs. not to come up with \$2000 in 30 days for an unexpected expense) Medicaid enrollees and commercially insured patients with solid tumor malignancies. **Methods:** The study was conducted at 3 community oncology practices in WA state. (ML41539, ISRCTN25569053) The ePRO had 15 common treatment-related symptoms from the PRO-CTCAE survey. 30 patients initiating systemic treatment wore a Samsung Galaxy 3 watch and completed the ePRO daily on study provided smartphones for 2 weeks. EPRO app adherence (ratio of completed to expected entries) was 91%. Smartwatch adherence (ratio of days with any biosensor data to number of days expected) was 86%. Composite symptom scores were calculated from ePRO responses using a published mapping algorithm (Range 0-3). Repeat symptoms, number of unique symptoms scores >1, and average heart rate (HR) were compared. **Results:** Participants' average age was 60 (68% female; 75% no comorbidity, 45% metastatic, 10% Medicaid, 13% reported financial fragility). Treatments: chemotherapy only (56%); immunotherapy only (11%); combination therapy (33%). Financially fragile patients had significantly higher average HR, unique symptoms, and repeat symptoms (e.g., >1 day with symptoms). The average composite symptom score over 2 weeks was significantly higher for Medicaid enrollees, and trended higher for financially fragile patients. 16% of daily composite symptom scores recorded by Medicaid patients were 2 or greater, versus 7% for non-Medicaid patients (p<0.001). **Conclusions:** Medicaid-insured and financially fragile patients may have more adverse responses to systemic therapy compared to more advantaged patients. If supported in larger studies, the findings may have profound implications for research aimed at improving clinical management in financially disadvantaged cancer patients. Research Sponsor: Genentech/Roche.

		Average HR (beats/min)		Composite symptom score		Number of repeated symptoms (>1 day)		Number of unique symptoms with composite score >1	
	N	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI
Financial Fragility									
Fragile	4	78.75	(78.73, 78.77)	0.32	(0.28, 0.37)	17.25	(6.37, 28.13)	6.25	(4.02, 8.48)
Not Fragile	20	76.13	(76.12, 76.14)	0.27	(0.25, 0.30)	14.50	(9.06, 19.94)	4.00	(2.88, 5.12)
Don't know Medicaid	6	76.20	(76.17, 76.20)	0.28	(0.24, 0.32)	12.20	(2.47, 21.93)	4.60	(2.60, 6.60)
Yes	3	78.05	(78.01, 78.08)	0.51	(0.45, 0.56)	24.00	(12.40, 35.60)	6.00	(3.38, 8.62)
No	27	76.34	(76.34, 76.35)	0.26	(0.24, 0.27)	13.18	(8.90, 17.47)	4.27	(3.31, 5.24)

1528

Poster Session

Team-based versus technology-based supportive cancer care (SCC): Assessment of implementation across 24 different clinical settings. *First Author: Sacha Moufarrej, Division of Oncology, Stanford University School of Medicine, Stanford, CA*

Background: Advanced care planning and symptom management, otherwise known as Supportive Cancer Care (SCC), are fundamental services that patients should receive after a cancer diagnosis. We launched a 24-clinic site cluster randomized clinical trial in July 2022 comparing two SCC delivery approaches: a team-based intervention in which patients engage in advanced care planning and symptom assessments with a lay health worker versus a technology-based intervention in which patients receive internet-based SCC education. The preliminary aim of this study is to evaluate clinic characteristics that may impact implementation and effectiveness of these SCC delivery approaches. **Methods:** We invited study staff at all 24 sites, including community oncology clinics, Kaiser Permanente clinics, Veterans Affairs facilities, safety-net hospitals, and academic centers, to participate in a survey and semi-structured interview. We used Consolidated Framework for Implementation Research (CFIR) and Reach, Effectiveness, Adoption, and Implementation (RE-AIM) frameworks to assess organizational culture, readiness, facilitators, and barriers to SCC delivery. Surveys were analyzed using descriptive statistics; interviews were analyzed using thematic analysis. **Results:** Among 30 interview participants across 24 clinics, of which 23 completed surveys, 9 (30%) were clinic principal investigators, 11 (36.7%) were research staff, and 10 (33.3%) were implementation staff. Survey respondents implementing team-based SCC were more confident that their approach: 1) accounted for patient care preferences (93.3%) and 2) had strong evidence (86.7%) than respondents implementing technology-based SCC (62.5% and 25.0% respectively). More respondents implementing team-based SCC expressed confidence in organization leadership (100%) and adequate resources for SCC (86.7%) than respondents implementing technology-based SCC (75.0%). Among interview participants, team-based approaches for SCC delivery were considered more effective, as they could: 1) reduce time burden for clinicians 2) tailor delivery to patient preferences; and 3) increase patient support. Participants believed that team-based approaches would also be more difficult and costly to implement. Barriers to both SCC delivery approaches include: a) limited technology access for patients, b) competing organization priorities which limit staffing and funding for SCC, and c) information overload for patients and caregivers. **Conclusions:** Implementation of SCC delivery approaches is needed but requires organizational leadership and implementation resources. Team-based approaches are considered more effective, but barriers such as staffing and funding may inhibit the scalability. Implementation evaluations are crucial to understand real-world applicability and scalability of SCC delivery. Research Sponsor: Patient-Centered Outcomes Research Institute (PCORI).

1530

Poster Session

Impact of geography on receipt of medical oncology consultation and neo-adjuvant chemotherapy for triple negative and HER2 positive breast cancer. *First Author: Elliott Kenneth Yee, University of Toronto, Toronto, ON, Canada*

Background: Consensus guidelines recommend consideration of neoadjuvant chemotherapy (NAC) for most patients with early-stage triple negative (TN) and HER2 positive (HER2+) breast cancer. Based on our previous work, most patients are not seen by a medical oncologist prior to surgery and do not receive NAC. Although potential barriers are not well understood, distance to cancer centres has been shown to mediate medical oncology referral and use of systemic therapy for other malignancies. We therefore aimed to characterize the impact of region of residence and cancer centre proximity on receipt of pre-treatment medical oncology consultation and NAC for patients with TN and HER2+ breast cancer. **Methods:** Using linked administrative healthcare datasets in Ontario, Canada, we performed a retrospective population-based geographic analysis of women diagnosed with stage I-III TN or HER2+ breast cancer from 2012-2019. Outcomes were pre-treatment medical oncology consultation and initiation of NAC. We created choropleth maps to assess the spatial distribution of outcomes across census divisions, displaying cancer centres and outcomes by colour gradient using geographic information system analysis. To assess the relationship between distance to the nearest cancer centre and outcomes, we performed a multivariable regression analysis adjusted for sociodemographic and clinical factors, including tumour extent and nodal status. **Results:** Within the cohort of 12,881 patients, there was no statistically significant relationship between incremental distance to the nearest cancer centre (≤ 5 vs. 5-10, 10-25, and ≥ 25 km) and rate of medical oncology consultation or receipt of NAC. Mapping analysis demonstrated high interregional outcome variability, ranging across census divisions from 12.2% to 64.3% for medical oncology consultation rate, and 9.3% to 64.3% for NAC rate. 77.7% of patients referred to medical oncology received NAC. **Conclusions:** Among patients with TN and HER2+ early breast cancer, rates of medical oncology consultation and NAC were not significantly impacted by distance to cancer centres but varied highly by region. This variability suggests that regional and/or provider practice patterns, rather than distance, may underlie discrepancies in referral for NAC. These findings can inform further studies and interventions aiming to improve equitable access to NAC for patients with TN and HER2+ breast cancer. Research Sponsor: Canadian Cancer Society Challenge Grant, Sunnybrook AFP Association through Innovation Fund of the Alternative Funding Plan.

1529

Poster Session

Dose rounding bevacizumab and its biosimilars to reduce drug waste in the oncology care model in a community oncology network. *First Author: Puneeth Indurial, The U.S. Oncology Network, McKesson, The Woodlands, TX*

Background: The Oncology Care Model (OCM) was a 6-year long Medicare value-based care (VBC) program that rewarded practices for decreasing TCOC compared to a benchmark price, while maintaining high-quality cancer care. Drug waste from partially used single dose vials (SDV) of expensive anti-neoplastic agents is a leading contributor to avoidable Total Cost of Care (TCOC) expenditures for payers. Dose rounding (DR) of biological anti-neoplastic agents, using recommendations (https://www.nccn.org/docs/default-source/clinical/order-templates/hopa.pdf?sfvrsn=3af91118_6) from the Hematology Oncology Pharmacists Association (HOPA) and endorsed by the National Comprehensive Cancer Network (NCCN), is a standard approach to mitigate the impact of drug waste. Many of the practices in The US Oncology Network (The Network) adopted a DR program for biologic agents in 2018 as a strategy to reduce drug waste and TCOC. We studied the impact of a DR initiative targeting bevacizumab and its biosimilars (B+B) on TCOC and drug waste expenditures for The Network practices participating in the OCM. **Methods:** Claims data for 14 practices in The Network participating in the OCM were assessed. Drug administration data for B+B was used to evaluate drug waste, total dose, TCOC, DR and the financial impact of drug waste reduction on TCOC from 2017 to 2021. **Results:** In 2017, prior to implementing DR, an average of 5.3% (range 4.6% to 5.5%) of the total dose of B+B was wasted, with ~25% of B+B administrations having waste in excess of 10% of the total dose. Implementation of the initiative led to a reduction of waste on 30% of the total administrations of B+B across 14 OCM participant practices in The Network. As a result of DR, B+B drug waste decreased by 55% to an average of 2.5% (range -2.3% to 2.7%) of the total dose in 2021. Decreasing drug waste resulted in TCOC reduction of approximately \$100 per member episode per month (0.97% of TCOC) for episodes with B+B administrations in the OCM. The highest waste reduction was seen with B+B administered for treatment of gastrointestinal cancers (colon, rectal, anal, gastroesophageal, or pancreatic cancers) compared to other cancer types (lung, brain, ovarian, etc.), and for B+B administrations where drug waste was greater than 10% of the total dose (~50% reduction). **Conclusions:** Drug waste contributes avoidable expenditures to the TCOC. Implementing strategies such as DR can offset the impact of drug waste and offer meaningful TCOC savings for VBC programs such as the OCM. A similar DR approach may be adopted for other high-cost biologic agents where drug waste results from partial use of SDVs. Research Sponsor: None.

1531

Poster Session

Implementation of a streamlined prior authorization process to improve cancer care delivery. *First Author: Aarti Sonia Bhardwaj, Division of Hematology and Medical Oncology, Icahn School of Medicine at Mount Sinai, New York, NY*

Background: Prior authorizations (PAs) for systemic cancer treatments are increasingly becoming a barrier to timely quality cancer care delivery. There is an extraordinary administrative burden placed on clinicians to complete peer to peers (P2P) and appeals when authorization specialists are unable to identify appropriate clinical data in the EHRs. This leads to delays in care, staff burnout and loss of revenue. At our tertiary academic cancer center, in partnership with our cancer registry and Epic teams, we propose shifting the clerical work required for intravenous chemotherapy PAs from clinicians to certified tumor registrars (CTRs) to improve documentation needed for authorization specialists and decrease PA associated clinician burnout. **Methods:** Clinicians first place the treatment plan order which goes to the CTR work queue. We leveraged the Epic staging smart form to consolidate and auto-populate a list of common data elements needed for PA (performance status, cancer biomarkers, stage, line of treatment, and goals of treatment). The CTRs then complete and validate all elements necessary for authorization specialists to obtain the PA. Our primary outcomes include: average monthly number of intravenous chemotherapy authorizations pending review (including P2P, appeals and authorizations requiring other clinical interventions from the primary team) during a pre (9/1/2021-9/30/22) and post-implementation (11/14/22-1/30/23) period. Analyses were conducted using descriptive statistics. **Results:** The average monthly number of authorizations pending review was 332 pre-implementation and 227 post-implementation, which is a 32% reduction. To account for temporal changes, when comparing December 2021 to January 2022 vs December 2022 and January 2023, the average number of referrals pending review was 276 vs 227 which is an 18% reduction. First line treatment regimens accounted for most regimens requiring review; 28% and 27% pre-implementation and post-implementation, respectively. Non-chemotherapeutics like lanreotide and feraheme had the highest pending review status pre and post-implementation respectively. Among chemo/immunotherapeutics, Nivolumab and Trastuzumab deruxtecan had the highest pending review status pre and post implementation, respectively. GI regimens had the highest number of regimens requiring review accounting for 17% vs 22% of all referrals pre and post implementation, respectively. **Conclusions:** By leveraging technology and increasing efficiencies of existing non-clinical staff workflows, we significantly decreased the number of ambulatory chemotherapy PAs that required further clinical review including P2P and appeals thereby improving efficient care delivery. Next steps include evaluation of sustained improvement, time to final authorization, revenue analysis and the impact on the well-being of clinicians. Research Sponsor: Office of well being and resilience grant.

1532

Poster Session

Best practices study to enhance the quality of multi-disciplinary teams in lung cancer care. *First Author: Marcos Gallego Llorente, Vintura, Baarn, Netherlands*

Background: Regular meetings at multi-disciplinary teams (MDTs) constitute a key moment in the care pathway in lung cancer, where physicians collectively discuss patient cases and decide on treatment plans. MDTs arguably increase the volume of patients treated, improve diagnosis, and positively impact on survival. However, the way MDTs are organized and function is variable across hospitals, countries and continents. Variations in MDT processes may lead to sub-optimal outcomes, such as inconsistencies on the numbers of patients treated with curative intent as well as variable 5-years survival rates for lung cancer. The importance of MDTs is ever increasing, as the therapeutical landscape is getting more complex every year, and treatments are evolving from a one-size-fits-all to a personalized approach. **Methods:** In this study, we gather the best practices in MDT processes, capabilities and governance in 24 leading hospitals throughout Europe and Canada. We map the MDT practices of each hospital into a coherent framework, and identify KPIs and best practices by conducting semi-structured interviews with health care professionals in each hospital and performing workshops with the entire MDT team. The primary research focuses on five key categories: access to the MDT, processes, technology (such as EMR, data sharing tools, and artificial intelligence), culture and capabilities. **Results:** We see a high variation in the way MDTs are organized, in time for discussion per patient, in the model of care and current MDT practices across the 24 hospitals in this project, along our five identified categories. We developed an MDT maturity model where we score individual elements within these five categories to identify the hospitals with the best MDT practices, and a total of 23 key success factors along the MDT process. The maturity model and the key success factors can be used as a self-assessment tool for MDT-teams for continuous quality improvement. **Conclusions:** MDTs have the potential to be a standard part of the patient care pathway, where excellence is consistently achieved when discussing patient cases. This work has identified the practices that are done best in leading hospitals and that have the potential to be progressively adopted. Furthermore, we see that the potential of decision support tools and other artificial intelligence is rarely leveraged by MDTs. Research Sponsor: AstraZeneca.

1534

Poster Session

Real-world experience of an in-house dihydropyrimidine dehydrogenase (DPYD) genotype test to guide fluoropyrimidine (FP) dosing at a multisite cancer hospital. *First Author: Jai Narendra Patel, Levine Cancer Institute, Atrium Health, Charlotte, NC*

Background: FPs, including 5-fluorouracil and capecitabine, are widely used to treat solid tumor malignancies like gastrointestinal (GI) cancers. One-third of patients (pts) develop severe toxicities which may lead to treatment delays or hospitalization. Toxicities can be partly due to genetic variations in *DPYD*. Herein, we describe the implementation of an in-house *DPYD* test and its impact on FP dosing at a multisite cancer hospital. **Methods:** This is an observational study of pts starting or continuing FP-based chemotherapy who received *DPYD* testing as part of routine care. Buccal swabs were collected in clinic and sent to an in-house lab for genotyping using a polymerase chain reaction-based Drug Metabolizing Enzyme assay that interrogates all 5 variants with moderate-to-strong evidence according to the Clinical Pharmacogenetics Implementation Consortium (CPIC) (c.1905+1G>A, c.2846A>T, c.1679T>G, c.1236G>A and c.557A>G). Phenotype translations and dosing were based on CPIC guidelines. Test results and dose recommendations were uploaded to the electronic medical record (EMR) and emailed to the care team. In April 2022, pre- and post-test EMR alerts were built to prompt test ordering and dose modifications. The primary objective was to evaluate the proportion of *DPYD* variant carriers in tested pts receiving FP. Secondly, we evaluated turnaround time and impact on FP dosing. **Results:** From March 2020-December 2022, 491 pts across 14 clinics received *DPYD* genotyping (54% male, 74% White, 20% Black, median age 53 years). GI cancers (~50% colorectal) represented 90% of the diagnoses. The median lab turnaround time was 3 (IQR 2-6) days. Pretreatment testing was ordered in 389 (79%) pts, of which 360 (93%) had results before cycle 1. Overall, 30 pts (6.1%) were heterozygous carriers (4.9% in pretreatment and 10.8% in reactive testing groups). Variants observed were c.1236G>A (n=13), c.2846A>T (n=8), c.1905+1G>A (*2A) (n=4), c.557A>G (n=4), and c.1679T>G (*13) (n=1). FP dose was modified in 27 (90%) pts (reduced in 25, avoided in 1, discontinued in 1). Of 19 carriers with pretreatment testing, 17 (90%) received an upfront dose reduction (mean reduction 42%; 3 had subsequent dose escalations); 1 avoided FP and 1 declined chemotherapy. Of 11 carriers with reactive testing, 9 had dose reductions (mean reduction 39%) and 2 discontinued FP due to toxicity. The mean FP dose intensity at cycle 1 was 56% in pretreatment carriers, 97% in reactive carriers, and 94% in wild type pts. **Conclusions:** *DPYD* genotype-guided FP dosing is feasible at a multisite cancer hospital. In-house rapid turnaround *DPYD* testing identified variant carriers and resulted in treatment/dose modifications for most carriers, potentially avoiding or mitigating severe toxicities and/or hospitalization, particularly with pretreatment testing. Toxicity evaluation is ongoing. Research Sponsor: Heineman Foundation of New York.

1533

Poster Session

Outpatient practice utilization for CAR-T and T cell engager in patients with lymphoma and multiple myeloma. *First Author: Radhika Bansal, Division of Hematology, Mayo Clinic, Rochester, MN*

Background: FDA-approved chimeric antigen receptor T-cell (CAR-T) and bispecific T cell engager (TCE) therapy are most commonly managed inpatient. Here we report our experience with hospital-based outpatient (HBO) management of patients (pts) receiving FDA-approved CAR-T or TCE and a predictive model for increased risk of early hospitalization (≤ 3 days post CAR-T). **Methods:** We reviewed the outcomes of pts who received FDA-approved CAR-T (axi-cel, brexu-cel, ide-cel, cilta-cel) or TCE (teclistamab) in the HBO unit between 3/2021 and 1/2023 at Mayo Clinic, Rochester. **Results:** HBO is closely integrated with inpatient practice and includes the same specialty trained clinical team. It is the first point of contact 24/7 for pts and triage evaluations. CAR-T and TCE are given on HBO followed by monitoring per REMS and as clinically needed until admission criteria is met. Remote patient monitoring (RPM) tools were used as part of outpatient monitoring. Out of 169 CAR-T pts, 87 (51%) were dosed with new indication/products (follicular lymphoma, mantle cell lymphoma, myeloma). Among those, 80 (92%) pts were dosed outpatient, among whom 21 (27%) were never hospitalized. CRS and ICANS incidences were comparable to that reported in registration studies. Median time to first admission from CAR-T infusion was 1 day (range, 0-9), with 31% (n=18/59) of admissions after day 3 post infusion. The most common cause of hospitalization was fever (n=40, 59%). Median length of hospital stay was 4 days (range, 1-49). Median time to tocilizumab (n=45, 80%), steroid (n=1, 2%), escalation of oxygen support (n=7, 12%), vasopressor (n=2, 3%), ventilator (n=1, 2%), hemodialysis (n=1, 2%) and ICU transfer (n=3, 5%) was 1 day (range, 0-31) after first admission. Use of bridging therapy, elevated CRP and LDH were predictive of early admission (ROC AUC 0.62). Four pts received teclistamab on HBO and enrolled in RPM. Data from more pts will be reported at ASCO. **Conclusions:** Our expanded study in CAR-T and TCE confirms that HBO is feasible and that CAR-T and TCE can be safely dosed outpatient. Approximately 31% of pts were admitted after 3 days from CAR-T infusion, and 27% of our pts were never admitted. Variables associated with aggressive disease can predict early hospitalization in pts receiving FDA-approved CAR-T. Extension of HBO practice to TCE is feasible. Research Sponsor: None.

Teclistamab RPM data.				
	Pt 1	Pt 2	Pt 3	Pt 4
Age, years	71	38	65	66
Gender	Female	Female	Male	Male
Prior lines of therapy	5	3	6	6
RPM days (ongoing)	13	17	13	3
Alerts/Entries	4/227	28/699	9/469	1/106
Time to respond to alert, hrs, Median (range)	1.0 (0.4,11.0)	1.3 (0.1,12.0)	1.5 (0.2,12.0)	1.1
Alert response, Called pt	3	11	3	1
Alert response, HBO visit scheduled	0	4	0	0

1535

Poster Session

Decreasing the burden of febrile neutropenia through dynamic remote patient monitoring: The DEFENDER program. *First Author: Joshua Pritchett, Mayo Clinic, Rochester, MN*

Background: Ambulatory management of select patients with febrile neutropenia (FN) may substantially decrease patients' burden of illness and improve their quality of life, and is recommended by American Society of Clinical Oncology (ASCO) guidelines. However, in the United States, inpatient management remains the universal standard. We hereby report the health care utilization associated with the DEFENDER remote patient monitoring (RPM) program, which leverages technology and virtual centralized nurse monitoring to facilitate ambulatory management of FN as an alternative to hospital-based care. **Methods:** Adult patients with cancer hospitalized with FN were assessed daily for eligibility to participate in the DEFENDER program. Eligibility criteria included MASCC score > 21 (per ASCO guidelines), and clinical judgment of the attending provider. Patients receiving cellular therapy (CAR-T, BMT) in the prior 100 days were excluded. Eligible patients agreeing to participate in the 30-day program were provided a kit containing cellular-enabled, pre-connected devices to facilitate monitoring, including twice-daily vital signs and electronic symptom questionnaires. Data were EHR-integrated in real-time and embedded decision trees facilitated alerts for adverse trends. RPM nurses responded to alerts and escalated care as indicated by pre-specified care pathways. Program assessment was performed at 20 weeks after full implementation. The primary outcome was the mean proportion of evaluable days spent inpatient (mPEDI) within 30 days of eligibility compared between those who participated in the program vs. those who declined. **Results:** 35 patients were offered participation in the DEFENDER program. Of these, 17 participated and 18 declined. Baseline characteristics are provided. Participating patients experienced mPEDI of 6.9% (Standard Error [SE], 3.7%), compared with 17.7% (SE, 3.6%) for patients who declined participation. Due to small sample size, this difference (10.8%) did not reach statistical significance (Wilcoxon Rank Sums p-value, 0.15). 30-day mortality did not differ between groups. Mean inpatient days were also lower for patients participating in the program. Additionally, when readmitted, patients participating in RPM experienced a trend toward shorter length of stay and lower rates of intensive care unit utilization. **Conclusions:** A trend towards decreased burden of inpatient care is evident among patients participating in the DEFENDER program. Further studies are warranted to assess comparative effectiveness of this model vs usual care. Research Sponsor: None.

	Participated	Declined
n	17	18
Median Age, years (range)	60 (24-76)	59 (25-79)
% Female	41%	50%
mPEDI (30d)	6.90%	17.70%
Mean inpatient days (30d)	1.9	4.7
All-cause mortality (30d)	1	1
Readmissions (30d): mean inpatient days	3	6.9
Readmissions (30d): ICU utilization rate	17%	38%
Readmissions (30d): mean ICU days	1.0	2.0

1536

Poster Session

Outcomes on the hematology malignancy hospitalist service: A model for inpatient care. *First Author: Alaina J. Kessler, Icahn School of Medicine at Mount Sinai, New York, NY*

Background: The use of oncology hospitalists has been shown to improve quality outcomes among hospitalized patients, though there is limited data on the use of hospitalists to care for patients with hematologic malignancies. The Hematology Malignancy Hospitalist Service (HMHS) was created in efforts to decrease patient volume on the primary hematology malignancy services at an academic hospital. Patients with active oncologic issues requiring specialty oncology management were cared for by oncologists on the primary leukemia, lymphoma, and myeloma services while patients with acute medicine-related issues were cared for by medicine hospitalists on HMHS. **Methods:** Criteria were established based on level of acuity and reason for admission to HMHS, which was comprised of a hospitalist attending and nurse practitioner. New admissions to HMHS were evaluated by the primary hematology malignancy service team as consultants and remained involved in patient care as deemed appropriate. Oncology attendings continued to care for patients on the primary leukemia, lymphoma, and myeloma services. We conducted a retrospective analysis from 6/28/21 through 6/30/22 excluding 1/2/22 to 2/6/22 when HMHS was paused due to the COVID Omicron surge. We compared length of stay (LOS), discharge before noon (DBN), and 30-day readmission rates of patients admitted to the HMHS service and those admitted to the primary services to assess for differences in outcomes. **Results:** There were a total of 95 (12%) admissions to HMHS and 669 (88%) to the primary services; 35.6% patients were white, 21.7% Black, and 10.3% Asian and 26.3% patients identified as Hispanic. The average age was 61.6 years. The average LOS in days was 9 ± 9.09 , 16.03 ± 14.96 , 11.41 ± 14.88 , and 12.68 ± 11.40 ($p = 0.005$) for patients admitted to HMHS, leukemia, lymphoma and myeloma services, respectively. DBN on HMHS (6%) was similar to the leukemia service (6%) and improved compared to the lymphoma service (11%) and myeloma service (7%); $p = 0.66$. The 30-day readmission rate was also improved on HMHS (12%) compared to leukemia (21%), lymphoma (21%), and myeloma (18%); $p=0.25$. **Conclusions:** The development and implementation of a medicine hospitalist-driven hematology malignancy service significantly improved LOS without a negative impact on 30-day readmission rates when compared to a primary hematology malignancy service model. The addition of medicine hospitalists to the inpatient care of patients with hematologic malignancies demonstrates improvement in healthcare utilization. This is an important area for future evaluation to determine the most appropriate patients to admit to these services and assess other important outcomes. Research Sponsor: None.

1538

Poster Session

Overcoming barriers and improving genetic testing completion rate for hereditary cancer in an underserved population at a large safety net hospital. *First Author: Autumn Vara, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Genetic testing is a routine practice in oncology care as outcomes of germline testing may impact surgical recommendations, open therapeutic options, as well as inform patients and family members of their cancer risks. Lyndon B. Johnson Hospital (LBJ) is a safety-net hospital that mainly serves low income and uninsured patients (pts), and LBJ oncology clinic is staffed by MD Anderson Medical Oncology faculty and fellows. Pre-test counseling with a certified genetic counselor was offered once a week by referral and transitioned to virtual template at the start of the COVID-19 pandemic. This transition in addition to barriers unique to the underserved population led to a decrease in test completion rates and introduced a backlog as patients were re-referred for completion of testing. We discuss our strategies in decreasing a 9-month backlog over the course of one year. **Methods:** Re-introduction of an on-site general oncology genetic counselor twice a week was implemented in addition to maintaining the virtual platform once a week. The on-site genetic counselor was embedded in the physician's clinic and rotated to ensure coverage for all clinic days. Manual chart review was conducted by on-site genetic counselor and patients were rescheduled to in-person template in conjunction with other same day appointments to improve no-show rate. Patients electing to proceed with germline testing signed appropriate written consent, patient assistance financial forms, and submitted samples prior to leaving clinic. **Results:** From January 2019 through December 2022, a total of 1716 patients including re-referrals were scheduled and 728 patients seen. When genetic counseling service was available as referral outside of oncology clinic, the completed visit rate was 48%, which decreased to 26% in 2020 after COVID-19 transition to virtual. The visit completion rate did improve to 36% in 2021 but the most improvement was seen with genetic counselor embedded in physician clinic with 69% in 2022. The number of genetic testing also increased with 79 ordered in 2021 to 211 ordered in 2022. Of those patients who met national criteria for germline testing and expressed verbal consent, 47% completed germline testing in 2021 which improved to 83% in 2022. **Conclusions:** In our experience, telehealth genetic services is not ideal in the underserved population as there are unique barriers. On-site embedded genetic counseling helps eliminate barriers by allowing patients to complete all steps necessary prior to leaving clinic, leading to successful test completion rates and improved quality of care. Research Sponsor: None.

	2019	2020	2021	2022
	In-Person (referral)	Virtual	Virtual	Virtual / In-Person (Embedded in Physician Clinic)
Completed Visits (%)	48%	26%	36%	34% / 69%
Absolute Number of Genetic Tests Ordered	NA	NA	79	211
Completed Genetic Tests by Eligible Pts (%)	NA	NA	47%	83%

1537

Poster Session

Are we ready to mitigate time toxicity of cancer care? Oncologists' perceptions on digital interventions to fast-track cancer care. *First Author: Erin Mary Bange, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Patients spend substantial time receiving cancer care, and innovative strategies to decrease time toxicity are needed. We have shown that a text-based triage can identify patients tolerating checkpoint inhibitors (ICI) without toxicity who could safely fast-track directly to ICI infusion. However, oncologists' readiness to implement this strategy is unknown. **Methods:** This sequential mixed-methods study included oncologists treating solid-tumor patients with ICIs at Penn Medicine. In phase 1, participants completed a 26-item survey assessing readiness to implement a digital strategy, using the Acceptability, Appropriateness, and Feasibility of Intervention Measures (AIM, IAM, and FIM), as well as perspectives of time toxicity. Each measure consisted of 4 items on a 5-point Likert scale for which means (M) and standard errors (SE) were calculated. In phase 2, a focus group (FG) was led by Penn's Mixed Methods Research Lab to better understand the barriers and facilitators to implementing a digital strategy among oncologists. The FG transcript was reviewed and coded in NVivo with identification of emerging themes. **Results:** 32 faculty members were eligible, of whom 17 (53%) completed the survey and 14 (44%) participated in the FG. Respondents were 53% (n=9) female, 65% (n=11) White, and 53% (n=9) full-time clinicians (non-research faculty); 41% (n=7) reported > 10 years in practice. Quantitative analysis identified infusion (n=11, 65%), commuting (n=11, 65%), and waiting for the physician (n=8, 47%) as the top 3 sources of time toxicity among oncologists. Most agreed that novel interventions are needed to improve the patient-experience (M=4.9, SE=0.08) on a Likert scale of agreeability (1-5, 5=strongly agree). On this scale, our text-based digital strategy to allow patients to fast-track care was found to be acceptable (M=3.8, SE=0.1), appropriate (M=3.8, SE=0.1), and feasible (M=3.9, SE=0.1). Qualitative analysis revealed the following major themes: 1) barriers to implementing a text-based digital strategy including a) health system built for clinician convenience, b) concern with being viewed as "slackers" by administration, c) concerns about overlooking symptoms, d) difficulties identifying appropriate patients, and e) communication issues; and 2) facilitators to adopting this new strategy including a) openness to change, 2) utilizing strengths of care team, and 3) optimism of this digital tool. **Conclusions:** Oncologists recognize time toxicity is a common complication of cancer care. Digital interventions to triage patients who are not experiencing treatment toxicity—thereby reducing time toxicity—were deemed acceptable, appropriate, and feasible. To integrate this technology, further research is required to address key barriers to uptake in routine care. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology; U.S. National Institutes of Health.

1539

Poster Session

Antineoplastic and immunomodulating agent effects on immunization outcomes. *First Author: Jacob New, Department of Medicine, Scripps Clinic, La Jolla, CA*

Background: Oncologists face a challenge in advising patients on the infection risk associated with antineoplastic and immunomodulating medications, as the extent of risk posed by each medication is not well understood. The rapid administration of COVID-19 immunizations across the population provides an opportunity to assess the influence of immunosuppressing medications on infection outcomes post-vaccination. This study evaluated the effect of antineoplastic and immunomodulating medications as classified by the World Health Organization Anatomical Therapeutic Chemical Classification System (WHO ATC) on post-vaccination risk of COVID-19 infection and antibody response to multiple SARS-CoV-2 epitopes using serial serologic assessments. **Methods:** At a large, tertiary healthcare system in San Diego, we conducted an observational cohort study from December 11, 2020, to September 22, 2022, comparing vaccinated adult patients taking WHO ATC-classified immunosuppressing medications ("immunosuppressed" group) with matched control patients not prescribed these medications ("immunocompetent" group) for the outcome of PCR+ COVID-19 infection. A subset of immunosuppressed and immunocompetent individuals was consented to provide serial assessments of antibody response to multiple SARS-CoV-2 epitopes using the Genalyte serologic platform. **Results:** 12,709 vaccinated immunosuppressed patients and 197,151 immunocompetent controls were identified for matched analysis. Receiving an immunosuppressing medication conferred increased risk of COVID-19 infection post-immunization (HR: 1.5, 95% CI: 1.38 – 1.63, $p < 0.0001$). Among immunosuppressing medications, PD1/PD-L1 inhibiting monoclonal antibodies and calcineurin inhibitors were associated with increased risk of COVID-19 infection (HR: 2.33, 95% CI: 1.35 – 4.04, $p = 0.0038$; HR 2.72, 95% CI: 1.78 – 4.16, respectively). Receiving three and four COVID-19 immunizations reduced this risk, except in patients taking calcineurin inhibitors. Among 87 consented participants, 218 samples from multiple timepoints revealed a decreased antibody response to both spike S1 and S2 subunits following third and fourth immunization. Despite decreased seroconversion, this study found medications like CD20 inhibiting monoclonal antibodies and folic acid analogs did not increase the post-immunization risk of COVID-19. **Conclusions:** These results help elucidate the relationship between antineoplastic and immunomodulating medications and COVID-19 immunization outcomes. In our patients, seroconversion efficacy did not always correspond to post-immunization infection, consistent with COVID-19 disease risk being multifactorial. The findings of this study inform oncologists' shared decision-making process in advising patients of the risk of infection associated with immunomodulating medications and the potential impact on their vaccination response. Research Sponsor: Scripps Health Research Innovation Grant; U.S. National Institutes of Health.

1540

Poster Session

Genomic therapy matching in rare and refractory cancers: Updated results from a retrospective cohort study in the Molecular Screening and Therapeutic (MoST) program. *First Author: Frank Po-Yen Lin, NHMRC Clinical Trials Centre, The University of Sydney, Sydney, NSW, Australia*

Background: Biomarker actionability and therapy matching are two central concepts in precision oncology. However, the best strategy to align therapy with genomic alterations remains unclear. Here we report the updated results from a cohort study conducted in an Australian precision oncology program (MoST, ACTRN12616000908437), examining a therapy matching strategy based on comprehensive genomic profiling (CGP) results. **Methods:** All patients (pts) with rare or advanced solid tumours undergoing CGP from 2016 to 2021 after exhausting standard treatments were included. The primary outcome was overall survival (OS) from the date of CGP result, estimated using the Kaplan-Meier method. Pts were grouped according to tiers of actionability determined by matching against the TOPOGRAPH knowledge base (<https://topograph.info>) and stratified into clinically active (Tier 1-3, therapies with evidence from prospective trials), investigational (Tier 3B and 4, therapies with evidence from another cancer type, preclinical, or retrospective studies), or unmatched tier groups. To assess between-group differences in OS, hazard ratios (HR) were estimated in a time-varying Cox regression model adjusting for time to initiation of subsequent therapy. **Results:** This updated analysis included 3,383 pts (79% rare and less common). The median follow-up was 22.6 months (mo). For 2,065 pts who did not receive treatment after CGP, the median OS (mOS) was 8.2 mo (95% CI 7.4 to 9.0). For 1,318 pts who received ≥ 1 line of therapy after CGP, the mOS was 14.1 mo (13.4 to 15.2). 1,270 pts (38%) carried a genomic alteration linked to clinically active therapies (Tier 1-3). Of these, 116 (3.4%) received matched treatment after CGP, experiencing longer survival compared with 410 (32.2%) that received only unmatched therapy (mOS 21.2 v 12.8 mo, HR 0.58, 0.45 to 0.76, $P < 0.001$). Whilst receiving a matched therapy in the investigational tier group ($n=133$, T3B/4) did not show significant differences in outcomes (mOS 14.5 v unmatched 12.8 mo, $n=536$, HR 0.88, 0.72 to 1.08, $p=0.24$), exploratory analyses identified differences in survival for a subset of 41 pts with Switch/Sucrose Non-Fermentable complex mutations receiving matched Tier 4 therapies (mOS 30.1 v 9.6 mo, HR 0.29, 0.17 to 0.51, $P < 0.0001$). Pts receiving repurposed drugs that matched solely on biomarkers in non-cognate cancer types (Tier 3B) showed no survival difference over unmatched therapy ($n=35$ v 469, mOS 13.6 v 12.5 mo, HR 0.96, 0.65 to 1.41, $p=0.83$). **Conclusions:** This study provides insight into how biomarker-linked therapies can be rationally prioritised in rare and advanced cancer populations. Addressing the barriers of access to Tier 1-3 therapies may broaden the utility of genomic biomarker testing. Off-label drug repurposing without direct supporting evidence should only be undertaken in a clinical trial setting. Research Sponsor: Office for Health and Medical Research, State of New South Wales; Australian Federal Government.

1542

Poster Session

Distribution of alternate site infusion providers in the US. *First Author: Cindy Revol, Trilliant Health, Brentwood, TN*

Background: Spurred by the pandemic, chemotherapy treatments provided by alternate site infusion providers have been increasing. This diversification has the potential to increase access to care and improve patient satisfaction. However, it is currently unknown how equitably distributed these non-traditional infusion settings are, and whether these newer entrants are entering markets with need or markets with ample supply. In addition, many community oncologists are concerned about the ability to retain control over a patient's treatment and preserve the profits earned from drug infusions. Further, there are concerns regarding the lack of robust data on the safety of alternate site chemotherapy infusions. Industry analysts anticipate steady expansion in US markets for alternate site infusion with chemotherapy being a strong driver of growth. The objective of this study was to examine the distribution of alternate site infusion services across the US. **Methods:** Leveraging the Medicare home health infusion (MHHI) provider database from CMS, we calculated the rate of MHHI providers per 1000 Medicare beneficiaries in each US state. We reviewed company information to determine the geographic footprint of 3 alternate site infusion providers. **Results:** The median MHHI rate was 0.013 per 1000 beneficiaries (CO), the average rate was 0.031, with a minimum of 0 (ND, SD, WY) and a maximum of 0.202 (IL). ND, SD, WY, IN, KY, and OK have the lowest concentration of MHHI providers, whereas OR, KS, WA, NE, CA, and IL have the highest concentration. 3 alternate site infusion providers are Option Care, UnitedHealth's Optum Infusion Pharmacy, and Coram, CVS Specialty Infusion Services. Option Care has 162 in-person infusion centers located in 45 states. Option Care's presence is highest in CA (24), FL (9), WA (9), OH (8), VA (8), and TX (7). UnitedHealth's Optum Infusion Pharmacy has 30 in-person infusion suites located in 20 states, primarily concentrated in FL (6) and CA (4), but also provides home infusions in all 50 states. Like MHHI providers, neither of these alternate-site providers have locations in ND, SD, or WY. Coram announced a pilot with Cancer Treatment Centers of America in 2021 to provide home chemotherapy to patients in GA, but it is unclear if that pilot is ongoing; Coram provides home infusion therapy in 49 states. **Conclusions:** MHHI and alternate site infusion providers are in markets across the US. If alternate site chemotherapy infusion continues to grow, health system-owned and 3rd party entrant alternate site infusion providers are likely to prosper. Conversely, physician-owned practices could face competition and loss of important drug infusion revenue leading to increased consolidation among independent oncology providers. More research is needed to determine the impact on cost and patient outcomes of alternate site chemotherapy infusions – insights that will impact reimbursement and the rate at which these services continue to grow. Research Sponsor: Trilliant Health.

1541

Poster Session

Surgical care and outcomes in older patients with cancer through implementation of a pre-surgical toolkit (OPTI-Surg): Interim results of a phase III cluster randomized trial (Alliance A231601CD). *First Author: George J. Chang, MD Anderson Cancer Center, Houston, TX*

Background: Frailty is common in older adults undergoing major cancer surgery. Mounting evidence indicates multimodal interventions to optimize patient functional status by addressing vulnerabilities associated with frailty before surgery result in decreased complications and enhanced functional recovery. This study tested the effectiveness of OPTI-Surg, a surgical prehabilitation toolkit for improving surgical care and outcomes in older patients undergoing major cancer surgery. Here, we report results from the planned futility interim analysis (IA). **Methods:** Thoracic (T), gastrointestinal (GI), and urologic (GU) oncological surgery practices affiliated with NCI's Community Oncology Research Program were randomized 1:1:1, stratified by practice type, to usual care (control), OPTI-Surg toolkit, or OPTI-Surg with an implementation coach. The toolkit was implemented at the practice level. It consisted of the 12-item Edmonton Frail Scale and guided recommendations for interventions directed at identified vulnerabilities. Eligible patients were adults ≥ 70 years old undergoing curative intent surgery for lung, gastrointestinal, or urologic cancers. Primary outcome was 8-week post-operative function (weekly caloric expenditure) derived from the validated Community Healthy Activities Model Program for Seniors (CHAMPS) questionnaire. A linear mixed model was used to compare usual care to the 2 OPTI-Surg arms combined, controlling for baseline function. **Results:** From July 2019 to October 2021, 225 patients, 50% of the total accrual goal, were enrolled from 29 practices, triggering the IA. Study was suspended to new patient accrual March to June 2020 due to the COVID-19 pandemic. There were no differences in demographics by arm (mean age 76.2 years; 46.4% women; 79.6% white; 20.4% lung resection, 69.8% major GI surgery, 9.8% total cystectomy). Of the 225 patients, 140 (47 Usual Care, 93 OPTI-Surg) were evaluable for the IA. There was no significant difference in post-operative function between OPTI-Surg and usual care (mean decrease of 0.59 kcal/week for OPTI-Surg patients and 0.19 kcal/week for usual care patients, $p = 0.762$, intraclass correlation = 0.033). Based on the futility analysis, the DSMB recommended closure of recruitment on September 16, 2022. **Conclusions:** Implementation of the OPTI-Surg toolkit did not significantly improve functional outcomes 8 weeks after surgery for patients aged 70 and older undergoing major cancer surgery compared to usual care. Future analysis of implementation and ethnographic data may identify reasons why significant differences between the intervention and usual care arms were not observed, potentially including disruptions due to the COVID-19 pandemic. Clinical trial information: NCT03857620. Research Sponsor: U.S. National Institutes of Health.

1543

Poster Session

National lung cancer screening rates among women veterans within the Veterans' Health Administration. *First Author: Jennifer Bail, Birmingham VA Medical Center, Birmingham, AL*

Background: Lung cancer is the number one cause of cancer related death among women in the United States. United States Preventive Services Task Force (USPTF) lung cancer screening (LCS) guidelines recommend annual low dose computed tomography (LDCT) among high-risk populations. The data specifically on women veterans is sparse so we retrospectively examined LCS rates among women veterans within the VHA. **Methods:** Women veterans ages 50-80, current or former (quit within 15 years) smokers from 2013- 2021 were identified through the VA corporate data warehouse (CDW). Captured characteristics included: demographics, smoking history, and cancer screening history (lung, breast, cervical). Data was analyzed using R Studio software. **Results:** Women veterans with a history of smoking ($n=40,299$) tended to be aged ≥ 60 , white (66%), single (69%), unemployed (64%), urban dwelling (67%), and residing in Southeast U.S. (31%). Overall, cancer screening rates among women veterans was low (9% lung; 27% breast; 21% cervical). Of the women not screened for lung cancer (91%; $n=36,837$), 11% ($n=4,016$) had a personal history of cancer. While pack-year history was not documented for the vast majority (92%), 7% ($n=2,729$) reported a >30 pack-year smoking history (guideline at the time). Of these >30 pack-year smokers, 88% ($n=2,418$) were not screened for lung cancer. Other significant demographic predictors of increased LCS rates included Southeast Veterans Integrated Service Network (VISN region) and comorbidities such as bipolar disorder and diabetes likely due to increased exposure to healthcare. **Conclusions:** LCS rates, as well as breast and cervical, among women veterans within the VHA is low. The lack of documented pack-year history among women veterans with a history of smoking is concerning. Increased documentation of pack-year history may aid in identifying women for LCS. Efforts are ongoing nationally to implement an equitable centralized LCS program for all veterans and as part of that effort the Birmingham VA Health Care System has utilized their Lung precision Oncology program (LPOP) funding to pilot a structured lung cancer screening program within our Women's Health Clinic in 2022. Research Sponsor: None.

1544

Poster Session

Association between inpatient clinical nursing acuity and 30-day rehospitalization among hospitalized patients with advanced cancer. *First Author: Daniel E Lage, Massachusetts General Hospital, Boston, MA*

Background: Half of patients with advanced cancer experience multiple hospital readmissions, which are burdensome to patients and their family members. During hospitalization, nurses provide assistance with medication administration, activities of daily living (ADLs), and other care needs. However, it is not known how nursing support required during hospitalization may relate to hospital readmissions. Using data from a post-discharge supportive care trial, we analyzed the association between nursing acuity on day of discharge to home and 30-day rehospitalization among patients with advanced cancer. **Methods:** The data for this exploratory analysis came from a single-arm pilot trial (n=54) of a nurse practitioner-led supportive care telehealth intervention at Massachusetts General Hospital (MGH). We enrolled English-speaking adults with advanced breast, gastrointestinal, genitourinary, or thoracic cancers who had an unplanned hospitalization and were being discharged home without hospice. MGH uses the Harris Healthcare AcuityPlus workload and productivity system to measure patients' need for nursing care twice daily, in order to define nurse staffing levels. AcuityPlus groups patients into six levels of acuity (1=0-5 hours; 2=5-7 hours; 3=7-10 hours; 4=10-14 hours; 5=14-20 hours; 6=20+ hours). We conducted chart reviews to determine 30-day hospital readmission rates and analyzed the last AcuityPlus assessment before hospital discharge. We described rates of 30-day hospital readmissions by nursing acuity level. **Results:** From 01/07/21 to 05/28/21, we enrolled 54 patients (median age=65.0 years; 59.3% and 22.2% had advanced gastrointestinal or thoracic cancers, respectively). On day of discharge, no patients were classified as acuity level 1, while 25.9% of patients were classified as acuity level 2. 53.7% were in acuity level 3 and 20.4% were in acuity levels 4-6. Further, at discharge, 64.8% of patients received partial or extended assistance with ADLs, and 53.7% were assessed at least every 2 hours. At 30 days, 10 (18.5%) patients were readmitted to the hospital, all of whom were in acuity category 3 or higher on the day of discharge. No patients in acuity level 2 were readmitted. **Conclusions:** In this cohort of hospitalized patients with advanced cancer enrolled in a post-discharge supportive care study, overall need for nursing care, ADL support, and assessment was high, with over 70% of patients receiving at least 7 hours of nursing care on the day of discharge. While some nursing care received was influenced by inpatient nursing protocols, all readmitted patients had high nursing needs at discharge. These results support further study in larger cohorts of the relationship between inpatient nursing needs and likelihood of readmission in hospitalized patients with advanced cancer to improve support at home for recently hospitalized patients. Clinical trial information: NCT04640714. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology.

LBA1545

Poster Session

A randomized trial of patient navigation with symptom-monitoring in advanced lung cancer. *First Author: Vanita Noronha, Tata Memorial Centre, Mumbai, India*

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2023, issue of the *Journal of Clinical Oncology*.

1546

Poster Session

Evolving adjuvant estrogen therapy prescribing among breast oncology workforce. *First Author: Kayla Polcari, University of Chicago, Chicago, IL*

Background: An oncologist shortage and rising number of breast cancer survivors has created a strained workforce. Care models that incorporate advanced practice providers (APPs) are recommended to meet this rising demand, particularly during survivorship. The objective of this study is to describe the evolving oncology workforce using anti-estrogen prescribing as a surrogate for breast cancer survivorship care. **Methods:** We used Medicare Part D Public Use Files to identify prescribers of anti-estrogen therapy from 2013 to 2020. We included medications primarily prescribed in the adjuvant setting for estrogen receptor positive breast cancer, including anastrozole, letrozole, exemestane, tamoxifen, raloxifene, fulvestrant, and toremifene. We assessed the volume of physician and APP prescribers and claims by provider type using descriptive statistics and logistic regression. Individual prescribers were included if they had more than 10 claims. **Results:** The overall number of anti-estrogen claims did not change significantly from 2013 to 2020, with an average of 3,224,361 annually. There was a significant increase in APP prescribers from 7,815 (8.6%) in 2013 to 12,961 (18.3%) in 2020. There was a reduction in physician prescribers by 24,815 (9.7%) over the same period with an overall net decrease of total prescribers of 19,669 (21.7%). The average annual claims per individual prescriber rose from 2013 to 2020 (Physicians: 2013: 37.5 to 2020: 45.2, $p < 0.001$; APP: 2013: 28.2 to 2020: 37.0, $p < 0.001$). The percentage of claims attributed to APP prescribers rose substantially from 6.6% in 2013 to 15.5% in 2020. This represents an increase from 220,000 prescriptions in 2013 to over 480,000 in 2020. **Conclusions:** Our results indicate an ongoing shift in the provider composition responsible for delivering breast cancer survivorship care. Over the time frame analyzed, there was no significant change in number of prescription claims annually, but an overall decrease in providers. Thus, the rise in APP prescribers is not driven by an increased prescribing volume, but rather seems to reflect an evolving surgical oncology workforce. This has significant implications for the future access to and delivery of timely high-quality cancer care. Research Sponsor: None.

Year	Total Claims	Physician Prescribers	APP Prescribers	Physician Prescribers (%)	APP Prescribers (%)	Average Claims per Physician	Average Claims per APP	Physician Claims (%)	APP Claims (%)
2013	3,325,406	82,739	7,815	91.4	8.6	37.5	28.2	93.4	6.6
2014	3,056,733	78,518	7,252	91.5	8.5	36.1	31.1	92.6	7.4
2015	3,298,385	76,593	9,116	89.4	10.6	39.3	31.4	91.3	8.7
2016	3,333,303	73,296	9,974	88.0	12.0	41.1	32.4	90.3	9.7
2017	3,288,808	69,708	10,756	86.6	13.4	42.0	33.4	89.1	10.9
2018	3,241,158	65,693	11,527	85.1	14.9	43.2	34.8	87.6	12.4
2019	3,150,501	61,488	12,162	83.5	16.5	44.1	36.0	86.1	13.9
2020	3,100,595	57,924	12,961	81.7	18.3	45.2	37.0	84.5	15.5

1547

Poster Session

Effect of an oncology care management program on unplanned hospital admissions in a commercially insured population. *First Author: Wendy L. French, Optum Health Solutions, Eden Prairie, MN*

Background: Despite advances in cancer outcomes, costs of cancer care continue to rise. Acute care utilization contributes significantly to these costs. The Cancer Support Program's (CSP) care management services focus on providing education on symptom management, palliative care and advance care planning, addressing psychosocial needs and closing gaps in care in members with cancer who are at high risk for unplanned hospital admissions (UHA). **Methods:** Beginning 1/1/22, commercially insured members with an active cancer diagnosis were clinically stratified as high or low risk for UHA. All high-risk members were invited to participate in the CSP program. Individuals who agreed to participate received individualized telephonic care management support. Medical claims from 1/1/22 through 9/30/22 were evaluated, and rates of UHA were compared between participants and non-participants within the identified high-risk population for an average period of 4 months after identification (the period equivalent to the average enrollment period of participants). **Results:** The study population included 3,113 members who stratified as high risk. Of those, 36% were enrolled in the program. Reasons for non-enrollment include inability to reach (72%), member refused (27%) and bad contact information (1%). There were no statistically significant differences between the two groups' demographic composition except for age (the enrolled group had slightly more in the 51-64 age group [63% vs. 59%; $p < 0.001$] and slightly fewer in the > 65 age group [9% vs. 15%; $p < 0.001$]). There were 358 UHA in the participating group and 737 UHA in the non-participating group. When normalized, there were 1,179 UHA per thousand members per year (PTMPY), 99% CI [1,171 UHA, 1,184 UHA] (bootstrap) in the participating group and 1,526 UHA PTMPY, 99% CI [1,523 UHA, 1,535 UHA] (bootstrap) in the non-participating group. **Conclusions:** Early results show lower UHA rates for members who participated in the care management program, suggesting the program is effective in reducing acute care utilization within the high-risk population. Limitations of this study include potential enrollment bias, changes in risk status from clinical or social factors, and the potential for human error or inconsistency in the risk stratification process. Further study is underway to validate these results. Research Sponsor: None.

1548

Poster Session

1549

Poster Session

An AI tool for chest X-ray interpretation and lung cancer pre-screening in developing countries. *First Author: Iván Romarico González Espinoza, Hospital Angeles Puebla, Puebla, Mexico*

Background: The current lung cancer screening strategy has not had a major impact on public health, facing many challenges during its implementation in developing countries. Although chest radiography (CXR) is not the study of choice for screening; it is one of the most accessible studies used at all levels of care, so implementing an AI tool capable of CXR interpretation as well as lung cancer risk assessment on a large scale could improve the selection of patients for lung cancer screening. The aim of our study was to develop and evaluate this tool. **Methods:** The dataset used for this tool development was obtained from the NIH "ChestX-ray14" public database. The set was divided into 3 subgroups for training, testing, and validation in a ratio of 80/10/10% respectively. We performed a structuration of metadata and an exploratory analysis as well as preprocessing of the images to standardize their size and resolution before the training. A model based on the adaptation of the momentum for learning was used as an optimizer of the CNN algorithm used. Additionally, a questionnaire based on the PLCO clinical criteria was included for the identification of patients at high risk of developing lung cancer. **Results:** Standard performance metrics were evaluated as shown. **Conclusions:** Our model is comparable to certified radiologists in accuracy at identifying patterns of a CXR. The use of clinical patient information improves the pre-selection of patients with a high risk of developing lung cancer. In developing countries, the implementation of this tool on a large scale will allow more patients to be screened and early diagnosed. Research Sponsor: None.

Metric/Pattern	Cardiomegaly	Emphysema	Effusion	Hemia	Infiltration	Mass	Nodule	Atelectasis	Pneumothorax	Pleural Thickening	Pneumonia	Fibrosis	Edema	Consolidation
Accuracy	84.60%	90.30%	79.60%	77.20%	70.90%	84.60%	79.00%	74.50%	83.50%	76.00%	71.50%	75.80%	79.60%	71.10%
Sensitivity	88.24%	71.43%	85.09%	50.93%	54.69%	71.70%	53.06%	65.96%	75.00%	85.71%	73.58%	64.29%	75.00%	75.96%
Specificity	99.76%	99.10%	97.63%	99.87%	87.41%	98.18%	97.08%	95.52%	99.02%	99.46%	99.25%	99.34%	99.36%	98.40%

Deep learning-based approach to predict multiple genetic mutations in colorectal and lung cancer tissues using hematoxylin and eosin-stained whole-slide images. *First Author: Teppei Konishi, Biomy Inc., Tokyo, Japan*

Background: The presence of genetic mutations is a vital prognostic in many types of cancer. However, genomic testing is expensive and challenging to perform. In contrast, hematoxylin and eosin (H&E) staining is relatively inexpensive and straightforward. Thus, in this study, we propose a method of predicting the presence of genetic mutations using H&E-stained whole-slide images (WSIs). **Methods:** We divided each H&E-stained WSI into small pieces or "patches." We used a deep learning model to classify each patch based on the presence of tumor-containing regions. We then extracted image features from each tumor-containing patch using a deep learning-based feature extractor. We created image features for the entire WSI by concatenating the features of the patches. We then trained genetic mutation classification models using the WSI features as the input and the presence or absence of genetic mutations as the output. Finally, we evaluated the performance of these models using the area under the receiver operating characteristic curve (AUC). **Results:** First, we evaluated our methods using The Cancer Genome Atlas (TCGA) colorectal cancer dataset. We used H&E-stained WSIs and data associated with Microsatellite Instability (MSI) and BRAF gene mutations, which are directly relevant to therapeutic strategies, obtained from an independent clinical cohort of 566 patients with TCGA colon and rectum adenocarcinoma. We divided the data into training, validation, and test splits, comprising 367, 90, and 109 patients, respectively. We used the training and validation splits for model training and selection, and the test split for model evaluation. The AUC values of the classification models and associated 95% confidence intervals (CIs) were 0.721 (CI = 0.572–0.870) for MSI and 0.712 (CI = 0.547–0.877) for BRAF gene mutations. We also applied our approach to MUC16, KRAS, and ALK mutations using the TCGA lung cancer dataset. We divided 909 TCGA lung adenocarcinoma and lung squamous cell carcinoma patients into training, validation, and test splits, comprising 582, 146, and 181 patients, respectively. In contrast with those of the colorectal dataset, WSI image features were generated using all patches. The AUC values on the test splits were 0.897 (CI = 0.85–0.95) for MUC16, 0.845 (CI = 0.75–0.94) for KRAS, and 0.756 (CI = 0.57–0.94) for ALK mutations. **Conclusions:** We proposed an approach to predict the presence of genetic mutations using only H&E-stained WSIs and evaluated its performance using colorectal and lung cancer datasets. Our model has the potential to predict the presence of certain genetic mutations with superior performance. These predictions can be used to improve the accuracy of prognostic prediction using WSIs alone. Research Sponsor: Biomy Inc.

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Poster Session

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Poster Session

Gene expression-based machine learning approach to predict immunotherapy response and survival in patients with advanced cancer. *First Author: Zheng Zhang, Department of Urology, Peking University First Hospital; The Institution of Urology, Peking University; Beijing Key Laboratory of Urogenital Diseases (Male) Molecular Diagnosis and Treatment Center; National Urological Cancer Center, Beijing, China*

Background: Immune checkpoint blockades (ICBs) have drastically improved the clinical outcomes of cancer patients, while only ~30% of them get significant benefits from immunotherapy. TMB, PD-L1, TNB, GEP (Cristescu et al. 2018) and other conventional biomarkers can explain only ~60% of the ICB response, suggesting that novel factors are yet to be discovered. **Methods:** Gene expression profiles and clinical information of 672 patients were collected from IMvigor210 (n=348, bladder cancer), Pender et al. (n=98, 20 tumor types), Kim et al. (n=45, gastric cancer) and CheckMate (n=181, kidney cancer) cohorts, in which all patients were treated with ICBs. In each sample, gene expression intensities normalized by RPKM were ranked in descender order (range of 1-20000) and scaled into the 0-1 range lastly. To identify immune signatures that correlated with both response and survival, 1000+ immune genes were downloaded from InnatDB database, and their expression values were compared between the two groups of IMvigor210 data which were divided according to response (CR+PR vs. SD+PD, Wilcoxon test) or overall survival (≥mOS vs. <mOS, Cox survival analysis). Bayesian-regularization neural networks (BRNN) model was used to develop the risk model to predict ICB response and prognosis. 75% of IMvigor210 data were randomly selected as the training set, and the remaining 25% as the test set. The performance of predictor was independently validated in Pender et al., Kim et al., and CheckMate cohorts subsequently. ROC curves were used to evaluate the predictive accuracy to response. Survival plots were created using the Kaplan-Meier estimator, and data were analyzed by log-rank test. **Results:** 40 DEGs (including top20 DEGs positively correlated with ORR/OS and top20 DEGs negatively correlated with ORR/OS) were identified as immune signatures, in which each gene signature could significantly distinguish ICB response and survival. Our model outperformed TMB or GEP in the prediction of response in IMvigor210 (Model = 0.986 vs. TMB = 0.728 vs. GEP = 0.551), Pender et al. (Model = 0.757 vs. TMB = 0.593 vs. GEP = 0.621), Kim et al. (Model = 0.881 vs. GEP = 0.828), and CheckMate (Model = 0.927 vs. TMB = 0.543) cohorts when AUC was used as performance metric. Meanwhile, our model showed promising results for differentiating longer survivors from shorter survivors with p value < 0.0001, 0.064, 0.021, and 0.0006 in IMvigor210, Pender et al., Kim et al., and CheckMate cohorts respectively. **Conclusions:** We proposed a deep learning model to predict ICB response and survival, in which feature selection based on immune gene expression order, allowing all kinds of platforms and expression data types. Our model showed a robust prediction not only in bladder cancer, but also in other pan-cancer types. Research Sponsor: ChosenMed Technology (Zhejiang) Co., Ltd.

Prediction of cancer treatment response from histopathology images through imputed transcriptomics. *First Author: Danh-Tai Hoang, The Biological Data Science Institute, College of Science, The Australian National University, Canberra, Australia*

Background: In recent years, the use of tumour molecular profiling within the clinic has allowed for more accurate cancer diagnostics, as well as the delivery of precision oncology. Rapid advances in digital histopathology have allowed the extraction of clinically relevant information embedded in tumor slides by applying machine learning methods, capitalizing on recent advancements in image analysis via deep learning. However, as in many supervised learning approaches, predicting response to therapy using whole slide images (WSI) of tissue stained with hematoxylin and eosin (H&E) requires large datasets comprising matched imaging and response data, severely restricting the applicability of this approach. **Methods:** To overcome this critical challenge, we introduce here for the first time a generic methodology for generating WSI-based predictors of patients' response for a broad range of cancer types and therapies, which does not require matched WSI and response data for training. The approach, termed ENLIGHT-DeepPT, consists of: (1) DeepPT, a new deep-learning framework that predicts exome-wide tumor mRNA expression from slides, and (2) ENLIGHT, a recently published response prediction algorithm, applied here to predict response based on the DeepPT predicted expression values, instead of measured values. **Results:** First, we study the ability to predict tumor expression, showing that DeepPT successfully predicts transcriptomics in all 16 TCGA cohorts tested and generalizes well to two independent datasets. Second, aligned with our key aim, we analyze six independent clinical trial datasets of patients with different cancer types that were treated with various targeted and immune therapies, on which DeepPT was never trained. We show that ENLIGHT, without any adaptation, can successfully predict the true responders from the expression values imputed by DeepPT, using only H&E images: ENLIGHT-DeepPT successfully predicts true responders in these cohorts with an overall odds ratio of 2.19, increasing the baseline response rate by 38.8% on average among predicted responders. **Conclusions:** ENLIGHT-DeepPT is the first approach to successfully predict response to multiple targeted and immune cancer therapies directly from H&E slides, without requiring any drug-specific training data. ENLIGHT-DeepPT can provide rapid treatment recommendations without requiring tumor sequencing, bringing precision oncology to low-income countries and other situations where NGS is prohibitive. Research Sponsor: U.S. National Institutes of Health; Australian National University.

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Poster Session

Utilizing predictive modeling to identify patients at high risk of death from immune checkpoint inhibitor therapy-related pneumonitis. *First Author: Antonious Ziad Hazim, Mayo Clinic, Rochester, MN*

Background: Immune checkpoint inhibitor therapy-related (ICI) pneumonitis poses a significant challenge in patients with cancer. There is a need for predictive modeling to identify those at high risk of developing serious adverse events of ICI pneumonitis. **Methods:** A newly created database of cancer patients diagnosed with ICI pneumonitis seen at Mayo Clinic from 2014-2022 was utilized for exploratory data analysis. Modeling was used to determine if three clinical outcomes could be predicted, namely risk of death from: pneumonitis prior to starting immunotherapy, pneumonitis at time of diagnosis of ICI pneumonitis, and any cause at time of ICI pneumonitis diagnosis. The data consisted of 170 patients with annotation for 71 clinical features. Data was divided into features available at time of cancer diagnosis and at time of ICI pneumonitis diagnosis. Exploratory modeling was performed using the gradient boosting technique Xgboost (Chen, 2015) and conducted using k-fold balanced cross validation best practices as well as a train/test/validate schema with 70%/20%/10% data proportions, respectively. Model reverse engineering was done with Shapley statistics (Lundberg, 2017) to determine which features had the largest contribution per model. Once identified, only those highly weighted features were used for logistic regression analysis providing more reproducible predictions by decreasing model variance. **Results:** Risk of death from pneumonitis prior to starting immunotherapy was modeled with an area under the curve of the receiver operator characteristic (AUC-ROC) of 0.79 with the most contributory features including lymphocyte count, oxygen dependence, PFT values, and PD-L1 expression. Logistic regression produced an AUC-ROC of 0.87 (95% CI 0.72-1.0, $p < 0.0013$). Risk of death from pneumonitis at the time of ICI pneumonitis diagnosis was modeled with an AUC-ROC of 0.85 and the most contributory features were similar to the list described in the previous endpoint. Logistic regression produced an AUC-ROC of 0.89 (95% CI 0.81-0.96, $p < 0.0001$). Risk of death from any cause at the time of ICI pneumonitis diagnosis until follow up concluded by 12/2022 produced a model with an AUC-ROC of 0.75 with the most contributory features including supplemental oxygen, PFT values, basic laboratory values, and PD-L1 expression, among others. Logistic regression produced an AUC-ROC of 0.85 (95% CI 0.76-0.93, $p < 0.0001$). **Conclusions:** We demonstrate that commonly available clinical data can be used to identify patients at high risk of death from ICI pneumonitis. This study identified clinical features that were predictive in each scenario from which further concerted effort could produce a new clinical model to provide clinician decision support when considering immunotherapy. Further studies should be done to further elucidate feature interdependence and generalizability. Research Sponsor: None.

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Poster Session

Can synthetic data accurately mimic oncology clinical trials? *First Author: Samer El Kababji, CHEO Research Institute, Ottawa, ON, Canada*

Background: There is strong interest by researchers, the pharmaceutical industry, medical journal editors, funders of research, and regulators in sharing clinical trial data. Reusing data extracts the most utility possible from patient contributions. The majority of patients do want to share their data for secondary research purposes. However, data access for secondary analysis remains a challenge. A key reason why individual-level data is not made directly available to data users by authors and data custodians is concern over breaches of patient privacy. Synthetic data generation (SDG) is an effective way to address privacy concerns that can enable the broader sharing of clinical trial datasets. However, a key question is whether the reproducibility of the generated data is adequate to draw reliable conclusions. **Methods:** We synthesized datasets from five pragmatic breast cancer clinical trials performed by the REaCT group (<https://react.ohri.ca/>). A sequential synthesis method, a type of machine learning was performed. The published analysis of each trial was repeated on each synthetic dataset to evaluate reproducibility. We evaluated reproducibility on three criteria: (a) decision agreement: the direction and statistical significance of the primary endpoint effect estimates are the same as the real data, (b) estimate agreement: the parameter estimates from the synthetic data are within the 95% confidence interval of the real data, and (c) the confidence interval overlap between real and synthetic parameters is above 50%. In addition, we evaluated privacy using a membership disclosure metric. This evaluates the ability of an adversary to determine that a target individual was in the original dataset using the synthetic data, computed as an F1 classification accuracy score. **Results:** Our results show that decision and estimate agreements held true across all five trials, and the confidence interval overlap was high. The risks of membership disclosure are all below the established 0.2 threshold. **Conclusions:** In this study, we were able to successfully generate synthetic datasets that accurately replicated original data from 5 oncology trials and yielded the same results as in the original published studies, with a very low risk of membership disclosure. With proper modeling techniques, synthetic datasets can play a key role in data democratization and the reuse of oncology clinical trials. Research Sponsor: CHEO Research Institute.

Trial Name	NCT	Decision Agreement	Estimate Agreement	CI Overlap	Membership Disclosure*
REACT-G G2	NCT02428114 & NCT02816164	Y	Y	94%	0.06
REACT-HER2+	NCT02632435	Y	Y	70%	-0.11
REACT-ILIIAD	NCT02861859	Y	Y	97%	0.02
REACT-ZOL	NCT03664687	N/A**	81%***	73%***	0.02
REACT-BTL	NCT02721433	Y	Y	79%	0.18

* A commonly used F1 threshold for acceptable membership disclosure is less than 0.2 and can be negative. ** Not applicable because the published analysis was descriptive only. *** This is the average across all descriptive values.

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Poster Session

Clinically oriented prediction of patient response to targeted and immunotherapies from the tumor transcriptome. *First Author: Ranit Aharonov, Pangea Biomed, Tel Aviv, Israel*

Background: Precision oncology is gradually advancing into mainstream clinical practice, demonstrating significant survival benefits. However, eligibility and response rates remain limited in many cases, calling for better predictive biomarkers. **Methods:** We present ENLIGHT, a transcriptomics-based computational approach that identifies clinically relevant genetic interactions and uses them to predict a patient's response to a variety of therapies in multiple cancer types, importantly, without training on previous treatment response data. Consequently, in addition to its ability to predict patients' response to approved and well-studied therapies, ENLIGHT can predict the response to new treatments in early development, even before clinical data has accumulated. Accordingly, we study ENLIGHT in two translationally relevant scenarios: Personalized Oncology (PO), aimed at prioritizing approved treatments to a given patient, and Clinical Trial Design (CTD), selecting the subset of most likely responders in a patient cohort. **Results:** Evaluating ENLIGHT's performance on 21 blinded clinical trial datasets spanning 11 indications and 15 different drugs in the PO setting, we show that it can effectively predict a patient's treatment response across multiple therapies and cancer types, with an overall odds ratio of 2.59 ($p=3.41e-8$), and a 36% increase in response rate over the baseline ($p=3.30e-13$). Its prediction accuracy is better than other state-of-the-art transcriptomics-based signatures. Unlike most signatures that are prognostic or provide insights for only very few, specific treatments, ENLIGHT provides matching scores to a broad range of treatments. Quite strikingly, its performance is comparable to that of supervised predictors developed for specific indications and drugs. In combination with the IFN- γ signature, ENLIGHT achieves an odds ratio larger than 4 in predicting response to immune checkpoint therapy. In the CTD scenario, our results show that by excluding non-responders ENLIGHT can enhance clinical trial success for immunotherapies and other monoclonal antibodies, achieving > 90% of the response rate attainable under an optimal exclusion strategy. **Conclusions:** ENLIGHT is a powerful transcriptomics-based precision oncology pipeline developed by Pangea Biomed that broadly predicts response to both extant and novel targeted and immune therapies, going beyond context-specific biomarkers. Research Sponsor: Pangea Biomed; U.S. National Institutes of Health.

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Poster Session

Relevance and accuracy of ChatGPT-generated NGS reports with treatment recommendations for oncogene-driven NSCLC. *First Author: Zac Hamilton, University of Illinois Chicago, Chicago, IL*

Background: Next-generation sequencing (NGS) is a routine clinical practice in advanced NSCLC. NGS reports are information-dense and clinical interpretation remains a challenge. ChatGPT is a large language model (LLM) AI chatbot that can generate text in response to user-generated prompts. We sought to assess the clinical relevance and accuracy of ChatGPT-generated NGS reports with first-line (1L) treatment recommendations for NSCLC patients with targetable driver oncogenes. **Methods:** Eight driver oncogenes with FDA-approved targeted treatment for 1L stage IV NSCLC were identified in the latest NCCN Clinical Practice Guidelines available to the AI model (version 5, September 2021). The prompt, "Create a next-generation sequencing report with a list of first-line treatment options for a patient with stage IV non-small cell lung cancer with an [oncogenic driver]." was run in a separate "new chat" 10 times for each driver oncogene ($n=80$). Each ChatGPT output was recorded and scored. The Relevance Score (RS) awarded 1 point for every NCCN preferred option and 0.5 points for each "other recommended" treatment listed in the AI-generated output, divided by the maximum possible score for the driver oncogene. Spurious recommendations were awarded 0 points. The Accuracy Score (AS) represents reported treatment options listed in NCCN over the total number of treatments in a report. Percentage of reports listing an NCCN-preferred 1L therapy, a clinical trial as an option, and character and word count were also captured. **Results:** The average length of the AI-generated NGS reports was 117 words (range: 44 – 232). The median number of treatments recommended was 5 (range: 3 – 8). An oncogenic driver-specific preferred 1L treatment was included in 55 reports (68.8%), and a recommendation to explore clinical trials was listed in 43 reports (53.8%). The RS for the total sample was 0.59 (95% CI: 0.52 – 0.65), and the AS was 46.0% (95% CI: 40.2% – 51.8%). **Conclusions:** ChatGPT can rapidly generate concise NGS reports with treatment options for NSCLC with driver oncogenes. Recommendation relevance was moderate, and accuracy was limited with high variability across oncogenes. Overall, ChatGPT recommendations were promising given the complexity of the task with no prompting or training provided to the AI. As LLM AI platforms mature, they may generate more relevant and accurate NGS reports, offering a potentially valuable tool for NGS report annotation for clinicians, and increased accessibility for patients. Research Sponsor: RHN is a recipient of the Robert A. Winn Diversity in Clinical Trials Career Development Award, funded by Bristol Myers Squibb Foundation.

Oncogene	RS	Std Dev	AS (%)	Std Dev (%)
EGFR exon 19 del.	0.49	0.20	59.9	18.6
EGFR exon 21 L858R mut.	0.46	0.15	57.0	11.4
ALK rearrangement	0.75	0.13	73.6	21.9
ROS1 rearrangement	0.86	0.13	70.2	17.5
BRAF V600E mut.	0.67	0.00	20.3	2.8
NTRK1/2/3 gene fusion	1.00	0.00	48.7	11.1
Metex14 skipping mut.	0.10	0.19	7.3	13.4
RET rearrangement	0.37	0.15	31.2	11.4
Total	0.59	0.31	46.0%	26.6%

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Poster Session

Identification of genes encoding targets associated with adverse events in multiple myeloma. *First Author: Xuan Xu, Kansas State University–Olathe, Olathe, KS*

Background: Despite novel therapeutic options, understanding the toxicity profile of anti multiple myeloma (MM) drug regimens (AMDR) is vital. Data suggests adverse event (AE) profile is orchestrated by certain associated genes. The purpose of this study is to explore the interplay of genes, regimens, AEs and provide genetic evidence for a linkage between regimens and the presence of AEs. **Methods:** We examined a group of AMDRs retrieved from the FDA Adverse Event Reporting System. Drug-associated genes were obtained from the Drug Gene Interaction Database, DGIdb. Then, genes were imported to the Online Mendelian Inheritance in Man (OMIM) to search for the existing clinical synopses (features) in the peer reviewed biomedical material, or phenotypes when no data was available. Clinical synopses were then linked to MedDRA. Gene gene interaction was also determined through the Search Tool for the Retrieval of Interacting Genes/Proteins (STRING). We then constructed a detailed large MM pharmacogenetic network to illustrate the linkage among drugs, genes and MM via various expert integrated resources. AMDR responses were then assessed at the DNA and protein levels by modularizing genetic causation into different scenarios i) a direct drug effect on gene expression; ii) the secondary or tertiary effect of drug(s) on subsequent drug metabolism or disposition altering gene expression pathways; iii) modulation of another biological network that disturbs drug effect on gene expression resulting in exacerbating AE occurrence. **Results:** We found multiple genes including *CTLA4*, *NFKB1*, *PSMB8*, *CCND1* and *HLAA* were complicit/associated with different AEs including cardiac or hepatobiliary disorders or other serious events. Our results suggested the expression of *CTLA4* was influenced by multiple AMDRs from combinations of bortezomib (V), lenalidomide (R), melphalan (M), or dexamethasone (D). When AMDRs involve these agents, the occurrence of pericardial disorders due to the treatment exhibited high confidence. We also found carfilzomib (K) combinations (Kd or KRd) were associated with *PSMB8* which was likely to be the genetic factor concomitant with heart failures, cardiac arrhythmias, or hepatobiliary toxicities. Furthermore, our findings suggested *NFKB1*, thalidomide associated gene interacting with *PSMB8*, may present the same toxicity events in hepatobiliary disorders. **Conclusions:** Understanding the genomic basis of specific drug-AE combinations could reveal molecular mechanisms underlying drug-gene-AE associations and recognize the causality of AEs. When considering alternative agents in MM, our study offers insights for predicting treatment responses such as *PSMB8* which could potentially cause an off target effect of K on cardiomyocyte 20S beyond MM cells. Our plan is to integrate this novel computational biology approach with translational medicine to further investigate our observation. Research Sponsor: None.

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Poster Session

Lost in translation? Information exchange during breast cancer care and implications for technology design. *First Author: Megan Salwei, Vanderbilt University Medical Center, Nashville, TN*

Background: Almost 4 million women in the US have had breast cancer, with 300,000 women diagnosed each year. Treatment decision-making following breast cancer diagnosis can be challenging as there are often several clinically appropriate treatment options, each with differing impacts on patient short- and long-term quality of life. Further, patients must manage this information during a time of high emotional burden, which can hinder decision-making. Not surprisingly, studies have found that less than 50% of patients believe their treatment plan aligns with their preferences. Numerous decision aids have been developed to support patient decision-making. However, sustained use of decision aids is limited due to poor integration in clinical workflow. We need to better understand the complex workflows and needs of decision aid users - patients and breast cancer clinicians. In this study, we investigate the information exchange between patients and clinicians when making breast cancer treatment decisions and identify design requirements for patient-centered decision support tools. **Methods:** This study is part of a larger research project to design a COMputerized PATient-centered Collaborative Technology (COMPACT) to support personalized breast cancer decision-making. We observed clinicians at one academic medical center's breast center from February-August 2022. Participating clinicians were followed throughout their clinical shift. Using a tablet computer and smart pencil, we recorded all aspects of clinician workflow. Written notes were transcribed and uploaded into Dedoose. Two human factors researchers inductively coded each observation in a consensus-based process. **Results:** We observed 79 hours of clinical care and 119 patient encounters across 20 observations of various clinical roles. Overall, we found that patients with breast cancer must manage an enormous amount of highly complex information that includes technical medical terms, mathematical concepts (e.g., risk), and uncertainty. We identified over 20 distinct decisions that patients face during their cancer journey, which were interdependent and evolved over time. We identified numerous patient-specific factors that influenced treatment decision-making, such as the patient's work and family circumstances. For instance, one patient was organizing a conference and needed to plan her surgery around this event. Patients were frequently asked to remember and relay information across members of the care team, indicating inadequate system support of information transfer within the large cancer team. Based on these findings, we identified design requirements for interventions to support care coordination and patient-centered decision-making. **Conclusions:** These findings can inform the design of interventions to support breast cancer decision-making and improve patient-centered cancer care. Research Sponsor: Agency for Healthcare Research and Quality.

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Poster Session

An intelligent machine learning model for real-time early detection of undesirable cancer events: AIM2REDUCE. *First Author: Robert C. Grant, Princess Margaret Cancer Centre, Toronto, ON, Canada*

Background: Cancer and its treatment cause undesirable cancer events (UCEs). Automated warning systems could reduce the frequency and severity of UCEs by alerting the healthcare team and allocating preventative interventions. Most previous studies predicted single UCEs at the initiation of treatment. In AIM2REDUCE, we developed and evaluated a general-purpose system for predicting UCEs during outpatient systemic anti-cancer therapy. **Methods:** Each time a patient receives treatment, AIM2REDUCE applies machine learning to the preceding data in the electronic medical record (EMR) to predict future UCEs. We identified patients treated for aerodigestive cancers from the EMR at Princess Margaret Cancer Centre, who were randomly split into development, validation, and test cohorts. Features included cancer diagnosis, treatment sessions with doses, laboratory tests, and patient-reported symptoms. UCEs are listed in the Table. We trained LASSO regression and random forests models in the training cohort and tuned hyperparameters in the validation cohort using Bayesian optimization. We evaluated performance across discrimination, calibration, and net benefit in the test cohort. **Results:** The cohort included 5,760 patients who received 175,565 treatment sessions, with 13,612,746 unique data points across 102 features. Of these patients, 2,352 (40.8%) were female, the median age was 64.0 years (interquartile range 14.0), the most common diagnoses were lung cancer (2,071, 36.0%) and pancreatic cancer (926, 16.1%), and the most common treatment regimens were weekly gemcitabine (433, 7.5%) and maintenance pemetrexed (417, 7.2%). The Table shows the performance of AIM2REDUCE. **Conclusions:** We demonstrate that longitudinal machine learning systems trained using EMR data can accurately predict a wide range of UCEs. Based on these results, automated warning systems should be implemented and evaluated in real-time clinical practice. Research Sponsor: Princess Margaret Cancer Centre.

UCE prevalence and AIM2REDUCE prediction performance in the test cohort.				
UCE	Treatment-level rate	Patient-level rate	Area under the receiver-operating characteristic curve (95% CI)	Area under the precision-recall curve (95% CI)
Death ^a	34.2%	48.1%	0.757 (0.752-0.763)	0.627 (0.621-0.632)
Pain ^b	4.5%	22.0%	0.706 (0.701-0.712)	0.119 (0.112-0.125)
Fatigue ^b	5.5%	27.5%	0.708 (0.702-0.715)	0.122 (0.115-0.127)
Dyspnea ^b	3.3%	18.3%	0.747 (0.742-0.754)	0.107 (0.100-0.112)
Neutropenia ^c	19.1%	40.6%	0.782 (0.776-0.787)	0.422 (0.415-0.427)
Anemia ^c	19.2%	40.8%	0.913 (0.907-0.920)	0.718 (0.711-0.723)
Acute Kidney Injury ^d	3.8%	15.6%	0.848 (0.842-0.855)	0.307 (0.301-0.313)

^a Within 1 year. ^b Increase $\geq$ 4 ESAS points within 30 days. ^c CTCAE v5.0 grade 2+ within 30 days. ^d Stage 1+ KDIGO creatinine-based criteria within 30 days.

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Poster Session

Association of smoking history extracted from electronic health records (EHR) using machine-learning methods and tumor characteristics in patients with lung cancer. *First Author: Semanti Mukherjee, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Though smoking is a major risk factor for lung cancer, it has been a challenge to collect patients' smoking history information accurately from the EH due to data inconsistency and incompleteness. To address these challenges, we utilized a weak supervision methodology to automatically annotate smoking status of patients with lung cancer and correlated it with tumor characteristics. **Methods:** We analyzed 6,355 patients with lung cancer who underwent tumor profiling with MSK-IMPACT. In total, 14,555 unstructured clinical notes were extracted from EHR at the Memorial Sloan Kettering Cancer Center. The weak supervision methodology used a generative model for intermediate labels that were subsequently tuned by machine-learning classifier to generate the final labels. Clinical notes from a randomly sampled set of 564 patients were manually curated and used for performance assessment. The rest of the patients were split into training and validation datasets used for model training and hyperparameter tuning. Pack years were also extracted from clinical notes using Natural Language Processing. We next conducted multivariate analyses for primary and metastatic tumor samples separately to correlate smoking metrics with tumor characteristics including tumor mutation burden (TMB) and chromosomal instability, as inferred by the fraction of genome altered (FGA) after controlling for age at sequencing, gender, histological subtypes, ancestry, coverage and tumor purity. **Results:** The weak supervision classifier had almost perfect performance for 2-label classification model (ever smokers and never smokers) with macro F1-score: 97.7%, balanced accuracy: 97.1%, 97.1%, precision:98.4%, 98.4% and recall: 99.5%,94.6% respectively. For 3-label classification model (never smoker, former smoker, and current smoker), the macro F1-score was 79.8%; balanced accuracy: 97.1%, 86.7%, 71.2%, precision: 93.9%, 90.1%, 61.7%, recall: 96.1%, 93.3%, 46.0% respectively. Analyzing genomic data, we observed that smoking status (smoker vs. never smoker) and pack-years were associated with TMB in both primary and metastatic tumor samples ($p<2e-16$). FGA was marginally associated with smokers compared to never smokers in primary tumor samples ($p=0.06$). Among smokers diagnosed with lung adenocarcinoma, significantly high FGA in primary tumor samples was observed in males compared to females after adjusting for pack-years and other variables ($p=3.3e-3$). **Conclusions:** We demonstrated high performance of our approach for automated curation of smoking history from EHR. The genomic results confirmed distinct mutational patterns associated with smoking behavior in patients with lung cancer. We are currently exploring multimodal approaches by including chest CT images and "time of quitting" to improve performance of the 3-class model. Research Sponsor: U.S. National Institutes of Health.

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Poster Session

Early assessment of sotorasib for treatment of patients with advanced non-small cell lung cancer using real-world data in the United States. *First Author: Dvir Aran, Faculty of Biology, Technion-Israel Institute of Technology, Haifa, Israel*

Background: Sotorasib is the first small molecule for targeting tumors with KRAS G12C mutations. Despite promising early results which led to expedited approval, recent interim results from the phase III clinical trial suggest similar efficacy to standard-of-care chemotherapy docetaxel. Here we perform the first evaluation of sotorasib for the treatment of non-small cell lung cancer (NSCLC) in real-world setting. **Methods:** Elevance Health claims data was used. Lung cancer (LC) patients with sotorasib claims between June 2021-August 2022 were identified (assumed to be NSCLC). LC patients treated with docetaxel as second-line+ were used as control group. Potential confounding factors, including social determinant index (SDI), age, gender, Charlson Comorbidity Index (CCI), and metastases profile were addressed using inverse probability treatment weighting (IPTW). Outcomes were hospitalizations and real-world overall survival (rWOS), which was estimated using weighted Kaplan-Meier estimator. For comparison with the clinical trial population-level adjustments were performed. **Results:** Cohorts included 105 sotorasib-treated and 448 docetaxel-treated patients. Sotorasib-treated were primarily female, of older age and had more comorbidities. Post-treatment all-cause hospitalization rates were similar during the first 3 months (36% in both). Most common hospitalization diagnosis was gastrointestinal (GI) related which was uncommon in the control group (29% vs. 8%, $p < .001$). No evidence for liver toxicity was identified. For a subset of patients it was possible to perform survival analysis. Adjusted survival curves of RWD and the clinical trial (CodeBreak-100) were indistinguishable following population-level adjustment ($p = 0.92$). Adjusted RWD sotorasib and the control cohorts revealed non-significant difference in rWOS up to 6-months of follow-up (62% sotorasib vs. 55% docetaxel; $p = 0.1$). **Conclusions:** We present the first analysis of sotorasib in US real-world settings. This early analysis suggests that sotorasib does not provide survival benefit at 6-months follow-up. Sotorasib is associated with increased GI-related severe adverse events. RWD can be used to provide early information in expedited FDA approved treatments. Research Sponsor: None.

Baseline characteristics of sotorasib vs. docetaxel patients (RWD).

	Entire Cohort			rWOS subset		
	docetaxel	sotorasib	p-value	Docetaxel	sotorasib	p-value
N	448	105		311	39	
Gender (% female)	228 (50.9)	67 (63.8)	0.02	173 (55.6)	22 (56.4)	1.000
Age, mean (SD)	62.0 (8.4)	63.9 (8.7)	0.05	59.2 (6.4)	60.4 (5.4)	0.20
Metastasis (%)						
Liver	66 (14.7)	13 (12.4)	0.64	78 (25.1)	6 (15.4)	0.26
Bone	157 (35.0)	35 (33.3)	0.83	158 (50.8)	20 (51.3)	1.00
Brain	127 (28.3)	37 (35.2)	0.20	131 (42.1)	22 (56.4)	0.13
CCI, mean (SD)	1.0 (1.2)	1.5 (1.3)	0.001	1.0 (1.1)	1.1 (1.0)	0.53
SDI, mean (SD)	45.8 (26.9)	44.6 (28.1)	0.69	43.4 (26.3)	33.4 (23.7)	0.02

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Poster Session

Accuracy of a clinical decision support system in identifying patients at risk of cancer in primary care. *First Author: Bea Bakshi, C the Signs, Cambridge, MA*

Background: 85% of patients diagnosed with cancer are symptomatic at presentation. Yet a delay in diagnosis (e.g. missing a presentation) can result in late stage detection and poorer outcomes. Clinical decision support systems (CDSS) have been used in other fields to calculate risk and support standardization of care. However, little has been reported about successful implementation of CDSS with determining cancer risk. C the Signs is a CDSS which uses artificial intelligence, mapped with the latest evidence and guidance, to assist healthcare professionals in identifying patients at risk of cancer and determining the most appropriate pathway for diagnosis. The aim of this study is to assess the accuracy of C the Signs in a real-world setting. **Methods:** A retrospective observational study was conducted in the National Health Service in England utilizing all patients risk assessed for cancer through the Electronic Healthcare Record (EHR) integrated C the Signs platform between 1st January 2021 and 31st August 2022. A total of 118,677 patients were risk assessed. All patients were followed up for 6 months post risk assessment to determine outcome. A sub-analysis was performed on the patients who were flagged at risk of cancer through C the Signs and subsequently diagnosed with cancer to establish the CDSS's cancer origin accuracy (the ability for the system to accurately predict which cancer the patient is at risk of). **Results:** 7,295 patients were diagnosed with cancer within 6 months of a C the Signs risk assessment. 7,056 patients were successfully identified at risk of cancer by the CDSS with a sensitivity of 96.7%. There were 103,168 false positives with a specificity of 7.37%. Of the 8,453 patients who were identified as not at risk of cancer using the CDSS, 239 had a confirmed cancer diagnosis within 6 months of risk assessment (with a negative predictive value 97.2%). The cancer origin accuracy of C the Signs was 85.6% across all cancers. **Conclusions:** A cancer CDSS like C the Signs can be used to accurately identify patients at risk of cancer. More research is needed to understand the specificity and false positive rate, and the impact of identifying these patients with non-cancer disease. Research Sponsor: None.

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Poster Session

Natural language processing identification of documented mental health symptoms associated with risk of mental health disorders in patients with cancer. *First Author: Isabel D. Friesner, University of California, San Francisco, San Francisco, CA*

Background: Delayed diagnosis and care of mental health disorders (MHD) is a significant challenge in the care for patients with cancer. The objective of this study was to use natural language processing (NLP) to identify words related to mental health documented in clinical notes surrounding the time of cancer diagnosis and assess their predictive ability of future, new MHD. **Methods:** This single institution cohort study consisted of patients diagnosed with cancer between January 2012 and November 2022. Cancer and MHD were identified based on ICD-10 codes obtained from deidentified electronic health record data. MHD included psychotic disorders (F20-29), mood disorders (F30-39), and anxiety disorders (F40-48). The clinical Text Analysis Knowledge Extraction System was applied to deidentified clinical notes, and symptoms mapped to SNOMED concepts relevant to mental health were identified. These mental health symptoms were aggregated in the 15 days preceding and 15 days following a first cancer diagnosis and analyzed across MHD status. Patient characteristics including sex, age, race, cancer, and insurance were also analyzed. **Results:** This cohort consisted of 64,010 patients with cancer who had no documented MHD prior to cancer diagnosis, with a majority being 40-64 years old (45.8%) or 65+ (43.7%) and identifying as male (53.0%) or white (60.2%). Most patients had prostate (12.5%), hematologic (10.8%), or breast (10.3%) cancer and private insurance (46.2%). 9,825 (15.3%) patients developed a newly documented MHD, with a median time of 139 days (IQR: 40-466) from cancer diagnosis. The top five most common mental health documented symptoms for all patients were normal mood (23.3%), mental state finding (17.9%), worried (10.2%), feeling content (9.9%), and cognitive function finding (6.6%). Those who had a future MHD had higher documented rates across all mental health symptoms. Multivariate cox proportional hazards model identified 18-39 years old, female, white, and Medicaid or Medicare insurance as independent factors associated with an increased risk of a future, new MHD. Prostate cancer was associated with lower risk of a future MHD. Panic (OR 2.1 [95% CI 1.8-2.4]), feeling nervous (1.9 [1.5-2.4]), feeling guilt (1.9 [1.4-2.5]), mild anxiety (1.8 [1.4-2.4]), and feeling frustrated (1.4 [1.2-1.6]) were identified as the symptoms most strongly associated with an increased risk of a future MHD. **Conclusions:** NLP extracted mental health symptoms documented in clinical notes correlated with an increased risk of documented MHD. Computational approaches may be tools for improving the timely diagnosis of MHD and referral to specialty services. Further work is needed to investigate potential disparities in documentation and management of care for patients with cancer who develop MHD, including delays between documentation and eventual diagnosis. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology; Radiation Oncology Institute; University of California, San Francisco Computational Cancer grant.

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Poster Session

ALAN as an omic tool to build gene signatures and to stratify patients. *First Author: Hannah E. Bergom, University of Minnesota, Minneapolis, MN*

Background: Understanding aberrant gene behavior is critical towards devising clinical therapeutics or gene based diagnostic panels. Clustering and AI/ML have clinical utility, but they do not contextualize changes in gene behavior that result from differences in cell type, microenvironment, or prior treatments. Here, we developed the Algorithm for Linking Activity Networks (ALAN), an informatics algorithm that allows rapid functional comparisons of all detectable genes between clinically annotated patient cohorts. ALAN outputs quantify gene behavior without any additional inputs and can be applied on all forms of clinical omic data. We tested the utility of ALAN to identify the molecular features of resistance and novel precision therapeutics. **Methods:** We applied the ALAN algorithm in prostate tissue using whole-transcriptome sequencing (WTS) data from SU2C/PCF (n = 209, metastatic prostate cancer), TCGA (n = 493, primary prostate cancer), and GTEx (n = 245, benign prostate tissue). We conducted informatics analysis of whole-exome sequencing (WES) data from SU2C/PCF (n = 444 mPC), Fred Hutch (n = 130 mPC), and MCTP (n = 61 mPC) to identify mPC patients with amplifications in *RSPO2*. We scored an ALAN gene signature in a patient with single-cell RNA sequencing pre and post AR inhibition (n = 112, 83). We examined ChIP-seq data to evaluate binding of AR and Co-factors at the CD276 transcription regulatory sequences. **Results:** In mPCs, ALAN unbiasedly identified genes that prior studies have implicated as resistance mechanisms towards enzalutamide. In this process, ALAN nominated *RSPO2*, a secreted protein, as a potential resistant gene that has never been targeted in mPC. In recent studies, we found *RSPO2* amplifications in 19.7-28.5% of mPC. We utilized ALAN outputs to build a novel gene signature that was exclusively enriched (p-value < 0.0001) in the transcriptome collected from single cells of a post-resistant mPC sample. We also utilized ALAN to stratify the optimal mPC patients in receiving precision therapies against B7-H3 (CD276). B7-H3 is an immune regulatory molecule in the B7 superfamily that includes PD-L1 and CTLA-4 and has not been targeted in mPC. B7-H3 was unlike other B7 family members and exhibited robust association with AR co-factors and AR signaling. We confirmed ALAN findings as multiple B7-H3 transcriptional enhancers and promoters were bound by AR and AR-cofactors. **Conclusions:** ALAN is an algorithm that can be readily deployed on existing clinical omic data to build gene signatures, identify resistant genes, and risk stratify patients. ALAN nominated a novel therapeutic target, *RSPO2*, which is recurrently amplified in mPC patients. ALAN predicted that mPCs with high baseline levels of AR activity would be optimal candidates for B7-H3 precision therapeutics. Altogether, ALAN outputs should be considered for making clinical decisions that would benefit by comprehensive comparisons of all detectable genes. Research Sponsor: University of Minnesota Medical School.

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Poster Session

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Poster Session

Deep learning to estimate RECIST in patients with cancer treated in real-world settings. *First Author: Irbaz Bin Riaz, Dana-Farber Cancer Institute, Boston, MA*

Background: Creating large oncology clinical-genomic datasets is laborious and time-consuming. Deep learning approaches that extract RECIST outcomes at scale from observational electronic health records (EHR) data could tremendously facilitate precision oncology research. **Methods:** This retrospective study included patients with solid tumors treated on therapeutic clinical trials from 2004-2022 at Dana-Farber Cancer Institute with radiology reports in EHR and RECIST labels available from the tumor imaging metrics core. Each RECIST label was generated using corresponding radiology reports at a given time point. Patients were sampled into training, validation, and held-out test sets. A deep learning model (RECIST model) was trained to predict two outcomes: overall response and progressive disease at each time point, using reports from that time point and prior time points for each patient. This trained RECIST deep learning model was deployed on real-world radiology reports, and results were compared with true labels abstracted by trained human curators using the PRISMM framework. **Results:** This study included 5153 patients with a total of 99,318 radiological reports who had RECIST annotations (median age at protocol enrollment [IQR] 60 years [52-57]; females 61% [3133]; and white 90% [4653]). The most common cancer types included breast (n=1006; 20%) lung (n=573; 11%), and ovarian cancer (n=539; 10%). The training subset included 4121 (79.9%) patients, the validation subset 518 (10.1%), and the held-out test set 514 (9.9%) patients. In the test set, the results showed an AUC of 0.86, and 0.87 with the best F1 scores of 0.72 and 0.63 for predicting overall response, and progressive disease, respectively. The real-world data set included 4482 patients. RECIST model evaluation on real-world radiology reports showed good performance for ascertaining PRISMM annotations of progression from those reports (AUC 0.83, best F1 0.68), but poor performance for ascertaining PRISMM annotations of response (AUC 0.63, best F1 0.28). Evaluation metrics are outlined in the Table. **Conclusions:** This study demonstrated the feasibility of using deep learning approaches to predict RECIST outcomes from radiology reports for patients with solid cancer tumors. The results show that the deep learning model accurately predicted RECIST labels on a held-out test set and real-world radiology reports for the outcome of progressive disease. These findings could accelerate precision oncology research providing a scalable way of ascertaining cancer outcomes from observational EHR data. Research Sponsor: None.

Classification	Evaluation Metric	Validation subset	Held-out test set	Real world set
Primary Study Overall response	AUC	0.8526	0.8637	0.6326
	Average precision score	0.74	0.74	0.15
	Best F1 score	0.7138	0.7167	0.2811
Progressive disease	AUC	0.8691	0.8671	0.8329
	Average precision score	0.66	0.66	0.72
	Best F1 score	0.6423	0.6267	0.6778

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Poster Session

Trial eligibility criteria (EC) and diversity among patients with advanced non small cell lung cancer (advNSCLC). *First Author: Maneet Kaur, Flatiron Health, New York, NY*

Background: FDA guidance encourages using real world data in developing diversity plans for clinical trials. Diversity plans may incorporate more inclusive (or expanded) EC, which may increase enrollment of minoritized populations. Whether broadened EC affect the diversity of eligible participants is unknown. **Methods:** Using the nationwide Flatiron Health electronic health record-derived deidentified database, we included patients with advNSCLC from 1/17-11/30/22 with a line of therapy (LOT) (N=61596). EC were defined by FDA, NCI/CTEP, and ASCO/FoCR standards, and included ECOG, ALT, AST, ALP, bilirubin, eGFR, CrCl, HGB, ANC & PLT -90 to +7 days from first LOT. Claims-linkage identified brain mets (BM), congestive heart failure (CHF), hepatitis C (HCV) & B (HBV), HIV and myocardial infarction (MI) within 6 months of first LOT. Logistic regression estimated odds ratios (OR) for exclusion by criterion associated with gender, age, race/ethnicity and area-level socioeconomic status (SES). Adjusting for clinical characteristics, Cox regression estimated hazard ratios (HR) for real world overall survival (rWOS). **Results:** Female patients (vs male patients) had greater odds of exclusion by CrCl (OR 2.9), eGFR (OR 1.27) & BM (OR 1.30). Compared to non-Latinx (NL) white patients, NL Black patients had greater odds of exclusion by ECOG (OR 1.17), CrCl (OR 1.33), eGFR (OR 1.61), HGB (OR 2.2), ANC (OR 1.71), HIV (OR 5.31), CHF (OR 1.31), HBV (OR 2.29) and HCV (OR 2.73); NL Asian patients by ALT (OR 1.64), ALP (OR 1.71), CrCl (OR 1.63), BM (OR 1.45) and HBV (OR 26.2); and Latinx patients by ALP (OR 1.56), HIV (OR 2.23) and HCV (OR 1.47). Compared to younger patients (18-49), older patients (75-84) had greater odds of exclusion by ECOG (OR 2.12), bilirubin (OR 1.53), CrCl (OR 41.9), eGFR (OR 9.54), CHF (OR 4.9) and MI (OR 4.7). Patients with the lowest (vs highest) quintile of SES had greater odds of exclusion by ECOG (OR 1.29) and HGB (OR 1.52). Among patients with complete data on all non-claims criteria (N=22117), the impact of expanding EC on diversity is shown, except SES which was similar. Compared to standard EC, the group with expanded EC had lower rWOS (adj HR 1.32; 95% CI 1.28-1.37). **Conclusions:** Expanding EC has the potential to increase the proportion and absolute number of Black, older, and female patients in advNSCLC trials. The resulting more diverse eligible population may have different clinical outcomes compared to a cohort defined by more restrictive EC. Future work will explore generalizability of findings to other clinical contexts. Research Sponsor: This study was sponsored by Flatiron Health, Inc., which is an independent subsidiary of the Roche Group.

		Standard EC N=12411	Expanded EC N=20240	Change +63%	p
Age	18-64	5213 (42%)	7064 (35%)	+36%	<.001
	65-74	4699 (38%)	7498 (37%)	+60%	
	75+	2499 (20%)	5678 (28%)	+123%	
Gender	Female	5390 (43%)	9436 (47%)	+75%	<.001
Race/Ethnicity	Asian	324 (2.6%)	529 (2.6%)	+63%	<.001
	Latinx	387 (3.1%)	599 (3.0%)	+55%	
	NL Black	964 (7.8%)	1793 (8.9%)	+86%	
	NL White	8417 (68%)	13480 (67%)	+60%	
	Other/Unknown	2319 (19%)	3839 (19%)	+66%	

Impact of COVID-19 pandemic mitigation strategies on industry and NCI cancer treatment trials. *First Author: Joseph M. Unger, Fred Hutchinson Cancer Research Center, Seattle, WA*

Background: The onset of the COVID-19 pandemic resulted in major disruptions in enrollment and conduct of cancer clinical trials. In response, regulators allowed modifications to traditional trial processes to enable clinical research and care to continue. The American Society of Clinical Oncology and Friends of Cancer Research established a task force to evaluate how sponsors perceived the impact of these mitigation strategies on data quality and overall trial conduct. **Methods:** The study used a survey and live interviews of industry and National Cancer Institute (NCI) cooperative group sponsors of cancer treatment trials. Sponsors with trials active in the United States from January 2015-May 2022 were eligible. We assessed perceived impacts of the pandemic on protocol deviations, types of mitigation strategies, trial closures, dropouts, adverse events (AEs), and data integrity. Descriptive statistics were used for survey data summaries. Key findings from semi-structured interviews were described by theme. **Results:** Of forty-one eligible sponsors, 20 (49%; 15/36 industry and 5/5 cooperative group) completed the survey; eleven (55%; 7/15 industry and 4/5 cooperative group) were interviewed. Sixty percent of sponsors reported large portfolios (>10 trials) of phase II and/or phase III trials. The most widely adopted mitigation strategies were remote distribution of oral anticancer therapies (70%), remote consenting (65%), and remote symptom monitoring for AEs (65%). The proportion of sponsors reporting a “substantial” increase in protocol deviations compared to the pre-pandemic period dropped from 42% in the initial wave (March-April 2020) to 16% thereafter. Sponsors primarily reported “no change” in trial drop-out rates (77%), the number of trials closed due to low accrual (90%), or rates of AEs (81%) at any point during the pandemic. Overall, most (83%) respondents reported the pandemic had “minimal” (14) or “no” impact (1) on data integrity. In interviews, many sponsors reported persistent time delays in data entry related to labor shortages at sites. **Conclusions:** This study represents the first systematic evaluation of clinical trial sponsors about the impact of the COVID-19 pandemic on the conduct of cancer clinical trials. Remote clinical trial conduct mitigation strategies were broadly adopted. Despite an observed increase in protocol deviations, most sponsors reported the pandemic had minimal or no impact on data integrity. The COVID-19 pandemic impacted how cancer clinical trials were performed and has likely accelerated a trend towards greater flexibility in trial conduct that was already emerging, with potential benefits of reduced burden and improved access for patients and sites. Future work is planned to further quantify the impact of the pandemic and trial mitigation strategies on the quality of trial data both overall and for historically under-represented patient groups. Research Sponsor: None.

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Poster Session

Toxicity reporting consistency and subjective minimizing language use in colorectal cancer (CRC) and pancreatic cancer (PaC) clinical trials: A systematic review of phase III randomized controlled trials (RCTs) presented at ASCO between 2012-2022. *First Author: James Yu, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL*

Background: Objective and complete toxicity reporting in clinical trials is critical for patient-centered shared decision-making. Conference abstracts inform initial impressions of practice-changing treatments. **Methods:** We performed a systematic review of all abstracts of CRC and PaC phase 3 RCTs presented at ASCO annual meetings between 2012–2022; long-term follow-up, supportive care, and solely non-pharmacological studies were excluded. Objective minimization of adverse event (AE) reporting was defined as absent and/or incomplete reporting of cumulative grade 3-5 CTCAE (common terminology criteria for AE). We also assessed the use of subjective minimizing language (Chin-Yee et al ASH 2022), defined as use of “acceptable,” “tolerable,” “manageable”, “favorable” (primary minimization terms), or “feasible”, “safe”, “patients did well”, “limited” (secondary minimization terms), terms that falsely imply patients deemed the therapy as such. Presence/absence of PRO or QOL data was also assessed. **Results:** 63 RCTs met entry criteria (42 CRC, 21 PaC), detailed in Table. Most trials studied chemotherapy +/- other drugs (52; 83%). 17% of all abstracts did not provide any information on AE. Quantitative data on AEs were reported by 38 (60%) of abstracts. However, serious AE reporting was frequently absent (Table), with some trials reporting only specific toxicities (e.g. cytopenias) instead of cumulative CTCAE. Only 7 (11%) of abstracts noted the occurrence or absence of fatal AE. Any subjective-minimizing language was used in 15 (24%) abstracts. Notably, none of the abstracts using subjective-minimizing language provided information on fatal AE rates, nor reported on the patient perspective via QOL or PRO. Average grade ≥ 3 AE in the experimental arm were similar in abstracts with vs without minimizing language (44% vs 45%). **Conclusions:** Our systematic review of ph 3 RCTs in GI oncology presented at ASCO annual meetings reveals that subjective minimizing language is often used to describe serious toxicities, and without formally assessing the patient voice. Serious AE reporting is frequently absent or incomplete. Research Sponsor: None.

No. of abstracts	63 (Total)	42 (CRC)	21 (PaC)
No. of Pts, Mean (Range)	621 (40 - 6088)	719 (108-6088)	425 (40-1062)
Absent AE Reporting, No. (%)	11 (17%)	7 (17%)	4 (19%)
Absent Fatal AE reporting	56 (89%)	37 (88%)	19 (90%)
Absent Grade ≥ 3 CTCAE reporting	48 (76%)	30 (71%)	18 (86%)
Use of any subjective minimizing language	15 (24%)	8 (19%)	7 (33%)
Primary terms use	13 (21%)	8 (19%)	5 (24%)
Secondary term use	4 (6%)	2 (5%)	2 (10%)
Multiple minimization terms use	4 (6%)	3 (7%)	1 (5%)
Combined Subjective or Objective Toxicity minimization	60 (95%)	41 (98%)	19 (90%)

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Poster Session

Technology-enabled clinical trials: Intentional capture of source data (IDC) in the electronic-health record (EHR) and direct transfer to trial database (electronic data capture (EDC)) in a phase II multicenter trial. *First Author: Trevor Joseph Royce, Flatiron Health, New York, NY*

Background: Traditional data collection for clinical trials can be cumbersome and inefficient. FDA guidance now promotes capturing clinical trial source data in electronic form and transmitting it to the EDC, recognizing that this should reduce double data entry and improve data quality and timeliness. Electronic data originators can include the EHR, which can be used during routine clinical care and for gathering data during a clinical investigation. We evaluated a pilot of structured EHR data transfer to EDC in a clinical trial setting. **Methods:** IDC capability in the EHR was developed and applied to a subset of patients for an open label prospective Phase II study. EHR variables, that include free text, standard dictionaries (eg CTCAEv5, CDISC, First Databank), and derived responses, were mapped to the electronic case report form (eCRF). Bulk transmission of IDC clinical data (adverse events, AEs; concomitant medications, CMs; past medical history, PMH) from the EHR to EDC was executed at a designated time point during study conduct. We assessed the quantity (records) and quality (queries) of data captured and transferred, and timeliness of entry. Data to be used for the production analysis of the trial was collected via eCRF in an EDC system in parallel per usual standards. **Results:** Data for 102 patients across 8 sites of care by 99 different users was captured in the EHR via IDC from 3/1/2021 to 9/9/2022 and transferred from EHR to EDC in bulk on 9/9/22. 3,958 data records were transferred (852 AEs; 1,581 CMs; 1,525 PMHs). Of the AEs, 99% had an associated grade. Of the CMs and PMHs, none were copy-forwarded (all were entered *de novo*). Regarding queries in the EDC for transcription error validation among matching records, EHR data produced 205 opened edit check queries from 12 edit checks across all domains (149 AEs, 0 CMs, and 56 PMHs). Regarding timeliness, 95% of matched records were entered in IDC prior to entry in the production EDC. **Conclusions:** For an open label Phase II study, clinical trial source data was captured electronically through IDC using the EHR as the data originator, and directly bulk-transmitted to EDC. This may enable the elimination of transcription of source data entry into eCRF and result in more timely access to the data in the EDC. Additional investigation into how IDC with EHR-to-EDC compares in quality to traditional EDC is warranted. Planned follow up research includes interviewing site users to evaluate their experiences with IDC data entry. Research Sponsor: Genentech; Flatiron Health.

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Poster Session

The inclusion of health-related quality of life and other patient-reported outcomes in landmark trials for Food and Drug Administration oncology drug approvals: An analysis of cancer drug approvals between 2006 and 2022. *First Author: Ademola Samuel Ojo, Howard University Hospital, Washington, DC*

Background: How patients feel and function are essential elements of the clinical benefit of interventions which is often not captured by traditional measures of clinical benefit such as progression-free survival and overall survival. Health-related quality of life, functional status, symptom burden, and other patient-reported outcomes (PROs) assess the impact of interventions from the patient's point of view. The aim of this study is to assess the inclusion of PROs in landmark trials leading to FDA oncology drug approvals. **Methods:** This is a retrospective cross-sectional study of pivotal trials leading to FDA oncology approvals between January 2006 and December 2022 based on the FDA oncology approval notifications. The trial protocols of all pivotal trials were evaluated for inclusion of health-related quality of life or other PROs as an outcome measure. The approved therapies were classified into first-line, adjuvant/maintenance, and second or later line of treatment. Chi-square tests were used to assess the relationship between the line of treatment and the inclusion of PROs in the trial protocol. **Results:** There were 420 oncology approvals during the study period with the highest number of approvals in a single year in 2020 (56) and the least in 2007 (7). Lung cancer has the highest number of approvals (61, 14.5%) followed by lymphoma (50, 12%), leukemia (49, 11.7%), genitourinary malignancies (48, 11.4%), breast cancer (36, 8.6%), gastrointestinal malignancies (32, 7.6%), plasma cell disorders (30, 7.1%) melanoma (20, 4.8%), gynecological malignancies (20, 4.8%), hepatobiliary malignancies (14, 3.3%) and head/neck cancers (14, 3.3%). The approved therapies were first line (146, 34.8%), second or higher line (226, 53.8%), and adjuvant/maintenance therapies (48, 11.4%). PROs were included in 40.7% of the pivotal trials. There is a rising trend in the inclusion of PROs from 5.5% of pivotal trials in 2006 to 31% in 2022. Trials on first-line therapies are more likely to include PROs compared to second or higher-line therapies (44.5% vs 36.7%; $p = 0.13$). **Conclusions:** Although there is a rising trend in the inclusion of health-related quality of life and other PROs in pivotal trials for FDA oncology drug approvals, most pivotal trials did not include PROs as outcome measures. Research Sponsor: None.

Year	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	Total
First line																		
PRO included	0	1	2	1	2	4	1	4	4	2	1	2	9	11	12	5	4	65
PRO not included	7	1	2	1	3	1	4	2	1	5	3	8	14	12	8	8	8	81
Adjuvant/maintenance																		
PRO included	1	1	0	1	1	1	0	0	0	1	0	5	3	1	3	4	1	23
PRO not included	5	2	2	0	0	1	2	1	0	2	0	1	2	1	1	2	3	25
2nd or higher line																		
PRO included	0	1	0	2	1	2	3	2	4	12	5	7	7	6	10	13	8	83
PRO not included	5	1	2	3	2	3	8	4	9	6	9	15	12	18	19	18	14	143
Total	18	7	8	8	9	12	18	13	18	28	18	32	47	35	56	51	42	420

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Poster Session

Endpoints reported in phase 3 randomized clinical trials at ASCO 2022. *First Author: Laure-Anne Marie Nicole Teuwen, Department of oncology, Antwerp University Hospital, Edegem, Belgium*

Background: The goal of phase 3 randomized clinical trials (RCTs) is to show clinically meaningful benefit for patients. An analysis of phase 3 RCTs presented at the ASCO 2022 Annual Meeting (ASCO22) was undertaken to assess which endpoints were evaluated. **Methods:** A systematic analysis was undertaken of ASCO22 abstracts from phase 3 RCTs reporting primary, secondary, interim, updated, and subgroup analyses, as well as trials reporting methodology of currently enrolling studies. Trials that reported posthoc, exploratory, biomarker, and retrospective analyses of RCTs were excluded. Information from ASCO22 materials and clinical trial registration websites was recorded by two independent researchers. **Results:** In total, 166 RCTs were identified: 93 trials with 50,781 enrolled patients and 73 trials expected to enroll 52,098 patients. More trials reported on patients with locally advanced/metastatic cancer (64.5%) compared to localized cancer (35.5%). Funding source was pharmaceutical or biotechnology company in 62%. Within locally advanced/metastatic trials, overall survival (OS) was a primary endpoint in 40%, while progression-free survival (PFS) was a primary or co-primary endpoint in 45% and 13% respectively. Other primary endpoints included (invasive) disease-free survival ((i)DFS), event free survival (EFS), overall response rate and pathological complete response. In trials that did not include OS as a primary endpoint, OS was a secondary endpoint in 88% ($n = 56/64$). Within the localized group, trials were subdivided into adjuvant, neo-adjuvant, definitive and other categories. Within the adjuvant trials ($n = 27$), the most common primary endpoint was (i)DFS (37%), followed by OS (15%). Other primary endpoints included recurrence-free survival, invasive breast cancer free survival, metastasis-free survival, EFS, and PFS. Across all trials, quality of life (QOL) was never reported as a primary endpoint, however it was as a secondary or other outcome in 53% for locally advanced/metastatic trials and 42% for localized trials. When comparing the endpoints reported in the ASCO22 abstract and meeting materials with those listed on the trial registration website, discordance was noted in 14%. **Conclusions:** Phase 3 RCTs presented at ASCO22 represented participation from over 100,000 patients, however, fewer than half in locally advanced/metastatic cancer and fewer than one quarter in localized disease utilized OS as a primary endpoint. QOL was listed as an endpoint in roughly one half of all trials. Endpoints reported did not match registration data in a significant minority. Debate over which endpoints should be used for cancer RCTs should be informed by this data. Research Sponsor: None.

1571

Poster Session

Utilizing Drug Combo to improve the design of phase 1 trials for anticancer drugs. *First Author: Lei Wang, Department of Biomedical Informatics, The Ohio State University, Columbus, OH*

Background: Accurate prior knowledge of a single drug or drug combination on toxicity, pharmacokinetics (PK), maximum tolerated dose (MTD), and dose-limiting toxicity (DLT) can help oncologists and statisticians design an efficient phase 1 clinical trial. However, most of the relevant knowledge is shattered in various databases. More importantly, MTD and DLT are missing in any databases. This study constructed a comprehensive knowledge base with expert-curated MTD and DLT knowledge from published anticancer drug combination phase 1 clinical trial results. We also demonstrated the utility of the knowledgebase to design a more efficient phase 1 trial. **Methods:** Toxicity, pharmacology, and PK knowledge were integrated from publicly available data sources, including DrugBank, SIDER, and drug labels. An interdisciplinary team manually curated the MTD and DLT knowledge. Relevant papers were discovered by PubMed keyword search (drug name + MTD or RP2D). Details regarding patient eligibility, treatment information (dose, formula, and schedule), trial design method, dose levels, DLT definition, MTD or Recommended phase 2 dose, and DLT incident were curated in the structured data format and stored in a database. Rxnorm and MedDRA were used for normalizing drug names and DLT. **Results:** Currently, 2358 papers on cancer drugs phase 1 trial have been curated. Additionally, pharmacological and PK knowledge of 197 cancer drugs, ADE information from 1094 drug labels, and more than 500,000 pieces of DDI evidence were integrated into the knowledge base. This knowledge base (drugcombo.info) could help researchers design an efficient phase 1 trial. For example, based on knowledge from Drug Combo, the combination of nivolumab and axitinib did not have potential PK DDI and severe overlapping toxicity. The reviewing physician considered a phase 1b study to start at a curated 5 mg maximum dose of axitinib with dose reduction to 3 and 2 mg and maintenance of a 3-mg/kg dose of nivolumab based on guidelines. With such additional preliminary knowledge, the reviewing statistician felt the adaptive statistical methods could be applied to redesign this phase I combination trial and minimize patient exposure to sub-therapeutic dose levels. **Conclusions:** To our knowledge, Drug Combo is the first knowledge that integrated curated MTD and DLT knowledge. It would promote applying curated knowledge to better design phase I trials to treat cancer. Research Sponsor: U.S. National Institutes of Health.

1572

Poster Session

Streamlining regulatory review in a multicenter platform trial: Opportunity to enhance patient centered care and drive innovation and efficiency. *First Author: Alexis Colley, University of California, San Francisco, San Francisco, CA*

Background: In addition to being required by the Federal Policy for the Protection of Human Subjects for United States-based institutions that receive federal funding and are engaged in cooperative research projects, the use of a central Institutional Review Board (cIRB) has multiple benefits. Yet more advanced trial designs have unique needs and challenges that may hinder adoption of an efficient cIRB. Platform trials, which require both a master protocol and successive individual protocol amendments for each new agent, are prone to high regulatory burden that can slow trial recruitment, representing a significant workload for study personnel. Specific challenges for platform trials include high burden of new amendments and IRB review schedules staggered across sites, making it challenging to have all sites operating under the same amendment concurrently. **Methods:** Administrative assessments were collected over the course of the I-SPY2 trial. The primary outcome of interest was time from amendment submission to approval (calculated as the number of days from submission to the local IRB by the site investigators to approval by the local IRB). Quantitative data in terms of hours spent on regulatory tasks pre- and post-cIRB implementation was estimated. Site investigators were asked in December 2022 to complete a brief questionnaire to investigate perceptions on changes to workload and level of comfort using a cIRB. **Results:** Amendments were activated when 50% of high accruing sites had IRB approval. The number of sites with approval for an amendment to go live was < 25% prior to cIRB adoption, and 83% after. Following transition to the cIRB in February 2021, the mean time from amendment submission to approval decreased from 54.4 to 20.7 days by Jan 2023. Changes to the informed consent were possible once the cIRB was adopted, including: standardizing site-specific IRB language in a section of the consent, so it need not be adjusted with every new agent amendment; standardizing site-specific workflows; shortening consent and making it more patient friendly. The average time that CRCs spent on regulatory work at each site decreased by an average of 160 minutes, but was variable, revealing continued use of local IRB, other committees at some sites. A total of 14 respondents completed the survey; most respondents indicated that keeping up with the amendment approval process was easier post-cIRB and 94% were comfortable relying on a cIRB. The short time for cIRB approval revealed the inefficiency of other processes, including coverage analysis and building of drug order sets. **Conclusions:** Active engagement of cIRB leadership and IRB working group has enabled regulatory review that now takes less than 30 days. The cIRB is now the standard for the I-SPY family of trials. Other services can also be shared and will continue to drive efficiency and reduce the regulatory burden for sites. Research Sponsor: U.S. National Institutes of Health; Quantum Leap Healthcare Collaborative.

1574

Poster Session

Use of gender-neutral language in clinical trial protocols in select cancers. *First Author: Garima Gupta, University of Kentucky, Lexington, KY*

Background: Around 21% of Generation Z Americans self-identify as lesbian, gay, bisexual, transgender (LGBT), nearly double the proportion of millennials. Despite Affordable Care Act Section 1557 in 2020, transgender individuals continue to have poor access to quality cancer care, including clinical trials. The National Institutes of Health (NIH) recognizes that using gender-neutral language in healthcare is one of many ways to improve sexual and gender minorities (SGM) related health disparities. This study examines use of gender-neutral language in clinical trial protocols in select cancers. **Methods:** Data was collected from clinicaltrials.gov, a commonly used resource for patients and providers. Phase III clinical trials with all recruitment statuses in the US from 2017 to 2022 were included. Cancer types were limited to those with highest risk of using gender-biased language: breast, ovarian, endometrial, fallopian tube, cervical, prostate, testicular, and penile. For each trial, frequency of use of following terms was recorded by searching under study details section: male, female, she, her, he, his, him, man/men, woman/women, breastfeeding/nursing/lactating/pregnant mother or female or woman. Mean frequency was compared between 2017-19 and 2020-22 using Wilcoxon signed-rank test. Funder type, eligible sex, gender-based eligibility and gender eligibility description were also collected. Data were compared between 2017-19 (pre-1557) and 2020-22 (post-1557) using Fisher exact test. **Results:** 243 studies were included in the analysis; 130 were pre- and 113 were post-1557. 103/130 (80%) studies between 2017-19 and 78/113 (70%) between 2020-22 included at least one gender-biased term or "male/female" outside of eligible sex description ($p = 0.05$), depicting a trend towards improvement; stronger improvement was noted in non-NIH funded studies versus NIH-funded studies. Mean frequency of gender-biased terms was higher in 2017-19 compared to 2020-22 (2.25 vs 1.88, $p = 0.02$). 27/130 studies (21%) between 2017-19 and 21/113 (19%) of studies between 2020-22 required gender-based eligibility ($p = 0.40$). Amongst these, 100% of studies between 2017-19 and 95% of studies between 2020-22 either provided no description or used this clause incorrectly, commenting on sex assigned at birth and not gender identity. This indicates lack of awareness regarding difference between sex assigned at birth and gender identity. While it is evident to investigators during registration on clinicaltrials.gov that eligible sex refers to biological sex, it is not to anyone reviewing the trial for enrollment, resulting in implicit bias. **Conclusions:** Our study highlights the dire need to address SGM-related health disparities and brings attention towards paucity of gender-neutral language in clinical trial protocols. This step is critical in providing more inclusive care and capturing the rising population of LGBT individuals. Research Sponsor: None.

1573

Poster Session

Survival-inferred fragility index of FDA-approved cancer drugs using surrogate endpoints. *First Author: Jonathan Ofer, Davidoff Cancer Center, Rabin Medical Center–Beilinson Hospital, Petah Tikvah, Israel*

Background: The survival-inferred fragility index (SIFI) quantifies the robustness of positive trials by estimating the number of changes in a survival analysis that would render the results insignificant. Here, we use a variation of SIFI (SIFI-median) in which the median patient is reassigned between study groups until significance is lost. Our goal was to study the robustness of oncology randomized controlled trials (RCTs) leading to drug approval by the FDA based on surrogate time-to-event endpoints. **Methods:** In this cross-sectional study, we identified phase II-III RCTs between 2010 and 2020. We reconstructed individual patient data from published Kaplan-Meier plots of surrogate time-to-event endpoints and calculated the SIFI-median, i.e., the minimum number of median survivor reassignments from the intervention group to the control group that would cause the loss of statistical significance. **Results:** A total of 101 studies comprising 60697 patients met the inclusion criteria. The most common surrogate endpoint was PFS 86 (85.1%), followed by DFS 7 (6.9%). The SIFI-median was 23 (interquartile range [IQR], 12 to 37) and the SIFI-median as a proportion of sample size was 5.3% (IQR, 2.7% to 8.1%). Forty-five studies (44.5%) had SIFI-median less than 5% of the total sample size which was often less than the number of censored patients during early follow-up. The SIFI-median was less than 1% of the total sample size in 10 studies (9.9%). **Conclusions:** Low fragility indices indicates that the statistical conclusions of clinical studies could be reversed with a small number of variations. The lack of statistical robustness in multiple FDA-approved drugs suggests higher uncertainty in their clinical benefit. Research Sponsor: None.

ABSTRACT
WITHDRAWN

1576

Poster Session

Trends in U.S and global patient enrollment from 2014 to 2022 in lung cancer clinical trials supporting marketing applications: An FDA analysis. *First Author: Oladimeji Akinboro, Office of Oncologic Diseases, Office of New Drugs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, MD*

Background: Oncology drug development is an increasingly global endeavor, however it is unclear how enrollment in registration clinical trials for lung cancer have been impacted. Clinical trial data must be reflective of the intended population in order to be considered applicable to U.S patients and medical practice, and for FDA review. **Methods:** Registration clinical trials supporting lung cancer indications submitted to FDA from 2014 to 2022 were included. Patient enrollment per country was extracted for each trial, and countries were grouped into 9 global regions. The proportion of patients enrolled in the U.S and global regions were calculated for each trial. For the purpose of this analysis, MRCTs were defined as trials that enrolled at least 5% of patients from each of ≥ 3 global regions with no region accounting for $\geq 70\%$ of patient enrollment. Trial-level patient enrollment was aggregated into 3 triennia: 2014-2016, 2017-2019, and 2020-2022. **Results:** A total of 66 pivotal trials supporting 59 applications submitted to FDA were evaluated during the study period. Of these, 91% ($n=60$) were for non-small cell lung cancer while 9% ($n=6$) were for small cell lung cancer; 59% ($n=39$) were randomized controlled trials (RCTs) while 41% ($n=27$) were single-arm trials; 53% ($n=35$) were for biologics while 47% ($n=31$) were for non-biologics; and 86% ($n=30$) of the biologics-based regimens were anti-programmed death (ligand)-1 antibody-containing regimens. The proportion of trials with no U.S patient enrollment increased from 4.8% in 2014-2016 to 19.0% in 2020-2022 while those with $\geq 10\%$ U.S patient enrollment declined from 71.4% in 2014-2016 to 52.3% in 2020-2022. There was a decline in the proportion of trials conducted as MRCTs since 2014 from 85.7% in 2014-2016 to 66.7% in 2020-2022. **Conclusions:** This exploratory analysis suggests that there may be declining U.S patient enrollment in lung cancer pivotal trials, and the proportion of these trials conducted as MRCTs may also be declining. These patterns of decline appear to be driven by the countries selected for patient enrollment in RCTs rather than in single-arm trials. Pivotal trials that do not enroll U.S patients and are not conducted as true MRCTs may have limited applicability to U.S patients. Research Sponsor: None.

US patient enrollment in pivotal trials supporting applications for lung cancer indications submitted to FDA from 2014 to 2022.

	TRIENNIAL	TRIALS, <i>n</i>	US PATIENT ENROLLMENT, %			TRIALS CONDUCTED AS MRCTs, %
			0%	> 0% to < 10%	$\geq 10\%$	
ALL TRIALS (<i>N</i> =66)	2014-2016	21	4.8	23.8	71.4	85.7
	2017-2019	24	12.5	33.3	54.2	75.0
	2020-2022	21	19.0	28.6	52.3	66.7
RCTs (<i>N</i> =39)	2014-2016	13	7.7	38.5	53.8	92.3
	2017-2019	15	13.3	53.3	33.3	80.0
	2020-2022	11	36.4	45.5	18.2	81.8
Single-arm Trials (<i>N</i> =27)	2014-2016	8	0	0	100	75.0
	2017-2019	9	11.1	0	88.9	66.7
	2020-2022	10	0	10.0	90.0	50.0

MRCTs=multi-regional clinical trials; *N*=number; RCTs=randomized controlled trials.

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Poster Session

Quantifying the growth of clinical actionability in precision oncology using OncoKB. *First Author: Sarah P. Suehnholz, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: OncoKB (www.oncokb.org), Memorial Sloan Kettering's (MSK) precision oncology knowledge base, contains curated information about the oncogenic effect and therapeutic implications of somatic alterations in cancer and is the first cancer variant database to be partially recognized by the US-FDA. Individual mutations and structural alterations in OncoKB are assigned a level of evidence based on whether the alteration is a predictive biomarker of response or resistance to a genomically matched standard care or investigational drug in a specific cancer subtype. As of February 2023, OncoKB includes annotations for >6200 alterations in >700 cancer-associated genes, including 50 level 1 or 2 standard care genes (specified in the FDA drug label or professional guidelines) as well as 9 level 3A and 12 level 4 genes (predictive of drug response based on well-powered clinical studies or compelling biological evidence, respectively). OncoKB data is used internally to annotate >15,000 MSK patient sequencing reports annually, and its content is integrated into the cBioPortal for Cancer Genomics. **Methods:** To quantitate the expansion of the clinical actionability landscape in precision oncology, we annotated the clinical sequencing results of 47,271 solid tumor samples from the AACR Project GENIE cohort (GENIE 11.0 - public) using two versions of OncoKB, the first from March 2017 and the second from November 2022. **Results:** From 2017 to 2022, we observed a 22.7% increase in the fraction of samples with a standard care biomarker (levels 1 and 2), and a 21.4% decrease in the fraction of samples with a driver alteration that was not clinically actionable. The tumor agnostic approvals of the anti-PD1 antibody pembrolizumab in microsatellite instability high (MSI-H) and tumor mutational burden high (TMB-H) solid tumors resulted in a 11.1% increase of samples with a level 1 biomarker. In sum, of the 38,722 samples across 66 cancer types with limited to no actionability in 2017 (levels 3B, 4 or no level), 21.7% became clinically actionable (levels 1, 2 or 3A) by November 2022. This is an upper bound estimate as it includes samples that may have been eligible for an FDA-approved precision oncology therapy based on cancer subtype alone. **Conclusions:** Our analysis highlights the significant expansion of precision oncology-based therapeutic options for patients with cancer over the past 5 years, as well as the ongoing unmet need for novel precision oncology approaches designed to address oncogenic but not currently actionable drug targets. Research Sponsor: None.

Clinical actionability of solid tumor samples from AACR project GENIE cohort.

Highest OncoKB Level of Evidence	OncoKB version March 2017	OncoKB version Nov. 2022
Level 1 (including MSI-H)	7.7%	21.0%
Level 1 (only TMB-H)	0%	9.2%
Level 2	1.2%	1.4%
Level 3A	9.2%	4.3%
Level 3B	20.0%	13.6%
Level 4	8.6%	20.6%
Driver without actionability	44.2%	22.8%
No Driver or no alteration	9.1%	7.1%

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Poster Session

Clinical pathways innovation: A lesson on the value of clinician based feedback and collaboration with Flatiron Health. *First Author: Christopher Davella, Department of Hematology/Oncology, University of Pennsylvania, Philadelphia, PA*

Background: Clinical pathways have emerged as a strategy to provide value-based care by reducing treatment variation across oncology practice. Despite evidence for cost reduction and improved patient outcomes, adoption of clinical pathways has met resistance in the oncology community given concerns regarding the impact on workflow, and cost. Flatiron Assist, an EMR based pathways tool, is a promising solution to minimizing workflow friction by providing a novel, streamlined user interface. **Methods:** The Abramson Cancer Center at the University of Pennsylvania and Flatiron Health conducted a pilot study from August 2021-December 2022 to test the use of Flatiron Assist within its thoracic oncology practices. The goal of the pilot was to increase utilization as well as usability of the pathways tool over time through clinician and developer iterative collaboration. Penn's clinical pathways were incorporated into the tool and integrated into the EMR. An education program trained clinicians on the tool's functionality. Based on clinician feedback, the Penn team identified two areas of improvement for the tool: speed and organization of the tool keys and prompts. Changes made over time included: 1) increasing the speed of the tool 2) restructuring the organization of keys and prompts, and 3) creation of a "hot button" for three common clinical scenarios in order to increase efficiency. Speed of the application (session length in seconds), utilization of the hot button (number of sessions/overall sessions) and overall physician adoption (treatment ordering with Flatiron Assist/total thoracic orders) were calculated during the pilot. **Results:** Provider utilization of the pathways tool increased over time with a baseline adoption rate of 29% in August 2021 and a peak of 74% in April 2022. Median session length decreased over time from 106.4 seconds (August 2021) to 39.9 seconds (December 2022). Peak performance for session length was 38.2 seconds (November 2022). Usage of the hot button introduced in August 2022 has increased over time from 27.6% of sessions to 41.8% in November 2022. Thoracic providers ordered, on average, 1.7 new treatment plans per week, resulting in less than 1.5 extra minutes of work per week with optimal use of the pathways tool. **Conclusions:** Collaboration between Penn and Flatiron Health effectively reduced specific areas of friction associated with the use of Flatiron Assist. Changes made to the speed, button organization and functionality of the tool contributed to increased clinician utilization over time. Future development of EMR based pathway tools should incorporate clinician engagement and feedback. Research Sponsor: None.

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Poster Session

Completion rates and trends of the patient-reported outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) across 14 oncology clinical trials. *First Author: Jessica A Emerson, Clario, Philadelphia, PA*

Background: With growing emphasis on patient-centered regulatory decision making, there is a greater need to incorporate the patient's voice in oncology clinical trials. Regulatory guidelines outline core patient-reported outcomes (PROs) to include which can inform risk/benefit evaluation. Self-reported symptomatic adverse events (AE) form part of these core PROs, with the new 2023 draft FDA guidance acknowledging the benefits of including them to enhance the assessment of tolerability in early phase dose optimization trials. Given the clinical symptoms and disease burden in oncology, patient burden needs to be thoughtfully considered when incorporating PROs into trials. We assessed trends and feasibility of electronic data collection for symptomatic AEs by analyzing completion compliance and time to complete the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) across 14 oncology trials. **Methods:** All PRO-CTCAE were collected electronically on Clario Tablets. Operational data for completion status (completed or missed) and duration of time to complete the PRO-CTCAE in seconds was extracted. Completion rates over time were examined overall and for every 3-month interval (quarters Q1 to Q9+). The median was selected for analyses of time to complete to account for skewness. **Results:** The sample included 14 studies across Phase I-III trials across a range of cancers including multiple myeloma, mesothelioma and cancers of the lung, prostate, head/neck, gastric, breast, and ovary. Study durations were 24 weeks and up. The PRO-CTCAE form was completed 13,122 times and missed in 1,182 instances, giving an overall completion rate of 91.7%. On average, 25 questions (range 5-47) covered an average of 13 symptoms (range: 4-25). Completion rate was not associated with the number of questions asked or time since enrollment. The overall median time to complete the PRO-CTCAE was 82s (study-specific median range: 24s to 276s). Examining time to completion as a function of the number of questions revealed a significant positive association, such that each additional question added 5.2 seconds to the time it took to complete the assessment. **Conclusions:** Completion compliance was high for PRO-CTCAE and remained high regardless of study length and the number of questions included in the PRO-CTCAE form. This suggests that electronic PRO-CTCAE is a feasible solution for collecting self-reported symptomatic AEs. Although time to complete the form increased with the number of questions, results suggest that including a higher number of PRO-CTCAE questions does not negatively impact compliance rate. Our data showing high completion rates may also reflect the benefits of electronic PROs in reducing patient burden and enhancing data quality, as acknowledged by regulatory agencies. Research Sponsor: Clario.

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Poster Session

Association of remote, longitudinal patient-reported outcomes (PROs) and step counts with hospitalization or death among patients with advanced cancer undergoing chemotherapy: Secondary analysis of the PROStep randomized trial. *First Author: Ravi Bharat Parikh, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA*

Background: Patients with advanced cancer undergoing chemotherapy experience significant symptoms and declines in functional status, which are often associated with poor outcomes. Remote monitoring of PROs (symptoms) and step counts (functional status), may proactively identify patients at risk of hospitalization or death. Our objectives were to evaluate the association of 1) longitudinal PROs with step counts, and 2) PROs and step counts with hospitalization or death. **Methods:** The PROStep randomized trial (NCT04616768) enrolled 108 patients with advanced gastrointestinal (GI) or lung cancers undergoing cytotoxic chemotherapy at a large academic cancer center. Patients were randomized to weekly text-based monitoring of 8 PROs (each measured on a 0-4 scale) + continuous step count monitoring via Fitbit, vs usual care. This pre-planned secondary analysis included 57 of 75 patients randomized to the intervention who had PRO and step data. We analyzed associations between PROs and mean daily step count, and associations of PROs and step counts with the composite outcome of hospitalization or death, using bootstrapped generalized linear models to account for longitudinal data. **Results:** Among 57 evaluable patients, mean age was 57 years, 24 (42%) were female, 49 (86%) were White, 43 (75%) had advanced GI cancer, and 14 (25%) had advanced lung cancer. A 1-point weekly increase (on a 32-point scale) in aggregate PRO score was associated with 247 fewer mean daily steps (95% CI -277, -213, $p < 0.001$). PROs most strongly associated with step count decline were patient-reported activity level (daily step change -892), nausea (-677), and constipation (-524). 25 patients (44%) were hospitalized ($n = 21$) or died ($n = 8$). A 1-point weekly increase in aggregate PRO score was associated with 20% greater odds of hospitalization or death (adjusted odds ratio [aOR] 1.2, 95% CI 1.1, 1.4, $p = 0.008$). PROs most strongly associated with hospitalization/death were pain (aOR 3.2), decreased activity (aOR 3.2), dyspnea (aOR 2.6) and sadness (aOR 2.1). A decrease in 1000 steps was associated with 16% greater odds of hospitalization or death (aOR 1.2, 95% CI 1.0, 1.3, $p = 0.03$). Compared to baseline, mean daily step count decreased 6.7%, 8.5%, 16.2% in the 3, 2, and 1 weeks prior to hospitalization/death. Mean aggregate PRO score increased by 11.0%, 25.3%, 36.4% in the 3, 2, and 1 weeks prior to hospitalization/death. **Conclusions:** In this secondary analysis of a randomized trial, increased PRO-based symptom burden was associated with lower daily step count. Higher symptom burden and decreased step count were independently associated with and predictably worsened close to hospitalization or death. Future interventions should leverage longitudinal PRO and step data to identify risk for poor outcomes. Clinical trial information: NCT04616768. Research Sponsor: U.S. National Institutes of Health.

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Poster Session

The Tempus TIME trial portal and clinical trial enrollment. *First Author: Amol Rao, Memorial Care, Fountain Valley, CA*

Background: The TIME Trial Program is a research network that screens > 1 million patients daily via EMR integrations and NGS testing through an automated trial matching platform and human review. There are enormous complexities following patients longitudinally as their clinical status changes while accurately matching them with hundreds of studies. The TIME Trials Portal, which stores both clinical trial documents and patient status updates, allows for real-time communication between the TIME team and Clinical Sites. **Methods:** After both an automated and nursing review, eligible trial patients are uploaded into the TIME Trials Portal. This database tracks the patient's name, date of birth, biomarkers, clinical status, trial matches, free text comments, and upcoming physician, radiology, and laboratory appointments. To protect Personal Health Information, each Clinical Site can only view their own patients. Patient status is classified as Needs Review, Monitoring, Enrolled, Inactive. Each update is time-stamped and tracked. Enrolled patients have the trial name, consent date, and other pertinent information documented. **Results:** The data from 2020 to 2022 includes 71 TIME Sites. Over this period, 6,816 patients were added to the TIME Trials Portal for an average of 219 per month. Of these, 1,891 patients were no longer eligible due to worsening performance status, trial closure, death, and other causes. The TIME team provided 8,643 patient updates compared to 7,442 Clinical Site updates. Clinical Sites spent 1,231.7 hours using the TIME Therapies Portal resulting in 623 total consents. Data from 2022 alone, demonstrated that 30 (42.3%) Clinical Sites with EMR integrations were responsible for 4,491 (76.3% of the total) patient updates translating into 288 (82.1%) of all consents. Also in 2022, of the 27 (38%) Clinical Sites that updated their patient's status > 50 times consented 291 (82.9% of the total) patients. **Conclusions:** By 2022, the TIME Trials Portal was averaging approximately 400 new patients monthly resulting in a 13.1X increase in patients added from the program's inception. Clinical Sites updated the patient status over 7,400 times spending over 1,200 hours using the TIME Trials Portal. The highest-performing Clinical Sites, which enrolled approximately 80% of the total patients, included those with EMR integrations and/or > 50 patient updates yearly. The TIME Trials Portal enabled patient tracking and communication to facilitate clinical trial enrollment. Research Sponsor: Tempus Laboratories.

Tempus TIME trials portal (2020-2022).				
Data	2020	2021	2022	Total
Time Sites	31	55	71	71
EMR Integrated TIME Sites	14	23	30	30
Patients Added Total	365	1,691	4,789	6,816
Patients Added Monthly (Average)	48	141	399	219
Patients No Longer Trial Eligible	132	498	1,261	1,891
Patient Status Changes by TIME Team	542	2,081	6,020	8,643
Patient Updates by Clinical Sites	N/A	1,285	6,157	7,442
Clinical Site Hours on TIME Trial Portal	0	352.3	879.4	1,231.7
Consents	20	252	351	623

1582

Poster Session

Differences in perceptions and use of remote patient monitoring technology in rural cancer programs. *First Author: David Penberthy, Penn State Health, Hershey, PA*

Background: While the benefits and acceptability of remote patient monitoring (RPM) during cancer care are well documented, barriers to implementation and use of these digital technologies remain. Feasibility may be particularly restricted in rural settings. The Association of Community Cancer Centers (ACCC) surveyed U.S. cancer programs, patients with cancer and caregivers in various geographic settings to illuminate the current practice landscape and perceptions regarding the use of digital technologies to monitor patients for adverse events and collect patient reported outcomes (PROs). **Methods:** ACCC convened an expert advisory committee and patient advocacy partners to guide development of two surveys, one for cancer program staff and the other for patients/caregivers. Surveys were distributed between December 2022 and January 2023 and included 25 closed and open-ended questions. Exploratory analysis was performed and responses were compared between rural, suburban, and urban settings for both groups, with comparisons made by two tailed Fisher's exact test. **Results:** There were 128 cancer program staff and 162 patient/caregiver responses. Of staff respondents (52% physicians, 20% other clinicians, 21% administrators/managers), 58% work in urban, 30% suburban, and 13% rural settings. Of the patient/caregiver respondents (56% patients, 44% caregivers), 28% live in urban, 51% suburban, and 21% rural areas. 56% of rural, 24% of urban, and 26% of suburban respondents indicated that their cancer programs have not implemented and are not considering implementing RPM. Of rural program staff, 44% indicated they have no experience/familiarity with RPM, compared to 7% for urban and 13% for suburban staff ($p < .001$, $p = .03$, respectively). Fewer rural programs, as compared to urban, use secure text messaging (6% vs. 42%; $p = .008$) or automated phone surveys (6% vs. 34%; $p = .03$). More rural patients/caregivers compared to their urban/suburban counterparts indicated concerns about privacy (47% vs 27%; $p = .02$), concerns about the need to pay (44% vs. 19%; $p = .004$), and lack of strong cell service (5% vs 21%; $p = .007$) as barriers to RPM technology use. **Conclusions:** RPM is gaining momentum in academic and community cancer program settings; however, significant gaps exist in RPM experience and implementation for rural cancer programs. In addition to well-documented disparities in access to internet and cellular service for rural patients, perceptions about privacy and cost pose additional barriers. Secure text messaging and automated surveys are often used as example solutions to bridge digital literacy and access gaps, yet cancer programs in rural areas are less likely to use these technologies. Tailored patient/provider education, funding/reimbursement strategies, and advocacy for policies expanding technology infrastructure may be needed for cancer programs to equitably provide RPM technologies. Research Sponsor: This study was supported by AstraZeneca.

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Poster Session

Global adoption of remote technologies to enable patient-centric oncology clinical trials: Analysis by the Bloomberg New Economy International Cancer Coalition. *First Author: Robert Michael Daly, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Fewer than 5% of patients with cancer enroll in a clinical trial, partly due to the significant financial and logistical burden on patients, especially among underserved populations. The COVID-19 pandemic marked a significant shift in the adoption of remote technologies and decentralized trial operations by major pharmaceutical companies. We sought to determine the current global state of adoption of these technologies, understand factors that are driving or preventing adoption of them, and highlight aspirations and direction for industry to enable more patient-centric trials. **Methods:** The multi-stakeholder Bloomberg New Economy International Cancer Coalition composed of patient advocacy, industry, government regulators, and academic medical centers developed a survey directed to global biopharmaceutical companies of the Coalition with a focus on registrational clinical trials. The survey was organized into three main sections: 1) Impact of different remote monitoring and data collection technologies on patient-centricity; 2) Adoption of these technologies in oncology and all therapeutic areas; 3) Barriers/facilitators to adoption. **Results:** Administered from October 1 to December 31, 2022, a total of 8 companies completed the survey (response rate: 100%), representing 33% of oncology market by revenues in 2021. Across nearly all remote monitoring and data collection technologies, adoption in oncology trials lags that of all trials. In the current state, eDiary/eCOA is the most utilized technology with 56% and 51% adoption for all trials and oncology trials, respectively, whereas visits in local physician networks is the least adopted at 12% and 7%, respectively. Looking forward, the difference between the current and aspired adoption rate in 5 years for oncology is large, with respondents expecting a 40% or greater absolute adoption increase in 8 out of the 11 technologies (Table). Furthermore, respondents identified digitally enabled recruitment, local or mobile imaging capabilities, and local physician networks as those technologies that would be most impactful for improving patient-centricity in the long term. **Conclusions:** This survey is the first by a coalition of global stakeholders to determine the current state and future aspirations for the use of remote technologies in oncology clinical trials. These efforts may galvanize momentum towards greater adoption of enabling technologies supporting a new paradigm of trials that are more accessible, less burdensome, and more inclusive. Research Sponsor: None.

Remote technologies	Current State	5-Yr Aspiration
eDiary/eCOA	51%	81%
Digitally-enabled enrollment	26%	70%
Patient engagement dashboard	25%	79%
Digitally-enabled recruitment	20%	70%
Remote monitoring	13%	55%
Telemedicine visits	11%	58%
Mobile/local labs	11%	47%
Mobile/local imaging	9%	49%
Local physician networks	7%	51%

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Poster Session

Longitudinal changes in patient reported outcome measures in patients with cancer six months prior to death: A case-control study. *First Author: Samantha Tam, Henry Ford Health, Detroit, MI*

Background: Provider assessments consistently fall short in determining when cancer patients enter into the terminal phase of their disease. Despite prior desires to spend their last days outside an institution, patients often seek emergency room care and most report never having a palliative consultation at the time of their terminal admission. Patient reported outcome measures (PROMs) are derived directly from the patient and may provide insight into the experience near the end of life to facilitate earlier involvement of supportive oncology. This study aims to compare PROMs in the 6 months prior to death to those not dying among patients with cancer. **Methods:** This study uses a routine PROMs program implemented since September 2020 for all patients with a cancer diagnosis at a tertiary care hospital. This study focused on PROMs using 3 domains of the Patient Reported Outcomes Measurement Information System (PROMIS): physical function, pain interference, and fatigue; PROMs frequency mirrored patients' oncologic visits. Using a retrospective case-control study, patients who had died within 6 months of a PROMs response (cases) were compared to controls who were alive at the time of the case's death. Cases were matched 1:2 to controls by age at PROMs completion, gender, cancer disease site, and stage. Generalized estimating equation (GEE) models adjusted for age at PROMs completion, gender, cancer disease site, stage, and correlations between individual patient encounters were used to compare mean PROMs scores between cases and controls in each domain. **Results:** In total, 274 cases were compared to 270 unique controls. Univariate comparisons between cases and controls demonstrated significant differences only in Charlson Comorbidity Index (CCI), with cases demonstrating worse CCI (3.3 ± 2.5) compared to controls (2.3 ± 2.2 ; $p < 0.001$). Time from diagnosis to PROMs completion was not different between groups (4.08 versus 4.10 years, $p = 0.798$). Over the 6 months prior to death, 10.5%/15.0%/32.0% cases had severe pain/fatigue/physical function scores compared to 3.3%/3.7%/8.7% in controls ($p < 0.001$). GEE models demonstrated that cases had a higher mean fatigue score of 5.34 points (95% CI = 3.81 to 6.88), higher mean pain interference score of 4.92 points (95% CI = 3.42 to 6.43), and lower mean physical function score of 7.39 points (95% CI = -8.84 to -5.93) indicating more severe symptom scores for cases in all three domains. **Conclusions:** On average, patients experiencing death within 6 months of PROMs completion demonstrated worse physical functioning, pain interference, and fatigue scores compared to their age, gender, cancer disease site, and stage matched controls. The differences in PROMs scores represent a first step to improving understanding of PROMs during the terminal stage of disease and may guide indicators for earlier need of supportive oncology support. Research Sponsor: Henry Ford Foundation.

1587

Poster Session

Acceptability and effectiveness of digital prehabilitation and personalised support for patients with cancer in the UK National Health Service. *First Author: Venetia Wynter-Blyth, Onkohealth, London, United Kingdom*

Background: Prehabilitation is associated with increased tolerance to oncology treatments, reduced post-operative complications and hospitalisations. Most prehabilitation programmes are delivered in hospitals or community centres. However, large-scale implementation is limited by problems of access, workforce demands, travel costs and sustainability. Digital technology presents an opportunity to address concerns and broaden access. The aim of this study was to explore the feasibility, acceptability and effectiveness of a digital prehabilitation service. **Methods:** Since January 2022 a digital coaching model of physical, nutritional and psychological optimisation was implemented across a sample of NHS hospitals, provided by Onkohealth Ltd. Patients were onboarded onto the 12-week programme through a native app or, for those without access to smart technology, a web-based pathway. Baseline health metrics were collected through a combination of validated survey tools and wearable technology. Patients were matched to a personal health coach for ongoing guidance and support. The intervention combined digital behaviour change techniques with remote monitoring and real-time targeted support from their coach when the need is triggered. Self-reported physical activity (PA) was recorded and calculated as METS min week⁻¹. Psychological wellbeing outcomes and e-PROMs included self-efficacy, quality of life [EQ5D5L Health Utility (EQ-HU)] and a visual analogue scale (EQ-VAS)] before and after completion of the 12-week programme. **Results:** 303 patients were referred to the service. 228 (75.2%) accepted and started the programme. 167 (74%) followed an app-based programme. 24 patients (12.2%) discontinued. 103 patients, on different oncological pathways, completed the 12-week programme. 30 completed a median of 4 weeks pre-operatively. 12 started post-operatively. 61 received chemotherapy (neoadjuvant: 17; adjuvant: 23 and palliative: 21). A complete pre-post data set was available for 47 patients. There were significant improvements for all study metrics: PA mean difference 323 METS min week⁻¹ (95% CI 45 to 600), $p = 0.024$; distress mean difference -1.2 (95% CI -2.3 to -0.1), $p = 0.025$; anxiety mean difference -1.5 (95% CI -2.7 to -0.3), $p = 0.018$; depression mean difference -1.3 (95% CI -2.5 to -0.1), $p = 0.04$; EQ-HU median 0.71 (IQR 0.57-0.84) to median 0.77 (IQR 0.65-0.84), $p = 0.041$; EQ-VAS mean difference 15.4 (95% CI 5.7 to 25.0), $p = 0.003$; self efficacy mean difference 3.2 (95% CI 0.6 to 5.7), $p = 0.015$. **Conclusions:** This is the first study on the implementation and effectiveness of a digital model of prehabilitation and coaching for cancer patients. Patients respond positively in nearly all dimensions of physical and psychological health despite being on oncological treatments, with a significant improvement in self-efficacy, EQ-HU and EQ-VAS. Research Sponsor: None.

1586

Poster Session

Patient-reported usefulness of an intervention to promote job retention among women undergoing (neo)adjuvant breast cancer chemotherapy. *First Author: Victoria Susana Blinder, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Women who undergo (neo)adjuvant breast cancer chemotx are at risk of job loss, especially if they lack work accommodations. We developed TEAMWork (Talking to Employers And Medical staff about Work), an English/Spanish mobile application (app) to help women identify work accommodations relevant to their needs, negotiate with their employers to receive these accommodations, and communicate with the clinic team to manage symptoms. TEAMWork will be compared to a booklet as a job-retention tool in an ongoing randomized clinical trial (RCT). Here we present acceptability data based on RCT participants' perceptions of the app's usefulness. **Methods:** Eligible participants were women aged 18-64, who spoke English/Spanish, were able to use and had access to a smartphone/tablet, were undergoing or planned to undergo (neo)adjuvant chemotx for stage I-III breast cancer, and were working full or part time for pay. Women who had stopped working due to the diagnosis were eligible. Those who had stopped working for reasons unrelated to breast cancer (e.g., prior illness disability) were ineligible. Online surveys were self-administered or administered interview-style (per participant preference) at baseline and midway through the planned chemotx. In the second survey, participants were asked if they had used TEAMWork at all since enrollment; those who said they had used it were asked about the app's usefulness. **Results:** 58 participants received the app; 56 received the booklet. 64% were white, 18% were Black, and 12% were Asian; 7% were Hispanic. 4% were Spanish-speaking. 79% had at least a college education. When surveyed half-way through their chemotx regimen, 62% of those randomized to the app said they had used the app; only 25% of those randomized to the booklet said they had used the booklet ($p < 0.0001$). Among those who reported having used the app ($n=36$), 86% said they were very (44%) or somewhat (42%) satisfied with TEAMWork, and 94% said they thought TEAMWork would be very (61%) or somewhat (33%) helpful to other patients. Additional details about the perceived usefulness of the app are shown. **Conclusions:** Compared to participants randomized to the booklet, more than twice as many who received the app reported that they had used their assigned intervention. Among those who used it, the app was well-received and was deemed especially helpful for communicating with medical providers. Recruitment to the RCT is ongoing, and job retention results will be presented when data are mature. Efforts are under way to increase the diversity of the study sample based on ethnicity, language, and education. Clinical trial information: NCT03572374. Research Sponsor: U.S. National Institutes of Health.

Perceptions of TEAMWork among participants who used the app ($n=36$).

Using TEAMWork made it easier for me to . . .	Agree (%)
. . . remember my symptoms	72
. . . talk to doctors/nurses	58
. . . negotiate/ask for work accommodations	47
. . . talk to my boss/employer	36
. . . talk to my coworkers	36

1588

Poster Session

Comparison of publications between cancer sites in high impact factor journals. *First Author: Nikita Sinha, UNC Chapel Hill, Chapel Hill, NC*

Background: Prior studies have shown disparities in federal funding allocation by cancer site after accounting for mortality, incidence, and person-years of life lost. Whether disparities exist in publications in high impact factor journals is unknown. The aim of this study is to analyze research publications in high impact factor journals by cancer site relative to their burden from 2000 to 2018. **Methods:** Abstracts from the top 55 impact factor journals from 2000 to 2018 were extracted from PubMed. We developed an algorithm to search the title of the abstract to determine whether the abstract was about cancer and identify the cancer type. The algorithm was validated against the gold standard of human review in 1143 abstracts and yielded a sensitivity and a specificity of >95%. An article proportion for each cancer site was calculated (abstracts for a cancer site / total cancer abstracts). Article proportion was compared to cancer site-specific incidence, mortality and lethality from NCI's SEER database using scatter plots and non-parametric Wilcoxon signed rank test. **Results:** We identified 128,377 articles; 31,045 (24%) were about cancer. Cancers with the most publications in high impact factor journals were breast (22%), lung (11%), and colorectal (10%) cancer. Breast, lung and colorectal cancer were also well represented in high impact factor journals compared to their incidence, mortality, and lethality. Gynecologic (ovarian, cervical, and endometrial), pancreatic, hepatobiliary, and prostate cancers were poorly represented in all 3 metrics. Breast, lung, and colorectal cancer ranked in the top half of Article to Lethality scores, while the gynecologic, pancreatic, and hepatobiliary cancers were in the bottom half ($p < 0.05$ for all comparisons). Comparison of rankings by lethality versus by funding indicates relative underfunding of the gynecologic, pancreatic, hepatobiliary, and prostate cancers. **Conclusions:** Research publications in high impact factor journals by cancer site are not proportionate to individual societal cancer burden. Significant disparities exist between breast, lung, and colorectal cancer when compared to gynecologic, pancreatic, hepatobiliary, and prostate cancers relative to their disease burden. Underfunding of these cancer sites likely contributes to this publication gap. Research Sponsor: U.S. National Institutes of Health.

Rank	Cancer Type	Article to Lethality	p-value (to uterus)	p-value (to cervix)	p-value (to ovary)	p-value (to pancreas)	p-value (to liver)
1	Breast	427	<0.001	<0.001	<0.001	<0.001	<0.001
2	Prostate	23	<0.001	<0.001	<0.001	<0.001	<0.001
5	Colorectal	109	<0.001	<0.001	<0.001	<0.001	<0.001
7	Lung	59.9	<0.001	<0.001	<0.001	<0.001	<0.001
12	Ovary	21.9	0.261	<0.001	n/a	<0.001	<0.001
13	Uterus	20.9	n/a	<0.001	0.261	0.0014	<0.001
16	Pancreas	12.7	0.0014	0.0726	<0.001	n/a	0.088
17	Liver	10.4	<0.001	0.55	<0.001	0.088	n/a
18	Cervix	10.1	<0.001	n/a	<0.001	0.073	0.55

1589

Poster Session

Association of state policies regulating short-term limited-duration insurance plans and cancer stage at diagnosis. *First Author: Justin Michael Barnes, Department of Radiation Oncology, Washington University School of Medicine in St. Louis, St. Louis, MO*

Background: In 2018, federal regulations expanded access to short-term limited duration insurance (STLD) plans. STLD plans generally limit coverage of medical services and have no cost-sharing caps, which can delay a cancer diagnosis. Furthermore, uptake of STLD plans can destabilize individual insurance markets, leading to increased prices and subsequent barriers to care for comprehensive insurance plan enrollees. Several states introduced legislation prohibiting and/or limiting STLD plans, but it is unclear whether STLD plans or policies restricting their proliferation have affected cancer stage at diagnosis. **Methods:** Individuals ages 18-64 years with staged first primary malignancies diagnosed 2016-2019 were identified from the Surveillance, Epidemiology, and End Results (SEER) database. Difference-in-differences (DID) analyses evaluated changes in early-stage (stages 0 [breast and bladder only] through II) diagnoses from pre- (2016-2017) to post- STLD expansion (2019; 2018 was excluded as washout/phase-in period) between states with policies prohibiting and/or limiting STLD plans vs. states with no policies regulating STLD plans. In some states limiting but not prohibiting STLD plans, insurers stopped selling STLD plans; we conducted additional analyses by state STLD plan availability in 2019. Linear probability models utilized cluster-robust standard errors (clustered at state level) and adjusted for fixed state and year effects, sociodemographic covariates, and cancer site. Sensitivity analyses excluded states that expanded and/or substantially changed Medicaid eligibility during the study period. The plausibility of the parallel trends assumption was tested in adjusted models restricted to the pre-policy period (2016-2017) and was satisfied for all analyses. **Results:** 398,190 individuals were included. In adjusted DID analyses, early-stage diagnoses increased 0.95 percentage points (95% CI = 0.53 to 1.38, $p<.001$) in states that prohibited vs. did not regulate STLD plans, but there was no relative change in early-stage diagnoses in states with other policies limiting STLD plans ($p=.25$). Relative to states where STLD plans remained available, there was a nonsignificant increase in early-stage diagnoses in states where legislation stopped the sale of STLD plans, with greater evidence for an increase after excluding states with Medicaid eligibility changes (1.03, 95% CI = 0.71 to 1.35, $p<.001$). There were no differential changes in early-stage diagnoses by state group in falsification tests limited to individuals >65 years-old, who were Medicare-eligible. **Conclusions:** State legislation prohibiting and/or leading to the cessation of STLD plans was associated with an increased rate of early-stage cancer diagnoses. Alternatively, the proliferation of STLD plans was associated with a differential decreased rate of early-stage cancers. Research Sponsor: None.

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Poster Session

"It was so many hoops to jump through": Patient-reported administrative burden from disability, Family and Medical Leave Act (FMLA), and insurance appeals. *First Author: Fumiko Chino, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: A breast cancer (BC) diagnosis places physical, emotional, and financial stress on patients. The full spectrum of administrative burdens that patients carry, while simultaneously dealing with cancer treatment, is unexplored. **Methods:** From 6-7/2022, Breastcancer.org community members consented to an anonymous online survey in English or Spanish. The survey assessed patient-reported disability claims [short-term (ST) or long-term (LT)], FMLA application, and appeals of insurance claim denials. Multivariable analysis (MVA) modeled associations with 1) disability application and 2) helpfulness of FMLA. Eligibility included: US resident, age ≥ 18 , and BC diagnosis within 10 years. **Results:** Of 2,420 members screened, 1,710 met eligibility, and 1,437 completed the survey (84% participation rate). Nearly all (94%) identified as women; 60% identified as White, 27% Hispanic, 8% Black, or 4% Other race. Median age was 46 years (range: 19-85), and median time since diagnosis was 2 years (range: 0-10). 75% were on active treatment; 11% had metastatic disease. About one-third of respondents (32%) applied for ST disability, and 26% for LT disability (10% applied for both). A lower proportion of White patients applied for disability (ST: 17% White, 25% Black, 33% Hispanic; LT: 9%, 15%, 35%, both $p<0.001$). Patients with metastatic disease applied for LT disability more often (23% vs 16% non-metastatic, $p=0.01$). Although most were approved (74% ST, 63% LT); about one-quarter (23% ST, 29% LT) found disability very/extremely difficult to apply for, with no variation by race, ethnicity, or disease status (all $p>.05$). On MVA, Hispanic patients (OR=5.39, 95%CI 3.96-7.34) and those with metastatic disease (OR=1.52, 95%CI 1.01-2.30) had increased odds of filing for disability. Of respondents who filed for FMLA (27%), 25% found it a very/extremely difficult application. Of 289 FMLA recipients, one-half found it very/extremely helpful. On MVA, longer time since diagnosis was associated with perceived helpfulness (OR=1.16, 95%CI 1.03-1.30). One-third of respondents filed an appeal of an insurance denial: this was more common among those with metastatic disease (41% vs 32% non-metastatic, $p=0.02$) and less common in White patients (26% White, 39% Black, 45% Hispanic; $p<0.001$). Of respondents who appealed, most (57%) filed between 2-5 times; patients with metastatic disease were more likely to have to file >5 times (18% vs 7%, $p=0.005$). **Conclusions:** Patient administrative burden impacted one-third of BC patients, with larger burdens on historically marginalized or minoritized groups (e.g., Black and Hispanic patients; those with metastatic disease). State and national legislative priorities should work to standardize and streamline application processes so patients can have the financial stability to focus on cancer treatment and recovery goals. Research Sponsor: This work was sponsored by Gilead Sciences Inc., Pfizer Inc., and Lilly.

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Poster Session

Clinical practice guideline descriptions of oncologic drugs granted FDA accelerated approval: A cross-sectional study. *First Author: Maryam Mooghali, Yale School of Medicine, New Haven, CT*

Background: The Food and Drug Administration's (FDA's) accelerated approval (AA) pathway allows drugs to be approved using surrogate endpoints, while requiring that sponsors complete postmarketing requirement (PMR) studies verifying clinical benefit. Subsequently, FDA determines whether AA can be converted to standard approval or be withdrawn. It is unclear whether clinical practice guidelines reflect PMR results or FDA regulatory decisions. As most drugs granted AA are cancer therapies, we investigated whether and how National Comprehensive Cancer Network (NCCN) guidelines reflect underlying evidence supporting AAs and subsequent FDA decisions. **Methods:** In this cross-sectional study, we used Drugs@FDA to identify drug indications granted AA by FDA for oncologic indications from 2016-2018, PMR status and results, and whether AA was converted to regular approval or withdrawn. We excluded pediatric and tumor-agnostic indications. PMR studies were classified as positive if the results from primary efficacy endpoint were statistically significant ($P<0.05$) favoring the drug. For each AA indication, we searched relevant NCCN guidelines for their recommendations and examined if AA status, PMR results, and updated FDA decisions were reflected. **Results:** Among 36 oncology drug indications granted AA from 2016 to 2018, 29 (81%) NCCN guidelines did not mention that the drug was approved via AA pathway or had not yet verified clinical benefit. For all 36 (100%) indications, NCCN guidelines did not state that approval was based on surrogate endpoints. As of December 31, 2022, among 16 drug indications that were converted to standard approval, 13 (81%) guidelines reflected FDA's updated decisions. Among 8 indications withdrawn after AA, 5 (63%) guidelines reflected the withdrawn status. Of 6 drug indications with negative PMR study results that were withdrawn, 2 (33%) were still recommended in NCCN guidelines thereafter. **Conclusions:** NCCN guidelines do not consistently reflect FDA regulatory status or PMR study results, highlighting the need for more up-to-date and accurate information to guide clinical practice. Research Sponsor: Arnold Ventures.

NCCN Guidelines' recommendations for cancer drugs granted FDA AA, N (%) ^a						
PMR results	Total drug indications converted to standard approval	Guidelines reflecting conversion to standard approval	Guidelines reflecting all PMR results for those converted to standard approval	Total drug indications withdrawn [†]	Guidelines reflecting withdrawal	Guidelines reflecting PMR results for those withdrawn
All positive	13	10 (77%)	11 (85%)	0	0 (0%)	0 (0%)
Mixed positive and negative	2	2 (100%)	1 (50%)	1	0 (0%)	0 (0%)
All negative / negative and pending	1	1 (100%)	0 (0%)	6	4 (67%)	3 (50%)

^a12 drug indications have not yet been converted or withdrawn, 2 (17%) of which had negative PMR results. 11 drug indication withdrawal was based on a terminated PMR; withdrawal was reflected in guidelines.

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Poster Session

Trends in new and persistent opioid use in older adults with cancer. *First Author: Laura Van Metre Baum, Yale School of Medicine, Department of Medicine, New Haven, CT*

Background: While ongoing efforts to decrease opioid use have dramatically altered the prescribing landscape, the impact on patients with cancer is not well understood. We examined trends in new and persistent opioid use in opioid-naïve older patients with and without cancer in the United States. **Methods:** This retrospective cohort study used SEER-Medicare linked data for patients with solid tumors malignancies diagnosed from 2012 through 2017, and a random sample of patients without cancer. We included patients who did not receive opioids for 3 months prior to the diagnosis or randomly assigned index date. We identified new opioid use (claim in 0-90 days after diagnosis/index date), early persistent opioid use (claims in days 0-90 and 91-180), and long-term persistent opioid use (claims in days 0-90 and 91-180 and months 13-15). Further analysis focused on 4 clinical strata: non-cancer, metastatic cancer, cancer treated with surgery alone, and cancer treated with surgery plus chemotherapy and/or radiotherapy ("surgery+"). We calculated relative changes in the predicted probability of opioid use from 2012 to 2017 based on a logit model adjusted for patient demographics. **Results:** We identified 238,470 eligible patients with cancer (mean age 76.3 years). Among patients with cancer, 46.4% had new opioid use; use was higher among those receiving surgery+ (70.6%), those treated with surgery alone (58.8%) and those with metastatic cancer (50.0%), compared to patients without cancer (6.9%). From 2012 to 2017, the predicted probability of new opioid use declined in all groups, with lower relative decline in the cancer subgroups (6.8% surgery+; 9.5% surgery alone; 10.2% metastatic cancer) compared to the non-cancer comparator (24.7%). For instance, in patients with metastatic cancer, predicted probability of new use decreased from 52.4 to 47.1% (10.2%) vs. 8.0 to 6.0% (24.7%) in patients without cancer. Relative decline in predicted probability of long-term persistent opioid use was lower in the surgical cancer strata (44.2% surgery+; 46.1% surgery alone) vs. the non-cancer comparator (54.0%). **Conclusions:** While opioid use remains common in patients with cancer, new and persistent opioid use declined over time in all patients, though with steeper relative declines in non-cancer compared to cancer populations. Our study suggests important but tempered effects of the changing opioid climate on patients with cancer. Research Sponsor: Food and Drug Administration (FDA) of the U.S. Department of Health and Human Services (HHS).

Opioid use by clinical stratum (2012–2017).				
Clinical stratum	N	% New opioid use	% Early persistent opioid use	% Long-term persistent opioid use [*]
Non-cancer	287,914	6.9	2.0	0.9
All cancer	238,470	46.4	11.2	3.8
Metastatic cancer	32,516	50.0	15.8	n/a**
Non-metastatic cancer treated with surgery only	43,425	58.8	10.7	3.2
Non-metastatic cancer treated with surgery+	26,007	70.6	15.9	4.8

^{*}Restricted to patients alive at 1 year. ^{**}Sub-group analyses restricted to non-metastatic disease.

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Poster Session

Cost-effectiveness of trastuzumab deruxtecan in HER2 low metastatic breast cancer. *First Author: James Dickerson, Stanford Hospital & Clinics, Stanford, CA*

Background: In recent years, metastatic breast cancer treatment has been revolutionized by new therapies that improve overall survival in phase three randomized clinical trials. These drugs are often more expensive than traditional cytotoxics. In 2022, the Destiny-Breast04 trial results showed that trastuzumab deruxtecan (T-DXd) improved survival in HER2 low metastatic breast cancer patients; FDA approval shortly thereafter greatly expanded the potential market capitalization of T-DXd. While the trial demonstrated T-DXd's clinical efficacy, its cost-effectiveness remains unknown.

Methods: We developed a decision-analytic state transition Markov model to simulate a hypothetical cohort of HER2 low metastatic breast cancer patients to assess the cost-effectiveness of T-DXd compared to a physician's choice chemotherapy from a US healthcare payer perspective over a lifetime horizon. Each month, simulated patients could remain progression-free, progress, have a non-interstitial lung disease (ILD) treatment-related adverse event leading to drug discontinuation (TRAE), have ILD leading to drug discontinuation, progress after either a TRAE or ILD, or die. Patients with either a TRAE or ILD were presumed to be progression free directly after discontinuation of the offending agent, and hence eligible for a different therapy. We calibrated the model to outcome data from the Destiny-Breast04 trial, supplemented with data from other relevant metastatic breast cancer clinical trials. Health-related quality-of-life weights were derived from studies of metastatic breast cancer patients. Drug prices (2020 USD) were extracted from the Federal Supply Schedule. Outcomes included discounted (3% annual) quality-adjusted life years (QALYs), life years, lifetime costs, and incremental cost-effectiveness ratios (ICER). We varied T-DXd price and efficacy in a two-way sensitivity analysis to assess our findings' robustness.

Results: Modeled life expectancies with T-DXd and chemotherapy were 26.5 and 21.5 months, respectively (T-DXd: 1.19 QALYs; chemotherapy: 0.93 QALYs). Discounted lifetime costs were 315,000 for T-DXd and 203,000 for chemotherapy; T-DXd cost 431,000 per QALY gained, surpassing a cost effectiveness threshold of 150,000 per QALY gained. The two-way sensitivity analysis showed that, across a range of plausible efficacies, T-DXd would need a price reduction of approximately 50% to be cost-effective at the \$150,000 threshold. **Conclusions:** While providing clinical benefits, our model-based analysis finds that at current prices, T-DXd for HER2 low metastatic breast cancer is not cost-effective at traditional thresholds. Substantial price reduction for T-DXd to a level much closer to prices of comparator cytotoxics could greatly increase the value for money T-DXd provides patients. Research Sponsor: AHRQ 5T32HS026128.

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Poster Session

Race and ethnicity reporting by US federal standards in high-impact phase 2/3 oncology clinical trial publications. *First Author: Kekoa A. Tappara, Stanford Cancer Institute, Palo Alto, CA*

Background: There are 5 races defined by the US Office of Management & Budget (OMB): White, Black, Asian, American Indian and Alaska Native (AIAN), and Native Hawaiian and other Pacific Islander (NHOPI) with Hispanic ethnicity. Despite the existing 1997 race standards, race reporting in oncology clinical trials is still dismal. Here we aim to 1) quantify cancer trial publications reporting race/ethnicity, 2) determine representation in published trials, and 3) identify geographic patterns of reporting race/ethnicity by 1st author. **Methods:** PubMed/Embase were queried for phase 2/3 clinical trials of the 6 most common cancers, published in 4 high-impact journals between 2012-2022, each reviewed by 2 independent reviewers. Trials were excluded for non-US 1st author and those including multiple cancers. Representation quotients (RQ) for each race were calculated by dividing the percent of clinical trial patients by the proportion of year-matched, site-specific incident cancers in the US (Cancer in North America data). RQ of 1 represents equal clinical trial representation compared to US cancer incidence. Trial characteristics were recorded. Descriptive statistics were calculated. RQ statistics were calculated using Kruskal-Wallis tests with Bonferroni Corrections (P_{BC}) for multiple testing. **Results:** Of 1,149 publications assessed, 342 were included (224 JCO, 84 NEJM, 18 Lancet, and 16 JAMA) with 258,123 patients, 60% phase 3, and 45% US Northeast 1st author. By cancer site, 31% breast, 24% lung, 18% prostate, 18% kidney/bladder, 5% colorectal, and 4% endometrial publications were included. Race was reported in 245 publications (72%) varying by journal: 81% JAMA, 78% Lancet, 72% JCO, and 67% NEJM. Specific race/ethnicity were reported in 239 publications (70%) for White, 201 (59%) for Black, 185 (54%) for Asian, 62 (18%) for Hispanic, 48 (14%) for AIAN, and 29 (9%) for NHOPI patients. Among publications reporting race, RQ varied after adjusting for multiple testing ($P_{BC} < .001$) with median (IQR) RQ of 1.0 (0.9-1.1) for White, 0.6 (0.1-2.7) for Asian, 0.4 (0.1-0.7) for Black, 0.0 (0.0-0.0) for AIAN, and 0.00 (0.0-0.0) for NHOPI patients. Stratified by cancer, RQ significantly differed by race for all cancers ($P_{BC} < .001$), except colorectal ($P_{BC} = .004$) and endometrial cancer ($P_{BC} > .99$). NHOPI was the only race with median RQ of 0.00 for all cancers. AIAN and NHOPI race reporting by 1st author was observed most in CA, while Hispanic was observed most in TX. **Conclusions:** While 72% of phase 2/3 cancer clinical trials published in high-impact journals report race, 91% do not report NHOPI race. Indigenous patients have the lowest reporting in cancer clinical trials. Our findings support a call to action to mandate consistent race/ethnicity reporting for publication. US clinical trialists and publishers should comply with mandated US OMB federal reporting guidelines in oncology publications. Research Sponsor: Stanford Cancer Institute – Women Cancer Center's Innovation Award; Stanford Cancer Institute – SCI Fellowship Award; Stanford Cancer Institute – Cancer Innovation Award.

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Poster Session

Data transparency and demographic representation in approval packages of FDA-approved oncology drugs from 2012-2021. *First Author: Jingyi Liu, Brigham and Women's Hospital, Boston, MA*

Background: Over the past decade, the U.S. Food and Drug Administration (FDA) has leveraged regulations and guidance documents to accelerate improvements in demographic reporting and encourage adequate representation of minorities in clinical trials. This cross-sectional study aims to assess the impact of these interventions by characterizing demographic data reporting and representation by sex, age, and racial and ethnic identity in pivotal trials supporting novel cancer therapeutics approved by the FDA from 2012 through 2021. **Methods:** Study demographic data were abstracted from FDA drug approval packages and US cancer population demographic data was abstracted from US Cancer Statistics. The percentages of trials reporting sex, age, racial and ethnic identity of participants in drug approval packages were calculated and participation to prevalence ratios (PPRs) were calculated by dividing the percentage of participants in each demographic by the percentage of the US cancer population in each group. PPRs were constructed for each pivotal trial by cancer type. Adequate representation was defined as PPR 0.8-1.2 and the proportion of trials which were adequately representative of each demographic was calculated and trended over time. **Results:** From 2012 through 2021, the FDA approved 118 cancer therapeutics, based on 131 pivotal trials. For drugs approved 2012-2016, the majority of associated pivotal trials reported participation based on sex (100% of trials), age (100%) and White (98%), Black (75%) or Asian (84%) racial identity, but not American Indian or Alaskan Native racial identity (18%) or Hispanic ethnic identity (41%). For drugs approved 2017-2021, there were no significant improvements in demographic data reporting, although there was a trend towards increased reporting on Hispanic ethnic identity from 2012-2016 (41%) to 2017-2021 (65%) ($p = 0.06$). For drugs approved 2012-2016, most pivotal trials adequately represented female participants (78% of trials) and participants identifying as White (87%), but few pivotal trials adequately represented older adults (7%), participants identifying as Black (11%), American Indian or Alaskan Native (0%), Asian (18%) or Hispanic (5%). Representation in pivotal trials did not significantly improve for any demographic for drugs approved 2017-2021 ($p > 0.05$). **Conclusions:** This study found that the last decade's efforts to improve demographic data transparency and representation in clinical trials have not yet borne fruit for novel cancer therapeutics. More consequential FDA regulations may be necessary. Beyond the FDA, demographic data transparency and adequate minority representation in oncology clinical trials is an all-stakeholder responsibility. A more just clinical trial infrastructure requires greater collaboration between the FDA, sponsors, enrollers, contract research organizations and cooperative groups. Research Sponsor: None.

1596

Poster Session

Association of participation in Medicare's Oncology Care Model with spending, utilization, and quality outcomes among commercially insured and Medicare Advantage members: A national difference-in-differences analysis. *First Author: Samyukta Mullangi, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Medicare's Oncology Care Model (OCM) was a voluntary, episode-based model between 2016 and 2021 that provided participating practices with additional payments to fund care enhancements such as extended clinical hours and urgent care. While it resulted in net losses for traditional Medicare beneficiaries, the OCM may have had "spillover" improvements on spending, utilization, and quality for commercially insured (CM) and Medicare Advantage (MA) members who were not targeted by the program. **Methods:** This retrospective analysis used claims from Elevance Health, a large national payer, to identify commercially insured and Medicare Advantage members diagnosed with breast, colorectal, lung, prostate, and pancreatic cancer initiating systemic therapy between 2014 to 2021. We identified 85 OCM practices and 581 matched non-OCM practices based on episode, practice, demographic, and market factors. The exposure variable was participation in the OCM model. All outcomes were defined in 6-month episodes; the primary outcome was overall inflation-adjusted spending; secondary outcomes included hospitalization and emergency room visits, and end-of-life acute care utilization. We utilized adjusted difference-in-differences linear probability models, with state-level fixed effects to control for market price variability, to estimate the association between OCM participation and all outcomes. **Results:** We studied 45,296 episodes of care in OCM practices and 122,231 episodes in non-OCM practices among CM and MA members during the post-implementation period. OCM participation was associated with a \$5,275 (SE \$749.40) reduction in total allowed spending ($p < 0.001$), driven by reductions in outpatient and systemic therapy spending. OCM was associated with improvements in end-of-life utilization and ED visits but none in hospitalizations and timely chemotherapy initiation. **Conclusions:** Participation in the OCM was associated with modest spillover spending benefit onto CM and MA members, but minimal utilization and quality benefits. Resultant practice innovations may have benefited non-targeted patients. Evaluations limited to targeted patients may have underestimated the full impact of the OCM. Research Sponsor: None.

	OCM practices		Non-OCM practices		
Outcomes (6-month episodes)	2014-2015	2016-2021	2014-2015	2016-2021	Difference-in-differences
Spending, \$					
Total allowed	44,054	46,966	48,671	58,553	-5,275***
Outpatient	36,458	38,903	40,928	49,785	-4,485***
Systemic therapy	16,341	18,931	18,883	24,710	-2,161**
Utilization, % of episodes					
Hospitalization	19.5	20.1	20.2	20.2	0.34
ED visit	15.8	16.1	15.1	16.3	-0.39
Quality, % of episodes					
Hospitalization in last 30 days of life	41.0	44.6	41.0	46.6	-2.09
Chemotherapy in last 14 days of life	5.4	5.1	4.9	5.2	-0.38

*** $p < 0.05$. ** $p < 0.01$.

1597

Poster Session

Is Medicare Advantage associated with more favorable health care access, acute care utilization, and affordability among beneficiaries with cancer?
First Author: Vishal R. Patel, Dell Medical School, The University of Texas at Austin, Austin, TX

Background: The Medicare Advantage (MA) program provides care to nearly half of Medicare beneficiaries, including a rapidly growing population of cancer survivors. Although MA was designed to optimize healthcare access, outcomes, and affordability, it is unknown whether these effects have been achieved in cancer survivors. **Methods:** We performed a cross-sectional study of Medicare beneficiaries ≥65 years with a self-reported history of cancer in the 2019 National Health Interview Survey. We used multivariable logistic regression to evaluate the association between Medicare program type (MA vs traditional Medicare, TM) and measures of healthcare access, acute care utilization, and affordability. **Results:** We identified 4,451 beneficiaries with a history of cancer, corresponding to 26.6 million weighted cancer survivors in 2019. Of beneficiaries, 35.8% were enrolled in MA while 64.2% were enrolled in TM. The age, sex, racial and ethnic composition, household income, primary site of cancer, and comorbidity burden of MA and TM beneficiaries were similar. In adjusted analysis, there were no differences in health care access or acute care utilization between TM and MA beneficiaries. However, survivors enrolled in MA were more likely to worry about (34.3% vs 29.4%; aOR, 1.3 [95% CI, 1.1-1.5]) or have problems paying (13.6% vs 11.1%; aOR, 1.4 [95% CI, 1.1-1.8]) medical bills. **Conclusions:** MA beneficiaries with a previous cancer diagnosis more often struggle paying medical bills despite similar healthcare access and preventive care as TM. Despite generous benefits and attractive incentives for care coordination and health management, privately run MA plans may not be more cost-effective than TM for cancer survivors. Our study informs ongoing congressional deliberations to re-evaluate the role of MA in promoting equity among beneficiaries. Research Sponsor: None.

Outcomes among beneficiaries by type of Medicare plan.				
Health outcomes (in last year)	MA Beneficiaries, % ^a	TM Beneficiaries, % ^a	aOR (95% CI) ^b	P value
Has a usual source of care	95.5	94.8	1.2 (0.8-1.8)	0.29
Had a doctor visit	98.2	97.7	1.3 (0.9-2.2)	0.33
Met aerobic physical activity recommendations	31.8	32.3	1.0 (0.7-1.3)	0.78
Visited an urgent care clinic ≥2x	9.9	11.1	0.9 (0.7-1.2)	0.37
Visited an ED	28.3	29.6	0.9 (0.8-1.1)	0.41
Had an overnight hospitalization	20.4	20.5	1.0 (0.8-1.2)	0.96
Worried about paying medical bills	34.3	29.4	1.3 (1.1-1.5)	0.01
Had problems paying medical bills	13.6	11.1	1.4 (1.1-1.8)	0.02
Delayed care to save money	4.3	3.9	1.3 (0.8-1.9)	0.32
Delayed filling medications to save money	5.5	5.0	1.1 (0.8-1.5)	0.66
Skipped medications to save money	4.3	3.2	1.5 (1.2-3)	0.06

ORs presented with TM as reference. ^a Percent answering yes. ^b Adjusted for age, sex, education, race/ethnicity, annual income, primary site of cancer, number of chronic diseases, region of residence, metropolitan status & survey year.

1598

Poster Session

Dosage optimization in drug development: An FDA Project Optimus analysis of postmarketing requirements issued to repair the cracks.
First Author: Brian Heiss, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, MD

Background: Dosage optimization (DO) is a critical aspect of oncology drug development. Because of this, the US FDA, through Project Optimus, has focused on reforming the DO and dosage selection paradigm for oncology products. When approving products, FDA may determine that although the recommended dosage possesses a favorable benefit:risk (BR) profile, there are significant safety concerns that require evaluation of alternative dosages to potentially improve the BR profile. Such postmarketing requirements (PMRs)—issued as a condition of approval—are examined here to better understand the characteristics and potential limitations of DO studies in the postmarketing setting. **Methods:** Between Jan. 1, 2010 to Dec. 31, 2022, oncology new molecular entities (NMEs) and original applications for biologics, hereafter referred to as new drugs, approved by CDER with at least one PMR issued for DO were identified in the FDA electronic records database. The designs and results of the associated trials or analyses for these PMRs, along with the status of the PMRs, were collected and evaluated. **Results:** There were 24 PMRs issued for 21 new drugs (15% of 138 total approved new drugs). The most common drug classes were: tyrosine kinase inhibitors (TKIs) (10), antibody drug conjugates (ADCs) (3), or GTPase Inhibitors (2). The following trials or analyses were planned to address these PMRs: randomized dose-comparison trials (18), non-randomized dose-finding trials (2), food effect trials (2), exposure-response analysis (1), and pending (1). The planned sample sizes for the 18 dose-comparison trials were 3 with <100 patients, 4 with 100 to 199 patients, 7 with 200 to 500 patients, and 4 with >500 patients. The dose-comparison trials used the following (co)primary endpoints: response rate (12), safety (7), OS (3), and PFS (2). Fourteen PMRs were either fulfilled (11) or released (3). Of the 11 fulfilled PMRs, 8 led to dosage changes for 5 new drugs (cabazitaxel, carfilzomib, ponatinib, ceritinib, and pexidartinib), and 3 did not lead to dosage changes. Ten PMRs are ongoing. The median time from issuance to fulfillment or release (not including ongoing PMRs) was 6 years (range: 0.7 to 8.3). **Conclusions:** A high proportion (15%) of new drugs required a PMR, which generally involved conducting a randomized trial with a substantial patient enrollment to evaluate an alternative dosage(s). This process was slow with a median of 6 years to fulfill a PMR. DO in the premarket setting has the potential to rapidly maximize BR, avoiding both patient exposure to unnecessary toxicity and large, resource-intensive, multi-year postmarketing trials. Project Optimus is working with stakeholders to advance a DO paradigm that occurs early and throughout premarket development to ensure an optimized recommended dosage at the time of approval. Research Sponsor: None.

1599

Poster Session

Association of accelerated approval (AA) status with National Comprehensive Cancer Network (NCCN) guideline recommendation for cancer drug indications: A cross-sectional study.
First Author: Edward Robert Scheffer Cliff, Program on Regulation, Therapeutics and Law, Boston, MA

Background: Many oncology drugs are approved via FDA's accelerated approval pathway based on trials showing changes to surrogate measures only 'reasonably likely' to predict clinical benefit. Despite this preliminary evidence, accelerated approval drugs are incorporated into clinical practice and included in guidelines. We assessed NCCN evidence and preference ratings for drugs with accelerated vs traditional approval. **Methods:** Accelerated approval oncology drugs were identified using an FDA list as of June 30 2022. Drug labelling revealed other oncology indications of these drugs. Accelerated approvals were stratified if they had been converted to traditional approval after confirmatory studies or withdrawn. Indications with no NCCN guidelines or tumor-agnostic approvals were excluded. Relevant NCCN guidelines were reviewed as of Oct 19 2022. Each indication was assessed for ratings of level of evidence and treatment preference. Levels of evidence included category 1 (consensus, high-level evidence), 2A (consensus, lower-level evidence), 2B (lower-level evidence without consensus), or 3 (major disagreement). Treatment preference rankings included preferred, alternative preferred, other recommended, or useful in certain circumstances. **Results:** Among 315 indications for 100 drugs, 156 (50%) had traditional approval and 159 (50%) had current or previous accelerated approval. Among accelerated approval indications, 78 (49%) had been converted to traditional approval and 21 (13%) withdrawn. Among all indications, 105 (33%) were rated as category 1 evidence, 185 (59%) as 2A, 6 (2%) as 2B, and 2 (0.6%) as 3. The treatment preference for 153 (49%) was preferred, for 55 (17%) was recommended, for 5 (2%) was alternative preferred, and for 38 (12%) was useful in certain circumstances. Compared to traditional approval, accelerated approval indications less often had category 1 evidence (3% v 47%), and were less often listed as preferred (40% v 58%). Converted accelerated approval indications had mid-range ratings for evidence (38% category 1) and treatment preference (47% preferred). 11 withdrawn accelerated approval indications remained in NCCN guidelines. **Conclusions:** In most cases, NCCN guidelines identified accelerated approval indications as having lower evidence than traditionally approved cancer drugs. Many traditional approvals and conversions from accelerated approvals had only category 2A evidence, suggesting better evidence is needed for traditional approval of oncology drugs. But in about half of accelerated approval indications withdrawn by the drug's manufacturer, NCCN continued recommending the drug. Professional organizations like NCCN should ensure their guidelines reflect that accelerated approval drugs are being marketed based on preliminary evidence. Research Sponsor: Arnold Ventures.

1600

Poster Session

System-wide approach on biosimilars adoption in oncology: Strategic plan on switching and cost savings.
First Author: Suwicha Limvorasak, Cedars-Sinai Medical Center, Los Angeles, CA

Background: Biosimilars provide competitive, lower-cost alternatives to biologic drugs in cancer treatment. As more agents become available in the US, institutions have to implement a strategy for successful adoption that is feasible, safe and provide price competition among biosimilar manufacturers. **Methods:** We aimed to standardize biosimilar utilization across the Cedars-Sinai Health System (CSHS) by integrating institutionally developed clinical pathways and insurance prior-authorization into the existing electronic health record (EHR). The initial study was limited to bevacizumab, rituximab and trastuzumab. To align with CSHS guideline recommendations, biosimilar indications for use were reviewed by each disease related group (DRG). Biosimilar brands for each drug were selected through a formulary process vetted by the Pharmacy & Therapeutics Committee. Physicians were permitted to opt-out of switching via an option provided within the electronic order set. To test feasibility of this approach, patients were divided into two groups as 1) main medical center (Cedars Sinai Medical Center) and 2) Cedars-Sinai Cancer affiliated sites. Feasibility was defined as a compliance rate of 80% or greater at the main medical center and 75% or greater at the affiliated sites. This study was powered to detect a minimum difference at 5.7% and 8.9%, respectively. **Results:** Between January 2021 to September 2022, a total of 1,139 cancer patients who initiated treatment with bevacizumab, rituximab or trastuzumab were identified through the EHR, of whom 650 were eligible (age 18-96; 61% female, 39% male). Using our approach, the compliance rate was 86% at the main site (p<0.001, 95%CI: 82.5-89.1) and 88% (p<0.001, 95%CI: 82.1-91.7) at the affiliated sites, resulting in a 56% improvement from baseline (86% vs. 55%, p<0.001). Among 14% of patients who did not switch to institutional-preferred biosimilar brands, the most common reasons for this were payer mandated use of an alternate brand (5%), off-label indication (4%), enrolled in patient assistance program (3%) and physician preference (2%). Five patients (<1%) did not switch to biosimilars due to history of infusion reactions. Insurance type (HMO, PPO, Medicare, others) was not associated with non-compliance (p=0.876). Cost savings were projected to be over \$4 million over a duration of two years. **Conclusions:** Enterprise-wide switching to one specific biosimilar brand is feasible and facilitated through leveraging of the EHR. This approach optimized existing organizational infrastructure to standardize biosimilar utilization and promote substantial cost savings. Research Sponsor: NCCN/Pfizer Biosimilar Project Funding.

	Main medical center (n=450)	Affiliated sites (n=200)
Switching to preferred biosimilar brand(s)		
Bevacizumab	78%	76%
Rituximab	92%	91%
Trastuzumab	92%	98%
Total	86%	88%
Not switching to preferred biosimilar brand(s)		
Use other biosimilar brand(s)	5%	1%
Use reference brand(s)	9%	11%

1601

Poster Session

Correlation between Oncotype DX, Predict, and Nottingham Prognostic Index on HR+, HER2- early breast cancer treatment: The current value of molecular testing. *First Author: Leticia Campoverde, University of Miami Hospital/Jackson Memorial Hospital, Miami, FL*

Background: The Oncotype DX Breast Recurrence Score (ODX) assay is a 21-gene assay validated in hormone receptor-positive, HER2 negative invasive breast cancer (BC) to predict chemotherapy benefit and risk of distant recurrence at 10 years regardless of node status and is also a strong predictor of mortality. ODX can minimize the misuse of chemotherapy, financial burden, and improve clinical outcomes. ODX is not widely used in Ecuador due to socio-economic and healthcare access disparities; instead, many physicians stratify patients' risk according to clinicopathological and immunohistochemical features. We aim to compare the differences between ODX and two of the most common stratification clinical tools: Predict Score (PS) and Nottingham prognostic index (NPI). **Methods:** Retrospective analysis of women with early BC who underwent ODX testing in Ecuador from May 2020 to January 2023. Inclusion criteria: early BC (T1-T3 / N0-N1a); estrogen receptor (ER) positive; HER2 negative by immunohistochemistry; and available data of tumor size, grade, lymph node status, and Ki67 proliferation index. Exclusion criteria: patients with recurrent BC, incomplete pathology, or immunohistochemistry data. PS and NPI were calculated using online tools. The correlation between PS, NPI, and ODX scores was analyzed using Spearman's correlation coefficient in SPSS. **Results:** 77 patients underwent ODX testing, of which 58 patients (mean age 55 years old) met the inclusion criteria. Invasive breast carcinoma not otherwise specified was the most common type (48 patients (82%). Risk scores generated by PS correlated strongly with NPI for all patients ($r=0.47$; $p \leq 0.001$). A strong correlation was also found between ODX and NPI (0.79 , $p<0.027$). Risk scores were then stratified by patient risk category. For low-risk patients, 68% of correspondence between ODX and PS was found, and 98% between ODX and NPI. Intermediate-risk patients showed a correspondence between ODX and PS of 5% and 9% for ODX and NPI. High-risk patients showed a correspondence of 50% between ODX and PS and 17% between ODX and NPI. **Conclusions:** ODX risk recurrence for low-risk patients is highly correlated with PS and NPI. For intermediate and high-risk patients determined by PS and NPI, ODX testing provided valuable and prognostic information and should be considered to guide adjuvant treatment. Research Sponsor: None.

Risk stratification according to ODX, PS and NPI.

ODX	PS	NPI
Low risk (0-15 pts. and < 50 y/o, or 0-25 pts. and > 50 y/o) 45 (78%)	Low risk (<3 pts.) 34 (59%)	Excellent prognosis (<2.4 pts.) 15 (26%)
Low-intermediate risk (16-20 pts. and < 50 y/o) 5 (9%)		Good prognosis (2.4 -3.4 pts.) 31 (53%)
Intermediate risk (21-25 pts. and < 50 y/o) 1 (3%)	Intermediate risk (3-5 pts.) 20 (34%)	Moderate prognosis (3.41-5.4 pts.) 11 (19%)
High risk (> 26 pts.) 6 (10%)	High risk (>5 pts.) 3 (5%)	Poor prognosis (> 5.4 pts.) 1 (3%)

Pts: points.

1603

Poster Session

Use and value of self-management (SM) recommendations in a real-world evidence study evaluating digital patient monitoring (DPM) of patients (pts) receiving cancer care. *First Author: Manuela Eicher, University of Lausanne, Lausanne, Switzerland*

Background: SM includes pts' abilities and activities to manage symptoms, treatment (tx), and any problems inherent to a chronic condition. Tailored SM support is recommended in cancer care. DPM enables pts to systematically self-report disease- or tx-related symptoms, communicate directly with healthcare professionals (HCPs), and access support materials. This observational study evaluated the real-world use of the Symptom Navi Program (SNP; Bern, Switzerland) SM materials on the Kaiku Health DPM platform (Helsinki, Finland) in collaboration with F. Hoffmann-La Roche Ltd (Roche; Basel, Switzerland). **Methods:** Adults diagnosed with locally advanced or metastatic non-small/small cell lung cancer, or any stage HER2-positive breast cancer being treated with locally approved and reimbursed drugs with an expected tx duration of >3 months, had access to a DPM solution that provided disease- and tx-tailored modules, including SNP SM recommendations for selected mild or moderate symptoms. The co-primary endpoints were DPM adoption and adherence. Here we report secondary endpoints; the perceived clinical impact, DPM module and service experience (assessed via Customer Effort Score [CES] and Customer Satisfaction Score [CSS]), and use of DPM features such as SM recommendations, via a DPM tool questionnaire. **Results:** Of the 89 enrolled pts, 66 had completed the DPM tool questionnaire at Week 6 of DPM use (data cutoff: June 9, 2022). Among the educational content, the symptom feedback library was accessed most. Pts spent up to a median of 12 minutes on Roche educational or SNP SM materials. The majority of pts (45/66 (68%)) considered the symptom questionnaires to cover all/most of the symptoms they experienced; 18/66 (27%) experienced only fair/partial symptom coverage; 49% (25/51) of pts whose symptoms were not covered contacted their HCP team. 34 pts (52%) took action based on the symptom questionnaire feedback; the most common action was SM recommendations applied according to symptom level (21/66 (32%)), followed by sending a message via the platform to the care team (8/66 (12%)). Half of pts found the SNP SM recommendations helpful/very helpful and 22 pts agreed that the SNP SM recommendations almost always/sometimes supported them in delaying contacting an HCP at an emergency room. At Week 6, the CES was 80%, CSS was 71%, and 48% (32/66) of pts felt that this service improved their care. **Conclusions:** Pt feedback showed that SNP SM recommendations were the most used action in response to the symptom questionnaire feedback and were perceived by most to be helpful/very helpful. These results support the use of SM recommendations in pts with cancer to help them self-manage tx-related symptoms experienced; future studies are needed to further explore their impact and usefulness, and to form recommendations for routine use in clinical practice. Research Sponsor: F. Hoffmann-La Roche Ltd.

1602

Poster Session

Telemedicine-supervised cancer therapy for patients with an aggressive lymphoma and metastatic lung cancer in the U.S. Veterans Affairs National TeleOncology Service. *First Author: Chenyu Lin, Durham VA Medical Center and Duke University, Durham, NC*

Background: Telemedicine is increasingly used in cancer care but has mostly been applied to surveillance and oral therapy rather than parenteral treatments. In the U.S. Veterans Affairs National TeleOncology service (NTO), patients receive intravenous cancer treatments locally under remote supervision from a disease-specialized oncologist. We analyzed care delivered by the NTO for patients with an aggressive lymphoma (AL) and metastatic lung cancer (mLC). **Methods:** The demographics of veterans with AL and mLC enrolled in NTO between 2020-2023 were compared to patients receiving in-person care at the VA. From these NTO cohorts, two subsets of patients receiving 1st line therapy for diffuse large B cell lymphoma (DLBCL) and stage IV non-small cell lung cancer (NSCLC) were extracted and compared to control arms of in-person care matched 1:4 by stage, age, PDL1 (NSCLC), and cytogenetics (DLBCL). Fisher's exact test was used for categorical variables, t test for continuous variables, log rank for survival, and negative binomial for count outcomes. **Results:** 140 patients with AL or mLC (40 DLBCL, 13 Hodgkin, 2 Burkitt, 61 NSCLC, 24 SCLC) were enrolled in NTO, spanning 12 U.S. states. Compared to in-person care ($n = 7,561$), NTO had more rural (56% vs. 34%, $p < 0.001$) and white patients (89% vs. 77%, $p = 0.002$). With a median follow-up of 256 days (IQR, 154 - 415), NTO mLC and AL patients had a median of 15 and 17 telemedicine visits, respectively. 13 of 55 AL (24%) and 56 of 85 mLC (66%) patients received systemic therapy of any line, while 38 (69%) of AL were on surveillance. 7 mLC and 2 AL patients were referred externally for care. 11 patients with DLBCL and 30 patients with stage IV NSCLC started 1st line therapy while in NTO, which were compared to matched controls. NTO and matched control had similar mean time from referral to first appointment and from diagnosis to first treatment. There were no significant differences in progression-free survival between NTO and matched controls for NSCLC (HR 1.1, 95% CI 0.7-1.8) or DLBCL (HR 0.5, 95% CI 0.1-2.3). COVID infections in the first 12 months and number of ED visits in the first 3 months of treatment were not statistically different from controls. **Conclusions:** The NTO service demonstrates the feasibility of infusional chemioimmunotherapy administration under the direction of a remote tele-oncologist. This model has the potential to improve access to specialized oncology care for rural populations and provides a framework for decentralized clinical trials. Research Sponsor: U.S. National Institutes of Health.

Patients starting 1st line therapy.

	DLBCL NTO (n = 11)	DLBCL Controls (n = 44)	p-value	NSCLC NTO (n = 30)	NSCLC Controls (n = 120)	p-value
Referral to appt, mean days	15	14	0.85	19	18	0.64
Diagnosis to treatment, mean days	38	33	0.49	41	43	0.72
COVID infections	0%	20%	0.18	13%	8%	0.48
ED visits, rate ratio	0.71 (95% CI, 0.26-1.66)			0.84 (95% CI, 0.49-1.40)		

1604

Poster Session

SpotCheck: A skin cancer diagnostic clinical trial comparing dermoscopy-enhanced telemedicine to in-person evaluation. *First Author: Jenne P. Ingrassia, NYU Langone Health, New York City, NY*

Background: Low socioeconomic status and long distances to a diagnosing provider are factors associated with poor melanoma outcomes, including advanced stage at presentation. Telemedicine offers improved access to diagnostic services for patients in medically underserved communities. Dermoscopy is an established skin imaging method with greater diagnostic accuracy for skin cancers compared to naked eye examination alone. We evaluated the safety and efficacy of a dermoscopy-enhanced, store-and-forward telemedicine-based skin cancer diagnostic platform in a prospective clinical trial. **Methods:** Participants were recruited primarily through advertisements in local newspapers. Subjects with self-identified skin lesions concerning for malignancy could have up to three lesions evaluated. Clinical and dermoscopic images of each lesion were captured, and were stored-and-forwarded to a team of three dermatologists (TeleTeam) working remotely, and independently. Participants were also evaluated face-to-face by a dermatologist (F2F). Participants were offered biopsies by the F2F (if needed) at the time of the visit, or at a follow up visit if the biopsy was only recommended by one or more members of the TeleTeam. The TeleTeam was blinded to the F2F recommendations. **Results:** We enrolled 146 subjects with 375 lesions of concern for skin cancer between September 2020 and December 2022. Baseline characteristics: 94 (64%) female; median age 65 years (range: 25-90 years); 92 (63%) non-Hispanic White; 22 (15%) Black; 11 (7%) Hispanic White; 8 (6%) Asian; 13 (9%) other or preferred not to say. Nineteen participants (13%) had a prior skin cancer including 2 with melanoma (one also with basal cell carcinoma (BCC)), and 17 with keratinocyte cancers (BCC and/or squamous cell carcinoma (SCC)). Overall, 363/375 (97%) skin lesions were clinically or histopathologically benign; 14/146 (10%) patients had a malignant or atypical skin growth. These included 12 skin cancers: 1 stage IA melanoma (0.5mm in thickness); 1 in-situ melanoma; 8 BCC; 2 in-situ SCC; and 2 moderately or severely atypical nevi. F2F recommended biopsy for both melanomas, 7 BCC and 1 SCC. TeleTeam recommended biopsy for both melanomas, 7 BCC, 2 SCC, and both moderately or severely atypical nevi. F2F identified 10/14 malignant or atypical skin growths; the TeleTeam identified 13/14. The benign:malignant ratio of the F2F and TeleTeam recommended biopsies were 2.7:1 and 5.8:1, respectively. The TeleTeam benign:malignant ratio decreased to 4.5:1 after the first 35 subjects were evaluated. **Conclusions:** Dermoscopy-enhanced telemedicine evaluation appears to be a safe and effective method to triage skin lesions for in-person medical evaluation and biopsy to diagnose skin cancer. Deployment of this diagnostic modality may help reduce melanoma health disparities arising in communities lacking dermatologists. Clinical trial information: NCT04411810. Research Sponsor: Melanoma Research Alliance; Sergei S. Zlinkoff Foundation for Medical Education; Ronald O. Perleman Department of Dermatology Orbusch Brand Pilot Program for Diseases of the Skin.

1605

Poster Session

A study to assess the diagnostic performance of a digital remote monitoring tool for patients with cancer: The POSITEA-VA study. *First Author: Charles Georges Parnot, Cureety, Dinan, France*

Background: Remote monitoring of cancer patients is known to improve survival by allowing early reporting and management of adverse events (AEs). Moreover, there is growing interest in connected, digital tools to monitor AEs by collecting patient-reported outcomes (PROs). However, countless PRO data can be overwhelming for daily clinical practice. To be simple and efficient, PRO tools should provide clear and actionable information to practitioners. In this study, we sought to validate an algorithm, Cureety TechCare, that proposes a simple clinical classification derived from AEs reported by patients. The primary objective was to assess the diagnostic performance of the algorithm using real-life data collected by the Cureety digital platform. **Methods:** Cancer patients using the Cureety Tech Care medical device were prompted to complete, at least once a week on their phone or computer, a PRO questionnaire personalized to their treatment and disease. An algorithm then computed, from the reported AEs, a simple "clinical classification" indicative of the patient's health state, with just four possible levels: red, orange, yellow, green (from most to less at-risk). These classifications allow the medical team to efficiently prioritize patients most at risk, by considering the patient either "flagged" as needing additional phone or in-person follow-up (red or orange), or "not flagged" (yellow or green). For this observational study, 400 questionnaires were randomly selected from patients that used the Cureety platform between October 1st, 2019, and September 30th, 2022. The questionnaire data were then independently assessed by 2 oncologists who were blinded to the Cureety TechCare classification. These expert classifications provided the references to calculate the sensitivity (ratio of true positive in the "flagged" group) and specificity (ratio of true negative in the "not flagged" group) of the algorithm. **Results:** Out of the 400 patients, 60 were in the "flagged" group based on the expert evaluations (with 47 true positives from the algorithm) and 340 in the "not flagged" group (with 321 true negatives). The sensitivity of Cureety TechCare was 78.3% (95% CI: 67.9%-88.8%), and its specificity was 94.4% (95% CI: 92.0%-96.9%). In addition, the algorithm correctly marked as "flagged" 95.8% (23/24) of the most at-risk patients, identified as "red" by the experts. **Conclusions:** The study demonstrated satisfactory accuracy of Cureety TechCare against a clinician-driven assessment. Its use to complement standard of care is thus clinically relevant, and it can be trusted as a useful supplementary indicator of the patient's health state. The simplicity of the output makes it particularly useful as a tool to prioritize care, with a clear four-level, color-coded clinical classification to represent the combined AEs reported by the patient. Clinical trial information: NCT05653609. Research Sponsor: None.

1607

Poster Session

Impact of state policies on telehealth use among the privately insured with newly diagnosed cancer. *First Author: Ya-Chen Tina Shih, MD Anderson Cancer Center, Houston, TX*

Background: The COVID-19 public health emergency (PHE), declared on January 31, 2020, relaxed many telemedicine restrictions. Yet there remains wide variation across states on the coverage and reimbursement of telemedicine services and rules to permit practicing across state lines. Research has shown expanded access to telemedicine is beneficial to cancer patients, making it important to understand the relationship between state policies and the use of telemedicine. **Methods:** We identified privately insured non-elderly patients newly diagnosed with any of five common cancers (female breast, prostate, lung, colorectal, and lymphoma) between March 2019 and March 2021 from Optum Clinformatics Data Mart. We characterized state telehealth policies by parity status (coverage & payment parity, coverage parity only, and none) and rules for cross-state practice (allowed with vs. without limitations). We applied interrupted time series analysis to examine the trend of telemedicine use before and after the declaration of COVID-19 PHE and conducted multivariable logistic regression to examine the association between state policies and telemedicine use while controlling for other confounders. **Results:** Of the 10,813 privately insured non-elderly patients, the adjusted rate of telemedicine use was 23.6%. The average age was 53.2 (SD = 9.24). Race/ethnicity distribution was 71.20% non-Hispanic White, 10.07% non-Hispanic Black, 8.56% Hispanics, 3.77% Asians, and 6.39% others. Lymphoma, female breast, colorectal, lung, and prostate cancer accounted for 10.55%, 46.55%, 13.27%, 7.56%, and 22.07% of patients. A sharp increase was observed early on (from 32.4% in March 2020 to 42.5% in April 2020), followed by a steady decline, down to < 15% by March 2021. Compared to patients residing in states with coverage and payment parity, those in states with only coverage parity and no parity were significantly less likely to use telemedicine (OR = 0.79, 95% CI: [0.71 – 0.88]; OR = 0.77, [0.68 – 0.87]). Patients residing in states with more restrictions/regulations on cross-state practice were significantly less likely to use telemedicine (OR = 0.84, [0.76 – 0.93]) than those in states that were less restrictive. Other factors predicting lower likelihood of telemedicine use included older age (OR = 0.69 [0.62-0.77] for age 50-64 vs. 20-49), non-Hispanic Black (OR = 0.84 [0.72 – 0.98] vs. non-Hispanic White), colorectal cancer (OR = 0.82 [0.70 – 0.96] vs. female breast), and more recent diagnosis. **Conclusions:** With the approaching end of COVID-19 PHE, states are deciding whether to permanently relax certain telemedicine policies or return to existing more restrictive policies. Our study suggests patients residing in states that move toward less generous parity and more restrictive cross-state practice rules may be less likely to benefit from telemedicine. Research Sponsor: None.

1606

Poster Session

Trends and disparities in oncology telehealth after the initial pandemic era. *First Author: Michael Jisoo Lee, San Francisco Medical Center, Kaiser Permanente Northern California, San Francisco, CA*

Background: While the COVID pandemic elevated the usage of telehealth to unprecedented levels, it remains unclear whether telehealth use is sustained after the initial pandemic era, and whether there remain demographic differences in telehealth utilization. In this study, we compared telehealth trends amongst different demographic populations in a large integrated healthcare system. **Methods:** Utilization of various visit types (office, video, telephone) was investigated in this population-based retrospective cohort study at 22 Kaiser Permanente Northern California Hematology and Oncology clinics from 10/1/2020 to 6/1/2022. We explored trends associated with the COVID 19 pandemic and after the initial pandemic era as well as demographic differences, using Chi-square for categorical and the Mann-Whitney U Test for non-parametric comparisons. **Results:** During the study period, there were 341,089 hematology/oncology visits with MD/DO providers, including 83,756 (24.5%) office, 125,162 (36.7%) video, and 132,171 (38.7%) telephone. Total monthly visits remained stable, with a monthly average of 1,765 (10.9%) for new visits and 14,476 (89.1%) for return visits. Monthly telehealth visits (telephone + video) peaked in January, 2021 (85.6% of total visits) and subsequently declined by June, 2022 (68.7% of total visits). Telephone visits increased from 46.1% of telehealth visits to 58.9% over the study period. Amongst telehealth visits, video visits remained popular for new appointments (56.9%) while telephone visits were more common for return appointments (60.7%). After the initial pandemic era, telehealth utilization continued to differ amongst different demographic populations. Video visits remained a significantly higher fraction of all visits ($p < 0.01$) in: (1) less than 45 year-old (60.0%) compared to older than 80 year-old (33.2%); (2) primary English speakers (50.7%) compared to those who require an interpreter (41.5%); (3) patients with commercial insurance (58.2%) compared to those with Medicaid (47.0%) or Medicare (45.2%); (4) non-Hispanic Whites (51.4%) and Asians (52.2%) compared to Hispanic Whites (45.0%) and Blacks (43.6%); (5) patients with the lowest neighborhood deprivation index (NDI) quartile (living in the least deprived neighborhood) (54.0%) vs the highest quartile (46.1%). **Conclusions:** After the initial pandemic era, telehealth utilization declined slightly over time but remained a common method of providing oncology care. Video visits continued to be widely utilized for initial visits whereas there was a shift to telephone visits for follow up appointments over time. Disparities in telehealth, especially in video visits, continued to be seen in various demographic populations by age, English proficiency, insurance plan, race/ethnicity and neighborhood deprivation index. Continued high utilization of telehealth should inform policy and practices in the post-pandemic era. Research Sponsor: Kaiser Permanente.

TPS1608

Poster Session

Korean Precision Medicine Networking Group study of molecular profiling guided therapy based on genomic alterations in advanced solid tumors (KOSMOS) II (KCSG AL 22-09). *First Author: Sun Young Kim, Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea*

Background: Next-generation sequencing (NGS) has been introduced to many Korean institutions as molecular diagnostics for cancers since 2017, when it was reimbursed by the National Health Insurance Service. However, molecularly-guided treatment (MGT) options based on NGS results have been limited due to the strict regulation for prescribing outside of the approved indication, lack of clinical trial availability, and limited access to molecular tumor boards (MTB) in most institutions. Given our previous KOSMOS study results, which showed MGT was available for 54% (124/198) of patients based on local NGS (ESMO Open 2022;7(6, Suppl 1); 100653), KOSMOS-II study was designed to demonstrate MGT would be feasible and effective via a nation-wide precision medicine platform. **Methods:** This national, prospective, pragmatic, multi-cohort study comprised of a framework to screen pts with metastatic solid tumors for actionable genetic alterations (GA) based on local NGS testing and to recommend MGT by a remote and centralized MTB held weekly or biweekly. MGT can be one of the following options: Tier 1, the therapeutic use of investigational drugs targeting GAs including ALK, EGFR, ERBB2, BRAF, FH, ROS1, RET, or high tumor mutational burden; Tier 2, drugs that are allowed for treatment outside of the approved indications by the National Health Insurance; Tier3, clinical trials matched for GA recommended by MTB. To estimate the proportion of patients receiving MGT to be $50 \pm 3.25\%$ with 95% confidence interval, we will enroll 1,000 pts, considering 5% drop-out rate. The clinical benefit rate of MGT beyond 16 ± 2 weeks is the second co-primary endpoint, which is expected to be 30% with type I error of 5% and 90% power. Pts must have progressed ≥ 1 or more lines of therapies; have undergone NGS testing; are able to provide the Variant Call Format (vcf) file of the NGS results. MTB determines clinical actionability of GA and recommends MGT if possible, according to Tier 1,2, or 3. The vcf files and matched clinical information will be deposited to the repository of National Center Center Korea and will be curated in a de-identified clinico-genomic database. As of Feb 2023, 139 of planned 1,000 have been enrolled. Clinical trial information: NCT05525858. Research Sponsor: Ministry of Health and Welfare, South Korea; Roche Korea.

TPS1609

Poster Session

Open label single arm study to assess the implementation of home based daratumumab administration in patients being treated for multiple myeloma. *First Author: Adam F Binder, Sidney Kimmel Cancer Center at Thomas Jefferson University, Philadelphia, PA*

Background: Multiple myeloma (MM) is an incurable hematologic malignancy that has a high burden of care for patients and their caregivers. Over the last two decades, the treatment landscape for MM has changed dramatically. However, treatment burden with frequent visits to offices and the hospital is high. We need innovative care delivery models to alleviate these burdens. Chemotherapy at home remains uncommon in the US, though models for its use exist globally. In these models, home-based chemotherapy is safe, preferred by patients, and can be administered at lower cost. Herein, we propose a home-based subcutaneous daratumumab and hyaluronidase-fihj (dara) program for patients with MM. We hypothesize that this program will be feasible, reduce patient treatment and financial burden, and improve quality of life.

Methods: We designed an open label single arm study to assess the implementation of home administration of dara. The primary objective is to evaluate (n=20) treatment satisfaction of patients, using the Cancer Therapy Satisfaction Questionnaire (CTSQ), when they receive care at home as compared to the standard of care (SOC). Secondary outcomes include evaluating adherence to home delivery, quality of life (EORTC QLQ-30), financial burden (COST survey), safety of home administration, and barriers to home administration. At the end of the study, we will conduct semi-structured interviews to assess patient experience with home administration of chemotherapy. Patients will be eligible for study participation if they have a diagnosis of multiple myeloma, are in the monthly phase of dara treatment and are treated with either monotherapy or in combination with oral agents. All participants who are interested and eligible will be on study for 8 cycles of dara (2 cycles of dara in the infusion center (IC) followed by 4 cycles at home and then 2 cycles in the IC). During the home administration phase, 1-3 days prior, patients will go to a local lab or have at home labs. On day of at home dara, the drug will be mixed and packaged by our pharmacy, and then delivered at room temperature to the patient's home by our home infusion courier. The patient will take pre-medications 1-3 hours prior to nurse arrival. The nurse arrives, confirm pre-medications were taken. Pre-treatment vitals and post treatment vitals will be obtained. Drug will be administered as per label instructions. At the beginning of each cycle, patient reported outcome surveys and quality of life surveys will be collected. During the home administration phase, details on barriers to maintaining adherence (i.e. issues with storage, delivery, disposal of medication) will be collected. The study opened for enrollment on November 8th, 2022. As of February 1st 2023, 9 patients have consented and 5 patients are on-treatment. Clinical trial information: NCT05511428. Research Sponsor: Janssen.

TPS1611

Poster Session

Progress report of a cross-organ and biomarker-based platform study: BELIEVE trial NCCH1901. *First Author: Yayoi Ando, National Cancer Center Hospital, Chuo-Ku, Japan*

Background: Cancer Genomic Medicine (CGM) has been developing and more patients have received the comprehensive genomic profiling (GCP) test under national healthcare system in Japan. However, the number of patients who could receive the genomically matched therapy based on the results of CGP tests was limited. To improve the drug accessibility, we initiated a cross-organ, biomarker-based clinical trial (NCCH1901, the BELIEVE trial). It was a platform trial and could be considered as the Japanese counterpart to the National Cancer Institute's Molecular Analysis for Therapy Choice (NCI-MATCH) study in the United States. **Methods:** It was a multi-institutional joint research nationwide led by NCCH with a master's protocol. Several drug cohorts were pre-established, allowing patients to participate in molecularly targeted treatments recommended as a result of CGP test. All drugs were provided for free from the pharmaceutical companies. The objective of this trial was to administer off-label drugs for the respective genomic abnormalities and collect efficacy and safety data for patients of the drugs. The primary endpoint was the response rate based on the best overall response for up to 16 weeks. This trial has been conducted under both of the Japanese Clinical Trial Act and the patient-proposed healthcare services which enable patients to receive unapproved, off-label drugs partially covered by National Health Insurance. The protocol and the informed consent forms were approved by the National Cancer Center Hospital (NCCH) certified review board and the Ministry of Health, Labour and Welfare (MHLW). The trial was registered in the Japan Registry of Clinical Trials (jRCTs031190104). As of January 31, 2023, we have 20 drug cohorts and the planned number of enrollments for each cohort was 50 with the target lesions and 30 without the target lesions. There were more than 500 patients so far. The most common cancer was brain tumours, followed by carcinoma of endocrine organs and the colorectal cancer. *BRAF* mutation and *ERBB2* amplification were the frequent genomic abnormalities registered in this trial. Five drug cohorts have already finished recruiting and 2 drug cohorts assessed their efficacies. We are still continuing to discuss several pharmaceutical companies to increase the drugs cohorts in this platform. This trial is now recruiting the patients and is contributing significantly to increase the treatment opportunity for the cancer patients. Clinical trial information: jRCTs031190104. Research Sponsor: the Japan Agency for Medical Research and Development; ONO PHARMACEUTICAL CO., LTD and Otsuka Pharmaceutical Co., Ltd.

TPS1610

Poster Session

Screening for high frequency malignant disease (SHIELD). *First Author: HA NGUYEN, Guardant Health, Inc. (Redwood City, CA), Redwood City, CA*

Background: Insufficient adherence to guideline recommended cancer screening undermines the effectiveness of current modalities to improve cancer related outcomes, resulting in an unmet clinical need. Implementation of a convenient blood-based cancer screening option, utilizing a test with high sensitivity and specificity, has the potential to address this unmet need. We aim to evaluate the performance of a blood-based multi-cancer screening test in a population of screen eligible individuals across multiple cancer types, encompassing a diverse representation of racial and ethnic groups. **Methods:** SHIELD (Screening for High Frequency Malignant Disease; NCT#05117840) is a prospective, observational, multi-center basket study in the United States and Europe designed to recruit individuals undergoing screening across multiple cancer types. The study's primary objective is to evaluate the performance of a blood-based multi-cancer screening test (GuardantLUNAR-2, Guardant Health, US) to detect cancer in screen-relevant individuals compared to the reference standard cancer screening modality. Each study cohort represents a unique cancer type(s). Eligible individuals consent to whole blood collection within 90 days of the standard of care screening for the respective cancer type. Clinical diagnoses, e.g., cancer, are made per standard of care. Primary outcomes: sensitivity, specificity, negative and positive predictive value of the blood-based multi-cancer screening test. Secondary outcomes: number of screen-detected cancers, early and late-stage screen-detected cancers per 1000 screened individuals. One- and two-year clinical outcomes are collected by implementing HIPAA compliant, patient-level linkage of trial data with real-world data sources (Medidata, USA) to which patients consent subsequent to main study consent. Cohort A: Lung cancer screening. Eligibility is aligned with USPSTF screening recommendations; age 50-80 years with > 20 pack-year smoking history who are current smokers or quit within the past 15 years, without any history of cancer or preinvasive lung lesions, and without recent surgery or trauma. This cohort will enroll 9,000 subjects over 24 months at up to 120 global sites. This cohort was initiated in January 2022. As of January 2023, 94 study sites have been activated with 4,977 individuals consented and 4,866 individuals enrolled (defined as study blood sample collected). To date, 4679/4977 (94%) individuals consented to the linkage process. Cohort A is on track to meet enrollment targets by the end of 2023 and on track for final primary outcome data collection by December 2024. Clinical trial information: NCT05117840. Research Sponsor: Guardant Health.

TPS1612

Poster Session

Infrastructure for rare cancer in the Netherlands: Towards a comprehensive platform for early detection and diagnosis of rare cancers (FORCE). *First Author: Carolina R.C. Pieterman, The Netherlands Cancer Institute Amsterdam/UMC Utrecht ENETS Centre of Excellence, Department of Endocrine Oncology, Utrecht, Netherlands*

Background: One in five patients with cancer has a rare type of tumor. For these patients, randomized controlled trials are often infeasible and, compared to patients with a more common tumor, their prognosis is poor due to late or incorrect diagnosis and fewer available treatment options. Moreover, most patients with rare cancer do not benefit yet from recent developments in ultrasensitive profiling of circulating cell-free DNA (USccfDNA). In some more common cancers, USccfDNA has improved early primary detection, detection of minimal residual disease (MRD), and early recurrence. The information needed to apply USccfDNA in most rare cancers is lacking, which delays innovation of personalized treatments and deprives these patients of a chance for a better outcome. FORCE aims to improve treatment outcomes for patients with rare cancers by systematically collecting their clinical data, tumor tissue and peripheral blood components. **Methods:** Retrospectively and prospectively collected data are used to build a data warehouse that provides comprehensive insight into the long-term biology of a rare cancer. The data warehouse is visualized as a train. The locomotive represents the infrastructure, which uses web-based tools for FAIR, comprehensive, multidisciplinary, data collection, workflow support and storage. The built-in "Call-me-in" module enables anyone who has been diagnosed with a rare tumor to collaborate and contribute their data to FORCE under strict privacy regulations. Each train carriage represents the data concerning a coherent set of rare tumor types, reflecting the ten domains defined by European Reference Network (ERN) Rare Adult Solid Cancers (EURACAN). Neuroendocrine neoplasms (NEN, EURACAN domain 4) is the first carriage joined to the FORCE infrastructure and serves as a use-case for the FORCE infrastructure. Currently, the first patients are being included in the prospective multicenter clinical biobank that makes optimal use of existing (data) infrastructure. A legal joint data registry agreement has been developed to enable a shared clinical biobank with a federated structure, and facilitate sharing of data and samples among participating institutes. FORCE-NEN has also developed a governance structure for the carriage and its relation to the central FORCE infrastructure. Both documents will serve as an adaptable template for other carriages. FORCE is now available for further international collaboration. We established a unique infrastructure in the Netherlands that combines the collection of clinical data, tumor and peripheral blood components of patients with a rare tumor, starting with NEN. The FORCE infrastructure will enable studies to optimize early primary detection, detection of minimal residual disease (MRD), and early recurrence by USccfDNA assays and facilitate future clinical trials. Research Sponsor: Koninkrijk Wilhelmina Fonds (KWF, the Dutch cancer foundation).

TPS1613

Poster Session

The PLATON Network: An interactive platform for precision oncology. *First Author: Salah-Eddin Al-Batran, Institut für Klinische Krebsforschung IKF GmbH am Krankenhaus Nordwest, Frankfurt Am Main, Germany*

Background: To increase the access of patients to precision oncology and personalized medicine, we need not only to undertake molecular profiling but rather we need to interlink patients, physicians and researchers using modern technological opportunities, increasing the likelihood of providing new therapies to patients with suitable targets. The PLATON Network (NCT05489250, IKF-T008) addresses these important issues. **Methods:** The PLATON Network (PLATON) is an interactive structure aiming at improving personalized medicine for all tumor entities (starting with upper GI tumors). The goal of the PLATON Network is to provide a platform for connecting medical practitioners, researchers and patients to personalized cancer treatments. The platform combines comprehensive molecular profiling, data on active clinical trials, remote data access with networking solutions, implemented substudies and associated educational and discussion forums. The main elements of PLATON are: a Platform-study design, an interactive Cloud-based WebApp, Networking, a Molecular Pathology Case Discussion Board, an educational forum, and a BioDataBank. The network will be composed of a global network of cancer centers and cancer specialists who can submit genomic data of their patients to PLATON. The WebApp allows members and associated scientists to view each other's current patients' clinical and molecular data and get into contact with the treating physicians or identify patients for ongoing biomarker-driven clinical trials using advanced algorithms. The PLATON Network also offers molecular testing via Foundation CDx and CDx Liquid for standardized NGS testing and functions as an umbrella for substudies within the platform design. PLATON enrolls patients during first line treatment and collects information on routine clinical data (baseline data, medical history, histopathology reports, treatment decisions, etc.). During follow up, all anti tumor therapy lines, tumor response and survival data are recorded. Importantly, quality of life data is captured monthly under therapy (with EORTC QLQ-30, -BIL21, -HCC18, -PAN26, -STO22 and EQ-5D-5L) and at further follow up (with EQ-5D-5L). So far, 110 cancer centers have joined the PLATON network. Over 200 patients with upper GI tumors received comprehensive molecular profiling and 162 cases were reviewed and discussed in the Molecular Pathology Case Discussion Board. Five sub-projects/-studies have been initiated under the umbrella of PLATON. The educational forum is in the planning stage. PLATON is conducted by the Institute of Clinical Cancer Research (IKF) in Frankfurt with the supervision of an independent scientific steering committee. Research Sponsor: Institute of Clinical Cancer Research at Krankenhaus Nordwest, Frankfurt am Main, Germany.

TPS1615

Poster Session

Mixed-methods clinical trial to evaluate the feasibility of the CURATE.AI optimised digital cognitive rehabilitation therapeutic (COR-Tx) in patients post brain radiotherapy. *First Author: Marlena N. Raczowska, The N.1 Institute for Health, National University of Singapore, Singapore, Singapore*

Background: Cognitive decline may be exacerbated, in brain tumour patients, by prior radiotherapy (RT). Traditional interventions to mitigate this typically involve fixed dose or intensity pharmacological and/or cognitive rehabilitation therapies that often elicit sub-optimal or no response, due to the dynamically evolving patient state and low adherence. Personalised digital therapeutics (DTx) may be more effective for this population. Further, gamification has previously shown to induce positive health behavioural change and improve intervention adherence. To this end, we have developed the CURATE.AI COR-Tx platform, a gamified DTx, that combines a previously validated, small-data artificial intelligence-derived dose optimisation technology with digital multitasking cognitive training. This novel DTx dynamically personalises treatment by using the patient's own longitudinal performance data to generate an evolving digital avatar that guides training intensity throughout the intervention. Herein, we aim to evaluate feasibility, user experience and usability of the DTx platform in brain tumour patients post-RT. **Methods:** This is a prospective, mixed-methods, interventional, single-arm, decentralised feasibility clinical trial. The primary objective is to evaluate feasibility of the CURATE.AI COR-Tx platform as both a digital intervention (DI) and digital diagnostic (DD) for cognitive function in 15 patients with brain tumour post-RT. The personalised and home-based DI involves completing three 12-min sessions per week for 10 weeks, starting 1 month post-RT. Cognitive function will be assessed via a combined non-digital cognitive evaluation and a DD session at five time points: prior to RT, pre- & post-DI and 16- and 32-weeks post-DI. Feasibility outcomes relating to acceptability, demand, implementation, practicality and limited efficacy testing and additional secondary and exploratory outcomes relating to usability and user experience will be collected by the clinical team and through semi-structured patient interviews and a study team focus group discussion at study completion. We will adopt a mixed-methods approach for data analysis. Feasibility of the CURATE.AI COR-Tx platform will be evaluated through thematic analysis for qualitative outcomes (acceptability and practicality), and descriptive and correlational analysis for quantitative outcomes (demand and implementation). We will adopt the CONSORT traffic light system to decide on future expansion into a large-scale randomised control trial. This trial began in April 2021 and has enrolled 14 of planned 15 patients at the time of submission. Clinical trial information: NCT04848935. Research Sponsor: Singapore Cancer Society; National Research Foundation Singapore.

TPS1614

Poster Session

Electronic collection of cancer patient-reported outcomes using a novel digital oncology platform: A multi-site randomized controlled trial. *First Author: Chris Fidyk, Vinehealth Digital Limited, London, United Kingdom*

Background: Cancer is the leading contributor of disease burden worldwide, and incidence rates are estimated to rise 47% by 2040. With increasing numbers of people living with cancer, alongside healthcare workforce shortages, current models for cancer monitoring and surveillance are unsustainable. Within the UK's National Health Service (NHS), this is exacerbated by a rising backlog following the COVID-19 pandemic. Furthermore, a 2020 Macmillan Cancer Support survey showed that current patient information and support is scattered, inaccessible, and poorly personalized. There is an urgent need for effective personalized tools to support cancer patient self-management and data collection to enable healthcare professional (HCP) monitoring and remote follow-up. **Methods:** A multi-site randomized controlled trial is underway within the NHS to evaluate the implementation of a novel digital oncology platform (Vinehealth) for personalized support. Vinehealth consists of a mobile patient application, integrated wearables data, and a clinician dashboard. The study aims to recruit 180 patients across 8 NHS Trusts diagnosed with (i) colorectal, breast, or lung cancer undergoing adjuvant systemic treatment (chemotherapy +/- targeted therapies) post surgery, or (ii) asymptomatic breast cancer undergoing neoadjuvant treatment. A power calculation was conducted relating to the primary objective demonstrating the efficacy in improvement of QoL in the interventional arm, providing 80% power and at a significance level of 0.05. Enrolled patients will be randomized (1:1) between standard of care (SoC) and interventional arms (SoC plus Vinehealth platform). The main objective is to assess if implementation of Vinehealth improves patients' quality of life (QoL) compared to SoC based on EQ-5D-5L, EORTC QLQ-C30, and FACT-G (PWB) questionnaires. Secondary objectives include assessing patient compliance with electronic patient-reported outcome (ePRO) data collection and patient self-management of symptoms. The study will further evaluate whether Vinehealth improves the process of care (assessed through medication adherence) and reduces emergency healthcare utilization (including ED/GP visits/admissions and acute oncology hotline use). Questionnaires are completed by all patients at baseline, 6, 12, 18 and 24 weeks. Qualitative interviews will be conducted with a subset of interventional arm patients and HCPs from each NHS Trust to understand engagement with the Vinehealth platform. To our knowledge, this is the first multi-site RCT within the NHS to evaluate the impact of a digital oncology platform on cancer patients' QoL, ePRO compliance, process of care, and healthcare utilization. The trial is expected to end by September 2023 with results being reported in January 2024. Clinical trial information: ISRCTN44293246. Research Sponsor: Innovate UK.

TPS1616

Poster Session

Liquid biopsy-informed precision oncology study to evaluate utility of plasma genomic profiling for therapy selection. *First Author: Jessica Tao, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD*

Background: Liquid biopsies have enabled a transformation in the management of patients with cancer as they have the potential to detect, characterize, and monitor tumor burden. However, the increasing complexity involved in the integration of genomic data into clinical practice has presented challenges with the practical implementation of liquid biopsies in clinical cancer care. To address these challenges, multidisciplinary teams comprised of experts within oncology, genetics, pathology, and informatics have created Molecular Tumor Boards (MTBs), which can improve clinical outcomes for cancer patients by efficiently utilizing the technologies created by the rapidly expanding precision oncology industry. Nevertheless, there remains a gap in the optimal implementation and interpretation of these diagnostic findings to maximize patient outcomes and access to standard of care therapies and clinical trials. **Methods:** We instigated a prospective observational liquid biopsy-informed precision oncology study, in which patients with metastatic solid tumors will be matched with genotype-driven therapies via serial liquid biopsies (NCT05585684). Liquid biopsy-derived genotypes will be generated through a clinical NGS assay (PGDX Plasma Focus) and will be annotated by an automated ensemble approach for variant actionability assessment, developed by the Johns Hopkins MTB, followed by a treatment recommendation. Key eligibility criteria include patients ≥ 18 years old, with ECOG performance status of 0-1 and with metastatic disease that have relapsed or progressed after standard of care first-line therapies or patients for which first-line standard of care therapeutic options are not expected to yield a clinical response. The primary objectives of the trial focus on feasibility of the approach and evaluating the fraction of patients with actionable mutations, for which the MTB recommendation is enacted upon. Unique to this study, a recommendation to not pursue genotype-targeted therapy is equally considered for personalized clinical decision making. Secondary objectives are to investigate whether enacting upon MTB recommendations improves progression-free and overall survival and perform a comparative analysis with tumor-based NGS. Exploratory objectives are to determine if serial molecular profiling after initiation of systemic treatment is sufficient to determine therapeutic response, compare with RECIST radiographic response and determine whether changes in liquid biopsy dynamics correlate with progression-free and overall survival. This study will enroll 150 patients with solid tumors, including lung, esophageal, breast, and head and neck cancer and mesothelioma to evaluate the clinical utility of liquid biopsy genomic profiling. Patient accrual for this study initiated in February 2023. Clinical trial information: NCT05585684. Research Sponsor: Personal Genome Diagnostics/Labcorp.

TPS1617

Poster Session

An interventional study of the impact of digital patient monitoring (DPM) on health outcomes, healthcare resource utilization, and feasibility of a combination with at-home treatment (tx) for delivery of systemic anticancer tx in clinical practice. *First Author: Sanna Iivanainen, Oulu University Hospital, Oulu, Finland*

Background: Disease- and tx-related symptoms negatively affect quality of life and may become life-threatening. There is a need for improved understanding, prevention, reduction and mitigation of symptoms, and tools to facilitate remote tracking of pt-reported outcomes (PROs) and support self-management of symptoms. As anticancer txs are increasingly given outside of the clinical settings, DPM tools are becoming more important to support remote symptom management. DPM can improve clinical care and pt outcomes; however, broad adoption requires proven usability and demonstration of real-world clinical utility/impact. ORIGAMA (NCT05694013) is an interventional, open-label, multi-country platform study investigating the clinical utility of DPM tools with specific txs. ORIGAMA will assess atezolizumab (atezo)-specific Roche DPM Modules (F. Hoffmann-La Roche Ltd, Basel, Switzerland; hosted on Kaiku Health DPM platform [Helsinki, Finland]) in two cohorts, to study the impact of DPM on clinical outcomes and healthcare resource utilization, and its feasibility to support at-home tx administration. **Methods:** Adult pts with ECOG PS of 0–2, an email address, and access to an internet-capable device and internet connection are eligible. In Cohort A, systemic tx-naïve pts with metastatic non-small cell lung cancer (NSCLC), extensive-stage SCLC, or Child–Pugh A unresectable hepatocellular carcinoma, with a life expectancy of ≥ 12 weeks (wks) will be randomized 1:1 to a locally approved anticancer regimen of intravenous atezo and local standard-of-care (SoC) support with/without access to the Roche DPM Module. Pts will receive tx until progressive disease or per local SoC. Cohort B will assess the Roche DPM Module in pts receiving 3 cycles of subcutaneous atezo in a hospital setting, followed by 13 cycles of at-home administration by a healthcare professional. Eligible pts have programmed-death ligand 1-positive (expression on $\geq 1\%$ of tumor cells), NSCLC (Stages IIB, IIIA, IIIB [T3–N2]), have completed adjuvant chemotherapy 4–12 wks prior to randomization, and must have a complete resection. Future cohorts may be added to investigate digital health solutions in other tx settings. The primary endpoints are the mean difference in change of the pt-reported Total Symptom Interference Score at Wk 12 from baseline (Cohort A), and flexible care adoption rate at Cycle 6 (Cohort B). The primary analysis for Cohort A will occur when all randomized pts have been followed for ≥ 12 wks and for Cohort B when all pts have completed 16 cycles of tx. Other endpoints include safety and PROs. An exploratory analysis of overall survival will be performed. ~400 pts in Cohort A and 40 pts in Cohort B will be enrolled. Recruitment has started; the first pt to be enrolled in February 2023. Clinical trial information: NCT05694013. Research Sponsor: F. Hoffmann-La Roche Ltd.

ABSTRACT WITHDRAWN

2001

Oral Abstract Session

Evaluating the diagnostic performance of ^{18}F -fluciclovine for detection of recurrent brain metastases after radiation therapy: Results from a prospective phase 2 trial. *First Author: Rupesh Kotecha, Miami Cancer Institute, Miami, FL*

Background: Differentiating radiation necrosis from tumor progression remains one of the most commonly encountered and clinically challenging scenarios after radiation therapy (RT) for brain metastases (BM). PURSUE (NCT04410367) evaluated the diagnostic performance of ^{18}F -fluciclovine, an amino acid PET radiopharmaceutical, based on various lesion metrics, to establish image interpretation criteria (IIC) for suspected recurrent BM after RT. **Methods:** Patients with solid tumor BM were enrolled across 7 US sites if they had a previously irradiated 'reference' lesion equivocal on MRI for recurrence and were planned for craniotomy. ^{18}F -Fluciclovine PET (185 MBq) took place <42 days post-MRI and 1-21 days pre-craniotomy. The primary endpoint was the diagnostic performance (sensitivity, specificity, positive-, and negative-predictive value [PPV/NPV]) of different thresholds of lesion ^{18}F -fluciclovine uptake on qualitative, visual reads vs central histopathological analysis. Lesion ^{18}F -fluciclovine uptake was assessed qualitatively by 3 independent blinded readers who visually rated the uptake as 'mild' (up to blood pool), 'moderate' (above blood pool to parotid), or 'marked' (above parotid). Secondary endpoints included the diagnostic performance based on different thresholds of quantitative (e.g., lesion SUV) and dynamic measures of uptake. A committee, including 2 expert imaging physicians independent to PURSUE, reviewed all data in round-table meetings to establish the IIC, which were subsequently used to assess diagnostic performance. **Results:** All 23 reference lesions in 23 subjects underwent histopathological analysis, with 10 (43%) confirmed as recurrent tumor. The highest performing qualitative measure was 'marked', rendering a sensitivity of 92-100%, with variable specificity of 40-80% across readers. SUV_{max} was a reader-independent, high-performing quantitative metric on ROC analysis (AUC 0.87, SUV_{max} threshold 4.8 conferring a sensitivity of 80% and specificity of 85%). Dynamic measures did not provide added diagnostic value. After analyzing these metrics, the committee established IIC as: Lesions with ^{18}F -fluciclovine uptake of a SUV_{max} equal to or greater than 4.8, or visually greater than the parotid gland, should be considered suspicious for recurrence. Otherwise, recurrence should be considered unlikely. Application of the IIC resulted in a sensitivity of 80%, specificity of 77-85%, PPV of 73-80%, and NPV of 83-85% across the readers. **Conclusions:** This is the first prospective multicenter trial to evaluate PET characteristics of suspected recurrent BM after RT, verified by histopathology. Qualitative and quantitative IIC show ^{18}F -fluciclovine to be a high-performing diagnostic tool. These IIC will help evaluate the diagnostic performance of ^{18}F -fluciclovine PET in future trials. Clinical trial information: NCT04410367. Research Sponsor: Blue Earth Diagnostics.

2002

Oral Abstract Session

Phase II study of short course hypofractionated proton beam therapy incorporating ^{18}F -DOPA-PET/MRI for elderly patients with newly diagnosed glioblastoma. *First Author: Sujay A. Vora, Mayo Clinic Arizona, Scottsdale, AZ*

Background: Elderly patients with glioblastoma have a poor prognosis with phase III trials reporting median overall survival (OS) and global time to deterioration of 6-9 and 1.2 months respectively. ^{18}F -DOPA (3,4-dihydroxy-6-[^{18}F]-fluoro-L-phenylalanine) positron emission tomography (PET) is sensitive and specific for identifying regions of high density and biologically aggressive glioblastoma. Proton beam therapy (PBT) can spare more healthy tissue that may improve quality of life for this patient population. With improved targeting of disease along with dosimetric advantages of PBT, this phase II trial tested whether hypofractionated PBT can offer both improved survival and quality of life. **Methods:** Patients with newly diagnosed glioblastoma aged ≥ 65 years without contraindications to ^{18}F -DOPA were eligible. Target volumes were defined by PET (tumor/normal brain $\text{SUV} \geq 2.0$) and MRI areas of contrast enhancement including surgical cavity. Patients received dose escalated hypofractionated PBT of 35-40 GyE to PET/MRI over 5-10 treatments with 10 mm margin. Patients received concurrent/adjuvant temozolomide. With an alpha of 0.1, 18 of 39 patients would be required to be alive at 12 months for the study to be considered a success. Kaplan-Meier/Cox regression analysis was performed for progression free survival (PFS) and OS. Toxicities were evaluated with CTCAE v4.0. Patients completed EORTC BN20, QLQ-C30, and MMSE questionnaires. Time to deterioration, defined as a 10-point decrease in the score of the function domain or 10-point increase in score of symptom domain, was evaluated. **Results:** Between 5/2019-6/2021, 43 patients were enrolled, with 4 patients withdrawing due to progression/insurance denial prior to beginning protocol therapy. The median age was 70.2 yrs. and median follow-up was 12.5 months. MGMT methylation was present in 13 (33%). Tumors were multifocal in 10 (26%) and unifocal in 29 (74%). The primary endpoint was met with median PFS/OS was 6.5/12.9 months for all patients and for MGMT methylated patients 11.9/29.8 months respectively. Grade 3 baseline adjusted treatment related adverse events included 1 (3%) confusion, 2 (5%) fatigue, and 1 (3%) seizure. There were no grade 4/5 events. Multivariate analysis revealed MGMT unmethylated, ECOG 2 and biopsy only patients had worse survival. PET volume was more predictive than MRI volume for OS with PET volume > 26 cc having a hazard ratio of 3.7. The median time to global deterioration per QLC-C30 was 6.3 months. **Conclusions:** This phase II trial incorporating ^{18}F -DOPA PET-guided dose escalated hypofractionated proton beam treatment for elderly patients with glioblastoma met its primary endpoint for improved OS and patient reported quality of life compared to historical controls. Further investigation is warranted. Clinical trial information: NCT03778294. Research Sponsor: Marley/Matheson.

ABSTRACT WITHDRAWN

2004

Oral Abstract Session

PD1 inhibition and G1TR agonism in combination with fractionated stereotactic radiotherapy for the treatment of recurrent glioblastoma: A phase 2, multi-arm study. *First Author: Stephen Joseph Bagley, University of Pennsylvania, Philadelphia, PA*

Background: Despite preclinical evidence that fractionated stereotactic radiotherapy (FSRT) is immunostimulatory, there remains a paucity of data regarding immune effects of FSRT in patients treated with immune checkpoint blockade (ICB). To evaluate the immune impact of FSRT in glioblastoma (GBM), which is refractory to single-agent ICB, and to evaluate the efficacy of the addition of FSRT to ICB for this disease, we conducted a phase 2 trial of the combination of retifanlimab (anti-PD1), INCAGN01876 (G1TR agonist), and FSRT (8 Gy x 3 fractions) in patients with recurrent GBM (rGBM). **Methods:** This single-center trial enrolled patients with no prior bevacizumab and dexamethasone dose $\leq$ 2mg/day. The study included a single-arm, primary efficacy cohort (Cohort A) treated with retifanlimab, INCAGN01876, and FSRT, and a two-arm neoadjuvant window-of-opportunity cohort (Cohort B) for patients needing tumor resection. In Cohort B, patients on Arm B1 received single doses of retifanlimab/INCAGN01876 plus FSRT prior to surgical resection, and patients on Arm B2 received single doses of retifanlimab/INCAGN01876 without FSRT prior to surgical resection. We used flow cytometry on tumor tissue and peripheral blood mononuclear cells and plasma proteomics to explore the immune consequences of neoadjuvant ICB, with vs. without neoadjuvant FSRT. Primary endpoint: ORR in Cohort A (null hypothesis, ORR 5%; alternative hypothesis, ORR 25%; $n = 16$ for 80% power, $\alpha = 0.05$). Secondary endpoints: progression-free survival (PFS) and overall survival (OS), separately in Cohorts A, B1, B2. Data cut-off: January 18, 2023. **Results:** 32 evaluable patients: Cohort A, $n = 16$; Cohort B, $n = 16$ (Arm B1, $n = 8$; Arm B2, $n = 8$). Median follow-up time: 20 months. Most common grade 3/4 treatment-related adverse events: cerebral edema (34%), fatigue (16%). Efficacy in Cohort A: no objective responses, best response of stable disease in 9/16 patients (56%), median PFS 3.9 months (95% CI 2.1–6.2 months), median OS 9.4 months (95% CI 8.2–10.6 months). Median PFS and OS were significantly longer in Cohort B1 (neoadjuvant immunotherapy + FSRT) vs. Cohort B2 (neoadjuvant immunotherapy, no FSRT): PFS 11.7 vs. 2.0 months ($p = 0.0002$), OS 20.1 vs. 9.4 months ($p = 0.001$). Inflammatory cytokine responses were stronger and more sustained in Cohort B1 vs. Cohort B2, with concomitant increases in proliferative T cell responses. **Conclusions:** The combination of retifanlimab, INCAGN01876, and FSRT did not demonstrate efficacy in patients with rGBM when administered without surgical resection. However, among patients receiving neoadjuvant immunotherapy prior to surgical resection, the addition of neoadjuvant FSRT was associated with a significant survival advantage as well as increased inflammatory and cellular immune responses. Neoadjuvant FSRT + ICB warrants further evaluation in rGBM. Clinical trial information: NCT04225039. Research Sponsor: Incyte; Conquer Cancer Foundation of the American Society of Clinical Oncology.

2006

Oral Abstract Session

Phase II trial of pembrolizumab in patients with brain metastases.

First Author: Priscilla Kaliopi Brastianos, Massachusetts General Hospital and Harvard Medical School, Boston, MA

Background: Brain metastases are an increasing challenge in oncology due to increasing incidence and limited treatments. Recent studies suggest that brain metastases harbor a tumor microenvironment characterized by immunosuppressive phenotypes, which contribute to treatment resistance. Therefore, a logical therapeutic strategy for brain metastases is to evaluate immune-based strategies that augment T cell cytotoxicity. **Methods:** This study was designed as an open-label, single-stage, single-arm phase 2 clinical trial evaluating the intracranial efficacy of pembrolizumab, a PD-1 inhibitor, in patients with brain metastases of diverse histologies. The target accrual was 58 patients to achieve at least 52 evaluable patients (i.e., received at least one dose of pembrolizumab). The primary endpoint was intracranial benefit, defined as a best response of complete response, partial response, or stable disease by RANO criteria during treatment. The study design compared a null intracranial benefit rate of 10% against an alternative of 24%. If at least 8 patients among the total of 52 had intracranial benefit, the primary efficacy endpoint would be met and pembrolizumab would be considered worthy of further study in this patient population. This design has a type-I error of 10% and power of 89% (target type-II error of 15%). **Results:** In the 57 evaluable patients, median age was 53 (range 28–80) and 81% were female. Tumor histologies included breast ($n = 35$), non-small cell lung cancer ($n = 7$), melanoma ($n = 2$), small-cell lung cancer ($n = 2$), sarcoma ($n = 2$), ovarian ($n = 1$), pituitary carcinoma ($n = 1$), pituitary neuroendocrine tumor ($n = 1$), esophageal adenocarcinoma ($n = 1$), prostate ($n = 1$), renal cell carcinoma ($n = 1$), neuroendocrine carcinoma ($n = 1$), unknown primary ($n = 1$) and sinonasal adenocystic carcinoma ($n = 1$). For the patients with breast cancer, 16 patients had HER-2 positive disease, 17 patients had hormone receptor-positive disease, and 11 patients had the triple-negative subtype. The study met its primary endpoint and achieved an intracranial benefit rate of 42.1% (90% confidence interval [CI]: 31–54%). In addition, seven patients, who had either breast cancer, melanoma or sarcoma, had durable intracranial anti-tumor activity (> 2 years). The extracranial benefit rate in patients with evaluable extracranial disease based on RECIST 1.1 criteria was 45% (18/40; 90% CI: 31–59%). Median overall survival was 8.0 months (90% CI: 5.5–8.7 months). Grade 4 toxicities at least possibly related to treatment were observed in 2 patients: cerebral edema ($n = 2$). Thirteen patients discontinued treatment for adverse events. **Conclusions:** Our study of pembrolizumab met overall primary endpoint for intracranial benefit in patients with brain metastases. These results suggest that PD-1 blockade may serve as the backbone of therapeutic strategies for a select group of patients with brain metastases and warrants further evaluation. Clinical trial information: NCT02886585. Research Sponsor: Merck Sharp & Dohme; Massachusetts General Hospital.

2005

Oral Abstract Session

Anti-telomerase vaccine in patients with newly diagnosed, unmethylated MGMT glioblastoma: A phase II study. *First Author: Antoine F Carpentier, Hôpital Saint-Louis, Paris, France*

Background: TERT, a subunit of the telomerase complex, is largely expressed in almost all cancers. Among those cancers, glioblastomas (GBM) harbor the highest incidence of activating mutations within the TERT promoter (over 85% of patients). This high incidence underlies the potential role of TERT in oncogenesis, and points out TERT as a highly relevant tumor target in GBM. UCPvax is a therapeutic vaccine composed of two CD4 helper peptides derived from TERT, combined with the montanide adjuvant. We conducted a phase IIa trial to test the immunogenicity, safety and efficacy of UCPvax in patients with newly diagnosed GBM. **Methods:** Key inclusion criteria were: histologically confirmed, non-mutated IDH1 glioblastoma, unmethylated MGMT promoter status, previous treatment with concomitant radiotherapy and temozolomide (TMZ), Karnofsky Performance status (KPS) $\geq 70\%$, steroids < 10 mg/day equivalent prednisone, and lymphocytes count $\geq 0.8 \times 10^9/L$. One month after completion of radiation/TMZ, patients started UCPvax vaccinations on days 1, 8, 15, 29, 36 and 43, then every two months until tumor progression, without additional cure of TMZ. Peripheral blood mononuclear cells were collected before treatment, at 1 and 2 months after treatment and, at each vaccination boost. The primary endpoint was an anti-TERT specific CD4 T-cell response measured *ex vivo* in peripheral blood using IFN-gamma ELISPOT at 2 months. Secondary endpoints included safety, overall survival (OS) and progression-free survival (PFS). **Results:** Thirty-one adult patients (median age 60-yr old, median KPS 90%) were included in this study. All patients received at least one vaccination, and vaccinations were given for 4.5 months on average (min 2–max 14). At baseline, only one patient had a pre-existing anti-TERT CD4 T-cell response (3%). After immunizations, *de novo* induction and/or amplification of an anti-TERT response were found in 29/30 pts (97%). An epitope spread response against other tumor-associated antigens was detected in 12/25 pts (48%). No severe (grade 3–4) toxicity was attributable to the vaccination. All patients developed local skin reactions ($\leq$ grade 2), 16 patients complained of transient asthenia ($\leq$ grade 2), and 13 patients experienced local pain ($\leq$ grade 2). In the intent-to-treat population ($n=31$), the PFS was 8.9 months (95% CI: 7.6–10.6) and the median OS was 17.9 months (95% CI: 16–23). Two years after diagnosis, 26% of the patients were still alive. OS was significantly improved in the patients developing an epitope spread response vs the others (19.3 vs 15.8 months, respectively, $p=0.03$). **Conclusions:** UCPvax is highly immunogenic and provides an interesting OS rate in this population of poor prognosis, unmethylated MGMT GBM patients. These data support further clinical studies of UCPvax in GBM patients. Clinical trial information: NCT04280848. Research Sponsor: PHRC.

2007

Oral Abstract Session

INB-200 phase I study of gene modified autologous gamma-delta ($\gamma\delta$) T cells in patients with newly diagnosed glioblastoma multiforme (GBM) receiving maintenance temozolomide (TMZ). *First Author: Mina Lobbous, University of Alabama at Birmingham, Birmingham, AL*

Background: MHC unrestricted $\gamma\delta$ T cells target NKG2D ligands upregulated on tumor cells. IN8bio's DeltEx chemotherapy resistant cell therapy (CRCT), is a novel $\gamma\delta$ T cell genetically engineered to express MGMT to convey temozolomide (TMZ) resistance and allow combination therapy. NCT04165941, a Phase 1 trial assessing the safety of single and multiple infusions of autologous CRCT cells presents updated safety and efficacy data. **Methods:** Adult newly diagnosed GBM patients with adequate organ function and KPS $\geq 70\%$ are enrolled. Cells engineered from apheresis were infused through a Rickham catheter placed during surgery. Cohorts (C) 1, 2 and 3 each receive 1, 3 and 6 doses of cells respectively on day (D) 1 of each 28-day maintenance cycle. Patients receive 1×10^7 $\gamma\delta$ T cells intratumorally with 150 mg/m² of TMZ intravenously on D1 of maintenance with the standard Stupp maintenance regimen on D2-5. Primary endpoint is safety; secondary endpoints include progression free and overall survival. Immunologic and genomic correlative analyses are being conducted. Dose limiting toxicities (DLTs) are defined as treatment related $\geq$ grade 3 cardiopulmonary or hepatic toxicity, grade 4 toxicity exceeding 72 hours or neurologic deterioration that exceeds 2 weeks. **Results:** 15 patients (53% male; median age 69 (range: 21–76); 80% IDH-WT, 66.7% MGMT unmethylated) were enrolled with 8 dosed ($N=3$ in C1, 4 in C2, 1 in C3). No patients experienced DLTs, cytokine release syndrome (CRS), or neurotoxicity (ICANS). The most common adverse events (AEs) were Grade 1/2 events including fever, fatigue, nausea, headache, platelet count decreased, incision site pain attributable to TMZ, radiotherapy or disease. One subject had Grade 3 treatment related AEs of UTI, dehydration, and thrombocytopenia. Three evaluable C1 patients have PFS of 8.3, 11.9, 7.4 months and OS of 15.6, 17.7 and 9.6 months respectively. In C2, four patients have been dosed, with no DLTs in 3 evaluable patients; 2 remain progression free at 18.9 and 14.8 months, while a third died without relapse due to pulmonary embolus at 8.7 months. One C3 patient has completed 5 of 6 planned doses without DLT. Patient recruitment continues with anticipated completion in 2023. **Conclusions:** Data demonstrates that single, repeat doses of CRCT gamma delta T cells have manageable toxicity with continued encouraging trend in PFS and warrants further assessment. Clinical trial information: NCT04165941. Research Sponsor: IN8bio, Inc.

2008

Oral Abstract Session

Belzutifan treatment for von Hippel-Lindau (VHL) disease-associated central nervous system (CNS) hemangioblastomas (HBs) in the phase 2 LITESPARK-004 study. *First Author: Othon Iliopoulos, Massachusetts General Hospital Cancer Center and Harvard Medical School, Boston, MA*

Background: Patients (pts) with VHL disease are at risk for developing multiorgan tumors and cysts, including CNS HBs. The first-in-class hypoxia-inducible factor 2 α (HIF-2 α) inhibitor belzutifan showed clinically meaningful antitumor activity in VHL disease-associated renal cell carcinoma (RCC) and other neoplasms in the ongoing, single-arm, phase 2 LITESPARK-004 study (NCT03401788). We present updated results for the subgroup of pts with CNS HBs. **Methods:** Adults with a VHL disease diagnosis based on germline VHL alteration, ≥ 1 measurable RCC tumor, no RCC tumor > 3 cm or other VHL tumor requiring immediate surgical intervention, no evidence of metastatic disease, no prior systemic anticancer treatment, and an ECOG PS score of 0 or 1 received belzutifan 120 mg orally once daily. End points evaluated in pts with CNS HBs included objective response rate (ORR), duration of response (DOR), time to response (TTR), and progression-free survival (PFS) per RECIST v1.1 by an independent review committee; linear growth rate (LGR); and safety. CNS HBs were assessed using 2 methodologies: 1) with measurable (≥ 1 cm) and/or nonmeasurable disease at baseline and with associated cysts, if present; and 2) with measurable disease at baseline, excluding associated cysts, if present, from the lesion measurement. **Results:** Of 61 enrolled pts, 50 (82%) had ≥ 1 CNS HB evaluable at baseline, and 22 (59%) pts had undergone ≥ 1 CNS-related surgery within 4 years prior to starting belzutifan treatment. As of the April 1, 2022 data cutoff date, median study follow-up for pts with CNS HBs was 38.0 mo (range, 36.1–46.1). ORR was 44% (n = 22; 95% CI, 30–59; 4 CRs, 18 PRs), and DCR was 90% (n = 45; 95% CI, 78–97). Median TTR was 5.4 mo (range, 2.3–33.1), and median DOR was not reached (NR; range, 3.7+ to 38.7+ mo). Median PFS was NR (95% CI, 38 mo to NR). After initiating belzutifan, median LGR for all evaluable pts was -1.6 mm/year (range, -7.0 to 3.1). Of all pts, 25/50 (50%) had ≥ 1 measurable CNS HBs, excluding any associated cysts. For these pts, ORR was 76% (95% CI, 55–91; 1 CR, 18 PRs), and DCR was 96% (n = 24; 95% CI, 80–100). Median TTR was 3.1 mo (range, 2.5–27.8), and median DOR was NR (range, 3.7+ to 38.7+ mo). Median PFS was NR (95% CI, 36 mo to NR). After initiating belzutifan, median LGR was -1.1 mm/year (range, -3.9 to -0.1). Of all pts, 1/50 (2%) underwent a CNS-related surgery after starting belzutifan. Two (3%) pts discontinued treatment due to treatment-related adverse events. **Conclusions:** With more than 3 years of treatment with belzutifan, consistent and durable antitumor activity was observed in pts with CNS HBs, which is consistent with findings in other VHL disease-associated neoplasms. Using different methodologies of assessing tumors, our data demonstrated that belzutifan induced the shrinkage of VHL disease-related CNS HBs with or without the presence of associated cysts. Clinical trial information: NCT03401788. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA; The Intramural Research Program of the National Institutes of Health, National Cancer Institute Center for Cancer Research, and a grant (U01 CA236489) from the National Cancer Institute.

2010

Clinical Science Symposium

Prognostic evaluation of surgical re-resection for recurrent glioblastoma using the novel RANO classification for extent of resection: A report of the RANO resect group. *First Author: Philipp Karschnia, Department of Neurosurgery, Ludwig-Maximilians-University, Munich, Germany*

Background: The clinical effects of re-resection for recurrent glioblastoma remain controversial, and the role of post-operative tumor volume is unclear since leaving certain tumor volumes deliberately behind cannot be ethically justified. A surgical classification system was previously proposed for stratification based upon residual contrast-enhancing (CE) tumor: RANO class 1 was defined as 'supramaximal CE resection' (including non-CE tumor removal), class 2 as 'maximal CE resection', class 3 as 'submaximal CE resection', and class 4 as 'biopsy'. We aimed to (I) explore the prognostic role of extent of re-resection using this classification and (II) define clinical factors which consolidate the effects of re-resection. **Methods:** The RANO resect group retrospectively compiled a global, eight-center cohort of patients with first recurrence from a previously resected glioblastoma. The combined associations of re-resection and clinical factors with outcome were analyzed. Kaplan-Meier survival analysis and log-rank test were applied to calculate survival, and Cox's proportional hazard regression models to adjust for multiple variables (significance level: $p \leq 0.05$). A propensity score-matched analysis was constructed to mimic a randomized clinical trial comparing the different RANO classes. **Results:** We encountered 681 patients with first recurrence of IDH-wildtype glioblastoma, including 310 patients who underwent re-resection at first recurrence. The use of re-resection was associated with prolonged survival also when stratifying for molecular and clinical confounders on multivariate analysis including pre-operative tumor volume, MGMT promotor status, and non-surgical therapies (HR: 0.65, CI: 0.5–0.8; $p = 0.001$); and ≤ 1 cm³ residual CE tumor translated into improved survival compared to non-surgical management. Accordingly, 'maximal resection' (class 2) had superior survival compared to 'submaximal resection' (class 3) (median OS after recurrence: 12 vs. 9 months; $p = 0.003$). Adjuvant chemotherapy further augmented the beneficial effects of lower residual CE tumor. Conversely, 'supramaximal resection' of non-CE tumor (class 1) was not associated with prolonged survival but frequently accompanied by post-operative deficits, hampering further treatment. The prognostic role of residual CE tumor was confirmed in propensity score analyses. **Conclusions:** Extent of resection for recurrent glioblastoma as quantified by residual CE tumor is highly prognostic and the RANO resect classification may serve to stratify patients accordingly. Chemotherapy may favorably contribute to the prognostic associations of re-resection. When pursuing resection of non-CE tumor, intraoperative mapping strategies to minimize the risk of post-operative deficits are recommended. Research Sponsor: None.

2009

Clinical Science Symposium

Clinical and analytical validation of a targeted gene expression biomarker predicting meningioma outcomes and radiotherapy responses. *First Author: William Cheng Chen, UCSF Department of Radiation Oncology, San Francisco, CA*

Background: Surgery is the mainstay of treatment for meningioma, the most common primary intracranial tumor, but improvements in meningioma risk stratification are needed and current indications for postoperative radiotherapy are controversial. Here we report multicenter clinical and analytical validation of a gene expression biomarker using 1856 retrospective and prospective meningiomas from 12 institutions across 3 continents. Our results reveal the gene expression biomarker provides additional information for meningioma outcomes compared to other classification systems, including prediction of radiotherapy responses. **Methods:** Gene expression profiling and regularized Cox regression was performed on a discovery cohort of 173 meningiomas to generate a 34-gene expression biomarker and continuous risk score for local recurrence. The model and thresholds for low, intermediate, and high-risk scores were locked and applied to 3 validation cohorts: a multicenter retrospective clinical validation cohort (N = 6 centers, N = 866 meningiomas, median follow-up 5.2 years), a prospective investigator-blinded clinical validation cohort from RTOG 0539 (N = 103 meningiomas, median follow-up 8.4 years), and an analytical validation set for test/re-test and FFPE/frozen analyses, as well as comparison across different platforms for gene expression quantification (N = 8 centers, N = 1219 meningiomas). Gene expression biomarker performance was compared to 9 contemporary molecular classification systems. Favorable versus unfavorable meningiomas were defined as gene expression low risk with any resection, or gene expression intermediate risk with gross-total resection (favorable), versus gene expression intermediate risk with subtotal resection, or gene expression high risk with any resection (unfavorable). **Results:** The biomarker outperformed WHO grade (5-year local freedom from recurrence [LFFR] delta-AUC 0.11, 95% CI 0.07–0.17, $p < 0.001$) and all other classification systems for LFFR and OS on multivariate analysis, achieving a negative predictive value for recurrence at 5-years of 91.9%. The biomarker was predictive for LFFR after postoperative radiotherapy, with a hazard ratio of 0.33 for unfavorable primary WHO grade 2 meningiomas (95% CI 0.14–0.76, $P = 0.009$), and 0.54 for unfavorable propensity-matched meningiomas across all WHO grades (95% CI 0.37–0.78, $p = 0.0001$). The biomarker reclassified 39.8% of prospectively collected meningiomas from RTOG 0539, including downstaging 30.5% of patients who received postoperative radiotherapy, and was independently prognostic for overall survival on multivariate analysis. **Conclusions:** A targeted gene expression biomarker improves discrimination of meningioma outcomes compared to recent classification systems and predicts postoperative radiotherapy responses. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology.

2011

Clinical Science Symposium

A genomic score to predict local control among patients with brain metastases managed with radiation. *First Author: Nayan Lamba, Brigham and Women's Hospital, Boston, MA*

Background: Clinical predictors of local recurrence following radiation among patients with brain metastases (BrM) provide limited explanatory power. As a result, radiation doses and fractionation schemes are prescribed with a "one-size-fits-all" approach. We sought to develop a DNA-based signature of radiation-based efficacy among patients with BrM, utilizing readily testable genes, to identify subpopulations at greater vs. lesser risk of recurrence. **Methods:** We retrospectively identified 570 patients with 1,487 distinct BrM managed with whole-brain (WBRT) or stereotactic radiation therapy (SRS/SRT) at a tertiary cancer center (2013–2020) for whom next-generation sequencing panel data (OncoPanel, 239 genes) were available on at least one tumor specimen. Local recurrence was assessed in a manner consistent with Response Assessment in Neuro-Oncology – Brain Metastases guidelines (i.e., radiographic enlargement of $>20\%$ in maximal cross-sectional diameter). Enlarging lesions managed with salvage treatment prior to $>20\%$ enlargement were considered to have recurred on the date of salvage therapy. Fine/Gray's competing risks regression was utilized to compare local recurrence on a per-metastasis level among patients with vs. without somatic alterations of likely biological significance across 84 OncoPanel genes with a mutational frequency $>0.5\%$. Genes with a q-value <0.10 were utilized to develop a numeric "Brain-Radiation Prediction Score" ("Brain-RPS") to quantify local recurrence risk. **Results:** Genomic alterations of potential biological relevance in 11 (ATM, MYCL, PALB2, FAS, PRDM1, PAX5, CDKN1B, EZH2, NBN, DIS3, MDM4) and two genes (FBXW7 and AURKA) were associated with a decreased or increased risk of local recurrence, respectively (q-value <0.10). Weighted scores corresponding to the strength of association with local failure for each gene were summed to calculate a patient-level RPS. On multivariable Fine/Gray's competing risks regression, RPS [1.66 (1.44–1.92, $p < 0.001$)], metastasis-associated edema [1.89 (1.38–2.59), $p < 0.001$] and receipt of WBRT without SRS/SRT or neurosurgical resection [2.73 (1.78–4.20), $p < 0.001$] were independent predictors of local failure. **Conclusions:** We developed a genomic score that can be calculated from an extracranial or intracranial site to quantify local recurrence risk following brain-directed radiation. Prior attempts to develop a biomarker-based radiation response signature have not been BrM-specific and have primarily relied on RNA-based measures of radiosensitivity, limiting their utility in clinical practice. To our knowledge, this represents the first study to systematically correlate DNA-based alterations with radiation-based outcomes among patients with BrM. If validated, Brain-RPS has potential to facilitate clinical trials aimed at genomic personalization of radiation treatment among patients with BrM. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology.

2012

Clinical Science Symposium

External validation and nomogram for risk factors of CNS metastasis in patients with clinically localized melanoma. *First Author: Merve Hasanov, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Surveillance for CNS mets is not routinely performed in CLM due to lack of evidence-based guidelines. We previously reported factors associated with CNS mets in CLM in a single institution study (MD Anderson Cancer Center; MDA). However, external validation of predictors is needed to develop evidence-based surveillance strategies. **Methods:** Demographics, primary tumor characteristics, and clinical events were collected for pts diagnosed with AJCC 8th edition Stage I-II melanoma in 1998-2014 in two institutions: MDA and Melanoma Institute Australia (MIA). Cumulative incidence of CNS mets was determined by competing risks method, including death; pts without CNS mets and alive at last follow-up (FU) were censored. The external validation of the MDA prognostic model was determined by calibration and discrimination using data from MIA. A ratio of observed and predicted outcomes (O/P ratio) was used to summarize calibration. An O/P ratio of 1 indicates perfect calibration, < 1 too high, and > 1 too low. The prediction model's discriminative ability was obtained by area under operating characteristic curve (AUC), ranging from 0.5 (none) to 1.0 (perfect) discrimination. Nomograms for predicting Cumulative Incidence of CNS mets were produced. **Results:** MDA and MIA cohorts included 4,332 and 9,610 pts, respectively. Pts and clinical characteristics were similar in the cohorts. Median FU time was longer for MDA than MIA (88.9 vs. 26.3 months). The 2-, 5-, 10-year (yr), and final cumulative incidence of CNS mets were 1.5%, 4.9%, 7.8%, and 11.0% for MDA and 1.4%, 4.7%, 7.9%, and 10.8% for MIA pts, respectively. The initial MDA predictive model considered for validation included gender, primary tumor site, melanoma subtype, Breslow thickness (BT), ulceration, mitotic rate (MR), lymphovascular invasion and perineural invasion. External validation of the predictive model was performed at 2, 5, and 10 yrs. The original model's validation properties were not ideal with the predicted estimates overestimating the observed values; thus the model was refined. The final reduced model evaluated included primary tumor site, melanoma subtype, BT, and MR. For calibration, O/P ratio (95% CI) for this model was 0.96 (0.75, 1.17) at 2 yrs, 0.97 (0.84, 1.11) at 5 yrs, and 1.03 (0.91, 1.15) at 10 years. The AUCs (95% CI) for 2, 5, and 10 yrs were 0.75 (0.70, 0.81), 0.71 (0.68, 0.75), and 0.69 (0.65, 0.72), respectively. The reduced model had similar AUCs with, but better calibration results than the original model. Nomograms of pts with high- and low-risk of CNS mets will be presented. A risk calculator will be available. **Conclusions:** A validated nomogram including primary tumor site, melanoma subtype, BT, MR can predict risk of CNS mets in CLM. This nomogram/risk calculator will help stratify CLM pts for CNS mets risk and facilitate development of personalized CNS surveillance strategies. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology.

2014

Poster Discussion Session

A radiomic-based predictive model of lung adenocarcinoma brain metastases and molecular subtypes. *First Author: Xiancheng Wu, Department of Medicine, Division of Internal Medicine, University of Pittsburgh, Pittsburgh, PA*

Background: Non-small cell lung cancer (NSCLC) comprises the largest portion of brain metastases (BM) from solid cancer with 40% of patients developing BM during the course of their disease. There are currently no reliable prediction tools for identifying patients at risk for BM, especially in the early-stage setting where MRI screening is not performed. Furthermore, in the later stage setting, brain MRI are only performed annually. Therefore, there is a critical need to identify high-risk patients for BM that could benefit from MRI surveillance. **Methods:** We identified 162 lung adenocarcinoma (LUAD) patients with (N = 66) or without (N = 96) BM that had treatment-naïve CT scans with a segmentable lesion. The tumor, surrounding ground glass opacity and necrosis were segmented via 3D slicer to create a volume of interest for radiomic texture analysis and 400 features were extracted. The Least Absolute Shrinkage and Selection Operator (LASSO) logistic regression feature selection method was used to select the most relevant features and models were built using the machine learning method XGBoost classifier. Training and testing sets with random splitting was used for cross validation. We report the accuracy, sensitivity, specificity, and area under the curve (AUC) for each model. **Results:** Among the extracted features that LASSO deemed as most discriminative for development of BM, we identified the most relevant features using XGBoost that predicted BM with 79% accuracy, 83% sensitivity, 72% specificity, and 79% AUC ($p = 0.01$) in the overall population. The addition of ground glass opacity and necrosis to the model did not significantly improve performance. Furthermore, the model distinguished those with metachronous vs synchronous BM with 84% accuracy, 83% sensitivity, 86% specificity, and 83% AUC ($p = 0.04$). Our model held up across molecular subtypes (*EGFR* and *KRAS* mutant). Importantly, the model was predictive in early-stage patients with 92% accuracy, 96% sensitivity, 83% specificity, and 95% AUC ($p = 0.0005$). Moreover, our model predicted for high vs. low overall survival, and was BM-specific as it was not predictive of other sites of metastases. We further developed a model from the CT features that correctly classified *KRAS* mutant vs. *KRAS* wild type LUAD with 77% accuracy, 73% sensitivity, 80% specificity, and 80% AUC ($p = 0.002$). **Conclusions:** Utilizing a radiomics approach, we were able to predict BM from primary lung CT features including in stage I and II disease, predict synchronous vs metachronous BM, and distinguish distinct molecular LUAD subtypes. We are currently validating our BM prediction model in a large independent cohort and developing models to classify targetable LUAD-BM molecular alterations utilizing brain MRI scans. These studies will identify patients that require MRI surveillance in the early-stage setting and more intensive surveillance in the late-stage setting for BM. Research Sponsor: Department of Defense.

2013

Poster Discussion Session

Pretreatment clinical parameters associated with intracranial progression burden following an initial stereotactic radiosurgery course in a multi-institutional brain metastases cohort. *First Author: Christina C Huang, Department of Radiation Oncology, Duke University Medical Center, Durham, NC*

Background: While brain metastasis (BM) velocity is a valuable prognostic metric at time of intracranial progression (ICP), pre-SRS risk factors for post-SRS high-burden intracranial progression (ICP) remain poorly characterized. We hypothesized that pre-SRS clinical parameters are associated with subsequent high-burden (ICP), defined as either ≥ 5 (ICP5) or new/progressive ≥ 11 BMs (ICP11). **Methods:** All patients completing an initial SRS course for BMs at two institutions from 1/2015-12/2020 were retrospectively identified. Patients with prior whole brain radiation therapy (WBRT) and/or BM resection were eligible. Demographic and clinical parameters were collected. ICP was defined as any radiographic concern for distant and/or in-field progression per multidisciplinary consensus. Overall survival (OS) and freedom from ICP were estimated via the Kaplan Meier method. Cox models assessed association between parameters and freedom from ICP5 and ICP11. **Results:** We identified 1383 patients completed SRS, with a median follow up of 8.7 months. Patients were 54.8% female, 45.6% with KPS ≥ 90 , and a median of 63.4 years old. Primary tumor types included non-small cell lung (48.7%), breast (14.7%), and melanoma (8.5%). 46.9% had oligometastatic disease (≤ 5 metastatic foci: including BMs) at SRS, and 53.4% underwent SRS for > 1 BM. 10.3% of patients had undergone prior WBRT and 26.1% surgical resection. 555 patients (40.1%) experienced ICP following SRS, of whom 72.6% had 1-4, 11.5% had 5-10, and 15.9% had ≥ 11 new/progressive BMs. Among patients with ICP, 6-month freedom from ICP was 35.5% (95% CI: 31.1-40.5%) for those with 1-4 BMs at time of ICP, 29.7% (95% CI: 20.4-43.3%) for 5-10 BMs, and 20.5% (95% CI: 13.5-30.1%) for ≥ 11 BMs ($p = 0.016$). Respective 12-month OS rates were 56.8% (95% CI: 52.1-61.9%), 46.0% (95% CI: 35.1-60.1%), and 38.7% (95% CI: 29.4-50.9%; $p < 0.001$). Neurologic symptoms at time of ICP were observed in 21.1% of patients with 1-4 BMs, 28.1% with 5-10 BMs, and 50.0% with new/progressive ≥ 11 BMs ($p < 0.001$). On multivariable analysis, superior freedom from high-burden ICP was associated with the following pre-SRS parameters: oligometastatic burden (ICP5: HR 0.68, 95% CI: 0.47-0.99; ICP11: 0.59, 95% CI: 0.36-0.97), no prior immunotherapy (ICP11: HR 0.57, 95% CI: 0.34-0.57), and a single BM at time of initial SRS (1 vs 2 BM, ICP 5: HR 0.51, 95% CI: 0.31-0.82; ICP11: HR 0.45, 95% CI: 0.24-0.84), while primary tumor type was not associated with ICP5 or ICP11. **Conclusions:** Pre-SRS parameters including polymetastatic burden, prior receipt of immunotherapy, and > 1 BM were associated with post-SRS high-burden ICP. High burden ICP developed earlier following SRS completion and was associated with higher rates of neurologic decline and inferior OS. Research Sponsor: None.

2015

Poster Discussion Session

Longitudinal single-cell (sc) immune profiling of cerebrospinal fluid (CSF) from melanoma patients (pts) with leptomeningeal disease (LMD) treated with intrathecal (IT) and intravenous (IV) nivolumab (N). *First Author: Golnaz Morad, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: LMD is associated with an extremely poor prognosis in melanoma pts, who currently have very limited treatment options. Our group previously reported initial safety and efficacy results from the dose escalation portion of a first in human phase I/IB trial using IT and IV N (NCT03025256) in melanoma LMD pts. Here we present longitudinal sc profiling of immune cells in CSF from a subset of pts in this trial to better understand the immune composition of this unique microenvironment and features associated with treatment and outcomes. **Methods:** 39 CSF samples were collected longitudinally from 5 long survivors (LS; IT N number of doses received 10-92) and 5 rapid progressors (RP; IT N doses 2-9) and profiled by sc RNA sequencing. Raw FASTQ reads were aligned to the GRCh38 human reference genome using Cell Ranger v6.0.0 to generate the count matrix. All samples were aggregated by Seurat v4.3.0 and data integration was performed using Harmony v0.1.0. Cells were filtered by following criteria: (1) $> 20\%$ mitochondrial content, or (2) $\text{express} < 100$ or $> 2,500$ -5,000 genes, according to sample specific distribution. Empty droplets and doublets were identified by EmptyDrops function from the R package DropletUtils v1.18.0 and DoubletFinder v2.0.3, respectively. We applied normalization, FindVariableFeatures ($n = 2,000$), scaling, PCA, UMAP and FindClusters to summarize the integrated samples and determine cell clusters. Cell types were annotated based on (1) canonical marker genes using FindAllMarkers, (2) published gene expression signatures, and (3) reference-based tool using Symphony v0.1.0 on published data: GSE164378 and GSE158803. Statistical analysis was conducted using the Wilcoxon rank-sum test. **Results:** A total of 10 patients were included in this pilot analysis. Five pts were LS (2 males; IT dose 5 mg, 1 pt; 10 mg, 2 pts; 20 mg, 2 pts; 2 BRAF mutant; 5 negative CSF cytology at baseline) and 5 pts were RP (3 males; IT dose 5 mg, 1 pt; 20 mg, 2 pts; 50 mg, 2 pts; 4 BRAF mutant; 4 positive CSF cytology at baseline). At baseline [prior to cycle (C)1 of IT N], LS pts had a higher percentage of NK cells (relative to total immune cells; $P = 0.036$) and mucosal-associated invariant T cells (relative to total T cells; $P = 0.021$) than RP pts. Prior to C2, LS had a significantly higher percentage of T cells (relative to all cells; $P = 0.036$). The abundance of immune cells and tumor cells were not different between the two groups at C3, at which point pts have received two doses of IT N and one dose of IV N. **Conclusions:** Exploratory sc analysis of longitudinal CSF samples of LMD pts suggest that baseline immune features may predict outcomes with IT N. Analysis of additional pts is ongoing to provide further insights. Research Sponsor: Dr. Miriam and Sheldon G. Adelson Medical Research Foundation; U.S. National Institutes of Health; Bristol-Myers Squibb.

2016

Poster Discussion Session

Long-term survival with IDH wildtype glioblastoma: First results from the ETERNITY Brain Tumor Funders' Collaborative Consortium (EORTC 1419). First Author: Michael Weller, Department of Neurology, University Hospital and University of Zurich, Zürich, Switzerland

Background: Median survival with glioblastoma remains in the range of 12 months on population levels. Only few patients survive for more than 5 years. Patient and disease features associated with long-term survival remain poorly defined. **Methods:** European Organization for Research and Treatment of Cancer (EORTC) 1419 (ETERNITY) is a registry study supported by the Brain Tumor Funders Collaborative in the US and by the EORTC Brain Tumor Group. Patients with glioblastoma surviving at least 5 years from diagnosis were identified at 24 sites in Europe, US, and Australia. In patients with isocitrate dehydrogenase (IDH) wildtype tumors, prognostic factors were analyzed using the Kaplan-Meier method and the Cox proportional hazards model. A population-based reference cohort was obtained from the Cantonal cancer registry Zurich. **Results:** At the cut-off of July 2020, 280 patients with histologically centrally confirmed glioblastoma (189 IDH wildtype, 80 IDH mutant, 11 not otherwise specified) had been registered. In the IDH wildtype population, median age was 56 years (range 24-78 years), 96 patients (50.8%) were female, 139 patients (74.3%) had tumors with O⁶-methylguanine DNA methyltransferase (MGMT) promoter methylation. Median overall survival was 9.9 years (95% CI 7.9–11.9). Patients without recurrence experienced longer median survival (not reached) than patients with one or more recurrences (8.92 years) ($p < 0.001$) and had a high rate of MGMT promoter unmethylated tumors. **Conclusions:** Freedom from progression is a powerful predictor of overall survival in long-term survivors with glioblastoma. Never relapsing patients often have MGMT promoter-unmethylated glioblastoma and may represent a distinct subtype of glioblastoma. Clinical trial information: NCT03770468. Research Sponsor: Brain Tumor Funders' Collaborative; EORTC Brain Tumor Group.

2019

Poster Discussion Session

BORTEM-17: A phase IB/II single arm, multicentre study investigating the efficacy of sequential bortezomib and temozolomide in recurrent GBM with unmethylated MGMT promoter—The results of an interim analysis. First Author: Dorota Gopen, Haukeland University Hospital, Department of Oncology, Bergen, Norway

Background: Glioblastoma (GBM) is the most frequent, lethal primary brain tumor in adults. Patients harboring tumors with functional O⁶ methylguanine DNA methyltransferase (MGMT) DNA enzyme gain limited benefit from temozolomide therapy. As shown in preclinical studies, bortezomib depletes the MGMT enzyme, restoring the tumor's susceptibility to temozolomide, if administered in a precise schedule when the MGMT enzyme is depleted. We hypothesized that recurrent GBM patients with unmethylated MGMT promoter may obtain clinical benefit from sequential BTZ and TMZ treatment. **Methods:** BORTEM-17 is a multicenter, open label, single arm, non-randomized phase IB/II trial to investigate potential survival benefit for recurrent glioblastoma patients administered bortezomib 48hrs prior to temozolomide. Sample size is calculated to 63 patients, of whom 10 included in phase IB. The doses of bortezomib is 1.3mg/m² intravenously days 1, 4, and 7 during 4-week cycle, and temozolomide 200mg/m² days 5-7. The control group is a retrospective cohort of 467 patients treated at 2 referral hospitals in Norway from January 2015 to December 2017. For the survival analysis, the patients included in BORTEM-17 (n=44) were compared with MGMT unmethylated control, age matched patients (n=116). The pre-defined interim analysis was performed after inclusion of 15 patients and as more than 2 of 15 patients had clinical benefit, the study was continued. **Results:** Until January 2023, 44 patients with median age 55 years (range 25-69), 30 males and 14 females were treated. Median KPS was 90 (70-100) and median NANO score 1 (0-7). The interim analysis was performed after inclusion of 15 patients in the phase IB and II and clinical benefit was observed in 5 patients. Two of them had tumor volume reduction and three experienced stable disease. The study proceeded to the next step. No treatment related deaths were observed. The most common adverse effects included hematological toxicity, gastrointestinal symptoms, muscle weakness, lower back pain and fatigue. Patients that progressed during the BORTEM-17 trial and were fit for further therapy received treatment at their physician's discretion. The preliminary data analysis after 44 of planned 63 patients were treated indicate prolonged median survival for BORTEM-17 patients 19.0 months vs 12.2 months of control MGMT unmethylated age matched patients. Median survival after recruitment is 5.5 months (1.0-23.8). **Conclusions:** The sequential BTZ+TMZ therapy is safe, feasible and effective as indicated by preliminary data when 70% of planned MGMT unmethylated patients have been included. Preliminary data indicate that the combination of BTZ and TMZ may offer an additional line of treatment with limited toxicity to the group of patients with particularly dismal prognosis. Clinical trial information: NCT03643549. Research Sponsor: Norwegian Cancer Society and KLINBEFORSK Norway.

2017

Poster Discussion Session

RANO 2.0: Proposal for an update to the Response Assessment in Neuro-Oncology (RANO) criteria for high- and low-grade gliomas in adults. First Author: Patrick Y. Wen, Dana-Farber Cancer Institute, Boston, MA

Background: Response Assessment in Neuro-Oncology (RANO) criteria for high-grade and low-grade glioma (HGG and LGG) were developed to improve reliability of response assessment in glioma trials. Several limitations of the original RANO criteria have been reported. **Methods:** To address limitations of the original RANO criteria, a large cohort of patients with newly diagnosed and recurrent glioblastoma were evaluated comparing RANO-HGG with modified RANO (mRANO) and immunotherapy RANO (iRANO) criteria to inform the following proposed updates (RANO 2.0). **Results:** Based on the 2021 WHO classification of glioma, we recommend a single common set of criteria for all gliomas regardless of WHO grade and IDH mutational status. These criteria will be used for all trials regardless of the treatment modalities being evaluated. In newly diagnosed glioblastoma, the post-radiotherapy MRI, usually obtained approximately 4 weeks after completion of radiotherapy, rather than the post-surgical MRI as proposed in original RANO criteria, will be used as the baseline for comparison of subsequent scans. Since the incidence of pseudoprogression is high in the first 3 months following radiotherapy, confirmation of progression during this period with a repeat MRI (in 4-8 weeks) will be required for determining radiographic progression of disease (PD) if the patient is clinically stable. However, confirmation scans are not mandatory after this period nor for recurrent tumors since these scans do not appear to improve reliability in determining progression. For agents with a high likelihood of producing pseudoprogression such as viral therapies and some other immunotherapies, mandatory confirmation of progression with a repeat MRI is an option. The primary measurement will remain the 2-dimensional maximum cross-sectional area of tumor as the simplest method, but where resources are available, volumetric measurements are an option. For IDH wild-type tumors with contrast enhancement, non-enhancing tumor will no longer be evaluated with the possible exception of patients receiving antiangiogenic therapies. However, in tumors with a significant non-enhancing component, both the contrast enhancing and non-enhancing components will be evaluated as target lesions. **Conclusions:** We hope that these and other proposed changes by the RANO working group will improve response assessment in glioma clinical trials and help the development of more effective therapy for patients. Research Sponsor: None.

2020

Poster Discussion Session

EO2401 (E) peptide immunotherapy + nivolumab (N) +/- bevacizumab (B) in recurrent glioblastoma (GB): EOGBM1-18/ROSALIE. First Author: Wolfgang Wick, Universitätsklinikum Heidelberg and German Cancer Research Center, Heidelberg, Germany

Background: EO2401 was designed to activate/expand existing memory T cells recognizing specific protein sequences from gut bacteria, which cross-react with tumor associated antigens (TAAs). E contains 3 CD8 HLA-A2 epitopes with mimicry to GB-TAAs (IL13Rα2, BIRC5, and FOXM1) and the CD4 epitope UCP2. **Methods:** Patients (pt) at 1st progression GB received E (300 µg/peptide, q2w x4 then q4w) with N (3 mg/kg q2w) in cohorts: 1a E x2 → EN; 2a/1, 2a/2 and 2b EN from start; 2c EN x2 → surgery → EN; 3/1 and 3/2 EN + B (10mg/kg q2w) (Table). **Results:** Among 100 treated pt EN +/- B was well tolerated, with E associated events limited to local skin reactions (45% of pt; 96% Grades 1/2, and 4% Grade 3) and N/B-tox consistent with historical data. EN induced immune response against all 3 mimics in 94% of 35 tested pt (all pt responded against at least 2 mimics), detectable as early as 2 weeks after first EN, and with durations beyond 10 months. Cross-reactivity against human peptides found in 89%. **Conclusions:** EN +/- B was well tolerated and generated fast and durable immune responses. EN survival like current standards. Delayed N was not advantageous for outcome. sLDB increased trt duration of EN, and improved efficacy. Continuous B plus EN further improved efficacy. Neo-/adjuvant EN was clinically feasible. Updated data, including C3/2 to confirm C3/1, to be presented. Clinical trial information: NCT04116658. Research Sponsor: Enterome.

Cohort 01/16/23	Ongoing treatment (trt) (pt)	Trt duration ^a	Disease Control Rate ^b	Duration of disease control ^c	Objective response rate PR+CR	Progression- free survival ^d	Survival ^e	Follow-up survival ^f ; pt alive
2a/1 (n=23) EN ^g	0%	1.4 (0.03- 11.2)	22%	3.6 (1.8- 10.2)	9%	1.6 (0.4-11.9)	9.0 (2.8-24.7)	22.1 9%
1a (n=21) ^h E → EN ^g	0% ^g	2.8 (0.03- 23.9)	33%	4.1 (2.7- 24.0)	5%	1.8 (0.2-24.0)	9.5 (0.4-29.4)	10.0 19%
2a/2 (n=15) ^h EN ^g	20%	3.2 (0.5-11.0)	40%	NR (5.2-9.0)	13%	3.6 (0.0-9.5)	12.6 (1.9-14.7)	10.8 47%
2b (n=6) ^h EN ^g	33%	7.9 (2.3-10.9)	83%	9.0 (5.0-9.2)	NA ^g	7.3 (1.9-9.2)	11.9 (10.1- 12.4)	11.5 50%
2c (n=9) ^h EN ^g peri-op	67%	NR (0.5-8.5)	88% ^g	NR (0.5-8.0)	NA ^g	NR (0.4-8.0)	NR (1.1-8.5)	5.6 100%
3/1 (n=11) ENB ^g	9%	5.0 (0.5-20.2)	91%	6.0 (3.1- 20.2)	55%	6.0 (0.0-20.2)	14.5 (3.0-20.2)	17.2 45%
3/2 (n=15) ENB ^g	73%	3.3 (1.4-4.2)	92% ^g	3.3 (1.7-3.7)	33% ^g	3.0 (0.0-3.7)	NR (1.4-4.4)	3.0 93%

NA not applicable; NR not reached.

^aMeasurable disease; ^b3 pt in safety lead-in; ^cOption for symptom driven, time-limited, low-dose B (sLDB; 5 mg/kg q2w), median of 3 doses to 1a=10 pt (56%); NA for 3 pt safety lead-in; 2a/2=5 pt (33%); 2b=1 pt (33%); NA for 3 initial pt; 2c=3 pt (33%); ^dE mono in 1 pt as individual use after 24 mo study period; ^eNon-measurable disease, adjuvant post-surgery in 4 of 6 pt; ^fpt with stable disease (SD), partial- or complete response (PR/CR) per iRECIST; ^gMedian (range) in months per Kaplan-Meier; ^hDCR = n=8 (1 pt early), ORR NA, only 2x E admin pre-surgery; ⁱDCR and ORR n=12 (3 pt early), ORR also unconfirmed.

2021

Poster Discussion Session

Immune profiling in patients with glioblastoma treated with VT1021 in a phase I/II expansion study. *First Author: Jian Jennifer Chen, Vigeo Therapeutics, Inc., Cambridge, MA*

Background: The cyclic peptide VT1021 is a first-in-class therapeutic agent that has been shown to inhibit tumor growth via stimulation of thrombospondin-1 (TSP-1) and reprogramming the immune tumor microenvironment (TME) in preclinical models. Subsequently, VT1021 has been tested in a phase I/II clinical study in solid tumors (NCT03364400) and has advanced to a phase II/III clinical study in glioblastoma (NCT03970447). VT1021 has demonstrated promising single-agent clinical activity against recurrent glioblastoma (rGBM) in a phase I/II expansion study. Among 22 evaluable subjects with rGBM, 3 had complete response (CR), 1 had partial response (PR), and 6 had stable disease (SD) with an average study duration of over 120 days. One subject has been on VT1021 treatment for > 900 days with no measurable lesion left. The overall disease control rate (DCR) was 45%. Here, we sought to examine the peripheral immune cell profile(s) in response to VT1021 and explore the association between these profiles and clinical responses in rGBM subjects. **Methods:** In the phase I/II expansion study, 22 evaluable rGBM subjects received VT1021 at a dose of 11.8 mg/kg (twice per week intravenously) until disease progression. Peripheral blood samples were collected from all evaluable subjects; immune cell profiles were analyzed by flow cytometry. **Results:** The immune profiles following VT1021 treatment on day 1 did not vary significantly among rGBM subjects, regardless of response. Intriguingly, after long-term VT1021 treatment (day 53), our analysis of the immune profiles revealed beneficial and sustained changes in three cytotoxic T Cell (CTL) parameters and PD-L1⁺ MDSCs that correlated with response. Specifically, CR/PR subjects showed a 20% increase in total CTLs (Pre 33.79% vs. 6hr 40.42%), a 66% increase in proliferating CTLs (Pre 1.37% vs. 6hr 2.28%) and a 63% increase in CTL/Treg ratio (Pre 7.85 vs. 6hr 12.81) on day 53 of VT1021 treatment. In contrast, SD and PD subjects exhibited no change or decrease in these three CTL parameters, respectively. We also observed that CR/PR subjects experienced a sustained decrease in PD-L1⁺ MDSCs after VT1021 treatment (day 1 Pre 95.96% vs. day 53 Pre 92.66% and day 53 6hr 88.06%). Conversely, the sustained decrease of PD-L1⁺ MDSCs after VT1021 treatment was not observed in SD and PD subjects. **Conclusions:** Here we report that the durable responses of peripheral immune cells to VT1021 may be associated with better clinical outcomes in rGBM subjects. These findings are consistent with the MOA of TSP-1 to reprogram the TME by stimulating immune and inflammatory cell functions. While the interpretation of our data is limited by the lack of a control arm and the small sample size, the results provide a signal and warrant continued analysis of these parameters in the ongoing phase II/III trial. Research Sponsor: Vigeo therapeutics.

2022

Poster Discussion Session

Ombipepimut dosing emulsion (ODE) + bevacizumab (bev) vs bev alone in patients (pts) with recurrent or progressive glioblastoma (rGBM).

First Author: Samuel Aaron Goldlust, John Theurer Cancer Center, Hackensack University Medical Center, Hackensack, NJ

Background: ODE is an investigational cancer vaccine derived from Wilms tumor 1. WIZARD was a randomized, adaptive, phase 3 study to test ODE + bev vs bev in rGBM pts (NCT03149003). Patients were stratified prior to randomization based upon KPS [60 or 70] vs [80 to 100] and extent of resection at initial diagnosis. Patients with low KPS (e.g., 60) are generally underrepresented in clinical trials. **Methods:** Pts ≥18 years with GBM at first recurrence were enrolled. Overall survival (OS) was the primary endpoint; the key secondary endpoint was the 12-month OS rate. The primary and the key secondary endpoints were tested using 1-sided test with an overall significance level 2.5%. The Lan-DeMets error spending function based upon O'Brien-Fleming stopping boundaries was used to adjust the significance level for the interim and final analyses. **Results:** From April 2018 to Aug 2021, 217 pts were randomized 1:1; 109 to ODE + bev and 108 to bev. OS was analyzed after 185 events with a median follow-up of 31.8 months (mo). Pts at baseline had a median age of 60 years, 45.2% reported corticosteroid use, 29% had KPS 60 or 70, 7.8% had tumors that harbored IDH1 or 2 mutations, and the median tumor volume was 10,532 mm³. Baseline characteristics between treatment arms were balanced in the ITT and KPS subgroups. Pts with KPS 60 or 70 had more corticosteroid use, worse NANO scores, and larger tumor burden than those with KPS 80-100. The study did not meet its primary endpoint of OS by ITT (ODE + bev: 10.2 mo vs bev: 9.4 mo, 1-sided p-value: 0.2159). Pts with KPS 60 or 70 had longer OS when treated with ODE + bev (8.2 vs 6.3 mo, 45% death risk reduction, 1-side p value: 0.0119). Grade 1 or 2 injection site reaction was the most common TEAE in the ODE + bev arm. No clinically significant difference in safety was noted between KPS subgroups. **Conclusions:** The data in pts with KPS 60 or 70 suggested benefit with ODE + bev that was consistent across different endpoints and that warrants further validation. Clinical trial information: NCT03149003. Research Sponsor: Sumitomo Pharma Oncology.

Efficacy outcomes by KPS subgroup (ITT population).

Endpoints	KPS 60 or 70 ODE +Bev (N = 32)	KPS 60 or 70 Bev (N = 31)	KPS 80-100 ODE +Bev (N = 77)	KPS 80-100 Bev (N = 77)
mOS (mo), 95% CI	8.2 (4.3,10.5)	6.3 (4.1,7.4)	10.6 (8.5,12.8)	10.6 (9.4,12.8)
12 mo OS rate (%)	29.5	12.9	41.3	39.5
mOS excluding IDH1 or 2, 95% CI	8.2 (5.8, 1.10)	6.3 (4.1, 7.4)	9.8(7.9,11.7)	10.6(9.4,12.8)
mPFS (mo), 95% CI	4.8 (3.5, 8.1)	2.9 (1.9, 3.7)	5.3 (3.9, 5.6)	5.5 (3.7, 8.5)
ORR % (n/N)	21.9 (7/32)	12.9 (4/31)	20.8 (16/77)	13.0 (10/77)
DCR % (n/N)	78.1 (25/32)	45.2 (14/31)	80.5(62/77)	50.6(39/77)
Without neurological progression at 6 mo (%)	56	28	69	65

Progression free survival: PFS; overall response rate: ORR; disease control rate: DCR using mRANO by central review.

LBA2023

Poster Discussion Session

A randomised phase II multicentre study of ipilimumab with temozolomide vs temozolomide alone after surgery and chemoradiotherapy in patients with recently diagnosed glioblastoma: Ipi-Glio. *First Author: Paul James Mulholland, University College Hospital-London, London, United Kingdom*

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2023, issue of the *Journal of Clinical Oncology*.

2024

Poster Discussion Session

Final analysis of 2-THE-TOP: A phase 2 study of TTFIELDS (Optune) plus pembrolizumab plus maintenance temozolomide (TMZ) in patients with newly diagnosed glioblastoma. *First Author: David D. Tran, Department of Neurological Surgery, Norris Comprehensive Cancer Center, University of Southern California, Los Angeles, CA*

Background: TTFIELDS induce anti-tumor immunity via simultaneous activation of type-1 interferon (T1IFN) pathways of the STING and AIM2 inflammasomes and immunogenic cell death. Thus, TTFIELDS-treated GBM cells may provide a complete in situ vaccination platform and synergize with immune checkpoint inhibitors to prolong survival in GBM patients. **Methods:** We enrolled 26 newly diagnosed GBM patients in a pilot phase 2 study combining TTFIELDS, pembrolizumab and maintenance temozolomide (TMZ). To distinguish immune effects of TTFIELDS from those of pembrolizumab, TTFIELDS was started at cycle 1 of TMZ while pembrolizumab (200 mg IV every 3 weeks) at cycle 2 of TMZ. Primary endpoints were progression-free survival (PFS) versus case-matched controls treated with TTFIELDS plus TMZ only in the EF-14 study. Secondary endpoints included overall survival (OS), toxicity, and signature and mechanism of response by multiomics analyses of PBMCs and tumors. **Results:** The median age was 60.5 years. Fourteen (54%) had biopsy only or partial resection. Nineteen (73%) had unmethylated MGMT and 3 (11.5%) had an IDH mutation. Median PFS was 12.0 months versus 5.8 months in a case-matched control cohort of 26 patients (HR = 0.466; 95% CI: 0.234-0.936; Log Rank $P = 0.007$). Twelve-month PFS was 50.0% versus 28.2% in controls; $P = 0.058$. Median OS was 24.8 months versus 14.7 months in controls (HR = 0.388; 95% CI: 0.194-0.775; $P = 0.039$). Two-year OS was 52.4% versus 12.0% in controls; $P = 0.004$. Six of 15 (40%) patients with measurable disease achieved partial to complete response. In a Cox regression analysis adjusting for key prognostic factors, P -value reached 0.0317 for PFS and 0.0074 for OS. The most common serious adverse events were thromboses, seizures, and metabolic disturbances in 4 (15%), 3 (11.5%), and 2 (7.7%) patients, respectively. Molecular analyses prior to the addition of pembrolizumab confirmed robust T cell activation by TTFIELDS via the T1IFN trajectory, as evidenced by a high correlation between TCRab clonal expansion and T1IFN responsive plasmacytoid dendritic cells (Spearman coefficient = -0.8; $P = 0.014$) and defined a T cell-based gene signature of TTFIELDS effects. Subsequently, the ability of the top expanded TCRab clones to adapt to the everchanging tumor microenvironment through successful clonal switching by 2 months after the addition of pembrolizumab strongly predicted response to the triple combination in a Cox HR fit model for OS with a concordance rate of 0.876, Log Rank $P = 0.031$. **Conclusions:** The triple combination was well tolerated and demonstrated promising efficacy in newly diagnosed GBM. Multiomics analyses confirmed the robust in situ immunizing property of TTFIELDS with synergy with pembrolizumab and identified potential signatures of response to TTFIELDS and the triple combination. Correlative analysis will be updated. Clinical trial information: NCT03405792. Research Sponsor: Novocure.

2025

Poster Session

Short-length DNA fragments in plasma to predict clinical outcome in unresected glioblastoma patients. *First Author: Maxime Fontanilles, INSERM UMR 1245 Brain And Cancer Genomics, Rouen, France*

Background: Early prediction of therapeutic response is an important issue in glioblastoma patients. Cell-free DNA (cfDNA) concentration in plasma shown potential prognostic value. cfDNA release is influenced by non-tumor parameters. Short-length cfDNA (sDNA) may better reflect tumor evolution. The aim was to investigate plasmatic sDNA as prognostic marker in unresected glioblastoma patients. **Methods:** An ancillary study of a prospective trial was conducted (GLIOPLAK trial). Patients had newly diagnosed and histomolecular confirmed glioblastoma *IDH* wild-type (WHO 2021 classification). Patients with resected tumor were excluded. All patients underwent radiotherapy/temozolomide (RT/TMZ) schedule after biopsy. Plasmas were collected at three times during first-line treatment: before (pre-), after (post-) RT and at the time of disease progression/relapse. Cell-free DNA (cfDNA) was extracted from plasma using the QIAamp circulating nucleic acid kit (Qiagen). Short-length DNA (sDNA) fragments (equal or lower than 250 bp length) concentration was calculated based on AUC after automated electrophoresis using 4200 TapeStation System. Primary objective was to investigate the impact on survival of sDNA during RT/TMZ phase. Secondary objectives were to explore the association between tumor volume, corticosteroid exposition and sDNA. **Results:** Thirty-eight patients were included: median age was 63 [interquartile range 55-66], 84.2% (n=32) had Karnofsky index higher than 80% at baseline and median overall survival (OS) was 13.3 months [CI 95% 11.5; 15.5]. sDNA was detected in 69.4% at the pre-RT time (mean 722.3 pg/ml $\pm$ sd 1257.7) and in 83.3% at the post-RT-time (686.1 pg/ml $\pm$ 1217.1). One third of the patients experienced a sDNA decrease between pre- and post-RT time. Presence of sDNA at the pre-RT time was associated with improved OS: median of 11.7 months [9.8-19.6] in the sDNA(+) group (n=25) versus 8.8 months [5.5-NA] in the sDNA(-) group (n=11), HR 0.309 [0.133-0.716], log rank p=0.004. Decrease of sDNA concentration was also associated with better outcome compared to stability or increase of sDNA between pre- and post-RT: respectively median OS 14.1 vs 10.1 months, 0.424 [0.197-0.909], p=0.02. Corticosteroid exposition and dose were not correlated to sDNA concentration at pre-RT or sDNA variation (respectively correlation coefficient 0.081 and 0.047). At pre-RT, presence of sDNA was independent of tumor volume: mean 265.0 cm³ $\pm$ 84.7 in sDNA(+) group vs 237.7 cm³ $\pm$ 115.7 in sDNA(-) group, p=0.492. Total circulating cfDNA concentration did not influence OS in our cohort. **Conclusions:** sDNA during the RT/TMZ phase is an independent prognostic marker in unresected glioblastoma patients. The role of sDNA as a biomarker for adaptive treatment after RT as well as non-invasive molecular characterization tool can be explored in dedicated trial. Clinical trial information: NCT02617745. Research Sponsor: Cancer Centre Henri Becquerel; Association de Recherche Contre les Tumeurs Cérébrales (ARTC).

2027

Poster Session

ctDNA detection in patients with brain metastases arising from solid tumors. *First Author: Laura Alder, Duke University Medical Center, Durham, NC*

Background: While circulating tumor DNA (ctDNA) is a routine tool for therapeutics in metastatic solid tumors, data in those with stable and active brain metastases (BrMs) is limited. We assessed genomic alterations in ctDNA from patients (pts) with solid tumor BrMs in three groups: isolated BrMs/stable extracranial disease (iCNS), concurrent brain and extracranial progression (cCNS), and extracranial progression with no active BrMs at ctDNA draw (eCNS). We also compared ctDNA alterations between pts with and without BrMs. **Methods:** Pts with BrMs and a Guardant 360 profile (n=253) from the Duke Molecular Registry of Tumors between 01/2014 – 12/2020 were identified. Intracranial and extracranial disease status were determined via investigator assessment (RECIST and RANO-BM criteria) within 30 days of ctDNA test. Mutant allele fraction (MAF) was defined as the % of mutant alleles divided by total alleles at a given loci. Differences in mean ranks of the MAF % maximum were compared using the Kruskal-Wallis test and pairwise comparisons with the Dwass, Steel, Critchlow-Fligner multiple comparisons post-hoc procedure. We compared differences in MAF >1% using the chi-square test. **Results:** Among the 253 pts with BrMs: 29 (12%) had iCNS, 160 (63%) cCNS, and 64 (25%) eCNS. The two most common tumor types were breast (BC, 12.0%) and non-small cell lung cancer (NSCLC, 76.4%). Median MAF was lower in the iCNS group (1.6%) vs cCNS (4.8%) p=0.002, but eCNS did not differ (2.6%). In pts with BC BrMs, *ESR1* mutations were most frequent in the iCNS group (67%), followed cCNS (54%) then eCNS (18%) (p = 0.09) as were *PIK3CA* mutations, iCNS(50%), cCNS (46%), and eCNS (27%), p = 0.55. In pts with NSCLC BrMs, *EGFR* mutations were most frequent in the iCNS followed by cCNS then eCNS (67%, 40% and 37%, p = 0.08). *KRAS* mutations were more frequent in cCNS followed by eCNS and iCNS (30%, 17% and 6% p = 0.031). Patients with no BrMs (n=449) included 24% breast and 76% NSCLC. In the ctDNA, *ESR1* and *BRCA2* mutations were more frequent in pts with BC BrMs than those without (60% vs 25%, p<0.001) and (17% vs 5%, p=0.022), respectively. Mutations in *EGFR* were more frequent in pts with BrMs vs without (36% vs 17%, p<0.001). Sequencing from both BrMs tissue and ctDNA were available for 8 pts (4cCNS and 4 iCNS). 7 of these (87.5%) had identical mutations in tumor and ctDNA. **Conclusions:** This study illustrates the feasibility of detecting actionable mutations from ctDNA among pts with BrMs, with and without extracranial disease. A higher frequency of actionable mutations in several targetable genes was observed in ctDNA when comparing pts with and without BrMs, thus providing therapeutic opportunities. Additional studies comparing ctDNA and alterations in BrMs tissue are needed to determine if ctDNA can be considered a surrogate to support treatment decisions. Research Sponsor: None.

2026

Poster Session

Association of CDK4 amplification with duration of response to bevacizumab in glioblastoma. *First Author: John L. Villano, University of Kentucky, Lexington, KY*

Background: Bevacizumab remains the standard second line therapy in glioblastoma (GBM) with reported improved progression free survival, but not overall survival. We investigated a large clinico-genomic database of GBM patients treated with bevacizumab for molecular alterations associated with treatment outcome. **Methods:** Molecular profiles of GBM were tested by next-generation sequencing (NGS) of DNA (592 genes, NextSeq or whole-exome sequencing, Novaseq) and RNA (whole transcriptome sequencing, NovaSeq) at Caris Life Sciences (Phoenix, AZ). Gene amplification was determined by NGS with a threshold of ≥ 6 copies. Real-world survival information was obtained from insurance claims data. Time-on-treatment (TOT) of bevacizumab was calculated from start to finish of treatment while post-bevacizumab overall survival (bevOS) from start of bevacizumab to last day of contact. Short-term (ST) and long-term (LT) responders were defined as those with TOT ≤ 6 months and ≥ 1 year, respectively. Kaplan-Meier estimates were calculated and significance was determined as p values of < 0.05 . For molecular comparisons, Fisher's exact tests and Mann-Whitney U were used when appropriate. **Results:** Among the total of 383 ST and 107 LT patients identified, no significant difference in gender or age were seen. The LT cohort had significantly longer bevOS compared to the ST cohort (HR 0.27, [95% CI: 0.28-0.35], p < 0.0001). Interestingly, CDK4 amplification was seen in 23% (18/78) of LT patients but only 7% (21/300, p = 0.0002) of ST. When investigating the total cohort of 498 GBM treated with bevacizumab, CDK4 amplified patients demonstrated significantly improved TOT compared to non-amplified (HR: 0.639, [0.48-0.85, p = 0.002]). Conversely, the ST cohort had significantly more *EGFR* amplifications than the LT cohort (43%, 130/300 vs. 19%, 15/79, p < 0.0001). In the total bevacizumab-treated cohort, *EGFR*-amplified GBM had significantly worse TOT on bevacizumab than non-*EGFR* amplified GBM (HR 1.387, [1.15-1.67], p < 0.001). No associations were seen in other alterations explored including *PIK3CA* mutation (HR = 0.81 [0.587-1.113], p = 0.2), *EGFR* mutation (HR: 1.209, [0.977-1.495], p = 0.1) or *RAF1* (HR: 0.647, [0.318-1.317], p = 0.2). **Conclusions:** Using a large clinical genomic database with GBM subjected to comprehensive molecular profiling, we demonstrated that amplification of CDK4 and *EGFR* were associated with long-term and short-term responses to bevacizumab, respectively. This warrants further investigation in independent cohorts controlled for age and other prognostic factors. If confirmed, a genetic basis for treatment optimization may provide meaningful clinical outcomes. Research Sponsor: University of Kentucky; CARIS.

2028

Poster Session

Evaluating the diagnostic performance of leptomeningeal diagnosis with CNSide compared to standard cytology. *First Author: Haley Appel, Miami Cancer Institute, Baptist Health South Florida, Miami, FL*

Background: Prior reports cited detection rates of leptomeningeal metastases (LM) using CNSide vs standard CSF cytology of 78% vs 55% in NSCLC and 84% vs 52% in various solid tumor cohorts. The objective of this study was to compare the real-world performance of the CNSide assay in diagnosing LM versus CSF cytology from lumbar puncture (LP) and established EANO-ESMD LM diagnostic criteria (EANO). **Methods:** We retrospectively analyzed all neuro-oncology patients from January, 2020 to December, 2022 with suspected LM who underwent LP with CSF cytology and CNSide. The CNSide assay included tumor cells (CSF-TCs) and cell-free DNA (cfDNA). LM diagnostic probability was defined by EANO criteria. Descriptive statistics and confusion matrix were calculated. **Results:** 87 patients (66 [76%] women) met eligibility criteria for inclusion with median age of 63 (23-87) years; 35 (40%) had uncontrolled systemic disease. The most common primary histologies were breast (45%) and lung (41%); 33% of primary lung cancers harbored molecular alterations, while primary breast cancers expressed hormone receptors in 69% and *HER2* alterations in 10%. Across all primary histologies, 53 (61%) cases harbored molecular alterations, of which 27 (31%) had molecular alterations also detected by CNSide. For 7 (8%) cases with negative cytology and CNSide, CNSide detected alterations by cfDNA assays. LM was diagnosed by CSF cytology in 23 (27%) cases, consistent with confirmed LM by EANO. 36 (41%) cases had confirmed LM by CSF cytology or CNSide; all cytology positive and equivocal cases were detected by CNSide. Patients with negative CSF cytology were further defined as probable (19, 23%), possible (35, 42%), or (7, 8%) lack of evidence by EANO. Modifying EANO criteria to include both standard CSF cytology and CNSide led to 36 (41%) confirmed LM cases, an increase of 13 cases in addition to the 23 cytology positive cases (+56.5%). Compared to CNSide, standard CSF cytology had a sensitivity of 70%, but an expected 100% specificity. Compared to the established higher specificity of CNSide, EANO had 100% sensitivity, but only 18% specificity for diagnosing LM, assuming all EANO possible, probable, or confirmed cases were positive, while specificity improved to 74% with slight decrease sensitivity to 94% if only probable or confirmed cases were considered positive. **Conclusions:** In the largest, retrospective, single institution, real-world study, implementation of CNSide showed increased sensitivity relative to standard cytology and increased specificity relative to EANO criteria, and provided clinically relevant, cell-based molecular and cell-free DNA analyses. CNSide increased the diagnostic yield by 56.5%. Research Sponsor: None.

2029

Poster Session

Leptomeningeal carcinomatosis and brain metastases in gastroesophageal carcinoma: A real-world analysis of outcomes, clinical and pathologic characteristics. *First Author: Thais Baccili Cury Megid, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada*

Background: Brain metastasis (BM) and Leptomeningeal Carcinomatosis (LC) are uncommon complications in gastroesophageal carcinoma (GEC) patients (pts). These patients have a poor prognosis and are challenging to study. We described the clinicopathologic features and outcomes in the largest real-world cohort of CNS metastasis in GEC pts. **Methods:** We conducted a single-center retrospective study of GEC pts treated at the Princess Margaret Cancer Centre from 2007 to 2021 who developed BM. Clinicopathologic characteristics and treatment modalities were reviewed. Survival was calculated from the date of BM or LC diagnosis until date of death/last follow-up using the Kaplan-Meier method. A multivariable Cox proportional hazards regression model was used to examine the association of baseline covariates and survival. **Results:** Of 3283 consecutive pts with GEC, 101 (3.08%) were diagnosed with BM and 20 with LC (0.61%). Most pts with BM were male (75.3%), non-Asian (93%), with a primary gastroesophageal junction tumor (47%) and adenocarcinoma histology (86%). Among pts with known HER2 status (N=48), 60% were HER2 positive (defined as IHC 3+ or IHC 2+/FISH+). All patients with LC had adenocarcinoma histology; most were signet-ring subtype (85%), poorly differentiated (80%) histology and only 15% (2/13) were HER2 positive. Median survival was 0.8; 3.8; and 7.7 months (mo) in BM pts treated with palliative care only, radiation only and surgery followed by radiation, respectively ($p < 0.001$). In LC, median survival was 0.7 mo in pts who had palliative care only (7/20) and 2.7 mo for those (13/20) who had whole brain radiation therapy (WBRT) ($p = .008$). Multivariate analysis showed a higher probability of death in patients with number of BM ≥ 4 ($p = 0.02$) and predicted superior survival in patients who received radiation and surgery followed by radiation ($p = 0.02$). **Conclusions:** This is the most comprehensive summary of clinicopathologic characteristics and survival in patients with GEC and BM and LC disease to date. Biomarker analysis reveals an enriched frequency of HER2 expression in BM, while this is uncommon in pts with LC. BM pts who were treated with surgery followed by radiation had a significantly improved OS. WBRT benefited patients with LC over palliative care alone. These findings add to our understanding for the management of this understudied population with poor survival. Research Sponsor: None.

BM pts	Median Survival (months) (95%CI)
Palliative Care	0.76 (0.20, 4.26)
Radiation (WBRT/SRS)	3.8 (2.16, 5.85)
Surgery followed by Radiation	7.71 (5.76, 16.45)
	$p \text{ value} < 0.001$
LC pts	
Palliative Care	0.7 (0, 1.58)
WBRT	2.7 (1.35, 6.0)
	$p < 0.008$

2031

Poster Session

INTRAMET: Results of a prospective, single-arm, open-label phase II trial of intraoperative radiotherapy after resection of brain metastases. *First Author: Stefanie Brehmer, Department of Neurosurgery, University Medical Center Mannheim, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany*

Background: Brain metastases (BM) occur in about 10-20% of all cancer patients during the course of their disease. The current standard of care for lesions that cause mass effects is neurosurgical resection followed by adjuvant radiotherapy of the resection cavity. We here report efficacy data of the INTRAMET trial (NCT03226483), which tested intraoperative radiation therapy (IORT) using a high-dose, single fraction to the tumor bed. **Methods:** Patients ≥ 18 years and Karnofsky (KPS) ≥ 50 with suspected BM were included. A frozen-section confirmed metastasis and technically applicable IORT were mandatory. Exclusion criteria were surgical or MRI contraindications, meningeal infiltration, or IORT Dmax doses exceeding 8 Gy at risk structures. IORT was performed after tumor resection in the operating room with a mobile low energy X-ray device emitting a spherical radiation field with a sharp dose gradient. A dose of 30Gy was prescribed to the surface of the resection cavity. The primary endpoint was cumulative local control rate (LCR). Secondary endpoints were incidence of other (distant) BM (RCR), overall survival (OS), time to the next systemic treatment and adverse event rates (AE). **Results:** In total, 35 of the originally 50 planned patients were recruited. After a pre-specified interim analysis, the study was prematurely halted due to good safety and outcomes profiles. 54.3% were men, the mean age was 64 (45-85) years. The mean follow-up was 25.7 (0.8-64.5) month. At the time of this report, 51.4% of patients were alive. 68.6% primary histologies corresponded to lung primaries. The LCR was 94.3% (95% CI 82.9-98.8%) and RCR was 57.1% (95% CI 40.7-72.4%). 8.6% patients or lesions developed out of field leptomeningeal progression. The mean OS was 37.4 months (95% CI 28.9-46.9). For those patients undergoing salvage whole brain RT (WBRT), the median initiation time was 147 (20-601) days with a significant survival benefit for those not requiring WBRT ($p = 0.027$). No significant survival differences were identified according to primary histology ($p = 0.618$), immunotherapy ($p = 0.928$), seizures at baseline ($p = 0.169$), KPS ($p = 0.056$) or radionecrosis appearance ($p = 0.214$). Mean time to next systemic treatment was 45.0 (95% CI 35.1-54.8) days. No G4-5 AE related to IORT occurred. The overall radionecrosis (RN) rate was 20% ($n = 5$ G1, $n = 1$ G2, $n = 1$ G3). No risk factors could be associated to RN. Post-surgical seizures were present in 28.6% patients, with eloquent localizations as the only predictive factor ($p = 0.008$). **Conclusions:** IORT for resected BM yields excellent local control rates and has a toxicity profile similar to those reported in post-operative SRS trials. By easing a prompt initiation of subsequent systemic treatments, IORT might shorten the overall treatment courses of many cancer patients. Clinical trial information: NCT03226483. Research Sponsor: None.

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Poster Session

A radiomics model developed from pre-metastatic brain magnetic resonance imaging to predict brain metastasis in non-small-cell lung cancer: Evidence to the seed-and-soil theory. *First Author: Xiao Chu, Department of Radiation Oncology, Fudan University Shanghai Cancer Center, Shanghai, China*

Background: Steven Paget's "seed and soil" theory suggests that both the primary tumor and the target host organ play important roles in successful metastasis development. In this proof-of-concept study, we proposed that inter-individual differences exist in the brain's congeniality for developing brain metastasis (BM), and validated the theory via developing a non-invasive radiomics BM prediction model. **Methods:** 256 non-small cell lung cancer (NSCLC) patients with no BM at baseline brain magnetic resonance imaging (MRI) were selected, 128 patients developed BM within three years after diagnosis and 128 remained BM-free. For radiomics analysis, both the BM and non-BM groups were randomly distributed into training and testing datasets at a 70%-30% ratio. Baseline brain MRI (representing the soil) and chest computed tomography (CT, representing the seed) radiomics features were extracted to develop the BM prediction models. We first developed radiomics models using the training dataset and subsequently validated the models in the testing dataset. A radiomics BM score (RadBM score) was generated and BM-free survival were compared between RadBM score-high and RadBM score-low groups. **Results:** The radiomics model developed from baseline brain MRI features alone can predict BM development in NSCLC patients. Furthermore, a fusion model integrating brain MRI features with primary tumor CT features (seed-and-soil model) provided synergetic effect and was more efficient in predicting BM (areas under the receiver operating characteristic curve 0.84 [95% confidence interval: 0.80-0.89] and 0.80 [95% confidence interval: 0.71-0.88] in the training and testing datasets, respectively). BM-free survival was significantly shorter in the RadBM score-high group versus the RadBM score-low group (Log-rank $P < 0.001$). Cumulative BM rate at 3-year were 75.8% and 24.2% for RadBM score-high and RadBM score-low group, respectively. **Conclusions:** The results demonstrated that intrinsic features of a non-metastatic organ exert a significant impact on metastasis development, which is first-in-class in metastasis prediction studies and provided novel evidence for the "seed-and-soil" theory of tumor metastasis. Radiomics BM prediction model utilizing both pre-metastatic brain and primary tumor features might provide a useful tool for identifying NSCLC patients more prone to develop BM and providing individualized management for these patients. Research Sponsor: National Natural Science Foundation of China (81902973, 82001903); Beijing Xisike Clinical Oncology Research Foundation (Y-2020Sciclone/qn-0041).

2032

Poster Session

Risk of brain metastases in metastatic non-small cell lung cancer without baseline brain metastasis: Pooled analysis of individualized patient data from three randomized clinical trials involving first-line atezolizumab treatment. *First Author: Yue Zhou, Fudan University Shanghai Cancer Center, Shanghai, Shanghai, China*

Background: Data on the efficacy of immune checkpoint inhibitors on delaying or preventing the occurrence of brain metastases (BMs) in metastatic NSCLC without initial BMs is limited. We explored the benefit of first-line atezolizumab versus chemotherapy in the occurrence of BMs in patients without baseline BMs. **Methods:** Individual patient data from IMpower1301, IMpower131, and IMpower150 were pooled. All patients in the intention to treat population were analyzed. Primary endpoints included BM free survival (BMFS) and the cumulative incidence of BM. Patients without baseline BMs were categorized into two groups: patients who received treatment including atezolizumab (atezolizumab group) and patients who received comparator chemotherapies (chemotherapy group). **Results:** In 2543 patients without baseline BMs, 87 (3.4%) developed BM, including 58 (3.4%) and 29 (3.4%) in the atezolizumab group and the chemotherapy group, respectively. The median BMFS was 8.31 months (95% CI 7.79-8.67). The cumulative incidence of BM at 6 months, 12 months, and 24 months was 1.9%, 3.1%, and 3.8%, respectively. Compared to the chemotherapy group, BMFS was significantly improved in the atezolizumab group (8.6 months versus 7.3 months, $p < 0.001$). After taking the competing risk events into account, no significant difference of the cumulative incidence of BM was observed between the two groups ($p = 0.671$), suggesting that the significantly better BMFS in the atezolizumab group analyzed by Kaplan-Meier method should be due to the lower incidence of extracranial progression or death. Baseline bone metastasis and non-squamous NSCLC were identified as two risk factors for BM. **Conclusions:** In patients with NSCLC without baseline BMs, first-line atezolizumab improved BMFS but not the cumulative incidence of BM compared to chemotherapy, indicating that atezolizumab could not reduce the intrinsic risk of intracranial tumor spreading. Research Sponsor: None.

Cumulative incidence (%) of BM for patients without baseline BMs.

	All	Atezolizumab group	Chemotherapy group
6 months	1.84	1.92	1.69
12 months	3.12	3.22	2.94
24 months	3.78	3.79	3.76

BM, brain metastasis.

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Poster Session

The prognostic role of ventricular size and its dynamics in patients with leptomeningeal metastases from solid tumors. *First Author: Emilie Le Rhun, University Hospital Zurich, Zurich, Switzerland*

Background: Hydrocephalus is a common radiological sign in patients with leptomeningeal metastasis (LM) from solid tumors and can be assessed using the Evans index (EI) with high interrater agreement. Normal ranges of EI values have been defined as 0.27 ± 0.05 for females and 0.28 ± 0.06 for males aged 65-69 for the diagnostic work-up of dementia. **Methods:** We retrospectively assembled a cohort of 113 adult patients with a diagnosis of LM from solid extra-central nervous system tumors and explored the association of ventricular size assessed by the EI at diagnosis, of its modification between diagnosis and evaluation at first follow-up (> 21 days after diagnosis), and at first progression, with outcome. **Results:** Median age was 58.2 years (interquartile range (IQR) 46.1-65.7), 41 patients (36%) were male, the most frequent cancers were lung cancer ($n = 39$, 35%), breast cancer ($n = 36$, 32%) and melanoma ($n = 23$, 20%). The median EI at baseline was 0.28 (IQR 0.26-0.31) and the EI value was 0.27 or more in 67 patients (59%) and 0.30 or more in 37 patients (33%). Among patients with MRI follow-up, the EI was increased in 19 of 47 patients (40%), including 9 of 47 patients (30%) and 10 of 47 patients (59%), respectively, without and with LM progression at first follow-up. At LM progression, an increase of EI was noted in 18 of 34 patients (53%). The median LM-specific progression-free (LM-PFS) survival was 1.8 months (IQR 0.8-3.7). The baseline EI was not significantly associated with LM-PFS (numerical values: $p = 0.299$). Median LM-PFS was 2.7 months (IQR 1.2-5.0) with an EI of 0.26 or less versus 1.3 months (IQR 0.6-3.1) with an EI of 0.27 or more ($p = 0.296$). It was 2.5 months (IQR 0.9-6) with an EI of 0.29 or less versus 1.1 months (IQR 0.5-2.4) with an EI of 0.30 or more ($p = 0.147$). An increase of 0.01 or more of the baseline EI first evaluation was associated with inferior LM-PFS ($p = 0.007$). The median overall survival was 2.9 months (IQR 1-7.2). The baseline EI was not associated with survival ($p = 0.067$), however, patients with a baseline EI of 0.26 or less had a longer survival than those with an EI of 0.27 or more (5.3 months, IQR 2.4-10.8, versus 1.3 months, IQR 0.6-4.1) ($p = 0.006$). Median survival was 3.7 months (IQR 1.4-8.3) with an EI of 0.29 or less versus 1.8 months (IQR 0.8-4.1) with an EI of 0.30 or more ($p = 0.109$). Among patients with follow-up scans available, median overall survival was 9.7 months (IQR 5.6-21.4) for patients with stable or decreased EI at first follow-up as opposed to 6.4 months (IQR 3.2-10.5) for those with an increase in the EI ($p = 0.292$). **Conclusions:** The EI at baseline is prognostic in LM on univariate analysis. An increase of EI during the follow-up is associated with inferior LM-PFS. Expanding the sample size and evaluation of confounding factors such as prior or concurrent treatment will help to better define the role of EI assessments in LM. Research Sponsor: None.

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Poster Session

HER2-low breast cancer brain metastases: Incidence and treatment implications. *First Author: Rania Chehade, University of Toronto, Sunnybrook Hospital, Toronto, ON, Canada*

Background: Brain metastases (BrM) are a major cause of morbidity and mortality among women with breast cancer (BC). Central nervous system (CNS)-penetrating systemic therapies for patients with HER2-negative BrM are lacking; this is particularly problematic for patients with triple negative disease (TNBC) who have a high likelihood of developing BrM. Given CNS activity of trastuzumab deruxtecan, efficacy for patients with HER2-low BrM is of interest. **Methods:** A retrospective study of two cohorts of patients who underwent surgery for BC BrM at Sunnybrook Health Sciences Centre between 1999-2013 and 2008-2018 were identified. Estrogen receptor, progesterone receptor, and human epidermal growth factor receptor-2 (HER2) status were assessed based on 2018 ASCO/CAP guidelines. HER2-zero was defined as immunohistochemistry (IHC) 0; HER2-low was defined as IHC 1+ or IHC 2+ with fluorescence in situ hybridization (FISH) negative status. HER2-positive was defined as IHC 3+ or IHC 2+ with positive FISH. Clinicopathological features were recorded. We also assessed the prognostic association between extent of HER2 expression and i) brain-specific progression free survival (bsPFS), as well as ii) overall survival (OS). **Results:** Out of 137 patients with resected BrM, tissue for HER2 assessment was available in 74.5% ($n=102$) of cases. In this cohort, the median age at BrM diagnosis was 53.5 (range, 32-85). 18.6% ($n=19$) had leptomeningeal disease and 68.6% ($n=70$) had extracranial disease. 53% ($n=54$) of the BrM were HER2-positive; 29.4% ($n=30$) were HER2-low and 17.6% ($n=18$) had HER2-zero status. Among BrM that were triple negative based on ASCO/CAP guidelines, 14 out of 22 cases (63.6%) were re-classified as being HER2-low. 15/25 (60%) BrM that were hormone receptor positive/HER2 negative (HR+/HER2-) based on ASCO/CAP guidelines were re-classified as being HER2-low. In total, 51 patients had matched primary breast and BrM tissue available; results of HER2 status when categorized as HER2-zero, HER2-low and HER2-positive were concordant in 82.3% ($n = 42/51$) of cases (Cohen's kappa 0.58, $p=0.0719$). In 7 cases, the primary breast tissue was HER2-zero whereas the BrM was either HER2-low ($n=5$) or HER2-positive ($n=2$). In only one case (2%), expression of HER2 was lower in the BrM (HER2-low) compared to the primary BC (HER2-positive). Median time from primary BC to the development of BrM was 35 months (IQR, 14-69) in the overall cohort; patients with HER2-zero BrM had a numerically longer time to development of BrM (45.8 months), compared to those with HER2-low (35 months) and HER2-positive (35 months) BrM ($p=0.948$). There was no significant association between HER2-zero, HER2-low and HER2-positive status in BrM and either bsPFS or OS. **Conclusions:** Among patients with surgically resected BrM, a high proportion of those with metastatic TNBC and HR+/HER2-negative disease have "HER2-low" BrM with potential to benefit from HER2-targeted therapy. Research Sponsor: None.

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Poster Session

A systematic review and meta-analysis of intrathecal versus alternate routes of delivery for HER2-targeted therapies in patients with HER2+ breast cancer leptomeningeal metastases. *First Author: Anna-Maria Lazaratos, Université de Montréal, Montreal, QC, Canada*

Background: Patients with HER2+ breast cancer (BC) frequently develop leptomeningeal metastases (LM). While HER2-targeted therapies have demonstrated efficacy in the neoadjuvant, adjuvant, and metastatic settings, including for parenchymal brain metastases, their efficacy for patients with LM has not been studied in a randomized controlled trial. However, several single-armed prospective studies, case series and case reports have studied oral, intravenous (IV), or intrathecally (IT) administered HER2-targeted therapy regimens for patients with HER2+ BCLM. **Methods:** We conducted a systematic review and meta-analysis of individual patient data to evaluate the efficacy of HER2-targeted therapies in HER2+ BCLM in accordance with PRISMA guidelines. Targeted therapies evaluated were trastuzumab (IT or IV), pertuzumab, lapatinib, neratinib, tucatinib, trastuzumab-emtansine (T-DM1) and trastuzumab-deruxtecan (TDXd). The primary endpoint was overall survival (OS), with progression-free survival (PFS) as a secondary endpoint. To assess differences between groups, shared frailty Cox regression models were used to estimate the hazard ratio (HR), 95% confidence interval (CI) and p-value. **Results:** 7780 abstracts were screened, identifying 44 publications with 200 patients, corresponding to 257 lines of HER2-targeted therapy for BC LM which met inclusion criteria. In univariable (OS: HR=0.9, 95% CI: 0.64-1.4, $P=0.76$; PFS: HR=0.8, 95% CI: 0.57-1.2, $P=0.35$) and multivariable (OS: HR=1.4, 95% CI: 0.68-3.1, $P=0.4$; PFS: HR=0.8, 95% CI: 0.41-1.7, $P=0.6$) analyses, we observed no significant difference between IT, oral or IV administration of HER2-targeted therapy. Meanwhile, ECOG performance status remained independently associated with prolonged OS (HR=2.2, 95% CI: 1.5-3.2, $P<0.001$) and PFS (HR=2.2, 95% CI: 1.5-3.2, $P<0.001$ and HR=1.9, 95% CI: 1.4-2.8, $P<0.001$) in the final multivariable model. ECOG status was not associated with route of trastuzumab delivery ($P>0.40$). Anti-HER2 monoclonal antibody-based regimens did not demonstrate superiority over HER2 tyrosine kinase inhibitors (OS: $P=0.647$; PFS: $P=0.983$). In a cohort of 7 patients, TDXd demonstrated improved OS compared to other HER2-targeted therapies and compared to T-DM1 ($P<0.05$). **Conclusions:** The results of this meta-analysis suggest that IT administration of HER2-targeted therapy for patients with HER2+ BCLM confers no additional benefit over oral and/or IV treatment regimens. We also present the first evidence supporting the efficacy of TDXd compared to alternative strategies for this patient population. Although the number of patients receiving TDXd in this cohort is small, this novel agent offers promise for this patient population and requires further investigation in prospective studies. Research Sponsor: None.

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Poster Session

Assessment of electronic health record (EHR)-based machine learning (ML) in predicting risk of brain metastasis among patients with early-stage non-small-cell lung cancer (eNSCLC). *First Author: Hossein Honarvar, ConcertAI, Cambridge, MA*

Background: Among patients (pts) with eNSCLC, development of brain metastasis (BM) is a poor prognostic sign, but routine surveillance for BM is not recommended post-therapy. EHR-based ML algorithms may identify pts who would benefit from active brain MRI surveillance and/or treatment intensification in the early-stage setting. **Methods:** ConcertAI Patient360 database, consisting of structured and curated EHR records from pts receiving care in ~900 US oncology clinics, was used to identify pts diagnosed with stage IB-IIIA NSCLC without prior evidence of BM between Jan 2010 – December 2021. Presence of BM was identified from human curation of patient documents. Gradient boosting (GB), random forest (RF), and logistic regression (LR) algorithms with 3-fold cross-validation were trained and compared to predict risk of BM at two landmarks: 18 and 24 months (mos) from initial diagnosis (index). Pts who did not develop BM and either died or were lost to follow-up prior to landmark times were removed. Feature importance was defined using Shapley Additive Explanation (SHAP)-derived marginal odds ratios (OR). Due to low prevalence of BM, AUPRC was used as performance metric. Pts in the 1st and 4th quartiles of predicted probabilities from GB model were flagged as low-risk vs. high-risk. **Results:** Among 7473 pts in 18 mos model, median age was 68.4 years (IQR 13.2), 50.5% were female, and 10.9% were black. Demographics were similar for 6863 pts in 24 mos model. 6.4% and 8.3% developed BM at 18 and 24 mos. Ability of GB, RF, and LR models to predict BM was similar with validation AUPRC of 0.109 at 18 mos and 0.137 at 24 mos. In the GB model, BM prevalence in high-risk vs. low-risk group was 10.3% vs. 3.1% at 18 mos and 13.4% vs. 4.4% at 24 mos. In both landmark models, NO stage and surgery within 90 days after index diagnosis were protective against BM, while presence of EGFR targetable mutations, adenocarcinoma (AD) histology, higher platelets (PLT), and history of pneumonia were risk factors. A glucose-by-histology interaction was found: For pts with normal blood glucose (GLU), risk of BM was independent of histology, for pts with high GLU, AD conferred greater risk of BM. **Conclusions:** An EHR-based ML model identified risk factors for developing BM among pts with eNSCLC and may identify pts who would benefit from active brain MRI surveillance and treatment intensification. Research Sponsor: ConcertAI.

Feature importance (mean OR, 95% CI).		
Feature	18-mos BM risk	24-mos BM risk
Surgery	0.86 (0.61, 0.97)	0.86 (0.60, 0.99)
NO stage	0.89 (0.69, 0.98)	0.87 (0.61, 1)
AD histology	1.14 (1, 1.45)	1.18 (1, 1.82)
EGFR exon 19 deletion or L858R	1.13 (1, 1.50)	1.15 (1, 1.53)
History of pneumonia	1.07 (1, 1.24)	1.10 (1, 1.43)
PLT > 330 vs < 205 10 ³ /mL	1.06 (1, 1.31)	1.07 (1, 1.32)
Interactions % BM		
GLU: histology	GLU $\geq$ 107: (AD = 11.4, non-AD = 6.0); GLU < 107: (8.2, 8.8)	(14.4, 6.7); (10.9, 10.8)

2037

Poster Session

Large-scale clinico-genomic models of solid tumor CNS metastasis.

First Author: Justin Jee, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Central nervous system (CNS) metastasis is a major cause of cancer death and morbidity, but the clinico-genomic covariates of CNS metastasis have been studied in small cohorts. We sought to i) determine whether models predicting patient time to CNS metastasis (ttCNS) trained on a large, automatically annotated clinico-genomic dataset could stratify ttCNS risk in an external, manually curated cohort and ii) use these data to study the genomic risk factors for metastasis at scale.

Methods: We leveraged the AACR Project GENIE Biopharma Collaborative (BPC), a structured curation of electronic health records at four cancer centers using the PRISMM method, to train natural language processing (NLP) algorithms to annotate metastatic sites from radiology reports. We applied these algorithms to all reports for MSK patients with tumor sequencing with our FDA-authorized targeted sequencing platform. We used the resulting clinico-genomic data to train random survival forests (RSF) to predict radiographically confirmed ttCNS from time of sample acquisition for patients with non-small cell lung (NSCLC, N = 7,263), breast (BRC, N = 5,195; HR+ N = 4,050, HER2+ N = 879, triple-negative (TNBC) N = 866), and colorectal cancer (CRC, N = 4,320) using stage, gene-level pathogenic alterations, pre-existing metastatic sites, histopathology, prior and current treatment, and patient demographics as variables, excluding those reaching the endpoint prior to sample acquisition. We also predicted time to bone, liver, and adrenal metastases. RSFs were validated in the manually curated, non-MSK BPC cohort. **Results:** RSFs had predictive power for ttCNS in validation datasets (NSCLC c-index: 0.66, BRC: 0.71 (HR+ only: 0.71, HER2+ only: 0.69, TNBC: 0.62), CRC: 0.67, all $p < 0.001$). Pre-existing metastatic involvement, and genomic, histopathologic and clinical features had non-overlapping information for predicting ttCNS. We explored genomic covariates of ttCNS and other sites using Cox proportional hazards models adjusted for disease stage. Within individual cancer types, the hazard ratios of gene-level changes leading to the four considered sites of metastasis were correlated (Pearson R = 0.71-0.98); in all cancer types the highest correlations were between ttCNS and ttAdrenal metastases. Across cancer types, genomic alterations leading to metastatic sites were less correlated (R = -0.22-0.48). For example, CDKN2A/B and MYC alterations shortened ttCNS in NSCLC and HR+ BRC but not in HR- BRC. PTEN was associated with shortened ttCNS in TNBC and NSCLC but not CRC and other breast subtypes. **Conclusions:** Automatically annotated cohorts provide a means of studying drivers of metastasis at scale. Pre-existing non-CNS sites are associated with shorter ttCNS. Genomic alterations predisposing to CNS metastases frequently predispose to other organ metastases, although in general the genomics of organotropism are highly cancer-specific. Research Sponsor: U.S. National Institutes of Health.

2039

Poster Session

Multi-cancer brain metastasis risk score development and validation using 220,246 whole transcriptomes and machine learning. *First Author: Jim Abraham, Caris Life Sciences, Phoenix, AZ*

Background: Brain metastases occur in multiple cancer types with higher prevalence in lung, breast, melanoma, and GI cancers. The prognoses of patients who develop brain metastases are very poor and identification of brain metastasis risk could be useful for prognostication, monitoring, and therapy selection. **Methods:** Data from the whole transcriptome of 220,246 tumor profiles were analyzed and multiple machine learning models were trained on various molecular subtypes. The dataset was split 50% for training and the other 50% for testing. UMAP was employed for dimensionality reduction and the patterns learned across the entirety of the training dataset irrespective of brain metastasis were leveraged on the testing data set. Patients with brain metastasis were identified using the presence of ICD-10 code C79.31 (Secondary malignant neoplasm of the brain). As the absence of C79.31 could be due to the event not happening yet, patients without brain metastasis were stratified into groups based on 3, 4 or greater than 5 years without a C79.31 ICD-10 code. The brain metastasis risk score was defined by empirical evaluation of the positive predictive value in 7 groups of risk probabilities. The validation set contained 1,217 patients with brain metastasis and 4,631 without an observed brain metastasis within 3 years. **Results:** In the validation set, the prevalence of brain metastases within the risk scores across all cancer types ranged from 4% with the lowest risk score to 94% in the highest with 71% of cases receiving the lowest 2 risk scores, 15% the 2 intermediate risk scores, and 14% the 3 highest risk scores. For breast, lung and colon cancers, the prevalence of brain metastasis ranged from 4-10% in patients with the lowest risk scores to 92-100% in patients with the highest however the distribution of cases with each risk score was markedly different across cancer type. Breast cancer had 62% of cases receiving the lowest 2 risk scores versus 27% in lung, and 92% in colon. Breast cancer had 18% of cases receiving the 3 highest risk scores while lung had 42% and colon only 2% of cases with those 3 highest scores. **Conclusions:** Whole transcriptome data can be leveraged by a machine learning platform that employs dimensionality reduction techniques along with transfer learning to predict the risk of brain metastasis. This tool can be used to augment the clinical picture of cancer patients an unmet clinical opportunity to inform prognosis, monitoring, and therapeutic selection. Research Sponsor: None.

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Poster Session

Surgically targeted radiation therapy (STaRT) for recurrent glioblastoma: Initial outcomes from a prospective multicenter registry. *First Author: Ahmad Ozair, Miami Cancer Institute, Baptist Health South Florida, Miami, FL*

Background: Surgically targeted radiation therapy (STaRT), using a novel bioresorbable collagen brachytherapy device containing 4 Cesium-131 sources, is FDA-cleared for use as adjuvant radiation therapy (RT) post-resection in both newly diagnosed and recurrent intracranial neoplasms. Intraoperative initiation of brachytherapy potentially minimizes post-resection tumor regrowth with a favorable dosimetric profile compared to external beam radiation. This work sought to determine early patterns of care and the safety of this approach in recurrent GBM. **Methods:** This prospective multi-institutional observational study (NCT04427384) included recurrent GBM patients who underwent maximum safe resection (MSR) and permanent implantation of the device(s) (GammaTile, GT Medical Technologies, Tempe, AZ, US). Descriptive and comparative analyses regarding patient characteristics and early clinical outcomes were performed. Toxicities were categorized using the CTCAE v5.0 adverse event (AE) criteria. **Results:** During 10/2020-01/2023, 14 participating sites enrolled 45 patients with recurrent GBM for STaRT; 2 patients had two sites treated for a total of 47 implants. 67% of patients were treated at the first recurrence, 24% at the second, and 13% at the third, respectively. The median age was 61 (range 28-75), 36% were female, and 23% were > 65 years. 85% of patients received prior same-site RT with the median time from last RT to implantation of 14.6 months (range 3.5-57). The median maximum preoperative size was 4.2 cm (range 1.6-7.0) and the median volume was 20.8 cm³ (range 0.8-130). 68% of resections were gross-total, 17% near-total, and 15% sub-total; the median time needed for device implantation was 5 minutes (range 1.0-13). Median follow-up was 5.2 months (range 0.6-23.2). Median Karnofsky performance status (KPS) at screening, at initial postoperative assessment, and 3 months were all 80 (range 40-100). 7 attributed AEs occurred in 13% (6/45) of patients, all grade 3 AEs: 2 CSF leaks, 2 seizures, 1 cerebral edema, 1 pseudomeningocele, and 1 left hemiparesis. All except one were coded as related to both radiation and surgery; the patient with pseudomeningocele experienced a seizure at 47 days that was considered related to radiation alone. **Conclusions:** Early data from this prospective registry demonstrate the feasibility and safety of STaRT in recurrent GBM. Data on 6-month progression-free survival will be presented at the conference. A prospective randomized trial of adjuvant systemic therapy (AST) +MSR+STaRT versus MSR+AST is planned for initiation in 2023. Research Sponsor: GT Medical Technologies.

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Poster Session

Cerebrospinal fluid immunological cytokines to predict intracranial tumor response to immunotherapy in non-small cell lung cancer patients with brain metastases: GASTO 1060. *First Author: Likun Chen, Department of Medical Oncology, Sun Yat-sen University Cancer Center, Guangzhou, China*

Background: Immunotherapy has been the standard first-line therapy in patients with advanced non-small cell lung cancer (NSCLC), and shown a certain efficacy for patients with brain metastases. However, the appropriate predictive biomarkers for intracranial tumor response to immunotherapy are unclear. We conducted this prospective study to explore the immunological cytokines in cerebrospinal fluid (CSF) to predict intracranial tumor response to immunotherapy in NSCLC patients with brain metastases. **Methods:** We prospectively enrolled treatment-naïve, EGFR/ALK wild-type NSCLC patients with brain metastases in this study. Patients received chemotherapy plus camrelizumab (a humanized anti-PD-1 monoclonal antibody) as first-line treatment, and paired plasma and cerebrospinal fluid (CSF) samples were collected at baseline and first treatment evaluation (8-week). All samples were detected for 92 Immunology cytokines using the Olink panels, and were explored for predictive biomarkers to immunotherapy. The Mann-Whitney U test was performed to compare the immunological cytokine expression between intracranial response and non-response groups. And logistic LASSO regression model was used to variate selection and develop a CSF immuno-cytokine model to predict intracranial tumor response. **Results:** Between April 2020 and May 2022, a total of 28 patients were enrolled this study. At baseline, most immunological cytokines were significantly lower in paired CSF than in plasma, whereas a subset including CD83, PTN, TNFRSF21, TWEAK, ICOSLG, DCN, IL-18 and MCP-1 were increasing expressed in CSF samples. For patients with objective intracranial tumor response compared to patients with non-response, the baseline CSF levels of LAMP3 were significantly higher, whereas the CXCL10, IL-12, CXCL11, IL-18, TIE2, HGF and PDCD1 levels were significantly lower. And patients with lower HGF, IL-18 or PDCD1 levels had significantly longer intracranial progression-free survival to immunotherapy. The above CSF immunological cytokines were significantly decreased at first treatment evaluation in patients with intracranial tumor response. Our logistic CSF immuno-cytokine model selected TIE2, IL-18, LAMP3, PDCD1 and IL-12 that were significantly associated with intracranial tumor response, and yielded a mean AUC of 0.91, compared to PD-L1 expression (mean AUC of 0.72). **Conclusions:** Immunological cytokines in CSF could predict intracranial tumor response to immunotherapy in NSCLC patients with brain metastases, and findings require validation in a larger prospective cohort. Research Sponsor: None.

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Poster Session

Analysis of tumor progression among patients with glioma after COVID-19 infection. *First Author: Tim Gregory, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: As of January 2023, there have been 6.7 million worldwide deaths attributed to SARS-CoV-2 COVID-19, which has impacted outcomes and medical care for all patients. Relatively little is known about the direct effects mediated by the virus on CNS tumor biology, despite the fact that viral neurotropism is well described, various coronavirus receptors have been observed in glioblastoma (GBM) tissues, and differential monocytic infiltration has been proposed to dysregulate the immune microenvironment. We detected a trend of rapid progression following COVID-19 infection among several patients with primary brain tumor patients and sought to systematically evaluate the pace of progression among infected patients in our institution. **Methods:** A single-institutional database of COVID-19 patients and an electronic medical record (EMR) search tool were used to identify a total cohort of 67 patients with glioma for retrospective analysis. This included 38 GBMs, 18 IDH-mutant gliomas, 5 ependymomas, 2 pilocytic astrocytomas, 1 diffuse midline glioma, 1 diffuse hemispheric glioma, and 1 ganglioglioma patients, each of whom had a documented COVID-19 infection between June 2020-December 2022. Hyperprogression was defined as tumor increase $\geq 40\%$ compared to previous scan using RECIST size criteria. **Results:** Thirty-nine (58%) patients experienced tumor progression following COVID-19 infection at a median of 34 days (range=1-734 days) after testing positive for COVID-19. Twenty-two (56%) had received COVID-19 vaccine before their infection and 5 (13%) had asymptomatic infections. Twenty-two patients had measurably increased tumor area by a median of 63% (range=10-2,900%), 18 of which constituted hyperprogression; 16 patients developed multifocal disease, 8 developed new nodular enhancement, 3 developed leptomeningeal disease (LMD), and 2 experienced increased infiltrative disease alone. Ten patients' presentation with new glioma was preceded by COVID-19 infection by a median of 31 days. GBM patients represented the majority of progression events, among whom 59% progressed within 60 days of documented infection (median 25 days). This subgroup of GBM with rapid progression within 60 days had a mOS from infection of 5.2 months; 89% had TERT promoter mutations and 42% had MGMT promoter methylation. **Conclusions:** Glioma patients appear to have disease progression at an accelerated pace in the first two months after COVID-19 infection. This suggests that glioma patients should continue observing strict precautions to prevent infection and should be clinically monitored vigilantly after infection, with consideration for short interval imaging during treatment. These preliminary data warrant further investigation exploring changes of immune cell infiltration in the tumor microenvironment and the possible correlation between tumor progression and COVID-19. Research Sponsor: None.

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Poster Session

An exploratory clinical trial on intra-lumbar injection of B7H3-specific allogeneic universal CAR-T cells in patients with recurrent high-grade gliomas. *First Author: Xiaoyun Shang, T-MAXIMUM Pharmaceutical (Suzhou) Co., Ltd., Suzhou, China*

Background: No standard-of-care treatment was established for recurrent high-grade gliomas (rHGGs) yet. Intrathecal infusion of autologous chimeric antigen receptor-T (CAR-T) cells has displayed potent anti-tumor activity in one patient (Brown et al. N Engl J Med 2016). We evaluated the safety, efficacy, pharmacokinetic (PK) and pharmacodynamic (PD) characteristics of B7H3-specific allogeneic universal CAR-T (B7H3 UCAR-T) cells in patients with rHGGs. **Methods:** Eligible patients who had received standard treatment for newly-diagnosed high-grade gliomas but failed were treated with 2.5×10^7 B7H3 UCAR-T cells via intra-lumbar injection every month. Eligibility criteria included histologic and/or cytologic rHGGs, B7H3-positive antigen expression rate of $>50\%$ in tumor tissue and Karnofsky performance status (KPS) ≥ 40 . The primary endpoint was treatment-related adverse events (TAEs); secondary endpoints include overall survival (OS) and objective response rate (ORR); exploratory endpoints were PK and PD characteristics of B7H3 UCAR-T cells. **Results:** In the 7 patients enrolled, 4 (57.1%) were female, 5 (71.4%) glioblastoma (WHO Grade IV) and 2 (28.6%) diffuse midline glioma (WHO Grade IV), and the mean age was 40.4 years. The most common reported TAEs were increased cerebrospinal fluid (CSF) IL-6 (7/7, 100%), headache (7/7, 100%), increased blood IL-6 (6/7, 86%) and fever (6/7, 86%). No adverse events of grade 3 or greater related to B7H3 UCAR-T cells were reported. All the adverse events recovered or relieved after treatment. No typical or severe systemic cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS) or graft versus host disease (GvHD) were observed during the study period. Based on Immunotherapy Response Assessment in Neuro-Oncology (iRANO), 3 of 7 patients had response to therapy (42.9%; 95% CI: 15.8 to 75.0) and 7 of 7 patients were stable disease (100%; 95% CI: 64.6 to 100). As of cutoff date (January 30, 2023), two patients died. The median OS was not reached (95% CI: 12.9 to could not be estimated). The median follow-up for OS was 15.6 months (95% CI: 14.7 to 16.1). OS rate at 12 months was 85.7% (95% CI: 48.7 to 97.4). The CAR DNA copy numbers increased 1 day after each administration and persist at least 1 month in cerebrospinal fluid. IL-6 concentrations in CSF and peripheral blood increased after each administration while the change and concentration values in peripheral blood were much lower than those in CSF. **Conclusions:** In patients with rHGGs, B7H3 UCAR-T cells was not associated with any toxic effects of grade 3 or higher. B7H3 UCAR-T cells resulted in a significantly longer overall survival and a higher objective response rate than history data. B7H3 UCAR-T cells persist well in patients. Clinical trial information: ChiCTR2100047968. Research Sponsor: T-MAXIMUM Pharmaceuticals (Suzhou) Co., Ltd.

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Poster Session

Safety, efficacy, and biomarker analysis of response to engineered tumor-infiltrating lymphocytes secreting anti-PD-1 antibody in recurrent glioblastoma: An open-label, two-arms, phase 1 study. *First Author: Yu Yao, Department of Neurosurgery, Huashan Hospital, Shanghai Medical College, Fudan University, Shanghai, China*

Background: Adoptive cell therapy using tumor-infiltrating lymphocytes (TILs) is effective against solid tumors with convincing evidence. But T-cells infused were exhausted when they encountered PD-1-mediated immunosuppression in the microenvironment. Here, we generated a modified autologous TILs secreting antibody targeting PD-1 (PD1-TIL), and conducted a first-in-human, two arms, phase 1 study (NCT03347097) in recurrent glioblastoma who had a poor prognosis with estimated 6-9 months of median overall survival (OS). **Methods:** Patients were included to be treated with PD1-TIL or TIL cell products intravenously every one month following surgery. The primary endpoint was safety and feasibility. The secondary endpoints were disease control rate (DCR), OS, immunologic responses and biomarker analysis. The clinical response to cell therapy was assessed by MRI according to iRANO criteria. Here, patients with clinical benefit (CR, PR, and SD) were defined as responder. **Results:** A total of 21 consecutive patients (median age 45 years, range 20-64) received infusions of cell products (7 patients for PD1-TIL with 1 excluded, 14 patients for TIL with 2 excluded). 52% (11/21) and 29% (6/21) of 21 patients had methylated MGMT promoter and IDH1/2 mutant respectively. No significant differences in baseline characteristics between groups were found. Both of PD1-TIL and TIL infusions were well tolerated with no unexpected high-grade adverse events. Of 7 evaluable patients in PD1-TIL group, 1 had PR for more than 26 months, 2 had SD lasting for 7.7 months and 24 months, and 4 had PD after infusion. The DCR, 1-year and 2-years survival rates in PD1-TIL group were 43% (3/7), 86% (6/7) and 29% (2/7) respectively. In TIL group, 3 patients had SD and the others had PD. The DCR, 1-year and 2-years survival rates in TIL group were half of that in PD1-TIL group. Survival analysis showed that patients treated by PD1-TIL had extended OS than those received TIL (16.1 vs. 11.2 months, $P = 0.047$). Among 21 patients, clinical responders had significantly improved OS (30.9 vs. 10.7 months, $P = 0.001$) than non-responders. We also found a high capacity for engraftment and persistence of infused TILs in peripheral blood which could be detectable at 6 months after treatment. Existence of neoantigen-reactive T cell clonotypes in cell products may be important for responding because missing of missense mutations predicted to generate a neoantigen after cell therapy was a remarkable signature in responders. Responsive tumors were also associated with tumor microenvironment profiles. **Conclusions:** This first-in-human study establish the preliminary feasibility, safety and encouraging efficacy of PD1-antibody-secreting TILs, and may constitute a new treatment strategy by T-cell genetic engineering in glioblastoma. Clinical trial information: NCT03347097. Research Sponsor: National Key R&D Program of China; National Natural Science Foundation of China.

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Poster Session

Lisavanbulin in patients with recurrent glioblastoma: Phase 2a results and a consolidated analysis of response-predictive biomarkers. *First Author: Juanita Suzanne Lopez, The Royal Marsden NHS Foundation Trust, Sutton, United Kingdom*

Background: Lisavanbulin (BAL101553, prodrug of BAL27862) destabilizes microtubules and promotes tumor cell death by modulating the spindle assembly checkpoint. BAL27862 is a lipophilic small molecule shown in rodents to penetrate the brain, with antitumor activity in orthotopic glioblastoma (GBM) models. In the Phase 1 part of this study¹ (NCT02490800), 2 of 5 patients with recurrent IDH-mutated G4 astrocytoma treated at active dose levels (15-30 mg/day) showed long-lasting objective responses and strong end-binding protein 1 (EB1) expression in GBM tissue by IHC. EB1 is a regulator protein on microtubules. **Methods:** The objective of the Phase 2 study was to investigate prospectively the response-predictive value of EB1, and to identify RNA-based response signatures in patients with recurrent GBM. A Simon's two-stage design was used with an objective response rate (ORR) $\geq 2/9$ required in Stage 1 to enable a final ORR $\geq 6/19$. A prescreening program identified patients with EB1-positive archival GBM tissue. All patients received 25 mg oral lisavanbulin once daily. RNA-seq was performed on archival GBM tissues. **Results:** GBM tissue samples from 64 of 629 patients (10.2%) obtained from 13 sites in four countries were EB1-positive, and 18 of these patients received lisavanbulin. Of 9 patients with measurable disease evaluable for response in Stage 1, one patient had a partial response, and another had a 44% target lesion area reduction. Despite sustained activity in these patients, formal stage transition criteria were not met, and the study was closed. IHC testing for EB1 did not show sufficient enrichment for response, but it is thought that IDH status may play a role. In addition, RNA-seq analyses identified a five-gene signature that is distinct from expression patterns observed with EB1-IHC positivity, and predicts current responses irrespective of IDH status. This signature is characterized by homeobox gene downregulation, which may be implicated in the control of microtubule dynamics. **Conclusions:** This Phase 2a study supports previous study results that lisavanbulin is associated with durable responses and clinical benefit in a subset of patients with GBM. RNA-seq analyses of GBM samples suggest further evaluation of the lisavanbulin predictive response signature. ¹Lopez et al, JCO 2019; 37,15 suppl, 2025. Clinical trial information: NCT02490800. Research Sponsor: Basilea Pharmaceutica International Ltd.

Study phase and tumor characteristics of patients with GBM or G4 astrocytoma	Number of patients treated with 15-30 mg/day lisavanbulin	Number of patients with Objective response	Best response and treatment duration (months) in patients ongoing on 31 Dec 2022
Phase 1, IDH mut	5	2	CR (49), PR (56)
Phase 1, IDH wt or unknown	11	0	-
Phase 2, IDH wt, measurable	9	1	PR (11), SD (13)
Phase 2, IDH wt, non-measurable	4	-	SD (15), SD (11), SD (5)
Phase 2, IDH wt, non-evaluable	5	-	-

2045

Poster Session

A single-arm, phase 2 clinical trial of abemaciclib in adult patients with recurrent grade 3 oligodendroglioma. *First Author: Stephen Joseph Bagley, Hospital of the University of Pennsylvania, Philadelphia, PA*

Background: Oligodendroglioma is a malignant glial neoplasm arising primarily in young adults. Although radiotherapy (RT) and chemotherapy result in durable disease control, tumor recurrence is inevitable and life-limiting. The cyclin D1-CDK4 axis is frequently dysregulated in recurrent oligodendroglioma. Abemaciclib is a selective CDK4/6 inhibitor that has been shown to achieve pharmacologically-relevant concentrations in brain tumor tissue. **Methods:** We conducted a single-center, single-arm, phase 2 trial evaluating the efficacy of abemaciclib in patients with recurrent oligodendroglioma, IDH-mutant and 1p/19q-codeleted, WHO Grade 3, following prior RT and ≥ 1 line of alkylating chemotherapy. Patients received abemaciclib 200mg twice daily. Primary endpoint was progression-free survival status at 6 months (PFS-6). Ten patients were needed for 80% power to detect the difference between the null (PFS-6 = 50%) and alternative (PFS-6 = 85%) hypotheses; one-sided $\alpha = 0.05$. Modified RANO criteria were used for patients with enhancing tumors and RANO low-grade glioma criteria for patients with nonenhancing tumors. **Results:** Between November 2019 - August 2022, 10 patients were enrolled (Baseline Characteristics). Most common treatment-related adverse event (trAE) was grade 1-2 diarrhea, occurring in all 10 patients. Grade 3-4 trAEs included grade 4 thrombocytopenia (n=2), grade 3 neutropenia (n=1), grade 3 fatigue (n=2), and grade 3 ALT increase (n=1). In patients with enhancing tumor (n=9), best response was partial response in 2 patients (ORR=22.2%; DOR 13.1 and 7.7 months, respectively), stable disease (SD) in 3 patients (33.3%; duration of SD 17.0, 6.7, and 2.5 months, respectively), progressive disease in 3 patients (33.3%), and not evaluable in 1 patient (11.1%). In the patient with nonenhancing tumor, best response was SD (duration 10.2 months). Median PFS was 7.7 months (95% CI, 1.7 – 13.1 months); median overall survival was not reached (median follow-up 17 months). The study's primary endpoint was not met; 5/10 patients (50%) were alive and progression-free at 6 months, below the minimum required (8/10) to consider abemaciclib worthy of further investigation. **Conclusions:** Despite objective responses and durable disease control in a small subset of patients, the efficacy of abemaciclib in recurrent grade 3 oligodendroglioma was not adequate to warrant further clinical evaluation of abemaciclib monotherapy in unselected patients. Correlative studies are ongoing to identify which patients with oligodendroglioma may benefit from abemaciclib. Clinical trial information: NCT03969706. Research Sponsor: Eli Lilly.

Characteristic	
Age at enrollment, years (median, IQR)	50 (44, 55)
Female gender, n (%)	5 (50)
Karnofsky Performance Status ≥ 90 , n (%)	9 (90)
Median time since original diagnosis, years (range)	14.3 (3.9, 19.7)
Median time since last systemic therapy, months (range)	6.7 (0.4, 132)
No. prior lines of systemic therapy, n (%)	
1, 5 (50)	
2, 0	
3, 1 (10)	
≥ 4 , 4 (40)	

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Poster Session

Final results of phase 2 trial of personal dendritic cell (DC) vaccines loaded with autologous tumor antigens (ATA) in newly diagnosed glioblastoma (GBM). *First Author: Daniela Annenelie Bota, University of California Irvine, Irvine, CA*

Background: Standard GBM therapy is associated with early progression and poor overall survival (OS). DC-ATA AV-GBM-1, a personal vaccine consisting of autologous DC pulsed with ATA, was investigated in a multicenter trial in patients with newly diagnosed GBM. **Methods:** Key eligibility criteria for surgical collection of tumor were clinical suspicion of new primary GBM & age 18-70 years. ATA lysate was prepared from irradiated tumor cells that were self-renewing in serum-free media. Autologous monocytes (MC) were collected by leukapheresis. Prior to initiating concurrent radiation therapy (RT) and temozolomide (TMZ), patients were enrolled with intent-to-treat (ITT) with DC-ATA after RT/TMZ. Eligibility included confirmation of primary GBM, availability of ATA & MC, KPS > 70 and plans for RT/TMZ. DC-ATA was manufactured during RT/TMZ. MC were differentiated into DC by culturing with IL-4 & GM-CSF, then DC were incubated with ATA. DC-ATA was suspended in 500 mg GM-CSF just prior to s.c. injections at weeks 1, 2, 3, 8, 12, 16, 20, & 24 (8 doses). Patients were not excluded based on apparent disease progression or PFS. Standard adjuvant TMZ regimens were started after the 3 weekly injections. Primary endpoint was $> 75\%$ OS 14.6 months from ITT enrollment. Secondary endpoints included median OS & progression-free survival (PFS). **Results:** Cell line and MC collection were successful for 97% of patients. Median age of the 60 ITT enrollees was 59 years. 3 patients withdrew before starting DC-ATA; 57 received 392 injections; 68% received all 8. Most common AE attributed to DC-ATA were local injection site reactions (16%) & flu-like symptoms (10%), but 33% experienced seizures. After 3 years of follow up, OS at 14.6 mos is 52.7% (95% CI 39.8, 65.8), median OS 16.0 mos (95% CI 12.9, 21.7) & median PFS 10.4 mos (95% CI 8.6, 11.6). OS rates at 1, 2, & 3 years are 70.1%, 32.4%, & 23.2%. Longer OS was associated with 8 DC-ATA doses ($p < 0.0001$), on < 2 mg/day dexamethasone (dex) at start of DC-ATA ($p = 0.005$), > 6 cycles of adjuvant TMZ ($p = 0.0054$), & KPS 90 or 100 ($p = 0.010$) at enrollment. Independent variables per multivariate Cox regression analysis were 8 DC-ATA doses, dex dose, IDH mutated, TMZ > 6 cycles, & MGMT promoter methylated. Concurrent TMZ regimens included TMZ alone (n = 28), TMZ + anti-VEGF (n = 14), & TMZ + tumor treating fields (TTF) (n = 10); 8 received no concurrent TMZ. OS was longer in patients treated with concurrent TMZ alone compared to no TMZ ($p = 0.0003$), TMZ + anti-VEGF ($p = 0.045$) or TMZ + TTF ($p = 0.045$). The only common features among 7 patients progression-free at 3 years are 8 DC-ATA injections, age < 60 , & < 2 mg dex. **Conclusions:** DC-ATA was reliably produced and injections well-tolerated in combination with various TMZ-based regimens, but the primary OS objective was not achieved. PFS was encouraging, but did not translate into improved OS, perhaps because DC-ATA was limited to 8 injections. Clinical trial information: NCT03400917. Research Sponsor: AIWITA Biomedical, Inc.

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Poster Session

Phase I/IIa study of concomitant radiotherapy with olaparib and temozolomide in unresectable high grade glioma patients: OLA-TMZ-RTE-01.

First Author: Dinu Stefan, Centre François Baclesse, Radiation Oncology Department, Caen, France

Background: Although the Stupp protocol (radiotherapy + temozolomide (TMZ)) remains the mainstay of glioblastoma (GBM) first line treatment after extended surgery, the prognosis is still poor. PARP inhibitors, such as olaparib, may improve GBM outcomes by enhancing cytotoxic effects of ionizing radiation and TMZ. The non-dividing nature of normal brain cells allows a dedicated tumor radiosensitization. We implemented a phase I/IIa trial to assess safety and efficacy of olaparib combined with TMZ concomitant with intensity modulated radiotherapy (IMRT) as a first line treatment in unresectable GBM patients (pts). We herein present results of the phase I step. **Methods:** Based on the Stupp protocol, 2 treatment periods were considered. The radiotherapy period (RT) occurs after surgery: pts received IMRT (60 Gy/30 fractions/6 wks), oral TMZ (75 mg/m²) during IMRT, and olaparib orally given at the same dose until 4 wks after the end of IMRT. For the maintenance period (MT) from 4 wks after IMRT, pts received TMZ (150 mg/m², days D) 1-5 every 28 days, for 6 cycles) plus olaparib at the MT dose level up to disease progression or unacceptable toxicity. The phase I included 2 sequential dose escalations (DE1, DE2) of olaparib to split both periods for DLT (Dose Limiting Toxicities) assessment. Olaparib dose levels (DL) were: 50 mg Q12H D1-3 (DL1), 100 mg Q12H D1-3 (DL2) or D1-5 (DL3), 200 mg Q12H D1-3 (DL4) or D1-5 (DL5) or 200 mg Q12H continuously (DL6). Pts in DE1 received olaparib only during RT to determine the MTD1 (Maximum-Tolerated Dose), by assessing DLT on this period. Next, after olaparib administered at MTD1 during RT, pts in DE2 received olaparib during MT to determine MTD2 ($\leq$ MTD1) during the MT period, assessing DLT from the first 2 cycles. DE1 and DE2 were performed by a TITE-CRM (Time-To-Event Continual Reassessment Method). **Results:** From 2017 to 2021, 30 pts were enrolled: 20 (67%) men, median age 59 yrs [range 25-70]. 16 and 11 pts were assessable for determining MTD1 and MTD2, respectively. In DE1, 2 pts received olaparib at DL1, 6 at DL2, 6 at DL3, 1 at DL4 and 1 at DL5. 4 pts observed DLT (3 at DL3, 1 at DL5): thrombocytopenia G3-4 (n=4) + neutropenia G4 (n=2). MTD1 was defined as DL2 with estimated probability of DLT of 22.1% [95%CI 8-40.5]. In DE2, 2 pts were treated at DL1, 9 at DL2. 1 pt observed DLT at DL2: thrombocytopenia G4. MTD2 was defined as DL2 with estimated probability of DLT of 13.3% [0.2-0.35]. No interruption of IMRT for toxicity was observed. Excepted DLT, permanent olaparib discontinuation for toxicity was observed in 1 pt during RT and 2 pts during MT. Toxicity induced temporary TMZ interruption in 4 pts, none with permanent discontinuation. No toxic death was observed. **Conclusions:** Olaparib 100 mg Q12H D1-3 in concomitant with the Stupp protocol has an acceptable safety profile in unresectable GBM pts: it warrants efficacy determination, in the ongoing phase IIa step. Clinical trial information: NCT03212742. Research Sponsor: French Cancer Institute and French Health Ministry (ref: PHRC-K15-135, INCa-DGOS_9780); Astra-Zeneca for Olaparib supply.

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Poster Session

Potential predictive biomarker for response to radiotherapy and CXCL12 inhibition in glioblastoma in the phase I/II GLORIA trial. *First Author: Frank Anton Giordano, Department of Radiation Oncology, University Medical Center Mannheim, University of Heidelberg, Mannheim, Germany*

Background: Standard of care (SOC) treatment achieves poor clinical outcomes in patients with glioblastoma (GBM), particularly in the absence of MGMT promoter hypermethylation. Preclinical models suggest that GBM recurrence is facilitated by CXCL12-mediated recruitment of bone marrow-derived cells capable of vasculogenesis after radiotherapy (RT). We have recently reported favorable safety and feasibility data of the phase I/II GLORIA trial, which combines RT and the CXCL12-neutralizing L-RNA aptamer olaptesed pegol (NOX-A12) in patients with newly diagnosed, incompletely resected or unresected GBM lacking MGMT promoter hypermethylation (NCT04121455). Here we report on clinical outcomes and their correlation with potential biomarkers. **Methods:** 10 patients with newly diagnosed incompletely resected (n=8) or biopsied (n=2) GBM with ECOG=2, age ≥ 18 and without MGMT promoter hypermethylation were enrolled. All patients received standard RT (60 Gy in 30 fractions or 40.05 Gy in 15 fractions) and escalating dose levels of continuous (24/7) i.v. infusions of NOX-A12 for 26 weeks. While the previously reported primary endpoint was safety, secondary efficacy endpoints included progression-free survival (PFS) and overall survival (OS). Biomarker assessment was performed with a six-plex immunofluorescence staining (CODEX) of neuropathologically confirmed tumor areas of pretreatment tissues for CXCL12, CD31 (endothelial cells), GFAP (glioma cells), CD68 (macrophages, microglia), α SMA (pericytes), Ki-67 (proliferating cells) and a nuclear marker. An independent patient cohort treated with SOC (n=15) matched by clinical and histopathological features was used for comparisons of efficacy and biomarker assessment. **Results:** Median PFS of the GLORIA cohort was 5.7 (range 1.9–8.5) months and the median OS was 12.7 (4.7–18.4) months. Biomarker analyses revealed that a higher frequency of CXCL12 expressing endothelial and glioma cells (EG12 score) significantly correlated with PFS ($r=0.87$; $p=0.005$) in patients treated with RT and NOX-A12, but not with SOC ($r=0.10$; $p=0.724$). GLORIA patients with a high EG12 score (median classifier) had a significantly longer PFS than those with lower scores (3.0 vs. 6.0 months; $p=0.031$) and a trend towards prolonged OS (11.1 vs. 15.8 months; $p=0.075$). These correlations were not seen in the reference cohort treated with SOC (PFS: 6.0 vs. 4.6 months; $p=0.502$; OS: 10.0 vs. 9.6 months; $p=0.243$). **Conclusions:** We show superior clinical efficacy of RT and NOX-A12 in patients with high frequency of CXCL12 expressing endothelial and glioma cells, suggesting the use of the EG12 score as a novel predictive biomarker for CXCL12-directed therapies in GBM. Clinical trial information: NCT04121455. Research Sponsor: TME Pharma AG.

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Poster Session

Post-marketing surveillance safety analysis of patients with CNS malignancies treated with tumor treating fields (TTFields) therapy between 2011–2022. *First Author: Maciej M. Mrugala, Department of Neurology and Hematology-Oncology, Mayo Clinic Cancer Center, Phoenix, AZ*

Background: Glioblastoma (GBM) has a poor prognosis. Standard treatments are associated with systemic toxicity, further increasing the disease burden in this patient population. Tumor Treating Fields (TTFields) are electric fields that disrupt cancer cell processes which affect cancer cell viability, and are generated by a portable, wearable device which is locoregional and noninvasive. TTFields therapy was approved by the FDA for the treatment of newly diagnosed (nd) and recurrent (r) GBM based on the phase 3 EF-14 (TTFields therapy 200 kHz + temozolomide) and EF-11 (TTFields 200 kHz) studies, respectively. TTFields therapy is also approved for pleural mesothelioma. We report an updated global, post-marketing surveillance (PMS) safety analysis of patients with CNS malignancies treated with TTFields therapy over an 11-year timeframe. This analysis represents the largest dataset of TTFields therapy use to date. **Methods:** Unsolicited safety data were collected from routine post-marketing activities for patients (N = 25,898) in North America, Europe, Middle East and Africa and Japan, from October 2011 to March 2022. AEs were stratified by diagnosis, age, and sex and categorized using MedDRA version 25.1. **Results:** Diagnoses were ndGBM (68%), rGBM (26%), anaplastic astrocytoma/oligodendroglioma (4%) and other (2%). Baseline demographics were reflective of real-world practice: median (range) age was 59 (3–103) years; two-thirds of patients were male. Most (69%) patients were 18–65 years; 0.4% were < 18 years, and 30% were > 65 years. All-cause and TTFields-related AEs occurred in 18,798 (73%) and 14,599 (56%), patients, respectively. The most common device-related AE was skin reaction (43% patients overall). There were no major differences in occurrence of this AE between pediatric, adult, and elderly groups (39%, 42%, and 45%, respectively), or between males and females (41% and 46%, respectively). The incidence of device-related skin reactions was higher in ndGBM than rGBM (46% vs 34%, respectively), in line with previous reports. Only 405 (2%) of patients overall reported an AE of treatment-related ‘quality-of-life decreased’. In line with the phase 3 studies, there were no treatment-related systemic AEs. **Conclusions:** In this updated global PMS safety analysis, TTFields therapy demonstrated a tolerable safety profile in patients with CNS malignancies, with no new safety findings. In line with previous real-world and clinical data, most AEs were localized, non-serious skin events, which were consistent between age groups. Such events can typically be managed easily using prophylaxis and topical therapies, together with optimization of caregiver techniques. Importantly, no TTFields therapy-related systemic AEs were detected. Research Sponsor: Novocure Ltd.

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Poster Session

A phase 0 pharmacokinetic trigger trial of infigratinib in patients with recurrent high-grade glioma. *First Author: Nader Sanai, Ivy Brain Tumor Center, Phoenix, AZ*

Background: This Phase 0 trial evaluates tumor pharmacokinetic (PK) and pharmacodynamic (PD) responses of fibroblast growth factor receptor (FGFR) inhibitor, infigratinib, in participants with recurrent high-grade glioma carrying FGFR1 K656E or FGFR3 K650E mutation or FGFR3-TACC3 translocation. Patients with high unbound drug concentrations in the gadolinium-nonenhancing tumor region were graduated to a therapeutic regimen of infigratinib. **Methods:** Recurrent high-grade glioma patients received 7 days of infigratinib (125 mg QD) prior to planned resection at 7–9 hours following the last dose. Tumor tissue (enhancing and nonenhancing regions), cerebrospinal fluid (CSF), and plasma were collected. Total and unbound infigratinib concentrations were measured using validated LC-MS/MS methods. A PK ‘trigger’ determined eligibility for the therapeutic expansion phase and was defined as unbound [infigratinib] > 5-fold biochemical IC50 (i.e., 5 nM) in non-enhancing tumor. PD response was assessed by quantification of percentage of positive pERK, MIB-1, and Cleaved Caspase 3 cells in the surgical tissue compared to baseline archival/biopsy tissue. Patients with tumors exceeding the PK threshold for unbound drug concentration were eligible for expansion phase therapeutic dosing of infigratinib. **Results:** Seven patients were enrolled into the Phase 0 study with 3 patients who met the PK threshold continued to the expansion phase. In non-enhancing tumor region, the mean unbound concentration of infigratinib was 3.5 nM (n=7). The mean non-enhancing tumor-to-plasma coefficient for unbound drug (Kp,uu) was calculated to be 1.4. The suppression of pERK levels and MIB-1 levels was observed in 17% (1/6) and 67% (4/6) of the patients, respectively. At a median follow-up of 16.3 months [range: 2.8–18.7 months], the median progression-free survival (PFS) was 2.8 months (n=3). One patient remains on treatment. No grade 3+ toxicities were observed, and no adverse events resulted in discontinuation of therapy. **Conclusions:** Despite relatively high unbound tumor-to-plasma (Kp,uu) value, infigratinib achieves sub-optimal unbound drug concentration in the non-enhancing brain tumor tissue. Pharmacodynamic response with archival tissue as comparator did not reveal inhibition of pERK. Clinical trial information: NCT04424966. Research Sponsor: The Ben and Catherine Ivy Foundation and Barrow Neurological Foundation.

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Poster Session

Safety and efficacy of tumor treating fields (TTFields) prior and concomitant to radiotherapy in patients with newly diagnosed glioblastoma: Results from PriCoTTF. *First Author: Seid Kebir, Department of Neurology and Center for Translational Neuro- and Behavioral Sciences (C-TNBS), Division of Clinical Neurooncology, University Medicine Essen, University Duisburg-Essen, Essen, Germany*

Background: Tumor Treating Fields (TTFields) therapy is a locoregional, antimitotic cancer modality that utilizes electric fields delivered non-invasively to the tumor region using arrays. Preclinical findings have demonstrated that TTFields have an enhanced inhibitory effect on glioblastoma (GBM) cell proliferation when used concomitantly with radiotherapy (RT). These results provided the rationale for the phase 1/2 PriCoTTF study that investigated the safety and efficacy of TTFields therapy initiated prior and concomitant to radio-chemotherapy in adult patients with newly diagnosed (nd)GBM. **Methods:** TTFields therapy was initiated following surgery and continued concomitant with radio-chemotherapy and adjuvant chemotherapy for a total of approximately 9 months. TTFields rechallenge was permitted upon GBM recurrence. RT was conducted with arrays placed on the patients’ scalp. The primary endpoint was safety and tolerability gauged by a series of pre-selected treatment-limiting toxicities (TLTs). **Results:** The baseline characteristics of 33 patients enrolled to date were typical for GBM, except for a small proportion of patients with gross total resection (22.5%). The frequency of adverse events (AEs) grade ≥ 3 was comparable to other studies in GBM. Of note, grade ≥ 3 skin AEs only occurred in 2 patients (6%) and no patients developed a TLT. The median duration of TTFields therapy was 8.4 months. Median overall survival (OS) was not reached (48% of events had occurred), which precluded conclusions regarding efficacy. However, notably, multivariable Cox regression found that OS was independently associated with the number of days patients achieved > 23 h TTFields therapy (HR 0.96, 95% CI 0.93–0.99, P = 0.008). **Conclusions:** The PriCoTTF study met its primary endpoint by finding that TTFields therapy concomitant with RT was well tolerated in patients with ndGBM. This included that high-grade skin toxicities were rare. Longer follow up is needed to estimate the efficacy of TTFields therapy in this setting, and will need to consider the relatively low overall duration of TTFields therapy and proportion of patients who received GTR. Research Sponsor: Novocure Ltd.

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Poster Session

H3.3-K27M neontigen vaccine elicits anti-tumor T cell immunity against diffuse intrinsic pontine glioma: The phase I ENACTING trial. *First Author: Yang Zhang, Beijing Tiantan Hospital, Capital Medical University, Beijing, China*

Background: Diffuse intrinsic pontine glioma (DIPG) harboring H3.3-K27M mutation is a malignant pediatric brain tumor with a >90% mortality rate within two-year of diagnosis. Current therapeutic options for DIPG are limited. Aiming to improve therapeutic outcomes, we herein report the preliminary findings of a phase I trial studying a neontigen peptide vaccine targeting H3.3-K27M. **Methods:** ENACTING is an open-label, single center, two-armed phase 1 trial to assess the safety and T cell immunity of a neontigen peptide vaccine against H3.3-K27M. Patients aged ≥ 5 years old with newly diagnosed DIPG were consented and screened. HLA-A*02+ / H3.3-K27M+ patients were enrolled to a two-arm study: Arm A consists of subjects receiving open debulking surgery, and Arm B consists of subjects without surgery eligibilities who received stereotactic biopsy. All patients subsequently received conformal radiotherapy and neontigen vaccine treatment designed to elicit both CD4+ and CD8+ T cell immune response. Vaccine was administered intramuscularly in combination with polyinosinic-polycytidylic acid-poly-L-lysine carboxymethylcellulose (Poly-ICLC). The primary objective is to evaluate the safety (AEs graded by CTCAE v4.03) and survival outcomes. Secondary objectives include maximum tolerated dose (MTD) and immunological responses. **Results:** As of Jan 2023, 11 patients have been treated, with 7 in Arm A and 4 in Arm B. No grade 3–4 treatment-related adverse events have been observed, with fever (81.9%) and injection site pain (54.5%) being the most common AEs. Among 10 efficacy-assessable patients, median progression-free survival (mPFS) and median overall survival (mOS) were 11.4 months (95% CI: 5.8–14.7) and 15.4 months (95% CI: 7.53–not reached), respectively. One-year OS rate was 66.7% (95% CI: 42–100%). One patient was assessed as complete response (CR). T cell responses against neontigen were detected and H3.3-K27M mutation-specific CD4+ and CD8+ TCR clones were validated. **Conclusions:** The H3.3-K27M neontigen vaccine was well tolerated. Initial results from this ongoing study suggest that, compared with other current therapies against DIPG, H3.3-K27M peptide vaccination may provide superior patient survival outcomes. Clinical trial information: NCT04749641. Research Sponsor: Guangdong TCRcure Biopharma Technology Co., Ltd, Guangzhou, China.

Clinical efficacy and adverse events.				
Efficacy (n=10)		Treatment-Related Adverse Events (n=11)		
		All grades	Grade 3	Grade 4
Complete response	1 (10%)	Fever 9 (81.9%)	0	0
Partial response	0 (0)	Injection site pain 6 (54.5%)	0	0
Stable disease	9 (90%)	Bloating 1 (9.1%)	0	0
Progressive disease	0 (0)	Abdominal pain 1 (9.1%)	0	0
Disease control rate	100%	Vomiting 1 (9.1%)	0	0
12-month overall survival	66.7% (95% CI: 42–100%)	Increased blood LDH 1 (9.1%)	0	0
Median progression-free survival	11.4 months (95% CI: 5.8–14.7)	Proteinuria 1 (9.1%)	0	0
Median overall survival	15.4 months (95% CI: 7.53–NR)	Hypocalcemia 1 (9.1%)	0	0

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Poster Session

Phase 1 study of pritimumab in brain cancer. *First Author: Jose Arganda Carrillo, Pacific Neuroscience Institute and Saint John's Cancer Institute at Providence Saint John's Health Center, Santa Monica, CA*

Background: Pritumumab, a fully human IgG1 (kappa) monoclonal antibody (mAb), was originally isolated from a patient with cervical carcinoma. This classical example of a natural human anti-cancer antibody recognizes an altered form of the cytoskeletal protein vimentin, referred to as ectodomain vimentin (EDV). EDV is an ideal target for immunotherapy as it is expressed on the surface of tumor cells and is significantly overexpressed in glioblastomas (GBM). A multi-center phase 1 study was performed to assess the safety and pharmacokinetics of Pritumumab (NCT04396717). **Methods:** Eligible patients included age ≥ 18 years, histologically confirmed diagnosis of a central nervous system cancer, and have failed prior standard therapy. Exclusion criteria included insufficient time from prior therapy characterized as less than 28 days from cytotoxic therapy, less than 14 days from non-cytotoxic investigational agent, and less than 7 days for non-cytotoxic or immunotherapy agent. Dose Escalation Schema: Five cohort arms with up to 6 patients at each dose level included Cohort 1 (1.6 mg/kg), Cohort 2 (4.8 mg/kg), Cohort 3 (8.0 mg/kg), Cohort 4 (12.0 mg/kg), and Cohort 5 (16.2 mg/kg) on weekly 3+3 dosing schedule. Dose escalation was based on the dose-limiting toxicities (DLT) encountered through Day 28 of treatment. Pharmacokinetics: Blood and CSF samples were collected for pharmacokinetic (PK) analysis both pre- and post-dose. **Results:** 24 patients provided informed consent and 9 were excluded for not meeting eligibility. 15 patients received the investigational agent and were evaluable for safety and efficacy analyses. 12/15 patients had a diagnosis of glioblastoma and one patient each had anaplastic astrocytoma, oligodendroglioma, and non-small lung cancer with brain metastases. 13 patients discontinued treatment due to disease progression, one due to PI discretion for an unrelated CNS infection, and one withdrew for personal reasons. One partial response showed nearly a 98.0% and 40.8% reduction in 2 tumor lesions for 17 months on study. There were no dose-limiting toxicities to this natural human IgG mAb. The most common adverse events at least possibly attributed to Pritumumab were fatigue (53.3%) and constipation (33.3%). Other rare side effects, possibly related to Pritumumab, occurred at 6.7% were nausea, joint tenderness, dehydration, hypomagnesemia, neuropathy, pruritus, scalp dryness, dry skin (face), and depression. There were no Grade 3, 4, or 5 adverse events attributed to pritimumab. Preliminary pharmacokinetic (PK) data shows volume of distribution as 38.36 mL/kg and clearance of Pritumumab as 0.1305 mL/h/kg. The half-life of Pritumumab was found to be 12.5 days. **Conclusions:** Single agent Pritumumab is safe up to a dose of 16.2 mg/kg every 7 days in brain tumor patients. A phase 2 study is being planned as single agent and in combination with checkpoint inhibitors in both recurrent gliomas and upfront with chemoradiation in newly diagnosed gliomas. Clinical trial information: NCT04396717. Research Sponsor: Nascent Biotech, Inc.

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Poster Session

New ESMO scale for clinical actionability of molecular targets (ESCAT) for gliomas based on a multicentric real world data cohort using next-generation sequencing (NGS). *First Author: Oriol Mirallas, Vall d'Hebron University Hospital and Institute of Oncology (VHIO), Barcelona, Spain*

Background: The ESMO ESCAT scale rank molecular alterations (MA) based on the published evidence supporting their clinical use. Building on our proposal for the first ESCAT classification for primary brain tumors (pBT) [Mirallas *et al.* ESMO 2022], we aim to describe the clinical actionability of NGS in a multicentric glioma cohort and gather clinical factors that enrich patients with MA to justify performing NGS. **Methods:** A multicentric retrospective study included pts with molecular profiling using NGS methods (Foundation Medicine, local NGS, Caris, OncoPrint, and fusion panels). Clinical actionability was classified using the ESCAT scale; Tier 1 (ready for clinical implementation), Tier 2 (alteration-drug match with antitumor activity), Tier 3 (supported in other tumor types), and Tier 4 (preclinical evidence). Clinical factors considered for enrichment were diagnosis of glioblastoma (GBM), sex, and age ≤ 40 years, differences between groups were determined using Chi-squared test. The overall survival (OS) was calculated through Kaplan-Meier method and cox hazard ratio were fitted. **Results:** A total of 361 pts with NGS performed between Feb 2018 and Dec 2022 at 4 hospitals in Spain. Median age was 51.5 (range, 3.3-83.8), 77% had ECOG ≥ 1 , 39.2% were women, 23.4% were 40 or younger, 20.8% had IDH1mut, and 73.5% had a diagnosis of GBM. The distribution of MA according to ESCAT was: 10 pts ESCAT 1 (5 BRAFV600E mut, 5 NTRK 1-3 fusions); 75 pts ESCAT 2 (67 IDH1 mut, 6 FGFR-TACC rearrangement, 4 FGFR 1-3 mut, 3 IDH2 mut); 105 pts ESCAT 3 (98 PIK3CA/PTEN mut, 12 PTEN loss, 11 H3K27M mut, 6 BRAF fusion, 2 MET mut, 1 FGFR3 amplification); 93 pts ESCAT 4 (119 TERT mut, 77 EGFR gain, 67 CDKN2A loss, 58 CDKN2B loss, 48 EGFRvIII rearrangement, 46 ATRX mut, 40 EGFR mut, 8 ATM mut). Prevalence of Tier 1-2 MA was 23.6%. In relation to enrichment factors: 12% > 40 y pts had ESCAT1-2 vs 61% in ≤ 40 y ($p < 0.001$), pts with GBM had a 11% prevalence vs 61% non-GBM ($p < 0.001$), and non-gender differences were seen. The median OS for Tier 1-2 was 135 months (95% CI 166-99) vs Tier 3-4 of 24 months (95% CI 21.5-29.6). Significantly worse OS was observed for Tier 3-4 gliomas (HR: 4.11; 2.84-5.95, $p < 0.001$), and remained significant after adjusting for histology and hospital center ($p < 0.01$). **Conclusions:** The prevalence of ESCAT Tier 1-2 alterations is high in gliomas suggesting that molecular profiling should be offered, at least, in tertiary centers where these techniques are available. Potential enrichment factors to offer NGS were age and non-GBM pBT, but not gender. Research Sponsor: VHIO.

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Poster Session

Zotiraciclib (TG02) for newly diagnosed glioblastoma in the elderly or for recurrent glioblastoma: The EORTC 1608 STEAM trial. *First Author: Emilie Le Rhun, University Hospital Zurich, Zurich, Switzerland*

Background: Zotiraciclib (TG02) is an oral multi-cyclin dependent kinase (CDK) inhibitor, including CDK-9, that inhibits tumor growth down-stream via depletion of survival proteins such as MCL-1 and MYC. MCL-1 and MYC are frequently overexpressed in glioblastoma. **Methods:** The EORTC 1608 (NCT03224104) (STEAM) phase 1b trial had a three parallel group (A,B,C) open-label, non-randomized, multicenter design. Groups A and B explored the maximum tolerated dose (MTD) of zotiraciclib in elderly patients (more than 65 years) with IDH1^{R132H}-non-mutant newly diagnosed glioblastoma or anaplastic astrocytoma, in combination with hypofractionated radiotherapy alone (group A) or temozolomide alone (group B), based on O⁶-methylguanine DNA methyltransferase promoter methylation status determined centrally. Group C explored single agent activity of zotiraciclib in IDH1^{R132H}-non-mutant glioblastoma or anaplastic astrocytoma at first relapse after temozolomide chemoradiotherapy with a primary endpoint of progression-free survival at 6 months. Secondary objectives included efficacy, quality of life, and safety. **Results:** The MTD was 150 mg in combination with radiotherapy alone (group A, n=12) or temozolomide alone (group B, n=9) in elderly patients. Two dose-limiting toxicities were observed at 150 mg, one in group A (grade 3 seizure) and one in group B (multiple grade 1 events). Main toxicities included neutropenia, gastro-intestinal disorders, and hepatotoxicity. Progression-free survival at 6 months in group C (n=50) was 6.7%. **Conclusions:** Zotiraciclib exhibits overlapping toxicity with alkylating agents and low clinical activity as a single agent. Larger randomized trials may be required to explore activity in combination with radiotherapy or temozolomide. Clinical trial information: NCT03224104. Research Sponsor: Cothra.

2056

Poster Session

Distinct molecular features and potential therapeutic strategies for spinal cord gliomas. *First Author: Frances Elaine Chow, Department of Neurological Surgery, Norris Comprehensive Cancer Center, University of Southern California, Los Angeles, CA*

Background: Spinal cord gliomas (SCG) are rare primary CNS tumors with varied prognosis. Standard treatment remains poorly defined, as no clear survival advantage exists with extensive resection, radiation, or chemotherapy. Mounting evidence suggests that tumors from different regions of the CNS harbor unique molecular signatures. In a retrospective study, we comprehensively characterized molecular alterations to identify potential therapeutic strategies in the largest cohort of SCG reported to date. **Methods:** We performed centralized pathology review and analyzed SCG with next-generation sequencing of DNA (592 gene NextSeq or WES, Novaseq), RNA (WTS, NovaSeq) and pyrosequencing (MGMT promoter methylation, MGMTme). We estimated tumor microenvironment cell infiltration by quantiseq & Epithelial-Mesenchymal Transition (EMT) by RNAseq. We used X2/Fisher's-exact/Mann-Whitney U tests for comparison & determined significance ($p < 0.05$), adjusting for multiple comparison by the Benjamini-Hochberg method ($q < 0.05$). **Results:** We analyzed 39 surgically accessible SCG (19 high grade, 17 low grade, 3 NOS); ependymomas were excluded. The most common alterations were mutations in H3F3A (31%), TP53 (25%), ATRX (21%), NF1 (18%) & BRAF fusion (19%). H3F3A mutations occurred exclusively in high grade SCG (63%, $q < 0.05$) while BRAF fusions occurred exclusively in low grade SCG (60%, $p < 0.05$). TP53 mutations were more prevalent in high grade SCG (50% vs. 8%, $p < 0.05$). Compared to intracranial gliomas ($n = 6732$), SCG harbor significantly more frequent H3F3A (31% vs. 1.6%), KRAS mutations (10% vs. 0.7%) & BRAF fusions (19% vs. 0.7%) but less frequent TERT (4.3% vs. 66%) & PTEN (0 vs. 27%) mutations or EGFR amplification (0 vs. 28%) (all $q < 0.05$). SCG rarely harbor the canonical intracranial alterations IDH1 (2.6% vs. 17%), EGFRvIII (0 vs. 17%) or MGMTme (19% vs. 47%) ($p < 0.05$). SCG have greater penetration of immune infiltrates of DCs (median cell fraction/MCF: 13% vs. 9%), T regs (positive percent: 47% vs. 26%) & B cells (MCF: 9% vs. 7%), with less penetration of monocytes (MCF: 0 vs. 2%) ($q < 0.05$). EMT score associates with high grade glioma in intracranial disease ($q < 0.05$) but does not recapitulate in SCG ($p > 0.05$). **Conclusions:** Clinical management of SCG is currently drawn from experience with intracranial gliomas. Our results identify unique molecular features of SCG suggesting an underlying biology distinct from intracranial gliomas. In SCG, H3F3A mutations are exclusive to high grade while BRAF fusions are exclusive to low grade; SCG rarely harbor canonical intracranial alterations such as IDH1, EGFR or MGMTme; and SCG have greater penetration of DCs with less penetration of monocytes. We provide a biological explanation for limited effectiveness of current therapies in SCG with potential implications for chemotherapy, targeted and immunotherapy. Our work underscores the need for investigations dedicated uniquely to SCG. Research Sponsor: U.S. National Institutes of Health.

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Poster Session

Prospective phase I study of checkpoint blockade for the treatment of patients with newly diagnosed high-grade glioma prior to radiochemotherapy: Results of nivolumab plus ipilimumab treatment arm. *First Author: Santosh Kesari, Saint John's Cancer Institute at Providence Saint John's Health Center, Santa Monica, CA*

Background: The limited success of checkpoint inhibitors (CPI) targeting the programmed death-1 (PD-1) axis in the adjuvant setting for glioblastoma has prompted a deeper understanding of the brain tumor and immune microenvironment and evaluating how the sequence of immunotherapy administration impacts antitumor response. We initiated a feasibility study (NCT03425292) of postoperative nivolumab (anti-PD-1) monotherapy and combination therapy in adults with newly diagnosed high-grade gliomas (HGG) prior to radiotherapy. **Methods:** Within six weeks from surgical resection of newly diagnosed HGG, patients in study Arm 3 received nivolumab 300 mg every 2 weeks and ipilimumab 1 mg/kg every 6 weeks until disease progression or unacceptable toxicity. The primary endpoint was the rate of dose-limiting toxicities (DLT). Secondary objectives included adverse events, antitumor activity and pharmacodynamic effects of study treatment. Next-generation sequencing (NGS) was performed on archival tumor specimens before treatment and at the time of subsequent surgery. **Results:** Fifteen patients were treated with nivolumab plus ipilimumab. 27% (4/15) of patients were receiving dexamethasone at treatment initiation. MGMT promoter was methylated in 5 tumors, unmethylated in 9, and equivocal in one. The most common treatment-related adverse events (AEs) were rash, pruritus, fatigue, nausea, and anorexia. Grade 3 AEs were lipase increased (n = 2), anorexia (n = 1), pruritus (n = 1), and rash (n = 3), and Grade 4 cerebral edema occurred in 1 patient. Median progression-free survival (mPFS) was 1.3 months and median overall survival (mOS) was 19.3 months. Paired tumor specimens obtained before and after treatment were analyzed in six patients and revealed molecular changes in response to treatment as well as differences between patients with shrinking tumors versus progressing tumors. **Conclusions:** We show that nivolumab plus ipilimumab can be safely administered prior to radiation. To our knowledge, this is the first study in which checkpoint blockade therapy was administered for newly diagnosed glioblastoma prior to standard radiotherapy. Despite the short mPFS, mOS was suggestive of a potential long-term benefit from early CPI exposure, and three patients deferred chemoradiation greater than seven months. Analysis of other study arms is ongoing. Clinical trial information: NCT03425292. Research Sponsor: PHASE ONE – The Road to Curing Cancer; Glen Turner, Jamie Siminoff.

2059

Poster Session

Real-world experience with tumor treating fields (TTFields) in newly diagnosed glioblastoma: A survival meta-analysis with systematic review. *First Author: Matthew T. Ballo, Department of Radiation Oncology, West Cancer Center, Germantown, TN*

Background: Tumor Treating Fields (TTFields) are electric fields that exert forces on cancer cells, disrupting processes critical for cancer cell viability and tumor progression. TTFields therapy became an FDA-approved treatment option for patients with newly diagnosed glioblastoma (GBM) in 2015 on the basis of the randomized controlled EF-14 study (NCT00916409). Subsequent approvals worldwide and increased adoption of TTFields has led to the question of whether or not a consistent survival benefit has been observed in the real-world setting, and whether device usage has played a role. **Methods:** A literature search was conducted using PubMed, Embase, and the Cochrane Library to identify clinical studies evaluating overall survival in adult patients with GBM treated with TTFields therapy. Comparative studies and single-cohort studies reporting on survival outcomes were included in the analysis. Inter-study heterogeneity was assessed using the Cochran Q test and quantified using the Higgins I² statistic. Survival curves were pooled using a distribution-free random-effects method. **Results:** Our review identified 8 studies evaluating the clinical efficacy of TTFields therapy in newly diagnosed GBM, with patients spanning diverse geographic regions. Of these 8, 6 studies (reporting on a total of 1378 patients) compared the addition of TTFields therapy to standard of care (SOC) vs SOC alone, and were included in a pooled analysis for overall survival. Meta-analysis of comparative studies indicated a significant improvement in overall survival for patients treated with TTFields therapy vs those not receiving treatment (hazard ratio [HR]: 0.62; 95% CI, 0.52–0.73; $P < 0.001$). Inter-study heterogeneity was examined, and a sensitivity analysis indicated the pooled effect was robust and not dependent on any individual study. Among post-approval studies, the pooled median overall survival was 22.2 months (95% CI, 17.3–42.6) for TTFields-treated patients and 17.3 months (95% CI, 13.6–22.0) for the non-TTFields group. Rates of gross total resection were generally higher in the real-world setting, irrespective of TTFields use. Furthermore, among studies reporting data on TTFields device usage, an average device usage rate of 75% or higher was found to consistently associate with prolonged survival when compared to an average usage rate below 75% (pooled HR: 0.63; 95% CI, 0.48–0.83; $P = 0.001$). **Conclusions:** Meta-analysis of comparative studies suggests a significant survival benefit with TTFields therapy added to standard radiochemotherapy for patients with newly diagnosed GBM, and that a 75% usage rate may be meaningful in the real-world setting. Research Sponsor: Novocure.

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Poster Session

Lisavanbulin (BAL101553), a novel, oral microtubule destabilizer plus radiation in patients with newly diagnosed, MGMT promoter unmethylated glioblastoma: A phase 1 Adult Brain Tumor Consortium study (ABTC1601). *First Author: Matthias Holdhoff, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD*

Background: Lisavanbulin (BAL101553, prodrug of BAL27862) is a novel, oral microtubule destabilizer that leads to cell death mediated by modulating the spindle assembly checkpoint. It has promising antitumoral activity in orthotopic glioblastoma (GBM) models in combination with radiation (RT) ± temozolomide (TMZ), including in MGMT promoter unmethylated (uMGMT) tumors. Lisavanbulin is a lipophilic and small molecule (MW 387), and data in rodents showed its ability to cross the blood-brain barrier (brain-plasma ratio 1:1). **Methods:** This multicenter phase 1 study was to determine the MTD of oral Lisavanbulin in combination with standard RT (60 Gy in 30 fractions) in patients with newly diagnosed uMGMT GBM. Dose escalation followed a modified 3+3 design. The safety evaluation period ended 4 weeks after completion of radiation, which was also the end of study. Patients were allowed to continue treatment with standard adjuvant TMZ as per treating physician's recommendation. **Results:** Twenty-six patients with uMGMT GBM (median age 64y, 42.3% male, 61.5% with gross total resection, median KPS 80) were enrolled. Two GBM harbored an IDH1 mutation. Patients were treated at 5 different dose levels of Lisavanbulin administered once daily for 6 weeks concomitantly with RT: Lisavanbulin 4 mg (5 pts), 6 mg (5 pts), 8 mg (7 pts), 12 mg (5 pts), and 15 mg (4 pts). The initial starting dose was 8 mg. Due to Grade 4 aseptic meningoencephalitis in the first patient, the study was held and the dose decreased to 4 mg. Dose escalation resumed and continued to 15 mg with 1 DLT of Grade 2 confusion and memory impairment observed at 12 mg. A planned dose expansion was not conducted due to discontinuation of funding. Grade 3 AEs were hypertension (2), seizure (2), cognitive disturbance (1), cerebral edema (1), hyponatremia (1), and lymphopenia (1); no additional grade 4 AE was observed other than the 1 case of aseptic meningoencephalitis. Median OS was 12.8 months (95%CI: 9.1–18.3 months). At data cut-off, 8 subjects (30.8%) were still alive. 38.5% subjects had no information on disease progression and were censored during the estimation of PFS. The median PFS was 7.7 months (95%CI: 3.0–9.5 months). **Conclusions:** The maximum studied safe dose for Lisavanbulin in combination with RT in newly diagnosed uMGMT GBM was determined at 15 mg daily during radiation. Overall, the safety of this combination was acceptable. Next steps in developing Lisavanbulin in newly diagnosed GBM include safety studies in combination with TMZ and of TMZ+RT in MGMT promoter methylated GBM prior to formally studying efficacy in a prospective randomized trial. Clinical trial information: NCT03250299. Research Sponsor: U.S. National Institutes of Health.

2060

Poster Session

Safety and feasibility of JAK inhibitor ruxolitinib in newly-diagnosed high-grade gliomas (CRUX): Final toxicity report. *First Author: Manmeet Singh Ahluwalia, Miami Cancer Institute, Baptist Health South Florida, Miami, FL*

Background: Dysregulation of the JAK/STAT pathway in newly-diagnosed high-grade gliomas (nHGG) is linked to enhanced survival and proliferation of tumor cells. Ruxolitinib, a small molecule inhibitor of JAK1, JAK2, and JAK3, limits glioma growth in preclinical models. This concept was explored in a phase I trial (NCT03514069), whose final report on toxicity is presented here. **Methods:** This non-randomized prospective study included 60 WHO Grade 3-4 nHGG patients who received standard of care (SOC) therapy along with ruxolitinib in a 3+3 dose-escalation design; level 1 of 10 mg BID, level 2 of 15 mg BID, level 3 of 20 mg BID, level -1 of 5 mg BID. The primary study objective was the determination of the maximum tolerated dose (MTD) of ruxolitinib in combination with chemoradiation. The secondary objective was the determination of safety, overall survival (OS), and progression-free survival (PFS). The exploratory aims were to investigate relationships between clinical outcomes and genomic signatures. **Results:** 60 patients were enrolled, with a median age of 60.5 years (range 22–78). 23 (38%) patients were female and 37 (62%) were male. 29 (48%) were MGMT unmethylated and received ruxolitinib with radiation of 60 Gy over 6 weeks. 31 (52%) patients were MGMT methylated and received ruxolitinib with 75 mg/m² of temozolomide (TMZ) with radiation of 60 Gy over 6 weeks. The 1-year OS rate was 77% for all GBM patients; 62% for arm 1 (unmethylated MGMT) and 93% for arm 2 (methylated MGMT). Median OS for arm 1 was 18.1 months (10.1, NA) and was not reached for arm 2. MTD for both cohorts was 20 mg BID. No dose-limiting toxicities were observed. Toxicities attributable to study medications included four grade 4 AEs including seizure, respiratory distress, somnolence, and thromboembolic event along with 14 grade 3 adverse events (AEs), including respiratory distress, seizure, gait disturbance, weakness, thrombocytopenia, cognitive disturbance, urinary retention, and meningitis. **Conclusions:** Ruxolitinib therapy is safe and feasible in combination with TMZ and radiation. Efficacy of ruxolitinib plus SOC appears promising compared to historical benchmarks for both MGMT methylated and MGMT unmethylated cohorts. A randomized phase 2 trial is planned. Clinical trial information: NCT03514069. Research Sponsor: Cleveland Clinic.

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Poster Session

Phase I and pharmacodynamic study of arsenic trioxide plus radiotherapy for newly diagnosed glioblastoma. *First Author: Samuel Ryu, Stony Brook University School of Medicine, Stony Brook, NY*

Background: Arsenic Trioxide (ATO) demonstrated prolonged survival in a transplanted rodent glioblastoma (GBM) model. Given the lack of effective therapies before temozolomide was available, the NCI funded NABTT Brain Tumor Consortium initiated a Phase I study of ATO with radiation in patients with newly diagnosed glioblastoma. Dose escalations using two different schedules of ATO were studied. **Methods:** Patients with newly diagnosed GBM (MGMT and IDH mutation status unknown) were assigned to receive ATO once or twice weekly during the 6-week course of radiation. The starting ATO dose was 0.25 mg/kg. This was escalated by 0.05 mg/kg until an MTD was reached. Patients did not receive ATO or other adjuvant therapy once the radiation was completed. As ATO affected tumor vasculature and blood flow in experimental imaging studies, perfusion MRIs were obtained before ATO administration and one and six weeks later. Survival was a secondary endpoint. **Results:** Thirty-one patients were enrolled: median age 54.9 years, 68% male, 77% patients KPS >90, 77% had tumor resection. The MTD was determined to be 0.4mg/kg on the weekly schedule and 0.3mg/kg on the biweekly schedule. ATO was well tolerated with 81% of patients completing the 6 weeks combined treatment. Major dose limiting toxicities were increased aspartate and alanine aminotransferases and one case of hyperkalemia. For all patients the median overall survival (mOS) was 17.7 months and the median progression-free survival (mPFS) was 5.4 months. However, there was a significant survival difference between the two ATO dose schedules across all doses with a mOS of 22.8 months in the biweekly schedule, vs 12.1 months in the weekly schedule ($P = 0.039$). There was a similar difference in mPFS (10.2 months vs 3.2 months, respectively, $P = 0.004$). Similarly, there were significant differences in perfusion imaging between the two ATO dose schedules with relative cerebral blood flow showing a significant decrease after one week of ATO treatment on the biweekly schedule ($p = 0.007$). **Conclusions:** The MTDs of ATO in patients with GBM administered once or twice weekly for six weeks with standard radiation were determined. This regimen was well tolerated. Survival in patients on the biweekly schedule was much better (22.8 months) than expected in patients not receiving temozolomide. In addition, patients on biweekly ATO also had significant changes on MRI perfusion studies suggesting a pharmacodynamic effect of this agent. These findings should be explored further in patients with newly diagnosed MGMT unmethylated GBM where temozolomide has very limited activity. Clinical trial information: NCT00045565. Research Sponsor: U.S. National Institutes of Health.

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Poster Session

Depth of radiographic response (DpR) and time to tumor regrowth (TTG) to predict overall survival following anti-VEGF therapy in recurrent glioblastoma. *First Author: Benjamin M. Ellingson, University of California Los Angeles, Los Angeles, CA*

Background: Anti-angiogenic therapies, anti-VEGF agents, cause high radiographic response rates due to reduction in vascular permeability. However, we theorized the degree of tumor shrinkage combined with the duration of response might be a more meaningful measure of tumor control and may better reflect real patient benefit. In the current study, we investigate the association between model-derived parameters describing enhancing tumor volumetric dynamics and overall survival (OS) in recurrent glioblastoma treated with anti-VEGF therapy from multiple clinical trials. **Methods:** N=134 patients treated with bevacizumab +/- irinotecan (BRAIN Trial; NCT00345163) and N=121 patients treated with cabozantinib (XL184-201; NCT00704288) were used to identify potential imaging biomarkers, and N=63 patients in the bevacizumab control arm in a phase III trial (GLOBE Trial; NCT02511405) were used as a validation dataset. Enhancing tumor volumes were estimated using T1 subtraction maps, and a biexponential model was used to model tumor response (d) and regrowth (g) rates, as well as time to tumor regrowth (TTG), the inflection point where the tumor stops shrinking and starts to regrow, and the depth of response (DpR) after initiation of anti-VEGF therapy for each patient. Log-rank, univariate, and multivariable Cox regression were used to quantify the relationship of these parameters and OS. **Results:** Optimized thresholds based on maximum hazard ratio occurred at $d=0.11$ months⁻¹ ($P=5 \times 10^{-9}$ training; $P=0.0082$ validation); $g=0.07$ months⁻¹ ($P=5 \times 10^{-20}$ training; $P<0.0001$ validation); TTG of 3.8 months ($P=6 \times 10^{-17}$ training; $P<0.0001$ validation); and DpR of 11.3% ($P=0.0026$ training; $P=0.0177$ validation). Univariate and multivariable Cox regression using these thresholds and controlling for age and baseline tumor volume confirmed that d , g , TTG, and DpR were all significant and independent predictors of OS in both phase II training and phase III validation datasets ($P<0.01$). Additionally, patients exhibiting combinations of a high DpR and/or long TTG showed differential median OS, while patients with favorable diffusion MR phenotypes exhibited a longer OS and significantly longer TTG. **Conclusions:** Volumetric response and regrowth rates, TTG, and DpR using a biexponential model are significant and independent predictors of OS in recurrent glioblastoma treated with anti-VEGF therapy. Clinical trial information: NCT00345163; NCT00704288; NCT02511405. Research Sponsor: U.S. National Institutes of Health.

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Poster Session

Efficacy of function-enhanced, re-activatable, dual-specific CAR T cells pre-loaded with oncolytic virus for immunotherapy of high-grade glioma. *First Author: Mason Webb, Mayo Clinic, Rochester, MN*

Background: While cancer therapeutics have made tremendous progress within the past several decades, this benefit has not been seen in many primary cancers of the brain. Particularly confounding have been high-grade gliomas (HGG), which retain a dismal prognosis. Currently, novel therapies are being explored to rise to this unmet, critical need. One such therapy are CAR T cells, immune cells which have been engineered to target malignancy-specific antigens. Unfortunately, the efficacy of CAR T cell therapies against solid tumors is significantly limited, in large part due to impaired expansion/persistence in the immune suppressive tumor microenvironment (TME). Here we show that *in vivo* reactivation of CAR T cells through their native T Cell Receptor (TCR) by an oncolytic virus (OV) has therapeutic benefit in HGG. **Methods:** An EGFRvIII third-generation MSGV1 retroviral CAR construct containing the CD28, 4-1BB, and CD3z moieties, in tandem with the scFv derived from the human monoclonal antibody 139 and the marker Thy1.1 (38) was used to generate our CAR T cells. C57Bl/6 mice were used for *in vivo* experiments and both B16- and CT2A-EGFRvIII murine glioma cell lines were injected in the brain to model HGG. OVs and CAR T cells were given systemically by tail vein. OVs used include reovirus, vesicular stomatitis virus, and adenovirus. **Results:** By using OV in combination with EGFRvIII CAR T cells, we were able to generate a CD8 CAR population with TCR specificity for both the EGFRvIII and OV epitopes. These dual-specific (DS) CAR T expressed a memory phenotype and persisted for much longer than conventional CAR T cells. Further, we showed that these DS CAR T cells are more cytotoxic and can respond more rapidly than their conventional counterparts. We created a novel delivery mechanism for this combination OV + CAR T therapy using virus-loaded CAR T cells to bypass initial antiviral clearance from the immune system. Treatment with these OV-loaded CAR T cells lead to significant benefit in mice with HGG tumors which could be further enhanced by a systemic boost with OV, which rapidly re-activated DS CAR T cells against tumor and resulted in long-term cures of greater than 80% of treated animals. **Conclusions:** These promising results show that DS CAR T cells can overcome the critical therapeutic challenge of CAR T as a treatment for solid tumors. Given these promising results, we will go on to develop a clinical trial in which CAR T cells will be pre-loaded with OV and administered intravenously to patients with HGG, followed by systemic boosting with virus to re-activate DS CAR T cells against their tumor. Research Sponsor: Mayo Foundation; Mayo Clinic Ventures.

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Poster Session

Ultrasensitive detection and monitoring of central nervous system tumors from plasma using personalized whole-genome ctDNA profiling. *First Author: Ivy Tran, NYU Langone Health, New York, NY*

Background: Patients with the central nervous system (CNS) tumors are largely followed up by imaging. Current plasma-based liquid biopsy techniques have limited utility in neuro-oncology due to a low circulating cell-free tumor DNA (ctDNA) burden, blood-brain barrier, and low number of mutations in coding regions. Whole genome sequencing (WGS)-derived patient specific mutational signature from a matched tumor-normal WGS can provide a personalized, highly sensitive and specific approach to detect mutations in ctDNA and provide blood-based monitoring in brain tumor patients. Furthermore, it can be performed on lower amount of peripheral blood since WGS requires less sequencing depth compared to targeted ctDNA panels. **Methods:** We have profiled a cohort of 28 extra- and intra-axial adult and pediatric brain tumors including adult and pediatric low- and high-grade glioma (9), meningiomas (11), medulloblastomas (5), ependymomas (2), neurocytoma (1). Tumor DNA was extracted from archival pathology tissue, normal DNA from unsorted white blood cells, and ctDNA from 1-2 mL of post-surgery plasma. WGS was performed with 40x coverage for Tumor-Normal DNA and 20x for ctDNA. Using WGS of matched Tumor-Normal and plasma samples, we derived a personalized mutational pattern using SNVs, indels, and copy numbers for quantification and ultrasensitive detection of ctDNA in plasma samples. An AI-based error suppression model was implemented to filter out the noise in the cell-free DNA (cfDNA) while the personalized mutational signature was used to detect the ctDNA in the cfDNA and to amplify the somatic signal to determine the Tumor Fraction at the time of diagnosis, during the therapy or surveillance period. The ctDNA Tumor Fraction (TF) was compared to the clinical status and MRI-based imaging. **Results:** All subtypes of brain tumors contained enough mutations to derive personalized mutational signatures. Most mutations were distributed in the noncoding DNA. TF correlated with clinical status and with the disease course on imaging at given time points reaching a 10^{-4} minimal residual disease detection sensitivity. We were able to detect ctDNA across all WHO grades ranging from WHO 1 meningioma to WHO 4 glioblastoma and medulloblastoma. Furthermore, we were able to detect tumor-specific copy number aberrations such as MYCN amplification in plasma samples and mutational signatures. **Conclusions:** Here we demonstrate that patient-specific WGS tumor signature in ctDNA from plasma can be used for sensitive monitoring of adults and children with primary low- and high-grade CNS tumors. Research Sponsor: Internal funding; C2i Genomics Inc.

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Poster Session

Immune checkpoint inhibitor (ICI) therapy in glioblastoma: Institutional experience at the Massachusetts General Hospital (MGH). *First Author: John Yohan Rhee, Massachusetts General Hospital, Boston, MA*

Background: Immune checkpoint inhibitors (ICI) have resulted in promising outcomes in systemic cancer but response in glioblastoma (GBM) has not met early expectations based on early clinical trial results. Conflicting data exists regarding the incidence of pseudoprogression after ICI in brain tumors. Here, we present our institutional experience of the radiographic response following ICI therapy in GBM both at initial diagnosis and recurrence. **Methods:** We retrospectively identified IDH-wildtype GBM (per 2021 WHO criteria) patients treated either at time of initial diagnosis or at recurrence with nivolumab, pembrolizumab, or durvalumab between 2015 and 2022 at MGH. Overall radiographic and clinical responses after initiation of ICI were assessed in both groups. **Results:** 56 pts (18 female, 38 male) were identified (average age 58.6). Eight (14.3%) patients had ICI-related non-hematological toxicities, including granulomatous folliculitis, arthritis and myositis, headache, acneiform rash, transaminitis, and gastritis). Four (7.1%) of the eight patients had to discontinue treatment due to ICI-related severe toxicity (hepatitis and/or gastritis) and were not included in the final response assessment. Of the remaining 52 patients, none had evidence of pseudoprogression related to ICI. We did not identify any complete response (CR) or partial response (PR) secondary to ICI monotherapy. In the 13 patients treated at initial diagnosis, the following radiographic responses were seen: CR=0, PR=0, stable disease (SD)=5 (38.5%), and progressive disease (PD)=8 (61.5%). In the 39 patients treated at disease recurrence, the responses were: CR=0, PR=4 (10.3%), SD=10 (33.3%), PD= 22 (56.4%). Noteworthy, all patients with PR were concurrently treated with bevacizumab. **Conclusions:** 0/52 patients showed radiographic response after ICI monotherapy. While treatment was overall tolerated, ICI therapy was discontinued due to toxicity in 7% of patients. Pseudoprogression attributable to ICI was not seen in any of the patients treated. Research Sponsor: None.

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Poster Session

Phase I study of BTK inhibitor ibrutinib with temozolomide and radiation in newly-diagnosed glioblastoma (EQUILIBRIUM): Final trial report. *First Author: Manmeet Singh Ahluwalia, Miami Cancer Institute, Baptist Health South Florida, Miami, FL*

Background: Novel therapeutic strategies are urgently needed in newly-diagnosed glioblastoma (GBM). Ibrutinib, an oral small molecule inhibitor of BTK, is currently being investigated for several B-cell malignancies and solid tumors. Preclinical evidence suggests ibrutinib in inhibiting cancer stem cell in glioblastoma. We sought to investigate the safety and tolerability of ibrutinib in nGBM. **Methods:** A non-randomized, prospective phase I trial was conducted in nGBM patients with Karnofsky performance status $\geq 70\%$ and normal organ function, who received standard of care chemoradiation plus ibrutinib in a 3+3 dose-escalation design (level 1: 420 mg daily, level 2: 560 mg daily, level -1: 280 mg daily). Primary study objective was to determine maximum tolerated dose (MTD) of ibrutinib in combination with radiotherapy (RT) of 60 Gy over 6 weeks with/without 75 mg/m² of temozolomide (TMZ). Secondary objective was to determine safety, overall survival (OS), and progression-free survival. **Results:** 26 patients were enrolled, with 12 (46%) females. Median age was 61.5 years (range 76-22). 15 (58%) patients were MGMT methylated and 11 (42%) were unmethylated. Dose-limiting toxicities (DLTs) were observed at all dose levels of ibrutinib plus RT (ibru+RT) cohort. MTD of ibrutinib was noted to be 420 mg daily with RT+TMZ. All MGMT methylated and 2 unmethylated patients received ibrutinib+RT+TMZ. Remaining 9 unmethylated received ibru+RT. In ibru+RT+TMZ, median cycles of TMZ were 4 (range 0-6) and of ibrutinib were 3 (range 0-26). EGFR amplification status was available for 22 patients, of which 8 (36%) were amplified. Survival outcomes are described, stratified using log-rank test. **Conclusions:** 420 mg of ibrutinib daily is safe and feasible in combination with TMZ and radiation in nGBM. Outcomes of ibrutinib appears promising compared to historical survival data in the MGMT methylated cohorts. Further trials are planned. Clinical trial information: NCT03535350. Research Sponsor: None.

Group	N	Median OS, [months (95%CI)]	1-year OS, [% (95%CI)]	2-year OS [% (95%CI)]	3-year OS, [% (95%CI)]
Overall	26	21.9 (18.8-NA)	80 (66-97)	42 (26-70)	0.19 (7-50)
MGMT Methylated	15	26.0 (22.0-NA)	100 (100-100)	56 (34-95)	35 (15-82)
MGMT Unmethylated	11	14.0 (8.54-NA)	51 (28-94)	2 (6-70)	NA
Received ibrutinib+RT+TMZ	17	26.0 (21.8-NA)	100 (100-100)	52 (31-90)	33 (14-77)
Received ibrutinib+RT	9	10.6 (8.54-NA)	44 (21-92)	22 (7-75)	NA
EGFR Amplified	8	29.5 (21.9-NA)	88 (67-100)	73 (47-100)	39 (14-100)
EGFR Non-Amplified	14	21.8 (16.6-NA)	85 (67-100)	38 (17-84)	13 (2-76)

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Poster Session

Vulnerability to immune therapy in BRAF- and MYB-altered pediatric gliomas. *First Author: Michael DeCuyper, Ann and Robert H Lurie Children's Hospital, Chicago, IL*

Background: The frequency and expression of predictive immune biomarkers in pediatric gliomas is relatively unknown. Here, we sought to define predictive signatures of immunotherapy responders by examining immune checkpoint expression, immune cell population signatures, and gene amplifications in a variety of pediatric gliomas. **Methods:** We profiled a cohort of pediatric, adolescent, and young adult glioma samples submitted to Caris Life Sciences (Phoenix, AZ) for analysis (N = 207). The cohort was further stratified by driver mutations: IDH mutant (N = 103), H3-3A mutant (N = 36), MYB-altered (N = 4), BRAF-altered (N = 39), and IDH wild type (IDH WT) (N = 25). De-identified next generation DNA sequencing (592-gene or whole exome) and RNA (whole transcriptome) sequencing were used to determine tumor-infiltrating immune cell signatures and immune checkpoint protein expression. Transcriptomic signatures predictive of response to immunotherapy (T cell inflamed score) and replication stress response defect (RSRD) score were calculated on transcripts per million (TPM) values. Immune cell fractions were estimated using RNA deconvolution (quanTIseq). **Results:** BRAF-altered tumors showed the highest IFN gamma signature (a clinically relevant inflammatory biomarker), a high pro-inflammatory M1 macrophage signature, and very high CD4+/CD8+ T cell signatures compared to other tumor groups. IDH mutant, but not WT gliomas, were relatively deficient in T cell infiltration but revealed an increase in dendritic cell signatures. IDH WT gliomas showed more T cell enrichment but higher immune suppressive checkpoint expression. H3-3A mutant tumors showed relatively low immune cell infiltration and immune checkpoint expression. Pro-inflammatory M1 macrophages were lower in the high-grade glioma microenvironment compared to low-grade. Immune suppressive M2 macrophages were elevated in the IDH WT microenvironment relative to other gliomas. There was no apparent difference in the frequency of PD-1+ T cells and tumor-expressed PD-L1 among the various molecularly defined pediatric glioma groups. **Conclusions:** In general, BRAF- and MYB-altered gliomas displayed high immune activation relative to other tumors. IDH WT tumors have an immune suppressive microenvironment with relatively high immune checkpoint expression. Based on predictive markers, BRAF- and MYB-driven gliomas show signatures suggesting the possibility of a greater response to immunotherapies than IDH WT/mutant gliomas or H3-3A gliomas. Research Sponsor: None.

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Poster Session

Interrogating drug action and immune response in organotypic glioma microenvironment. *First Author: Jiyong Liang, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: The glioma tumor microenvironment is characteristic of a high level of heterogeneity and a profoundly immune suppressive phenotype as driven by the presence of glioma stem cells and abundant innate immune cells of the myeloid lineages, rendering glioblastomas (GBM) recalcitrant to conventional treatments and immunotherapies. To address the full complexity of the brain tumor with its diverse components, we have developed an organotypic slice culture system to overcome several limitations of the other preclinical models and allow interrogation of drug action and immunomodulatory agents in human GBM *ex vivo*. **Methods:** We performed extensive characterization of the organotypic glioma slice system and optimization of the *ex vivo* tissue culture conditions, and determined the longitudinal dynamics of slice cell viability, relative tumor versus immune cellularity, and responses to a selection of therapeutic agents and cytokines by multiplexed flow cytometry and single cell transcriptome (scRNA seq) profiling. **Results:** Single cell transcriptomic analysis showed that both tumor and immune cell heterogeneity were preserved *ex vivo* for the two-week observation time, which exhibited tumor-type specific gene expression profiles suggesting cooperative interactions among cell populations. Consistent with the findings in fresh tumor specimens and an immune suppressive microenvironment, we found a scarcity of T lymphocytes in IDH mutant gliomas, whereas abundant T cells were found in recurrent GBM slices that persisted *ex vivo*. Additional analyses revealed that T cell infiltration in GBM was associated with the mesenchymal-like molecular phenotype, which exhibited remarkable intratumor heterogeneity highlighting the presence of stem-like cells and a unique cell population expressing aberrant cancer genes and antigen presenting molecules. We further found that T cells in organotypic GBM slices acquired a potent effector phenotype in response to cytokine-induced reprogramming of microglia and tumor-associated macrophages. In addition, scRNA seq also revealed a population of cancer-associated fibroblast-like cells that are present in all tumors sequenced, which may function to mediate the interactions between immune and tumor cells as our data suggested. **Conclusions:** We demonstrated that the organotypic slice culture system we developed is compatible with genomic, pharmacological, and immunotherapeutic manipulations and provided data showing that organotypic slice culture preserves glioma microenvironment *ex vivo* allowing acquisition of crucial information of response of heterogeneous patient tumor tissue to the agent tested. This method represents a unique mechanism by which therapy development can be facilitated in an *ex vivo* setting. Research Sponsor: MD Anderson MoonShot Program.

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Poster Session

A phase 0/2 trigger trial of niraparib in patients with newly diagnosed glioblastoma. *First Author: Shweta Mehta, Ivy Brain Tumor Center, Phoenix, AZ*

Background: Poly (ADP-ribose) polymerase (PARP) mediates DNA damage response; niraparib is an investigational PARP1/2-selective inhibitor. This Phase 0 study evaluates newly-diagnosed glioblastoma (GBM) tumor pharmacokinetics (PK) and pharmacodynamics (PD), graduating patients with O6-methylguanine methyltransferase (MGMT) unmethylated tumors into a therapeutic regimen of niraparib plus fractionated radiotherapy when high unbound drug concentrations are present in gadolinium-enhancing tumor. **Methods:** Patients with presumed newly-diagnosed GBM were enrolled in a phase 0 study receiving 4 days of niraparib (300/200 mg QD) prior to planned resection 3-5 or 8-12 hours following the last dose. Tumor tissue (enhancing and non-enhancing regions), cerebrospinal fluid (CSF), and plasma were collected. Total and unbound niraparib concentrations were measured using validated LC-MS/MS methods. PARP inhibition was assessed by quantification of PAR induction after 10 Gy ex vivo irradiation in surgical tissue compared to non-irradiated control tissue. A PK 'trigger' determined eligibility for the therapeutic expansion phase and was defined as unbound [niraparib] > 5-fold biochemical IC50 (i.e., 19 nM) in non-enhancing tumor. Patients with MGMT unmethylated tumors exceeding this PK threshold were eligible for expansion phase dosing of niraparib plus radiotherapy followed by a maintenance phase of niraparib. **Results:** All patients (n=35) enrolled in the phase 0 portion of the study met the PK threshold. In non-enhancing tumor regions, the mean unbound concentration of niraparib was 253.2 nM in 32 evaluable GBM patients. The suppression of PAR levels after ex vivo radiation was observed in 75% of the patients (18/24). Eleven out of 18 patients with unmethylated tumors enrolled in phase 2. Five of the 6 initial patients enrolled in phase 2 experienced thrombocytopenia related to niraparib, and 3/5 cases were deemed serious and life-threatening. Consequently, starting dose in both phases was lowered to 200 mg, and no serious AEs were observed thereafter. At a median follow-up of 8.1 months [range: 6.0-12.9 months], PFS6 was 64% (n=11) with 4 patients remaining on treatment and 5 patients ongoing survival follow-up. **Conclusions:** Niraparib achieves pharmacologically-relevant concentrations in non-enhancing, newly-diagnosed GBM tissue in excess of any other studied PARP inhibitor. Clinical trial information: NCT05076513. Research Sponsor: The Ben and Catherine Ivy Foundation; Barrow Neurological Foundation.

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Poster Session

Intra-operative desorption-electrospray ionization mass-spectrometry for real-time diagnosis, margin assessment, and maximization of brain cancer resection. *First Author: Diogo Garcia, Mayo Clinic Florida, Jacksonville, FL*

Background: Despite advances in our understanding of brain cancer, the ability to discern between infiltrated and non-infiltrated tissue with current adjuncts, remains elusive. Isocitrate dehydrogenase (IDH) mutation is unique to IDH-mut glioma cells and can be used as a surrogate for tumor infiltration. Further, emerging evidence has shown unique signatures in brain cancer lipidomic profiling, with lipid metabolism playing a key role in brain cancer biology. Here, we aimed to evaluate the impact of desorption electrospray ionization-mass spectrometry (DESI-MS) as a near real-time method to determine infiltration status and the use of DESI-MS to perform intra-operative histological diagnosis. **Methods:** This is a prospective multi-institution cohort study using intra-operative DESI-MS on freshly obtained tumor samples to evaluate 2-hydroxyglutarate (2HG), with post-hoc validation by review by a board-certified neuropathologist. For tumor cell estimation and tissue diagnosis, high-throughput DESI-MS was used for rapid analysis of high-density arrays using lipidomic profiling. Analysis of the data was performed using a pre-written algorithm employing a combination of Python- and MATLAB-based custom software allowing results in less than a second per sample. **Results:** A total of 496 tumor biopsies from 72 patients have been analyzed. Earlier iterations focused on absolute quantitation of 2HG in 247 biopsies from 49 patients to determine IDH genotype yielding sensitivity, specificity, and accuracy values of 89, 100, and 94% for core biopsies (71). Improvement in accuracy was obtained with relative measurement of 2HG in comparison to glutamate allowing for detection of IDH-mut infiltration at the margin, resulting in 93% sensitivity, 100% specificity, and 98% accuracy with turnover times averaging 3 minutes in 183 biopsies from 23 patients. Margin assessment beyond the limits of neuro-navigation and surgeon assessment showed tumor infiltration in 88% of margin biopsies from IDH mutant tumors (30 of 34 biopsies) with 100% accuracy. Intra-operative tissue diagnosis was pursued in 66 unique tumor samples using DESI-MS lipidomic profiling, including samples of normal brain parenchyma, gliomas, meningiomas and pituitary adenomas, split into two microarray sets (36 and 40 samples). Using estimated principal components as input features, high accuracy (> 90%; ROC AUCs $\geq$ 0.89) was obtained for supervised tissue classification using simple machine learning algorithms. **Conclusions:** We present a novel system for intra-operative evaluation of tumor infiltration at the margin in gliomas and for intra-operative tissue diagnosis of brain cancer. Our method identified tumor infiltration beyond the surgical margins and serves as a foundation for future uses employing DESI-MS to allow for molecularly guided surgery in IDH-mut gliomas. Research Sponsor: U.S. National Institutes of Health.

2070

Poster Session

Investigation of leptomeningeal disease in high grade glioma and characterization of molecular alterations. *First Author: Madison L. Shoaf, Emory University, Atlanta, GA*

Background: Leptomeningeal disease (LMD) is a challenging complication of high grade glioma (HGG) and questions remain regarding risk factors, molecular associations, and optimal treatment. Here we report updated results on a larger cohort from our previously reported multicenter study (Shoaf 2022, Neuro-Oncology). **Methods:** Patients with molecularly-profiled HGG (Caris Life Sciences; Phoenix, AZ) with LMD at 3 institutions were included. NextGen Sequencing of DNA (592 gene or whole exome) and RNA (whole transcriptome) were tested. Medical records were reviewed for clinicopathologic characteristics and outcome. Kaplan-Meier estimates of survival were performed using Cox's proportional hazard model. Mann-Whitney U or Chi-square tests were applied for molecular comparison as appropriate and adjusted for multiple comparisons. **Results:** Seventy-two patients (female: 20, male: 52; median age: 54.5y) were identified, comprising 65 grade 4 tumors (glioblastoma [GBM]: 62; gliosarcoma: 2; H3K27M diffuse midline glioma: 1), 5 grade 3 tumors (astrocytoma: 4; pleomorphic xanthoastrocytoma: 1), and 1 astrocytoma NOS. LMD diagnosed at glioma diagnosis (n=23) vs. recurrence (n=44) was associated with longer post-LMD survival [pLMD-OS: 16.9m vs. 5.5m, p<0.0001] but similar overall survival [mOS: 16.9m vs. 20.9m; p=0.36]. Pathology-diagnosed LMD (n=15) vs. MRI-diagnosed LMD (n=54) was associated with longer post-LMD survival [pLMD-OS: 15.2m vs. 6.2m, p=0.0002] but similar overall survival [mOS: 16.9m vs. 20.9m; p=0.72]. Post-LMD survival [pLMD-OS: 8.7m vs. 6.8m, p=0.33] and overall survival [mOS: 21.1m vs. 20.9m, p=0.20] were similar for supratentorial (n=45) vs. infratentorial/spinal (n=10) locations, and post-LMD survival did not significantly differ for symptomatic (n=40) vs. asymptomatic (n=22) patients [pLMD-OS: 6.6m vs. 10.5m, p=0.13]. pTERT mutation (73%), MGMT methylation (38%), EGFR amplification (31%), and PTEN mutation (28%) were the most prevalent molecular alterations in this group. Comparison of grade 4 LMD tumors with an independent GBM cohort (n=5431) suggested a male predominance (73.4% vs. 58.5%, p=0.016) and a trend towards more frequent mutations in RB1 (25% vs. 9.2%, p=0.002) and MDM4 (12.7% vs. 4.3%, p=0.01) and amplification of WIF1 (6.1% vs. 0.3%, p=0.006), CHIC2 (17.0% vs. 5.2%, p=0.002), and LGR5 (5.9% vs. 0.4%, p=0.012). The expression of immune checkpoint-related genes was similar, although a trend towards immunologically "colder" tumors in the LMD cohort was observed. However, these effects were not significant after correcting for multiple comparisons. **Conclusions:** LMD is more common in male patients and may be associated with various genomic alterations and tumor microenvironment differences. Overall survival does not differ from patients without LMD, but these differences may provide clues to the pathogenesis and treatment resistance of GBM. Research Sponsor: None.

2072

Poster Session

Intraoperative glioma characterization using time-resolved fluorescence spectroscopy. *First Author: Simon Menaker, Cedars-Sinai Medical Center, Los Angeles, CA*

Background: Extent of surgical resection significantly improves progression-free and overall survival in glioma patients. Due to the infiltrative nature of gliomas, tumor margin detection is often difficult, and current intraoperative visualization methods are limited. Time-resolved fluorescence spectroscopy (TRFS) has the potential of differentiating glioma from normal brain tissue, thereby maximizing extent and safety of resection. **Methods:** Twenty-seven preoperative patients diagnosed with glioma met inclusion criteria for an IRB-approved study aimed to assess the accuracy of TRFS relative to tissue histopathology for differentiating glioma from normal cortex (NC), normal white matter (NWM), and white matter with edema (WME). A multi-channel TRFS system was developed for in vivo brain tissue and tumor characterization during glioma surgery. A custom-designed fiber optic probe was used to deliver ultrafast laser pulses to tissue regions of interest and collect fluorescence signals, with simultaneous registration to intraoperative neuronavigation. The fluorescence light was collected using a photomultiplier tube and digitized across six wavelength bands. Biopsies were taken at each measurement site for evaluation by a blinded neuropathologist to determine the accuracy of TRFS, which was calculated using parameters derived from the recorded fluorescence pulse and used to characterize tissue signatures. **Results:** During surgical resection of 27 patients, 162TRFS measurements were collected in vivo followed by biopsy of the same tissue. Samples from brain tumors (39 low grade gliomas (LGG, WHO grade I to III), 35 high grade gliomas (HGG, WHO grade IV)) were compared with 47 samples of normal brain tissue (NC and NWM). The time-resolved system was able to differentiate LGG from normal tissue with 97% sensitivity and 93% specificity (93% PPV and 98% NPV). When all tumor grades were tested, the sensitivity dropped to 91% (96% PPV and 86% NPV), which we believe reflects the heterogeneity of HGG. HGG alone showed a sensitivity of 83% and specificity of 93% (91% PPV and 88% NPV). Normal cortex had the fastest decays across all wavelength bands among different tissue types, WME had longer decays compared to other tissue types at all wavelengths, and HGG had a variable but predictably different fluorescence decay pattern. **Conclusions:** TRFS is an intraoperative tool that can distinguish glioma from normal brain tissue and has the potential to maximize safe surgical resection. Research Sponsor: Cedars-Sinai Medical Center.

2073

Poster Session

Detection of methylation-based prognostic signatures in liquid biopsy specimens from patients with meningiomas. *First Author: Grayson Herrgott, Henry Ford Health, Detroit, MI*

Background: Detection of distinct epigenetic biomarkers in circulating cell-free DNA (cfDNA) of liquid biopsy (LB) specimens (e.g. blood) fosters opportunity for prognostication of central nervous system (CNS) tumors and has not been thoroughly explored in patients with meningiomas. **Methods:** We profiled the cfDNA methylome (EPIC array) in serum from patients with meningiomas (MNG; n = 93) and harnessed internal and external meningioma tissue methylome data with reported follow up (n = 77). To predict recurrence risk (RR), we consolidated a tissue cohort with at least 5 years of follow up and divided them into confirmed recurrence (CR; either reported progressive disease in post-surgical imaging, or additional resections following initial surgery) and confirmed no-recurrence (CNR: no confirmed disease progression w/in at least 5-years of follow-up). Then through application of an iterative process consisting of multiple tissue- and serum-based supervised analyses, we identified risk-specific methylation markers with potential for serum application. which, when inputted into a random forest algorithm allowed for segregation of both tumor tissue and liquid biopsy specimens according to recurrence risk. We estimated immune cell composition using MethylCIBERSORT, where a reference methylome atlas of chosen immune cell types was utilized to deconvolute the MNG samples. **Results:** The resulting recurrence risk classifier demonstrated an appreciable predictive power in classifying samples as high or low recurrence risk across the tumor tissue cohort (ACC: 87.7%, CUI+: 86.4%). When compared to another classifier of rivaling purpose, our model demonstrated statistically significant agreement across primary meningioma samples ($\kappa = 0.269$, $p = 0.01$), and more accurately predicted samples to recur across expanded time windows (time to recurrence > 5 yrs). Across resulting liquid biopsy classifications, recurrence risk subgroups were analogous with reported risk factors, including WHO grade, extent of resection, and tumor location. Recurrence risk subgroups also demonstrated differential estimated immune cell contributions, with low-risk samples exhibiting a "hot" profile, or enrichment of B-Cells, CD56- and CD4 T-Cells, and natural killer cells. Notably, the estimated neutrophil to lymphocyte ratio, previously purported to be relevant to tumor prognosis, was appreciably higher for those meningioma samples with the highest recurrence risk. **Conclusions:** DNA methylation markers identified in the serum are suitable for the development of machine learning-based models which present high predictive power to prognosticate patients with meningioma and estimate a differential immune profile across recurrence risk groups. After validation in an external cohort, this noninvasive approach may improve the presurgical therapeutic management of patients with meningiomas. Research Sponsor: Hermelin Brain Tumor Center.

2075

Poster Session

3D volume growth rate evaluation in the EORTC-BTG-1320 clinical trial for recurrent WHO grade 2 and 3 meningiomas. *First Author: Emeline Tabouret, Aix-Marseille Univ, APHM, CNRS, INP, Inst Neurophysiopathol, CHU Timone, Service de Neurooncologie, Marseille, France*

Background: We previously reported that tumor 3D volume growth rate (3DVGR) classification could help in the assessment of drug activity in patients with meningioma (Graillon *et al.* 2021). This classification segregates meningioma response into three main classes and a total of five subclasses (class 1 = volume decrease $\geq 25\%$; 2A = tumor stabilization; 2B = 3DVGR severe slowdown; 3A and 3B = respective low and quick progression) based on the 3DVGR before and under treatment. The EORTC-BTG-1320 clinical trial was a randomized phase II trial evaluating the use of trabectedin for recurrent WHO 2 or 3 meningioma (Preusser *et al.* 2022). Objective: To evaluate the discriminative value of 3DVGR classification for response and clinical benefit prediction in the EORTC-BTG-1320 clinical trial. **Methods:** All patients with at least one available additional MRI before inclusion were included. 3D volume was evaluated on all consecutive MRI until progression. 3DVGR classification was applied on them as previously described. Clinical benefit was defined as neurological and/or functional status improvement and/or steroid decrease or discontinuation. **Results:** 17 patients were included in this post-hoc analysis with a median age of 58 years (range, 38-73). Treatments were trabectedin, bevacizumab, hydroxyurea or palliative care in 9, 3, 2 and 3 patients respectively. At first evaluation, 3DVGR classes were 1, 2A, 2B, 3A, 3B and not evaluable in 8%, 15%, 8%, 23%, 38% and 8%, respectively. Best 3DVGR classification was 1, 2A, 3A, 3B and not evaluable in 15%, 31%, 15%, 31% and 8%, respectively. 3DVGR did not differ by methylation subgroups and NF2 or CDKN2A alterations. All patients with progression-free survival longer than 6 months presented with best 3DVGR class 1 or 2. In contrast, all patients with PFS shorter than 6 months presented with best 3DVGR class 3 or not evaluable due to early progression. Median overall survival was 34.7 months for the entire cohort. 3DVGR classes 1 and 2 (combined) had a median overall survival of 34.7 months *versus* 7.2 months for class 3. Best objective response according to modified Macdonald response criteria were stable disease, progression or undetermined in 8, 6 and 3 patients respectively. Regarding the 8 stable patients, they were segregated into classes 1, 2, 3 or undetermined by the 3DVGR classification in 2, 4, 1 and 1 patients, respectively. Finally, all class 1 patients, 75% of class 2 patients and only 17% of class 3 patients presented with clinical benefit (neurological and/or functional status improvement and/or steroid decrease or discontinuation), respectively. **Conclusions:** Tumor 3DVGR classification may be helpful to discriminate early signal of treatment activity in an independent randomized phase II clinical trial. Clinical trial information: NCT02234050. Research Sponsor: PharmaMar, S.A.

2074

Poster Session

FOXC1 expression in meningiomas. *First Author: Michelle Wedemeyer, Nationwide Children's Hospital, Columbus, OH*

Background: Meningiomas account for nearly 1/3 of brain tumors and are characterized by a low mutational burden and dysregulation of DNA methylation. The promoter of FOXC1 is hypomethylated relative to dura in meningiomas of all grades and knockdown of FOXC1 in murine models causes craniofacial hypoplasia and absent frontal dura, suggesting a role as a meningeal identity gene. Here we perform a multi-omic analysis of FOXC1 expression in a large cohort of meningiomas. **Methods:** A total of 555 meningiomas (148 grade I, 255 grade II and 87 grade III) were analyzed with next-generation DNA sequencing (592 gene NextSeq panel; n=150 or Agilent WES whole exome sequencing, n=405) and whole mRNA (WTS, NovaSeq, 555) at Caris Life Sciences (Phoenix, AZ). Top quartile transcripts per million (TPM) for FOXC1 expression were considered high (FOXC1-H) and bottom quartile low (FOXC1-L). Immune cell infiltration was estimated using RNA deconvolution by QuantiSeq to calculate median cell fractions (MCF) or positive percentages (PP). Data were analyzed using X2/Fisher's-exact/Mann-Whitney U tests. A p-value < 0.05 after BH correction was considered significant. **Results:** Median FOXC1 expression was 33 TPM. Expression of FOXC1 transcript was higher in lower grade tumors (I: 34, II: 29, III: 27, $q < 0.05$). NF2 mutations were significantly more common in FOXC1-L than FOXC1-H tumors (45% vs. 68%, $q < 0.05$). Although a higher percentage of FOXC1-H meningiomas harbored TERT promoter mutations (2% vs. 9%, $p < 0.05$) and a higher percentage of FOXC1-L meningiomas harbored a TRAF7 mutation (19% vs. 5.5%, $p < 0.05$), these differences were not significant after correction for multiple comparisons. Programmed cell death ligand1 (PD-L1/CD274, 2.27 vs. 492) and MHC-I (HLA-A: 58 vs. 109, HLA-B: 59 vs. 74, and HLA-C: 61 vs. 101) transcripts were more highly expressed in FOXC1-H than FOXC1-L tumors. FOXC1-L tumors exhibited significantly more B cells (MCF: 5% vs. 4%), M1 Macrophages (MCF: 2% vs. 1%), CD8+ T cells (PP: 27% vs. 7%), and a higher interferon gamma transcript signature than FOXC1-H. Infiltrates of NK cells (MCF: 3.5% vs. 4.3%) and dendritic cells (MCF: 6% vs. 8%) were higher in FOXC1-H (all $q < 0.05$). **Conclusions:** The craniofacial patterning transcription factor FOXC1 was found to be widely expressed in a large cohort of meningiomas and its expression is inversely correlated with WHO tumor grade. Multi-omic analysis reveals a significant relationship between FOXC1 transcript levels and key markers of the immune environment including PD-L1 transcript expression. These data suggest that FOXC1 is a marker of meningiomas in addition to its role as a meningeal identity marker during development. Functional studies are warranted to determine whether FOXC1 is necessary for meningioma growth, whether FOXC1 plays a direct immunomodulatory role in meningiomas, and whether the lower FOXC1 expression levels in high grade tumors represent a more embryonic phenotype. Research Sponsor: None.

2076

Poster Session

The ketogenic diet plus standard of care for adults with recently diagnosed glioblastoma: Results from a phase 1 trial. *First Author: Lj Amaral, Cedars-Sinai, Los Angeles, CA*

Background: Facing limited treatment options, brain tumor patients are often highly motivated to use complementary therapies, including diet, to help themselves. There is now an abundance of preclinical evidence suggesting possible benefit with a ketogenic diet (KD) for brain tumor patients, but clinical evidence is still limited. Thus, we conducted a single-arm, phase 1 safety and feasibility trial of a KD among patients with recently diagnosed glioblastoma (GBM) during standard-of-care (SOC) treatment. **Methods:** Adults with GBM within 3 months of diagnosis followed a supervised 16-week diet intervention of a standard 3:1 KD (Fat(g):Carbohydrate+Protein(g)) plus SOC chemoradiation. Primary outcome was safety, evaluated by weekly assessments of weight and body mass index (BMI). Secondary outcomes included feasibility (pre-specified as > 50% of patients maintaining blood ketone levels > 0.3 mM over 50% of study days), progression-free survival (PFS), overall survival (OS), health-related quality-of-life (QOL), and cognitive function. Twice daily blood glucose and ketone levels, weight/BMI, physical activity, and sleep were assessed by remote monitoring. **Results:** Seventeen patients were evaluable: 53% women, median age 55, median Karnofsky Performance Status 85. All participants met the primary safety objective with no instances of excessive weight loss or related serious adverse events. Adherence to KD was high: all 17 patients maintained nutritional ketosis (≥ 0.3 mM/dL) > 50% of study days, where 14 patients maintained nutritional ketosis > 85% of study days. Median time to ketosis from diet initiation was 3 days. Diet-related AEs were mild and manageable; no patients came off study due to inability to tolerate KD. Median progression-free survival (PFS) and overall survival (OS) were 12.5 months and 28.6 months from KD initiation respectively. QOL, symptom control, and cognitive function remained stable or improved, although these did not reach statistical significance. **Conclusions:** This phase 1 trial demonstrates that KD is safe and feasible for GBM patients receiving SOC, may improve outcomes, and provides a foundation for future randomized trials to assess efficacy. Clinical trial information: NCT03451799. Research Sponsor: Cedars Sinai.

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Poster Session

Osmotic blood-brain barrier disruption with mannitol followed by methotrexate, rituximab, and carboplatin in treating patients with newly diagnosed primary central nervous system lymphoma. *First Author: Prakash Ambady, Providence Brain and Spine Institute, Portland, OR*

Background: Osmotic blood-brain barrier disruption (BBBD) uses intra-arterial (IA) mannitol to open the neuro-vascular unit to enhance delivery of therapeutic agents to the brain. We report the results of a multi-institutional, single arm, phase 2 study evaluating the efficacy and safety of BBBD-enhanced chemotherapy in combination with immunotherapy in patients with newly diagnosed primary central nervous system lymphoma (PCNSL). PCNSL is a rare non-Hodgkin's lymphoma that is limited to the brain, cerebrospinal fluid, spinal cord and/or the vitreoretinal compartment. **Methods:** Non-immunocompromised subjects with newly diagnosed PCNSL received rituximab IV over 5 hours on day 1. On days 2 and 3, under general anesthesia in the angiography suite, subjects received IA mannitol immediately followed by IA methotrexate over 10 minutes, and then IA carboplatin over 10 minutes. Subjects received sodium thiosulfate IV for hearing protection at 4 and 8 hours after each carboplatin dose. Treatment was repeated every month for up to 12 courses in the absence of disease progression or unacceptable toxicity. Per institutional recommendations, further accrual was terminated during the COVID-19 pandemic. Contrast MRI was used for response assessment based on IPCG criteria. **Results:** Twenty subjects (10 F, 10 M, Median KPS = 80; range 40-100) received a median of 8 cycles at 3 US institutions. Sixteen radiographic complete responses (80%) and 1 partial response were documented, 3 subjects were not evaluable (2 withdrew consent and 1 unrelated death). Median PFS was 55.2 months (95% CI :10.3 – not reached) and Median Overall survival was 82.8 months (95% CI :19.8-145.8). Fourteen patients (82% of evaluable patients) had grade 3 or 4 adverse events (AE). Grade 4 AEs (n = 14 in n = 7 patients) included neurologic toxicities (ischemia, cervical cord inflammation, neuropathy) and blood/bone marrow toxicities (lymphopenia, neutropenia, granulocytopenia). There were no treatment-related deaths. **Conclusions:** We demonstrate the feasibility of performing BBBD in a multi-institutional setting with excellent PFS and OS in patients without whole brain radiation or autologous transplant. Our CR rates, PFS and OS are comparable to other IV high-dose MTX regimens, with acceptable toxicity profile and no documented treatment-related deaths. Clinical trial information: NCT00293475. Research Sponsor: U.S. National Institutes of Health; Jonathan D. Lewis Foundation and the Walter S. and Lucienne Driskill Foundation.

2079

Poster Session

MTHFR polymorphisms and neurotoxicity and overall survival after methotrexate-based therapy in primary CNS lymphoma. *First Author: Philipp Karschnia, Department of Neurosurgery, Ludwig-Maximilians-University, Munich, Germany*

Background: The folate-antagonist methotrexate (HD-MTX) is an integral to induction chemotherapy for primary CNS lymphoma (PCNSL); however, it can be associated with toxicities, including injury to cerebral white matter known as leukoencephalopathy. Methylene tetrahydrofolate Reductase (MTHFR) is involved in intracellular folate metabolism, and MTHFR polymorphisms may affect CNS-specific side effects of HD-MTX. Here, we evaluated the possible association of MTHFR polymorphisms and HD-MTX related CNS toxicity. **Methods:** We retrospectively searched our institutional database at the Massachusetts General Hospital for newly diagnosed PCNSL patients treated with HD-MTX (without use of radiotherapy or intrathecal chemotherapy). MTHFR polymorphisms were correlated with evolution of leukoencephalopathy over a time period of five years and patient outcomes. ROC curves were generated to estimate the diagnostic ability of specific MTHFR genotypes. Survival was calculated using Kaplan-Meier survival analysis and log-rank test. The significance level was set at $p \leq 0.05$. **Results:** Among 68 PCNSL patients, MTHFR polymorphisms were found in 60 individuals (88.2%; 677C>T: 29 patients, 1298A>C: 18 patients, combined 677C>T & 1298A>C: 13 patients). Neither MTX clearance nor disease response to HD-MTX was affected by specific genotypes, and complete response was achieved in 72.1% of patients by induction with HD-MTX-based therapy. However, the 1298A>C genotype was associated with increased frequency and severity of leukoencephalopathy over time ($\chi^2 = 7.43$). Such genotype predicted treatment-induced leukoencephalopathy with a sensitivity of 71.0% and a specificity of 62.2% (ROC: $p = 0.019$). While progression-free survival did not differ in genotype-based subgroups, overall survival was significantly lower when the 1298A>C genotype was present. **Conclusions:** The MTHFR 1298A>C genotype may serve to identify PCNSL patients at elevated risk for HD-MTX-induced leukoencephalopathy. This was associated with reduced overall survival, potentially due to decreased functional status in patients less suitable for aggressive subsequent therapies. Research Sponsor: None.

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Poster Session

Belzutifan treatment of Von Hippel-Lindau (VHL) related central nervous system (CNS) hemangioblastomas (HBs): A single institution experience. *First Author: Othon Iliopoulos, Massachusetts General Hospital Cancer Center and Harvard Medical School, Boston, MA*

Background: Patients with inactivating germline mutations in the VHL gene develop CNS (brain and/or spine) HBs and/or renal cancers, pheochromocytomas and pancreatic neuroendocrine tumors. The oral HIF2a inhibitor belzutifan has been approved by FDA for the treatment of VHL-related HBs. We present here data on a cohort of VHL patients with CNS HBs treated with belzutifan in a single institution. **Methods:** Adult VHL patients, with radiologically documented CNS (brain and/or spine) HBs that displayed documented growth within the last 6 months prior to therapy, were treated with an initial dose of 120 mg belzutifan orally per day. Target lesions included HBs > 0.4cm long in one maximal cross-sectional diameter. Lesions were imaged by MRI at 1.5, 3, 6 months after initiation of treatment and at 6-month intervals thereafter. Solid enhancing lesions, associated cysts and peritumoral edema were recorded and quantified. Tumor sizes were evaluated by RECIST 1.1 criteria and volumetric analysis. All patients were evaluated and treated in the Hemangioblastoma Center and the VHL Clinic of the Massachusetts General Hospital Cancer Center. **Results:** At the time of analysis, 9 females and ten 10 male VHL patients (n=19) have been treated. Median age at treatment initiation was 36 yo (range 19-59). Median follow up is 12 months (range 1-19.5 months). Two patients were not yet evaluable for response. Of 17 evaluable patients, 8 had a PR (ORR 47%; 95% CI, 34-60), 8 had SD and 1 patient had progression (PD, 5.8%). Two patients had dose reduction to 80 mg/d because of anemia. No patient had grade 3 or greater toxicity and no patient experienced a CNS related toxicity during treatment. Volumetric analysis of solid and cystic components of the lesions, VHL germline mutations and other correlates of response to belzutifan will be presented. **Conclusions:** Real world data collected at a single institution confirm the high response rate of both solid and cystic components of CNS HBs to the FDA approved HIF2a inhibitor, belzutifan. Belzutifan was well tolerated. Further prospective controlled studies addressing the optimal dose, schedule and duration of treatment of HBs with belzutifan are required. Research Sponsor: None.

TPS2080

Poster Session

The clinical relevance of margins in frameless stereotactic radiosurgery for intact brain metastases: A randomized trial of 0 vs 2 mm margins. *First Author: Aditya Juloori, Department of Radiation and Cellular Oncology, University of Chicago, Chicago, IL*

Background: Stereotactic radiosurgery (SRS) is a commonly utilized treatment strategy for brain metastases which offers a relatively low rate of morbidity and high rate of local control. SRS delivers an ablative dose of radiation in a single session to a limited target volume while minimizing dose to surrounding normal tissue. Image-guided linear accelerator (LINAC)-based frameless SRS has enabled effective, safe delivery of high dose radiation without the discomfort and logistical complications associated with use of a rigid frame. Localization errors during frameless SRS vary depending on the specific LINAC configuration and immobilization technique. The clinical relevance of potential inaccuracies in localization with frameless SRS remains controversial. When employing frameless systems, many centers will account for set-up uncertainties by adding a circumferential margin of 1-3 mm around the GTV to create a planning target volume (PTV). This PTV expansion ensures adequate tumor coverage if target motion occurs, but exposes more normal brain tissue to radiation and may increase the risk of adverse events, chiefly radionecrosis. There is limited literature available to guide radiation oncologists on the appropriate choice of margin size, if any, for frameless SRS. There are no randomized data evaluating the safety and efficacy of omitting the margin entirely. Given the paucity of data examining margin extent and the potentially significant consequences for treatment efficacy and morbidity, we propose a phase II randomized prospective clinical trial evaluating 0 vs 2 mm marginal GTV to PTV expansions for treating patients with intact brain metastases with frameless SRS. **Methods:** Eligible patients will have brain metastases from solid tumors with ECOG performance status of 0-2 and life expectancy of >3 months. Patients must have 1 - 5 newly diagnosed well-circumscribed, measurable intraparenchymal brain metastases with maximum tumor diameter ≤ 3.0 cm. At least one lesion must be ≥ 0.5 cm in maximum diameter to be considered measurable. SRS will be delivered in a single fraction to either 20 Gy or 18 Gy dependent on tumor size. Importantly, PTV margin randomization is blinded and occurs after delineation of tumor volume by radiation oncologist to not bias contouring based on knowledge of margin randomization. This is two-armed multi-center phase II randomized controlled trial. The trial is powered to demonstrate non-inferiority of the experimental arm with regard to the primary endpoint of local PFS at 6 months and the superiority of the experimental arm with regard to the secondary endpoint of radionecrosis or pseudoprogression. We expect the total study duration, from the start of screening for the first participant until the end of follow-up for the last one, to be approximately six years. We plan to accrue 166 patients to this trial at all sites. Clinical trial information: NCT02747303. Research Sponsor: None.

TPS2081

Poster Session

A phase 0/1a study of BI 907828 concentrations in brain tissue and a nonrandomized, open-label, dose escalation study of BI 907828 in combination with radiotherapy in patients with newly diagnosed glioblastoma (GBM). *First Author: Jann Nagina Sarkaria, Mayo Clinic, Rochester, MN*

Background: Murine double minute 2 (MDM2) directly regulates the stability of the tumor suppressor p53, and dysregulation of this pathway can critically disrupt cellular response to genomic stress and lead to cell death. BI 907828 is a highly potent inhibitor of the MDM2-p53 interface that triggers accumulation of p53 and subsequent apoptosis in multiple GBM patient-derived xenografts (PDXs) with wild-type p53. Moreover, the combination of BI 907828 and radiotherapy provides significant survival extension in multiple orthotopic GBM PDXs. **Methods:** An integrated Phase 0/1 trial design is being used to evaluate the potential for BI 907828 to achieve a therapeutic concentration in brain tumor tissue and to test the safety of the combination with radiation. The co-primary endpoints for the Phase 0 study are i) measured total concentration of BI 907828 and ii) calculated unbound concentration of BI 907828 in contrast and non-contrast enhancing regions of tumor. Key inclusion criteria for the Phase 0 study are patients at least 18 years of age, ECOG performance status of 0 or 1, histologic or radiologic new diagnosis of GBM, and planned surgical resection. The first approximately 6 patients enrolled in the Phase 0 will be treated at the starting dose of 30 mg, and the future patients enrolled will be dosed at higher levels (45 mg or 60 mg) provided there are no safety concerns. If dose-limiting toxicities (DLTs) are encountered, then a Bayesian Logistic Regression Model (BLRM) with overdose control will be used to guide the dose level decisions for the additional patients. Multiple, image-registered tumor samples and intra-operative plasma samples will be analyzed for BI 907828 by LC-MS/MS. Intra-tumoral variation in BI 907828 will be correlated with pharmacodynamic effects of MDM2 inhibition (elevation of p53, p21, MDM2, GDF15, PUMA). Those patients completing the Phase 0 study and who meet additional eligibility criteria can enroll on the Phase 1a portion of the study. The pathologic inclusion criteria are TP53 wild-type, IDH1/2 wild-type, MGMT unmethylated GBM. Co-primary endpoints for the Phase 1a trial are i) occurrence of DLTs during and within 21 days after completion of radiation therapy, and ii) occurrence of adverse events throughout the treatment period. Tolerability of inter-patient dose-escalation of BI 907828 (30, 45, 60 mg) combined with radiation therapy (60 Gy in 30 fractions) will be evaluated with dose-escalation guided by a two-parameter BLRM with overdose control. Patients will remain on BI 907828 monotherapy following completion of radiotherapy until progression. To date, two patients have enrolled on the Phase 0 study, and one patient went on to enroll on the Phase 1a portion of the study. Clinical trial information: NCT05376800. Research Sponsor: Boehringer Ingelheim.

TPS2083

Poster Session

Phase 3 TRIDENT study (EF-32): Tumor treating fields (TTFields; 200 kHz) concomitant with chemoradiation, and maintenance TTFields therapy/temozolomide in newly diagnosed glioblastoma. *First Author: Wenying Shi, Department of Radiation Oncology, Thomas Jefferson University, Philadelphia, PA*

Background: Tumor Treating Fields (TTFields) therapy, a noninvasive and locoregional antimitotic cancer treatment modality, is approved for newly diagnosed (nd), recurrent glioblastoma (r) GBM and mesothelioma. In patients with ndGBM, progression-free survival (PFS) and overall survival (OS) were significantly improved with TTFields therapy/temozolomide (TMZ) vs TMZ alone in the pivotal EF-14 study, leading to FDA approval in ndGBM. To avoid potential impedance of radiotherapy (RT), TTFields therapy was administered following RT/TMZ; however, preclinical studies have demonstrated that TTFields therapy enhances the therapeutic effect of RT. **Methods:** TRIDENT (EF-32; NCT04471844), a phase 3, global, randomized study, will evaluate TTFields therapy concomitant with RT/TMZ in patients ≥ 18 years of age (≥ 22 years in the US) with histologically-confirmed ndGBM, ≥ 3 months life expectancy, and ≥ 70 Karnofsky performance status. Patients will be stratified on the basis of MGMT promoter methylation status and extent of resections. Approximately 950 patients will be assigned 1:1 to continuous TTFields therapy (200 KHz, ≥ 18 h/day) concomitant with RT/TMZ (experimental arm) or RT/TMZ alone (control arm). Patients in the experimental arm will receive TTFields therapy continuously from the first day of chemoradiation. Patients in the control group will begin TTFields at the same time as maintenance TMZ, approximately one month after completion of chemoradiation. TTFields therapy will continue in both treatment groups until second disease progression (PFS2) or 24 months (if clinically able). The primary endpoint is median OS, and secondary endpoints include PFS, 1- and 2-year survival rates, objective response rate, PFS2, 6- and 12-month PFS rates, safety, and quality of life (EORTC QoL questionnaires). The ability of TTFields therapy to extend OS in a dose-dependent manner is an exploratory endpoint. The sample size is powered for a hazard ratio of < 0.8 with a 5% type I error. The hypothesis that first-line TTFields therapy/RT/TMZ can significantly improve OS vs RT/TMZ will be tested using a stratified log-rank test. The study is expected to enroll patients at 150 sites, with enrollment currently open in 9 countries. Clinical trial information: NCT04471844. Research Sponsor: Novocure.

TPS2082

Poster Session

A first-in-human pharmacodynamic evaluation of dual polyamine depletion for patients with high-grade gliomas. *First Author: Cecile Riviere-Cazaux, Mayo Clinic, Rochester, MN*

Background: No drug has improved survival for patients with high-grade gliomas (HGGs) since temozolomide in 2005. Relatively little is known about the live response of *in situ* gliomas to therapeutic intervention. Phase 0 studies that leverage access to the live human glioma *in situ*, including via microdialysis to sample the live glioma microenvironment, provide an attractive and feasible solution to this problem. We performed intraoperative microdialysis to evaluate the extracellular metabolome of divergent regions in 15 HGG resections. Our data revealed a conserved metabolic signature of HGGs and a novel glioma-associated metabolite, guanidinoacetate (GAA). Pathways enriched in this tumor signature included methionine and polyamine metabolism. Although GAA is typically converted to creatine, we hypothesize that the high flux of ornithine through ornithine decarboxylase (ODC) results in excess GAA accumulation. As such, in a Phase 0 trial, we will evaluate *in situ* glioma responses to polyamine depletion via ODC inhibition (Difluoromethylornithine, DFMO), with or without blockade of polyamine uptake (AMXT 1501), to identify candidate extracellular biomarkers of target engagement and cytotoxicity. **Methods:** Patients will be recruited who are undergoing a clinically indicated subtotal resection for a known or suspected high-grade glioma (NCT05717153). At the end of the surgery, two microdialysis catheters will be implanted for post-operative microdialysis, one in residual tumor and one in brain adjacent to tumor for an internal control. Beginning on post-operative day (POD) 1, patients will be randomized to one of the following three groups, including administration of vehicle, DFMO (500 mg, PO, BID) and AMXT 1501 (600 mg, PO, BID): 1) DFMO + AMXT 1501 (POD1-5); 2) Vehicle (POD1-POD2), followed by DFMO + AMXT 1501 (POD3-POD5); 3) DFMO alone (POD1-POD2), followed by DFMO + AMXT 1501 (POD3-POD5). Throughout this time, extracellular metabolite levels of polyamines, guanidinoacetate, and glutamate will be quantified from microdialysate collected every two hours from intraoperatively implanted 100 kDa microdialysis catheters. The primary outcome of this study is to determine how polyamine depletion impacts extracellular intratumoral guanidinoacetate abundance. The secondary outcomes of this study are to (1) determine the impact of polyamine depletion on polyamine abundance and the global extracellular metabolome within live human gliomas, *in situ*, and (2) assess the feasibility of longitudinal microdialysis for pharmacodynamic analysis within live human gliomas *in situ* in the post-operative setting. Clinical trial information: NCT05717153. Research Sponsor: U.S. National Institutes of Health.

TPS2084

Poster Session

Low-intensity focused ultrasound with systemic microbubble oscillators for blood-brain barrier disruption for liquid biopsy in glioblastoma (LIBERATE). *First Author: Manmeet Singh Ahluwalia, Miami Cancer Institute, Baptist Health South Florida, Miami, FL*

Background: Liquid biopsy in glioblastoma (GBM) is hindered by a lack of requisite circulating-free DNA (cfDNA) levels in blood due to the blood-brain barrier (BBB). This results in challenges to the identification of blood-based biomarkers and the development of novel biomarker-driven systemic therapies. Real-time image-guided low intensity focused ultrasound (LIFU) combined with IV microbubble oscillators (DEFINITY), non-invasively causes BBB disruption (BBBD). This clinical trial aims to evaluate the utility of LIFU for increasing cfDNA in blood for liquid biopsy in GBM. **Methods:** LIBERATE is a prospective, multi-center, self-controlled, ongoing, pivotal trial evaluating safety and technical efficacy of LIFU for BBBD to increase cfDNA in blood for GBM. Patients aged > 18 -80 years with suspected GBM planned for tumor biopsy or resection at eleven centers in North America are being included. Patients with multifocal tumors or tumors arising from deep midline, thalamus, cerebellum, or brainstem are excluded. Patients are administered IV oscillating microbubbles for enhancing sonication, after which MR-guided BBBD using a 220 kHz LIFU device is performed with real-time acoustic feedback for effective cavitation. Before and after procedure, phlebotomies and MRI brain are performed to evaluate outcomes. The primary study endpoint is defined, per subject, as the ratio between their cfDNA level in blood 1-hour post-LIFU compared to cfDNA level in blood pre-procedure. The primary study hypothesis is that BBBD with LIFU leads to ≥ 2 -fold increase in cfDNA in blood. The secondary hypothesis is that there exists $\geq 75\%$ agreement between biomarker pattern in cfDNA sample from 1-hour post-LIFU sample and biomarker pattern in tumor tissue obtained later. The trial has been powered to evaluate both primary and secondary hypotheses. Based on an assumed true agreement rate of 91% and a one-sided alpha of 0.025, an exact test for binomial proportions provides a sample of $N=50$ with 84% power for the secondary hypothesis. Exploratory endpoints include (1) sensitivity of detection of known somatic mutations in cfDNA from blood samples collected before and after LIFU, (2) estimation of cfDNA levels post-LIFU in samples collected at 30 minutes, 1 hour, 2 hour, and 3 hour to determine time of greatest yield, (3) correlation of MRI parameters related to grading of BBBD and biomarkers positive in cfDNA from post-LIFU blood samples. Patient enrollment commenced in 2022 and 7 patients have been recruited by 02/13/2023. Clinical trial information: NCT05383872. Research Sponsor: Insightec.

TPS2085

Poster Session

Efficacy and safety study of neoadjuvant efineptakin alfa (NT-17) and pembrolizumab in recurrent glioblastoma. *First Author: Mason Webb, Mayo Clinic, Rochester, MN*

Background: Glioblastoma (GBM) is the most common and aggressive form of brain tumor in adults. Despite maximal surgical resection, irradiation, and chemotherapy, median overall survival (OS) remains at only 30 weeks for recurrent GBM (rGBM) patients, emphasizing the need for novel treatments. GBM tumors are immunologically 'cold,' in that they have an immune-suppressive microenvironment with a low number of tumor-infiltrating lymphocytes (TIL). Interleukin 7 (IL-7) plays a key role in T cell development and survival. The physiological level of IL-7 increases to stimulate T cell expansion in lymphopenic condition. Previous studies have shown that lymphopenic GBM patients have shorter survival. However, their IL-7 levels are unexpectedly low. Efineptakin alfa (NT-17), a long-acting IL-7, has been shown to increase effector CD8 T cells and reduce suppressor T-regulatory cells in murine GBM models, with subsequently improved OS. Further, we recently completed a Phase I study which showed that NT-17 is safe, well-tolerated, and increased absolute lymphocyte counts (ALC) in newly diagnosed GBM patients. Phase II dosing was determined through this Phase I study reaching maximum tolerated dose. Thus, we hypothesized that NT-17 may reverse GBM-associated immune suppression and potentiate the effect of an immune checkpoint inhibitor, leading to an increase in TILs and improved survival. Our preliminary data suggests that combining NT-17 with pembrolizumab, an anti-PD-1 antibody, improves survival in murine glioma models. The purpose of this study is to evaluate the safety and efficacy of combining NT-17 and pembrolizumab in rGBM patients. **Methods:** This is an open-label single arm one-stage Phase II study of NT-17 and pembrolizumab as neoadjuvant and adjuvant therapy with surgery for adult patients with rGBM. We plan to enroll 30 evaluable patients, including a 6-patient safety run-in. Key eligibility criteria include candidates willing to undergo clinically indicated resection or biopsy, age ≥ 18 years, Karnofsky performance status ≥ 70 , and dexamethasone dose > 2 mg/day ≤ 2 days prior to registration. The primary endpoint is a 9-month OS rate. Secondary endpoints include progression-free survival, objective response rate, changes in ALC, and adverse events profile. The correlative endpoints include studies to assess the anti-glioma immune response, changes in T cell subsets, T cell effector function, cytokine analysis, and immunohistochemical analysis of GBM tissue. Longitudinal cerebrospinal fluid proteomics is optional. This study opened on 1/20/2023. Two of the planned 30 patients had been enrolled by submission on 2/14/2023. Clinical trial information: NCT05465954. Research Sponsor: Supported in part by a research grant from Investigator-Initiated Studies Program of Merck Sharp & Dohme LLC.; The Ivy Foundation; Mayo Clinic Comprehensive Cancer Center; Humor to Fight the Tumor.

TPS2087

Poster Session

Phase II trial of combination pembrolizumab, olaparib, and temozolomide for patients with recurrent glioma. *First Author: Lauren Schaff, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Diffuse gliomas are primary brain tumors characterized by substantial morbidity and mortality. Standard treatment includes maximal safe surgical resection followed by combination radiation and chemotherapy. Despite aggressive treatment, diffuse gliomas inevitably recur. Alkylating agents, and in particular temozolomide, play an important role in the treatment of gliomas, resulting in single-strand DNA breakages which require PARP activity for detection and repair. Gliomas with mutations in *isocitrate dehydrogenase (IDH) 1 or 2* have an accumulation of 2-hydroxyglutarate (2HG) which results in a *BRCA*-like state of homologous recombination deficiency (HRD). When PARP is inhibited in the setting of HRD, single-strand DNA damage progresses to double-strand breaks resulting in synthetic lethality. PARP inhibition has also been shown to increase mutational burden and neoantigen expression ("immune-priming") and increases tumor-infiltrating lymphocytes and expression of PD-L1. Here, we present an ongoing clinical trial combining the checkpoint inhibitor pembrolizumab, the PARP inhibitor olaparib, and temozolomide for treatment of recurrent gliomas with HRD. **Methods:** This is an open-label, non-randomized phase II trial of combination pembrolizumab, olaparib, and temozolomide for patients with recurrent glioma. The main study cohort (A) will consist of 52 patients with recurrent enhancing grade 2 or 3 IDH-mutant gliomas. An exploratory cohort (B) will consist of 5 patients with recurrent IDH-wildtype gliomas and mutations associated HRD. Study intervention is administered in 21-day cycles and includes pembrolizumab (200mg IV q3 weeks day 1), olaparib (200mg bid orally days 8-14) and temozolomide (50mg/m² orally days 8-14). The primary outcome is overall response rate (ORR) in cohort A. Secondary objectives include safety and toxicity of triplet therapy, overall and progression-free survival, and best radiographic response. Exploratory objectives will describe outcomes in the IDH-wildtype cohort and associate response to tumor markers obtained through archival tissue and cell free DNA of cerebrospinal fluid. The trial includes a 6-patient safety lead-in to assess tolerability of triplet therapy. Cohort A patients must have grade 2 or 3 IDH-mutant glioma without known CDKN2A/B loss. Patients in Cohort B must have IDH-wildtype glioma with an alternate deleterious mutation involved in homologous recombination. Additional inclusion criteria include age ≥ 18 , ECOG 0-1, and glioma recurrent after prior therapy with measurable disease by RANO. Patients must be on a stable dose of corticosteroids not to exceed 2mg/day. There are no restrictions regarding number of recurrences or prior therapies if an appropriate washout has been completed. To date, seven of 57 patients have enrolled. The safety-lead in was completed without dose-limiting toxicities. Clinical trial information: NCT05188508. Research Sponsor: MSKCC; Merck.

TPS2086

Poster Session

Phase 1b multicenter study to evaluate CHM 1101 in patients with recurrent or progressive glioblastoma. *First Author: Jason Blair Litten, Chimeric Therapeutics, Carlton, Australia*

Background: Glioblastoma multiforme (GBM) is the most common and most aggressive primary brain tumor. More than 300,000 new cases are diagnosed globally with over 250,000 deaths each year (Sung H, et al. *CA Cancer J Clin.* 2021). Patients with recurrent GBM have a poor prognosis, with limited treatment options and a median survival of less than 1 year (Gallego. *Curr Oncol.* 2015). While prior attempts to treat GBM with chimeric antigen receptor (CAR) T-cells have been limited by tumor heterogeneity, chlorotoxin (CLTX)-directed CAR T-cells in mice demonstrated broad anti-tumor activity and prolonged survival with no off-tumor toxicity or antigen escape (Wang, et al. *Sci Transl Med*, 2020). CLTX, a 36-amino acid peptide identified in scorpion venom, selectively binds to malignant glioma cells through matrix metalloproteinase-2 (MMP2) and clinical administration of CLTX-based biologics has been well tolerated in patients (Mamelak, et al. *J Clin Oncol*, 2005, Patil, et al. *Neurosurgery*, 2019). CHM 1101 is the first CAR T to utilize CLTX as its tumor targeting domain for autologous CAR T-cell therapy. A single-center first-in-human phase 1 study of CHM 1101 in patients with recurrent GBM is ongoing. **Methods:** Clinical Trial NCT05627323 is a phase 1b, multi-center study of CHM 1101 in adult subjects with MMP2+ recurrent or progressive GBM after standard therapy. After leukapheresis and tumor resection, pts will receive CHM 1101 at Dose Level 1 (240×10^6 CAR T cells) or Dose Level 2 (440×10^6 CAR T-cells), divided across 3 once-weekly intracranial (intracavitary and intraventricular) administrations; after disease assessment at 28 days, additional doses of CHM 1101 can be administered on a weekly schedule. Eligible subjects have a prior histologically confirmed diagnosis of a grade 4 GBM, a grade 2 or 3 malignant glioma with radiographic progression consistent with a grade 4 GBM (IDH wild type), grade 4 diffuse astrocytoma (IDH mutant), or a unifocal relapse of GBM. MMP2+ tumor expression is confirmed by IHC ($\geq 20\%$ moderate/high MMP2 score [2+ or 3+]). The primary endpoint is safety; key secondary endpoints include feasibility, progression-free survival, overall survival, response rate (RANO criteria), and cellular kinetics. Recruitment is ongoing. Clinical trial information: NCT05627323. Research Sponsor: Chimeric Therapeutics.

2501

Oral Abstract Session

Initial results from the phase 2A trial of visugromab (CTL-002) + nivolumab in advanced/metastatic anti-PD1-L1 relapsed/refractory solid tumors (The GDFATHER-TRIAL). *First Author: Ignacio Melero Bermejo, Laboratory of Immunology, Clínica Universitaria de Navarra, Pamplona, Spain*

Background: Increasing evidence has emerged that Growth and Differentiation Factor 15 (GDF-15) plays a critical role in tumoral immunosuppression. Apart from blocking immune-cell entry into the tumor microenvironment, GDF-15 also has a major impact on the formation of the immune synapse. Many tumors overexpress GDF-15 and have hijacked this mechanism to block immunotherapy success. Here we report initial results of the phase 2a part of the GDF-15 neutralizing antibody visugromab (CTL-002) in combination with nivolumab. **Methods:** At cut-off date (06-Feb-2023), a total of 79 pts with advanced/metastatic solid tumors have been enrolled and were treated with visugromab 10 mg/kg Q2W in combination with nivolumab 240 mg Q2W in the phase 2a expansion part of the CTL-002-001 phase 1/2 trial (NCT04725474). The primary endpoint of the phase 2a expansion is the Objective Response Rate (ORR) according to RECIST v1.1. Tumor assessments were performed every 8 weeks and patients had to be relapsed/refractory to a minimum of 12 weeks continuous prior anti-PD1/-PD-L1-containing therapy, with relapse or progression after initial response to have occurred on continued anti-PD1/PD-L1 therapy. Phase 2a contained several indication-specific expansion cohorts (e.g. NSCLC, Bladder Cancer, HCC, Melanoma), following a Simon 2-stage design, and two cohorts were already expanded to stage 2 in light of initial responses observed. An additional expansion cohort is a pan-tumor basket cohort with sequential tumor biopsies for biomarker analyses. A key component of this multi-arm trial is an extensive translational research program to identify response-predictive tumor and immunologic marker and pattern. **Results:** Across several expansion cohorts, durable tumor regressions were observed, including several partial responses (PR) and one complete response (CR) in heavily pretreated patients with a median of 3 prior lines of systemic therapy for advanced/metastatic cancer, including at least one prior line of anti-PD1/-PD-L1 therapy and being relapsed/refractory to it. In NSCLC, so far 13 pts underwent at least one tumor assessment. Of these, two experienced a PR (one confirmed), three additional tumor shrinkage > 5% (TS) and one longer-term SD (LT-SD) were seen. In bladder cancer, 7 patients underwent at least one tumor assessment with 1 confirmed CR, 1 TS and 1 LT-SD. The treatment was overall well tolerated. **Conclusions:** These initial phase 2a results demonstrate promising clinical activity for the combination of visugromab and nivolumab in heavily pretreated anti-PD1/-PD-L1 refractory/relapsed solid tumor patients across various indications, including induction of confirmed partial and complete responses. Extensive biomarker evaluations are ongoing to further evaluate potential response-predictive markers identified during phase 1 development. Clinical trial information: NCT04725474. Research Sponsor: Catalm GmbH.

2503

Oral Abstract Session

Tumor mutational burden (TMB) measurement from an FDA-approved assay and real-world overall survival (rWOS) on single-agent immune checkpoint inhibitors (ICI) in over 8,000 patients across 24 cancer types. *First Author: David R. Gandara, Division of Hematology/Oncology, Department of Medicine, UC Davis Comprehensive Cancer Center, Sacramento, CA*

Background: There is controversy around the applicability of TMB across cancer types and reliability between assays from different manufacturers. The KEYNOTE 158 trial supported FDA approval of the Foundation Medicine test (FoundationOne CDx) at TMB ≥ 10 mut/Mb as a solid tumor companion diagnostic (CDx) for single-agent pembrolizumab in 2nd+ line. Using a large real-world dataset with validated rWOS endpoint data, we evaluated the clinical validity of the TMB measurement by the FDA approved test in over 8,000 patients across 24 cancer types who received single agent ICI. **Methods:** Following a prespecified analysis plan, this study used the nationwide (US-based) de-identified Flatiron Health-Foundation Medicine clinico-genomic database (FH-FMI CGDB), with data originating from approximately 280 US cancer clinics (~800 sites of care). The overall cohort included patients from 24 cancer types of interest with adv/metastatic disease treated with single-agent anti-PD(L)1 therapy in the FH network between 1/1/2011 - 9/30/2022. This study used the TMB algorithm from the FDA-approved test supporting solid tumor CDx and composite mortality variable validated against the national death index. Relative hazards of death by TMB interval were assessed using Cox PH models adjusted for ECOG PS, prior treatment, sex, age, opioid rx pre-therapy, genetic ancestry, and socioeconomic assessment. Multi-solid tumor cohort Cox models were additionally adjusted for MSI status, with baseline hazards stratified by cancer type. **Results:** 8,440 patients from 24 cancer types met inclusion criteria for the overall cohort. Adjusting for aforementioned factors, the hazards of death (HR, (95% CI)) across the entire cohort, relative to TMB < 5, was 0.95 (0.89 - 1.02) for TMB 5-10, 0.79 (0.73 - 0.85) for TMB 10-20, and 0.52 (0.47 - 0.58) for TMB 20+. Adjusted Cox models comparing TMB ≥ 10 vs. TMB < 10 were pre-specified for cancer types with at least 15 death events in each group: breast 0.51 (0.35 - 0.76), colorectal 0.37 (0.27 - 0.49), cancers of unknown primary 0.52 (0.30 - 0.90), endometrial 0.38 (0.26 - 0.55), gastric 0.46 (0.34 - 0.62), head & neck 0.49 (0.33 - 0.73), melanoma 0.55 (0.43 - 0.71), non-small cell lung 0.76 (0.71 - 0.83), small cell lung 0.69 (0.44 - 1.09), and urothelial 0.63 (0.53 - 0.75). Additional individual tumor types, stratification by MSI status, and time to next treatment associations to be presented at conference. **Conclusions:** Across a heterogeneous cohort, and within individual cancer types with sufficient power, elevated TMB using the TMB measurement based on the FDA-approved test associated with more favorable rWOS on ICI than for similar patients with lower TMB levels. Completed and ongoing randomized controlled trials are encouraged to report out subgroup analyses comparing ICI vs. comparator arm by TMB level. Research Sponsor: Foundation Medicine; Flatiron Health.

2502

Oral Abstract Session

Initial results from a first-in-human, phase I study of immunomodulatory aryl hydrocarbon receptor (AhR) inhibitor BAY2416964 in patients with advanced solid tumors. *First Author: Ecaterina Elena Dumbrava, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: AhR activation is involved in tumor growth, immunomodulation, and resistance to immune checkpoint inhibitors. BAY2416964 is a novel, potent, oral AhR inhibitor (AhRi) that antagonizes AhR ligand-induced immunosuppressive effects, resulting in enhanced proinflammatory activity of antigen-presenting cells and T cells and reduced activity of immunosuppressive myeloid cells. **Methods:** A first-in-human, Phase I clinical trial of AhRi BAY2416964 (NCT04069026) is evaluating its safety, pharmacokinetics, pharmacodynamics, recommended Phase II dose, and anti-tumor activity per RECIST v1.1 and iRECIST. BAY2416964 was administered orally in patients with advanced solid tumors in a dose-escalation cohort using a modified toxicity probability interval (mTPI) design. The initial expansion cohorts enrolled patients with non-small-cell lung cancer (NSCLC) and head and neck squamous cell carcinoma (HNSCC). **Results:** As of November 4, 2022, 72 patients had been treated with BAY2416964: 39 patients in dose escalation and 33 patients in the initial dose expansion treated with 500 mg twice daily (25 NSCLC, 8 HNSCC). The most common tumor types enrolled in dose escalation were colorectal cancer ($n=12$), breast cancer ($n=6$), and pancreatic cancer ($n=4$). Median age was 61 years (range 35-80). 51/72 (70.8%) patients had received ≥ 3 lines of therapy (including 16 [22.2%] who had received ≥ 6 lines) and 47/72 (65.3%) had received immune checkpoint inhibitors. Drug-related treatment-emergent adverse events (TEAEs) of all grades reported in $\geq 10\%$ of patients were nausea (13.9%; 1.4% grade 3) and fatigue (11.1%; 1.4% grade 3). Most drug-related TEAEs were grade 1 or 2; 9 (12.5%) patients experienced drug-related grade 3 TEAEs and no patients experienced drug-related grade ≥ 4 TEAEs. No dose-limiting toxicities were observed. Two patients in dose expansion discontinued treatment due to drug-related TEAEs. Plasma exposure to BAY2416964 increased according to dose and food intake. Analysis of biomarkers demonstrated evidence of target engagement and an increase in immune activation at the doses tested. Of 67 patients evaluable for response by RECIST, 22 (32.8%) had stable disease per RECIST v1.1, including 1 with thymoma in dose escalation achieving an iRECIST partial response. **Conclusions:** BAY2416964 was well tolerated across all dose levels and regimens tested. Initial evaluation of biomarkers shows BAY2416964 inhibits AhR and modulates immune functions. Encouraging preliminary anti-tumor activity was observed in heavily pretreated patients. The disease-specific dose-expansion part of this study is ongoing. The observed manageable safety profile also supports combination therapies. Clinical trial information: NCT04069026. Research Sponsor: Funding by Bayer AG, medical writing support provided by Complete HealthVizion.

2504

Oral Abstract Session

Evaluation of change in RECIST tumor size and survival in patients with rare cancers treated with checkpoint inhibitor therapy (SWOG S1609). *First Author: Megan Othus, Fred Hutchinson Cancer Center, Seattle, WA*

Background: RECIST has been used for over twenty years to evaluate changes in tumor burden. At each scan, the sum of maximum diameters of "target" lesions are measured. Changes in the sum are categorized into an "objective status" at each scan, including complete and partial response and stable and progressive disease. Prior research among patients treated with chemotherapy did not find a threshold effect corresponding to the RECIST categories; instead a linear association was observed. Herein we use a unique clinical trial resource, a basket trial of patients with rare cancer treated with combination anti-CTLA-4 and anti-PD-1 therapy, to evaluate the association between quantitative change in RECIST tumor burden and survival among patients treated with checkpoint inhibitor therapy. **Methods:** The study population was 796 patients enrolled on the S1609 DART (Dual Anti-CTLA-4 & Anti-PD-1 blockade in Rare Tumors) trial, a basket immunotherapy trial evaluating ipilimumab plus nivolumab across solid rare tumor subtypes. The analysis population was 720 patients; patients not eligible ($n=50$; mostly due to non-rare diagnosis), THOSE who did not receive protocol therapy ($n=22$), OR WHOSE DISEASE WAS NOT evaluated by RECIST ($n=4$; gestational trophoblastic disease evaluated by -hCG) were excluded. All patients had RECIST-measurable disease at study entry. Associations between overall and progression-free survival (OS and PFS) and change in tumor burden between baseline and the first scan were evaluated using log-rank tests and Cox regression models stratified by basket. Landmark analyses (at day 65) controlled for lead-time bias. Linear regression models and R^2 were estimated for median and 2-year estimates across tumor change intervals. **Results:** The median age of the cohort was 61, 52% were the distribution of percent change in tumor burden at the first scan. The linear correlation between median and 6-month PFS and change in tumor burden had $R^2=0.92$ and 0.74 ; median and 1-year OS had $R^2=0.79$ and 0.79 . Martingale residuals for both PFS and OS showed linear trends up to tumor increase of +50% with no thresholds at definitions of partial response or stable disease. **Conclusions:** This is the first evaluation of the association between numeric changes in RECIST tumor burden among patients receiving checkpoint therapy. Our results suggest that similar to results among patients who received chemotherapy there is a linear correlation with PFS and OS. As a consequence, the thresholds for RECIST categories do not correspond to thresholds in patient outcomes. Research Sponsor: U.S. National Institutes of Health; Bristol-Myers Squibb.

% change in RECIST tumor burden, $n=720$.

% change	N
-51 to -100	75
-50 to -31	36
-30 to -21	20
-20 to -11	31
-10 to -6	18
-5 to -1	33
0 to +5	40
+5 to +9	32
+10 to +19	39
+20	311
New lesion	85

2505

Oral Abstract Session

Interim update of the ATRC-101 phase 1b trial in advanced solid tumors.

First Author: Bartosz Chmielowski, University of California Los Angeles, Jonsson Comprehensive Cancer Center, Los Angeles, CA

Background: ATRC-101 monoclonal antibody targets tumor-specific ribonucleoprotein complex (RNP) and elicits anti-tumor immunity, innate and adaptive, in preclinical models. **Methods:** Phase 1b is evaluating ATRC-101 as monotherapy, every 3 (3M) or 2 (2M) weeks (wk), and ATRC-101 in combination with pembrolizumab (3P) in participants (pts) with advanced solid tumors. ATRC-101 target expression is determined by CAP-CLIA IHC assay. For pts described herein, pre-treatment (tx) tumor biopsies were assessed for target expression by IHC retrospectively or prospectively. Enrollment in 3M and 3P is currently open to pts who are target positive (RNP+ve) by IHC with an H-score ≥ 50 . Objectives are safety (primary), PK, immunogenicity, recommended dose for expansion, activity by RECIST1.1 and biomarker analyses in pre-tx and on-tx tumors. **Results:** As of Nov 18th, 2022, 67 pts received ≥ 1 dose of ATRC-101 (median prior tx 5, range 1-12). Tumor types were colorectal (CRC, 28), ovarian (10), breast (9), melanoma (8), non-small cell lung (NSCLC, 6), head and neck squamous cell (3), urothelial (1), esophageal (1) and small bowel (1). Tx emergent adverse events (TEAEs) Grade ≥ 3 occurred in 22 (33%) pts and were related to ATRC-101 in 2 (3%). No tx discontinuations or dose reductions related to ATRC-101. RECIST1.1 best overall responses in efficacy evaluable 61 pts included 1 complete response (CR) in RNP+ve melanoma (3P, 10mg/kg), and 1 partial response (PR) in RNP+ve NSCLC (3M, 30mg/kg). Further, disease stabilized (SD) in 24 pts (39%) and 35 pts had disease progression (PD, 57%) with evidence of association between anti-tumor activity and target expression. Of 24 SD, 22 were in monotherapy cohorts and included 9 CRC pts with highly refractory disease. **Conclusions:** ATRC-101 alone and in combination with pembrolizumab continues to be well tolerated with evidence of anti-tumor activity. Interim data support ongoing enrollment of pts with RNP+ve pre-tx tumors. Updated and new data including durability of disease control will be presented. Clinical trial information: NCT04244552. Research Sponsor: Atreca.

Safety and efficacy summary.

Cohort	3M	3M	2M	3M	2M	3M	2M	3M	2M	3P	3P
ATRC-101 dose, mg/kg	0.3	1	1	3	3	10	10	30	30	10	30
N=67 Safety, n	3	3	3	9	3	7	4	24	4	3	4
Cycles	11	7	9	39	26	19	27	111	20	30	28
Pts with ≥ 1 TEAE, n (%)	3	3	3	9 (100)	3	7 (100)	4	23 (96)	4	3 (75)	3 (75)
Pts with ≥ 1 Grade ≥ 3 TEAE, n (%)	1 (33)	1 (33)	1 (33)	3 (33)	0	3 (43)	1 (25)	9 (38)	2 (50)	1 (33)	0
Pts with ≥ 1 Grade ≥ 3 tx-related TEAE, n (%)	0	0	0	1 (11)	0	1 (14)	0	0	0	0	0
				Headache		Small bowel obstruction					
N=61 Efficacy, n	3	3	3	9	3	4	4	23	4	3	2
RECIST1.1 best response, n (%)											
CR	-	-	-	-	-	-	-	-	-	1 (33)	-
SD	-	-	-	-	-	-	-	1 (4)	-	-	-
PD	-	1 (33)	-	5 (56)	1 (33)	2 (50)	2 (50)	9 (39)	2 (50)	-	2
PR	3	2 (67)	3	4 (44)	2 (67)	2 (50)	2 (50)	13	2 (50)	2 (67)	(100)
Disease Control (CR, PR, SD) by Target expression H-Score pre-tx, n											
≥ 50	0	0	0	0	1	1	0	6	1	1	2
< 50	0	0	0	1	0	1	0	3	1	0	0
Unknown	0	1	0	4	0	0	2	1	0	0	0

3M = ATRC-101 every 3 wk; 2M = ATRC-101 every 2 wk; 3P = ATRC-101 every 3 wk + pembrolizumab (200 mg every 3 wk or 400 mg every 6 wk).

2507

Oral Abstract Session

Phase I study of the bifunctional anti-PD-L1/TGF- β RII agent SHR-1701 combined with SHR2554, an EZH2 inhibitor, in patients with previously treated advanced lymphoma and solid tumors. First Author: Kaichao Feng, Department of Bio-therapeutic, The First Medical Center, Chinese PLA General Hospital, Beijing, China

Background: Despite the remarkable successes of cancer immunotherapies, the majority of patients (pts) experience only partial response and most pts will progress. Enhancer of zeste homolog 2 (EZH2) as an epigenetic target for cancer therapy has been shown to enhanced antigen presentation and synergize with immunotherapy in preclinical studies. This study investigates the safety and efficacy of SHR-1701 (anti-PD-L1/TGF- β RII) plus SHR2554 (EZH2i) in pts with pretreated advanced lymphoma and solid tumors. **Methods:** This open-label, single-arm, phase 1 study enrolled pts with pretreated advanced lymphoma and solid tumors. Escalating doses of SHR2554 (300–350mg bid) plus fixed-dose SHR-1701 (30mg/kg q3w) were evaluated in the dose-escalation phase. SHR2554 at the recommended phase 2 dose (RP2D) plus SHR-1701 were administered in the dose-expansion phase. The primary end point was determination of the RP2D of SHR2554 plus SHR-1701. Secondary end points included safety and preliminary activity. **Results:** By January 6, 2023, 33 patients were enrolled (dose-escalation: n=7; dose-expansion, n=26). No dose-limiting toxicities were observed, and RP2D was established as SHR2554 350mg bid plus SHR-1701 30mg/kg q3w. Treatment-related adverse events (TRAEs) occurred in 13 of 32 patients (40.6%), mainly including platelet count decreased (21.9%), anemia (15.6%) and vomiting (15.6%). The most common Grade ≥ 3 TRAEs were anemia (3.1%) and fever (3.1%). In the efficacy-evaluable population (n = 26), objective response rate (ORR) was 57.7%, including 2 complete response (CR) achieved by patients with Metastatic Renal Cell Carcinoma and classical Hodgkin lymphoma (cHL). 16 patients with relapsed/refractory classical Hodgkin lymphoma (cHL) after a median of 10 prior lines of therapy have been enrolled. 16 (100%) cHL pts had received prior anti-PD1/PD-L1 antibody therapy, and 15 (93.8%) prior epigenetic therapies, such as decitabine or chidamide. Out of 14 cHL-evaluable patients, ORR was 100% and the CR rate was 7.1%. **Conclusions:** SHR-1701 combined with SHR2554 showed acceptable safety profile and encouraging antitumor activity in immunotherapy-pretreated cHL, establishing the foundation for further exploration. Clinical trial information: NCT04407741. Research Sponsor: None.

2508

Oral Abstract Session

Phase 1/2 Study of DF1001, a novel tri-specific, NK cell engager therapy targeting HER2, in patients with advanced solid tumors: Phase 1 DF1001 monotherapy dose-escalation results. First Author: Howard Safran, Brown University School of Medicine-Rhode Island Hospital, Providence, RI

Background: DF1001 is a first in class, Tri-specific, NK cell Engager Therapy (TriNKET), that uses HER2 as an anchor to modulate innate and adaptive immunity. DF1001 redirects both NK and CD8 T cells to reprogram the tumor microenvironment, turning cold tumors hot. DF1001-001 (NCT04143711) is an ongoing phase I/II, first in human study investigating the safety, tolerability, clinical and biologic activity of DF1001. The safety, pharmacokinetic (PK), pharmacodynamic (PD) and efficacy data from the phase 1 monotherapy escalation and safety/PK/PD expansion is presented in this report. **Methods:** The Phase 1 dose escalation of DF1001-001 evaluated doses ranging from 0.000052-15mg/kg in patients with advanced and/or refractory solid tumors. Safety/PK/PD expansions, mandating paired biopsies, enrolled at doses 0.52-15mg/kg for biomarker assessment in patients with at least HER2 1+ expressing tumors. The primary objective of the Phase 1 study was to evaluate the safety of DF1001. The secondary objective was to assess efficacy. **Results:** As of 8 Dec 2022, 36 patients were treated in the dose escalation and 68 patients were treated in the safety/PK/PD expansion. 63% of the patients were female with a median age of 61 years. Most common tumor types included breast (38%), urothelial carcinoma (10%), esophageal (8%), non-small cell lung (7%) and colorectal (7%) cancer. Treatment Related Adverse Events (TRAE) were reported in 79% of patients. TRAEs were mostly low grade (86% were Grade 1-2) and rarely led to treatment discontinuation. No Grade 4 or 5 TRAEs were reported. The most common TRAEs were infusion related reactions (26%), asthenia (15%) and fatigue (12%). No dose limiting toxicities were detected, and the MTD has not been reached. Best overall response (BoR) of Partial Response (PR) by RECIST 1.1 was observed in 5 patients, with duration of up to 13 months, and 22 patients experienced stable disease (SD), for a Clinical Benefit Rate (CBR) of 39.7%. Responders included patients with refractory lung and breast cancer, whose tumors expressed HER2 1+ to 3+ by IHC. Biomarker analysis in responders demonstrated increases in inflammatory cytokines and chemokines by gene expression profiling, and consonant increases in NK and CD8 cells in the tumor microenvironment, consistent with TriNKET mechanism of action (MOA). **Conclusions:** In this dose escalation study, DF1001 is shown to be a safe and well-tolerated novel NK cell engager therapy targeting HER2. DF1001 monotherapy demonstrates promising anti-tumor activity in treatment refractory patients with a spectrum of HER2 expression as well as MOA consistent pharmacodynamic changes in the tumor. This promising data set supports further exploration of DF1001 alone, and in combination with other compounds, as a potential novel therapeutic option for patients with solid tumors. Clinical trial information: NCT04143711. Research Sponsor: Dragonfly Therapeutics, Inc.

2509

Clinical Science Symposium

Clinical and immune phenotypes associated with immune checkpoint inhibitor-induced autoimmune diabetes. First Author: Karina Nicole Ruiz-Esteves, Massachusetts General Hospital, Boston, MA

Background: ICI-induced autoimmune diabetes (ICI-DM) is an immune-related adverse event (IrAE) that affects approximately 1% of patients who receive ICI. Most reports of ICI-DM suggest that it resembles fulminant type 1 diabetes, with low or absent endogenous insulin production at presentation. However, milder cases have recently been reported, suggesting a more heterogeneous disease. In this study, we identified distinct clinical phenotypes of ICI-DM that may improve individualized approaches to management. **Methods:** We performed a retrospective chart review of 16,582 patients treated with either anti-PD1, anti-PDL1, anti-CTLA4, or combination between 2010 and 2022 in a multi-centered academic hospital system. We identified patients with ICI-DM as those with a new diagnosis of type 1 diabetes or drug-induced diabetes and a prescription for medium- or long-acting insulin following ICI therapy; cases were confirmed by chart review by two board-certified endocrinologists. To phenotype ICI-DM based on endogenous insulin production, we reviewed all patients with ICI-DM who had a C-peptide level in our system, which allowed us to identify and subdivide 57 cases of ICI-DM. These patients were further characterized at both initial presentation and up to 30 months of follow-up. **Results:** We identified six distinct groups of ICI-DM based on the presence (A+) or absence (A-) of diabetes-specific autoantibodies, further divided by level of endogenous insulin production, preserved (B+), low (B+/-) or undetectable (B-). In our cohort, A+B- patients showed to have the lowest time to diagnosis (median 45 days) and high rates of both DKA and hospitalization (67%) at presentation. At the other end of the spectrum, A-B+ patients had a longer time to diagnosis (median 176 days) and no evidence of DKA or hospitalization at presentation. Surprisingly, all groups had similar insulin requirements without significant dosage variations at 30-month follow up. Elevated lipase levels varied widely across groups with the highest rate (66.7%) reported in the A+B- cohort. The prevalence of thyroiditis in our cohort was highest in the A-B- group but did not seem to follow any specific distribution. **Conclusions:** Our study examined the largest data set to date of deep clinical phenotyping of patients with ICI-DM. We define at least three distinct subsets of ICI-DM, with A+B- patients being most similar to the initially described cases of fulminant type 1 diabetes. Patients with negative antibodies seem to have a milder form of the disease. Our findings also suggest significant heterogeneity and distinct underlying mechanisms amongst cases of ICI-DM. Further studies will be needed to elucidate whether these findings could extrapolate to other individual IrAEs, which may also encompass distinct phenotypes with distinct mechanisms. Research Sponsor: Mass General Brigham.

2510

Clinical Science Symposium

First-line treatment of fecal microbiota transplantation for immune-mediated colitis. *First Author: Yinghong Wang, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: The management of moderate to severe immune-mediated colitis (IMC) includes immunosuppression with steroids and/or biologic agents. Long-term immunosuppression increases the risk for infections and steroid side-effects. Fecal microbiota transplantation (FMT) is increasingly used for the treatment of refractory IMC but has not been studied in the front-line setting. Here we aim to test the hypothesis that front-line FMT can alleviate IMC symptoms while reducing unnecessary exposure to steroids and their complications. **Methods:** We will report interim data from a prospective clinical trial exploring the efficacy and safety of FMT as a first-line treatment for IMC. To be included, patients had to 1) have symptoms of immune-mediated diarrhea or colitis grade ≥ 2 within 45 days of FMT and 2) not have received any immunosuppressive treatment for IMC or any other indication around the time of FMT. **Results:** Seven patients have been enrolled in the trial thus far. Patients received front-line FMT within a median of 35 days (IQR: 18-57 days) from IMC onset. Five (71.4%) patients had symptom improvement within a median of 1 day (IQR: 1-5 days) after FMT. The only FMT-related adverse events reported were transient fever and self-resolving abdominal cramping in three patients (42.8%) within the first week of FMT. All patients stopped immunotherapy due to IMC. Six (85.7%) were able to resume cancer treatment after FMT with 4 patients (57.1%) resuming immunotherapy. Four patients (57.1%) had colitis remission by the end of the study period, with one additional patient showing signs of symptom improvement but passing away before IMC outcome could be assessed. **Conclusions:** This study is the first to evaluate the safety and efficacy of front-line FMT for the treatment of IMC. While more patients are needed before final conclusions can be drawn, our initial results suggest that FMT can be an effective first-line treatment for IMC that can be delivered in a timely manner and quickly provide symptom relief in a majority of patients while avoiding the use of steroids and allowing the safe resumption of immunotherapy. Therefore, first-line FMT may be a safe and effective steroid sparing alternative to the current standard of care treatment for IMC. Clinical trial information: NCT04038619. Research Sponsor: Adopt a scientist, The University of Texas MD Anderson Cancer Center Internal Funding.

Characteristic	No. (%) (n=7)
Median days from initial IMC to FMT (IQR)	35 (18-57)
Symptom improvement after FMT	5 (71.4%)
Median days from FMT to symptom improvement (IQR)	1 (1-5)
FMT-related complications within 30 days	3 (42.8%)
Colitis remission at the last follow up, n=6	4 (83.3%)

2512

Rapid Abstract Session

Baseline autoantibody profiling in patients with NSCLC with pre-existing autoimmune diseases or who had received prior anti-PD-1 therapy before enrolling in the TAIL study. *First Author: Delys Rodriguez-Abreu, Complejo Hospitalario Universitario Insular-Materno Infantil, Las Palmas De Gran Canaria, Spain*

Background: Patients (pts) with pre-existing autoimmune diseases (AID) and prior immune checkpoint inhibitor (ICI) experience were historically excluded from studies with ICIs. Moreover, about 50% pts with pre-existing autoimmunity have a flare up when given ICI therapies (1). In this post-hoc exploratory analysis, we characterized the baseline autoantibody (AAb) profiles and evaluated its correlation with efficacy and safety outcomes in NSCLC pts with either pre-existing AID or who had prior ICI therapy and received atezolizumab in the TAIL study (2). **Methods:** Plasma samples were obtained from 57 NSCLC pts prior to receiving atezolizumab (TAIL study, NCT03285763). AAb testing was performed using tailored immuno-oncology bead-based antigen arrays comprising 1,340 tumor, AID and immune pathway antigens (3, 4). The cohort includes 39 pts with prior ICI therapy or prior AID (experimental group) and 18 pts without prior ICI therapy or AID (control group). Differences in IgG AABs were compared between the experimental and control group in pts with or w/o irAE and overall survival (OS) longer or shorter than 11.1 months (median OS in overall population in TAIL). Furthermore, the AAb profiles of a subgroup of pts with therapeutic benefit (OS ≥ 11.1 months) and no or low grade irAEs (standard toxicity grade ≤ 2) were analyzed. Statistical analysis included 2-way permutation-based ANOVA (factors: outcome, study group) and Significance Analysis of Microarrays (SAM). **Results:** While pre-treatment AABs were detected in the overall cohort, significant differences in AAB were observed between the experimental and control group at baseline, which were associated with OS and irAEs. In experimental group pts, pre-existing AABs to AQP4 and NCOA1 predicted the development of irAEs. Differences were also observed in AABs predicting longer OS. AABs to CENPT were specifically identified in pts in the experimental group with longer OS, whereas AABs to SOX5 were elevated in pts of the control group with longer OS. In the subgroup of pts with therapeutic benefit and no or low risk of irAE, AABs to IL6, CENPT and the cancer testis antigens NY-ESO-2 and MAGEB2 were elevated in the experimental group. **Conclusions:** This AAB analysis provides important preliminary data in helping to understand the drivers of clinical outcomes with ICIs in pts with pre-existing AID and prior ICI therapy. The findings seem biologically plausible as some of the identified antigens refer to the breach of tolerance to classical AAB targets e.g. CENPT, AQP4 and to an immune response to classic tumor antigens e.g. NY-ESO-2 and MAGEB2. Further validation of the AAB profiling approach is warranted to shed insights on potential therapeutically actionable antigens and generate data orthogonal to efforts to identify biomarkers that are predictive of efficacy and safety outcomes with ICI therapies. Research Sponsor: F. Hoffmann-La Roche.

2511

Clinical Science Symposium

Identifying molecular targets for rational immunosuppressive strategies in patients with immune checkpoint therapy-induced myocarditis and myositis. *First Author: Bilal Ahmed Siddiqui, MD Anderson Cancer Center, Houston, TX*

Background: Immune checkpoint therapies (ICTs) can induce durable anti-tumor responses but also life-threatening immune-related adverse events (irAEs). Myocarditis, myositis, and myasthenia gravis (MG) are rare, often concurrent irAEs with mortality up to 40%. Steroids are the standard first-line treatment and have significant adverse events with prolonged use. We and others have identified serum autoantibodies in these irAEs, suggestive of B cell contribution to pathogenesis. Furthermore, although prior studies have shown T cells and myeloid cells in inflamed muscle tissue, their specific subtype and role in disease pathogenesis have yet to be defined. This understanding may contribute to the development of more effective immunosuppressive strategies. Hypothesis: In addition to T cells, plasma B and myeloid cells contribute to the pathogenesis of ICT-induced myocarditis, myositis, and MG. **Methods:** We enrolled patients with suspected ICT-induced myocarditis, myositis, and MG on an IRB-approved laboratory protocol. Diagnosis required: 1) symptoms requiring hospitalization; 2) elevated serum markers (creatinine kinase $\geq 5\times$ normal, troponin >99 th percentile or detection of autoantibodies for MG); and 3) positive biopsy, electromyography, or cardiac MRI. Patients underwent standard diagnostic testing (including endomyocardial and/or skeletal muscle biopsy) and treatment as clinically indicated. **Results:** 23 patients were enrolled (n=13, confirmed irAE; n=10, negative control). Most patients received combination ICT (10/13, 77%). Anti-striated muscle and/or acetylcholine receptor binding antibodies were detected in 7/13 patients (54%), including 3 without MG (known to have both T and B cell etiologies). Single cell RNA sequencing of patient tissue (confirmed irAEs: cardiac n=10, skeletal n=9; control: cardiac n=4, skeletal n=5) identified specific populations of myeloid and CD8⁺ T cells conserved between inflamed cardiac and skeletal muscle. **Conclusions:** Specific populations of T cells, myeloid cells, and plasma B cells are potential targets for rational immunosuppressive strategies in ICT-induced myocarditis and myositis and will be tested in murine models to inform future clinical trial design. Research Sponsor: Parker Institute for Cancer Immunotherapy.

	Distribution of irAEs, n (%)
Myositis	1 (8)
Myositis + Myocarditis	6 (46)
Myositis + Myocarditis + MG	4 (31)
Myocarditis	1 (8)
MG	1 (8)

2513

Rapid Abstract Session

Targeting CD47 in lymphoid malignancies with CAR T cells. *First Author: Alexander Paul Boardman, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Despite major therapeutic advances of chimeric antigen receptor (CAR) T cells directed against CD19 in relapsed and refractory non-Hodgkin lymphoma (NHL), two thirds of patients experience relapse within the first two years. Nearly one third of these relapses are associated with CD19 antigen-loss escape thus leveraging alternate CAR targets may improve outcomes. CD47, an anti-phagocytic "don't eat me" receptor known to be overexpressed in NHL, is an ideal CAR target as it is potentially indispensable for tumor progression. **Methods:** CD47-CAR binding domains were engineered either as a camelid single variable heavy chain nanobody (CD47-VHH-CAR) or as the CD47 binding domain of cognate receptor SIRP α (SIRP α -CAR), each combined with a CD28 costimulatory domain and a CD3 ζ activation domain with two mutated ITAMs (1XX). In vitro co-culture assays were performed with lymphoid mouse tumor cell lines BM185 and A20. For in vivo experiments, syngeneic BALB/c mice were sublethally irradiated for lymphodepletion then injected intravenously with 1×10^5 luciferase⁺ BM185 cells. Two days later, mice were injected with 2×10^6 CAR T cells, and bioluminescence imaging was performed to monitor tumor progression. For bio-localization experiments, CAR T cells were co-transduced with a separate vector encoding luciferase. **Results:** CD47-CAR T cell expansion in vitro was hindered due to fratricide, which can be rescued by CD47 CRISPR knockout. Both CD47-VHH-CAR and SIRP α -CAR T cells exhibited potent and specific in vitro lysis of BM185 and A20 cells. CD47-VHH-CAR T cells showed transient anti-leukemia activity, however, survival was not significantly prolonged. T cell bio-localization analysis revealed that, compared to CD19-CAR T cells, CD47-VHH-CAR T cells exhibited prolonged retention in the thorax with minimal bone marrow trafficking, suggesting CD47 antigen-specific pulmonary sequestration, and inferior expansion. SIRP α -CAR T cells engineered to secrete pro-inflammatory cytokine IL-18 significantly improved CAR T cell expansion, resulting in bone marrow trafficking and clearance of BM185 tumor. However, recipients of IL-18-secreting SIRP α -CAR T cells experienced lethal CAR T cell-related toxicity. To improve the safety of CD47-CAR T cells, we engineered an NFAT-responsive vector expressing the CD47-CAR modified with E. coli-derived dihydrofolate reductase drug destabilization domain to limit CD47-CAR expression to T cells exposed to the stabilizing antibiotic trimethoprim and receiving a licensing NFAT signal from a CD19-CAR. **Conclusions:** In vivo activity of CD47-targeting CAR T cells is limited by thoracic retention and limited expansion, which can be partially overcome by overexpression of IL-18, though enhanced toxicity precludes survival prolongation. Our findings suggest that strategies to spatiotemporally restrict CAR expression or activation will be necessary to achieve safe and efficacious CD47-CAR T cell activity. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology.

2514

Rapid Abstract Session

Association of common inherited *NOD2* mutations with exceptional response to immune checkpoint inhibitors. *First Author: Megan Babette Barnett, Garvan Institute of Medical Research, Darlinghurst, NSW, Australia*

Background: Melanomas and lung cancers usually display a large burden of somatically mutated proteins, yet only a subset of individuals can be induced to mount a therapeutic immune response against tumours. Inherited mutations in immune regulatory genes may be one factor predisposing to a heightened immune response with addition of an immune stimulus. **Methods:** Germline whole genome sequencing (WGS) was performed in a patient with exceptional response (ExR) to targeted radiotherapy for metastatic melanoma (complete abscopal response). A target variant gene was identified, and interrogated within a prospectively recruited cohort of patients with ExR or non-response to anti-PD1 for non-small cell lung cancer (NSCLC). Results were experimentally tested in mice and validated in an independent mixed cancer clinical cohort. **Results:** Compound heterozygous variants in *NOD2* were found within the patient with abscopal response (expected genotype frequency 1.3 in 10,000), whose cancer regression occurred concurrently with a flare of pre-existing Crohn's colitis (a *NOD2*-associated condition). Patients treated with anti-PD1 for NSCLC were prospectively recruited (n=144). Individuals with ExR to PD1 were selected, defined by progression-free survival (PFS) ≥ 2 years and ≥ 1 CTCAE grade 2 or higher immune-related adverse event (n=40). Median follow-up was 41 months (median PFS not reached). Patients with best response of progressive disease were selected for comparison (n=18, median PFS 2.76m, 95% CI, 2.1-3.81). WGS from blood was analysed for all human *NOD2* variants known to impair *NOD2* signalling. Of ExR patients, 25% carried 1 or more functional *NOD2* variants, totalling 11 of 80 alleles (13.8%); more than twice the expected allele frequency (6.58%, p=0.0199). Within non-responders, 1 patient carried a variant *NOD2* allele (1 of 36 alleles, 2.78%). The association between *NOD2* loss-of-function and heightened immune response to anti-PD1 was experimentally tested in *Nod2*-null C57BL/6J (*Nod2*^{ts}) mice. *Nod2*^{ts} mice transplanted with a syngeneic cell line and treated with anti-PD1 showed greater tumour response compared with *Nod2*^{wild-type} littermates (60-day OS 41.67% vs 0%, p<0.01). Flow cytometry of tumours showed greater proportion of (CD44^{hi} CD62L^{low}) CD8⁺ and CD4⁺ effector memory differentiated cells within *Nod2*^{ts} versus *Nod2*^{wild-type} animals (p<0.05). Results were validated within an independent clinical cohort (n=105). Overall response rate to PD1 in patients with mutant vs wild-type *NOD2* was 50% versus 15% (p=0.03). **Conclusions:** These results provide four complementary lines of evidence that common inherited defects in the immune regulatory gene *NOD2* promote exceptional immune response following acute triggers to control cancer. *NOD2* may be a biomarker for treatment stratification or a therapeutic target to enhance anti-PD1 response. Research Sponsor: None.

2516

Rapid Abstract Session

Association of ctDNA tumor fraction with survival in advanced non-small cell lung cancer (NSCLC) treated with maintenance durvalumab in the UNICANCER SAFIRO2-Lung/IFCT1301 trial. *First Author: Filippo Gustavo Dall'Olio, Cancer Medicine Department, Institut Gustave Roussy, Villejuif, France*

Background: ctDNA shed is a promising biomarker for cancer immunotherapy, with patients (pts) having higher concentration of plasma ctDNA being reported to have poorer outcome. Its role in the maintenance setting with immune checkpoint inhibitors remains unexplored. In SAFIRO2-Lung, advanced NSCLC pts were enrolled to receive a platinum-based chemotherapy. After 4 cycles, if stable or in response, pts with no targetable alterations were oriented to the immunotherapy sub-study and randomized between maintenance durvalumab or Standard of Care (SoC) (PMID 35802649). Durvalumab prolonged survival only in the PD-L1 $\geq 1\%$ subgroup. Here we explored Tumor Fraction (TF) as determined by Low-Pass Whole Genome Sequencing as a biomarker for immunotherapy irrespective of PD-L1. **Methods:** SAFIRO2-Lung (NCT02117167) is a multicentric, randomized phase 2 clinical trial. Plasma samples were obtained at randomization, just before maintenance treatment initiation. DNA was extracted using the Maxwell RSC ccfDNA Plasma Kit (Promega, AS1840). Sequencing libraries were prepared using the Low Input SureSelectXT protocol (Agilent, G9916A). Pooled libraries were sequenced on a NovaSeq 6000 platform (Illumina) as 2 × 150 bp paired-end reads (NovaSeq 6000 SP Reagent Kit v1.5). Genomic copy number aberrations and TF were investigated using the ichorCNA (V0.2.0) tool. TF $\geq 2\%$ was considered positive. For the survival analyses, a landmark approach was performed, by considering the randomization date as the landmark time. Progression Free Survival (PFS) was the primary endpoint, defined as the time from randomization until the date of objective radiological disease progression, clinical progression or death. The secondary endpoint was Overall Survival (OS). **Results:** 50 out of 121 plasma samples from pts randomized to durvalumab were analyzed for the feasibility part. 34 pts (68%) were < 65 years, 33 (66%) were male. PD-L1 expression was available for 18 pts and 39% of them had PD-L1 $\geq 1\%$. Median TF was 1.1%, 8 pts (16%) had a TF $\geq 2\%$, ranging from 2.2% to 23.3%. TF at randomization was marginally correlated with the presence of liver metastases (p 0.063) and with the sum of target lesions (p 0.081). No significant correlation was observed with PD-L1 positivity. Pts with TF $\geq 2\%$ had lower median PFS 1.7months (m) (95% CI 1.2 – 4.2) vs 5.8m (95% CI 2.9 – 7.5) for those with TF < 2%, p 0.0003. Similarly, median OS was lower for pts with TF > 2% 10.4m (95% CI 4.2 – 18.7) vs 25.9m (95% CI 18.2 – NR) for those with TF < 2%, p 0.0002. Data will be presented on the whole cohort, including control group receiving SoC, to discriminate between a prognostic or a predictive value of TF. **Conclusions:** TF was positive in 16% of pts randomized to durvalumab in the SAFIRO2-Lung trial. This population seems to have a limited benefit from maintenance durvalumab after induction chemotherapy. Clinical trial information: NCT02117167. Research Sponsor: Unicancer.

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Rapid Abstract Session

Intestinal microbiome characterization in immune checkpoint inhibition (ICI) resistant disease. *First Author: Pavlina Spiliopoulou, Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, ON, Canada*

Background: The gut microbiome modifies response to ICI treatment. Despite durable response rates seen with ICI, most pts do not benefit from treatment (primary resistance) or have only a period of disease control (acquired resistance). The Immune Resistance Interrogation Study (IRIS, NCT03702309) is a prospective pan-cancer study that aims at characterizing ICI-resistant disease through multiomic and gut microbial composition profiling. Herein we compare the gut microbial diversity of pts with PR vs AR to PD-1/PD-L1 based treatment as part of the wider IRIS framework. **Methods:** Patients who progressed after anti-PD1/PD-L1-based ICI were classified into 2 groups. Acquired resistance (AR): complete response (CR), partial response (PR) or stable disease (SD) for ≥ 6 months (m) with subsequent (PD) or PD after ≥ 3 m from last dose of adjuvant ICI; or primary resistance (PR): PD at first imaging, SD but progressed ≤ 6 m or progression ≤ 3 m from last dose of adjuvant ICI. Stool samples were collected at time of PD and underwent DNA extraction and metagenomic sequencing. Species-level Shannon diversity indices were calculated and compared using unpaired Wilcoxon test. Principal component analysis (PCA) of Bray-Curtis dissimilarity indices was performed to assess differences in taxonomic composition. **Results:** Stool samples from 62 pts (PR n=38; AR n=24) were evaluated. Tumor types were melanoma n=37 (60%), head and neck n=17/62 (27%), gastrointestinal n=3/62 (5%), gynaecological n=2/62 (3%) and other n=3/61 (5%). Most pts n=59/62 (95%) were treated with palliative intent, and n= 3/62 (5%) with adjuvant therapy. Anti-PD-1/PD-L1 monotherapy was received by 32/62 (52%) pts and n=30/62 (48%) received combination anti-PD-1/PD-L1 with either anti-CTLA-4 inhibition, experimental immunotherapy, chemotherapy, or targeted treatment. The median Shannon diversity index was similar between pts with PR (median: 3.5; range: 2.5 - 4.3) vs AR (median: 3.4; range: 0.9 – 3.9; p = 0.7). There were no differences in composition by group by PCA of Bray-Curtis dissimilarity indices. Abundance testing did not reveal any differentially abundant species between pts with AR vs PR while controlling for antibiotic use within 1m of sampling and type of treatment. No taxa were significantly different between AR and PR; top taxa per group are shown. **Conclusions:** Primary analysis showed no significant differences in gut microbial composition between primary vs acquired resistance to ICI. Comparative analysis between ICI-resistance samples and ICI-naïve samples from historical patient cohorts is underway. These results will be collated with other analyses from IRIS to create a multi-modal characterisation of ICI resistance. Clinical trial information: NCT03702309. Research Sponsor: Princess Margaret Foundation funding.

ICI-resistance	Differentially abundant taxa	Fold change
Primary	Clostridium disporicum	3.6 log fold change, q-val: 0.36
Acquired	Bacteroides fragilis	3.8 log fold-change, q-val: 0.12

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Poster Discussion Session

Phase 1 results with anti-CD19 allogeneic CAR T ALLO-501/501A in relapsed/refractory large B-cell lymphoma (r/r LBCL). *First Author: Frederick L. Locke, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL*

Background: Approximately 50% to 60% of pts with r/r LBCL will either not achieve a complete response (CR) or will relapse with current treatments and require additional therapy. Autologous anti-CD19 chimeric antigen receptor T (CAR T) therapies have revolutionized the care of patients whose disease progresses following standard therapies, but patient-specific manufacturing processes and long wait times to treatment present challenges for their broad clinical use. Allogeneic (healthy-donor-derived), off-the-shelf, anti-CD19 (CAR T) treatment promises broader and more rapid access to one-dose treatment with curative intent. Initial phase 1 data for the anti-CD19 AlloCAR T cell product ALLO-501 (NCT03939026) and successor, ALLO-501A (NCT04416984), demonstrated a manageable safety profile with no dose-limiting toxicities (DLTs), and efficacy comparable to autologous CAR T therapy in pts with r/r LBCL who were autologous CAR T-naïve. This update provides additional follow up and a focus on participants who received the conditioning regimen and cells made with an optimized manufacturing process currently under study in the first potentially pivotal trial for an allogeneic CAR T product. **Methods:** In these two multicenter, single-arm, open-label, phase 1 trials, a cohort of autologous CAR T-naïve pts with r/r LBCL underwent 3-day lymphodepletion (LD) with FCA90, fludarabine (F, 30 mg/m²/day), cyclophosphamide (C, 300 mg/m²/day), and ALLO-647 (A [anti-CD 52 mAb] 30 mg/day; total dose: 90 mg) followed by a single dose of ALLO-501 or ALLO-501A produced by the Allo manufacturing process. **Results:** As of Jan 26, 2023, 12 pts received the FCA90 LD regimen and CAR T therapy with 100% receiving product per specifications with a median time from enrollment to LD of 3 days. Median follow-up time (actual) was 7.1 months (range: 1.4, 36.0). No DLTs, severe (Gr3+) cytokine-release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), or graft-versus-host disease (GVHD) events occurred. An overall response rate and a CR rate of 66.7% and 58.3%, respectively, were observed. Median DOR was 23.1 months. Among 8 pts with the opportunity to be followed for 6 months, 5 (62.5%) had achieved CR and 4 (50.0%) sustained CR through 6 months. Analyses of vector copy number pharmacokinetics at Days 28 and 56 documented substantial and sustained expansion of CAR T cells. **Conclusions:** A one-time dose of allogeneic CAR T therapy following LD with FCA90 provided durable responses with a manageable safety profile in patients with r/r LBCL comparable to those treated with autologous CAR T cells. This treatment enables rapid access to off-the-shelf treatment with a median time from trial enrollment to treatment of 3 days. These findings support broader evaluation of ALLO-501A in the ongoing, first potentially pivotal phase 2 trial (ALPHA2) of off-the-shelf allogeneic CAR T cells. Clinical trial information: NCT03939026. Research Sponsor: Allogene Therapeutics.

2518

Poster Discussion Session

CLDN6 CAR-T cell therapy of relapsed/refractory solid tumors ± a CLDN6-encoding mRNA vaccine: Dose escalation data from the BNT211-01 phase 1 trial using an automated product. *First Author: Andreas Mackensen, Friedrich-Alexander University Erlangen-Nuremberg, Erlangen, Germany*

Background: We are developing a chimeric antigen receptor (CAR)-T cell therapy targeting claudin 6 (CLDN6), an oncofetal antigen that is undetectable in healthy somatic tissue and highly expressed in various solid cancers. Autologous CLDN6 CAR-T cells are being tested alone and in combination with CLDN6-encoding CAR-T cell Amplifying RNA Vaccine (CARVac), a nanoparticulate RNA vaccine designed to stimulate and expand CLDN6 CAR-T cells. **Methods:** The ongoing first-in-human trial BNT211-01 evaluates the safety and feasibility of CLDN6 CAR-T cell transfer ± CARVac in lymphodepleted patients with relapsed/refractory solid tumors. Patients are pre-screened for CLDN6 expression with a cut-off of 50% positivity of intermediate or strong intensity by immunohistochemistry staining. Key endpoints are safety, tolerability, and anti-tumor activity. Pharmacokinetics of adoptively transferred CAR-T cells in peripheral blood is monitored by quantitative PCR. Dose escalation proceeds according to a classical 3+3 design, testing CLDN6 CAR-T cells at each dose level as both as monotherapy and in combination with CARVac. We previously reported results from 22 patients from 4 dose escalation cohorts with a manual CAR-T production process ± CARVac (ESMO-IO LBA38) which followed the same methodology. We observed durable responses along with a manageable safety profile, in line with commercial CAR-T products used to treat B-cell malignancies. No on-target/off-tumor toxicity and only a single case of (grade 1) neurotoxicity was observed. Given the encouraging efficacy, we have implemented an automated process to scale-up manufacturing. Accordingly, we are repeating the dose escalation with an automated CAR-T cell product, and with a modified CARVac regimen. As of 1st February 2023, 7 patients with epithelial ovarian carcinoma (EOC), 4 with testicular germ cell tumors (GCT), and a further 5 patients with tumors of various indications have been infused with CAR-T cells up to DL2. We intend to submit efficacy, safety and CAR T-cell pharmacokinetics data from 5 cohorts treated with 1x10⁶, 1x10⁷ or 1x10⁸ CLDN6 CAR-T cells ± CARVac with a data cut-off of March 14th, 2023 from ≥17 treated patients as a late-breaking abstract. Clinical trial information: NCT04503278. Research Sponsor: BioNTech SE.

2520

Poster Discussion Session

A phase 1/2a study of T3011, an oncolytic HSV expressing IL-12 and PD-1 antibody, administered via intratumoral (IT) injection as monotherapy in advanced solid tumors. *First Author: Dongmei Ji, Fudan University Shanghai Cancer Center, Shanghai, China*

Background: T3011, a replication-competent, genetically modified, next-generation oncolytic herpes simplex viruses (oHSV), deletes one copy of ICP34.5 and retains ICP47, thus maximizing replication activity and virulence attenuation of the virus. Moreover, T3011 was inserted with biologically active IL-12 and anti-PD-1 antibody genes. Therefore, while lysing tumor cells, T3011 can significantly improve the tumor microenvironment and elicit the body's specific anti-tumor immunity. **Methods:** An open-label, dose escalation and expansion study of T3011 administered via IT injection as a single agent in patients (pts) with advanced solid tumors. Pts who progressed on or were intolerable to the standard of care were eligible and received T3011 IT therapy Q2W in several dose cohorts (2.5x10⁵ ~ 1x10⁸ PFU/mL). The primary endpoints were safety and tolerability. Key secondary endpoints were PK/PD profile, efficacy endpoints including ORR, DCR, DOR, PFS by investigator per RECIST1.1 and OS. **Results:** As of 18 Jan. 2023, 90 Pts received T3011 monotherapy. Median follow-up time is 5.7(0.5-22.5) months. No DLT events were reported. Treatment-related adverse events (TRAEs) were observed in 66.7% pts (≥G3 TRAEs and treatment discontinuation both in 2.2% [2/90]), and treatment-related SAEs occurred in 2.2% (2/90) pts. The most frequently reported TRAEs (≥5%) were pyrexia (21.1%, 19/90), influenza like illness (8.9%, 8/90), TSH increased (6.7%, 6/90), proteinuria (6.7%, 6/90), facial edema, white blood cell count decreased, AST increased and anemia (5.6%, 5/90, each). MTD was not reached, RP2D was determined as 1x10⁸ PFU/mL. Over 80% of pts had viral DNA undetected in their blood, urine and saliva after injection. Moreover, almost all injection site and occlusive dressing samples that tested positive for viral DNA were confirmed to be free of viral activity. The confirmed ORR was 11% (6/55), DCR was 49% (27/55) in 55 pts (HNSCC, sarcoma, melanoma, breast cancer, etc.) treated under RP2D evaluable for tumor response. The median PFS was 2.8 mos (95%CI: 1.84, 4.60) in all 76 Pts received T3011(RP2D). 19 head and neck squamous-cell carcinoma (HNSCC) pts progressed on platinum-based chemotherapy and anti-PD-1/PD-L1 therapy treated with T3011(RP2D), median PFS was 3.9 mos (95%CI: 0.89, NA; 1 pt failed from chemotherapy only for PFS analysis set). 12 HNSCC pts had at least one tumor evaluation post-dose, the confirmed ORR and DCR was 25% (3/12) and 50% (6/12) respectively. **Conclusions:** The safety profile and clinical compliance of T3011 IT therapy are excellent. T3011 injected locally will not spread to blood, urine and saliva, regional shedding doesn't raise the possibility of transmission to the local and systemic environment. The encouraging anti-tumor activity of T3011 monotherapy in advanced HNSCC pts supports further evaluation in phase II studies. Clinical trial information: NCT05602792. Research Sponsor: ImmVira Co. LTD.

2519

Poster Discussion Session

A phase I/II trial investigating safety and efficacy of autologous TAC01-HER2 in relapsed or refractory solid tumors. *First Author: Benjamin L. Schlechter, DFCI/BWH cancer center, Boston, MA*

Background: Despite recent therapeutic developments for patients with advanced, metastatic, unresectable HER2+ solid cancers, significant unmet medical needs still exist, especially in tumors other than breast and gastric. The T cell antigen coupler (TAC) technology is a novel approach to modifying T cells, allowing them to recognize and treat HER2+ solid tumors. The TAC receptor redirects T cells to tumor cells, and upon tumor cell recognition, co-opts the natural T cell receptor (TCR) to yield safer anti-tumor responses versus chimeric antigen receptor (CAR) T cells. In preclinical studies, TAC T cells led to complete tumor clearance in mouse models of human cancer, without any TAC-related toxicities. **Methods:** In the ongoing clinical trial (NCT04727151), TAC01-HER2 treatment of HER2+ solid tumors is hypothesized to result in safe and effective anti-tumor responses. Subjects undergo leukapheresis, bridging therapy (if needed) while their TAC01-HER2 are engineered, lymphodepletion chemotherapy (LDC), and finally TAC01-HER2 infusion. In phase I dose escalation, the primary objective is to evaluate the safety of TAC01-HER2 at increasing doses of 0.3, 0.8, 3, and 8 x 10⁵ cells/kg in HER2+ solid tumors (1+, 2+ or 3+ as identified by immunohistochemistry) in adult subjects who have progressed after ≥2 lines of systemic therapy. Dose limiting toxicities (DLTs) are assessed up to 28 days from cell infusion. In Phase II, dose expansion groups will further evaluate the safety, efficacy, and pharmacokinetics of the optimal TAC01-HER2 dose in HER2+ breast and other solid tumor types. **Results:** As of 10 Feb 2023, 18 patients have been treated in Cohorts 1-4 with breast, colorectal, gall bladder, gastroesophageal junction, gastric, esophageal, lung, and ovarian cancers. One DLT event of grade 3 pneumonitis has been reported in one subject in Cohort 4 (8 x 10⁵ cells/kg). No neurotoxicity has been reported. Most subjects treated at Cohorts 3 and 4 experienced Grade ≤2 CRS which resolved with standard therapy. Twelve subjects have reported a total of 21 serious adverse events, 17 unrelated to TAC01-HER2 except for one Grade 3 pneumonitis, one Grade 1 and two Grade 2 CRS. Most adverse events were related to LDC or the underlying malignancy. At Cohort 2 (0.8 x 10⁵ cells/kg), a partial response was observed in a subject with refractory metastatic gastric adenocarcinoma (3+ HER2) at 1st scan, with a 35% reduction in measurable disease and clinical benefit was maintained for 4 months. A 55% disease control rate was observed at Cohorts 2-4 at 1st scan. **Conclusions:** Dose escalation of TAC01-HER2 is ongoing, with seven subjects treated and three more scheduled in Cohort 4. These results in a heavily pre-treated cancer population show manageable safety and promising clinical activity with a novel T cell therapy that may have broad clinical applicability in HER+ cancers. Clinical trial information: NCT04727151. Research Sponsor: Triumvira.

2521

Poster Discussion Session

Safety and early biologic effects of phase 1 PERIO-01 trial of pressure-enabled drug delivery (PEDD) of TLR9 agonist SD-101 and immune checkpoint inhibition (ICI) in uveal melanoma metastatic to the liver (MUM). *First Author: Kamaneh Montazeri, Massachusetts General Hospital, Boston, MA*

Background: Delivery barriers due to intratumoral pressure and immunosuppression related to myeloid-derived suppressor cells (MDSC) in liver tumors have created challenges for immunotherapy. TLR9 agonists seem to improve response to ICI. PERIO-01 is a first-in-man trial of PEDD of SD-101 using hepatic arterial infusion (HAI) with ICI in MUM. **Methods:** PERIO-01 is an open-label phase 1 trial of SD-101 given by HAI in MUM (NCT04935229). The study consists of dose-escalation cohorts of SD-101 alone (Cohort A), with nivolumab (Cohort B), or nivolumab + ipilimumab (Cohort C). SD-101 is delivered over 2 cycles, with 3 weekly doses per cycle. Blood, liver metastasis (LM) and normal liver biopsies are collected for correlative studies. **Results:** At data cutoff, 33 patients were enrolled, 30 of whom received at least one dose of SD-101, 13 in Cohort A (2, 4, and 8 mg), 15 patients in Cohort B (2 mg and 4 mg) and 2 patients in Cohort C (2 mg). The median age was 63 years of equal gender. Only 3 patients were treatment-naïve and 2 were HLA-A*02:01+ who received prior tebentafusp. Nine subjects had 4-7 LM and 4 had > 10. The median index LM size was 4.7 cm. Only one patient experienced a grade ≥3 adverse event (AE) related to SD-101, which was increased liver enzymes. All AEs related to cytokine release syndrome have been low-grade with the most common being fever (9), chills (5), and dizziness (4). Treatment resulted in high liver drug levels (median at 2 mg = 1540 ng/g and 8 mg = 2325 ng/g, p = 0.035), with only transient exposure in the periphery (< 4 hours) and a maximum peak serum level of 554 mg/ml 30 minutes post-infusion. Increases in serum IL-18 and IFNγ were noted, with highest levels at 8 mg. Expansion of natural killer cells were detected in 9 of 10 patients from flow cytometry data peripherally. Monocytic MDSC levels were decreased in 5 of 5 patients on immunofluorescence, and NanoString analysis revealed decreases in ARG-1 and IDO-1 gene levels up to 100 days from initial treatment. Broad immunostimulatory gene expression changes were noted in tumor and normal liver following SD-101, including increases in IFNB1 and IL-9. Using the available samples from 13 patients, 7 of 10 had decrease in ctDNA, with complete clearance in 3, along with circulating tumor cell decreases in 6 of 13. In cohort B at 2 mg, 5 of 6 with available response data have stable disease with a median duration of disease control of 12 weeks (range = 7.5-24) at data cutoff. **Conclusions:** HAI of SD-101 has been well tolerated and associated with encouraging immunologic activity. Evidence of biologic effects at the lower doses of SD-101 with nivolumab is encouraging and enrollment with escalation continues in Cohorts B and C. Clinical trial information: NCT04935229. Research Sponsor: TriSalus Life Sciences.

2522

Poster Discussion Session

The immune microenvironment in hormone positive, HER2 negative breast cancer: A focus on tumour infiltrating lymphocytes, spatial phenotypes and tertiary lymphoid structures. *First Author: Mairi Lucas, St Vincents University Hospital, Dublin, Ireland*

Background: Hormone positive, HER 2 negative breast cancer (ER+/HER2-) has traditionally been considered an immune cold tumour subtype. Research to date indicates that TILs in ER+/HER2- breast cancer may be a negative prognostic marker. However, there is a paucity of data in this area regarding immune subpopulations and spatial phenotypes. Tertiary lymphoid structures (TLS) have been associated with improved prognosis and response to immunotherapy in other solid organ malignancies. We aim to explore the immune microenvironment in early stage ER+/HER2- breast cancer with a focus on tumour infiltrating lymphocytes, spatial phenotypes and tertiary lymphoid structures (TLS). **Methods:** Full face sections of archival tissue samples from patients with early stage ER+/HER2- breast cancer were stained with CD45 antibody (DAKA clone M0701) via the automated Leica Bond III system. Open source digital pathology analysis software, Qupath, was utilised to identify positive cells and calculate the percentage of positive CD45 staining cells (CD45%) within the tumour area. Spatial analysis was done to divide tumour area into three spatial phenotypes; Immune cold -lacking immune infiltrate; Immune excluded- immune cells restricted to the tumour periphery and immune hot - immune cells infiltrating the tumour core. A tissue micro array (TMA) was created and stained manually with a multiplex chromogenic immunohistochemistry panel for CD20/CD3/DCLamp to identify immune subpopulations associated with tertiary lymphoid structures. **Results:** A total of 409 patient samples were included in the analysis. 89% (n=367) of samples had a CD45% of 0-10%. CD45% stratification by 21-gene-recurrence score(RS) into Low, Intermediate and High showed a statistically higher CD45% in those with a High RS compared to Low RS (p value= 0.0015). We identified a trend towards worse disease free survival (DFS) in the CD45%high group which did not reach statistical significance. The immune hot spatial phenotype was associated with a worse DFS (p value = 0.034) with no statistically significant difference in DFS between immune cold and immune excluded phenotypes. The majority of samples had minimal immune infiltrate. Staining with a TLS panel revealed that samples with a significant infiltrate could broadly be divided into T cell only infiltrate or those with the presence of TLS, the significance of this is unclear. **Conclusions:** The majority of ER+/HER2- breast cancer samples had low numbers of TILs, however there is clear heterogeneity within this subgroup. Spatial elements and immune cell subpopulations may further guide the value of TILs in prognosis in this breast cancer subtype. Research Sponsor: Royal College of Surgeons Ireland.

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Poster Discussion Session

A phase 1 study of AGEN2373, a novel CD137 agonist antibody designed to avoid hepatotoxicity, in patients with advanced solid tumors. *First Author: Minal A. Barve, Mary Crowley Cancer Research Center, Dallas, TX*

Background: We present results from the completely enrolled monotherapy arm of the first-in-human dose escalation study of AGEN2373, a novel CD137 agonist antibody engineered to maximize efficacy by circumventing the dose-limiting hepatotoxicity reported for prior CD137 agonists (NCT04121676). AGEN2373 binds to a unique epitope of CD137 on effector T and NK cells in the tumor and tumor-draining lymph nodes, promoting co-engagement of activating Fcγ receptors. CD137 (4-1BB) is a tumor necrosis factor receptor superfamily protein and co-stimulatory receptor that promotes anti-tumor activity of adaptive and innate immune cells, making it an attractive target for immunotherapy. **Methods:** 46 patients (pts) received AGEN2373 IV every 2 weeks (Q2W), Q3W, or Q4W at doses between 0.03 and 10 mg/kg in a 3+3 design. Key endpoints included safety, tolerability, PK, preliminary efficacy, and PD markers. Imaging was Q8W. **Results:** Pts were enrolled between Oct 2019 and May 2022 with a median follow-up of 7.2 months. The median age was 64 (range 33-82). The most common tumor types were colorectal cancer, 13 pts (28%) and sarcoma, 8 (17%). Median prior therapies were 4 (range 1-14) including 48% with prior immunotherapy. There were no dose-limiting toxicities (DLTs) and no treatment-related hepatitis. 37% of pts had treatment-related AEs (TRAEs). TRAEs >10% were limited to fatigue (17%) and nausea (15%). There were no G3, 4 or 5 TRAEs. Pharmacokinetic parameters including half-life, clearance, and volume of distribution were consistent with a human IgG1 Fc backbone. Induction of soluble CD137 was dose dependent with 2 mg/kg as the lowest saturating dose and minimum predicted efficacious dose. In 19 pts treated at 2 mg/kg or higher who had at least one post-baseline scan, the overall response rate (ORR) was 11% (n=2); 37% had SD (n=7) resulting in a disease control rate (DCR) (CR, PR or SD) of 47%. Notable responses include: a pt with vulvar SCC who had progressed rapidly on pembrolizumab and had a confirmed partial response (cPR) while remaining on AGEN2373 x 2 mg/kg q2w for ~40 wks, and a pt with ampullary carcinoma with 4 prior regimens had a cPR on AGEN2373 x 6 mg/kg q3w with complete resolution of the pancreatic lesion. A pt with CRPC had a 38% tumor reduction in liver target lesions (confirmed) on AGEN2373 x 10mg/kg q3w but was non-evaluable due to palliative radiation to bone metastases. **Conclusions:** AGEN2373 showed objective responses as monotherapy in heavily pretreated pts with solid tumors and was well-tolerated with no evidence of hepatotoxicity. This distinguishes AGEN2373 from previous CD137-targeted agents that reported dose-limiting hepatotoxicity. Combination therapy with botensilimab, a novel Fc-enhanced CTLA-4 antagonist, is being studied in pts with PD(L)-1 pretreated melanoma. Clinical trial information: NCT04121676. Research Sponsor: Agenus; Gilead.

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Poster Discussion Session

A phase 1a dose-escalation study of PY159, a monoclonal antibody targeting TREM1 (triggering receptor expressed on myeloid cells 1). *First Author: Ira Seth Winer, Barbara Ann Karmanos Cancer Institute, Detroit, MI*

Background: This study aimed to characterize the safety of PY159 (an agonist antibody to TREM1 that reprograms immunosuppressive intratumoral myeloid cells) as a single agent and in combination with pembrolizumab in subjects with advanced refractory solid tumors, including subjects refractory to immune checkpoint inhibitors. **Methods:** Two strata were evaluated, PY159 as a single agent and in combination with pembrolizumab, using an accelerated 3+3 dose escalation study design. Dosing was intravenous once every 3 weeks. Disease assessment by RECIST 1.1 was performed every 6 weeks. The single-agent stratum included 7 dose levels of PY159 (range, 0.01–10 mg/kg). The combination stratum included 4 dose levels of PY159 (range, 0.3–10 mg/kg). Pharmacokinetics were evaluated at specified time points. Archival tumor tissue was analyzed for TREM1 expression by immunohistochemistry. Based on preclinical immunohistochemistry data, HR+ HER2- and triple-negative breast cancer, gastric cancer, pancreatic cancer, head and neck cancer, non-small cell lung cancer, and gynecologic cancers were studied. **Results:** Thirty-seven subjects (median age 65 years; range 29–86 years; 22 female and 15 male) with an ECOG PS <2 were enrolled and all but 5 were RECIST-evaluable (3 withdrew consent, 1 sustained a TEAE, and 1 had a DLT, an asymptomatic grade-3 transaminitis). Twenty subjects received single-agent PY159 and 17 received PY159 in combination with pembrolizumab. Four subjects experienced a grade-3 TRAE, 14 a low-grade immune-related reaction, 18 an SAE (related in 2), and 14 an immune-related adverse event (arthralgias). There were no SUSARs. Five subjects sustained high-grade TRAE resulting in discontinuation. TREM1 levels in the tumors ranged from 0 to 15%. Pharmacokinetic parameters were linear beyond the 0.3 mg/kg dose, dose proportional with a half-life of 8–9 days, and unaffected by pembrolizumab. Radiographic response included 2 partial responses (1 each in an ovarian and pancreatic cancer subject) and stable disease in 9 subjects, ranging from 12 to 96+ weeks. Two subjects continue receiving PY159. **Conclusions:** PY159 was well tolerated, with an acceptable safety profile, as a single agent and in combination with pembrolizumab. A dose for expansion was derived and enrollment of subjects with 7 prespecified cancers is ongoing. Clinical trial information: NCT04682431. Research Sponsor: Pionyr Immunotherapeutics.

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Poster Discussion Session

First-in-human, phase 1a dose finding of LVGN6051 CD137/4-1BB agonistic antibody with or without pembrolizumab in patients with advanced solid tumors. *First Author: Adil Daud, University of California-San Francisco, San Francisco, CA*

Background: LVGN6051 is a conditional 4-1BB agonistic monoclonal antibody with Fcγ-receptor IIB selective binding in the tumor microenvironment for optimal activity. Preclinical studies showed potent antitumor activity by LVGN6051 alone and in combination with anti-PD-1 antibody. **Methods:** We conducted this first in human (FIH) multicenter phase 1 dose escalation study in the US. Eligible pts with advanced solid tumor malignancies received escalating doses of LVGN6051 alone or in combination with pembrolizumab 200 mg IV Q3W until unacceptable toxicity, progressive disease, or withdrawal of consent. **Results:** As of Jan 23, 2023, 55 pts were enrolled and received LVGN6051 alone with the dose range of 0.003–7 mg/kg (n=18), or combination therapy of LVGN6051 2 mg/kg + pembrolizumab (n=22) or LVGN6051 4 mg/kg + pembrolizumab (n=15). The median age was 58 years (range 20-83) and number of prior therapies was 5; 46 pts (84%) had ECOG PS 1 and 21 pts (38%) had received prior immune checkpoint inhibitors (ICI). In pts who received LVGN6051 alone, the MTD was not reached up to 7 mg/kg and the RP2D was selected as 4 mg/kg IV Q3W for tolerance. The RP2D for combination therapy was established as LVGN6051 4 mg/kg and pembrolizumab 200 mg IV Q3W. Pts received a median of 2.8 months and a mean of 4.0 months (range 0.5 – 19.2) of study treatment. 33 pts (60%) experienced any grade treatment-related adverse events (TRAEs) with noteworthy (> 5%) AST increased (27%), ALT increased (26%), thrombocytopenia (16%), infusion related reaction (IRR) (9%), fatigue (7%), lipase increased (6%), nausea (6%) and chills (6%), 14 pts (25%), 14 pts (25%), 14 pts (25%) and 13 combination therapy, showed ≥ grade 3 TRAEs: AST increased (11%), ALT increased (9%), thrombocytopenia (7%), fatigue (4%), IRR (2%), lipase increased (2%) and nausea (2%). 6 drug-related serious adverse events and 1 DLT (grade 4 thrombocytopenia), all in combination therapy, were reported. In 42 evaluable pts, the disease control rate (DCR) was 50%. Combination therapy showed that target lesions were reduced by 57%, 42% and 48% in melanoma (n=2) and pancreatic cancer (n=1), respectively. Among 11 melanoma pts (10 had progressed on anti-CTLA4 and anti-PD-1 therapy), 2 PR and 5 SD were observed per RECIST 1.1, including one being treated for 19+ months (26+ cycles). Pts with HNSqCC (n=1) and CRPC (n=1) also showed remarkable tumor shrinkage. Paired tumor biopsies for single cell RNAseq biomarker exploration confirmed activation of effector T cells following LVGN6051 treatment. **Conclusions:** We established the RP2Ds of LVGN6051 alone and in combination with pembrolizumab in this FIH phase 1a study. These regimens were well tolerated. Preliminary efficacy data showed encouraging anti-tumor activity in heavily pretreated pts who had progressed on ICI. Phase 1b dose expansion for the combination therapy is ongoing in pts with melanoma, GI malignancies and NSCLC. Clinical trial information: NCT04130542. Research Sponsor: Lyngen Biopharma Holdings Limited.

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Poster Discussion Session

A phase 1/2 study of the TORC1/2 inhibitor onataseritib combined with toripalimab in patients with advanced solid tumors. *First Author: Pei Shu, Clinical Trial Center, National Medical Products Administration Key Laboratory for Clinical Research and Evaluation of Innovative Drugs, West China Hospital, Sichuan University, Chengdu, China*

Background: Pre-clinical studies suggest synergistic activity of the combination of inhibitors of mTOR with a PD-1 antibody in solid tumors. Here we report updated results of a phase 1/2 open-label, dose escalation and expansion trial of the oral TORC1/2 inhibitor, onataseritib (ATG-008) in combination with toripalimab (tori), a PD-1 monoclonal antibody, in patients (pts) with advanced solid tumors. **Methods:** This study consists of dose escalation and dose expansion. The primary objective in the dose escalation phase was to evaluate safety and tolerability of onataseritib combined with tori, followed by a dose expansion phase to assess antitumor efficacy and verify the safety and tolerability profile of the combination therapy. Primary endpoints included maximum tolerated dose (MTD), recommended phase II dose (RP2D) and efficacy of the combination. Other endpoints included pharmacokinetics and exploratory biomarkers of drug activity. Prior PI3K/AKT/mTOR inhibitor therapy was excluded, regardless of PD-L1 expression. Onataseritib was administered orally once a day (QD) at three dose levels (15, 20 and 30mg) in combination with tori at the approved dose of 240 mg, once every 21 days (Q3W). **Results:** As of Oct 21, 2022 cut-off, 46 advanced solid tumor pts were enrolled with 10 pts in the dose escalation phase and 36 pts in the dose expansion phase. Median age was 53 years. Baseline ECOG scores were 0 (13 pts) and 1 (33 pts) with a median of 2 prior lines of therapy (0-7); 27 pts had stage IV disease. Twenty-one cervical cancer (CC) pts were enrolled in total with the similar baseline characteristics. No dose-limiting toxicity was reported in dose escalation phase. The study did not reach MTD. Forty-five pts (97.8%) had ≥ 1 TEAEs; 32 (69.6%) pts had grade ≥ 3 TEAEs. The most common grade ≥ 3 TEAEs included lymphocyte count decreased (23.9%), rash (19.6%) and hyperglycemia (10.9%). The RP2D for onataseritib was determined to be 15 mg in combination with the recommended dose of tori. Among the 46 treated pts, ORR was 26.1% (12/46, all confirmed), and DCR was 73.9%. In 21 pts with CC, ORR was 52.4%, including 1 CR and 10 PR, and DCR was 90.5%. One CC pt with negative PD-L1 expression achieved CR and remains on treatment after 883 days. The ORR was 75% (6/8) and 41.7% (5/12) for CC pts with PD-L1 positive and negative expressions, respectively. One CC pt with prior anti-PD-1 therapy also reached PR. Another PR was achieved in nasopharyngeal carcinoma (NPC) for over 2 years. Median PFS in all treated pts and CC cohort was 4.3 months(m) and 7.2 m, respectively. Pharmacokinetic profiles of ATG-008 in combination with PD-1 antibody were similar to ATG-008 monotherapy, across Asia Pacific and U.S. patient populations. **Conclusions:** Onataseritib in combination with tori is tolerable with encouraging response rate and disease stabilisation in pts with advanced solid tumors, especially in CC pts. Expansion enrolment for CC and NPC is ongoing. Clinical trial information: NCT04337463. Research Sponsor: Antengene Corporation.

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Poster Discussion Session

AMPLIFY-201, a first-in-human safety and efficacy trial of adjuvant ELI-002 2P immunotherapy for patients with high-relapse risk with KRAS G12D- or G12R-mutated pancreatic and colorectal cancer. *First Author: Eileen Mary O'Reilly, Memorial Sloan Kettering Cancer Center, Weill Cornell Medical College, New York, NY*

Background: RAS mutations occur in 25% of solid tumors with G12D being the most frequent variant. ELI-002 2P is a vaccine comprised of lymph-node targeted Amphiphile (Amph)-modified G12D and G12R mutant KRAS peptides with an Amph-modified CpG oligonucleotide adjuvant designed to expand polyfunctional mutant KRAS-specific T cells. Preclinical amphiphile data (relative to non-amphiphile controls) showed increased immunogenicity, tumor clearance and survival in mouse models. **Methods:** This first-in-human multicenter phase I trial assessed safety, immunogenicity and antitumor activity using a novel adjuvant trial design in patients (pts) with minimal residual disease (MRD) following standard of care treatment. Eligibility: elevated circulating tumor DNA (ctDNA) and/or serum tumor biomarker elevation (CA19-9/CEA), and KRAS/NRAS mutation. In a 3+3 dose escalation, n=22 received a subcutaneous course of 6 prime and 4 booster injections of fixed dose Amph-peptides (1.4 mg), admixed with escalating Amph-CpG-7909 (Table). Dose escalation based on observed safety in first 28 days. Safety, antitumor activity including biomarker reduction/clearance and relapse free survival using Immune Response Evaluation Criteria in Solid Tumors (IRECIST) were assessed. Immunogenicity assessed by direct ex vivo Fluorespot and intracellular cytokine staining of peripheral blood mononuclear cells (T-cell responders = ≥ 2 -fold increase over baseline) and by tumor CD3 immunohistochemistry in subset who underwent a biopsy. **Results:** No dose-limiting toxicities, treatment related SAEs or cytokine release syndrome were observed, and no maximum tolerated dose was identified. Safety: all grade 1, fatigue (19%), headache (19%), and injection site reaction (9.5%). Biomarker reduction was observed in 15/19 (79%) and in 5/5 at highest doses; clearance of MRD was observed in 4/19 (21% - n=2 pancreas, n=2 colorectal). Polyfunctional mKRAS-specific T cell responses observed in 80% of pts (n=12/15), with both CD8+ and CD4+ T cell responses for most, and CD3+ T cells observed on biopsies. The recommended phase 2 dose (RP2D) is 10.0 mg Amph-CpG-7909. **Conclusions:** ELI-002 2P, evaluated in a novel MRD+ trial, was safe with ctDNA and serum tumor biomarker reduction and clearance and notable immune responses. The RP2D is the start dose for a phase 1/randomized phase 2 study evaluating a new seven peptide formulation for G12 D, R, V, S, A, C, and G13D mutated solid tumors (NCT05726864). Clinical trial information: NCT04853017. Research Sponsor: Elicio Therapeutics.

ELI-002 Amph-CpG Dose Level	0.1 mg	0.5 mg	2.5 mg	5.0 mg	10.0 mg
Number of pts/mKRAS G12D or G12R	3/DDD	6/DDDDD	5/DRDD	5/DRDD	3/RRD
Safety (DLT)	0/3 (0%)	0/6 (0%)	0/5 (0%)	0/5 (0%)	0/3 (0%)
Biomarker reduction/clearance	2/3 (67%)	5/6 (83%)	3/5 (60%)	3/3* (100%)	2/2* (100%)
T cell response	2/3 (67%)	5/6 (83%)	2/3 (67%)*	3/3 (100%)*	*

*Subset of pts evaluable at data cut.

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Poster Discussion Session

A phase 1 dose-escalation study of RiMO-301 with palliative radiation in advanced tumors. *First Author: Matthew Koshy, University of Chicago, Chicago, IL*

Background: Nanoscale metal-organic frameworks (MOFs) are a new class of organic-inorganic hybrid nanomaterials constructed from metal centers and organic ligands. Preclinical studies have shown that nanoscale MOFs can enhance the antitumor effects of ionizing radiation via a unique radiotherapy-radiodynamic therapy mode of action, and MOFs plus radiation can enhance the immunotherapeutic effects of immune checkpoint inhibitors. RiMO-301 is a hafnium-based MOF which enhances radiotherapy and checkpoint blockade immunotherapy without showing systemic toxicity in preclinical models. RiMO-301 is the first MOF to enter clinical trials on human patients. **Methods:** This is a multicenter, open-label, first-in-human dose-escalation phase I trial of RiMO-301 [NCT03444714]. The primary objective is to determine the maximum tolerated dose (MTD) of locally injected RiMO-301 with or without the PD-1 inhibitor pembrolizumab in patients treated with concurrent palliative doses of radiation (20 Gy in 5 fractions or 30 Gy in 10 fractions) using a 3+3 design. The MTD is defined as the dose associated with dose-limiting toxicity (DLT) in less than 33% of patients. The secondary objective is to evaluate antitumor response (objective response rate, ORR) using RECIST and iRECIST criteria. **Results:** A total of 25 patients were enrolled and treated with escalating doses of RiMO-301 (relative to tumor volumes). No protocol defined DLT was reported. The observed possibly treatment related adverse events included mild dermatitis radiation, mild dysgeusia, diarrhea, mild hypotension (30 days post treatment) and mild dizziness (30 days post treatment). One patient each experienced a Grade 2 alanine aminotransferase increase 45 days post treatment, a Grade 2 dry mouth, and a Grade 3 pain at the injection site. Nineteen patients were evaluable, with 13 and 6 patients, respectively, for RiMO-301 without and with pembrolizumab treatments. By iRECIST criteria, RiMO-301 without pembrolizumab demonstrated 38.5% (5/13) ORR (1 complete response and 4 partial responses) with 2 additional patients experiencing 20-30% tumor size reduction. RiMO-301 with pembrolizumab exhibited 66.7% (4/6) ORR with the 2 remaining patients showing 15-20% tumor size reduction. Preliminary pharmacokinetic analysis indicated that the hafnium concentrations in the systemic circulation were either below or barely above the level of detection. **Conclusions:** RiMO-301 with or without pembrolizumab was well tolerated and demonstrated promising signs of efficacy in patients with advanced tumors when treated with concurrent palliative radiotherapy. The results support the use of RiMO-301 as a potential radio-enhancer and will prompt further phase 2 studies in the development of RiMO-301 for patients undergoing radiotherapy. Clinical trial information: NCT03444714. Research Sponsor: Coordination Pharmaceuticals Inc.

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Poster Session

Phase 1 first-in-human study of PF-07257876, a novel CD47/PD-L1 bispecific checkpoint inhibitor, in patients with PD-1/PD-L1-refractory and -naïve advanced solid tumors. *First Author: Benedito A. Carneiro, Legorreta Cancer Center, Brown University, Providence, RI*

Background: Tumor expression of the antiphagocytic protein CD47 (integrin associated protein) may lead to immunotherapy resistance (IO-R). PF-07257876 is a novel, IgG1, Fc-active, bispecific antibody targeting CD47 and PD-L1 designed to reverse IO-R, decrease anemia risk, and eliminate a priming dose. We report a Phase 1 dose escalation study (NCT04881045) in patients (pts) with advanced solid tumors, both IO-refractory and IO-naïve. **Methods:** The study enrolled pts ≥ 18 yrs with advanced non-small-cell lung carcinoma (NSCLC) and squamous cell carcinoma of the head and neck (SCCHN) with PD-L1 expression $>1\%$ post anti-PD-1/PD-L1 therapy. Pts with other PD-L1+ tumors known to express CD47 were included (prior IO not required). Pts received PF-07257876 at escalating dose levels in 28-day cycles. Primary objectives were safety (dose-limiting toxicity [DLT] rate), tolerability, and determination of Recommended Phase 2 Dose (RP2D). Secondary and exploratory objectives included pharmacokinetics (PK), blood receptor occupancy (RO), CD47 levels by immunohistochemistry (IHC), tissue biopsy findings, and objective response rate (ORR) per RECIST v.1.1. **Results:** As of 200CT2022, 18 pts were enrolled (NSCLC: n = 6; SCCHN: n = 4; other: n = 8). Median (range) age 68 (46–79) yrs. PF-07257876 was given at ascending doses, 150–2400 mg by subcutaneous (SC) injection or SC infusion every 2 weeks. 16 (89%) pts had treatment-related adverse events (TRAEs): Grades 1/2: n = 12 (67%); Grade 3: n = 1 (6%); Grade 4: n = 3 (17%); no Grade 5. Most common TRAEs: injection site reaction/erythema (n = 13, 72%), thrombocytopenia (n = 6, 33%), anemia (n = 5, 28%), and nausea (n = 4, 22%). DLTs occurred in 2 of 3 pts at the highest tested dose (Grade 4 neutropenia and thrombocytopenia, n = 1; Grade 4 thrombocytopenia, n = 1; both pts recovered). One pt with IO-R SCCHN had a confirmed partial response (duration of response 16 wks). ORR was 5.6% (1/18). Drug exposure increase after 1st dose was not dose proportional. Blood RO was $> 95\%$ for PD-L1 and $> 70\%$ for CD47 with drug exposure. All pts' baseline CD47 IHC levels were moderate to high. Pharmacodynamics cytokine profiling showed notable dose-response increases of IFN γ , TNF α , CXCL9/10, CCL3/4, without IL-6 increase. **Conclusions:** PF-07257876 was well tolerated with manageable toxicity. Incidence and grade of anemia or thrombocytopenia were manageable. Target engagement of CD47 and PD-L1 in peripheral blood was high. Innate and adaptive cytokine modulation was observed. Antitumor activity was modest. Expansion is ongoing at 1800 mg. Clinical trial information: NCT04881045. Research Sponsor: Pfizer.

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Poster Session

A phase Ib trial of the VEGF fusion protein HB002.1T plus chemotherapy in patients with advanced solid tumors. *First Author: Junli Xue, Department of Medical Oncology, Shanghai East Hospital, Tongji University School of Medicine, Shanghai, China*

Background: HB002.1T is a recombinant human vascular endothelial growth factor receptor (VEGF)-IgG Fc fusion protein, which functions as a decoy receptor to bind VEGF-A, VEGF-B and placental growth factor (PlGF). In phase Ia, HB002.1T monotherapy showed encouraging anti-tumor activity in gallbladder cancer. **Methods:** This study aimed to evaluate efficacy and safety of HB002.1T plus chemotherapy (mainly based on platinum, paclitaxel, gemcitabine, etc.) in advanced solid tumors. The tumor assessment was evaluated by investigator according to RECIST v1.1. The study included part 1 and part 2, part 1 study was dose escalation (12mg/kg, 16mg/kg Q3W) and dose expansion conducted in patients (pts) with advanced solid tumors, part 2 study was dose expansion (16mg/kg Q3W) in specified tumors (cohort 1: ovarian and cervical, cohort 2: pancreatic, gallbladder and bile duct cancer). **Results:** As of Dec 20, 2022, 68 (42F/26M) advanced solid tumor pts were enrolled in the study with 32 pts in part 1 and 36 pts in part 2. 33.3% pts failed at least 3 lines of therapy before enrollment. 63 (92.6%) pts had stage IV disease. Median age was 58. It is to be noted that 12 efficacy assessment evaluable pts with ovarian cancer (1 with 12mg/kg in part 1, 11 with 16mg/kg in part 2) were all stage IV, which included 3 complete response (CR), 6 partial responses (PR) and 3 stable disease (SD). Median progression free survival (PFS) was 7.3 months and 6-month PFS rate was 58.3%. The ORR and DCR were 75%, 100% respectively. The most common treatment related adverse events (TRAEs) included neutropenia (9/12, 75.0%) and leukocytopenia (8/12, 66.7%). 8 (8/12, 66.7%) pts had grade ≥ 3 TRAEs, which neutropenia (4/12, 33.3%) and leukocytopenia (3/12, 25.0%) were commonly observed. Part 1: In 28 pts whose tumor assessment were available, including 1 gastric cancer patient achieved CR, 11 pts achieved PR (2 gastric, 2 ovarian, 2 cervical, 1 maxillary, 1 lung, 1 parotid, 1 nasopharynx, 1 pancreatic) and 15 achieved SD. Part 2: 32 pts were available for tumor assessment, including 4 achieved CR (3 ovarian, 1 cervical), 10 achieved PR (4 ovarian, 2 cervical, 3 biliary, 1 pancreatic), and 16 achieved SD. Overall, in Part 1 and 2, TRAEs occurred in 64 (64/68, 94.1%) pts. The most common TRAEs were leukocytopenia (28/68, 41.2%), neutropenia (26/68, 38.2%) and proteinuria (25/68, 36.8%). 34 (34/68, 50.0%) pts had grade ≥ 3 TRAEs, which neutropenia (15/68, 22.1%) and leukocytopenia (11/68, 16.2%) were commonly observed. TRAE leading to discontinuation occurred in 3 pts. No death was reported related with HB002.1T. **Conclusions:** The Pts were well tolerated to 12mg/kg and 16mg/kg HB002.1T dose combined with chemotherapy, and HB002.1T showed acceptable safety profile. As well as, promising anti-tumor activity was observed in various tumors, especially in advanced ovarian cancer. More data is being accumulated, and confirmatory clinical trials are being prepared. Clinical trial information: NCT04802980. Research Sponsor: Shanghai Huaota Biopharma Co., Ltd.

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Poster Session

A phase 1 dose-escalation study to investigate the safety, efficacy, pharmacokinetics, and pharmacodynamic activity of cln-619 (Anti-MICA/B antibody) alone and in combination with pembrolizumab in patients with advanced solid tumors. *First Author: Judy S. Wang, Sarah Cannon Research Institute at Florida Cancer Specialists, Sarasota, FL*

Background: MICA and MICB are stress-induced ligands upregulated on the majority of human tumors. Engagement of MICA/B by the activating receptor NKG2D on NK cells and several subsets of T cells results in immune-mediated target cell lysis. However, proteases in the tumor microenvironment cleave cell surface MICA/B, enabling immune evasion. CLN-619 is a humanized MICA/B-specific IgG1 monoclonal antibody designed to prevent the proteolytic release of MICA/B, restoring immune-mediated tumor cell lysis. CLN-619 is expected to have broad anti-tumor activity. **Methods:** This phase 1, multicenter, open-label, first-in-human dose-escalation study (NCT05117476) enrolls patients (pts) with advanced solid tumors who progressed on available therapies, were intolerant to treatment, or refused noncurative standard treatment. CLN-619 alone (dose levels (DL) of 0.1, 0.3, 1, 3, 6, 10mg/kg) were administered intravenously every three weeks. Corticosteroid pre-medication for infusion related reaction (IRR) prophylaxis were required starting at the 3 mg/kg DL. A parallel dose-escalation is exploring CLN-619 (DL 1.0 mg/kg and higher) in combination with pembrolizumab. Response (RECIST 1.1) is assessed every 9 weeks. Data from the monotherapy dose escalation are described. **Results:** As of Dec 2, 2022, 23 pts (median age, 63 y, range 47-83) were enrolled, 48% were male and 61% had ECOG PS 1. Major tumor types included colon (4), cervical (3), lung (3) and prostate (3). All pts received prior systemic therapy (median 3, range 1-7); 12 patients had prior checkpoint inhibitor. The median number of CLN-619 cycles received was 2 (range, 0-8). Treatment-emergent adverse events (TEAEs) in $\geq 20\%$ of pts were abdominal pain (26%), nausea (22%), pyrexia (22%), and infusion related reaction (IRR) (22%). IRRs occurred at dose levels of 0.3 mg/kg and higher. All IRR occurred in Cycle 1 and resolved within 3 hours of onset. One case of Gr3 laryngeal edema occurred at the 10 mg/kg DL in the absence of required steroid premedication and led to dose discontinuation. No fatal TEAEs were reported. A nearly dose-proportional increase in CLN-619 exposure was observed between the 0.1 mg/kg and 10 mg/kg dose levels. CLN-619 half-life ranged from 87.6 to 307 hours for DL ranging from 0.1 mg/kg to 6 mg/kg. There was one confirmed complete response in a patient with recurrent salivary gland tumor who progressed following a complete response on a PD-1 blocking agent. Another patient with cervical cancer maintained SD for 9 cycles before progressing. **Conclusions:** CLN-619 therapy was well tolerated at doses ranging from 0.1 to 10 mg/kg and demonstrated monotherapy clinical activity, including objective response in a patient progressing after PD-1. Updated data from the dose-escalation portion of the trial will be presented. Clinical trial information: NCT05117476. Research Sponsor: Cullinan Oncology, Inc.

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Poster Session

A phase 1, first-in-human, open-label, dose escalation and dose expansion study of TST005 in patients with locally advanced or metastatic solid tumors. *First Author: Anthony W. Tolcher, NEXT Oncology, San Antonio, TX*

Background: TST005 is a novel bi-functional fusion protein combining a high affinity PD-L1 mAb and a differentiated TGF- β trap with improved stability. In pre-clinical study, TST005 showed no antibody-dependent dependent cytotoxicity (ADCC) or complement dependent cytotoxicity (CDC) activity. **Methods:** This is a Phase 1, dose escalation study with classic 3+3 design to evaluate the safety, tolerability, PK and pharmacodynamic and preliminary anti-tumor activity of TST005 and determine the maximum tolerated dose and/or the Recommended Phase 2 Dose (RP2D). Eligible solid tumor patients who have failed prior standard therapy(ies) and have received no more than one prior immune checkpoint inhibitor (ICI) treatment will be enrolled to receive TST005 intravenous (IV) infusion every 3 weeks until disease progression assessed by the Investigator per RECIST v1.1 and/or immune RECIST, or unacceptable toxicity. **Results:** The study is ongoing at 4 clinical centers in US and China. As of 31 Jan 2023, 18 eligible subjects have been enrolled into different TST005 dose levels: 2 at dose of 1mg/kg, 4 at 3 mg/kg, 4 at 10 mg/kg, 3 at 20 mg/kg, and 5 at the last dose level of 30 mg/kg. The enrollment is still ongoing. No DLT was observed so far. The most common treatment-emergent adverse events (TEAEs) ($> 10\%$) included: fatigue (38.9%), rash (22.2%), anemia (16.7%), myalgia (16.7%), and arthralgia, dehydration diarrhea, dry skin, hematuria, hypokalemia, pruritus, lymphocyte count decreased were 11.1%. 7 patients (38.9%) experienced $\geq$ Grade 3 (G3) TEAEs according to CTCAE V5.0, 1 of whom were considered as related to TST005: it was an infusion related reaction (G3), and caused discontinuation of treatment. Two subjects experienced IRRs (G2 and G3 respectively), both at the dose of 3mg/kg cohort. One subject of 30mg/kg dose cohort presented a squamous cell carcinoma of skin, which is known as a classic side effect of TGF- β directed therapies. The subject was discontinued from study and to receive resection. No treatment-related deaths occurred. TST005 demonstrated a nonlinear PK profile between 1 to 20 mg/kg with calculated $t_{1/2}$ of 4-9 days. ADA was observed in most ADA evaluable subjects, PK at doses ≥ 10 mg/kg were not impacted by ADA. At 20mg/kg, the receptor occupancy increased to $> 90\%$ immediately after infusion and remain at this level up to CD21. Start from 1mg/kg, serum TGF- β 1 was depleted immediately after dosing, sustained to next dose of TST005. 11 subjects had at least one post treatment tumor assessment per RECIST 1.1. 7 subjects (63.6%) had best overall response of SD. No PR or CR had been observed. **Conclusions:** TST005 monotherapy demonstrated a good safety and tolerability, nonlinear PK characteristics and significant target engagement in patients with advanced solid tumors. Continue investigation of TST005 as monotherapy or in combination with other therapies are warranted. Clinical trial information: NCT04958434. Research Sponsor: Suzhou Transcenta Therapeutics Co., Ltd.

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Poster Session

Leveraging innate immunity with AFM24, a novel CD16A and epidermal growth factor receptor (EGFR) bispecific innate cell engager: Interim results for the non-small cell lung cancer (NSCLC) cohort. *First Author: Anthony B. El-Khoueiry, University of Southern California, Norris Comprehensive Cancer Center, Los Angeles, CA*

Background: Patients with EGFR mutant NSCLC who progress on or after small molecule EGFR inhibitors have only limited treatment options. AFM24 is a tetravalent, bispecific innate cell engager that binds EGFR on solid tumor cells and CD16A on NK cells to redirect and enhance antitumor antibody-dependent cellular cytotoxicity, thus acting independently of the EGFR downstream signaling pathway and EGFR expression levels. The Phase 1 dose escalation phase of the presented study (NCT04259450) established the recommended Phase 2 dose of AFM24 monotherapy at 480 mg based on tolerability, receptor occupancy, and pharmacokinetics (PK). Correlative science data revealed an activation and enrichment of immune cells in the tumor microenvironment. **Methods:** The Phase 2a expansion phase is evaluating 480 mg AFM24 in patients with EGFR mutant NSCLC, relapsed or refractory to ≥ 1 prior lines of therapy; EGFR-positivity is defined as positive staining for EGFR in $\geq 1\%$ of tumor cells per local immunohistochemistry assay. The study follows Simon's two-stage design. The primary endpoint is overall response rate per local RECIST v1.1; secondary endpoints include safety, PK, and immunogenicity. Efficacy per iRECIST is an exploratory endpoint. AFM24 is administered intravenously once weekly in a 28-day cycle. Tumor assessments are performed at initial screening, cycles 2, 4, 6, 8, and every 3 cycles thereafter. **Results:** As of December 2022, 14 patients (median [range] age 55 [37-82]; 12 male; 11 Asian, 3 White) were enrolled; the median number of prior therapies was 2.5 (1-12). Median treatment duration with AFM24 was 6.7 weeks (1.0-26.1). Best objective response in 10 evaluable patients was confirmed partial response in 1 patient (change from baseline -45%); 4 patients exhibited stable disease, 1 was confirmed. Tumor shrinkage occurred in 2 patients with stable disease (-6%, -18%). The tumor control rate was 50%. Treatment-related adverse events (TRAEs) were reported in 13 patients; infusion related reactions (IRRs, 12), dermatitis acniform, neutrophil count decreased, decreased appetite, and myalgia (2 each) were most common. Grade ≥ 3 TRAEs occurred in 4 patients and included decreased neutrophil count (2), lymphopenia, and IRR (1 each). Grade 5 pneumonitis was observed in 1 patient with disease progression and multiple comorbidities; relation to AFM24 could not be ruled out. As of January 2023, enrollment is ongoing; results of the interim analysis will be presented. **Conclusions:** AFM24 demonstrated clinical activity and acceptable safety in heavily pretreated patients with EGFR mutant NSCLC. The novel mechanism of action of AFM24 could add to the therapeutic options for patients with EGFR expressing tumors and is under clinical evaluation as a single agent and in combination with atezolizumab or autologous NK cells. Clinical trial information: NCT04259450. Research Sponsor: Affimed GmbH.

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Poster Session

Clinical development of the bispecific PSMAxCD3 antibody CC-1. *First Author: Christopher Hackenbruch, University Hospital Tübingen, German Cancer Consortium (DKTK), Department of Internal Medicine, Clinical Collaboration Unit Translational Immunology, Tübingen, Germany*

Background: While being highly efficient in hematological malignancies, bispecific antibodies (bsAbs), alike CAR T cells, are yet not successful in solid tumors. Moreover, all available T cell-mobilizing strategies cause side effects that endanger patients and, in case of bsAbs, limit applicable doses and thus efficacy. We report on the clinical development of CC-1, a PSMAxCD3 bsAb, in an IgG-based format that induces fully target cell-restricted T cell activity (Zekri et al, EMBO Mol Med, 2020). Targeting PSMA, which is expressed on malignant cells and on the neovasculature, improves accessibility of the tumor site for immune effector cells as critical prerequisite for success in solid tumors. Notably, CC-1 binds a unique PSMA epitope which is expressed on malignant cells both of prostate carcinoma (PC) and 50% of patients with squamous cell carcinoma (SCC) of the lung. **Methods:** A FIH trial evaluating CC-1 with pre-emptive Tocilizumab included patients with metastatic castration resistant prostate carcinoma (mCRPC) (NCT04104607) and consisted of two parts. Dose escalation (n=10-66) using a novel intra-individual dose escalation design to rapidly reach the target dose of 826µg to determine safety, tolerability and maximum tolerated dose (MTD) (Labrenz et al, Pharm Stat, 2022). The dose expansion cohort exposed patients to CC-1 at MTD and explored efficacy to define RP2D (n=14). Our second phase I trial enrolls patients with SCC of the lung (NCT04496674) to receive CC-1 in combination with checkpoint inhibition. Based on the meanwhile available very favorable safety and preliminary efficacy data, a third phase I trial was initiated where CC-1 is evaluated as first line treatment in patients with hormone sensitive biochemical recurrence (BCR) of PC (NCT05646550), where tumor burden is low and accordingly lower side effects and long-lasting efficacy are expected. **Results:** Recruitment in the dose escalation part of the trial in mCRPC has been completed and the target dose was reached and MTD defined without DLT upon treatment of the 9th and 14th patient, respectively. 24 patients completed treatment, with the most frequently observed toxicity being cytokine release syndrome (CRS, max. 2°) (88%). Besides grade 1 to 2 hypertension (46%) and xerostomia (8%), no further CC-1 related toxicities were observed. A rapid and profound decline of elevated PSA levels was observed in all but one patient, with up to 60% reduction compared to baseline. So far 5 patients received multiple treatment cycles at MTD-level. One patient with SCC of the lung has been treated and CC-1 was escalated up to 153µg without occurrence of CRS. In the phase I trial in BCR of PC, the first three patients were enrolled in February 2023. **Conclusions:** CC-1 is a promising compound with a favourable toxicity profile and promising clinical activity. Details on study designs and updated data from the 3 clinical trials will be presented at the meeting. Clinical trial information: NCT04104607, NCT04496674, NCT05646550. Research Sponsor: German Cancer Research Center, German Cancer Consortium, AKF program of the University Tübingen, Helmholtz validation fund; Else-Kröner Fresenius Stiftung, Robert Bosch Center for Tumor Diseases (RBCT) at the Bosch Health Campus (BHC).

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Poster Session

Phase Ib/Ia safety and efficacy of PM8002, a bispecific antibody targeting PD-L1 and VEGF-A, as a monotherapy in patients with advanced solid tumors. *First Author: Ye Guo, Shanghai East Hospital, School of Medicine, Tongji University, Shanghai, China*

Background: PM8002 is a bispecific antibody targeting both PD-L1 and VEGF-A. We had completed dose escalation from 1mg/kg to 45mg/kg and had not found DLT/MTD. In a Phase Ib dose expansion and Phase Ia studies we are evaluating the safety and preliminary anti-tumor activity of PM8002 as a monotherapy. Here, we provide an update of PM8002 Phase Ib/Ia results. **Methods:** During Phase Ib dose-expansion and Phase Ia studies, the majority of patients received PM8002 at 20mg/kg Q2W or 30mg/kg Q3W as a monotherapy (recommended phase II doses). The primary endpoint was ORR with secondary endpoints/objectives including safety. **Results:** As of Feb 3, 2023, 263 patients of advanced solid tumor with prior 0 to 4 line systematic treatment had been enrolled (1mg/kg Q2W [n=1], 10mg/kg Q2W [n=1], 20mg/kg Q2W [n=190], 20mg/kg Q3W [n=4], 30mg/kg Q2W [n=4], 30mg/kg Q3W [n=52], and 45mg/kg Q3W [n=11]). The median duration of exposure was 10.6 weeks (range, 0.1—51.0). Of the 263 enrolled patients, 211 had completed their first evaluation for efficacy. The overall ORR, regardless of tumor type, was 15.2% (32/211) with 32 PRs (20 confirmed PRs), and the DCR was 75.4% (159/211) per RECIST 1.1. Twenty-five patients with cervical cancer had an ORR of 28% (7/25). Twenty-six patients with renal cell carcinoma had an ORR of 26.9% (7/26). Twenty-six patients with platinum-resistant ovarian cancer had an ORR of 15.4% (4/26), and 27 patients with NSCLC (with EGFR mutations) had an ORR of 18.5% (5/27). Any-grade TRAEs occurred in 68.8% patients (181/263), with 18.3% Grade ≥3 (48/263). The most common TRAEs were proteinuria (17.5%), hypertriglyceridemia (11.4%), Aspartate aminotransferase (9.9%), Alanine aminotransferase increased (9.5%), Hypoalbuminemia (8.7%), and increased gamma-glutamyl transferase levels (6.8%). Thirty-six patients (13.7%) discontinued PM8002 due to TRAEs. No death-related cases occurred, and most patients remain on treatment. **Conclusions:** PM8002 showed encouraging antitumor activity and good safety in patients with advanced solid tumors. Phase Ib/Ia of PM8002 as a monotherapy and Phase II combination trials of PM8002 with chemotherapy are ongoing for multiple indications. Clinical trial information: ChiCTR2000040552. Research Sponsor: Biotheus Inc.

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Poster Session

Preliminary results of a phase I dose escalation study of IMM2510, a PD-L1 and VEGF bispecific fusion protein, in patients with advanced tumors. *First Author: Xiangdong Cheng, Zhejiang Cancer Hospital, Hangzhou, China*

Background: It is well established that anti-PD-1/PD-L1 and anti-VEGF therapies have excellent synergic effects. Previous clinical trials showed that immunotherapy using anti-PD-1/PD-L1 combined with various VEGF/VEGFR targeting agents achieved better efficacy for advanced tumors. IMM2510 is a novel bispecific fusion protein targeting PD-L1 and VEGFs with good efficacy and safety profile verified by our preclinical study. Here we report the preliminary data of an ongoing phase I dose escalation clinical trial of IMM2510 in human. **Methods:** A phase I, multicenter, open labelled, dose escalation study, was designed to evaluate the safety, efficacy, pharmacokinetics (PK) and pharmacodynamics (PD) of IMM2510. Patients (pts) with advanced solid tumors who had undergone more than two prior lines of PD-1/PD-L1 or antiangiogenic inhibitor therapies were excluded. IMM2510 was administered intravenously Q2W by using accelerated titration (0.007 mg/kg, 0.03 mg/kg) followed by 3+3 dose escalation design (0.1 mg/kg, 0.3 mg/kg, 1.0 mg/kg, 3.0 mg/kg, 6.0 mg/kg, and 10.0 mg/kg) to evaluate the safety and to determine recommended phase II dose (RP2D). Anti-tumor activity was evaluated based on RECIST v1.1. **Results:** As of Dec 15, 2022, 22 pts had received IMM2510 at 8 dose levels (0.007 mg/kg-10.0 mg/kg), the median age was 55.5 yrs, the median prior line of therapy was 3, ranging 1-12. No DLT was observed. The most common TRAEs (≥ 20%) were infusion related reaction (IRR) (63.6%), diarrhea (22.7%), anemia (22.7%). 4 pts experienced G3 TRAEs, including IRR (4.5%), diarrhea (4.5%), pain in extremity (4.5%), C-reactive protein increased (4.5%), prolactin increased (4.5%) and lymphocyte count decreased (4.5%). No G4/G5 TRAE occurred. MTD had not been reached. Based on 17 evaluable pts, 1 confirmed PR was observed after 24-week of treatment at 3.0 mg/kg in an ongoing patient with lung squamous cell carcinoma who was IO resistant to prior therapies. Additionally, SDs were seen in 4 patients (1 ovarian serous carcinoma at 0.1 mg/kg, 1 cervical squamous cell carcinoma at 3.0 mg/kg, 1 malignant pleural mesothelioma at 6.0 mg/kg, and 1 breast invasive ductal carcinoma at 10.0 mg/kg). After the cut-off date, another NSCLC patient at 10.0 mg/kg achieved PR after 9-week of treatment and was ongoing on the study. Preliminary PK analysis demonstrated that T_{1/2} of IMM2510 was around 6 days at the high dose levels. PD data showed that at doses of 3.0 mg/kg or greater, the circulating VEGF-A was completely blocked after first administration till the end of treatment. **Conclusions:** These data indicated that IMM2510 is well tolerated at the dose levels evaluated, and preliminary anti-tumor efficacy in solid tumors is encouraging. The phase I/II is ongoing. Clinical trial information: chict20211203. Research Sponsor: ImmuneOnco Biopharmaceuticals (Shanghai) Inc.

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Poster Session

Preliminary results of a phase 1/2, first-in-human, open-label, dose escalation study of ZL-1211 (anti-Claudin 18.2 mAb) in patients with unresectable or metastatic solid tumors. *First Author: Sunil Sharma, Honor Health, Scottsdale, AZ*

Background: ZL-1211 is a humanized immunoglobulin G1 monoclonal antibody targeting Claudin18.2. Site mutations (S239D and I332E) were introduced in the Fc portion of ZL-1211 to enhance antibody dependent cellular cytotoxicity. Herein, we present the preliminary results from the ongoing dose escalation part of the study. **Methods:** This is a first-in-human, phase 1/2, multicenter, dose escalation/cohort expansion study of ZL-1211 administered intravenously to adult patients with Claudin 18.2-positive advanced solid tumors. A Bayesian optimal interval design with 3+3 run-in was adopted to assess 5 dose levels of ZL-1211 monotherapy (1 to 40 mg/kg biweekly) for phase 1 dose escalation, followed by phase 2 cohort expansion. The primary objectives were to determine the maximum tolerated dose and/or the recommended phase 2 dose, assess the safety/tolerability, and evaluate the preliminary antitumor activities of ZL-1211. Tumor assessments were performed every 8 weeks per RECIST v1.1. Blood samples were collected for pharmacokinetic (PK) analyses. **Results:** As of Dec 12, 2022, 19 patients (11 pancreatic cancer, 6 gastric cancer, 1 esophageal cancer, and 1 bile duct cancer) had been enrolled in the dose escalation phase to receive ZL-1211 at 1 mg/kg (n = 3), 5 mg/kg (n = 7), 10 mg/kg (n = 4), and 20 mg/kg (n = 5). The median age was 60 years and the majority of the patients (78.9%) received ≥ 2 lines of prior systemic therapy. No dose limiting toxicities (DLT) had been observed as of the cut-off date. The most common treatment-related adverse events (TRAEs) were gastrointestinal disorders, including nausea (11/19, 57.9%), vomiting (6/19, 31.6%), and abdominal pain (3/19, 15.8%). Other common TRAEs (≥ 15%) were hypoalbuminaemia (3/19, 15.8%) and infusion-related reactions (3/19, 15.8%). Grade 3 TRAEs occurred in 3 patients, 1 with nausea and vomiting, 1 with platelet count decreased, and 1 with anaemia, leukopenia, platelet count decreased, and weight decreased. No Grade ≥ 4 TRAEs were reported. Two patients experienced serious TRAEs: 1 reporting 2 cases each of grade 3 vomiting and nausea and 1 reporting a grade 3 platelet count decreased and a grade 2 abdominal pain, all of which had recovered. TRAEs led to treatment interruption in 5 patients (26.3%) and treatment withdrawal in 1 patient (5.3%). No TRAEs leading to death were reported. Six of 9 tumor-evaluable patients achieved stable disease as the best overall response. Three patients had tumor regression: 17.1% in a pancreatic cancer patient of the 5 mg/kg cohort; 14.5% in a pancreatic cancer patient and 24.9% in a gastric cancer patient in the 10 mg/kg cohort. Preliminary PK analyses revealed linear PK of ZL-1211 over the dose range tested. **Conclusions:** ZL-1211 displayed an acceptable safety/tolerability profile to date and demonstrated preliminary antitumor effects. Clinical trial information: NCT05065710. Research Sponsor: Zai Biopharmaceutical (Suzhou) Co., Ltd.

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Poster Session

A phase 1/2 study of a first-in-human immune-stimulating antibody conjugate (ISAC) BDC-1001 in patients with advanced HER2-expressing solid tumors. *First Author: Bob T. Li, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: BDC-1001 is a HER2-targeted immune-stimulating antibody conjugate (ISAC), designed to trigger local activation of the innate immune system and generate a durable tumor-targeted adaptive immune response. BDC-1001 incorporates a trastuzumab biosimilar (EG12014) conjugated to a proprietary TLR7/8 agonist using a non-cleavable linker and a cell membrane-impermeable payload. An international phase 1/2 study was initiated to evaluate the safety of BDC-1001 ± nivolumab (nivo) and to identify the recommended phase 2 dose (RP2D) considering PK/PD analyses and preliminary efficacy. **Methods:** Dose-escalation (3+3, +backfills) enrolled patients (pts) with HER2-positive (amplified, or IHC 3+) or HER2 low (IHC 2+ and not amplified) solid tumors who had progressed after standard therapies. BDC-1001 was given IV q3w, q2w, or q1w as monotherapy (mono; n=91) and q2w or q1w with nivo 240 mg q2w (combo; n=27). **Results:** As of Nov 23, 2022, 118 pts with 16 different tumor types, were enrolled with BDC-1001 doses ranging from 0.15 to 20 mg/kg. Mean age was 61 yrs with a median of 4 and 5 prior lines of therapy (range, 1-11; 1-14; prior anti-HER2 therapy (HER2Tx) [66%/70%], immunotherapy (IO) [23%/22%]) for mono and combo, respectively. Median follow-up time was 5.0-6.1 months. Treatment was well tolerated with only 1 DLT (Gr3 supraventricular tachycardia) at 8 mg/kg q1w combo cohort. Low-grade IRRs were the most common related TEAEs (mono, 26.5%; combo, 25.9%). A related SAE (Gr4, bronchopulmonary hemorrhage) was seen in 1 pt (mono, 1.1%). Antitumor activity was observed at a range of doses and malignancies. There were 4 confirmed (RECIST 1.1) durable PRs (all in MSS tumors with low/intermediate TMB, prior Tx: 1 HER2Tx, 1 IO) including 1 pt with colon cancer (CRC) in the 5 mg/kg q3w mono cohort, and 3 in the 20 mg/kg q2w cohorts (mono 1/7; combo 2/7; ovarian, biliary, and rectal cancers). After the data cut, an additional PR (unconfirmed) was reported at week 6 in a pt with CRC receiving 12m/kg 1wq combo. Ten additional pts had SD lasting ≥6 months (8 mono; 2 combo; prior Tx: 6 HER2Tx, 1 IO; e.g., ovarian, endometrial, colorectal, gastric). Durable SDs were most frequent in the q2w cohorts. BDC-1001 exposure (e.g., C_{min}) correlated with activity among pts in q2w cohorts. Increases in myeloid and T cell infiltration markers in post-Tx tumor biopsies align with mechanism of action (MoA). No anti-drug antibodies were detected. **Conclusions:** BDC-1001 mono and combo were well-tolerated. Targeted serum exposure levels were achieved, and encouraging clinical activity was noted in heavily pretreated pts with various HER2 positive tumors, especially in the 20 mg/kg q2w cohorts. Immune biomarker changes from plasma and tumor were consistent with MoA of this ISAC. These data support further development of BDC-1001 with phase 2 expansion in HER2-expressing solid tumors at the RP2D. Clinical trial information: NCT04278144. Research Sponsor: Bolt Biotherapeutics; Bristol-Myers Squibb.

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Poster Session

Selective recognition of over-expressed self-antigens in solid tumors using calibrated CAR-T therapy. *First Author: Farzad Haerizadeh, Bio4t2, San Diego, CA*

Background: CAR-T has shown promise in patients with a subset of solid tumors. Future development depends on identifying CAR-T that differentiate between normal and malignant cells. The PrismCore platform develops CAR-T targeting self-antigens using three principles: 1) identification of targets uniformly expressed on solid tumors, 2) over-expression on the surface of invasive cancers compared to healthy cells, and 3) elevated levels linked to tumor aggressiveness. PrismCore produces CAR-T for treating multiple solid tumor types by calibrating T-cell activity against self-antigens only when present at elevated densities. **Methods:** PrismCore generates CAR-T by combining computational biology with empirical observations to target over-expressed self-antigens. Proto-libraries of CARs are created using synthetic single-domain antibodies and structural/signaling components. Bio-screening is performed using combinatorial libraries generated through computational simulation. Lead CAR-T are identified through iterative *in vitro* and *in vivo* testing and evaluated for safety in non-human primates (NHP). **Results:** PrismCore platform has identified engineered T cells against several self-antigens, with the first CAR-T, termed B4t2-001, advanced to clinical testing against the target BT-001. Libraries (1E10 to 1E11) of camelid antibodies were designed, synthesized, and assessed. Selected antibody variants subsets were combinatorially assembled into CAR-Ts and rigorously screened against gradient of BT-001. Six candidates were advanced to further testing in mice to evaluate anti-tumor effect and sustained *in vivo* biological activity. B4t2-001 was evaluated in NHP that express basal levels of BT-001. No toxicity observed despite measurable circulating CAR-T and *in vitro* activity to NHP BT-001 when at high density. The turnaround from target selection to B4t2-001 for clinical evaluation was six months. **Conclusions:** We report pre-clinical data for B4t2-001 that safely and effectively targets BT-001 when overexpressed on tumors. This is a novel target for T-cell therapy and is at elevated levels on multiple different types of solid tumors. BT-001 participates in pathobiology, tumor invasion as well as metastasis, and level of expression inversely correlates with overall survival. B4t2-001 demonstrated target density-dependent response, potency, durability of effect and safety in preclinical models and is undergoing phase I clinical evaluation (NCT05621486) in patients with different types of solid tumors. Research Sponsor: Bridgeway Group.

Percentage of cases expressing BT-001.

Annual Global Cases (Millions) (2022)*			
Indication	New cases	Deaths	BT-001
Lung	2.2	1.7	>85%
Colorectal	1.9	0.93	>55%
Gastric	1.1	0.76	>85%
Pancreatic	0.5	0.46	>90%
Breast	2.2	0.68	>70%

*WHO and International Agency for Research on Cancer.

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Poster Session

Peri Cruiser CAR-T: An innovative platform to reduce on-target off-tumor toxicity of CAR-T therapy. *First Author: shuangshuang zhang, Suzhou Immunofoco Biotechnology Co., Ltd, Shanghai, shanghai, China*

Background: On-target off-tumor toxicity is a significant concern in Chimeric Antigen Receptor (CAR)-T therapies, especially for solid tumors, leading to adverse effects on normal tissues and impacting on treatment efficacy. To address this challenge, a modified form of CAR-T cells named Peri Cruiser CAR-T has been developed by using miRNA technology to knock down three adhesion genes that mediate T cell trans-endothelial migration to normal tissues, aiming to block the extravasation of CAR-T cells so that the on-target off-tumor toxicity could be prevented without compromising anti-tumor efficacy. In this study, we provided a proof of concept by using the epithelial cell adhesion molecule (EpCAM) as a targeting tumor-associated antigen (TAA). **Methods:** An miRNA cassette was incorporated into the vectors of anti-human or mouse EpCAM CARs. The knockdown efficiency, endothelial adhesion efficiency, effector functions and memory phenotypes *in vitro* were evaluated. To determine the toxicity *in vivo*, the anti-mouse EpCAM CAR-T cells were administered to non-tumor bearing NSG mice, and the body weight and T cell infiltration in normal tissues was evaluated. Anti-tumor efficacy was also evaluated in NSG mice with subcutaneous and metastatic tumor models by anti-human EpCAM CAR-T cells. **Results:** Our Peri Cruiser CAR-T platform was capable to effectively downregulate the target genes by 10 folds. The knockdown is stable after extended culture and antigen engagement *in vitro*. This knockdown of targeted genes significantly decreased T cell adhesion to endothelial cells and corresponding ligands, but did not affect T cell activation or effector functions such as cytotoxicity and IFN gamma release. Surprisingly, lowering the levels of these adhesion molecules improved the memory phenotypes of CAR-T cells as indicated by increased portion of CCR7+CD45RO+ cells. *In vivo* studies showed that conventional EpCAM CAR-T-injected mice experienced severe weight loss and all had to be sacrificed before day 8, the IHC staining of CD3 revealing massive infiltration of T cells in lung, liver, and kidney. However, the incorporation of the miRNA cassette prevented T cell infiltration in normal tissues, reversed the toxicity, and ensured the survival of all mice. The anti-tumor efficacy of these T cells was evaluated *in vivo* and found to decrease metastasis as effectively as the conventional CAR-T cells in a metastasis model of HCT116-Luc, although there was a slightly but not significantly decreased efficacy in a subcutaneous model of HCT116. **Conclusions:** The Peri Cruiser CAR-T platform can significantly improve the safety of CAR-T cells without compromising their efficacy to eliminate tumor cells in primary site and metastasis. This technology opens another avenue to safely target a variety of other TAA by CAR-T even when there is the potential of on-target off-tumor toxicity in normal tissues for those antigens. Research Sponsor: Suzhou Immunofoco Biotechnology Co., Ltd.

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Poster Session

A phase 1/2 study of the safety, tolerability, and preliminary efficacy of the anti-GITR monoclonal antibody, INCAGN01876, combined with immunotherapies (IO) in patients (Pts) with advanced cancers. *First Author: Martin Gutierrez, Hackensack University Medical Center, Hackensack, NJ*

Background: INCAGN01876 is a GITR agonist designed to induce antitumor immunity by promoting effector T cells while inhibiting Tregs. Recent clinical studies suggest that combining IO with immune agonists such as INCAGN01876 may extend clinical benefit in pts with cancer. **Methods:** This global open-label nonrandomized phase 1/2 study assessed the safety, tolerability, recommended phase 2 dose (RP2D), and efficacy of INCAGN01876 + nivolumab (NIVO) and/or ipilimumab (IPI) (NCT03126110). Eligible pts (≥18 y) had locally advanced/metastatic cancer. Phase 1 (dose escalation) consisted of 4 treatment groups: A, INCAGN01876 1, 3, 5, 10 mg/kg Q2W + NIVO 240 mg Q2W; B, INCAGN01876 1, 3, 5, 10 mg/kg for 2 doses then NIVO 240 mg Q2W; C, INCAGN01876 1, 3, 5 mg/kg Q2W + IPI 1 mg/kg Q6W; D, INCAGN01876 1 mg/kg Q2W + NIVO 3 mg/kg Q2W + IPI 1 mg/kg Q6W. INCAGN01876 RP2D was assessed via a 3+3+3 design. Phase 2 (dose expansion) evaluated INCAGN01876 RP2D in combination IO in select tumors; data will be presented elsewhere. **Results:** As of Nov 9, 2021, 51 pts (A, n=17; B, n=13; C, n=15; D, n=6) were enrolled (most common tumors: breast, gastric, and ovarian [each n=8]; prior PD-(L)1 therapy, n=12). One pt in D had DLTs (nonserious grade [gr] 3 pruritus and rash); MTD was not reached; INCAGN01876 300 mg Q2W was selected as RP2D. All pts in A, B, D, and 93.3% in C had TEAEs. Twenty-six pts had gr ≥3 TEAEs (A, n=10; B, n=5; C, n=7; D, n=4), most commonly, pneumothorax (A [5 mg/kg], n=2) and anemia (B [1, 5 mg/kg], n=2; C [1, 3, 5 mg/kg], n=3). INCAGN01876-related TEAEs occurred in 8, 6, 10, and 5 pts in A, B, C, and D, respectively. Most common immune-related AEs in A: pruritus (gr 1/2, n=2); in B: rash (gr 1, n=2), simultaneous rash and pruritus (gr 1, n=4); in C: pruritus (gr 1/2, n=2), rash (gr 1, n=2), simultaneous rash and pruritus (gr 1, n=2); in D: simultaneous pruritus and rash (gr 3, n=1); 3 pts (A [1 mg/kg], n=1; C [3 mg/kg], n=1; D, n=1) had infusion-related reactions. One pt in A (10 mg/kg Q2W) discontinued treatment due to a pneumonia TEAE. Best unconfirmed overall responses (per RECIST v1.1) were 1 complete response (CR; duration of response [DOR], 1065 days) in renal cancer and 1 partial response (PR; DOR, 573 days) in breast cancer in A; 1 CR (DOR, 876 days) in cervical cancer in B; 1 PR (DOR, 169 days) in ovarian cancer and 1 PR (DOR, 281 days) in lung cancer in C; none in D. The disease control rate was 35.3% in A, 23.1% in B, 33.3% in C, and 0% in D. **Conclusions:** INCAGN01876 plus NIVO and/or IPI was generally well tolerated in pts with advanced tumors; most common toxicities were mild to moderate pruritus and rash. No novel safety signals were seen. INCAGN01876 300 mg Q2W was selected as RP2D based on safety and preliminary PK/PD data and used for expansion in combination with NIVO or IPI. Clinical trial information: NCT03126110. Research Sponsor: Incyte Corporation.

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Poster Session

Effect of a novel expansion process on tumor-infiltrating lymphocyte (TIL) polyfunctionality, cytotoxicity, and expansion, while preserving cells in a less differentiated and more stem-like phenotype. *First Author: Andrew Yuhas, Iovance Biotherapeutics, Inc., San Carlos, CA*

Background: Adoptive cell therapy using autologous TIL has shown durable responses in patients with metastatic melanoma and some epithelial tumors (Chesney *JITC* 2022; Schoenfeld *SITC* 2021; O'Malley *SITC* 2021). Data suggest that maintaining a higher proportion of less differentiated and more stem-like TIL can associate with persistence and response in patients with metastatic melanoma (Krishna *Science* 2020; Rosenberg *Clin Cancer Res* 2011). Here, we describe a novel TIL expansion process that increases TIL expansion and preserves cells in a less-differentiated and more stem-like phenotype with enhanced functional output. **Methods:** Tumors of various histologies, including lung, breast, and renal cancer, were fragmented and expanded using either a standard process or a newly developed process that uses a different combination of cytokines during the pre-rapid expansion protocol (pre-REP) stage and another combination of cytokines and a pathway inhibitor during the REP stage to control T-cell activation and differentiation. The expansion potential, viability, and phenotypic and functional attributes of the final TIL products were evaluated by a variety of assays. **Results:** When compared with standard TIL expansion, the novel process increased yield and viability while preserving TIL in a less differentiated and more functional state, as evidenced by increased expression of the memory-associated markers CD27, CD28, CD62L, and IL-7R, with reduced expression of the activation markers CD38, CD39, and CD69, and lower levels of the inhibitory markers LAG3, TIM3, TIGIT, and TOX. Importantly, the novel process led to a pronounced increase in the tumor-homing marker CXCR3 as well as TIL polyfunctionality as evidenced by increased co-expression of IFN γ , TNF α , and IL-2 while showing an enrichment in genes associated with stem-like cells and a reduction in exhaustion-associated genes. Pseudotime trajectory analysis also demonstrated that the new expansion process maintained TIL in a less differentiated and more stem-like state. Together, these phenotypic and functional characteristics translated into increased cytotoxicity even after repeated stimulation. **Conclusions:** Our novel TIL expansion process improves multiple metrics that correlate with both TIL persistence and response, including enhanced polyfunctionality, reduced inhibitory receptor expression and a less differentiated and more stem-like phenotype, while increasing yield. These effects may translate into a more vigorous and less differentiated TIL infusion product with improved cytotoxicity and persistence. Research Sponsor: This study is sponsored by Iovance Biotherapeutics.

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Poster Session

A pilot study of lymphodepletion intensity for PBMC-derived, neoantigen-specific CD8+ T cells (Neo-Ts) therapy in patients with advanced solid tumors. *First Author: Dandan Li, Biotherapy Center, Sun Yat-sen University Cancer Center, Guangzhou, China*

Background: Adoptive T cell therapy (ACT) using neoantigen-specific CD8+ T cells (Neo-Ts) derived from patient PBMC was recently developed aiming to target individual patient's unique tumor mutations and increase treatment efficacy. But the optimal lymphodepletion intensity for Neo-T therapy has yet to be determined. **Methods:** In this phase I clinical trial (NCT02959905), we generated Neo-Ts from patients with locally advanced or metastatic melanoma or colon cancers that were refractory to standard therapies, and evaluated the effects of lymphodepletion at various dosages (high: 2x500 mg/m² cyclophosphamide and 2x25 mg/m² fludarabine; low: 1x500 mg/m² cyclophosphamide and 2x25 mg/m² fludarabine; and no lymphodepletion) during Neo-T therapy. The primary end point was safety and the secondary end point was objective response rate (ORR). **Results:** We showed that Neo-T therapy was safe with lymphodepletion at dosages from no lymphodepletion to high intensity. The median PFS was 7.1 months (95% CI: 3.7-9.8), and median overall survival (OS) was 16.8 months (95% CI: 11.9-31.7). The ORR was 33.3% (3/9) among all groups. Three patients achieved PR, two of them were in the group without lymphodepletion. One of the PR patients refractory to prior anti-PD-1 therapy also responded to Neo-T therapy. Neoantigen specific TCRs were examined in two responding patients and showed expansion and persistence after treatment. **Conclusions:** Neo-T therapy with low intensity lymphodepletion or no lymphodepletion could be a safe and promising regimen for advanced solid tumors. Clinical trial information: NCT02959905. Research Sponsor: None.

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Poster Session

AFNT-211: An FAS-41BB-enhanced TCR-T cell therapy with stem-like properties targeting KRAS G12V-expressing solid tumors. *First Author: Michele Hoffmann, Affini-T Therapeutics, Watertown, MA*

Background: KRAS is the most common oncogenic driver mutation in solid tumors, promoting the initiation and progression of many incurable cancers, including colorectal, pancreatic and lung cancer. While small molecule inhibitors to KRAS^{G12C} mutations have been approved, there are no targeted therapies available for patients with highly prevalent KRAS^{G12V} mutations. TCR-T cell therapies have demonstrated remarkable responses in clinical trials, but their durability has been limited by the immunosuppressive tumor microenvironment (TME). AFNT-211 is an autologous T cell therapy engineered to express an HLA-A*11:01 KRAS^{G12V}-specific TCR, further enhanced with CD8 α / β coreceptor and a FAS-41BB switch receptor to drive T cell persistence and durable clinical responses. CD8 α / β coreceptor enables a coordinated CD4+/CD8+ T cell response and FAS-41BB converts the FAS ligand (FASL) TME death signal into a costimulatory signal through 41BB activation. **Methods:** AFNT-211 was assessed for efficacy *in vitro* against a panel of KRAS^{G12V}-expressing tumor cell lines and *in vivo* using human xenograft mouse models. *In vitro* safety studies were performed to assess potential cross-reactivity, alloreactivity, and cytokine-independent growth. The clinical manufacturing process consists of autologous CD4+/CD8+ T cells transduced with lentivirus and expanded using culture conditions that drive robust expansion while preserving stem-like properties. Phenotypic and functional analyses of AFNT-211 were performed using flow cytometry and cell-based assays. **Results:** Coculture of AFNT-211 with a panel of KRAS^{G12V}-expressing tumor cell lines led to significant effector cytokine secretion, T cell proliferation, and tumor cell killing. The CD8 α / β coreceptor enabled CD4+ T cell recognition of KRAS^{G12V} and greater overall cytotoxicity. The FAS-41BB switch receptor dramatically augmented the magnitude and durability of the anti-tumor response against FASL-expressing tumor cells. XScan mutagenesis and potential off-target peptide testing revealed no significant cross-reactivities. No alloreactivity was observed against a panel of lymphoblastoid cell lines presenting the most frequent HLA types in the US population. Potent anti-tumor response was observed *in vivo* in a mouse xenograft model. Affini-T's Thrive manufacturing platform used for the production of AFNT-211 consistently delivers >30-40e⁹ TCR-engineered T cells with a high frequency of naive and central memory T cells expressing negligible markers of exhaustion. **Conclusions:** The AFNT-211 manufacturing process generates a large number of TCR-T cells with desirable stem-like properties optimized for clinical dosing. Preclinical data demonstrated a potent and safe profile for AFNT-211 that supports clinical development in HLA-A*11:01 patients with advanced/metastatic solid tumors harboring a KRAS G12V mutation. Research Sponsor: Affini-T therapeutics.

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Poster Session

A phase 1 dose escalation trial of ex-vivo expanded allogeneic cord blood-derived natural killer cell immunotherapy for pediatric solid tumor malignancies. *First Author: Sajad Khazal, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Despite aggressive multimodality therapy, survival outcomes of most patients with recurrent/refractory solid tumors remain dismal. Pre-clinical data have shown that natural killer (NK) cells play a significant role in controlling cancer progression, metastasis, and survival. In this phase I dose escalation trial, we evaluated the safety and phase 2 recommended dose of cord blood derived NK cells in children and young adults with recurrent/refractory pediatric solid tumors. **Methods:** Eligible patients were 1-40 years old. Cord blood donors were 4, 5, or 6/6 HLA matched. Ex-vivo, antigen presenting cell-mediated expansion of human cord blood derived NK cells was performed over 14 days. All patients received lymphodepleting regimen with cyclophosphamide (500 mg/m²/day) and etoposide (100 mg/m²/day) for 5 days (days -7 to -3) followed by 2 days rest and a single infusion of NK cells on Day 0. The study evaluated two dose levels using a standard 3+3 phase I trial design with an expansion cohort at the maximum tolerated dose. **Results:** Twelve patients (median age 16 years) received NK cells infusions. Tumor types included osteosarcoma (n = 7), Ewing sarcoma (n = 4), and synovial sarcoma (n = 1). Three patients received NK cells at dose level 1 (5 X 10⁷/Kg), and nine patients at dose level 2 (1 X 10⁸/Kg), which was determined to be the recommended Phase 2 dose. No dose-limiting toxicities were observed. Most adverse events were grade 1 and 2 (fatigue, dizziness, nausea and vomiting). Most frequently observed grade 3 and 4 adverse events were leukopenia, neutropenia, lymphopenia, and thrombocytopenia. No cytokine release syndrome or neurotoxicity was observed. Allogeneic NK cells were detected in recipients' peripheral blood as high as 100% of all NK cell populations and as late as 9 days post infusion. Of the 9 patients evaluable for tumor response, 3 patients (with osteosarcoma) had stable disease and 6 had progressive disease. **Conclusions:** Allogeneic ex-vivo expanded NK cells immunotherapy demonstrated favorable safety profile in patients with advanced pediatric solid tumors. Strategies to improve efficacy are warranted including using adjuvant therapy to increase persistence, more stringent selection strategies and gene editing approaches to increase alloreactivity against recipient tumor cells. Clinical trial information: NCT03420963. Research Sponsor: The University of Texas MD Anderson Cancer Center.

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Poster Session

Safety and efficacy of Sleeping Beauty TCR-T cells targeting shared *KRAS* and *TP53* mutations expressed by solid tumors in first-in-human phase 1 study. *First Author: Maria Pia Morelli, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Solid tumors present driver mutations in *KRAS*, *TP53*, and *EGFR* genes on their surface in the context of human leukocyte antigen (HLA) molecules to T-cell receptors (TCRs) expressed by T cells. Non-viral genetic engineering of patient T cells with the Sleeping Beauty transposon/transposase system can generate driver mutation-reactive TCR-T cells. **Methods:** This is a first-in-human phase 1/2 study of autologous Sleeping Beauty TCR-T cell therapy for patients with non-small cell lung (NSCLC), colorectal, endometrial, pancreatic, ovarian and bile duct cancer whose tumors contain at least one of the targeted driver mutations in *KRAS*, *TP53*, and *EGFR*. The primary objective of the phase 1 portion is to define the incidence of dose-limiting toxicities (DLTs) and the maximum tolerated dose or recommended phase 2 dose to be explored in disease specific cohorts during phase 2. Dose levels of 0.1×10^{10} (DL1), 1.7×10^{10} (DL2) or 7.15×10^{10} (DL3) TCR-T cells are being explored. Any of the six tumor types or 12 TCRs within the library can be used for the Phase 1 portion of the trial. **Results:** As of February 14, 2023, three patients have been treated with Sleeping Beauty TCR-T cells on this study. The first was a 34 year old female with stage IV mucinous adenocarcinoma NSCLC refractory to chemotherapy and immunotherapy who received DL1 (0.9×10^{10} TCR-T cells) targeting *KRAS*^{G12D} and HLA-A*11:01, second was a 54 year old female with stage IVA chemotherapy resistant colorectal cancer who received DL2 (6.4×10^{10} TCR-T cells) targeting p53^{R175H} and HLA-A*02:01 and the third was a 60 year old male with stage IV pancreatic cancer refractory to chemotherapy who received DL2 (5.8×10^{10} TCR-T cells) targeting *KRAS*^{G12V} and HLA-A*11:01. Overall, a manageable safety profile with no unexpected adverse events, DLTs or immune effector cell-associated neurotoxicity syndrome (ICANS) was observed. Patients 1, 2 and 3 had cytokine release syndrome grades 2, 3 and 1, respectively, that were self-limiting or resolved with standard management and anti-IL-6 antibody in the case of Patient 2. Best overall responses were partial response for Patient 1 with six month progression-free survival, stable disease for Patient 2 and progressive disease for Patient 3. Persistence of TCR-T cells was observed in all patients at last follow-up and out to 6 months in the case of Patient 1. Acceleration to DL3 is under consideration based on a continued manageable safety profile. **Conclusions:** This is the first-in-human experience administering Sleeping Beauty TCR-T cells. Signs of efficacy, safety and persistence of TCR-T cells was observed. Thus, this treatment has promise for patients with solid tumors expressing shared mutations in driver genes. The trial is actively enrolling new patients and treating at one of the two highest dose levels. Clinical trial information: NCT05194735. Research Sponsor: Alauos Therapeutics.

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Poster Session

Phase I results of human endogenous retrovirus type-E (HERV-E) TCR transduced T-cells in patients (pts) with metastatic clear cell renal cell carcinoma (mccRCC). *First Author: Rosa Nadal, Laboratory of Transplantation Immunotherapy, Cellular and Molecular Therapeutics Branch, NHLBI, NIH, Bethesda, MD*

Background: The CT-RCC HERV-E is expressed in the majority of ccRCC tumors with no expression in normal tissues. T-cells transduced to express a HERV-E TCR are cytotoxic to ccRCC and mediate tumor regression of human ccRCC in a murine model. We developed a method to manufacture HERV-E TCR transduced T-cells (HERV-E TCR) for clinical development. **Methods:** We conducted a phase I dose-escalation trial (DL1: 1×10^6 , DL2: 5×10^6 , DL3: 1×10^7 & DL4: 5×10^7 cells/kg) to evaluate the safety of adoptively infused HERV-E TCR in mcrRCC pts. HERV-E TCR contain T-cells engineered to express an HLA-A*11 restricted HERV-E TCR and a truncated CD34 cassette for *in vivo* monitoring. Eligible HLA-A*11 pts had mcrRCC, ECOG 0-1 & prior antiangiogenic & checkpoint inhibitors therapy unless contraindicated/unavailable. Cyclophosphamide & fludarabine were given followed by HERV-E TCR infusion & IL-2 administration. **Results:** 14 HLA-A*11+ pts (median age 56) were treated including 3 pts in each DLs 1-3 & 5 pts in DL4. 86% had ≥ 3 prior treatment lines (range 1-7); 36% had high-dose IL2, 57% ipilimumab-Nivolumab & 50% ≥ 3 lines of anti-VEGFR therapy. Bone, liver & brain metastases were present in 71%, 43%, and 14% of pts. All HERV-E TCR products met sterility, purity, and potency criteria for release and infusion (Table). No HERV-E TCR dose-limiting toxicities or treatment-related deaths occurred. Pts received a mean: 12 IL-2 doses (IQR 11-14). 57% pts had G3-4 febrile neutropenia & 7% G3-4 capillary leak syndrome. 1 pt experienced G2 skin rash possibly related to HERV-E TCR. Best response included 7% pts with partial response & 29% with stable disease ≥ 8 weeks. The mPFS: 62 days (IQR 31,90). At DL4, TCR transgene expression was detectable in PBMCs at a mean 6.3% (range (r) 0.02-25), 12.3% (r 0.01-61.2), 3.45% (r 0.00-13.7) & 2.89% (r 0.00-11.5) on days 4, 7, 14, & 21. HERV-E TCR were detected in the malignant pleural effusion of 1 pt. **Conclusions:** This is the first trial evaluating TCR-engineered T-cells targeting a human endogenous retrovirus in ccRCC. The manufacturing method utilized produced large numbers of highly purified CD8+ HERV-E reactive T-cells that were not associated with any dose limiting toxicities when given at doses up to 5×10^7 cells/kg. For pts in DL4, HERV-E TCR were observed to proliferate *in vivo*, traffic to a metastatic site, and induce tumor regression in one mcrRCC pts. Clinical trial information: NCT03354390. Research Sponsor: U.S. National Institutes of Health.

DL	Cell Viability (%)	CD34 + T Cells (%)	CD8 + T Cells (%)	CD8+/CD34+ T cells (%)	Vector Copy # (D10)	INF- γ Release Assay
Release Criteria	> 70%	> 25%	> 80%	> 25%	< 5 copies/cell	2 x over background
	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	-
DL1	94.6 (1.6)	86.7 (7.7)	99 (2.8)	84.2 (10.9)	1.9 (0.6)	+
DL2	90.2 (4.8)	90.6 (4.5)	95.4 (6.5)	87.9 (2.7)	1.9 (0.5)	+
DL3	88 (4.5)	93.4 (4.5)	99 (0.4)	91.8 (3.7)	2.3 (0)	+
DL4	95 (1.7)	90.3 (3.7)	98.5 (0.3)	90 (3.8)	2 (0.4)	+
All	94.6 (5.7)	90.4 (7.2)	98.6 (1.7)	89.6 (7.2)	2 (0.6)	+

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Poster Session

Effect of the killing style of individual CAR T cells on the clinicopathological behavior of therapeutic products in the clinic. *First Author: Ahmed Z Gad, Center for Cell and Gene Therapy, Texas Children's Hospital, Houston Methodist Hospital, Baylor College of Medicine, Houston, TX*

Background: CAR T cell products that signal through CD28 and 41BB are highly effective against B lineage leukemia, despite exhibiting distinct efficacy and toxicity profiles in patients. Specifically, CD28 has been linked to higher upfront lytic activity and toxicity, while 41BB induces longer CAR T cell persistence and more durable progression free survival. We reasoned that the killing style of individual CAR T cells can explain the clinicopathological behavior of CAR T cell products in the clinic. **Methods:** We studied the cellular kinetics of CD28 and 41BB signaling CD19 CAR T cell products approved in the clinic, their single cell killing behavior in high throughput, the molecular composition of the lipid rafts inside the CAR immune synapse (CARIS) they form with their target cells, and their CARIS mechanical properties, then corroborated these findings in one kinetic model to explain their distinct clinicopathological behavior in the clinic. **Results:** We discovered that tumor encounter polarizes CD28 CAR T cell products to a predominance of more differentiated CD8 effectors that rely on short-lived highly lethal synapses with tumor cells. CD28 CAR T cell mediated synapses are characterized by fast mechanical buildup and resolution and brisk shuttling of CAR and other associated molecules into the CARIS and rapid polarization of the killing machinery in a manner that supports a mastery of serial killing mediated by perforin and granzymes. In contrast, 41BB responds to tumor stimulation by a T_H2 -polarizing cytokine milieu that robustly expands a balanced CD4/CD8 population of effectors preserving a central memory phenotype. 41BB CAR T cells engage in lengthier synapses characterized by slower accumulation of CAR molecules in a mechanically tonic CARIS and rather collaborative yet lengthy Fas ligand-mediated killing process. **Conclusions:** We show here that CAR T cell signaling domains mediate distinct killing dynamics that can explain their behavior in patients. By understanding and potentially modulating these dynamics, the CAR T cell functionality and toxicity can be rationally optimized. Research Sponsor: Stand Up To Cancer (SU2C)—St. Baldrick's Foundation.

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Poster Session

Initial results from a first in human dose escalation trial of a novel immune stimulating oncolytic adenovirus, AdAPT-001^{TGF- β Trap}. *First Author: Anthony Paul Conley, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: As a class, oncolytic adenoviruses (OAV), modified agents of the common cold, specifically target and lyse tumor cells, and by expression of cytotoxic transgenes activate an immune response. AdAPT-001 is an OAV, which carries a transforming growth factor beta (TGF- β) trap that neutralizes the immunosuppressive and profibrotic cytokine, TGF- β . Preclinically, AdAPT-001^{TGF- β Trap} eradicates non-T-cell infiltrated tumors. The aim of this Phase 1 study was to assess the safety and tolerability and, secondarily, the efficacy of AdAPT-001^{TGF- β Trap} after single intra-tumoral injection (IT) (Phase 1a) and multidose IT injection (Phase 1b) in patients with advanced refractory solid tumors. **Methods:** This was an open label, single-arm, multicenter dose escalation design trial. AdAPT-001^{TGF- β Trap} was administered by intratumoral injection. 9 patients were in a single-dose group, where doses of 2.5×10^{11} , 5.0×10^{11} , 1.0×10^{12} viral particles (VPs), were tested, and 19 patients with a median age of 70, 5 median prior regimens, and a median ECOG score of 1 received AdAPT-001 every 2 weeks at 1.0×10^{12} VPs until progression. **Results:** AdAPT-001^{TGF- β Trap} was well tolerated with local inflammation, fever, and fatigue as the main side effects. No dose limiting toxicities, no grade 4 toxicities, or treatment-related serious adverse events (SAEs) were seen. Tumor types were sarcoma (n = 8), melanoma (n = 2), head & neck (n = 5), gastric (n = 1), rectal (n = 1), breast (n = 1), fallopian (n = 1). Biological activity (virus replication, local reactions, and tumor shrinkage) was observed. The duration of local reactions and virus replication suggested that dosing every 2 weeks was appropriate. The overall responses to treatment were as follows: 5 patients had durable stable disease for 6 months or more, 1 patient had a partial response, and 2 patients demonstrated pseudoprogression with inflammation of uninjected as well as the injected tumor, 5 patients had stable disease for approximately 2 months and 15 patients had progressive disease. 2 abscopal responses have been seen to date. The data also suggest a dose-response relationship, with higher and more frequent doses associated with better outcomes. Peripheral lymphocyte subset analysis and serum cytokine analysis are ongoing. **Conclusions:** AdAPT-001^{TGF- β Trap} is well tolerated and no dose limiting toxicities were observed with the single or multidosing protocol described. Evidence of an antitumor effect was seen. The recommended Phase 2 dose was 1.0×10^{12} VPs administered by intratumoral injection once every 2 weeks. Combination of AdAPT-001^{TGF- β Trap} with a checkpoint inhibitor is planned. Clinical trial information: NCT04673942. Research Sponsor: EpicentRx.

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Poster Session

Harnessing the power of tumor-infiltrating lymphocytes: A first-in-human study of GT201 as monotherapy in advanced solid tumors. *First Author: Yarong Liu, Grit Biotechnology, Shanghai, China*

Background: Genetically engineered TIL has shown features such as prolonged memory that can improve therapeutic efficacy in tumor mouse models. GT201 is an engineered TIL that expresses a membrane-bound IL-15 (mIL-15), and preclinical studies have demonstrated enhanced antitumor reactivity. A phase 1 study was initiated to evaluate the preliminary safety of GT201 and to identify Optimal Biological Dose (OBD) suitable for monotherapy expansion. **Methods:** The dose-escalation study (using TITE-BOIN design) intended to enroll patients (pts) with advanced treatment-refractory solid tumors. Once the OBD is identified, a monotherapy expansion phase will be opened for patients with various solid tumors. Enrolled patients were pre-conditioned with a nonmyeloablative (NMA) lymphodepletion regimen and treated by autologous infusion of the GMP-grade G201 cell product, followed with supportive low dose IL-2 administration. **Results:** As of January 17, 2023, the dose-escalation study enrolled 4 pts, all of whom were female with a median age of 52.6 years. The median number of infused TIL cells was 5.3E+09. All pts experienced TRAEs, with the majority being grade 1 or 2. The most common grade 3/4 TRAEs were lymphopenia (100%), leukopenia (25%) and neutropenia (25%), which were related to the NMA regimen. No dose-limiting toxicities (DLTs) or TIL-related grade ≥3 TRAEs were observed. Median time on study was 17 wks (6–30 wks). One pt with highly treatment-refractory cervical cancer experienced a confirmed partial response (PR) after 16 wks that was durable for 30 wks (RECIST 1.1). Two pts (cervical cancer and melanoma) experienced disease stabilization, while another malignant melanoma pt experienced progressive disease. Despite varying doses of TILs (5.0E+09 to 1.40E+10) and IL-2 (up to 3.0E+05 IU/kg), all patients receiving GT201 therapy showed robust T cell expansion post-infusion, with higher doses of IL-2 leading to more rapid TIL expansion. GT201 TILs could be detected in patients after one month post-infusion, indicating promising activation and long-term persistence of the infused TILs. Based on safety, tolerability, PKs, and preliminary efficacy, a TIL dose of 1.0E+10 and an IL-2 dose of 3.0E+05IU/kg was selected as the OBD for the study. **Conclusions:** The results of the first-in-human study of GT201, a mIL-15 expressed on TILs, demonstrate promising preliminary findings as a monotherapy in pts with advanced cancers. The administration of GT201 was associated with robust T cell expansion, as well as prolonged persistence of infused TILs. Results of mIL-15 expressed TIL demonstrates that GT201 has good tolerability with encouraging preliminary antitumor activity as a monotherapy. Further investigations, including correlative biomarker analyses and updated safety and clinical outcome data, will be presented at the meeting. Clinical trial information: NCT05430360. Research Sponsor: Grit Biotechnology.

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Poster Session

Preclinical evaluation of targeting PRAME with TCR mimic CAR T cells in AML. *First Author: Danielle Kirkey, Fred Hutchinson Cancer Center, Seattle, WA*

Background: Chimeric antigen receptor (CAR) T cell therapy has revolutionized cancer treatment, but has had limited success against AML in part due to overlap of cell surface antigens expressed in AML and normal hematopoietic cells. To identify AML-restricted targets, we interrogated the transcriptome from over 3000 AML patients and found PRAME (Preferentially Expressed Antigen in Melanoma), an intracellular protein, to be a highly expressed AML-restricted target. Using a novel approach to target intracellular antigens, we developed a PRAME CAR T cell using a TCR mimic (mTCR) antibody, which recognizes the PRAME peptide/HLA-A2 complex on the tumor cell surface. To conduct final IND-enabling studies, we generated an *in vivo* patient derived xenograft (PDX) model to treat with PRAME^{mTCR}CAR T cells. Here we demonstrate the *in vivo* activity of PRAME^{mTCR}CAR T cells against a PDX AML model. **Methods:** We used the VL and VH sequences from the PRAME TCR mimic antibody (Pr20) to construct the single chain fragment variable domain into the 41-BB/CD3ζ CAR vector. The PDX model was derived from a PRAME⁺/HLA-A2⁺ pediatric patient with AML. PDX cells were transduced with *fluciferase* for noninvasive bioluminescent IVIS imaging to monitor leukemic progression. PDX leukemia-bearing mice were treated with unmodified T-cells or PRAME^{mTCR}CAR T cells at 5x10⁵ cells (1:1 CD4:CD8) per mouse 1 week after leukemia injection. Leukemia burden was measured by IVIS imaging and peripheral blood analysis. **Results:** Treatment with PRAME^{mTCR}CAR T cells led to eradication of leukemia with all mice alive >100 days post-treatment, while control mice (unmodified T cells) had disease progression at Day 50 (p=0.001). Average leukemia burden in the control cohort was 3.5% at week 6 and 41.75% at week 11, while no leukemia was detected following CAR T cell treatment. In addition, the control arm had a marked expansion of leukemia with a 7.75 and 429.6 fold increase in radiance by IVIS at 6 and 11 weeks post-treatment. No significant increase in radiance was seen in the PRAME^{mTCR}CAR T cell treated group. Human T cells (CD45+/CD3+) were detectable in the peripheral blood at Day 7 and 14 post-treatment in both the unmodified and CAR T cell treated groups. **Conclusions:** We demonstrate the therapeutic potential of targeting PRAME with mTCR CAR T cells in AML. We show potent efficacy with eradication of leukemia in PDX-bearing mice following treatment with PRAME^{mTCR}CAR T cells resulting in prolonged survival. These results provide a novel approach to target PRAME with CAR T cells and provide compelling data to evaluate PRAME^{mTCR}CAR T cells for use in clinical trials against AML. Research Sponsor: Project StElla.

		Treatment	
		Unmodified T cell (N=5)	PRAME ^{mTCR} CAR T cell (N=5)
Time to development of leukemia (Days)		50.75	N/A
Survival at Day 100 post-treatment		40%	100%
Average Fold Change in radiance post-treatment	6 weeks	7.75	5.65
	11 weeks	429.6	3.95
% leukemia in peripheral blood	6 weeks	3.5%	undetectable
	11 weeks	41.75%	undetectable

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Poster Session

MT-6402, an engineered toxin body (ETB) targeting PD-L1: Interim efficacy and safety data. *First Author: Minal A. Barve, Mary Crowley Cancer Research Center, Dallas, TX*

Background: MT-6402, an engineered toxin body (ETB) , has been designed to be effective in patients (pts) previously treated with checkpoint inhibitors (CPIs) by utilizing 3 unique mechanisms of action (MOA): (i) remodeling of the tumor micro-environment by elimination of PD-L1⁺ immunosuppressive cells like myeloid-derived suppressor cells (MDSCs), (ii) direct cell kill of PD-L1⁺ expressing tumor cells, (iii) delivery of HLA-A*02 restricted cytomegalovirus (CMV) peptide pp65 to PD-L1 expressing cells to direct a CMV specific CD8 T-cell response against the tumor. **Methods:** Dose escalation continues with MT-6402 (QW in 4-week cycles) in pts with relapsed/refractory PD-L1⁺ solid tumors. After clearing doses of 16, 24, 32, 42 and 63 µg/kg, 83 µg/kg is being evaluated. Safety, tolerability, efficacy, pharmacokinetics, and pharmacodynamic data are reported. **Results:** MT-6402 at 63 µg/kg in 1 pt with metastatic nasopharyngeal carcinoma (NPC) who progressed after radiation, chemotherapy, and CPI (PD-L1 CPS=2%, not HLA-A*02) resulted in a PR (63% reduction in target lesion) after 2 cycles. This pt had an increase in CD8/CD4 and immune activation cytokines (IL-2, TNFα, IFNγ) consistent with elimination of MDSCs. A pt with NSCLC (osseous disease only) that had progressed after CPI showed resolution of 3/4 osseous metastases and decreased radiotracer uptake by the remaining bone metastasis. This patient had high PD-L1 tumor expression and HLA-A*02/CMV*. Complete CMV-specific T-cell extravasation was noted by C1D8 consistent with haplotype-specific CMV antigen delivery for presentation on the tumor surface by MHC class I. All cohorts had reductions in peripheral PD-L1⁺ MDSCs, monocytes and dendritic cells after MT-6402 without effect on PD-L1⁺ cells with the most depletion at the highest doses. Most pts displayed CD8⁺ T-cell expansion and elevations of serum IL-2 and TNFα, consistent with PD-L1-mediated immunotolerance. MT-6402 was well tolerated with 2 dose limiting toxicities reported: Grade (G)2 maculopapular rash at 24 µg/kg, G3 IRR at 63µg/kg. No G ≥ 4 AEs occurred. Infusion-Related Reactions in 3 pts (G1, G2, and G3) and Cytokine Release Syndrome (G1 [2 pts] at both 32 and 42µg/kg and G2 [1 pt] at 16µg/kg) occurred. **Conclusions:** MT-6402 utilizes three PD-L1-targeted and unique MOAs: direct cell-kill, reduced immunosuppression, and increased immunorecognition. As of Feb 2023, 5 dose cohorts have completed. MT-6402 was well tolerated without CLS or payload-derived toxicity as is observed with traditional immunotoxins and ADCs, respectively. A PR in 1 pt with CPI-refractory NPC (CPS 2%, CMV) and regression of osseous metastases in a pt with NSCLC (TPS 80%, HLA-A*02/CMV*) following disease progression on CPI occurred. These results show MT-6402 monotherapy activity though unique MOAs and provide rationale for MT-6402 dose expansion. Clinical trial information: NCT04795713. Research Sponsor: Molecular Templates, LLC.

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Poster Session

Product characteristics and clinical trial design for T-Plex: Multiplexed, enhanced T cell receptor engineered T cell therapy for solid tumors. *First Author: Shrikanta Chattopadhyay, TScan Therapeutics, Waltham, MA*

Background: Checkpoint immunotherapies have revolutionized the treatment of solid tumors yet durably benefit a minority of patients because they rely on endogenous anti-tumor T cells. In patients lacking functional anti-tumor T cells, a solution is engineering their T cells with exogenous T cell receptors (TCRs) to efficiently target and kill tumor cells. Initial clinical trials with TCR engineered T cell therapies (TCR-Ts) only produced partial, short-lasting responses because they targeted single tumor antigens. Solid tumors are notoriously heterogeneous not only with highly variable antigen expression levels but also with recently identified HLA gene losses occurring in up to 40% of solid tumors, enabling tumor cells to evade T cell attack. **Methods:** To overcome this heterogeneity, TScan has developed T-Plex, a multiplexed therapy comprising 2-3 different TCR-Ts, chosen from a collection of TCR-Ts called the ImmunoBank, to target different tumor antigens presented on different HLA types with confirmed tumor expression. **Results:** To deepen clinical responses, TCR-T cells are engineered to express the CD8α/β co-receptors that, in preclinical experiments, enable CD4+ helper T cells to become >100-fold more cytotoxic and secrete cytokines at >100-fold lower target antigen levels. Finally, to enable T cell persistence despite immunosuppressive TGF-β in the tumor microenvironment, engineered TCR-T cells express the dominant negative TGF-β receptor allowing ~10-fold improved proliferation and ~2-fold improved cytokine production in the presence of TGF-β. The inclusion of these additional genes is enabled by a transposon manufacturing system with no cargo limit. Patient selection for the Phase 1 study uses a separate screening protocol to identify patients any time during standard clinical care so they can rapidly enroll into the treatment protocol upon progression. Screening comprises germline HLA testing, then archival tumor testing for antigen expression and HLA loss. Treatment includes standard lymphodepletion followed by 2 doses of T-Plex infused 28 days apart. T-Plex initially starts with 2 TCR-Ts targeting different MAGE-A1 antigens presented either on HLA-A*02:01 or HLA-C*07:02. Dose escalation starts with testing the single TCR-Ts individually in dose levels 1 and 2. The two TCR-Ts will then be combined and escalated in dose levels 3 and 4. Additional TCR-Ts added to the ImmunoBank will go through dose levels 1 and 2 as single therapies before becoming available for multiplexed dose levels 3 and 4. Primary endpoints include safety and feasibility, secondary endpoints are response rates and duration of response and exploratory endpoints measure T cell persistence. **Conclusions:** Four additional TCR-Ts are on track to be added to the ImmunoBank in 2023 which makes 50-80% of patients with common solid tumors eligible for multiplexed TCR-T therapy. Research Sponsor: TScan Therapeutics.

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Poster Session

Preclinical testing of FOLR1-CAR T cells against osteosarcoma (OS). *First Author: Michelle Choe, Fred Hutchinson Cancer Center, Seattle, WA*

Background: Survival rates for OS are poor. Prior literature suggests folate receptor- α (FOLR1) overexpression in OS, making it a target for CAR T development. **Methods:** OS transcriptome data from TCGA, PCGP and NCI PIVOT programs were interrogated for FOLR1 gene expression. A 2nd generation FOLR1-CAR T cell was created by fusing the ScFv from farletuzumab (anti-FOLR1 monoclonal antibody) with a 4-1BB costimulatory and CD3 ζ cytotoxicity domain. Non-transduced (NT) T cells served as controls. *In vitro* functional analysis was performed against U2OS cell line using flow cytometry (FC) and Incucyte. U2OS xenograft in NSG mice was generated via intra-femoral inoculation for local tumor and via tail vein (TV) tumor injection for pulmonary disease. Tumor engraftment was confirmed by *in vivo* imaging system (IVIS). Disease progression was monitored by IVIS and CT imaging. 5 million T cells were administered via TV. Circulating human T cells (HTC) collected from retro-orbital peripheral blood (PB) were detected via FC. **Results:** FOLR1 transcript was expressed in >75% of OS in TCGA, PCGP and PIVOT. *In vitro* evaluation of FOLR1-CAR T demonstrated robust antitumor activity (E:T ratio 1:1) with cytotoxicity of 76.5% and 95.5% at 6 and 24 hrs. Disease progression was observed in NT T cell treated mice, with an average fold increase in IVIS radiance of 35.1 in local (n=2) and 142.8 in pulmonary disease (n=3) over 11 weeks (wks) versus complete resolution of local (n=2) and pulmonary disease (n=3) in FOLR1-CAR T treated mice (see table). NT T treated mice with local disease demonstrated significant bone destruction; no local tumors were found in FOLR1-CAR T treated mice. HTC (CD45+/CD3+) expansion was detected in PB one wk post-treatment (PT); in mice with metastasis 0.190% and 0.136% of live circulating cells were human T cells in FOLR1-CAR T and NT T treated mice, respectively. Improved overall survival was observed in FOLR1-CAR T treated mice (>100 vs 87.5 days). **Conclusions:** FOLR1-CAR T cells appear to have *in vivo* activity against U2OS cell line and support further testing of safety and feasibility in an early phase clinical trial for relapsed/refractory OS. Research Sponsor: Sam Day Foundation.

	Local Tumor		Pulmonary Disease	
	FOLR1 CAR T (n=2)	NT T (n=2)	FOLR1 CAR T (n=3)	NT T (n=3)
Average Fold Change in Radiance [p/s/cm ² /sr]	4 wks PT	-.988	1.382	-.805
	8 wks PT	-.632	30.716	-.816
	11 wks PT	-.998	35.125	-.848
HTC Average Contribution in Circulation	1 wk PT	.054%	.004%	.190%
	2 wks PT	.003%	.002%	.016%
	8 wks PT	.000%	.000%	.000%

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Poster Session

A subset of neutrophils as a predictive biomarker for immunotherapy response in patients with non-small-cell lung cancer and melanoma. *First Author: Yuval Shaked, Technion, Haifa, Israel*

Background: Despite the remarkable success of immunotherapy, only ~20-40% of cancer patients display an extended durable response. Pre-existing biomarkers for immunotherapy outcome are significantly limited in their predictive power, e.g., PDL-1 expression by tumor cells (AUC ~ 0.6-0.75). This requires additional efforts to search for new approaches to discover new biomarkers in immune-oncology. While mice are the most widely used and cost-effective model to study human disease, translating preclinical biomarkers into clinical practice faces significant obstacles – in part due to the lack of diverse or appropriate models. In this study we have taken a holistic approach to search for new biomarkers for immunotherapy outcomes, with the aim to improve translatability of the findings and their validity in cancer patients. **Methods:** Several pre-clinical models were used, each capturing one possible mechanistic aspect of immunotherapy response, such as tumor- and host-dependency, in order to reflect the variability seen in human cancers. These models have been analyzed for myeloid cell composition within tumors and peripheral blood using high throughput techniques such as single-cell RNA sequencing and mass cytometry, followed by rigorous bioinformatic tools. Peripheral blood mononuclear cells (PBMCs) were obtained from non-small cell lung cancer (NSCLC, n = 34) and melanoma (n = 38) patients prior to immune-checkpoint inhibitor backbone therapy as monotherapy or in combination with chemotherapy. These results were validated on additional human bulk mRNA datasets (n = 417). **Results:** Using the preclinical models, we identified interferon-stimulated, Ly6E^{hi} neutrophils as a pre-treatment, blood-borne biomarker for anti-PD1 response. These results were validated in PBMCs of advanced metastatic NSCLC and malignant melanoma patients predominately treated with immune checkpoint inhibitor-based therapy, with a high degree of accuracy (AUC ~ 0.9). These results were also validated in independent cohorts of immunotherapy-treated patients with other cancer types obtained from bulk mRNA datasets including renal cell carcinoma (n = 109), urothelial carcinoma (n = 228) and additional melanoma patients (n = 80). Functional studies revealed that Ly6E^{hi} neutrophils sensitize otherwise resistant tumors to anti-PD1 therapy, in part by directly activating cytotoxic T cells and contributing to tumor cell killing, while operate upstream of T cells in the immunotherapy response. **Conclusions:** Our study demonstrates a pragmatic approach to search for new, clinically relevant and functionally active cellular biomarkers for immunotherapy outcomes in humans. This study paves the way for a conceptual framework to advance the field of immuno-oncology by utilizing this approach for successful clinical trials. Research Sponsor: European Research Council.

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Poster Session

A novel platform to enrich for tumor-specific T cells in non-small-cell lung cancer. *First Author: Stephanie J Hachey, ImmunoTarget Therapeutics, Inc., Irvine, CA*

Background: To induce robust cellular immunity against non-small cell lung cancer (NSCLC), the leading cause of cancer-related death in the US, we have developed an innovative cell-based therapeutic platform technology to generate polyclonal, neoantigen-reactive T cells *in vitro*. **Methods:** Surgically resected NSCLC tissue and peripheral matched blood were collected from 17 patients under an IRB-approved protocol. From 3 of the patient-derived NSCLC specimens, methods were tested to enhance immunogenicity and stimulate neoantigen-specific immune responses. We then use a novel, human vascularized microtumor (VMT) platform to assess the sensitivity of tumor cells to T-cell mediated attack at the individual patient level. **Results:** The therapeutic platform induced a significant increase in T cell proliferation, interferon-gamma secretion, and blast phenotype of lymphocyte populations compared to T cells primed by standard methods. Interestingly, for one patient, immunosuppression of the T cell response with concomitant increase in CD96, an immune checkpoint receptor implicated in lung cancer progression, was observed in the tumor. Importantly, using sequencing data from one patient, an analytical and machine learning pipeline detected putative neoantigens using our therapeutic platform technology and not with standard methods. **Conclusions:** The therapeutic platform can be used to directly generate cell-based immunotherapies and to facilitate neoantigen discovery and development of targeted cancer immunotherapies. Our goal is to advance novel approaches to effectively mobilize anti-tumor immunity and overcome treatment resistance in NSCLC. Research Sponsor: U.S. National Institutes of Health.

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Poster Session

The exploratory case-control study on prediction of immune checkpoint inhibitor-induced thyroiditis by human leukocyte antigen types. *First Author: Yutaka Natori, Fukushima Medical University, Fukushima-Shi, Japan*

Background: Given the function of human leukocyte antigen (HLA) in immunity, variation of the HLA type could affect the development of immune-related adverse events (irAEs) that is induced by immune checkpoint inhibitors (ICIs). In this study, we examined whether HLA types of cancer patients could be a marker for the development of irAE thyroiditis. **Methods:** In the present case-control study, we randomly selected 20 cancer patients who received ICIs and developed thyroiditis (irAE thyroiditis group) and 51 who did not develop thyroiditis (No irAE thyroiditis group). The 51 patients were subdivided into 31 who did not develop any irAEs (No irAEs group) and 20 who developed irAEs other than thyroiditis (irAEs other than thyroiditis group). HLA types were classified at the amino acid sequence level (Field 2 resolution). Frequency of the HLA types of each group was compared. **Results:** There was no significant difference in HLA type prevalence, comparing the irAE thyroiditis group and the No irAE thyroiditis group. When comparing the irAE thyroiditis group with the No irAEs group, the irAE thyroiditis group had significantly higher HLA-X, HLA-Y, and HLA-Z (Tentative names are used here, and actual HLA types will be announced at the time of publication). This result suggested that irAEs other than thyroiditis in the control group could be noise. HLA-X had a specificity of 96.8% for the development of irAE thyroiditis. HLA-Y had a sensitivity of 80.0%. Patients carrying both HLA-X and HLA-Y had the highest specificity of 100.0%. There was a significant difference in frequency of HLA-Y between irAEs other than the thyroiditis group and the No irAEs group. HLA-Y may be a universal marker for any irAEs. On the other hand, HLA-X is a specific marker for thyroid irAE. The median time of onset of irAE thyroiditis in all patients was 72 days after ICI administration. Patients with both HLA-X and HLA-Y tended to have an earlier onset with a median onset time of 53 days. **Conclusions:** We found an association between specific HLA types and the development of irAE thyroiditis. The present study indicates that HLA types could be a predictive marker for the development of irAE thyroiditis. Research Sponsor: Japan Society for the Promotion of Science.

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Poster Session

C-reactive protein as a response biomarker to immune checkpoint blockade: A meta-analysis. *First Author: Alexander B Karol, Department of Medicine, Icahn School of Medicine at Mount Sinai, Mount Sinai Hospital, New York, NY*

Background: Tumor-promoting inflammation is a hallmark of cancer pathogenesis and is associated with poor outcomes and treatment resistance. C-reactive protein (CRP) is a routinely measured acute phase reactant whose synthesis is stimulated by cytokines and may thereby represent a surrogate for tumor promoting inflammation. Pre-treatment CRP has been associated with resistance to immune checkpoint blockade (ICB) in several studies. However, whether post-treatment changes in CRP correlate with ICB outcomes has not been systematically examined. **Methods:** We performed a systematic review to identify cohort studies or clinical trials in solid tumor patients receiving ICB therapy with CRP response comparator pairs (high/low) available. We included studies that had hazard ratio (HR) of overall survival (OS), progression-free survival (PFS), or odds ratio (OR) of objective response rate (ORR) available. We performed a meta-analysis using a random-effect model to evaluate if post-treatment changes in CRP are associated with ORR, PFS, or OS. Subgroup analysis for primary cancer type was performed. Heterogeneity was assessed using the I-squared statistic. **Results:** We screened 691 eligible studies; 19 met inclusion criteria and 2,101 patients were included. Patients experiencing post-ICB declines in CRP had improved ORR HR=4.67 [95% CI] [2.81-7.78] ($p<0.0001$, $I^2=42\%$), PFS HR=2.47 [1.98-3.09] ($p<0.0001$, $I^2=18\%$), and OS HR=2.28 [1.68-3.08] ($p<0.0001$, $I^2=56\%$). Heterogeneity among subgroups was low in ORR ($I^2=14.6\%$) and PFS analysis ($I^2=0\%$), and moderate in OS analysis ($I^2=64.2\%$). **Conclusions:** In patients receiving ICB therapy, post-treatment declines in CRP were associated with improved ORR, PFS, and OS across multiple histologies. These findings support the integration of on-treatment CRP decline as a clinically relevant response biomarker for novel therapies directed at modulating tumor-promoting inflammation. A meta-regression analysis will help determine optimal post-treatment CRP cutpoints. Pooled OR of ORR [95%CI] and HR [95%CI] of PFS and OS with subgroup analysis results and heterogeneity assessment. Research Sponsor: None.

Primary malignancy	Subgroup						
	Overall	Non-small cell lung cancer	Renal cell carcinoma	Melanoma	Urothelial carcinoma	Varied	Subgroup differences
ORR	4.67 [2.81, 7.78]	7.97 [3.54, 17.94]	3.85 [2.11, 7.00]	7.14 [2.31, 22.13]			$I^2=14.6\%$ ($P=0.31$)
PFS	2.47 [1.98, 3.09]	2.53 [1.79, 3.59]	2.55 [1.87, 3.46]				$I^2=0\%$ ($P=0.99$)
OS	2.28 [1.68, 3.08]	1.64 [1.16, 2.31]	3.90 [2.02, 7.54]	1.46 [1.03, 2.07]	3.17 [1.59, 6.34]	2.28 [1.68, 3.08]	$I^2=64.2\%$ ($P=0.02$)

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Poster Session

Clinical outcomes of immune checkpoint inhibitor treatment in patients with classic cold tumors identified to have a high tumor mutational burden via ctDNA. *First Author: Reagan Barnett, Guardant Health, Inc., Redwood City, CA*

Background: Some cancers, including breast, ovarian, pancreatic, and prostate cancers, are traditionally considered “cold” tumors, less likely to trigger an immune response and/or respond to immune checkpoint inhibitors (ICIs). However, some patients with these cancer types may benefit from ICIs. Here we investigate if a high blood tumor mutational burden (bTMB-H) may predict benefit to ICIs in such tumor types. **Methods:** We retrospectively queried the Guardant Health database for patients with advanced breast ($n=8531$), ovarian ($n=1106$), upper GI/pancreatic ($n=5110$), and prostate ($n=7153$) cancer who had ctDNA next-generation sequencing (Guardant360, Redwood City, CA) as part of routine clinical care from 2020-2022. Mutation profiles were evaluated for patients with bTMB-H (based on previously reported 80th percentiles for each tumor type, breast ≥ 15.31 mut/Mb, ovarian ≥ 14.98 mut/Mb, pancreatic ≥ 11.36 mut/Mb, prostate ≥ 13.4 mut/Mb) vs those with bTMB below this threshold (bTMB-L). A subset of cases were analyzed in a multi-institutional clinical cohort with a bTMB of ≥ 10 mut/Mb ($n=35$). **Results:** bTMB-H was observed in 9.5% of patients with breast cancer, 5.1% ovarian, 2.0% pancreatic, and 4.4% prostate. Genes more often mutated in patients with pTMB-H vs pTMB-L in each cancer type included *TP53* and *PIK3CA* in breast cancer; *TP53* and *CHEK2* in ovarian; *ATM* and *CHEK2* in pancreatic; *TP53* and *AR* in prostate (all p values <0.01). Patients in the clinical cohort ($n=35$) had a median age of 74 (range: 40-85) 29/35 White / 4/35 Black, 27 prostate, 1 breast, 3 upper GI. Patients underwent first ctDNA analysis after a median of 3 (range 0-11) lines of therapy. The median bTMB detected was 16.59 mut/Mb (range: 10.02-152.85); six patients (6/35) were MSI-H. Twenty-three patients received ICI after a median of 6 (range: 0-8) lines of therapy, either alone (9, 39%) or in combination with hormonal therapy (5, 22%), chemotherapy (3, 13%) or targeted therapy (6, 26%). The median time to progression on ICI was 5.0 (95% CI, 3.6-6.4) months and median duration of response was 19.8 months (12.1-20.2). The ORR for evaluable patients was 13% and 74% of patients had progressed on therapy at time of data cut-off. **Conclusions:** “Cold” tumors represent a meaningful portion of patients with advanced cancer in which ICIs are not typically leveraged, and ctDNA was a feasible tool for identifying patients with bTMB-H who achieved durable responses from ICI-based therapy. The efficacy in this clinical cohort of traditionally “cold” tumors approaches other pan-cancer cohorts that include more traditionally immunoresponsive tumor types; further research is warranted to explore predictive value of bTMB, including potential tumor-specific thresholds, for optimizing patient selection for ICIs. Research Sponsor: None.

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Poster Session

Blood-based assessment of patients with mismatch repair-deficient tumors enrolled in NCI-MATCH Arm Z1D (nivolumab). *First Author: Chris Alan Karlovich, Molecular Characterization Laboratory, Frederick National Laboratory for Cancer Research, Frederick, MD*

Background: NCI-MATCH was the largest precision medicine initiative conducted to date. Arm Z1D was a study of nivolumab in patients (pts) whose tumors were mismatch repair deficient (MMRd) by immunohistochemistry (IHC). Plasma was available for analysis of circulating tumor DNA (ctDNA), a component of cell-free DNA (cfDNA), in 39 of 47 pts enrolled to treatment. Large ctDNA gene panels that interrogate microsatellite instability (MSI), tumor mutational burden (TMB) and other complex biomarkers may provide an important complement to tumor-based assessments. **Methods:** 10–30 ng of cfDNA extracted from Streck tubes was tested with a modified version of the 523-gene TruSight[®] Oncology 500 ctDNA RUO assay (Illumina, San Diego, CA). Blood MSI (bMSI) status was calculated by interrogating ~2400 microsatellite sites and applying an experimentally validated cut-off. Blood TMB (bTMB) was calculated as total number of nonsynonymous and synonymous SNVs and Indels identified per Mb. Tumor sequencing was performed with the 143-gene OncoPrint Comprehensive Assay v2. Overlap of tumor and plasma gene panels was evaluated for concordance. MMRd was evaluated by MLH1 and MSH2 IHC expression. MSI PCR testing was performed on 7 microsatellite sites. Clinical response was assessed by RECIST v1.1 criteria. **Results:** ORR was 31% (12/39) for 39 MMRd patients with plasma samples. Among these, 34 pts (87%) were classified as MSI-high (MSI-H) by ctDNA at baseline. The 5 MSS cases included 1 CR, 2 PRs and 2 unevaluable for response. The median bTMB was 56.4 mut/Mb (range: 1.65 – 435 mut/Mb). All pts had at least one oncogenic/likely oncogenic alteration identified in plasma. Of 136 of these mutations identified in tumor, 107 (78.6%) were detected in plasma. The most frequently mutated genes in plasma included *TP53* ($n=26$ pts), *RNF43* ($n=16$ pts, all G659Vfs*41) and *PIK3CA* ($n=16$ pts). *MLH1* ($n=5$) and *MSH2* ($n=5$) mutations were also identified. *RNF43* G659Vfs*41, which was not interrogated by the targeted tumor panel, is known to be strongly associated with MSI-H status. In this heavily pre-treated cohort (median prior therapies = 3), variants in genes commonly associated with clonal hematopoiesis of indeterminate potential were identified in all pts. Changes in cfDNA tumor fraction tracked with clinical response in 4 of 4 pts where on-treatment blood was collected for TSO 500 assessment. **Conclusions:** 78.6% of oncogenic/likely oncogenic alterations found in tumor were also identified in plasma. 87% of MMRd pts by tumor IHC were defined as MSI-H by baseline ctDNA, and median bTMB was 56.4 mut/Mb. These data suggest blood-based MSI and TMB should be further explored as biomarkers for the non-invasive identification of patients who may be candidates for immune checkpoint blockade, particularly when tissue is limiting. Research Sponsor: U.S. National Institutes of Health; Illumina, Inc.

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Poster Session

Time-dependent efficacy of immune checkpoint inhibitors in the treatment of metastatic cancers: A meta-analysis. *First Author: Thierry Landre, Hôpitaux-Universitaires-Paris-Seine-St-Denis, AP-HP, Paris, France*

Background: Immune checkpoint inhibitors (ICIs) have been established as the standard of care for numerous advanced malignancies. Emerging evidence suggests that the time-of-day of administering these immunotherapies may impact patient outcomes. We sought to determine the consistency in the impact of ICI time-of-day infusion on survival of patients with metastatic cancer. **Methods:** We performed a meta-analysis of published studies that have reported on ICI time-of-day infusion and efficacy in patients with advanced solid tumors. Overall survival (OS) and progression free survival (PFS) were compared between patients who had received ICIs before and after the daily time cut-off of each study. Hazard ratios (HRs) with their 95% confidence interval (CI) were collected from the studies and pooled. **Results:** This meta-analysis identified 7 studies of 1019 patients (PS 0, 43%; PS 1, 39%; males, 65%; females, 35%) who had stage IV non-small cell lung cancer (NSCLC), urothelial cancer, renal cell carcinoma, or melanoma, and were treated with mostly anti-PD-1 (nivolumab or pembrolizumab), anti-PD-L1 (atezolizumab), and anti-CTLA-4 (ipilimumab) agents. The time cut-offs selected to stratify patterns of ICI infusion were 16:00 or 16:30 in 5 studies (based on differences in adaptive immune response reported in previous vaccination studies) and 13:00 (based on median time of ICI infusions) in 2 studies. The pooled analysis of OS results showed a statistically significant benefit in favor of patients receiving infusions in the morning or in the early part of the day with a HR: 0.49, [95% CI: 0.36-0.69] ($p<0.0001$). A similar benefit was observed for PFS with a HR: 0.56, [0.44-0.72] ($p<0.00001$). **Conclusions:** Patients with advanced cancers may benefit from earlier time-of-day ICI infusions. Our findings are consistent with established circadian mechanisms that control immune cell functions and trafficking over a 24-h period. Prospective randomized trials are warranted to establish ICI timing recommendations for optimizing treatment efficacy in patients with different cancer types and at minimal cost. Research Sponsor: None.

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Poster Session

Pan-cancer analysis of natural killer (NK) cell infiltration in human malignancies: Molecular features and clinical implications. *First Author: Nick Zorko, University of Minnesota, Minneapolis, MN*

Background: NK cells are part of the innate immune system that are not antigen-specific, but can be redirected to targets of interest using multiple strategies. Advantages of NK cells over T cells include the use of allogeneic off-the-shelf products and lower risk of cytokine release syndrome. Numerous NK-specific immunotherapies are under development for the treatment of cancer, although none are yet FDA-approved. Here, we conducted a pan-cancer analysis of NK cell abundance in >90,000 tumor samples across 45 cancer types using the Caris Precision Oncology Alliance (POA) database. Features of prostate cancer (PCa, n=3365) and renal cell carcinoma (RCC, n=1106) were explored in depth. **Methods:** DNA (targeted/whole-exome) and RNA (whole-transcriptome) sequencing was performed for patient tumors (N=90,916) submitted to Caris Life Sciences (Phoenix, AZ). NK cell fractions were inferred from RNA-seq data using quantTiseq (Finotello, 2019). Real-world overall survival (OS) was determined from insurance claims, and Kaplan-Meier estimates were calculated. Statistical significance was determined using χ^2 and Mann-Whitney U tests with corrections for multiple hypothesis testing where appropriate. **Results:** Median NK cell fractions ranged from 7-9% (medulloblastoma and gliomas) to 2% (thyroid and thymic cancers), with intermediate levels observed for PCa (4.6%) and RCC (3.1%). High (> median) NK cell fractions were associated with improved OS (hazard ratios, 0.28–0.84, $p<0.05$) for 28 of 45 cancer types, while 16 of 45 including low-grade glioma, GIST, and thyroid had HR <1.0 (0.264–0.997) with 95% CI crossing 1.0. Improved OS was notable in PCa (HR 0.46, 95% CI 0.38–0.56, $p<0.0001$) and RCC (HR 0.52; 95% CI 0.39–0.70, $p<0.0001$). Unexpectedly, tumors with higher NK infiltrates were less frequently PD-L1+ (SP142) by IHC in PCa (2.8% vs 5.4%, $p=0.08$) and RCC (12.4% vs 30.8%, $p<0.0001$) (i.e. an inverse relationship), despite a lack of correlation of NK infiltration with dMMR/MSI status or tumor mutation burden (TMB) in both cancers. Conversely, increased NK infiltration was associated with a 1.4- to 2.1-fold increased mRNA expression of immunomodulatory receptors *LAG3* and *TIGIT* in both PCa ($p<0.0001$) and RCC ($p<0.0001$), but a 1.4-fold decrease in *B7-H3* in RCC ($p<0.0001$). **Conclusions:** High NK cell infiltration is associated with improved OS in numerous cancer types, including many with inadequate therapeutic options. Our findings suggest broad deployment of NK engagers and CAR-NK products in a range of malignancies. The positive correlation between NK cells and *LAG3/TIGIT* suggest that combination approaches may be warranted. The inverse relationship between NK infiltrates and PD-L1, and lack of association with standard immune therapy markers (MSI status, TMB), indicates the potential use of NK cell approaches in situations where other immunotherapies are ineffective. Research Sponsor: Prostate Cancer Foundation; Department of Defense; Caris Life Sciences; U.S. National Institutes of Health.

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Poster Session

The prognostic ability of immune scoring system Immunoscore in patients with localized colon cancer: A systematic review and meta-analysis. *First Author: John Lois Padayao, St. Luke's Medical Center, Quezon City, Philippines*

Background: Assessment of tumor recurrence risk as well as prognosis in resectable colon cancer are still mainly based on the histopathological criteria of tumor invasion reflected in the TNM classification. Robust data in colorectal tumor research show the value of tumor microenvironment and tumor-infiltrating lymphocytes (TILs) as novel parameters to predict recurrence and survival. The utility of the derived tumor Immunoscore via digital pathology is now being promoted to refine the prognosis of early colon cancer patients together with the TNM staging to guide treatment decisions, but is not yet a recommendation in international consensus guidelines. This study assessed the prognostic value of this diagnostic tool in predicting clinical outcomes. **Methods:** A systematic literature search using PubMed, Embase, and Cochrane CENTRAL Library was conducted to identify observational or randomized controlled studies from January 2008 and December 2022 according to pre-specified inclusion and exclusion criteria which examined the relationship between Immunoscore and long-term prognosis (overall survival and disease free survival) in patients with localized colon cancer. Hazard ratios with 95% confidence interval for overall survival (OS) and disease-free survival (DFS) were extracted. Pooled estimates of the prognostic ability of Immunoscore were obtained using bivariate random effects model. Statistical heterogeneity between studies was evaluated with I^2 statistics and explored through sensitivity analysis. **Results:** A total of 5,718 patients from 11 studies were included in the meta-analysis. Moderate heterogeneity between studies for both DFS ($I^2=27\%$) and OS ($I^2=33\%$) was seen. The pooled analysis indicated that compared to those with high Immunoscore, colon cancer patients with low Immunoscore were associated with shorter disease-free survival (HR 1.75, 95% CI 1.53–2.49) and overall survival (HR 1.87 95% CI 1.45–2.13). In the subgroup analyses, this association was consistent across geographic regions and maximum time of follow up. **Conclusions:** A low Immunoscore was significantly associated with poorer clinical outcomes in terms of disease-free survival and overall survival. The use of Immunoscore provides valuable estimate of the risk of recurrence in patients with early colon cancer and has the potential to greatly affect treatment decisions in conjunction with the existing risk assessment system. Research Sponsor: None.

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Poster Session

Leflotolimod (TLR agonist) and ipilimumab in patients with advanced solid tumors: A phase I trial. *First Author: Mirella Nardo, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: The TLR-9 agonist lefotolimod (MGN1703) significantly increases the Th1 response in pre-clinical models and has demonstrated antitumor activity in early phase clinical trials. This trial assessed the safety and preliminary efficacy of the rational combination of lefotolimod with ipilimumab in patients (pts) with advanced solid tumors. **Methods:** This was a single-center, open-label, investigator-initiated, dose-finding, and expansion Phase I trial (ClinicalTrials.gov no. NCT02668777). Key inclusion criteria were histologically confirmed advanced solid tumor, ECOG performance status ≤ 2 ; age ≥ 18 years. Patients (pts) were enrolled at escalating doses of lefotolimod (15–120 mg/kg), subcutaneously (SC) administered weekly and a fixed dose of ipilimumab 3 mg/kg in a 3-week cycle. For the expansion cohort, lefotolimod was administered intratumorally (IT) at 15 mg weekly. The primary endpoint was safety and tolerability according to CTCAE v4.0, dose-limiting toxicity (DLT) and maximum tolerated dose (MTD)/recommended Phase II dose (RP2D) for the lefotolimod in this combination. The secondary endpoint was efficacy, evaluated according to Immune-Related Response Criteria (irRC). Exploratory endpoints included changes in the intratumoral T-cell microenvironment in pre- and post-treatment tumor biopsies and the correlation of immune biomarkers with response. **Results:** From March 2017 to February 2020, 28 pts were enrolled. Median age was 56 years (range: 19–92). Median prior lines of therapy was 4 (range: 0–12). Pts 1–4 received lefotolimod 15 mg SC, pts 5–8 received lefotolimod 30 mg SC, pts 9–12 received lefotolimod 60 mg SC, pts 13–19 received lefotolimod 120 mg SC, and pts 20–28 received lefotolimod 15 mg IT. Eleven pts had at least one treatment-related AE (TRAE). The most common TRAE was skin rash (n=4, 14.2%), followed by fatigue (n=3, 10.7%) and pruritis (n=2, 7.1%). There were no grade 4 or 5 AEs, none of the pts required dose reduction, and there was no discontinuation of treatment due to AEs. DLT and MTD were not reached and the RP2D was established as lefotolimod SC 120 mg weekly with ipilimumab 3mg/Kg every 3 weeks. Of the 28 pts, 8 pts had stable disease as best response. 7 pts could not be evaluated by irRC due to clinical progression before restaging, non-measurable lesions and withdrawal of consent. Paired biopsy samples were analyzed by flow cytometry. Pro-inflammatory immune conditioning of the tumor microenvironment by the combination of the TLR9 agonist MGN1703 in combination with ipilimumab showed increases in intra-tumoral CD8 T cell frequency, memory CD8 phenotype (CD45RO+) and proliferation (Ki67+). **Conclusions:** The combination of high subcutaneous doses or intra-tumoral administration of lefotolimod in combination with ipilimumab is safe and well tolerated in patients with advanced cancers, with preliminary antitumor activity observed. Clinical trial information: NCT02668777. Research Sponsor: U.S. National Institutes of Health; MD Anderson Cancer Center Support Grant (NIH/NCI P30 CA016672).

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Poster Session

Modi-1, anti-citrullinated neopeptide vaccine, alone and combined with checkpoint inhibitors in patients with head and neck, breast, renal, and ovarian cancers: ModiFy phase I/II basket clinical trial—Report after completion of monotherapy dose-finding. *First Author: Christian H.H Otten-smeier, The Clatterbridge Cancer Centre NHS Foundation Trust, Liverpool, United Kingdom*

Background: Stressful conditions in the tumor microenvironment induce autophagy, resulting in high levels of calcium in autophagosomes, in turn activating peptidyl-larginine deiminase enzymes; these convert arginine residues within polypeptides to citrulline and alter proteolytic cleavage. MHC-II presents these citrullinated peptides to CD4⁺ T cells. Modi-1 comprising three citrullinated, adjuvanted peptides targeting vimentin and enolase to inducing and expanding CD4⁺ T cells. At the tumor site the CD4⁺ T cells release proinflammatory cytokines including INF γ , further upregulating MHC class II. This enables presentation of endogenous citrullinated peptides on the tumor cells in a positive feed-forward loop. **Methods:** ModiFy is an open-label, multicohort, multicenter, adaptive Phase I/II basket trial for patients with unresectable Head and Neck Squamous Cell Carcinoma (SCCHN), Triple Negative Breast Cancer (TNBC), Renal Cell Carcinoma and High Grade Serous Ovarian Carcinoma (HGSOC). Patients are treated with Modi-1 alone or - if eligible for standard of care checkpoint inhibitor (CPI) monotherapy - Modi-1 + SoC CPI. The Modi-1 only expansion cohorts will recruit 16 patients per tumor type, Modi-1+CPI will recruit 21 patients per tumor type. Study objectives are safety, the breadth and strength of the cellular immune response, ORR, duration of response, PFS, and OS. **Results:** As of February 2023, the monotherapy dose-finding has completed. 3 patients received Modi-1v (vimentin only) 80 μ g/peptide and 3 patients received Modi-1 at 400 μ g/peptide (vimentin + enolase peptides) as part of the monotherapy dose escalation. No DLTs were observed, triggering enrolment into the monotherapy expansion cohorts. 20 evaluable pts have received Modi-1v (3 pts Modi-1v 80 μ g/peptide, 17 Modi-1 400 μ g/peptide): 16 had HGSOC, 2 TNBC, 2 SCCHN with 53 doses received; 2 patients have been treated beyond 24 weeks. All patients had skin reactions consistent with a delayed-type hypersensitivity reaction at injection sites. Vaccinations have been well tolerated with 71 adverse reactions in 15 patients reported. All were Grade 1 or 2 except for four Grade 3 reactions in 3 patients (anemia, fatigue, and injection site reactions). There have been no SAEs. Elevation in anti-CCP antibodies has not been seen. In 13 response-evaluable patients, best overall response by RECIST v1.1 included 1 PR (SCCHN), 6 SD and 6 PD. The study is currently enrolling into the combination with checkpoint inhibition dose escalation cohorts and the monotherapy expansion cohorts. **Conclusions:** Modi-1 is well tolerated, and the early monotherapy efficacy data are encouraging. Safety and early efficacy data are supportive of further development of combination with CPI. Clinical trial information: NCT05329532. Research Sponsor: Scancell Ltd.

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Poster Session

Investigation of synthetic lethality gene pairs in the DNA damage response pathway in response to immunotherapy in pan-cancer. *First Author: Hongyan Huang, Department of Oncology, Beijing Shijitan Hospital, Capital Medical University, Beijing, China*

Background: The concept of synthetic lethality (SL) refers to the phenomenon where the simultaneous loss of function of two genes leads to cell death, while the loss of function of either gene alone has no effect. PARP inhibitors target poly ADP ribose polymerase (PARP) enzymes, which are involved in DNA repair, are the successful cases of utilizing synthetic lethality-based therapy to treat cancers with DNA damage response (DDR) deficiency. The prognosis for cancer patients already has a combination of synthetic lethal mutations especially in DDR pathway can vary and it is not yet fully understood how these mutations may impact the response to immunotherapy. **Methods:** SL gene combinations in the DDR pathway were screened out from SynLethDB database (<http://histone.sce.ntu.edu.sg/SynLethDB/>). The immunotherapy cohort (Samstein 2019, n=1661) and non-immunotherapy cohort (Zehir 2017, n=10336) with solid tumor were used to Kaplan-Meier analyze the correlation between SL gene combinations and prognosis. TMB scores were compared between DDR co-mutation group and non DDR co-mutation group. For investigating the associations between immune infiltrates and genetic features, TIMER 2.0 database (<http://timer.cistrome.org/>) was conducted to estimation of immune infiltration levels on DDR mutation genes in pan-cancer. **Results:** 430 pairs of DDR mutation combinations were used to subgroup stratification, the DDR co-mutation group was associated with worse prognosis in non-immunotherapy cohort (HR=1.305, p<0.0001) but better in immunotherapy cohort (HR=0.741, p<0.0061). Interestingly, the TMB score in the DDR co-mutation group was significantly higher than non DDR co-mutation group (mean 50.03 vs 8.868, p<0.0001) in immunotherapy cohort. The high-frequency mutation combinations (>10%) were ATM-POLE (14.40%), ATM-ATR (13.60%), ATR-BRCA2 (13.60%), ATM-BRCA2 (12.00%) and BRCA2-RECQL4 (10.40%), respectively. Comparing common immune component with statistically significant under different DDR mutant genes, the ATM-POLE co-mutation tumor tended to have more CD4+ T cell infiltration while the ATM-ATR co-mutation tumor appeared to have more myeloid dendritic cell infiltration. **Conclusions:** The combinations of DDR SL mutation tumor might result to worse prognosis whereas these patients might benefit from immunotherapy. Our results will help to shed light on the complex interplay for the combinations of SL mutation in DDR pathway between cancer cells and the immune system and provide new insights into the development of effective cancer treatments. Research Sponsor: None.

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Poster Session

A phase 1 first-in-human study of interferon beta (IFN β) and membrane-stable CD40L expressing oncolytic virus (MEM-288) in solid tumors including non-small-cell lung cancer (NSCLC). *First Author: Andreas Nicholas Saltos, Moffitt Cancer Center, Tampa, FL*

Background: MEM-288 is a conditionally-replicative oncolytic adenovirus expressing human IFN β and a recombinant membrane-stable form of CD40L (MEM40L). Pre-clinical studies show MEM-288 induces robust dendritic cell-mediated systemic T cell responses capable of inhibiting abscopal tumor growth as monotherapy and synergizes with immune checkpoint inhibitors (ICI). **Methods:** MEM-288 is being evaluated in this Phase 1 open-label trial (NCT05076760) in pts with select solid tumors including NSCLC (a) refractory to standard therapy and (b) with a tumor lesion deemed feasible for biopsy and MEM-288 intratumoral (i.t.) injection. The primary objective is to determine using a BOIN design a recommended phase II dose of MEM-288 across 3 dose levels (DL1-3) spanning 1e10 to 1e11 viral particles by i.t. injection once every 3 weeks. Secondary objectives include efficacy assessment, including response rate of injected and non-injected tumors assessed separately. Tumor biopsies obtained immediately prior to the 1st and 2nd injections are used to explore biomarkers and anti-tumor immune responses. **Results:** As of February 2023, 12 pts (11 NSCLC and 1 pancreatic cancer; n = 3 DL1, n = 5 DL2, n = 4 DL3) have enrolled. The median number of MEM-288 i.t. injections was 2 (1-3), median age was 63 (39-76), and median prior lines of therapy was 3 (1-5). Radiology-guided injections were administered in superficial/palpable tumors and visceral lesions. No dose limiting toxicities occurred. Treatment-related adverse events observed in > 1 pt include grade 1 injection site reaction (42%) and chills (17%). Of 10 response-evaluable pts, 4 (40%) pts had shrinkage of injected tumor (range -26 to -54%); 3 (30%) PR and 1 (10%) SD. Multiple pts also had stabilization or shrinkage of distal non-injected lesions. Best overall response was 3 (30%) stable disease and 7 (70%) progressive disease. After a single MEM-288 injection, biopsies show decreased tumor cell percentage concomitant with substantial increases in overall CD8⁺ T cells, increased T clonotype diversity in both tumor and peripheral blood, and increased TCF1⁺ stem-like CD8⁺ T cells that are strongly associated with response to ICIs. Plasma cytokine analysis showed increases in IFN γ and of IFN-inducible cytokines and chemokines, supportive of stimulation of systemic response after MEM-288. Of note, a pt with strong stimulation of tumor and systemic T cell immunity after MEM-288 had subsequent CR (ongoing > 7 months) to docetaxel + ramucirumab following prior treatment failure with platinum doublet + ICI received before MEM-288. **Conclusions:** Preliminary safety, antitumor and immune response data are encouraging. Updated results and immune data from this study will be presented. An expansion arm is planned with combination MEM-288 and anti-PD1 antibody in pts with advanced NSCLC refractory to ICI. Clinical trial information: NCT05076760. Research Sponsor: Memgen.

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Poster Session

VirMAP for cancer: Characterization of the intratumoral virome in virally associated cancers and a resource for investigators. *First Author: Yongwoo David Seo, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: A major barrier to understanding the role of viruses in cancer progression has been the lack of sensitivity of current tools to assemble viral genomes in an untargeted way. Here, we utilize our novel VirMAP algorithm to identify eukaryotic and prokaryotic viruses associated with cancers, using RNA sequencing data from The Cancer Genome Atlas (TCGA). **Methods:** VirMAP was run on 16 TCGA RNASeq datasets of primary tumor tissues, with a focus on cancers with known viral associations (including cervical, head and neck, liver, stomach, esophagus and ovarian). Previously published survival data were used for exploratory analysis. Overall survival (OS) was assessed using the Kaplan-Meier method, and p-values were calculated using log-rank test. Multivariate analysis (MVA) was done using Cox proportional hazards model to control for age, sex, stage, and histology. **Results:** Viral sequence recovery (among 537 billion sequencing reads from 6185 patients) was at least equal to previously published algorithms such as Kraken, but with higher taxonomic resolution; overall recovery was 0.0041% from 16 tumor types. Cancers with high viral loads such as cervical cancer demonstrated high recovery rates (0.012% of all reads mapped to viral taxa, followed by 0.004% for liver, 0.0018% head and neck, 0.0016% stomach, 0.0009% esophageal, and 0.0002% ovarian). There was a wide range of viral signature richness, with cervical cancer showing the highest viral read count predominated by 18 different HPV serotypes; in contrast, stomach cancer had lower abundance but contained over 300 unique viral species. Exploratory analysis revealed novel correlations between viral signatures and OS. In cervical cancer, presence of HPV45 predicted worse survival (median OS 837 days vs 4086, p=0.0043); MVA demonstrated hazard ratio (HR) of 5.7 [2.6-11.4, p<0.0001]. In stomach cancer, patients often had more than one viral taxon present (mean 3.7, range 0-18); presence of seven or more unique taxa predicted worse OS (median OS 403 days vs 1153, p=0.0001). MVA showed HR of 1.1 for every additional taxon (p=0.0004). Across all 16 tumor types, the detection of phage virus was associated with worse OS (1073 days vs. 2094 days for non-phage virus and 2131 days for no virus, p<0.0001). **Conclusions:** VirMAP performs deep characterization of the tumor-associated virome in both high and low abundance settings, with generation of partial genome reconstructions and strain level taxonomic classification including phages. Further work is ongoing to optimize viral read normalization based on genome length, as well as subset analysis with disease-specific modifiers such as histology, race, and exposures. Utilizing publicly available platforms such as TCGA, clinical and correlative published data can be leveraged to better understand the nuanced pleiotropic effects of the tumor virome on cancer progression. Research Sponsor: None.

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Poster Session

Uliedlimab and toripalimab combination therapy in treatment naïve advanced NSCLC: Phase 1b/2 clinical trial results using CD73 as a potential predictive biomarker. *First Author: Qing Zhou, Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, Guangzhou 510080, China, Guangzhou, China*

Background: CD73 is a rate-limiting enzyme in adenosine pathway promoting immune suppression in tumor microenvironment. The role of CD73 as a novel target in cancer immune therapy is further supported by correlation between its high expression in tumors and poor prognosis in cancer pts. Here we evaluate safety and efficacy of uliedlimab, a differentiated CD73 antibody, in combination with toripalimab, a PD-1 antibody, in treatment naïve NSCLC pts. In particular, we investigate the correlation between clinical response and tumor CD73 expression to assess its value as a potential predictive biomarker, following a previous study where a correlation was indicated (Robert F, et al. ASCO 2021). **Methods:** Pts with treatment naïve advanced NSCLC (EGFR/ALK wild type) were enrolled in a dose-expansion cohort and received uliedlimab (20mg/kg or 30mg/kg Q3W) in combination with toripalimab 240mg Q3W. Safety, the primary endpoint, and clinical efficacy including ORR, determined by iRECIST, were evaluated. Baseline CD73 and PD-L1 expression in tumor specimens were measured by IHC. The cut-off value for CD73^{High} expression was assessed by ROC analysis for correlation with ORR. **Results:** As of 12/2/22, 66 pts were enrolled (median age 62.5 years, ECOG PS 0 40.6%, male 84.8% and never smokers 22.7%) and received at least one dose. Treatment-related adverse events (TRAEs) occurred in 86.4% of pts (Gr $\geq$ 3, 15.2%) with no grade 5 TRAE. One patient was discontinued due to TRAE (1.5%). Efficacy was analyzed in 48 pts who were enrolled at least 90 days prior to data cut-off, allowing for two assessments. Baseline PD-L1 and CD73 expression was available in 45 pts. 40% of tumor or immune cells with $\geq$ 1+ staining intensity by IHC was determined as a preliminary cut-off for CD73^{High} (the area under ROC curve =0.72, p=0.02). While ORR and DCR were 31.3% (15/48) and 79.2% (38/48) respectively in all pts, ORR appeared higher in CD73^{High} pts (50%, 9/18) and much lower in CD73^{Low} pts (14.8%, 4/27). Highest ORR was found in a cohort with CD73^{High} and PD-L1 TPS $\geq$ 1% (57.1%, 8/14). **Conclusions:** Uliedlimab and toripalimab combination therapy was well-tolerated in treatment naïve advanced NSCLC pts. Clinical response of the therapy seems to correlate with high tumor CD73 expression, indicating a potential value of CD73 as a predictive biomarker. The study warrants a biomarker-guided randomized clinical trial that is currently in preparation. Clinical trial information: NCT04322006. Research Sponsor: I-Mab Biopharma.

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Poster Session

Enhancing STING activation by cyclic dinucleotide-manganese particles for systemic cancer immunotherapy. *First Author: Xingwu Zhou, University of Michigan, Ann Arbor, MI*

Background: Activating the innate immune pathway of stimulator of interferon genes (STING) can elicit potent anti-tumor immunity via the production of type-I interferons (IFN-I). However, cyclic-dinucleotide (CDN) STING agonists have undesirable pharmacological properties. Most CDNs in clinical development are administered intratumorally, thus precluding their applications in treating metastasis, hematologic malignancies, and hard-to-reach solid tumors. Here, we report the development of a new nanoparticle system for the systemic delivery of CDN STING agonists with potent efficacy, favorable pharmaceutical properties, and acceptable safety profiles. **Methods:** Nutritional metal ions play crucial roles in modulating immune pathways, which could potentially be used for enhancing STING activation. We screened different metal ions and found that manganese ion (Mn^{2+}) achieved strong synergy with CDN STING agonists for inducing IFN-I production. We further developed a new nanoparticle system for co-delivery of Mn^{2+} and CDN for systemic cancer immunotherapy. **Results:** Mn^{2+} induced up to 77-fold enhancement in CDN-mediated STING activation. Mixing CDNs with Mn^{2+} resulted in the self-assembly of nanocrystals, and the lipid layer coating led to uniform nanoparticles. The resulting STING-activating CDN-Mn nanoparticle (SNP) given intravenously elicited IFN-I responses, attenuated the suppressive functions of myeloid cells, remodeled the immunosuppressive tumor microenvironment, and expanded CD8⁺ T cells for sustained tumor control. Intravenous SNP therapy resulted in robust anti-tumor efficacy in multiple murine tumor models, including a genetically engineered mouse model of MMTV-PyMT triple-negative breast cancer. We have also demonstrated the robust anti-tumor efficacy of SNP against VX2 head and neck squamous cell carcinomas (HNSCC) in New Zealand white rabbits. Mechanistically, the efficacy of intravenous SNP therapy was dependent on the host STING expression but independent of the tumor STING expression. In addition, the anti-tumor efficacy of SNP was decreased in mice lacking *Irfar1* or *Irfng1* expression in the B16F10 melanoma model, showing the crucial effects of IFN-I and IFN-II responses. Lastly, SNP was effectively uptaken by human PBMCs and elicited IFN-I responses when injected into fresh human tumor biopsies derived from HNSCC patients. **Conclusions:** SNP empowers highly effective systemic cancer immunotherapy via nanotechnology. It also underscores the potential of utilizing metal ions for immune-mediated disease treatment. Research Sponsor: U.S. National Institutes of Health.

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Poster Session

Phase 1 clinical trial results for NG-350A, a novel transgene-armed and tumor-selective vector: Differential effects of intravenous (IV) versus intra-tumoral (IT) dosing on immune pharmacodynamics (PD). *First Author: Minesh Patel, Akamis Bio, Abingdon, United Kingdom*

Background: Tumor-selective therapeutic viral vectors are often limited to IT delivery. NG-350A, a blood stable adenoviral vector, selectively replicates in tumors and expresses an agonist anti-CD40 payload. We assessed the impact of IV vs IT delivery during the phase 1 FORTITUDE study (NCT03852511). **Methods:** NG-350A was dose-escalated in separate IT or IV cohorts of patients (pts) with metastatic/advanced epithelial tumors. Pts received either 1 (Day[D1]) or 4 IT injections (D1, 8, 15, 22) of up to 1×10^{12} viral particles (vp) or 3 IV infusions completed in <9 days (doses of 1×10^{11} to 6×10^{12} vp). Serum samples were taken immediately after dosing (pharmacokinetics [PK]) and during follow-up (PD). Baseline and on-treatment (D15+) tumor biopsies were taken. **Results:** In total, 25 pts received NG-350A monotherapy, 9 by IT and 16 by IV dosing. Both IV and IT dosing elicited similar anti-drug (virus) antibody responses and limited viral shedding. Peak vp Cmax was variable with IT dosing but dose-related with IV dosing. Vector DNA was detected by qPCR in tumor biopsies after higher IV dose levels (including up to ~7 weeks post dosing) and IT injection. Dose-dependent, sustained and specific increases in inflammatory cytokines related to the expected effects and timing of the anti-CD40 transgene production (IL-12, IL-17A, IL-2, IFN- γ) were detected in serum of pts treated at higher IV doses. By contrast, limited evidence of such PD effects was seen with IT dosing. Transgene was not detectable in core needle biopsies; however, a novel serum biomarker assay detected transgene mRNA at D8 or D15 in five pts who received higher IV dose levels. Importantly, both IV and IT dosed NG-350A was well-tolerated, with no treatment-related SAEs occurring in >1 pt and no DLTs at the highest dose levels tested. No evidence of anti-CD40 transgene-related toxicity was seen with IV or IT dosing, with few hepatic AEs and no Grade ≥ 3 CRS. Follow-up for imaging was limited; however, stable disease was observed in 3/6 pts at IV Dose Level 3. **Conclusions:** This analysis provides the first clear evidence that an IV-dosed tumor-selective viral vector can drive expression of immuno-stimulatory payloads with functional PD consequences in advanced cancers. The improved PK and PD profile of IV vs IT dosed NG-350A also highlights the benefits of systemic delivery for such vectors. Dose-escalation of NG-350A + pembrolizumab to identify a dose for efficacy assessments continues in the FORTIFY study (NCT05165433). Clinical trial information: NCT03852511. Research Sponsor: Akamis Bio.

Key PK and PD outcomes by route of administration.

	IT D1 (n=6)	IT D1 2 (n=3)	IV D1 (n=6)	IV D1 2 (n=4)	IV D1 3 (n=6)
Peak PK Cmax (mean vp/mL)	2.3×10^6	1.2×10^7	8.0×10^6	1.0×10^8	2.3×10^8
Viral DNA detected in tumor biopsy (n)	3/6	3/3	0/6	1/1	5/6
Sustained cytokine response observed (n)	0/6	1/3	0/6	3/4*	2/6

*One pt had no follow-up beyond D1.

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Poster Session

T cell engager (TCE) score in patients treated with bispecific CD3 TCE in phase I clinical trials. *First Author: Noé Herbel, Gustave Roussy, Drug Development Department (DITEP), Villejuif, France*

Background: Immune prognostic scores, such as the Gustave Roussy Immune (GRIM) score have been investigated in patients (pts) treated with immune checkpoint blockers. We aimed to determine whether we could improve the selection of pts that could benefit from new immunotherapies such as bispecific CD3 T cell engagers (TCE) antibodies in pts treated in phase I clinical trials (CT), by building a new prognostic score. **Methods:** All patients treated with bispecific CD3 TCE in phase I CT from July 2018 to February 2023 at the Drug Development Department at Gustave Roussy were enrolled in the study. Univariate and multivariate analyses (UVA and MVA) were conducted on demographic, clinical and biological data to assess their prognostic value on progression free survival (PFS). MVA results were used to build a new prognostic score (TCE score). This score was then validated on overall survival (OS). The predictive ability (on PFS and OS) of the TCE score was assessed using Harrell's C index. It was compared with the GRIM and Royal Marsden Hospital (RMH) scores predictive ability on PFS and OS. **Results:** A total of 67 patients (47 men, 20 women) with metastatic solid cancer or advanced hematological cancer were included. Median age was 62 years old. The most represented tumor types were prostate cancer (33%), lymphoma (25%) and small cell lung carcinoma (24%). UVA on PFS showed that elevated C-reactive protein (CRP) (HR: 2.36; 95%CI: 1.35-4.16; $p = 2.10^{-3}$) and lactate dehydrogenase (LDH) (HR: 3.00; 95%CI: 1.63-5.53; $p = 2.10^{-4}$) were associated with a worst PFS. In MVA, LDH (HR: 2.49; 95%CI: 1.30-4.74, $p = 1.10^{-4}$) and CRP levels (HR: 1.92; 95%CI: 1.1-3.46; $p = 1.10^{-4}$) were independent negative prognostic factors for PFS. The TCE score was based on MVA results (CRP > 10g/L: +1; LDH > 250U/L: +1). It showed that pts with a high score (1-2) had a shorter PFS (median PFS: 2.8 months) and OS (median OS: 9.9 months) than low score (0) pts (median PFS: 5.8 months; median OS: not reached). TCE score's Harrell's C index for PFS was 0.63 and 0.64 for OS. For GRIM and RMH scores, Harrell's C index for PFS were respectively 0.60 and 0.55. For OS it was respectively 0.58 and 0.53. **Conclusions:** To select patients for Bispecific CD3 TCE phase I CT, we built a new prognostic score, based on LDH and CRP levels, that can be used as prognostic of PFS and OS. TCE score is more reliable than GRIM and RMH scores to prognose PFS and OS. Research Sponsor: None.

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Poster Session

A phase 1 study of the OX40 agonist, BGB-A445, with or without tislelizumab, an anti-PD-1 monoclonal antibody, in patients with advanced solid tumors. *First Author: Jayesh Desai, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia*

Background: OX40 is an immune costimulatory receptor, expressed on activated CD4⁺ and CD8⁺ T cells, which promotes T cell proliferation and survival in the tumor microenvironment. BGB-A445 is a novel monoclonal antibody (mAb) OX40 agonist that does not compete with endogenous OX40 ligand binding. BGB-A445 has demonstrated antitumor activity as a single agent and in combination with an anti-PD-1 mAb in preclinical studies. Here, we report data from the ongoing dose-escalation part of a multicenter, phase 1 dose escalation/expansion study (NCT04215978) of BGB-A445 alone or in combination with tislelizumab (TIS) in patients (pts) with advanced solid tumors. **Methods:** Eligible pts were enrolled into seven sequential dose escalation cohorts of BGB-A445 IV as monotherapy (Part A) or five increasing dose levels of BGB-A445 IV in combination with TIS 200 mg IV (Part B) on day 1 of 21-day cycles. Dose escalation was guided by a Bayesian (mTPI-2) approach. This study assessed safety, tolerability, pharmacokinetics (PK) profile, and preliminary antitumor activity (RECIST v1.1). **Results:** As of August 31, 2022, 59 pts were enrolled in Part A and 32 pts in Part B. Median (range) age was 59 years (28-80) and 61 years (37-75) in Parts A and B, respectively; 26 (44%) and 13 (41%) pts were male, respectively. $\geq$ Grade 3 treatment-emergent AEs (TEAEs) were reported in 24 (41%) and 17 (53%) pts in Parts A and B, respectively; the most commonly reported (≥ 3 reported) $\geq$ grade 3 TEAEs were gastrointestinal disorders (diarrhea, nausea, and abdominal pain). Serious TEAEs were reported in 23 (39%) pts in Part A and 16 (50%) in Part B. Treatment-related AEs leading to treatment discontinuation were reported in 1 (2%) pt in Part A and 0 (0%) pts in Part B. In Part A, all grade immune-mediated AEs (imAEs) were reported in 11 (19%) pts; no pts reported $\geq$ grade 3 imAEs. In Part B, all grade imAEs were reported in 14 (44%) pts; $\geq$ grade 3 imAEs were reported in 1 (3%) pt (one event each of rash maculopapular and diarrhea). There were no dose-limiting toxicities or concerning patterns of safety/tolerability observed. BGB-A445 PK (maximum concentration [C_{max}] and area under the curve from day 0 to 21 [AUC_{0-21}]) were linear and dose proportional in all tested dose ranges. In the efficacy-evaluable population of Parts A ($n=50$) and B ($n=30$), respectively, partial response was observed in 2 (4%) pts (unconfirmed) and 7 (23%) pts (confirmed); stable disease in 18 (36%) and 13 (43%) pts (confirmed), and progressive disease in 26 (52%) and 8 (27%) pts. **Conclusions:** In the dose escalation part of this study, BGB-A445 alone or in combination with TIS was generally well tolerated across all doses in pts with advanced solid tumors, and demonstrated preliminary antitumor activity as both a single and combination agent. The dose expansion part of the study is ongoing in pts with non-small cell lung cancer and head and neck squamous cell carcinoma. Clinical trial information: NCT04215978. Research Sponsor: BeiGene, Ltd.; The authors wish to thank all BGB-A317-A445-101 study investigators, research staff, and patients. This study was sponsored by BeiGene, Ltd. Medical writing support, under the direction of the authors, was provided by Adeline Lum Nde, PhD, of Ashfield Med-Comms, an Inizio company, and was funded by BeiGene, Ltd.

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Poster Session

IMPORT-201 (IMP-MEL): A phase 1 first-in-human dose finding/randomized phase 2 study of a novel iNKT agonist IMM60 and pembrolizumab for advanced melanoma and metastatic non-small cell lung cancer (NSCLC). *First Author: Nicholas Coupe, Oxford University Hospital, Oxford, United Kingdom*

Background: Invariant natural killer T-cells (iNKTs) share features of NK-like cells and T-cells, playing a role in both innate and adaptive immune responses. The importance of this relatively rare lymphocyte subset has generated interest due to its dual ability to have a direct cytotoxic effect on CD1d expressing tumors as well as to induce long-lasting antitumor CD8 T cell responses mediated by cross-priming and licensing of dendritic cells. While many current clinical approaches involve the use of allogeneic iNKT cells, here we describe initial clinical studies with IMM60, a synthetically derived agonist of iNKT cells formulated in a liposome (PORT-2). In preclinical studies, IMM60 treatment results in maturation of DCs and B cells and a potent stimulation of iNKT cell-derived IFN- γ . In murine efficacy studies, IMM60 demonstrated monotherapy activity in multiple PD-1 resistant models (e.g., B16-F10), as well as upregulation of PD-L1 expression on cancer cells and re-sensitization to PD-1 inhibition. **Methods:** The IMPORT-201 trial is a multicenter, international expansion of an open-label first-in-human phase I/II investigator initiated study (IMP-MEL). Ph 1 is currently enrolling patients with NSCLC or melanoma. IMM60-containing liposomes are administered IV Q3W at 3 escalating dose levels for 6 doses as monotherapy or with pembrolizumab 200mg Q3W. The Ph I portion of the study seeks to establish the recommended Ph 2 dose of IMM60 alone and in combination with pembrolizumab. The Ph 2 evaluates IMM60 monotherapy, PD-1 monotherapy, and the combination. **Results:** Eight patients with melanoma (n=4) or NSCLC (n=4) have been enrolled in the IMM60 monotherapy dose cohorts. These patients were heavily pretreated, having a median of 3.5 prior therapies (range 2-7). One patient with NSCLC has been enrolled to the IMM60 + pembrolizumab combination cohort. IMM60 was well tolerated with no treatment-related SAEs or G3-5 AEs, and no MTD was determined. The most common related AE is G1-2 fatigue, reported in 2 patients. In the monotherapy cohort, a preliminary review of individual target lesions showed 2 lesions that completely resolved, 1 lesion with 69% decrease in size, 10 lesions that were stable, and 6 lesions with >20% increase in size. Serum biomarker analysis demonstrated evidence of iNKT and NK activation, as well as increases in dendritic and CD86+ B cells. Pharmacokinetics demonstrate dose proportionality with a terminal half-life of ~8 hours. **Conclusions:** IMM60 is well tolerated as monotherapy and in combination with pembrolizumab at the doses tested. These data show that a single agent iNKT agonist can be safely administered in a heavily pre-treated population and initiate immune activation. The combination with pembrolizumab is ongoing, and updated results of the Ph 1 portion of the study will be reported. Clinical trial information: NCT05709821. Research Sponsor: Portage Biotech/iOx Therapeutics.

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Poster Session

Efficacy and safety of IBI110 in combination with sintilimab and lenvatinib in first-line of advanced hepatocellular carcinoma: Preliminary results from a phase Ib study. *First Author: Ming Liu, Key laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Peking University Cancer Hospital & Institute, Beijing, China*

Background: Sintilimab plus bevacizumab has been approved as first-line treatment in patients (pts) with advanced hepatocellular carcinoma (HCC). Dual inhibition of PD-1 and lymphocyte-activation gene 3 (LAG-3) may improve anti-tumor effect synergistically. IBI110 plus sintilimab has shown preliminary antitumor activity in advance solid tumors. This phase Ib cohort study evaluated the efficacy, tolerability, and safety of IBI110 in combination with sintilimab and lenvatinib as first-line treatment in pts with advanced HCC. **Methods:** This phase Ib study enrolled pts with histologically or cytologically diagnosed or clinically confirmed unresectable or metastatic hepatocellular carcinoma, no previous systemic treatment. Patients received IBI110 200mg IV Q3W and sintilimab 200mg IV Q3W, in combination with lenvatinib (weight <60kg: 8mg, weight $\geq$ 60 kg: 12mg) orally administered once daily, until disease progression, unacceptable toxicity or death. The primary objective was to evaluate the safety, tolerability, and efficacy of the combination therapy per RECIST v1.1. **Results:** As the data cutoff date on January 9th 2023, 28 pts were enrolled (median age: 59 years; ECOG PS=0: 6 pts; stage C per Barcelona Clinic Liver Cancer [BCLC]: 13 pts). All 28 pts were included for safety analysis. Treatment-related adverse events (TRAEs) of any grade occurred in 27 pts (96.4%) and the most frequent TRAEs included hypertension (50%), hypothyroidism (42.9%), neutrophil count decreased (39.3%). Grade $\geq$ 3 TRAEs occurred in 16 pts (57.1%) and grade $\geq$ 3 irAEs occurred in 4 (14.3%) pts. Two (7.1%, 2/28) pts experienced TRAE leading to drug discontinuation. One pt experienced investigator-assessed treatment related death. As of data cutoff, for 27 pts with at least one efficacy evaluation, the objective response rate (ORR) was 29.6% (95% CI, 13.8-50.2). The disease control rate (DCR) was 85.2% (95% CI, 66.3-95.8), and 11 pts were still in treatment. With a median follow up of 12.2 months (95%CI, 11.0-12.6), the median progression-free survival (PFS) was 9.9 months (95%CI, 5.7-NC) and the 9-month PFS rate was 54.5% (95%CI, 33.8-71.2). The median overall survival (OS) was not reached. **Conclusions:** In this phase Ib study, IBI110 in combination with sintilimab and lenvatinib as first line therapy demonstrated robust response and survival benefit with manageable safety profile in patients with advanced hepatocellular carcinoma. This combination therapy need to be further explored in this population. Clinical trial information: NCT04085185. Research Sponsor: Inovvent Biologics, Inc., China.

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Poster Session

Efficacy and safety of IBI110 in combination with sintilimab in first-line advanced HER2-negative gastric cancer or gastroesophageal junction cancer: Updated results from a phase Ib study. *First Author: Chenyu Mao, The First Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, China*

Background: Sintilimab plus oxaliplatin and capecitabine (XELOX) has become the standard of care in patients (pts) with untreated advanced, recurrent, or metastatic gastric or gastroesophageal junction adenocarcinoma (G/G/EJ AC) in China. Dual inhibition of PD-1 and lymphocyte-activation gene 3 (LAG-3) may further improve anti-tumor effect. The preliminary safety and efficacy data of IBI110 plus sintilimab and XELOX in pts with first-line G/G/EJ AC were previously presented (Chenyu Mao et al. ASCO 2022). Here, we presented updated safety and efficacy results of this study. **Methods:** This phase Ib study enrolled patients with previously untreated, unresectable, locally advanced or recurrent/metastatic HER2-negative G/G/EJ AC. Pts received IBI110 200mg IV Q3W and sintilimab 200mg IV Q3W plus XELOX (oxaliplatin 130 mg/m² Q3W and capecitabine 1000mg mg/m²/time twice daily [BID]) until disease progression, unacceptable toxicity or death. The primary objectives were to evaluate the safety, tolerability, and efficacy of the combination therapy per RECIST v1.1. **Results:** As of data cutoff January 9th 2023, 17 pts were assessed as evaluable (median age: 61 years; ECOG PS=1: 14 pts; all gastric cancer). All pts (17/17, 100%) experienced treatment-related adverse events (TRAEs) of any grade, and the most commonly TRAEs were neutrophil count decreased (64.7%), white blood cell count decreased (52.9%), platelet count decreased (52.9%). Grade $\geq$ 3 TRAEs occurred in 11 pts (64.7%), the most frequent grade $\geq$ 3 TRAEs were consistent with TRAEs of any grade. Investigator-assessed immune-mediated adverse events (irAEs) occurred in 10 pts (58.8%). Grade $\geq$ 3 irAEs occurred in 3 pts (17.6%), all led to discontinuation. No treatment-related death occurred. As data cutoff, among 17 efficacy-evaluable pts, the unconfirmed and confirmed objective response rate (ORR) were 88.2% (95% CI, 63.6-98.5) and 64.7% (95% CI, 38.3-85.8), respectively. The disease control rate (DCR) was 94.1% (95% CI, 71.3-99.9). With a median follow up of 13.1 months (95% CI, 7.1-NC), the median duration of response (DoR) and progression-free survival (PFS) were 11.6 months (95% CI, 2.5-14.4) and 12.9 months (95% CI, 3.8-15.8), respectively. The median overall survival (OS) was not reached, and the 12-months OS rate was 70.6% (95% CI, 43.1-86.6). **Conclusions:** IBI110 in combination with sintilimab and XELOX demonstrated manageable safety and encouraging efficacy results in patients with first-line gastric adenocarcinoma. This is the first positive trial to show clinical benefits of a LAG3 plus PD-1 inhibitor combined with chemotherapy for this population. Clinical trial information: NCT04085185. Research Sponsor: Inovvent Biologics, Inc.

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Poster Session

Dynamic change of immune phenotype assessed by artificial intelligence (AI)-powered analysis of tumor-infiltrating lymphocytes (TILs) during neoadjuvant durvalumab with or without tremelimumab (D+/-T) in head and neck squamous cell carcinoma (HNSCC). *First Author: Hyunwook Kim, Division of Medical Oncology, Department of Internal Medicine, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea*

Background: The results of a phase II trial evaluating preoperative durvalumab with or without tremelimumab (D+/-T) in resectable HNSCC (NCT03737968) suggest that the neoadjuvant immunotherapy is associated with pathologic tumor regression with manageable safety profiles. Here, we applied AI-powered spatial TIL analyzer, Lunit SCOPE IO, to tumor specimens of the patients included in the trial to assess the impact of spatial TIL density and inflamed immune phenotype (IIP) on immunotherapy responses. **Methods:** H&E-stained whole-slide images (WSIs) of pre- and post-treatment tumor specimens from HNSCC pts enrolled in the aforementioned D+/-T trial were collected. Patients with locally advanced but operable HNSCC were randomly assigned in 1:1 to receive a single dose of D (1,500mg) or D+T (1,500mg+75mg) followed by surgery, at Severance Hospital in Seoul, Korea. Lunit SCOPE IO was used to segment tumor epithelium and stroma to identify and quantify intratumoral TIL (iTIL) and stromal TIL. IIP was defined as the proportion of high iTIL area more than 33.3% of analyzable area. Clinical data and the combined positive scores (CPS) of PD-L1 were also collected. **Results:** A total of 39 paired tumor samples of pre- and post-treatment WSI (23 from D+T and 16 from D) were included. Overall, tumor regression grade 2 (TRG2, $\geq$ 50% of tumor regression) was achieved in 15.4% (6/39) pts, and downstaging after treatment was achieved in 35.9% (14/39) pts. By pre-treatment WSIs, 38.5% (15/39) samples were classified as IIP, and subgroups of D+T and D had 34.8% (8/23) and 43.8% (7/16), respectively. In the D+T arm, the proportions of TRG2 were 25% (2/8) in IIP versus 13.3% (2/15) in non-IIP, whereas D arm had 28.6% (2/7) TRG2 in IIP, but no TRG2 in non-IIP (0/9), respectively. Comparing the WSI of pre- and post-D+/-T samples, the proportion of IIP was significantly increased to 66.7% from 38.5 ($p=0.015$). The increase in IIP proportion was prominent in the D+T arm (34.8% to 69.6%, $p=0.043$), but not in the D arm (43.8% to 62.5%, $p=0.37$). Similarly, PD-L1 CPS increased after therapy, especially in the D+T group (mean CPS 6.0 to 20.7, $p=0.009$). Interestingly, pts who remained non-IIP in both pre- and post-treatment (25.6%, 10/39) had significantly poor prognosis compared to the others, as the 12-month disease-free survival (DFS) rate was 50.0% vs 93.1% (median DFS 13.4m vs not reached, hazard ratio [HR] 4.26, 95% confidence interval [CI] 1.32-13.8, $p=0.009$). This prognostic impact was prominent in the D+T arm (HR 6.75, 95% CI 1.49-30.6, $p=0.004$). **Conclusions:** Neoadjuvant durvalumab +/- tremelimumab promotes dynamic change toward inflamed immune phenotype, resulting in favorable clinical outcomes. Resistance mechanism of stand-still-non-inflamed patients even on D+/-T should be further investigated. Clinical trial information: NCT03737968. Research Sponsor: AstraZeneca; National Research Foundation of the Republic of Korea (NRF-2019M3A9B6065231 to Hye Ryun Kim, 2020R1F1A1073692 to Hyun Je Kim, 2021R1A2C2094629 to Hye Ryun Kim, and 2021R111A1A01059271 to Chang Gon Kim) funded by the Ministry of Science and ICT of Republic of Korea, and Information and Communications Technology and Severance Hospital Research Fund for Clinical Excellence (SHRC 2022-0001) funded by Yonsei University College of Medicine.

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Poster Session

Multiplexed trackable intratumor microdosing of the investigational STING agonist TAK-676 alone and in combination in the native tumor microenvironment of patients with head and neck cancer: A phase 0 trial. *First Author: Karthik Rajasekaran, The University of Pennsylvania, Philadelphia, PA*

Background: TAK-676 is a novel synthetic STING agonist developed to induce an inflammatory state through release of interferon (IFN), production of proinflammatory chemokines and cytokines, and activation of innate and adaptive immune cells in the tumor microenvironment (TME). To gain early mechanistic insights on the effects of TAK-676 in the native TME alone and in combination with standard-of-care chemotherapies, we completed a Phase 0 intratumoral microdosing trial in head and neck squamous cell carcinoma patients using the Comparative In Vivo Oncology (CIVO) platform. CIVO enables direct evaluation of biomarker response in trackable, distinct regions of drug exposure upon resection. These studies were designed to identify rational combinations that could be evaluated in future clinical trials with therapeutic intent. **Methods:** This IRB-approved study was conducted at four centers within the United States. Fifteen subjects provided Informed Consent and enrolled in the trial. Microdoses ($\leq 1/100^{\text{th}}$ systemic dose) of TAK-676, carboplatin, 5-FU, paclitaxel, and combinations thereof, were simultaneously injected via CIVO to eligible patients presenting with a surface-accessible primary or metastatic lesion ≥ 2 cm and planned surgical resection of the target lesion at 24 (n=8) or 72–96 (n=7) hours. Injection sites were identified via co-injection of fluorescent tracking markers (CIVO GLO). Multiplexed ISH, IHC, and spatial molecular profiling via GeoMx and CosMx were used to resolve molecular responses at each injection site. Patients were monitored for adverse events (AEs) for 28 days following injection. **Results:** TAK-676 exposure was associated with increased IFN signaling in all samples analyzed at the 24-hour cohort. This was accompanied by increased expression of pro-inflammatory cytokines and chemokines, “M1-like” macrophages, NK cells, and CD8+ T cells. Spatial profiling with GeoMx and CosMx revealed an IFN signature and elevated pro-inflammatory markers across multiple cell types throughout the TME. In addition, exposure to TAK-676 plus chemotherapy resulted in localized enhancement of apoptosis vs. chemotherapy alone across multiple tumors. The responses observed at 24 hours were transient and not detected in the 72–96-hour cohort. No AEs related to injection procedure or contents were reported. **Conclusions:** Intratumor microdosing via CIVO of TAK-676 alone and in combination with chemotherapy was shown to promote an early pro-inflammatory response, providing evidence of an on-target mechanism of action. The absence of effect at the late timepoints could be due to pharmacokinetics of drug exposure or compensatory signaling within the TME. In this Phase 0 clinical trial we safely demonstrated precise, mechanistic effects of TAK-676 on the native TME of intact human tumors. Clinical trial information: NCT04541108. Research Sponsor: Presage Biosciences, Inc.

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Poster Session

SpliceIO: A robust platform for the discovery and validation of splicing-derived neoantigens. *First Author: Gayatri Arun, Envisagenics Inc., Long Island, NY*

Background: Splicing dysregulation is a major hallmark of cancer, affecting tumor progression, metastasis, and therapy resistance. Aberrant alternative splicing plays a critical role in generating tumor-specific neoantigens targetable through an arsenal of immunotherapeutic modalities. Such neoantigens cannot be discovered using conventional DNA-based tools; they require specialized software for alternative splicing analysis using RNA-seq data. **Methods:** Envisagenics has developed SpliceIO, a proprietary software platform for splicing-derived neoantigen discovery. SpliceIO uses RNA-seq data to uncover extracellular neoantigens encoded by transmembrane proteins or presented to immune cells through the MHC complex. This predictive ensemble maximizes the value of RNA-seq data to predict fundamental aspects of neoantigen activity, such as their protein localization, MHC binding affinity, epitope accessibility and cancer pathway relevance. Here, we summarize the discovery and validation of novel splicing-derived neoantigens identified using SpliceIO in acute myeloid leukemia and colorectal cancer. **Results:** We analyzed $>10,000$ RNA-seq samples from the four tumor types and controls derived from 32 normal tissues. To maximize the prevalence of neoantigen target candidates in patient subpopulations, RNA-seq samples were pre-stratified using SpliceSlice, a proprietary software for spliceosomal profiling. As a result, patients sharing common spliceosome alterations were grouped into 11 coherent subsets that are distinct from normal tissue. Using this approach, we have discovered several promising candidates that we prioritized for experimental validations. SpliceIO target candidates were validated experimentally in cancer cell lines and primary tumor tissues to confirm RNA expression, translation, and membrane localization. Additionally, we performed proteomics to evaluate the presence of neopeptides generated from the unique splicing events. Using this approach, we have discovered and validated several tumor specific splicing derived neoantigens that are also recurrent in $>15\%$ of the population. **Conclusions:** Together, our results strongly support the role of aberrant splicing as a major source of tumor-specific neoantigens. Our combined computational and experimental approach promotes novel target discovery, enabling the development of novel immunotherapeutics for cancer treatment. Research Sponsor: U.S. National Institutes of Health; Envisagenics.

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Poster Session

The initial report of phase I trial of VG2025, a non-attenuated HSV-1 oncolytic virus expressing IL-12 and IL-15/RA payloads, in patients with advanced solid tumors. *First Author: Siqing Fu, Department of Investigational Cancer Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: VG2025 is a non-attenuated HSV-1 Oncolytic virus (OV). The wildtype neurovirulence is controlled by the Transcription and Translation Dual Regulation (TTDR) of ICP27 and ICP34.5 proteins. IL-12, IL-15, IL-15Ra payloads are controlled by tumor promoter CxCR4. The native promoter of ICP27 was replaced with a promoter for Carcinoembryonic Antigen (CEA). Here we report a first-in-human, open label, study to evaluate the safety, pharmacokinetics (PK), and biologic effects of VG2025 in patients (pts) with advanced solid tumors progressed after standard of care from China and United States. The study is actively recruiting. NCT05266612. **Methods:** Dose escalation follows a 3+3 design at 4 dose levels as intratumoral, and image guided injections into deep lesions on days 1 and 15 of each 28 days treatment cycle. PK and viral shedding (DNA), samples from biopsies, blood, urine, and swabs from injection site and other anatomical locations were analyzed by PCR. Changes of cytokines and lymphocyte subsets in blood were also observed as pharmacodynamic parameters. **Results:** As of 10 Jan 2023, 10 pts received doses of 1.0×10^8 and 2.0×10^8 PFU. 5 males and 5 females with the median age of 58 years were enrolled. 20% were PD(L1) refractory, 20% had 2 Prior lines of therapy and 60% ≥ 3 . The Median CEA level was 7.4. Tumor types were: 2 Duodenal Adeno Ca., 1 Pancreatic, 1 Ovarian, 1 Leiomyosarcoma, 1 Salivary Duct Ca., 1 Hepatocellular Ca (HCC), 1 Intrahepatic Cholangiocarcinoma (ICC), 1 Colorectal Ca (CRC) and 1 Colon Ca. No Dose Limiting Toxicities were observed. Any grade treatment-related AEs (TRAEs) was 70%, the most common TRAEs was fever 60%. Grade ≥ 3 TRAEs were 50% [3 pts had grade 4 Lymphocyte decreased (all recovered)], 1 had grade 3 COVID-19 and 1 had grade 3 nausea and vomiting. 4 pt had SAEs (2 cases of COVID-19, 1 Ascites and 1 Nausea and Vomiting). No TRAEs leading to dose reduction and treatment discontinuation. No pts had positive viral shedding. 4 pts were efficacy evaluable; ORR 25% (1 pt with ICC had confirmed PR with -45%) and DCR 100% based on RECIST v1.1. The PR pt had meaningful reductions in CEA levels. Tumor shrinkage was also observed in non-injected lesions demonstrating an abscopal effect. Nanostring analysis of paired biopsies from the PR pt demonstrate upregulation of genes for integrin signaling pathway, activation of CD8+ T cells and T cell-based immunity, upregulation of antigen-presenting MHC (HLA-DQA1 and HLA-DRB1) and chemokine receptor (CMKLR1) genes. Cellular immunity was activated by upregulation of Th1 cells, macrophage-associated genes and downregulation of Treg-associated genes. The results are consistent with the mechanism of action of VG2025. Analysis is ongoing with other subjects. **Conclusions:** Monotherapy activity was observed with an acceptable safety profile in heavily pretreated pts with advanced solid tumors. Clinical trial information: NCT05266612. Research Sponsor: Virogin Biotech Canada Ltd.; Virogin (Shanghai) Biotech Co. Ltd.

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Poster Session

Patient perspectives on BCMA-targeted therapies for multiple myeloma: A survey conducted in a patient advocacy group. *First Author: Jennifer M. Ahlstrom, HealthTree Foundation, Lehi, UT*

Background: The emergence of B-cell maturation antigen (BCMA) targeted therapies in multiple myeloma (MM) has led to improvements in clinical outcomes in patients with heavily pretreated disease. Little is known about patients' knowledge, decision-making process, and openness to these novel therapies that include chimeric antigen receptor (CAR) T-cell therapy and bispecific antibodies. This study aims to understand patient perspectives on these BCMA-targeted therapies. **Methods:** This is a cross-sectional survey completed by patients with MM enrolled in HealthTree Cure Hub, an online portal for patients with plasma cell dyscrasias to help navigate their disease. An 18-question survey was developed by the research team, then reviewed and adjusted by HealthTree's Patient Advocacy Panel and a physician panel. Responses were analyzed descriptively and reported in aggregate. **Results:** From 10/28/2022 to 1/12/2023, 325 patients with MM participated in the survey (mean age: 66 ± 8 years; 54% female; 90% White; years since diagnosis: 6.6 ± 4.7 ; lines of therapy: 3.0 ± 2.6). In general, 26% of patients were open to trying a new therapy right away and 43% were open but would like more information on safety and efficacy. BCMA-targeted therapies were well known with 92% of patients having heard about them. Among respondents for each question, 65% were likely or very likely to try a CAR T-cell therapy if offered and 74% were likely or very likely to try a bispecific therapy; while 17% and 13%, respectively, needed more information to decide. The most requested domains of information were efficacy, side effects (SEs), eligibility, and administration process for both CAR T-Cell and bispecific therapies. "How soon can I receive it" was ranked higher for bispecific therapy while "where can I receive it" was ranked higher for CAR T-cell therapy, relatively. The top attributes of therapy profiles were prolonged life, improved quality of life, longer progression-free survival, and tolerable SEs. To receive an effective therapy, the top acceptable trade-offs included frequent monitoring of SEs and initiating a new drug in a hospital setting, while patients were least willing to compromise on caregiver burden. Additionally, the most acceptable SEs were those that were asymptomatic but would need routine monitoring to prevent serious complications, and those that were cosmetic but non-life-threatening. **Conclusions:** This study found a high level of openness in patients with MM to try BCMA-targeted therapies if offered. Information on efficacy, safety, availability, and eligibility may assist patients on their decision-making. Patients were willing to accept certain trade-offs for a treatment that could be clinically beneficial. Incorporating patients' goals, values, and preferences alongside clinical factors and other considerations may further optimize treatment decisions and improve patient outcomes. Research Sponsor: Janssen.

2583

Poster Session

Use of proteomimetic polymers for delivery of tumor antigens and adjuvants through formation of stable electrostatic complexes with small molecule STING agonists. *First Author: Max Mu Wang, Medical Scientist Training Program, Northwestern University, Chicago, IL*

Background: Utilizing tumor antigens for the development of patient-specific cancer vaccines has been a promising therapeutic strategy. However, significant challenges remain in delivering subunit vaccine components to elicit anti-tumor immune responses. To overcome these, we developed rationally designed cancer vaccines using a new nanoplatform called the Protein-Like Polymer (PLP) with unique characteristics that allow for sustained delivery of tumor antigens in conjunction with immunomodulatory compounds. **Methods:** PLPs containing antigens were synthesized via ring-opening metathesis polymerization (ROMP) and characterized using HPLC, LC-MS, NMR, and GPC. A library of compounds were generated with different sidechain linkage chemistries (amide, ester, or disulfide linkage), DPs, and inclusion of PEG side chains. In vitro assays using gp100-specific T Cells were conducted with fluorescently labeled and non-labeled polymers. In vivo experiments were done using B16 murine melanoma transplanted tumor models. Ability of PLPs to co-deliver immunomodulatory compounds was tested using a small molecule STING agonist 2'3' cGAMP. **Results:** Conjugating antigens to the polymer backbone using a cleavable disulfide linkage, designed to be reduced intracellularly, resulted in the best subcellular localization and immune activation (higher levels of immune cell proliferation, cytokine production, and expression of activation markers). Incorporating a diluent amount of PEG side chains increased resistance to enzymatic degradation while improving bioactivity and cell uptake. In vivo studies using PLPs conjugated with melanoma-associated antigen gp100 showed the reductions in tumor size with increased immune cell proliferation and activation in a B16 melanoma model. Additionally, increasing the degree of polymerization, and therefore the density of antigen side chains per unit polymer, improved vaccine efficacy and resistance to proteolysis. Mice treated with STING agonists electrostatically coupled to PLPs showed significantly smaller tumors vs no-treatment at day 14 (0.038g vs 0.76g; $p < 0.0001$) and allowed for subcutaneous administration of the small molecule, which normally must be injected intratumorally. **Conclusions:** Our work demonstrates the potential of PLPs to overcome inherent difficulties associated with developing cancer vaccines. The modularity of the platform allows for complex nano-architectures including systems capable of delivering challenging compounds, ie small molecule STING agonists, subcutaneously through electrostatic coupling. This technology has the potential to revolutionize cancer vaccinology. Research Sponsor: U.S. National Institutes of Health.

2585

Poster Session

Relationship between tumor microenvironment (TME)-based histomic TGF β signature (TGFbs), stromal fibroblast recruitment, and exclusion of immune cells as immunotherapy resistance mechanisms. *First Author: Gahee Park, Lunit Inc., Seoul, South Korea*

Background: TGF- β activates fibroblasts within the TME and may be associated with poor response to immunotherapy. However, objective and reliable assessment of the TGFbs by gene expression profiling (GEP) is challenging. Using H&E whole-slide images (WSI) from The Cancer Genome Atlas (TCGA), we developed an artificial intelligence (AI) model to predict a normalized TGFbs, applying it to real-world datasets (RWDs) of advanced solid tumor patients treated with immunotherapy. **Methods:** The TGFbs was defined using the mean GEP values of the 'Hallmark TGF- β signaling' gene set. H&E WSIs of 23 carcinoma types from TCGA (n=6,945) were used to discover the association of the TGFbs with various cell types, including fibroblasts and tumor-infiltrating lymphocytes (TILs) detected by an AI model, Lunit SCOPE IO (AI-1). Another custom AI model (AI-2) to predict TGFbs was developed by integrating self-supervised and supervised features and other semantic content extracted by AI-1 with multilayered perceptron classifiers. TGFbs prediction scores from the AI-2 were applied to 5 different RWDs containing 1,792 immunotherapy-treated patients (> 16 primary tumor types). The immune-excluded phenotype (IEP) was defined by high stromal TIL and low intratumoral TIL density. **Results:** In the TCGA dataset, TGFbs and fibroblast density detected by AI-1 were closely correlated ($R=0.19$, $p<0.001$) compared to other cell types, with both highest in pancreatic adenocarcinoma (PAC)(median [interquartile range, IQR] 0.73 [0.66-0.80], 1306 [985-1588]/mm², respectively) and CMS4 colorectal cancer (0.61 [0.54-0.67], 868 [582-1128]/mm²) compared to other cancers (0.57 [0.47-0.66], 577 [295-890]/mm²). The AI-2 predicted TGFbs with area-under-the-curve of 0.781 on cross-validation within the TCGA dataset. The TGFbs of immunotherapy-treated RWDs were inferred from their corresponding H&E WSI, with scores comparable to those from the TCGA (0.42 [0.16-0.60] vs 0.58 [0.48-0.67]), with PAC having the highest TGFbs (0.65 [0.45-0.77]) in the RWD as well. Interestingly, TGFbs inferred scores and fibroblast density were significantly correlated ($R=0.7$, $p<0.001$) in the RWD and also significantly correlated with the IEP (0.52 [0.30-0.66]) compared to other immune phenotypes (0.42 [0.16-0.60], $p<0.001$). In the RWD, patients with inferred TGFbs in the upper 75% quartile had a poor clinical response to immunotherapy (objective response rate: 15.1% vs 20.7%, median progression-free survival 3.0 m vs 4.0 m, hazard ratio 1.21, 95% confidence interval 1.07-1.36, $p=0.002$). **Conclusions:** TGFbs is closely correlated with fibroblast density within the TME and may confer resistance to immunotherapy. Unique morphologic features of the TGFbs can be captured by AI, enabling scalable application to various datasets for clinical and translational research. Research Sponsor: None.

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Poster Session

Phase I study of MP0317, a FAP-dependent DARPIn, for tumor-localized CD40 activation in patients with advanced solid tumors. *First Author: Carlos A. Gomez-Roca, Institut Claudius Regaud, IUCT-Oncopole, Toulouse, France*

Background: CD40 is a master switch for both innate and adaptive immune systems. The clinical development of CD40 agonists has been hampered by dose-limiting toxicity (DLT) due to systemic CD40 activation and peripheral target-mediated drug disposition (TMDD). MP0317 is a CD40-agonistic DARPIn (designed ankyrin repeat protein), developed to reduce systemic toxicity. MP0317 is exclusively active in the presence of fibroblast activating protein (FAP) expressed by cancer associated fibroblasts in the tumor microenvironment. This allows reaching serum levels that overcome the TMDD and have the potential to deliver sustained and tumor-localized CD40 activation. Ongoing clinical testing aims at establishing its safety/tolerability profile, PK/PD characteristics, and a recommended dose for combination therapy. **Methods:** NCT05098405 is a Phase 1, multicenter, open label, dose escalation study followed by a safety expansion part in adult patients with advanced solid tumors. The dose escalation scheme uses an adaptive Bayesian logistic regression model with overdose control. Peripheral blood biomarkers are analyzed by immunoassays and flow cytometry, and baseline and on-treatment tumor biopsies are characterized by RNA sequencing and immunofluorescence. Eligible patients are enrolled into 9 sequentially escalating dose cohorts of MP0317 (0.03-10 mg/kg), administered IV 3-weekly (Q3W) or 1-weekly (Q1W) until disease progression or unacceptable toxicity. **Results:** At submission, 23 patients across 6 cohorts completed the study, with no DLT observed. Patient enrolling in higher dose cohorts is ongoing. The most frequent AE was grade 2 infusion related reaction in 5 patients. The 23 patients received ≥ 2 (range 2-8) doses (range 0.03 – 3 mg/kg) of MP0317 across five Q3W and one Q1W cohorts and completed the 28-day DLT period. PK data confirmed all patients were exposed to MP0317 with broadly dose-dependent C_{max} and no sign of accumulation. PD data was derived from patients dosed with 0.03 – 3 mg/kg. Soluble biomarkers (sFAP and sCD40) showed target engagement in periphery with signs of FAP saturation at ≥ 0.5 mg/kg. Colocalization of MP0317 with FAP and CD40 in the tumor was confirmed in 4 out of 8 evaluable paired tumor biopsies. Whole transcriptome and gene set enrichment analyses showed an upregulation of genes related to B-cell trafficking (CXCL3, CXCR5, CCR6, CCL20) upon treatment. Transient increase of IFN γ -induced chemokines (CXCL9, CXCL10) was observed, whereas the pro-inflammatory cytokines (TNF α , IL-2, IL-6, IL-8) were not upregulated. **Conclusions:** Clinical data and the lack of pro-inflammatory circulating cytokines confirm MP0317 is safe and well-tolerated, while analysis of paired pre- and on-treatment tumor biopsies suggests early evidence of tumor-localized CD40 activation. The current data enables further evaluation in a combination setting. Clinical trial information: NCT05098405. Research Sponsor: Molecular Partners AG.

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Poster Session

Clinical outcomes in phase 1 clinical trials (Ph1-CT) when treating patients (pts) with novel immunotherapy (IT) agents at early lines for advanced disease. *First Author: Juan José Soto, Medical Oncology Department-Phase 1 Functional Unit | Catalan Institute of Oncology (ICO), Hospitalet De Llobregat, Barcelona, Spain*

Background: Cancer pts can be offered IT drugs within Ph1-CT before having exhausted standard of care (SoC) therapies. However, whether this strategy may improve pts' outcomes remains unclear. We assess the benefits of receiving novel IT compounds within Ph1-CT at early lines for advanced disease. **Methods:** We retrospectively reviewed a correlative series of pts with advanced solid tumors treated with IT within Ph1-CT at the Phase 1 Unit of Catalan Institute of Oncology (ICO), Barcelona, Spain, from January 2018 to July 2022. Primary aim was to assess clinical outcomes measured by median progression-free survival (mPFS) and median overall survival (mOS) according to number of prior lines (PL) for recurrent/metastatic disease, prior IT, availability of alternative SoC in our country, IT biomarker-selected population and grade 3-4 toxicity (G3-4 Tox) by multivariate analysis (MVA). Overall response rate (ORR) was evaluated by RECIST 1.1. Clinical benefit rate (CBR) was defined as complete/partial response + stable disease for ≥ 6 months (m). PFS/QOS were calculated by Kaplan-Meier method. Log-rank test was used for comparisons. MVA was performed by Cox regression. **Results:** A total of 228 pts were assessed: IT monotherapy = 49 (21.5%), IT combinations = 179 (78.5%) (IT+IT = 111 [48.7%], IT+targeted therapy = 24 [10.5%], IT+others = 44 [19.3%]). Forty-nine (21.5%) pts were included according to IT biomarkers (PDL1, TIM3 expression, MSI-H, others). Median age was 62 y (24-83), 62.7% were men. All pts had ECOG ≤ 1 . The 4 most frequent cancer types were HNSCC (19.7%), NSCLC (15.4%), glioblastoma (10.5%) and urothelial (10.1%). Number of PL: 0 = 33 (14.5%) pts, 1 = 92 (40.3%) pts, $\geq 2 = 103$ (45.2%) pts. Sixty-three (27.6%) pts had received prior IT and 159 (69.7%) had alternative available SoC. Overall G3-4 Tox rate was 21.5% (20.6% in pts IT-treated). ORR and CBR were higher in pts IT-naïve than in pts IT-treated (21.2% vs 12.7% [$p=.18$] and 35.7% vs 25.4% [$p=.26$], respectively). With a median follow-up of 19m, overall mPFS and mOS were 3.5m (2.7-3.9) and 9.8m (8.5-11.5), respectively. In the MVA, lesser number of PL, SoC availability and biomarker selection positively impacted on mOS. After Ph1-CT treatment, 111 (48.7%) pts received further treatment: 19.3% within clinical trial, 29.4% with SoC. **Conclusions:** In our cohort of pts treated within IT Ph1-CT, those with less PL of treatment, with available alternative SoC and/or selected by biomarker achieved higher PFS and OS. These results suggest that treating pts with novel IT agents at early lines might positively impact on survival. Research Sponsor: None.

Variables	PFS(m)	OS(m)
PL		
≤ 1 / ≥ 2	4.3 / 2.4 p .0002	13.3 / 8.7 p .001
≤ 2 / ≥ 2	3.6 / 1.7 p .001	10.5 / 7.8 p .001
Prior IT (yes/no)	2.3 / 3.5 p .007	9.3 / 8.5 p .66
SoC available (yes/no)	3.8 / 2.1 p .0003	10.8 / 8.7 p .03
Biomarker selection (yes/no)	5.3 / 2.7 p .07	12 / 8 p .03
G3-4 Tox (yes/no)	5.4 / 2.8 p .001	13 / 8.9 p .058

ABSTRACT WITHDRAWN

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Poster Session

Patient-derived skin MicroOrganoSpheres and clinical response to immunotherapy. *First Author: Rikhia Chakraborty, Xilis, Durham, NC*

Background: Immunotherapies, including immune checkpoint inhibitors (ICI), have revolutionized the treatment of many cancers, producing significant improvements in survival in patients with many different cancers. However, the intended anti-tumor effects also result in a unique form of autoimmunity, known as immune-related adverse events (irAEs), which have emerged as a limiting factor for many immunotherapies. Cutaneous irAEs (cirAEs), the most frequently occurring ICI-related toxicities, have been associated with improved efficacy and survival but, in their severe forms, require systemic steroids and have in cases led to premature ICI discontinuation and fatality. There is a need for both robust biomarkers and adequate models that effectively predict which patients who develop irAEs may have improved outcomes. **Methods:** Using a microfluidic droplet technology that generates "mini" patient-derived organoids called MicroOrganoSpheres (MOS), we successfully generated skin MOS from skin biopsy samples in both healthy skin and tumor-involved skin that sustain the original patient skin immune microenvironment over three weeks. Using this model, we assessed skin cell toxicity and cytokine release in response to ICI and targeted therapies. **Results:** Clinical responses were largely consistent with the skin and tumor MOS assay readouts, indicating that MOS recapitulates the potential association between skin irAEs and efficacy. Matched pairs of patient melanoma and skin MOS showed good concordance with patient outcome indicating that MOS recapitulates the potential association between skin irAEs and efficacy. Enrichment of genes associated with atopic dermatitis, vitiligo, and psoriatic dermatitis were observed in MOS generated from skin of an ICI-sensitive patient compared to the MOS generated from skin of an ICI-resistant patient. These results indicated that the skin MOS platform can potentially predict the dermatological toxicity of ICI. As the MOS assay can be completed within 12 days after biopsy acquisition, this novel technology may enable personalized medicine approaches by prediction of cirAEs and efficacy for individual patients. **Conclusions:** This is the first study to date demonstrating the application of a patient-derived immune competent skin model deployable for assessing ICI efficacy and toxicity response. Matched tumor skin MOS from the same patients recapitulated the clinically observed association between ICI efficacy and toxicity and may provide key indicators for prospective irAE-predicting clinical trials. Research Sponsor: Xilis, Inc.

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Poster Session

Safety and efficacy of HB0025, an anti-PD-1/VEGF bispecific antibody fusion protein, in patients with advanced solid tumors: Preliminary results from an FIH trial. *First Author: Yiqun Du, Phase I Clinical Trial Center, Fudan University Shanghai Cancer Center, Shanghai, China*

Background: HB0025 is a recombinant humanized anti-PD-L1 monoclonal antibody-VEGFR1 fusion Protein. Nonclinical data both in vitro and vivo have shown high-affinity binding to both targets as well as the inhibition of tumor growth in animal models. Here, we present preliminary safety and efficacy data from a dose escalation phase I study of HB0025. **Methods:** Eligible patients (pts) were ≥ 18 years old (ECOG PS 0–1) who had advanced solid tumors (NSCLC, gynecological tumors, digestive system tumors, etc.) and failed standard treatment. This phase 1 dose escalation includes accelerated titration (0.01, 0.03, 0.1 and 0.3 mg/kg) and conventional 3+3 dose escalation (1.0, 3.0, 6.0, 10, 12, 20, and 30.0 mg/kg). HB0025 is administered intravenously every 14 days (Q2W). Objectives include evaluation of safety, pharmacokinetics (PK), pharmacodynamics (PD), immunogenicity, and antitumor activity. Adverse events (AEs) were reported with CTCAE v5.0 and DLTs were evaluated within a 28-day window. **Results:** As of Aug 30th 2022, 30 pts including 8 male and 22 female from Caucasian and Mongoloid have received HB0025 at doses of 0.01 mg/kg (n=1), 0.03 mg/kg (n=2), 0.1 mg/kg (n=1), 0.3 mg/kg (n=1), 1.0 mg/kg (n=3), 3.0 mg/kg (n=7), 6.0 mg/kg (n=7), 10.0 mg/kg (n=5), and 12.0 mg/kg (n=3) Q2W. Overall, the median age was 55 years and the median lines of previous treatment was four. Of the 22 evaluable pts dosed at ≥ 3 mg/kg Q2W, the ORR was 9.1% (2/22) and the disease control rate (DCR) was 50% [11/22]. Among the 2 responders, a CR (colorectal ca) pt whose prior therapy was no immune checkpoint inhibitor (ICI) or bevacizumab have continued more than 36 weeks; and a PR (NSCLC) pt with duration more than 18 weeks whose tumor was 60.2% regression and prior ICI failure. Till the date of submission, the therapy was continuing for the CR and PR pts. Treatment-related adverse events (TRAEs) occurred in 83.3% of pts. The grade 3 TRAEs occurred in 20% [6/30] and treatment-related SAEs occurred in 13.3% [4/30]. One DLT occurred in the 12.0 mg/kg cohort. No death occurred related to HB0025. TRAEs leading to treatment discontinuation occurred in 13.3% of pts [4/30]. The most frequent TRAEs were hypertriglyceridemia (23.3%), hypercholesterolemia (23.3%), anemia (16.7%), alanine aminotransferase increase (16.7%), and proteinuria (13.3%). **Conclusions:** HB0025 shows manageable safety and promising anti-tumor activity in pts with various solid tumors. To better characterize the risk-benefit profile, HB0025 is currently enrolled at 20.0 mg/kg Q2W and is being explored at doses 10 mg/kg in expansion cohorts. The future data, including PK, PD and ADA will be presented. Clinical trial information: NCT04678908. Research Sponsor: Huaota Biopharma, Inc.

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Poster Session

Efficacy and predictors of response of nivolumab in treatment-refractory MSI solid tumors: Results of a tumor-agnostic DRUP cohort. *First Author: Birgit Geurts, Department of Molecular Oncology & Immunology, Netherlands Cancer Institute, Amsterdam, Netherlands*

Background: Microsatellite unstable (MSI) tumors represent 4% of all cancer diagnoses and are known to be sensitive to immune checkpoint inhibitors (ICI). Despite the progress made, a significant proportion of patients with MSI tumors does not respond, highlighting the urgent need to identify additional predictive biomarkers. In this study, we evaluated the efficacy of the PD-1 inhibitor nivolumab across pre-treated solid MSI tumors and performed extensive biomarker analysis to better characterize ICI-effectiveness in this setting. **Methods:** Adult patients with MSI tumors who exhausted all standard of care treatment options were eligible for inclusion and were enrolled in the Drug Rediscovery Protocol (DRUP), a clinical trial that treats cancer patients with approved targeted- and immunotherapies outside their registered indication, based on their tumor molecular profile (NCT0295234). Patients were treated with nivolumab (four cycles of 240 mg every 2 weeks, followed by 480 mg every 4 weeks) until disease progression or unmanageable toxicity. Primary endpoint was clinical benefit (CB, objective response (OR) or stable disease ≥ 16 weeks). Whole genome sequencing and RNA sequencing were performed on pre-treatment biopsies to reveal potential predictors of response or resistance to anti-PD1. **Results:** 130 evaluable patients were enrolled with in total 16 different tumor types. CB was observed in 62% (95% CI 46 – 54) ($N = 80$) with an OR in 45% (95% CI 53 – 70) ($N = 58$). After a median follow-up of 14.5 months (95% CI 13 – 19), median progression free survival was 18 months (95% CI 9 – not reached) and median overall survival was not reached. HLA class I status and mutational burden were not significantly associated with CB. However, in depth biomarker analyses identified that mutational burden was predictive of CB in HLA-wildtype patients (52%) but not in HLA class I mutants (48%). Strikingly, in contrast to the paradigm that neoantigen-specific adaptive immunity is primarily involved in clearing MSI tumors, transcriptomics indicated that, compared to non-CB, CB was characterized by significantly higher expression of key modulators in innate immunity, including non-classical HLA transcripts ($P = 4.2 \times 10^{-3}$), NKGD2 ligands MICA/MICB ($P = 6.4 \times 10^{-3}$), killer immunoglobulin-like receptors ($P = 0.047$) and butyrophilins ($P = 0.024$). **Conclusions:** Nivolumab proved highly effective in pre-treated, advanced solid MSI tumors. Genomic analysis revealed that neoantigen burden only determined ICI-effectiveness in patients with wildtype HLA class I. Furthermore, transcriptomics revealed a central role of innate immunity in ICI-effectiveness in MSI tumors, which aligns with the fact that these tumors frequently lose HLA class I antigen presentation. Together, these results inform novel biomarker strategies to further refine precision medicine in this patient population. Clinical trial information: NCT0295234. Research Sponsor: The Dutch Cancer Society (KWF); Bristol Myers Squibb.

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Poster Session

Immunotherapy for localized dMMR/MSI tumors: First interim analysis of the IMHOTE trial. *First Author: Christelle De La Fouchardiere, Medical Oncology Department, Centre Leon Berard, Lyon I University, Lyon, France*

Background: Immune checkpoint inhibitors (ICI) have demonstrated their efficacy in advanced dMMR/MSI (deficient mismatch repair/microsatellite instability) tumors and increasing data are also accumulating in localized resectable stages with about 60% of pathological complete response rate. The goal of the IMHOTE trial is to assess the safety and efficacy of peri-operative pembrolizumab in localized dMMR/MSI tumors independently of their anatomical origin. **Methods:** IMHOTE is a prospective, multicenter, phase II study aimed to include 120 patients (pts) with localized resectable dMMR/MSI tumors, eligible for curative surgery. Pembrolizumab 400 mg flat dose is administered as a perioperative treatment with 1 or 2 doses every 6 weeks before surgery and thereafter every 6 weeks for one year. Primary objective is to evaluate the pathological complete response (pCR) rate defined as ypT0N0 stage. Secondary objectives are to assess major pathological response, centralized pathological review, safety, clinical response rate, recurrence-free survival and overall survival. Here, we present the interim analysis of safety and pathologic response data for the first 70 treated pts. **Results:** Median age was 67.5 years (26-89), 54.3% were males, and 42.0% were ECOG-PS 0. Surgery was performed in 54/70 pts including 27/35 colorectal (CRC), 16/21 oesogastric (OGC), 4/5 endometrial (EC) and 7/9 other (6 small intestine, 1 bile duct) (OC) cancers. 16 pts (22.9%) were not operated, mainly due to patient's decision following complete clinical response (n=7). Only one patient was not submitted to surgery because of disease progression. Focusing on the 54 operated pts, 31 and 23 pts received 1 and 2 neoadjuvant pembrolizumab doses respectively. The pCR rate was 38.9% (40.7%, 25.0%, 0.0% and 85.7% in CRC, OGC, EC and OC respectively). Grade 3-4 immune-related adverse events were observed in 4 (5.7%) patients including transaminases increase (n=1), arthritis (n=1), acute kidney injury (n=1) and pneumonitis (n=1). **Conclusions:** In this IMHOTE interim analysis, we observed a limited complete pathologic response rate to short-course neoadjuvant pembrolizumab. If we add patients in clinical complete response who chose not to be operated to those with pCR, our results compare with those previously reported. But we can also hypothesize that preoperative treatment duration should be prolonged to obtain more pCR. Overall, tolerance of pembrolizumab was acceptable without new safety signal. Centralized pathological review, major pathological response evaluation and clinical response rate analysis are ongoing. IMHOTE trial has been registered (first post: March 12th, 2021). Clinical trial information: NCT04795661. Research Sponsor: French Ministry of Health.

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Poster Session

Partial tumor irradiation plus pembrolizumab in treating large advanced solid tumor metastases. *First Author: Mark Charles Korpics, University of Chicago, Chicago, IL*

Background: We previously demonstrated the safety of stereotactic body radiotherapy followed by pembrolizumab (SBRT+P) in patients with advanced solid tumors. This phase 1 clinical trial was expanded to study the safety of partial tumor irradiation (partial-Rx). We assessed irradiated local failure (LF) and clinical outcomes with correlations to biomarkers including CD8-T-cell radiomics score (RS) and circulating cytokines. **Methods:** Patients received SBRT to 2-4 metastases and pembrolizumab ≤ 7 days after SBRT. Tumors < 65 cc received the full radiation dose (complete-Rx), whereas tumors > 65 cc received partial-Rx. Landmark analysis was used to assess the relationship between tumor response and overall survival (OS). Multivariable analysis was performed for RS and circulating cytokines. **Results:** In the combined (expansion plus original) cohort, 97 patients (219 metastases) were analyzed and received SBRT+P. Forty-six (47%) patients received > 1 partial-Rx treatment. There were 7 (7.2%) dose-limiting toxicities (DLTs). 1-year LF was 7.6% overall, and 13.3% and 5.4% for partial-Rx and complete-Rx tumors, respectively (hazard ratio 2.32, 95% confidence interval: 0.90-5.97, $p = 0.08$). The overall, unirradiated, and irradiated objective response rate was 22%, 12%, and 34%, respectively. Irradiated tumor response to SBRT+P was associated with prolonged OS; 1-year OS was 71% (responders), 42% (mixed-responders), and 0% (non-responders) ($p < 0.01$). High-RS was significantly associated with improved LF, progression-free survival (PFS), and OS. Elevated circulating IL-8 was independently associated with inferior PFS and OS. **Conclusions:** SBRT+P is safe in patients with large, advanced solid tumors. Additional studies are warranted to assess non-inferiority of complete versus partial irradiation of tumors in the setting of immunotherapy. Clinical trial information: NCT02608385. Research Sponsor: Merck Investigator Studies Program.

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Poster Session

Differences in real-world pembrolizumab dosing patterns (every 3 weeks versus every 6 weeks) across a large cancer center network. *First Author: Divya Natesan, University of Pittsburgh School of Medicine, Pittsburgh, PA*

Background: Pembrolizumab (pembro) is an intravenous immune checkpoint inhibitor used for anti-cancer treatment, with equivalent monotherapy dosing options of 200 mg every 3 weeks (Q3W) or 400 mg every 6 weeks (Q6W). Pembro Q6W dosing was approved for use in April 2020 after the Q3W dose had already been established. As pembro dosing patterns in real-world practice are not well-described, we evaluated this in a large cancer center network consisting of a central site (CS) and 36 community network sites (NS). **Methods:** We retrospectively reviewed the charts of all patients who received pembro monotherapy for cancer treatment between 4/2020 – 4/2022 at UPMC Hillman Cancer Center sites across the state of Pennsylvania, as well as sites in New York and Ohio. We performed statistical comparisons using the Fisher's exact test and Wilcoxon rank-sum test. **Results:** We identified 1,640 patients who received pembro monotherapy, including 377 patients at the CS and 1,263 patients in the NS, with characteristics displayed. Pembro Q6W dosing was significantly more common at the CS than in the NS (42% vs. 15%, $p < 0.0001$). When analyzed by tumor type, pembro Q6W dosing was significantly more common at the CS than in the NS for head & neck (53% vs. 11%, $p < 0.0001$), thoracic (49% vs. 15%, $p < 0.0001$), skin (60% vs. 19%, $p < 0.0001$), and genitourinary (30% vs. 16%, $p = 0.015$) cancers, but not for other tumor types. Within the NS, 30% (11/36) of sites only utilized pembro Q3W dosing and never administered Q6W dosing to patients. Of note, some patients who received pembro Q6W dosing received pembro Q3W dosing initially, either as part of a pembro-containing multidrug regimen or as monotherapy. Excluding patients initially treated with a multidrug regimen to reduce confounding factors, we found that of the patients who received pembro Q6W dosing, 47% (65/137) at the CS and 28% (48/169) in the NS were initially treated with pembro Q3W monotherapy before transitioning to Q6W monotherapy ($p = 0.0008$). **Conclusions:** In our large cancer center network, pembro Q6W dosing was significantly more common at the CS than in the NS. Switching from pembro Q3W to Q6W dosing was also significantly more common at the CS. Further work is needed to clarify the patient, provider, and institutional factors influencing differences in pembro dosing patterns in real-world practice, as well as the impact of dosing patterns on care delivery outcomes such as cost and accessibility. Research Sponsor: None.

	Central Site (N, %)	Network Sites (N, %)	p-value
Median Age (IQR)	69 (61-77)	71 (63-79)	0.011
Male Gender	230 (61.0)	722 (57.1)	0.191
Race			< 0.0001
White	322 (85.4)	1188 (94.1)	
Black	40 (10.6)	45 (3.6)	
Other/Unknown	15 (4.0)	30 (2.4)	
Hispanic Ethnicity	1 (0.3)	7 (0.6)	0.691
Median Days Since Diagnosis (IQR)	155 (26-585)	103 (23-489)	0.105
Pembro Q6W Dosing	157 (41.6)	185 (14.7)	< 0.0001

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Poster Session

Genomic alterations associated with response to immune checkpoint inhibitors in rare cancers: A biomarker exploration study from the Australian Molecular Screening and Therapeutics (MoST) Program. *First Author: Maya Kansara, Garvan Institute of Medical Research, Sydney, NSW, Australia*

Background: Despite immune checkpoint inhibitors (ICI) demonstrating efficacy in over 15 cancer types, evidence in most rare cancers remains scarce, reflecting the challenges of conducting prospective trials. This Australia-wide study reports real-world (RW) objective responses to ICIs targeting the programmed death-(ligand)1 (PD-1/PD-L1) pathway in a large precision oncology program, and associations between response and genomic alterations in rare cancers. **Methods:** This study was conducted within the framework of the MoST Program (ACTRN12616000908437), where adult patients (pts) with advanced solid tumors were screened using comprehensive genomic profiling (CGP). Only pts who received ICI after CGP were included in this analysis. The best overall response (BOR) to ICI was reported by the treating oncologist during the follow-up period. Best response was categorized as complete (CR), partial (PR), stable (SD), or progressive (PD). Two categories were defined: responders were individuals reported to have experienced CR or PR, while non-progressors were those with CR, PR, or SD. The association between tumor mutational burden (TMB) and response categories was assessed by area under the receiver operator characteristic curve (AUC). Odds ratios (OR) of specific genomic alterations associated with each category were also estimated. **Results:** Between Dec 2016 and Aug 2022, 4343 pts were screened; 3471 (80%) rare cancer pts, of whom 556 went on to 90 different ICI trials after undergoing CGP. In 273 pts treated with ICI where BOR was reported by the treating oncologist, the median survival was 17.3 months (95% CI 15.0 to 20.4). 13 pts (4.8%) had CR reported, including 8 pts with unapproved indications: 3 sarcomas, and 1 each, small cell carcinoma of unknown primary, adenoid cystic carcinoma, pituitary adenoma, thymoma, and pancreatic adenocarcinoma. 45 (16.5%) and 112 (41.0%) had PR and SD reported, respectively. High TMB, defined as ≥ 10 non-synonymous tumor mutations/megabase, was identified in 39 (14.3%) pts. TMB was associated with response (AUC 0.715, 0.630 to 0.800) and non-PD (AUC 0.600, 0.528 to 0.671) to ICI. Further exploratory analyses identified that alterations in *EP300* ($n = 7$, OR, 9.8, 1.9 to 52), *PTCH1* ($n = 6$, OR, 15.5, 1.7 to 141), *MSH6* and *KMT2D* ($n = 6$ each, OR, 7.7, 1.4 to 43), and *NFI* ($n = 10$, OR, 3.89, 1.1 to 13.9) were associated with CR/PR. Genomic *ARID1A* alterations ($n = 18$) were associated with non-PD (OR 5.16, 1.2 to 22.9), as were alterations in the SWI/SNF complex ($n = 20$, OR 3.64, 95% CI 1.0 to 12.8). **Conclusions:** Notwithstanding their limitations, these real-world data suggest that rare cancer patients may also benefit from ICI. Further prospective investigations into pan-cancer genomic biomarkers of response are warranted. Clinical trial information: ACTRN12616000908437. Research Sponsor: Government grants.

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Poster Session

Immune checkpoint inhibitor in high-risk oral potentially malignant disorders (IMPEDE study): An interim analysis on safety. *First Author: Andrea Alberti, Medical Oncology Unit, Department of Medical & Surgical Specialties, Radiological Sciences & Public Health, University of Brescia, ASST Spedali Civili, Brescia, Italy*

Background: Oral Potentially Malignant Disorders (OPMD) represent the most common oral precancerous condition, with a variable risk of malignant transformation. The most effective biomarker in predicting malignant transformation risk is loss of heterozygosity (LOH). Patients (pts) carrying OPMD with LOH at 3p14 and/or 9p21 plus LOH at another locus have an expected 3-year risk of developing oral cancer of 35%. This chromosomal profile is found in about 30% of OPMD. IMPEDE is a phase II, open-label, single-arm trial designed to evaluate the efficacy of PD-L1 inhibitor avelumab in reverting cancer transformation risk in OPMD with LOH. In this analysis, we report the first safety results, while data about treatment activity need longer follow up. **Methods:** During the screening period, pts undergo OPMD biopsy. If pathological diagnosis of dysplasia is confirmed, LOH valuation is performed and in case of positivity of this biomarker, subjects receive a short course of immunotherapy with avelumab 800 mg every 2 weeks for 4 total administrations. Follow-up after last avelumab dose is performed monthly and adverse event data are collected at every visit. Six months after treatment start, surgery and LOH re-assessment are performed. **Results:** Between November 2020 and December 2022, 49 pts were screened in 8 Italian centers. Of these, 16 pts (33%) had a LOH and 12 received the treatment (3 males, median age 65.5 years, range 49-81). Nine out of 12 treated patients had a previous oral cancer. After a median follow up of 14 months, 39 adverse events (AE) of any grade were reported, of these 18 were considered as immune related AEs (irAE). The most frequent AEs was grade 1 (G1) oral pain (4/12 pts), managed with local painkillers. Only three G2 irAEs were reported, namely amylase/lipase increase, psoriasis and fever. No grade 3-4 AEs were described, and no patient had to stop immunotherapy because of toxicities. Local excision after immunotherapy was not delayed by any treatment toxicities. **Conclusions:** This is the first trial with immunotherapy in an enriched population of OPMD selected according to LOH. First results support the feasibility of this approach, showing that immunotherapy with avelumab is safe and does not compromise subsequent local surgery. Clinical trial information: NCT04504552. Research Sponsor: Italian association for cancer research (AIRC).

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Poster Session

Phase II basket trial evaluating the efficacy of pembrolizumab (PE) combined with vorinostat (VO) in patients (pts) with recurrent and/or metastatic squamous cell carcinoma (SCC). *First Author: Christophe Le Tourneau, Curie Institute, Paris, France*

Background: Epigenetic modulation plays a major role in escaping tumor immunosurveillance and confers resistance to immune checkpoint inhibitors. Preclinical evidence suggests that modulating the epigenome might improve the efficacy of immunotherapy. **Patients and Methods:** PEVOsq is an open-label, non-randomized, multi-center, basket phase II trial, evaluating the efficacy of pembrolizumab in combination with vorinostat in patients with recurrent and/or metastatic squamous cell carcinoma of the cervix, head and neck, anus, vulva/vagina, penis, and lung. Patients had to be PD1/PD-L1 antagonist-naïve. There was no selection based on PD-L1 expression nor on HPV status, and no restriction in terms of prior lines of treatments. Pembrolizumab dose was 200 mg Q3W IV, and vorinostat 400 mg QD PO. Sample size was determined for each cohort using an A'Hern design. Primary endpoint was objective response rate (ORR) according to RECISTv1.1. Secondary endpoints included safety, progression-free survival (PFS), overall survival (OS), and duration of response (DOR). **Results:** Among 112 included patients, 111 were evaluable for safety and 107 for efficacy. The lung cohort was closed prematurely because of lack of enrollment. Median age was 61 years old [range: 18-85] and the median number of prior lines of therapies was 1 [range: 0-4]. ORR, PFS, G3/4 treatment related adverse events (TRAE), and OS are reported. 28 patients (26%) had an objective response and median DOR was 9.7 months [95%CI: 3.1-15.2]. Results per PD-L1 status will be presented at the meeting. Pembrolizumab and vorinostat were stopped for toxicity in 9% and 39% of patients, respectively. 60% of patients had a dose-reduced of vorinostat for toxicity. Pembrolizumab safety was as expected. Main vorinostat toxicities included hematological toxicity, gastrointestinal disorders, and asthenia and creatinine increase. **Conclusions:** Pembrolizumab combined with vorinostat showed encouraging antitumor activity in squamous cell carcinoma with unselected PD1/PD-L1 status, especially in cervical and anal cancer, although vorinostat dose had to be reduced because of toxicity in a substantial proportion of patients. Clinical trial information: NCT04357873. Research Sponsor: Fondation ARC; MSD; ERAPERMED; Agence National pour la recherche.

Efficacy and safety summary per cohorts.

Cohort	Primary endpoint ORR N (%)	Secondary endpoints		
		PFS (month) Median [95%CI]	OS (month) Median [95%CI]	G3/4 TRAEs N (%)
Cervix	9/23 (39)	4.2 [2.3-8.2]	10.3 [5.7-NR]	11/25 (44)
Anus	9/29 (31)	5.8 [2.7-11.0]	18.8 [12.8-NR]	18/29 (62)
Head and Neck	5/26 (19)	4.1 [1.5-4.4]	9.2 [6.8-14.4]	10/27 (37)
Vulva/Vagina	3/16 (19)	1.3 [1.1-4.3]	17.5 [2.3-NR]	4/17 (24)
Penis	2/11 (18)	2.4 [0.5-4.1]	4.4 [1.6-11.0]	5/11 (45)
Lung	0/2 (0)	NA	NA	1/2 (50)
Overall	28/107 (26)	4.0 [2.6-4.3]	11.1 [9.2-17.4]	49/111 (44)

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Poster Session

Retrospective analysis on association of ABO blood type and immune checkpoint inhibitor response. *First Author: Akshay Batra, University of Vermont, Burlington, VT*

Background: The presence or lack of a collection of antigenic cell surface markers on red blood cells makes up the ABO blood groups that contribute to various immunogenic neoantigens. Variations in the T-cell diversity and HLA haplotype with different blood types might affect a patient's response to Immune checkpoint inhibitors (ICIs). However, the association between the ABO blood type and ICIs is not well studied. **Methods:** We did a retrospective observational study to investigate the influence of ABO blood groups on patients receiving ICIs at the University of Vermont Cancer Centre. We examined the medical records of people who received ICIs as first-line therapy between January 2017 and June 2022 and collected demographic data, including age, sex, ethnicity, cancer stage, type and metastasis. We looked at overall survival and the occurrence of immune-related adverse events (irAEs) in different blood type subgroups and calculated relative risks. **Results:** A total of 288 cases were identified, out of which 169 had documented blood type, including 75 with A, 19 with B, 72 with O and 3 with AB blood type. The mean age was 63.71 years (Standard deviation (SD): 11.52), 58.6% were males, and ethnicity was 94.7% White, 1.2% Asian and 0.6% Hispanic. Lung cancer was most commonly identified at 41%, and 60% of total cancers were stage 4. The median ECOG status was 1 and the Charlson comorbidity index was 6. 36% of cases developed irAEs, whereas mortality was 39% during the study period. The relative risk of irAEs with blood type A and B compared to O was 0.89 and 0.83, respectively but wasn't statistically significant. The relative risk of irAEs of AB compared to O blood type was statistically significant at 2.63 (CI: 1.95-3.54). The relative risk of death in A and B blood types compared to O wasn't statistically significant. No patients in the AB blood group died. **Conclusions:** Clinically significant association wasn't found between different blood types and irAEs or mortality except for the increased risk of irAEs with AB compared to O. With the rapidly growing use of ICIs, prospective trials are needed to better understand the true risk of developing irAEs in patients with AB blood type. Research Sponsor: None.

Descriptive characteristics	RR (A to O)	RR (B to O)	RR (AB to O)
Adverse Events	0.89 (CI: 0.57-1.37)	0.83 (CI: 0.40-1.72)	2.63 (CI: 1.95-3.54)
Death	0.90 (CI: 0.61-1.32)	0.72 (CI: 0.35-1.48)	NA

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Poster Session

Phase 1B study of avelumab and whole brain radiotherapy (WBRT) in patients with leptomeningeal disease (LMD) from epithelial carcinomas: Final results and molecular analyses with single cell RNA sequencing. *First Author: Yolanda Pina, Moffitt Cancer Center, Tampa, FL*

Background: Leptomeningeal disease (LMD) from epithelial cancer has a dismal prognosis with median overall survival (OS) of 3-4 months (mo) using PD-1 axis blocking therapy. Preclinical studies showed that this combination promotes antigen presentation within the CSF compartment, increases BBB permeability and increases ingress of activated T cells into the meninges/CSF space. In an open-label phase 1B trial, we tested the safety and efficacy of Avelumab in combination with WBRT in patients with LMD (NCT0371768). **Methods:** Patients received concurrent Avelumab 800 mg IV q2 weeks for up to 5 cycles (until PD or unacceptable toxicity) with WBRT 3000 cGy in 10 daily fractions. Primary endpoints were safety/DLTs and 3-month OS. Secondary endpoints included CSF T-cell transcriptome trajectory i.e., single cell RNA sequencing (scRNAseq). Patients with prior PD-1/PD-L1/CTLA-4/CD137 targeting therapy within 6 mo were excluded. **Results:** 15 patients were enrolled with disease sites that included breast (8), lung (4), nasopharyngeal (1), ovary (1), and pancreas (1). Patients were 87% female, median age 59 range 32-82. One patient did not complete WBRT. Two of 15 patients had grade 3/4 immune-related AEs (i.e., hypoadrenalism, hypothyroidism, lymphopenia); 5 patients had treatment-related <grade 3 AEs, including hypoadrenalism, anemia, diarrhea, hypothyroidism, lymphopenia, thrombocytopenia, leukopenia). There were no grade 5 toxicities. Median follow up was 3.7 mo (range, 0.9-36.8 mo; 95% CI 1.3-14.7 mo). The median follow-up time for survival analyses of the study was 19.8 mo. Ten out of 15 patients (66.7%) were alive at 3 mo. Median OS was 10.5 (95% CI 1.2 - 19.8 mo). 1-year OS was 44% (95% CI: 19-68%). Median PFS was 4.3 mo (95% CI, 0.9-15.2 mo), Fig. 3B. Two patients remain alive and clinically well. scRNAseq analyses are underway; signatures correlated with outcomes in short versus long term survivors. **Conclusions:** The combination of Avelumab and WBRT is safe, well tolerated, and demonstrates encouraging activity in patients with LMD with an OS that is longer than other published series. Multiple platform interrogation of CSF will be used to explore mechanisms of LMD response and resistance. Functional studies of scRNAseq and short versus long term survivors should be further explored. Clinical trial information: NCT03719768. Research Sponsor: Pfizer.

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Poster Session

A phase 1/2 study of retifanlimab (INCMGA00012, Anti-PD-1), INCAGN02385 (Anti-LAG-3), and INCAGN02390 (Anti-TIM-3) combination therapy in patients (Pts) with advanced solid tumors. *First Author: Omid Hamid, The Angeles Clinic & Research Institute, A Cedars-Sinai Affiliate, Los Angeles, CA*

Background: In cancer treatment (tx), loss of T-cell function is associated with progressive expression of checkpoint (CP) molecules, and resistance or relapse following PD-(L)1 inhibitor therapy is a high unmet need. LAG-3 and TIM-3 are key CP pathways implicated in resistance to PD-1 inhibitors and have shown synergistic effects upon triple inhibition with PD-1 in a murine model. This open-label, nonrandomized phase 1/2 study (NCT04370704) aims to determine optimal doses and preliminary safety and efficacy for the monoclonal antibody combinations of INCAGN02385, INCAGN02390, and retifanlimab. Here we report initial safety and efficacy results. **Methods:** Study consists of 4 parts in phase 1 and 2 expansion cohorts in phase 2. In phase 1, parts 1 and 2 determined safety of INCAGN02385 350 mg Q2W + INCAGN02390 400 mg Q2W and INCAGN02385 350 mg Q2W + INCAGN02390 400 mg Q2W + retifanlimab 500 mg Q4W, respectively; parts 3 and 4 will test additional dosing schedules. Pts enrolled had previously treated (including PD-(L)1) locally advanced unresectable or metastatic solid tumors, with no prior LAG-3- or TIM-3-directed therapy. **Results:** As of June 28, 2021, 21 pts were enrolled in parts 1 (n=10) and 2 (n=11); 62% of pts were <65 years and 38% were male. Pts had median 3 (range 1-9) prior lines of therapy, including prior anti-PD-(L)1 (part 1, 8 pts; part 2, 11 pts); pt tumor types are listed. Nineteen pts discontinued tx, 1 due to toxicity. Nine pts in part 1 and 10 pts in part 2 had tx-emergent adverse events (TEAEs), most commonly anemia and diarrhea (each 30%) in part 1 and anemia (36%) in part 2 (all tx-unrelated). Serious tx-related TEAEs occurred in 1 pt in part 1 (grade [G]3 vasculitis) and 1 pt in part 2 (G3 myocarditis and pericardial effusion). Most common G $\geq$ 3 TEAE was G3 anemia (part 1, 2 pts; part 2, 3 pts); 1 pt in part 1 had a G5 TEAE of sepsis unrelated to tx, with COVID-19 infection. In part 2, 1 pt had an infusion-related reaction, and 1 pt had immune-related TEAEs of pericardial effusion and myocarditis (both G3 and tx-related), which resolved after steroid therapy and tx discontinuation. Best overall response in part 1 was stable disease, and in part 2 was a confirmed and durable partial response in 1 pt with CP therapy-refractory melanoma. **Conclusions:** Doublet anti-LAG-3 + anti-TIM-3 and triplet anti-LAG-3 + anti-TIM-3 + retifanlimab regimens in the study were generally well tolerated in heavily pretreated pts, with a safety profile consistent with that of CP monotherapy and no novel toxicities. Optimal doses of both combinations are to be further evaluated in the ongoing study in first-line tx of melanoma. Clinical trial information: NCT04370704. Research Sponsor: Incyte Corporation.

Tumor types.		
Tumor Type	Part 1 (N=10)	Part 2 (N=11)
Melanoma	3	5
Prostate	2	0
Renal	1	0
Cervical	1	1
Pancreatic	1	1
Anal	1	0
Gastrointestinal	1 (appendiceal)	1 (colorectal)
Lung	0	1
Head and neck	0	2

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Poster Session

A phase 1B dose escalation study of ETC-159 in combination with pembrolizumab in advanced or metastatic solid tumours. *First Author: David Shao Peng Tan, National University Cancer Institute, Singapore and Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore*

Background: ETC-159 is a small molecule porcupine inhibitor, in a prior Phase 1 study was safe as a monotherapy at 16 mg or at 24 mg with the addition of preventive denosumab for bone protection. In this Ph1B open-label trial the safety, MTD, PK and pharmacodynamics (PD) of ETC-159 in combination with pembrolizumab were determined (NCT02521844). **Methods:** Eligible patients had adequate organ function, advanced or metastatic solid malignancies and had failed standard treatments. Patients' refractory/resistant to prior PD-1 treatment were allowed and all patients had to have serum β -CTX levels below 600 pg/mL (or <1000 pg/mL and preventive denosumab). Dose escalation followed a 3+3 design with a DLT period of 42 days. ETC-159 was dosed orally QOD in 21-day cycles (8-24 mg); pembrolizumab was dosed IV at 200 mg Q3W. Day 1 and trough PK were determined for ETC-159 and pembrolizumab. Responses were assessed every 6 weeks (RECIST 1.1). **Results:** 20 patients were enrolled, 6 in the 8 mg cohort and 14 in the 16 mg cohort (50% M and 50% F, mean age of 51.4 y). All patients have been discontinued: 16 due to disease progression; 1 due to AEs, 2 developed contra-indication to denosumab & pembrolizumab, 1 withdrawal of consent. PK parameters of ETC-159 in the first cycle were consistent with prior single agent data. TEAEs were reported in all subjects in the study with most events being grade 1/2, with dysgeusia (65%), β -CTX increase (30%), fatigue (25%), constipation (20%), and nausea (20%) being the most common. DLTs were G3 colitis and G3 immune-related enteritis (16 mg, 2 patients), and pneumonitis and erythema with fever (8 mg, 1 patient). Other drug related SAEs were G2 thyroiditis, hematuria, and thrombocytopenia. No fractures or other drug related skeletal SAEs. Of the 15 evaluable patients, 6 (40%) demonstrated clinical benefit (1 PR, 5 SDs) in combination with pembrolizumab (2 ovarian, 1 lung, 1 pancreatic, 1 urachal, 1 MSS CRC patient with RSP0 fusion), at the first assessment, in a predominantly MSS population (65% MSS, 25% unknown, 10% MSI). Pharmacodynamics, (hair follicle *Axin2* reduction), was detected at both dose levels and was $\geq$ 80% from baseline on D15. **Conclusions:** ETC-159 + pembrolizumab was well tolerated; 8 mg of ETC-159 in combination with pembrolizumab was determined to be the MTD/ RD. Preliminary data suggest Wnt signaling inhibition in combination with checkpoint inhibition may provide clinical benefit in MSS patients. Clinical trial information: NCT02521844. Research Sponsor: A*Star Research Entities.

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Poster Session

IMM01 plus tislelizumab in patients with advanced solid tumors and lymphoma: An open-label, multicenter, phase 1b/2 dose escalation and expansion study (IMM01-04). *First Author: Zhengbo Song, Zhejiang Cancer Hospital, Hangzhou, China*

Background: IMM01, a recombinant SIRP α -Fc fusion protein, can activate macrophages to enhance anti-tumor activity by blocking CD47-SIRP α interaction. Based on preclinical results, IMM01 showed unique property of weak human erythrocyte conjugation. IMM01 plus tislelizumab has the potential to augment both innate and adaptive anti-tumor immune responses. **Methods:** This study included the phase 1b dose escalation part and the phase 2 dose expansion part. The dose escalation part was conducted with a standard 3+3 design to evaluate the safety, MTD/RP2D and anti-tumor activity in patients with advanced solid tumors. IMM01 (1.0, 1.5, 2.0 mg/kg) was administered once a week and tislelizumab (200mg) was administered once every 3 weeks. The results of the dose escalation part were reported here. **Results:** As of 26 Dec 2022, 14 pts were enrolled in the dose escalation part, including 5 NSCLC, 2 SCLC, 2 ESCC, 2 CRC, 1 HCC, 1 melanoma and 1 cervical carcinoma. Median age was 61 years (range 49-70). Median of prior therapies was 4 (range 1-10), and 13 pts (92.9%) received previous anti PD-1/L1 treatment. Treatment-related adverse events (TRAEs) occurred in 14 pts (100.0%) to date. Most TRAEs were grade 1-2. The most common TRAEs ($\geq$ 10%) of all grades were anaemia (85.7%), platelet count decreased (28.6%), asthenia (28.6%), white blood cell count decreased (21.4%), lymphocyte count decreased (21.4%), IRR (21.4%), proteinuria (21.4%), gamma-glutamyltransferase increased (14.3%), white blood cell count increased (14.3%), blood creatine phosphokinase MB increased (14.3%), neutrophil count decreased (14.3%), neutrophil count increased (14.3%), hyponatraemia (14.3%) and hyponatraemia (14.3%). The Grade 3-4 TRAEs were lymphocyte count decreased (21.4%), white blood cell count decreased (14.3%), platelet count decreased (14.3%), blood creatine phosphokinase MB increased (7.1%), blood pressure increased (7.1%) and anaemia (7.1%). No DLT occurred. No TRAE leading to treatment discontinuation was reported. 2 pts (14.3%) had treatment related SAE (2 platelet count decreased), they recovered without platelet transfusion and no bleeding occurred. In 14 pts, 1 pt had confirmed PR and 3 pts had SD. One heavily pre-treated NSCLC pt in the 2.0 mg/kg dose cohort had confirmed PR at Week 12, who was resistant to anti PD-1. One NSCLC pt in 1.5 mg/kg dose cohort and 2 pts (1 SCLC, 1 CRC) in 2.0 mg/kg dose cohort had SD. The treatments of these four pts are ongoing. **Conclusions:** Up to 2mg/kg IMM01 plus tislelizumab is well tolerated. The RP2D of IMM01 was determined as 2mg/kg, this was the highest IMM01 dose evaluated in human as a single agent. IMM01 plus tislelizumab showed preliminarily anti-tumor activity in patients with advanced solid tumors. The dose expansion part in advanced solid tumors and lymphoma is ongoing. Clinical trial information: chict20220791. Research Sponsor: ImmuneOnco Biopharmaceuticals (Shanghai) Inc.

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Poster Session

Deciphering primary and acquired immunotherapy resistance with whole genome and transcriptome analysis (WGTA). *First Author: Sofia Genta, Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, ON, Canada*

Background: Most cancer patients (pts) do not respond to antiPD1/PDL1 immune checkpoint inhibitors (ICI) or experience only a temporary benefit. Comprehensive molecular profiling with WGTA could broaden our understanding of the mechanisms contributing to primary (Pr) and acquired resistance (Ar) to ICI and identify novel predictive biomarkers. **Methods:** The Princess Margaret investigator-initiated Immune Resistance Interrogation Study (NCT04243720) aims to comprehensively characterize ICI-resistant cancers (Genta et al. ASCO 2021). Fresh tumor biopsies and blood samples were obtained from solid tumor pts at the time of PD on ICI-based treatment. DNA/RNA was extracted from tumor tissue and paired buffy coat and sequenced using an Illumina NovaSeq6000 system (2x150 paired reads for WG and 2X100 paired reads for WT). Copy number alterations (CNA), structural variants (SVs), mutation signatures and genes expression were assessed. Wald test in univariable and multi-variable logistic regression model was used for comparison. **Results:** As of January 2023, 73 pts (45 Pr/28 Ar) were enrolled. WGTA was completed in 22 pts (14 Pr/8 Ar). Key pt characteristics included: median age 60.5 years (range 26-79); male 68%/female 32%; melanoma 50%, squamous cell cancer of the head and neck 36%, and other tumor types 14%. Forty-one percent of the pts were treated with PD-1/PD-L1 inhibitor monotherapy and 59% with PD-1/PD-L1 inhibitor combinations. There were no significant differences in median tumor mutation burden (TMB, coding; 2.8, range 0.6-30.5 for Pr vs 4.4, range 1.6-12.8 for Ar), median percent genome altered by CNA (43% Pr vs 65% Ar) or median number of SVs (144, range 9-775, for Pr vs 76, range 25-924, for Ar pts). After performing RNA sequencing we observed a significantly higher expression of the epithelial mesenchymal transition (EMT) hallmark gene-set from msigDB and of 3 previously reported ICI-resistance gene expression signatures in Pr vs Ar ($p \leq 0.05$) in univariable analysis. The signatures included genes involved in the regulation of EMT, cellular de-differentiation and a cancer associated fibroblast (CAF) signature (IPRES signature, Hugo et al. Cell 2016; melanocytic plasticity signature [MPS], Pérez-Guijarro et al. Nat Med 2020; LRRC15 CAF signature, Dominguez et al. Cancer Discov. 2020). After adjusting for cancer type, the MPS signature was significantly associated with Pr vs Ar resistance in multivariable analysis ($p = 0.048$). **Conclusions:** No significant differences between Ar and Pr were observed in genomic features including TMB, CNAs and number of SVs. Cancers primary resistant to ICI were characterized by a higher expression of EMT, cell de-differentiation and CAF related genes, detected with transcriptome analysis. Our findings might indicate these features as possible driver of early ICI progression. Analysis of additional samples is ongoing. Research Sponsor: Marathon of Hope Cancer Centres Network; Dr. Siu's BMO Chair in Precision Genomics; University of Toronto.

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Poster Session

PD-1 inhibitors combined with radiotherapy and GM-CSF, sequentially followed by IL-2 (PRaG 2.0) regimen in advanced refractory solid tumors: A prospective, multicenter, single-arm clinical trial. *First Author: Pengfei Xing, The Second Affiliated Hospital of Soochow University, Suzhou, China*

Background: Low frequency of durable responses in patients treated with immune checkpoint inhibitors demands taking complementary strategies in order to boost immune responses against cancer. Our previous PRaG trial also demonstrated that PD-1 inhibitors in combination with radiotherapy and granulocyte macrophage-colony stimulating factor (GM-CSF) could improve clinical response in patients with advanced refractory solid tumors (ChiCTR1900026175). In an effort to further enhance efficacy, we conducted the PRaG 2.0 trial (ClinicalTrials.gov: NCT04892498) and optimized the PRaG regimen by incorporating interleukin-2 (IL-2). **Methods:** The PRaG 2.0 regimen was administered to patients with advanced refractory solid tumors who lacked or were unable to tolerate standard-of-care treatments. A treatment cycle consisted of radiotherapy (5 or 8Gy×2-3f) delivered for one metastatic lesion, PD-1 inhibitor dosing within one week after completion of radiotherapy, GM-CSF 200µg subcutaneous (SC) injection once daily for 7 days, and then sequentially followed by IL-2 2million IU SC once daily for 7 days. PRaG 2.0 regimen was repeated every 21 days for at least 2 cycles until no appropriate lesions for irradiation or reached the tolerance dose of normal tissues. Patients who could not continue radiotherapy and had not yet developed progression disease (PD) allowed PD-1 inhibitors to be continued as maintenance therapy until PD or unacceptable toxicity but no more than one year. The primary endpoint was Progression-Free Survival (PFS). **Results:** As of 31st October 2022, 51 patients were enrolled in the study, and 42 completed at least one tumor assessment. The median Progression-Free Survival (PFS) was 5.8 months, and the median overall survival (OS) was 13.5 months. The objective response rate (ORR) was 21.4%, and the disease control rate (DCR) was 61.9% according to RECIST version 1.1. Lower plasma levels of Interleukin (IL)-6 and IL-17 at baseline were found to be associated with improved PFS. Treatment-related adverse events (TRAE) experienced in 34 of 42 (78.6%) patients, with 4 patients (9.5%) experiencing Grade ≥ 3 TRAEs. TRAEs leading to discontinuation of all study treatments occurred in three patients (7.1%). **Conclusions:** The PRaG 2.0 trial demonstrates that PD-1 inhibitors in combination with radiotherapy, GM-CSF, and IL-2 could be a potential treatment regimen for patients with advanced refractory solid tumors, with an acceptable benefit/risk profile. Clinical trial information: NCT04892498. Research Sponsor: None.

2605

Poster Session

The impact of renin-angiotensin-aldosterone system inhibitors on immune checkpoint inhibitor-associated adverse cardiovascular events. *First Author: Cho Hung Chiang, National Taiwan University Hospital, Taipei, Taiwan*

Background: Immune checkpoint inhibitors (ICIs) are associated with adverse cardiovascular events that impair patient outcomes. Previous observational studies showed that renin-angiotensin-aldosterone system inhibitors (RAASi) may mitigate the cardiotoxicity associated with chemotherapeutic agents. However, the effects of RAASi on ICI-associated adverse cardiovascular events are unknown. **Methods:** We conducted a 1:1 propensity score-matched cohort study involving ICI-treated patients at two tertiary referral centers in Taiwan. The propensity score matching model includes age, sex, hypertension, diabetes mellitus, chronic kidney disease, Eastern Cooperative Oncology Group (ECOG) Performance Scale, cancer stage, and cancer type. The primary outcome was major adverse cardiovascular events (MACE), defined as a composite of myocardial infarction (MI), ischemic stroke, peripheral arterial occlusive disease (PAOD), pulmonary embolism (PE), deep venous thrombosis (DVT), heart failure, pericardial disease, myocarditis, and cardiac arrhythmias. The secondary outcomes were arterial thrombotic events (MI, ischemic stroke, PAOD) and venous thrombotic events (PE and DVT). **Results:** We identified 684 patients eligible for inclusion, from which 164 patients who received RAASi were matched to patients who did not receive RAASi. Over a median follow-up of 9.1 months, the incidence rate of MACE for RAASi and non-RAASi recipients was 6.5 and 13.9 per 100 patient-years, respectively, resulting in an incidence rate ratio of 0.47 [95% CI: 0.21–1.00] (p = 0.038). In a multivariate Cox proportional hazard model adjusting for cancer therapy, RAASi recipients had an approximately 60% reduction in the risk for MACE (HR, 0.37 [95% CI: 0.16–0.86], p = 0.021). In the secondary analysis, RAASi were associated with a reduction in venous thrombotic events (HR, 0.11 [95% CI: 0.02–0.63], p = 0.013), but not for arterial thrombotic events (HR, 0.47 [95% CI: 0.06–3.38], p = 0.45). **Conclusions:** In patients receiving ICI therapy, the use of RAASi is associated with a decreased cardiovascular risk, particularly for venous thrombotic events. Research Sponsor: None.

Outcomes	RAASi No. of cases	Non-RAASi No. of cases	Univariate hazard ratio (95% CI)	P-value	Multivariate hazard ratio ^a (95% CI)	P-value
Major adverse cardiovascular events	13 (8%)	18 (11%)	0.52 (0.25-1.07)	0.074	0.37 (0.16-0.86)	0.021
Arterial thrombotic events	3 (2%)	3 (2%)	0.60 (0.12-3.04)	0.54	0.47 (0.06-3.38)	0.45
Venous thrombotic events	3 (2%)	6 (4%)	0.34 (0.08-1.37)	0.130	0.11 (0.02-0.63)	0.013

^aMultivariate model adjusting for cancer therapy including antimetabolites, Vascular endothelial growth factors inhibitors, taxanes, tyrosine kinase inhibitors, monoclonal antibodies, vinca alkaloids, anthracyclines, topoisomerase inhibitors.

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Poster Session

Durvalumab + tremelimumab in biologically selected advanced/metastatic solid tumors. *First Author: Christelle De La Fouchardiere, Medical Oncology Department, Centre Leon Berard, Lyon I University, Lyon, France*

Background: Tremelimumab (T) in combination with Durvalumab (D) is approved by the FDA for the treatment of unresectable hepatocellular carcinoma and metastatic non-small cell lung cancer. We prospectively examined its clinical activity in a cohort of biologically-selected advanced/metastatic solid tumors from the MOST Plus clinical trial (NCT NCT02029001). **Methods:** Adult patients (pts) previously treated by at least one prior line but immunotherapy-naïve were eligible if their tumor harbored TMB-H (>10mut/Mb) and/or MSI/dMMR (by PCR and IHC tests), and/or PD1/PD-L1/CTLA4 amplification and/or POLD1 or POLE mutation. T was administered for up to 4 cycles (75mg, IV, Q4W) and D (1500mg, IV, Q4W) until disease progression, unacceptable toxicity or patient/investigator decision. Tumor response was assessed as per RECIST 1.1 and adverse events reported according to NCI-CTCAE v4.03. **Results:** 70 patients were enrolled (24 male, median age: 65 years [33-88], MSI n=56, TMB-H n=10, PDL1 and PDL2 ampl. n=1, POLE mut. n=1, MSH6 mut. n=1, MSH2 mut. n=1). The median number of prior lines of systemic therapy was 1 (range: 0-4). Main tumor types were colorectal (44%), endometrial (19%), and stomach (7%) carcinomas. As of October 2022, overall response (ORR) rate was 52.8% (21.4% CR, 31.4% PR). With a median follow-up of 37 months, median PFS and OS were 8.4 months [95% CI: 4.4- 22.1] and 37.2 months [95% CI: 10.4-NE], respectively. Median duration response of response was not reached. Overall, 24.3% of patients experienced at least one serious treatment-related (TR) adverse event. Two TR-deaths were reported (haemophagocytic lymphohistiocytosis and nephritis). ORR, median PFS and OS are reported. **Conclusions:** T+D is a highly efficient combination in biologically selected tumors leading to a high complete response rate. Enrolment is still ongoing, to further evaluate the utility of a maintenance treatment, i.e the optimal treatment duration. Clinical trial information: NCT02029001. Research Sponsor: Fondation ARC.

ORR, PFS and OS.

	MSI N=56	TMB-H N=10	Other N=4	All
CR % (n)	18.5% (n=13)	2.9% (n=2)	0%	21.4%
PR % (n)	30% (n=21)	1.4% (n=1)	0%	31.4%
mPFS (Months)[95%CI]	12.2[6.7 ; 37.2]	2.5[0.4 ; 14.8]	1.6[1.0 ; NR]	8.4[4.4 ; 22.1]
mOS (Months)[95%CI]	NR[18.6; NR]	5.3 [1.1; NR]	2.6 [1.2; NR]	37.2[10.4 ; NR]

2606

Poster Session

Updated results and biomarker analyses from the phase 2 trial (BBCAPX study) of sintilimab plus bevacizumab and CapeOx as first-line treatment in patients with RAS-mutant, microsatellite stable, unresectable metastatic colorectal cancer. *First Author: Ying Yuan, Department of Medical Oncology, Key Laboratory of Cancer Prevention and Intervention, Ministry of Education, The Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China*

Background: RAS-mutant and microsatellite stable (MSS) metastatic colorectal cancer (mCRC) patients have an immunosuppressive microenvironment and show a low response rate to immunotherapy. Sintilimab plus bevacizumab and CapeOX (BBCAPX) has proved its efficacy and safety in above unresectable mCRC patients (Xuefeng Fang et al. ASCO 2022). Here, we report updated efficacy, safety, progression-free survival (PFS) and biomarker analyses from this single arm, open-label, phase 2 trial (NCT05171660). **Methods:** RAS-mutant and MSS mCRC patients received sintilimab (200 mg, day 1) plus bevacizumab (7.5mg/kg, day 1) and oxaliplatin (135 mg/m², day 1) and capecitabine (1g/m², bid, day 1-14) of each 21-day cycle. Clinical response was assessed every 2 cycles via RECIST 1.1 criteria. Whole exome sequencing (WES) and 289 NanoString panel RNA sequencing was performed for tumor mutational burden, genomic alteration, immune microenvironment and other biomarker analysis. **Results:** 25 patients with unresectable metastases were enrolled after the assessment of CRC multidisciplinary team. 2 (8.0%) patients showed complete response (CR), 19 (76.0%) patients had a partial response (PR) and 4 (16.0%) had stable disease. Objective response rate (ORR) reached 84.0% and disease control rate was 100.0%. The median PFS was 18.2 months for the full analysis set. The most common treatment-related adverse events (TRAEs) in all grades were anemia (21/25, 84.0%), neutropenia (20/25, 80.0%) and hand-foot syndrome (14/25, 56.0%). The most frequent grade 3 or 4 TRAEs were neutropenia (3/25, 12.0%) and alanine transaminase increased (2/25, 8.0%). No grade 5 adverse events occurred. In biomarker exploration, after treatment, as compared with the baseline, the results of WES suggested 5 patients appeared TTN/OBSCN “double-hit” and copy number variants burden was significantly decreased in tumor tissues. Nanostring panel RNA sequencing analysis found that there was a better tumor immune microenvironment cell infiltration in CR/PR patients compared with non-CR/PR patients tumors as well as PFS-long group (< 12.5 months) compared with PFS-short group (≥ 12.5 months). **Conclusions:** Combination treatment of sintilimab plus bevacizumab and CapeOX as first-line treatment demonstrated a high ORR (84.0%) and a manageable safety profile in RAS-mutant, MSS unresectable mCRC. Exploratory biomarker assessment analysis showed some patients changed into “immune-hot” subtype after the treatment. We are launching a phase 3, randomized, open-label, multicentric clinical trial (NCT04194359) to further evaluate the effect, safety and prognostic biomarkers of this combination in RAS mutant, MSS mCRC patients when compared with that of bevacizumab and CapeOX. Clinical trial information: NCT05171660. Research Sponsor: Inovvent Biologics, Inc.

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Poster Session

Prospective cardiovascular surveillance of immune checkpoint inhibitor-based combination therapy in patients with early-stage, triple-negative breast cancer. *First Author: Vishnu Venkatesh, University of Texas Southwestern Medical Center, Dallas, TX*

Background: Both pembrolizumab and anthracyclines (AC) can cause adverse cardiovascular events; combination therapy is approved for high-risk, early-stage, triple-negative breast cancer (TNBC) and may further increase real-world cardiovascular risk. Cardiac surveillance with serial troponin measurements has been advocated in this population, though evidence supporting this approach is lacking. **Methods:** High-sensitivity troponin I (hs-TnI) was prospectively measured at baseline and with each treatment cycle in cancer patients receiving immune checkpoint inhibitors (ICI) at a single center as part of an institutional surveillance protocol for ICI-related adverse events from 2020-2022. Acute cardiac injury was defined as ≥ 1 abnormal hs-TnI value ($>17\text{ng/dL}$ in women and $>35\text{ng/dL}$ in men) with normal baseline hs-TnI, or at least 20% increase in hs-TnI from abnormal baseline. The incidence of acute cardiac injury and all-cause mortality were compared between patients receiving ICI in combination with AC versus ICI without AC. **Results:** Among 215 patients treated with ICI with baseline and ≥ 1 follow-up hs-TnI value, 28 patients (13%) received ICI with AC, all of whom were women with early-stage TNBC receiving pembrolizumab and AC-containing chemotherapy. 187 patients (87%) received ICI without AC for other oncological indications. Patients receiving ICI with AC were younger and more likely to be female than patients receiving ICI without AC ($p<0.001$) with lower rates of smoking, hypertension, and diabetes ($p<0.04$). Acute cardiac injury was observed in 33 patients, 21% of those receiving ICI with AC ($N=6$) and 14% of those receiving ICI without AC ($N=27$; $p=0.34$). Among these 33 patients, 2 patients were treated for ICI-associated myocarditis (1 receiving ICI with AC, 1 receiving ICI without AC); 67% of those receiving ICI with AC ($N=4$) were continued on ICI while only 30% of those receiving ICI without AC ($N=8$) were continued on ICI ($p=0.16$). The rate of all-cause mortality was significantly lower in patients receiving ICI with AC (0%) as compared to patients receiving ICI without AC (40%, $p<0.001$). **Conclusions:** Among women with early stage TNBC receiving pembrolizumab with AC, the rate of acute cardiac injury by surveillance troponin measurements was numerically but not statistically higher than for patients receiving ICI without AC for other oncological indications, though the rate of all-cause mortality was significantly lower. These findings suggest that surveillance troponin monitoring may have less clinical utility among women with early-stage TNBC receiving ICI-based combination therapy as compared to other patient populations receiving ICI. Further study is needed to understand the mechanistic and prognostic significance of acute cardiac injury in patients with TNBC receiving ICI-based combination chemotherapy. Research Sponsor: None.

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Poster Session

A novel method that leverages existing data to conduct comparative analyses of competing assets: Sugemalimab and agents targeting the PD-L1/PD-1 axis as an example. *First Author: Antonio Tito Fojo, Columbia University Medical Center, New York, NY*

Background: Non-small-cell lung cancer (NSCLC) remains the leading cause of cancer-related mortality worldwide. Numerous immune checkpoint inhibitors (ICIs) targeting the programmed cell death protein-1/programmed death ligand-1 (PD-1/PD-L1) axis have garnered regulatory approvals. A novel method of comparative analysis that discerns differences/similarities amongst such agents could reduce redundancy and hopefully enhance true competition. **Methods:** We've described an approach for assessing efficacy that assumes changes in tumor quantity result from two simultaneous processes – exponential decay of the treatment-sensitive fraction of tumor at rate d , and exponential growth of the resistant fraction at rate g . Using this method, the USFDA analyzed data from 9934 patients with NSCLC enrolled in registration trials treated with chemotherapy, targeted therapies, and immunotherapies concluding g is inversely associated with survival across treatment types and encouraging prospective studies to evaluate whether g derived from early tumor measurements might serve as an earlier clinical trial endpoint (Gong ASCO 2020). Using data provided by EQRx and CStone we analyzed the GEMSTONE-302 trial comparing chemotherapy +/- the PD-L1 inhibitor sugemalimab in first line NSCLC. **Results:** 88% of the data could be analyzed. Regression without growth was seen in 10-12% of both arms with indistinguishable d values. Evidence of tumor growth was estimable as a g value in 68-71% with statistically slower g values and longer tumor doubling times (TDT) seen with sugemalimab + chemotherapy [0.0012/day (0.0005-0.0022); TDT 578d] than placebo + chemotherapy [0.0025/day (0.0013-0.0035); TDT 277d] $p<0.0001$. A comparative analysis with FDA data from 1521 patients who received Combo ICI in front line, finds comparable/slightly slower g values for sugemalimab + chemotherapy using all or a fraction of the data. **Conclusions:** We used a method of analysis that estimates rates of tumor growth (g) to analyze the efficacy of the PD-L1 antagonist, sugemalimab, in NSCLC. Because time is included in our equations the intervals of assessment are rendered inconsequential, making this method of analysis ideal for virtual comparisons. We confirmed the value of sugemalimab in the first-line setting by demonstrating its data track very closely with data aggregated from randomized trials reported by the USFDA in patients treated with Combo ICI in front line. Because g values can be estimated with fewer data it can be leveraged for early decisions. Research Sponsor: None.

Median g by line/type of therapy.

Line of therapy	Type of therapy	N	Median g /day	TDT
USFDA [Gong, Abstract #9541 ASCO 2020]				
Front	Combo ICI	1521	0.0014/day	495 days
Front	Combo control	835	0.0019/day	365 days
GEMSTONE-302				
Front	Sugemalimab + Chemotherapy	320	0.0012/day	578 days
Front	Placebo + Chemotherapy	159	0.0025/day	277 days

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Poster Session

The controversial abscopal effect: A single-center experience about the combination of stereotactic radiotherapy with pembrolizumab in patients with metastatic dMMR/MSI-H colorectal cancer. *First Author: Annaliese Gandini, IRCCS Ospedale Policlinico San Martino, Genoa, Italy, Italy*

Background: Colorectal cancer (CRC) patients with mismatch repair system deficiency (dMMR/MSI-H) have shown impressive responses to immune checkpoint inhibitors in any lines of treatment. However, almost 30% of these patients are primary refractory and another 30% develop secondary resistance. Thus, many treatment combinations are being pursued to overcome resistance. One of the proposed strategies is the addition of radiotherapy to immunotherapy based on the potential abscopal effect and its consequent on-target and off-target activity. **Methods:** Between November 2019 and April 2021, we conducted a prospective interventional single-institution study to assess the feasibility, disease control and safety of the combination of pembrolizumab with stereotactic ablative radiotherapy (SABR) in a cohort of 14 consecutive dMMR CRC patients. SABR was administered in combination within the second or third cycle of Pembrolizumab 200 mg infused every 21 days. SABR was delivered on one or more targetable metastases with the ablative dose of 15 Gy in the first fraction followed by a second fraction of 5 Gy. **Results:** Fourteen patients were enrolled and 11 received radiotherapy in combination with Pembrolizumab as per protocol. Three patients who started Pembrolizumab never received radiotherapy due to deterioration of their general conditions, leading to death within two months. Two out of these three patients were $BRAF^{V600E}$ mutated. Five patients (35.7%) received Pembrolizumab as first line, 6 (43%) as second line and 3 (21%) as third or later lines. Six out of 14 patients (42.9%) harboured $BRAF^{V600E}$ mutation, 2 out of 14 (14.3%) RAS mutation and the others were RAS/BRAF wild type. Objective response was observed in 4 out of 14 patients (29%) and disease control was achieved in 7/14 patients (50%). Among these, six patients (42%) achieved a disease control lasting more than 15 months. This regimen caused substantial toxicity, mainly linked to SABR. Any grade TRAEs occurred in 50% of patients, with one patient with G1 event, three patients with G2 events, and two patients with G3 events (pneumonia, bowel perforation); no treatment-related deaths were observed. **Conclusions:** These data do not show hint of added efficacy of Pembrolizumab by SART in unresectable dMMR/MSI-H mCRC. Research Sponsor: IRCCS Ospedale Policlinico San Martino.

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Poster Session

DURTRERAD: A phase II open-label study evaluating feasibility and efficacy of durvalumab (D) and durvalumab plus tremelimumab (DT) in combination with radiotherapy (RT) in non-resectable locally advanced HPV-negative head and neck squamous cell carcinoma (LA-HNSCC). *First Author: Ulrich Keilholz, Charité-Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Charité Comprehensive Cancer Center, Berlin, Germany*

Background: Concurrent platinum-based chemo-RT is the standard treatment for LA-HNSCC, despite of limited efficacy in poor-risk patients and long-term toxicity. Targeting PD-L1 with D has activity in recurrent/metastatic (RM)-HNSCC, and the combination with the CTLA4 targeting agent T was considered to augment the immunotherapy efficacy of a chemotherapy-free regimen. Thus DURTRERAD was designed as a randomized two-arm phase II study to investigate, whether D or DT combined with RT was feasible in the patient population and a 1-year progression free survival rate of 50% was reached. **Methods:** The phase II study planned to enroll 60 patients in each treatment arm. Key selection criteria were patients with advanced HPV negative unresectable HNSCC planned for definitive radiotherapy. Treatments: First dose of immunotherapy 14 days prior to start of RT (70Gy over 7 weeks). D (1500mg q 3 weeks x 13) or DT (D: 1500mg q 3 weeks x 13 + T: 4 x 75 mg in weeks 5,9,13,17). Planned treatment duration was 51 weeks in both arms. Treatment was considered feasible in case of $<10\%$ treatment discontinuations. An interim analysis for feasibility was planned after treatment of 6 patients per arm and a utility analysis was performed after treatment of 18 patients, resulting in premature closure of the trial. **Results:** Patient accrual in 4 centers in Germany from 9/2018 - 9/2020. The interim feasibility analysis of DT revealed that 5/6 patients stopped treatment due to 1 grade 5 and 1 grade 4 immune related AE and 3 non-immune related AEs, respectively. Thus, the DT arm was prematurely terminated, and only the D monotherapy arm continued. Utility analysis of D monotherapy: One of 12 patients stopped treatment due to immune related toxicity, and 7 patients experienced disease progression on treatment or died within the first year. The median PFS was 39 weeks, the 1 year PFS rate was 42%. **Conclusions:** Even though D was previously proven as an active agent in RM-HNSCC, and there DT was not associated with increased toxicity, DT in combination with RT was not feasible in our poor prognostic, vulnerable patient cohort of HPV negative LA-HNSCC. D monotherapy in combination with RT was well tolerated, but revealed a low level of efficacy, when administered in the trial schedule, starting 2 weeks prior to RT. Similar to results in lung cancer, start of immunotherapy after completion of radiotherapy may be of interest. Clinical trial information: NCT03624231. Research Sponsor: Charité - Universitätsmedizin Berlin; AstraZeneca - Unrestricted Educational Grant.

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Poster Session

MyTACTIC: Efficacy and safety of atezolizumab (atezo) + chemotherapy (chemo) in patients (pts) with advanced unresectable/metastatic solid tumors with high tumor mutational burden (TMB-H) or high microsatellite instability (MSI-H)/deficient mismatch repair (dMMR). First Author: David R. Spigel, Department of Thoracic Medical Oncology, Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN

Background: MyTACTIC (NCT04632992) is a phase II, non-randomized, multi-arm basket study evaluating targeted therapies as single agents or combinations in pts with advanced solid tumors with specific biomarkers. We present the efficacy and safety of arm E from MyTACTIC: atezo + chemo in pts whose tumors have TMB-H and/or MSI-H/dMMR. **Methods:** Enrolled pts were ≥ 18 years old, with histologically/cytologically confirmed advanced unresectable/metastatic solid tumors with TMB-H (TMB ≥ 10 mut/Mb) and/or MSI-H/dMMR and ECOG PS ≤ 2 ; those with symptomatic/actively progressing CNS metastases were excluded. Pts received intravenous atezo 1200 mg every 21 days and physician's choice chemo (docetaxel; paclitaxel; capecitabine) until progressive disease (PD), toxicity or death. Primary endpoint: investigator-assessed confirmed objective response rate (cORR). Secondary endpoints included disease control rate (DCR; confirmed complete response [CR] + partial response [PR] + stable disease [SD] or non-CR/non-PD for ≥ 70 days), duration of response (DOR), progression-free survival (PFS) and safety. **Results:** At data cutoff (May 16, 2022), 25 pts with 10 tumor types had received atezo + chemo. Median age was 69 years (range 37–83), 88% of pts had ECOG PS ≤ 1 and 20 pts with metastatic disease had a median of 1 prior line of therapy (range 1–4). Twenty-three pts had TMB-H (2 missing), 7 had MSI-H and 7 had dMMR (12 missing); 7 pts had TMB-H and MSI-H/dMMR. cORR was 28.0% (7/25; 95% CI 12.1–49.4), including 1 CR (colon cancer) and 6 PRs. Responses were observed in 6/10 tumor types studied. cORR was 12.5% in pts with TMB-H alone (2/16) and 71.4% (5/7) in pts with TMB-H and MSI-H/dMMR. DCR was 32.0% (8/25; 95% CI 14.9–53.5). Median DOR and median PFS were 7.4 months (95% CI 7.4–not estimable) and 3.9 months (95% CI 2.2–8.4), respectively. The safety profile of atezo + chemo was consistent with previous reports for this combination. The most common treatment-related adverse events (TRAEs) were diarrhea (60%) and fatigue (32%). Grade 3/4 TRAEs occurred in 32% of pts and there were no serious or grade 5 TRAEs. **Conclusions:** In this small cohort, treatment with atezo + chemo demonstrated clinical activity in pts with advanced solid tumors with TMB-H and/or MSI-H/dMMR. Responses were observed in different tumor types and were numerically higher in pts whose tumors had both biomarkers vs those with TMB-H alone. Further analyses with a larger cohort and longer follow-up will be required to confirm these results. Clinical trial information: NCT04632992. Research Sponsor: This study is sponsored by Genentech, Inc. Third-party medical writing assistance, under the direction of authors, was provided by Vanessa Poon, BSc, of Ashfield MedComms, an Inizio company, and was funded by Genentech, Inc.

Tumor type	cORR n/N
Colon	2/11; 18%
Breast	1/5; 20%
Bladder	1/1
NSCLC	1/1
Uterine	1/1
Carcinoma of unknown primary	1/1
Esophageal (n=2)*, Neuroendocrine (n=1), Prostate (advanced unresectable n=1), Prostate (metastatic n=1)	0/5

*DCR: 50%; 1 pt had SD for ≥ 70 days.

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Poster Session

Pan-cancer analysis of IDO1 transcriptome expression and its impact on outcome in patients treated with immune checkpoint inhibitors. First Author: Yu Fujiwara, Department of Medicine, Icahn School of Medicine at Mount Sinai, Mount Sinai Beth Israel, New York, NY

Background: The immunosuppressive tumor microenvironment (TME) is a major component of resistance to immune checkpoint inhibitors (ICIs). Tryptophan catabolism is recognized as a metabolic pathway leading to immunosuppression and indoleamine 2,3-dioxygenase 1 (IDO1), an enzyme catabolizing tryptophan to kynurenine, has been investigated as a potential target. Analyzing the association of IDO1 and immune molecules in the TME could better elucidate the role of IDO1 as an immunotherapeutic strategy. Thus, we performed pan-cancer transcriptome analysis of IDO1 according to cancer types and immune molecules in the TME and evaluated survival outcomes in patients treated with ICIs based on IDO1 expression levels. **Methods:** Comprehensive transcriptome analysis of IDO1 and selected immune molecules in 514 patients with advanced solid tumors at the Moores Cancer Center at the University of California San Diego was performed. The rate of "High" (75–100 percentile), "Intermediate" (25–74), and "Low" (0–24) IDO1 RNA expression in each cancer type was calculated (rank compared to 735 controls). Univariate and multivariate analyses of the odds ratio (OR) for high IDO1 expression based on factors such as immune checkpoints, cancer types, microsatellite instability (MSI), and tumor mutational burden (TMB) were conducted. Additionally, progression-free survival (PFS) and overall survival (OS) from the time of ICI therapy based on IDO1 expression was compared by the Kaplan-Meier method. Multivariate analysis of survival outcomes was performed using the Cox proportional hazards model. **Results:** Overall, 91 of 514 patients (17.7%) were classified into "High", 228 (44.4%) into "Intermediate", and 195 (37.9%) into "Low" IDO1 RNA expression. High IDO1 expression was seen in uterine (54.2%), ovarian (37.2%), and lung cancer (25.0%). In multivariate analysis, high STAT1 and CD40 expression, ovarian cancer, and uterine cancer were correlated with high IDO1 expression. In patients treated with ICIs (N = 217), "High" IDO1 expression (N = 49) was associated with better PFS (HR = 0.57, 95%CI: 0.40–0.83, p = 0.003) and OS (HR = 0.52, 95%CI: 0.47–0.83, p = 0.006) than "Intermediate/Low" IDO1 expression (N = 168). Multivariate analysis incorporating age, sex, IDO1, PD-1, PD-L1, PD-L2, CTLA-4, LAG3, cancer types, TMB, and MSI revealed that IDO1 (HR = 0.28, 95%CI: 0.11–0.69, p = 0.006) and PD-1 (HR = 0.24, 95%CI: 0.09–0.65, p = 0.005) are independent predictive factors for longer OS. **Conclusions:** IDO1 RNA levels are high in $>25\%$ of uterine, ovarian, and lung cancers but differ from patient to patient between and within tumor types. High IDO1 levels correspond with longer PFS and OS from start of ICI therapy. These results suggest the importance of patient selection through pan-cancer molecular analysis and the potential role of IDO1 as a predictive marker for ICI therapy. Research Sponsor: U.S. National Institutes of Health.

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Poster Session

High transferrin receptor expression marks tumors with increased immune-effector infiltration and expression of targetable checkpoint molecules: Results of a multi-cancer analysis in solid tumors. First Author: Asaad Trabolsi, Jackson Memorial Hospital/ University of Miami, Miami, FL

Background: The cell-surface transferrin receptor, TFR1, encoded by *TFRC*, imports iron-bound transferrin into cells to drive tumor proliferation. We have found worse prognosis with high *TFRC* expression across multiple tumor types. The mechanism by which *TFRC* drives tumor cell-intrinsic oncogenesis is multifactorial, but its interaction with the tumor microenvironment (TME) has not been studied. Here, we assessed TME infiltration by immune effector populations and immune checkpoint expression. **Methods:** Tissue samples underwent comprehensive molecular profiling at Caris Life Sciences: Next-gen sequencing of DNA (592 Gene Panel, NextSeq, or whole exome sequencing, NovaSeq), RNA-seq (NovaSeq, whole transcriptome sequencing, WTS) and immunohistochemistry. RNA deconvolution analysis by the Microenvironment Cell Populations (MCP)-counter method quantified immune populations to assess T cells, B cells, natural killer cells (NK) and myeloid dendritic cells (MDC). Analyses compared quartiles of *TFRC* mRNA expression between Q4 (*TFRC*-H) high and Q1 (*TFRC*-L) low expressors. **Results:** Among 27,607 patients with non-small cell lung cancer (NSCLC), 5,332 with prostate cancer (PC), and 14,287 with colorectal cancer (CRC), *TFRC*-H tumors were associated with high tumor mutational burden (TMB-high, ≥ 10 mutations/MB), and *TP53* mutation (q<0.05). Multiple immune checkpoint genes showed significantly higher expression in *TFRC*-H relative to *TFRC*-L in all tumor types, including *CD274* (PDL1), *LAG3*, *PDCD1LG2* (PDL2), and *CTLA4* (Table; All values are statistically significant: q<0.05). Moreover, TME assessment by MCP-counter showed significantly increased infiltration by total T cells, CD8+ cells, B cells, NK cells, and MDCs in *TFRC*-H (Table). Finally, among patients who received Check-point inhibitors (CPI), *TFRC*-L had improved survival (HR=0.807 (95% CI 0.76 – 0.85) p<0.00001) in NSCLC but no difference was found in CRC or PC. **Conclusions:** Our study is the first to reveal the TME characteristics associated with *TFRC* expression in a variety of solid tumor types. We found *TFRC*-H tumors have increased infiltration by immune effector populations but also express significantly higher levels of immune checkpoint molecules, highlighting immune exhaustion. Altered iron metabolism has been shown to promote tumorigenesis and here we identify a new role for *TFRC* in remodeling the TME. TFR1-targeting therapeutic agents are in clinical development and warrant further investigation in combination with CPIs. Research Sponsor: None.

	Immunecheck point markers, <i>TFRC</i> -H Log2(TPM+1) fold change				<i>TFRC</i> H:L fold change			
	-	-	-	-	-	-	-	-
	PDL1	LAG3	PDL2	CTLA4	T cells	CD8	NK	B cells MDC
NSCLC	2.23	1.39	1.45	1.59	1.88	2.07	2.05	2.0 1.29
PC	2.06	1.39	1.38	1.54	2.34	2.23	2.47	2.64 2.39
CRC	2.08	1.27	1.31	1.71	2.33	2.14	2.50	2.11 1.96

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Poster Session

Distributional range of tumor mutational burden (TMB) across multiple cancer types emphasizing the importance of different cutoff values in different tumor types for clinical interpretation: A consensus statement from the SEQUOIA consortium. First Author: Wojciech Swat, Cancer Genomics and Molecular Pathology, Bioreference Laboratory, Elmwood Park, NJ

Background: The measurement of tumor mutational burden (TMB) is critical to select patients who are expected to respond to immune checkpoint inhibitors or immunotherapy (IO). The majority of the clinical guidelines on the interpretation & utility of TMB values are based on studies performed on lung cancer, setting a cutoff of 10. Laboratories that are using comprehensive genomic profiling (CGP) for tumor testing are reporting TMB values &/or interpretations (high/low) beyond lung cancer. Multiple studies have shown that the TMB signature is not universal, but rather tumor &/or even patient-specific. However, the pan-cancer trial for IO (KEYNOTE-158) failed to consider setting different cutoffs per tumor type. Currently, no major guidelines or consensus statements address the issue of reporting TMB as a biomarker beyond lung cancer. In the current study, the membership of the SEQUOIA (Sequencing & Oncology Informatics Academic Team) Consortium investigates the landscape of TMB values across multiple cancer types. **Methods:** We investigated TMB values in 11,670 patient samples (M = 6225; F = 5445) across 13 different tumor types & histological subtypes, including cancers with lung, colorectal, gastrointestinal, brain, prostate, pancreatic, biliary, endometrioid, ovarian, skin, hematological (CLL myeloma) & lymphoid origin. All samples were processed by a CGP panel of 523 genes. Multiple specimen types were included in the study consisting of tissue, blood, marrow, & lymph node. **Results:** The range of TMB values varied significantly across different cancer types & histological subtypes. The colorectal, melanoma & endometrial cancers have a wider range of TMB values (2–400 mutations/MB) relative to prostate, breast, myeloma, & serous cancers (0–30 mutations/MB). Along with the range, the mean, & median TMB values are also significantly varied across these tumor types. We also identified that a subset of patients exhibits high TMB (>30 mutations/MB) values across almost all types of cancer. **Conclusions:** TMB values & their association with response to immune checkpoint inhibitors are not very well studied in all cancer types, although a TMB cut-off of 10 mutations/MB was defined as TMB-high for FDA-approved IO in patients with unresectable or metastatic solid tumors. The range, mean, median, cut-offs & clinical interpretations of TMB-high & low for IO based therapies for different tumor types has not been well established. Our data confirm the wide range, mean, & median across different tumor types, & thus laboratories & oncologists need to be cautious in the clinical interpretation of TMB values for patient management. Future studies should assess responsiveness to IO in specific tumor types based on TMB value to determine tumor-specific TMB cutoff values. Research Sponsor: None.

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Poster Session

Quantitative 3D assessment of the lung cancer microenvironment using multi-resolution open-top light-sheet microscopy. *First Author: Caleb R Stoltzfus, Alpenglow Biosciences, Inc., Seattle, WA*

Background: Non-small cell lung cancer (NSCLC) tissue is a valuable resource for diagnosis, treatment planning, and drug development. Current 2D histopathological techniques introduce under-sampling error (i.e., a single 5 μm section represents 0.5% of a 1 mm thick biopsy), interobserver variability, and failure to capture the biology contained within the entire tissue sample. We have developed a suite of technologies to stain, chemically clarify, image, visualize, and analyze entire, intact lung tissue samples. Herein, we present analysis methods for comprehensive 3D assessment of intact NSCLC tissue. **Methods:** Human NSCLC tissue, stored frozen in optimal cutting temperature (OCT) compound, was fixed in 4% paraformaldehyde, stained with nuclear (TOPRO-3) and general protein (Eosin) fluorescent dyes, and optically cleared using a modified iDISCO protocol with ethyl cinnamate as the refractive index matching solution. Twenty tissue samples measuring 1-5 mm^3 in volume were imaged at 2 $\mu\text{m}/\text{pixel}$ resolution with a hybrid open-top light-sheet microscope. Smaller regions of interest (ROIs) with interesting pathologic features were re-imaged at higher resolution, 0.17 $\mu\text{m}/\text{pixel}$. Visualization and analysis was performed using Aivia software, custom spatial analysis software and python scripts. **Results:** All NSCLC tissue samples were successfully imaged in 3D at both low and high resolution. Computational approaches, such as machine learning, were used to segment and classify tumor cells and lymphocytes within the high resolution ROIs. In one example we quantified a 0.0045 mm^3 ROI containing 1×10^9 voxels. We segmented 1,474 unique objects, and classified 683 (46%) of the objects as lymphocytes and 309 (20%) of the cells as tumor cells. We found that on average the lymphocytes were within 12 μm of the nearest tumor cell. Additionally the tissue was broken into separate lymphocyte dense (58% of volume) and tumor dense regions (42% of volume). Further analysis is in progress to quantify more features, such as tertiary lymphoid structures, stromal cells, and fibrosis over the full 20 sample dataset. **Conclusions:** We successfully implemented 3D machine learning analysis pipelines using images from intact NSCLC tissue samples measuring up to 5 mm^3 . The imaging was performed using our custom hybrid open-top light-sheet microscope. This novel method enables us to identify and quantify key histological features such as tumor cells and lymphocytes within the tumor microenvironment. In addition, machine learning driven algorithms clustered cells into distinct tissue regions in 3D which enables a more precise assessment of disease state and heterogeneity. Further investigation is ongoing to link these results to patient outcomes. Research Sponsor: Alpenglow Biosciences.

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Poster Session

Genomic landscapes to characterize mismatch-repair deficiency (dMMR)/microsatellite instability-high (MSI-H) gastrointestinal (GI) cancers stratified by tumor mutation burden (TMB). *First Author: Jingyuan Wang, Norris Comprehensive Cancer Center, Keck School of Medicine, University of Southern California, Los Angeles, CA*

Background: TMB is a predictive biomarker for immune checkpoint inhibitor treatment in dMMR/MSI-H cancers. We aimed to characterize specific molecular features of a large cohort of dMMR/MSI-H GI tumors with a range of TMB levels. **Methods:** A total of 2272 GI tumors tested as dMMR/MSI-H were analyzed using Next-generation sequencing (NGS) and immunohistochemistry (IHC) (Caris Life Sciences, Phoenix, AZ). MMR/MSI status was evaluated by a combination of IHC, Fragment Analysis and NGS. TMB-H were defined using differing TMB cutoffs (10, 20, 50 mutations/Mb). Molecular features were compared in four groups (TMB < 10 vs 10-20 vs 20-50 vs ≥ 50 mutations/Mb) using Fisher-Exact or Chi-square and adjusted for multiple comparison by Benjamini-Hochberg. The impact of TMB on tumor immune environment was analyzed using a TCGA cohort. Significance was determined by adjusted (adj) $P < 0.05$. **Results:** Tumors with TMB over 10, 20, 50 mutations/Mb were observed in 95.38%, 86.05% and 14.47% respectively in the dMMR/MSI-H GI cohort. Compared to other groups, dMMR/MSI-H GI tumors with TMB over 50 mutations/Mb exhibited the highest mutations rates in *RNF43*, *MSH6*, *KMT2D*, *BRCA2* and *ASXL1* (Top 5, all $P_{\text{adj}} < 0.0001$). Among the four MMR genes, only *MLH1* mutation had no association with higher TMB. The rates of *CNNE1* amplification (i.e. the Cycle E1 gene) and HER2 overexpression were the highest in tumors with TMB below 10 mutations/Mb (all $P_{\text{adj}} < 0.05$). The association between PD-L1 positivity and TMB levels was only observed in gastroesophageal cancers ($P = 0.03$). The lymphocyte infiltration signature score, IFN γ response and M1 macrophage infiltration were significantly lower, while fraction of genome alterations was significantly increased in dMMR/MSI-H tumors with TMB below 10 mutations/Mb, compared to other subgroups (all $P < 0.05$). Neoantigens were significantly enriched in those with TMB over 50 mutations/Mb, compared to other subgroups ($P < 0.0001$). **Conclusions:** This is the largest study to investigate the distinct molecular landscape of dMMR/MSI-H GI cancers with different degrees (magnitude) of TMB. These data may inform our understanding of the efficacy of ICB in dMMR/MSI-H GI tumors. Research Sponsor: None.

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Poster Session

Incorporating long non-coding RNA (lncRNA) into genome-wide biomarker screening for prognostic gene signatures of immunotherapy outcomes. *First Author: Xuefeng Wang, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL*

Background: Emerging data have shown that long non-coding RNA (lncRNAs) have the potential to become biomarkers in cancers with potential roles in regulating cell proliferation, apoptosis, migration, invasion and maintenance of stemness during cancer development. In this research, we aimed for a genome-wide biomarker screening approach incorporating lncRNA in order to identify key molecules and pathways involved in ICI response and resistance. **Methods:** We utilized clinical and transcriptomic data collected under the Total Cancer Care Protocol (NCT03977402) and Avatar project within the Oncology Research Information Exchange Network (ORIEN). We analyzed RNA-seq data from a total of 875 ICI treated pts. A novel resampling-based technique with elastic net regression was utilized for genome-wide biomarker screening, in which Cox regression was used for survival outcomes and logistic regression for a 2-year-based dichotomized outcome. All search was done through 200 resampling steps, each consisting of randomly selecting 80% of pts and 80% of all gene signatures. Moreover, we searched the genes that are most complementary to the established immune cell scores (i.e., Ecotyper and xCell) by incorporating these scores into the regression adjustment. Finally, we applied the same approach to identify prognostic long non-coding RNA (lncRNA) signatures. All analyses were carried out on all ICI pts, as well as on subgroups stratified by cancer type. **Results:** Of 875 pts treated with ICI, 125 had melanoma, 143 had kidney cancer, 126 had non-small lung cancer, and 110 had head and neck cancer. The genome-wide selection method successfully identified a panel of top prognostic genes and pathways for all cancer types included. In melanoma, the top five prognostic genes were *ZDHHC2*, *CBX4*, *MET*, *NTN4*, and *HLA-DQA1*, with 80%, 78%, 77.5%, 77.5%, 76.5% resampling-based selection probability respectively; the top five lncRNAs were *AC073655.3*, *AC116348.3*, *PITPNA-AS1*, *AC011447.3*, and *AL021978.1*. When adjusting for the immune scores in the selection model, the top five prognostic protein-coding genes in melanoma were *TENM3*, *POLR2J3*, *SCCPDH*, *MET* and *SLAH1*, and the top five lncRNAs were *AC007620.2*, *PITPNA-AS1*, *HCG11*, *SLC25A5-AS1*, and *LINC02258*, respectively. **Conclusions:** Our analysis has successfully identified gene panels of mRNA and lncRNA molecules with potential roles related to ICI mechanisms of action. Ongoing analyses are further investigating the potential mechanisms and pathways linking these molecules and will be presented at the meeting. Research Sponsor: Oncology Research Information Exchange Network (ORIEN) Foundation; Community Foundation Tampa Bay.

Gene Type	Gene Name	Average Effect Size	Selection prob (Stability score)
Protein-coding genes	<i>ZDHHC2</i>	-0.713	0.80
	<i>CBX4</i>	0.161	0.78
	<i>MET</i>	0.125	0.775
	<i>NTN4</i>	-0.176	0.775
	<i>HLA-DQA1</i>	-0.070	0.765
LncRNAs	<i>AC073655.3</i>	0.288	0.855
	<i>AC116348.3</i>	-0.369	0.825
	<i>PITPNA-AS1</i>	1.282	0.810
	<i>AC011447.3</i>	-0.318	0.805
	<i>AL021978.1</i>	-0.183	0.805

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Poster Session

STK11 alterations as predictive biomarkers of resistance to immune checkpoint inhibitors in multiple cancers with mismatch repair gene alterations. *First Author: Michael Iglesia, Siteman Cancer Center, Washington University School of Medicine, St. Louis, MO*

Background: *STK11* is an important tumor suppressor gene that encodes for a serine-threonine kinase involved in a variety of metabolic functions. *STK11* alterations are associated with an inert or cold tumor microenvironment in KRAS-mutant lung adenocarcinoma, and are a major driver of primary resistance to immune checkpoint inhibitors (ICIs). Here, we explored *STK11* alterations as predictive biomarkers of resistance to ICIs in multiple solid tumors with mismatch repair (MMR) gene alterations. **Methods:** The cBioCancer Genomics Portal (cBioportal, <http://www.cbioportal.org>) was used to obtain genomic data. The association between *STK11* alterations and median overall survival (mOS) was explored in an ICI-treatment cohort comprising a total of 1572 evaluable patients. This cohort includes patients with cancers of the lung, colon, unknown primary, head and neck, gastroesophageal, bladder, skin (melanoma), brain, breast and kidney that had received at least one dose of ICI. These were then cross-referenced with patients who had MSK-IMPACT testing done in the context of routine clinical care. Kaplan-Meier survival curves were generated and compared using log-rank testing. **Results:** In the ICI-treated patients cohort (N = 1572), 96 patients (6.1%) had *STK11* alterations. Patients with *STK11* alterations had higher median tumor mutation burden (TMB) than patients without *STK11* alterations (8.81 mut/Mb vs. 5.87 mut/Mb, $p < 0.0001$). Yet, they had worse mOS (7 m, 95% CI: 6-13 m vs. 20 m, 95% CI: 18-22 m, $p < 0.001$). MMR alterations (not including gene promoter methylation) were identified in 103 (6.6%) and co-occurrence of *STK11* with MMR alterations was identified in 9 (0.6%) patients. Compared to patients without MMR or *STK11* alterations (N = 1382), the mOS was better in patients with MMR alterations without *STK11* alterations (N = 94) (59 m vs. 19 m, $p = 0.0004$) and trending for worse in patients with MMR and *STK11* alterations (N = 9) (5 m vs. 19 m, $p = 0.117$). The mOS was better in patients with MMR alterations without *STK11* alterations compared to patients with MMR and *STK11* alterations (59 m vs 5 m, $p = 0.016$). Controlling for KRAS mutation status, a multivariable Cox regression model shows that besides MMR and *STK11* alteration status ($p = 0.0008$), BRAF mutant status ($p = 0.0001$, HR 0.598; 95% CI, 0.459-0.779) was another biomarker associated with significantly better OS. Lung cancer diagnosis was associated with worse OS ($p = 0.0016$, HR 1.340; 95% CI, 1.117-1.607). **Conclusions:** In a large cohort of ICI-treated patients with multiple cancers, *STK11* alterations were associated with worse mOS despite having higher TMB. MMR alterations were only predictive of response to ICIs in patients without *STK11* alterations. Our findings suggest that *STK11* alterations in patients with MMR alterations could potentially identify patients who are less likely to respond to ICIs but more data are needed. Research Sponsor: None.

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Poster Session

The differential response to immune checkpoint inhibitors (ICIs) according to mismatch repair alterations in gastrointestinal (GI) non-colorectal cancers (non-CRCs) and the impact of dual vs. monotherapy ICIs on survival in GI (CRC and non-CRC) cancers. *First Author: Moh'd M. Khushman, Washington University in St. Louis, Siteman Cancer Center, St. Louis, MO*

Background: In patients with mismatch repair deficient (dMMR) colorectal cancers (CRCs), we previously reported that loss of expression of MSH2 and MSH6 (MutS co-loss) was associated with better response to ICIs and longer median overall survival (mOS) compared to loss of expression of MLH1 and PMS2 (MutL co-loss). Here, we expanded our analysis and included gastrointestinal (GI) non-CRCs and explored the impact of dual vs. monotherapy ICIs on mOS in GI (CRC and non-CRC) cancers. **Methods:** Specimens were profiled by next-generation sequencing (592, NextSeq; WES, WTS NovaSeq) (Caris Life Sciences, Phoenix, AZ). MMR/microsatellite instability (MSI) status was determined by immunohistochemistry (IHC) of MMR protein. Real world OS was extracted from insurance claims and calculated using Kaplan-Meier estimates for molecularly defined cohorts from first treatment with ICIs (Nivolumab, Nivo; Ipilimumab, ipi; or Pembrolizumab, pembro) to last contact. Statistical significance was determined using chi-square and Mann-Whitney U test with p-values adjusted for multiple comparisons ($q < 0.05$). **Results:** The GI non-CRC cohort (N=19,767) included cancers of the esophagus, stomach, gastroesophageal junction, pancreas, bile duct and small bowel with 97 (0.49%) patients having MutS co-loss, and 494 (4.03%) patients having MutL co-loss. MutS co-loss was associated with increased *KRAS* (45.4% vs 25.2%, $q < 0.01$), *CDKN2A* (29.2% vs 9.0%), *GNAS* (27.8% vs 7.8%) and *SMAD4* (17.5% vs 5.9%) mutations compared to MutL co-loss. Independent of treatment, MutS co-loss (N=74) had improved mOS compared to MutL co-loss (N=332) (40.4 m vs. 26.2 m, HR = 0.66; (95% CI: 0.46-0.95), $P=0.024$). In patients treated with ICIs, the mOS in MutS co-loss (N=21) was better compared to MutL co-loss (N=76) (not reached (NR) vs. 25.4 m, HR = 0.23 (95% CI: 0.07-0.75), $p=0.008$). At 3 years, more than 80% of the patients with MutS co-loss were alive. Of particular importance, when looking at all GI (CRC and non-CRC) patients, the mOS of MutL co-loss treated with ipi/nivo (N=18) trended for better mOS compared to MutL co-loss treated with pembro (N=215) (NR vs. 28.2m (HR=0.39; (95% CI: 0.14-1.07), $p=0.057$), while the mOS of MutS co-loss treated with ipi/nivo (N=6) was not different compared to MutS co-loss treated with pembro (N=44) (NR vs. NR, HR=0.75 (95% CI: 0.094-5.92), $p=0.78$). **Conclusions:** In ICI-treated GI non-CRCs, the mOS was longer in MutS co-loss compared to MutL co-loss. In ICI-treated GI (CRC and non-CRC) patients with MutL co-loss, there was a trend for better survival with ipi/nivo compared to pembro. Our data suggest that the MutS vs. MutL status may guide the choice of ICIs regimen (Dual vs. Monotherapy) but more data are needed. Research Sponsor: None.

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Poster Session

Spatial distribution of B cells and lymphocyte clusters for the treatment of non-small cell lung cancer. *First Author: Corinne Ramos, ImaBiotech, Loos, France*

Background: The presence of tertiary lymphoid structure (TLS) in tumor tissues has been reported to be a factor associated with a good prognosis in several types of cancers including non-small cell lung cancer (NSCLC). However, the relationship between TLS spatial organization and the treatment response remains unknown in NSCLC who received anti-PD-1 antibody. The purpose of this study was to evaluate the effect of the various stages of the spatial organization of the TLS from locally concentrated aggregates of immune cells, through clearly defined B cell follicles to mature follicles in NSCLC and its relationship with the tumor microenvironment on anti-PD1 treatment response. **Methods:** Frozen sections from retrospectively collected surgically resected NSCLC tumors treated with adjuvant pembrolizumab therapy were used. The TLS in tumor tissues was detected by high-plex imaging mass cytometry staining and the difference in TLS spatial organization was compared to the features of the tumor microenvironment and the objective response rate of the patients. **Results:** TLS identified and characterized according to their spatial organization within or adjacent to the tumor showed that the presence of tumor-associated TLS (TA-TLS) correlated with favorable response to anti-PD-1 therapy. The abundance and the spatial distribution of B cells allowed for a better definition of the correlation between B cell subsets with clinical outcomes showing that the heterogeneity in these TA-TLS influences the predictivity significance to anti-PD-1 therapy. **Conclusions:** Identifying the phenotypic heterogeneity of intratumor B cells and their functional connection to CD8 T cell helps optimally guide the anti-PD-1 treatment strategy. This spatial mechanistic insight also provides an exciting opportunity for translation of B cell-based immunotherapies into clinics complementary to existing T cells centric strategies. Research Sponsor: ImaBiotech.

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Poster Session

Artificial intelligence (AI)-powered spatial analysis of macrophages in tumor microenvironment and its association with interferon-gamma (IFNG) signature and immune phenotype (IP) in pan-cancer dataset. *First Author: Chiyeon Oum, Lunit Inc., Seoul, South Korea*

Background: Macrophages are known to play a crucial role in cancer progression, but few studies have reported macrophage spatial distribution and its association with genomic signatures and tumor-infiltrating lymphocytes (TIL). Here, we applied an AI-powered Whole Slide Image (WSI) analyzer in The Cancer Genome Atlas (TCGA) pan-cancer dataset to show correlation between specific localization of macrophage and anti-tumor activity, which is reflected by IFNG signature and IP based on spatial TIL density. **Methods:** For spatial macrophage analysis in TCGA pan-cancer dataset, we used Lunit SCOPE IO, an AI-powered H&E WSI analyzer, which identifies and quantifies various classes of cells such as tumor cell, macrophage, and TIL within cancer or stroma area. IPs were defined as follows: inflamed IP (IIP) as high intratumoral TIL (iTIL) and stromal TIL (sTIL); immune-excluded IP (IEP) as low iTIL and high sTIL; immune-desert IP (IDP) as low TIL overall. The immune cell profiling and quantification of the IFNG signature score were analyzed by using CIBERSORT and RSEM. **Results:** In TCGA dataset (N = 7,402), median macrophage density in total TME area (tMP) was 19.9 /mm² (interquartile range [IQR] 9.0-44.9), and it was highly enriched in lung adenocarcinoma (median 65.1, IQR 34.3-110.0), lung squamous cell carcinoma (61, 32.4-101.3), and head and neck squamous cell carcinoma (39.4, 19.6-77.3). Based on IP classification, tMP was highly enriched in IIP (37.8, 18.7-73.8) compared to IEP (25.5, 13.8-48.6) and IDP (8.9, 4.4-17.1). Interestingly, spatial analysis showed that intratumoral macrophage density (iMP) in IIP was highly enriched compared to the others (mean fold change 2.57) and the difference of stromal macrophage density (sMP) among IPs was relatively smaller (mean fold change x1.85). Classified into four groups based on median values of iMP and sMP, high-iMP/high-sMP group had the highest proportion of IIP (47.3% vs 18.7%, $p < 0.001$), whereas low-iMP/high-sMP group had the highest one of IEP (54.9% vs 32.3%, $p < 0.001$) compared to the others, respectively. Moreover, the high-iMP/high-sMP group had the highest level of IFNG signature score among 4 groups (x2.13 times higher, $p < 0.001$). Notably, both iMP and sMP were significantly correlated with CD68 expression (rho 0.292 and 0.287) but CSF1R expression was more strongly correlated with iMP (rho 0.259) compared to sMP (rho 0.078). **Conclusions:** IIP, IFNG signature, and CSF1R expression are more strongly correlated with intratumoral macrophage density versus stromal macrophage density, suggesting a relationship between macrophage location and function in the TME warranting further investigation. Research Sponsor: None.

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Poster Session

Role of HLA class-I antigen peptide loading complex components in immune evasion and treatment sensitivity in human lung cancer. *First Author: Adrien Costantini, Yale University, New Haven, CT*

Background: Determinants of sensitivity and resistance to immune checkpoint inhibitors (ICIs) are poorly understood. An intact HLA class-I antigen presentation machinery (APM) is necessary for tumor-antigen recognition by effector T-cells and disruptions to the APM can cause ICI resistance. The peptide loading complex (PLC) is a multi-chaperone complex located in the endoplasmic reticulum in which tapasin (Tap), calreticulin (CalR) and ERp57 play major roles. The PLC allows for optimal peptide selection and loading onto HLA class-I heavy chain and is critical for adequate cell surface presentation of peptide-HLA complexes. We studied the frequency and clinical significance of cancer-cell selective PLC protein defects in human NSCLC. **Methods:** Multiplex quantitative immunofluorescence (mQIF) was performed to simultaneously and spatially measure cytochrome (CK), Tap, CalR, ERp57 and CD8 protein levels in 1,031 primary NSCLCs from 5 independent cohorts represented in tissue microarrays. The protein levels were measured in CK-positive cancer-cells and in CK-negative stromal cells. The presence of lower marker levels in malignant cells relative to stromal cells within the same sample was considered as cancer-cell selective downregulation. Cohorts #1-3 included baseline samples from patients treated without ICIs and Cohort #4 included samples from patients treated with ICIs. Cohort #5 contained lung adenocarcinomas clinically tested for EGFR and KRAS mutations. The association between the levels of Tap, CalR and ERp57, their association with clinicopathologic variables, CD8+ T-cell levels and outcomes were studied. **Results:** mQIF analysis identified cancer-cell selective downregulation of Tap, CalR and/or ERp57 in 73%, 81%, 68% and 75% of cases from Cohorts #1-4, respectively. The most common PLC alterations were cancer-cell downregulation of Tap alone in Cohorts #1 (32%), #3 (34%) and #4 (36%); and Tap-CalR in Cohort #2 (29%). Tap and ERp57 levels were significantly higher in stage IV than in earlier stage tumors. The PLC marker levels and the frequency of cancer-cell selective downregulation were comparable across EGFR and KRAS mutated samples. NSCLCs with cancer-cell Tap downregulation had lower CD8+ T-cell infiltration and shorter OS across all cohorts that reached statistical significance in Cohort #4 (median OS 12.08 vs 21.00, HR=1.72, 95% CI 1.02-2.89, $p=0.034$). The cancer-cell selective downregulation of CalR was associated with shorter OS in cohorts #1 and #3. **Conclusions:** HLA class-I PLC components show variable levels in treatment naive NSCLCs. Downregulation of Tap in cancer-cells, alone or in combination with other PLC members occurs in up to 60% of cases and is associated with reduced CD8+ TILs and shorter OS preferentially in patients treated with ICIs. Cancer-cell Tap downregulation could mediate primary ICI resistance and has biomarker potential. Research Sponsor: U.S. National Institutes of Health; ERS, Fulbright, Fondation ARC; Merck.

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Poster Session

Pan-cancer associations of B7-H3 (CD276) transcriptional expression across human malignancies. *First Author: Justin Hwang, University of Minnesota, Minneapolis, MN*

Background: B7-H3 (CD276) is a transmembrane glycoprotein of the B7 superfamily that includes PD-L1 and CTLA-4. B7-H3 targeted therapeutics have demonstrated promising results in both solid tumors and hematologic cancers. To understand the applicability of B7-H3 targeted therapies, we characterized the landscape of clinical outcomes, genomic, transcriptomic, and immunological features associated with B7-H3 mRNA expression in > 93,000 samples across > 45 cancer types from a large real-world clinico-genomics database. **Methods:** DNA (592-gene/whole exome) and RNA (whole transcriptome) sequencing was performed for samples submitted to Caris Life Sciences (Phoenix, AZ). Differential expression of individual genes was analyzed, with pathway enrichment assessed by Gene Set Enrichment Analyses (GSEA). RNA deconvolution was used to estimate immune cell infiltration of tumor microenvironments using quanTseq (Finotello, 2019). Real-world overall survival (OS) was determined from insurance claims data and Kaplan-Meier estimates were calculated. Statistical significance was determined using χ^2 and Mann-Whitney U tests with Benjamini-Hochberg corrections for multiple hypothesis testing where appropriate. **Results:** B7-H3 mRNA displayed robust expression in many prevalent cancer types, including prostate, pancreatic, breast, colorectal, ovarian, and lung cancers (n = 3407, 4624, 8639, 12,862, 8004, and 13,502, respectively). High B7-H3 expression predicted worse OS in ovarian cancer (1.38 HR, 95% CI 1.23-1.53, p < 0.001) and lung adenocarcinoma (1.45 HR, 95% CI 1.34-1.57, p < 0.001), and better OS in prostate (0.84 HR, 95% CI 0.71-0.99, p < 0.05). Notably, high B7-H3 was detected in tumors with known driver mutations (e.g. *EGFR*, *ESR1*, *KRAS*, *SPOP*) or undruggable therapeutic targets (*TP53*, *APC*). When examining Hallmark gene signatures, we found that B7-H3-high samples demonstrated consistent enrichment for pathways involved in epithelial to mesenchymal transition (EMT), WNT, TGF- β , and Notch signaling (FDR < 0.05) across cancer types. Additionally, high B7-H3 expression was correlated with greater proportions of pro-inflammatory M1 macrophages but lower proportions of effector CD8+ T cells and NK cells across multiple cancer types. **Conclusions:** We demonstrate B7-H3 to be a promising pan-tumor target, with most solid tumors showing robust expression which is often associated with worse OS. In several major cancers, high B7-H3 expression was associated with mutational and transcriptomic repertoires not easily targeted by current precision therapies. We find B7-H3-high tumors to have increased potential for myeloid-driven immune induction, making them potentially more amenable to immunomodulatory therapies, in particular, those targeting B7-H3. Further work is warranted to elucidate different mechanistic interactions of B7-H3 with specific oncogenic pathways in each cancer type. Research Sponsor: Prostate Cancer Foundation; Department of Defense.

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Poster Session

Novel STK11 differentiation phenotype classifier STK11-DPC: Immunosuppressive tumor microenvironment (TME) and response to immune checkpoint blockade (ICB) in STK11-deficient NSCLC. *First Author: Jacob Kaufman, The James Cancer Hospital and Solove Research Institute, Columbus, OH*

Background: Loss of STK11 occurs in 20-25% of NSCLC and confers poor prognosis and resistance to ICB. STK11 loss affects lineage plasticity in murine models and differentiation phenotypes in patients. However, interactions between differentiation state, TME, and clinical outcomes are not well characterized. **Methods:** This is a retrospective and descriptive study across eight transcriptomic datasets of 2118 non-squamous NSCLC with 314 STK11 mutations, including 628 patients randomized to docetaxel or atezolizumab in the OAK and POPLAR clinical trials. STK11-DPC applies a validated gene signature to assess functional STK11 loss, then uses a rule-based classifier to define three differentiation lineages: "Neuroendocrine," "TTF1-Low," and "TTF1-Positive." TME is assessed by xCell immune deconvolution, and patient outcomes assessed by Cox proportional hazards regression models. **Results:** STK11-DPC significantly outperforms STK11 mutations in predicting decreased MHC-1, MHC-2, interferon-stimulated genes, and immune infiltration (P < 1e-8 for each). Each of the three differentiation groups has low immune infiltration compared to STK11 WT tumors, but we observe distinctive TME phenotypes corresponding to the Neuroendocrine and TTF1-Low groups. Neuroendocrine tumors have low expression of pro-inflammatory genes in the TNF/NF κ B and JAK/STAT signaling pathways (P < 1e-10), while TTF1-Low tumors show hallmarks of increased inflammation, with higher PMN-MDSC, CD8 and NK signatures, but relative exclusion of dendritic cells (P < 1e-6 for each). These differences persist after controlling for KRAS, KEAP1, and TP53 mutations. Conversely, STK11-deficient tumors in WT-like or TTF1-Positive groups have TME more similar to STK11-WT tumors and show increased immune infiltration. STK11-DPC was prognostic when applied to OAK and POPLAR, with worse OS in Neuroendocrine (HR 1.6, P = 0.006) and TTF1-Low (HR 2.4, P = 5.8e-10) groups. Survival in both arms was equally poor in these groups. In contrast, STK11-deficient tumors with WT-Like or TTF1-Positive phenotypes had better OS with atezolizumab compared to docetaxel (HR 0.5, P = 0.03). **Conclusions:** STK11-DPC is highly predictive of immune exclusion and NSCLC patient outcomes. It identifies STK11-deficient subsets with increased immune infiltration and improved ICB response, and two putatively immune-resistant subgroups with markedly different TME phenotypes: Neuroendocrine tumors have an anti-inflammatory phenotype, while TTF1-Low tumors exhibit chronic inflammation. Performance of STK11-DPC as a predictive biomarker warrants further validation in additional patient cohorts, while the apparent TME differences suggest distinct and non-overlapping mechanisms of ICB resistance and may guide development of precision treatment strategies. Research Sponsor: Lung Cancer Foundation of America.

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Poster Session

Clinical and biological activity of FLX475, an oral CCR4 antagonist, in advanced cancer. *First Author: Dirk G. Brockstedt, RAPT Therapeutics, Inc., South San Francisco, CA*

Background: FLX475 is a potent and selective CCR4 antagonist, designed to block the recruitment of immunosuppressive regulatory T cells (T_{reg}) into tumors without affecting healthy tissues. Blocking migration of T_{reg} into the tumor microenvironment (TME) has the potential to restore antitumor immunity and synergize with a variety of conventional and immunotherapy-based approaches to overcome immune resistance and broaden clinical efficacy. In a recent interim clinical update from the ongoing FLX475-02 Phase 1/2 trial, evidence of monotherapy and combination activity were reported. FLX475 monotherapy induced complete responses in two of the six evaluable subjects enrolled with EBV+ NK/T cell lymphoma. In checkpoint inhibitor naive non-small-cell lung cancer (NSCLC), 4/13 subjects (31%) had confirmed partial responses (PRs) following treatment with the combination of FLX475 and pembrolizumab. In this analysis we present biomarker data from patients with broad range of tumor types treated with FLX475 monotherapy. We provide evidence to substantiate the mechanism of action and support the combination of FLX475 with pembrolizumab. **Methods:** Flow cytometry was used to measure relative proportions of T_{reg} in the periphery. CD8 and FOXP3 positive cells in tumor biopsies were quantified by immunohistochemistry (IHC). Gene set enrichment analysis and immune deconvolution methods were used to interrogate RNAseq data derived from tumor biopsies. **Results:** FLX475 monotherapy results in a small but significant increase in proportion of circulating CD25+CD127-/low CD4+ T_{reg} by day 8 of treatment. IHC analysis revealed a trend towards increased CD8:FOXP3 ratio in the TME of patient biopsies. Transcriptomic profiles from tumor biopsies of FLX475 monotherapy treated patients exhibited significant changes in immune pathways likely to benefit the antitumor response. Using global gene expression analyses we identified that FLX475 monotherapy altered the transcriptome of tumors to resemble those from patients with favorable clinical outcome to anti-PD(L)-1 treatment. Consistent with the proposed mechanism of action, immune deconvolution identified that FLX475-treated patients experienced a decrease in T_{reg} cell populations. **Conclusions:** FLX475 monotherapy results in beneficial changes in the TME consistent with our proposed mechanism of action. FLX475 monotherapy is modifying the tumor microenvironment toward a phenotype associated with response to anti-PD-1/anti-PD-L1. Clinical trial information: NCT03674567. Research Sponsor: RAPT Therapeutics, Inc.

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Poster Session

Tracking plasticity along with proliferation and immune evasion using FOXC1, MKI67 and PDL1 for prediction of therapeutic response and risk for hyperprogressive disease with PD1/PDL1 inhibitors in advanced/metastatic cancers: Pan-tumor validation in clinical trial and real-world cohorts. *First Author: Partha S Ray, Onconostic Technologies, Evanston, IL*

Background: Accurate prediction of therapeutic response (TR) to treatment with immune checkpoint blockade (ICB) as well as any resultant durable clinical benefit in terms of improved progression-free survival (PFS) and overall survival (OS) is not consistently achieved with existing biomarkers like PDL1 or tumor mutational burden (TMB). We hypothesized that a multi-marker predictive biomarker strategy that tracks plasticity using FOXC1 expression, in parallel to tumor proliferation and immune evasion, using expression of MKI67 and PDL1, respectively, may demonstrate superior TR prediction, and also enable accurate prediction of risk for hyperprogressive disease (HPD). **Methods:** Pre-treatment tumor RNA-Seq data obtained from training/validation clinical trial cohorts and real-world patients diagnosed with advanced/metastatic non-small cell lung cancer (NSCLC, n=82/28) and melanoma (n=154/121) were analyzed for FOXC1, MKI67 and PDL1 expression, and correlated with overall response rate (ORR), PFS, OS and HPD, the latter defined as time-to-treatment-failure $\leq$ 2 months post-treatment initiation. Optimized biomarker cutoff values based on model area-under-curve were leave-one-out cross validated and cancer-type specific (CTS) prediction algorithms derived. The unmodified strategy was then validated in the independent, CTS validation datasets. **Results:** ORR prediction accuracy was confirmed in validation datasets with high accuracy: NSCLC AUC=0.96, OR=9.63 (0.98-94.54, 95%CI) p=0.03 and melanoma AUC=0.91, OR=3.85 (1.73-8.58, 95%CI), p=0.0005. Predicted Responders consistently displayed superior PFS and OS compared to predicted Non-Responders: NSCLC PFS HR=0.51 (0.32-0.82, 95%CI) p=0.007, OS HR=0.44 (0.27-0.73, 95%CI) p=0.003; melanoma PFS HR=0.45 (0.30-0.68, 95%CI) p=0.002, OS HR=0.43 (0.26-0.71, 95%CI) p=0.002. Patients at risk for HPD were identified with high accuracy: NSCLC AUC=0.96, OR=9.67 (2.95-31.73) p<0.0001; melanoma AUC=0.98, OR=44.36 (11.73-167.74, 95%CI) p<0.0001. **Conclusions:** Tracking multiple dimensions of cancer biology including plasticity (using FOXC1), as opposed to tracking immune evasion alone, proved to be a superior and accurate pan-cancer, tissue-agnostic predictor of TR to ICB therapy in advanced/metastatic tumors in terms of ORR, PFS, OS as well as HPD risk prediction. This approach merits further testing in prospective clinical trials. Research Sponsor: None.

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Poster Session

Phase I evaluation of PRGN-2009 alone and in combination with bintrafusp alfa in patients (pts) with recurrent/metastatic (R/M) HPV-associated cancers (HPV-C). *First Author: Charalampos S. Floudas, Center for Immunology, CCR, NCI, NIH, Bethesda, MD*

Background: Combinatorial treatments may improve efficacy in checkpoint blockade resistant (CBR) R/M HPV-C. PRGN-2009 is a gorilla adenovirus immunotherapy vaccine containing 35 non-HLA-restricted epitopes of HPV-16 and 18. We conducted a first-in-human Phase I study of PRGN-2009 alone and combined with bintrafusp alfa (BA), a bifunctional TGF- β “trap”/anti-PD-L1 fusion protein in adult pts with pretreated R/M HPV-C. We report safety and efficacy results. **Methods:** Pts received PRGN-2009 1×10^{11} or 5×10^{11} particle units (PU) SC Q2W for 3 times, then Q4W (dose escalation part, DEP) or the recommended phase 2 dose (RP2D) of PRGN-2009 plus BA 1200 mg IV Q2W (combination part, CP) until progressive disease, unacceptable toxicity or patient withdrawal. Primary endpoints were safety and RP2D; secondary endpoints included overall response rate (RECIST 1.1). Exploratory endpoints included the induction of HPV-16/18 specific T-cell responses in peripheral blood mononuclear cells collected pre- and post-PRGN-2009 treatment. **Results:** Between August 11, 2020, and May 5, 2022, 17 pts were enrolled. Median follow-up at data cutoff was 7.4 months and 18.6 months for the DEP and CP, respectively. In the DEP, 6 pts received PRGN-2009, for a median duration of 3.0 months (range 1.8-17.9). Five pts had ≥ 3 prior lines of anticancer therapy. There were no dose limiting toxicities. Adverse events (AE) related to treatment (TRA) were Grade 1-2 flu-like syndrome, injection site reactions, fatigue, rash. 5×10^{11} PU was selected as RP2D. Stable disease was noted in 4 pts, longest duration being 14.9 months. In the CP, 11 high-risk HPV positive pts received PRGN-2009 with BA for a median duration of 10.0 months (range 0.5-23.0). Four pts (36.3%) had received ≥ 3 prior treatment lines; 10 pts (90.9%) were CBR. Grade 3 TRAEs occurred in 1 pt (9.1%); duodenal hemorrhage [DH] attributable to BA; 2 pts (18.1%) had grade 4 TRAEs (DH, pharyngeal mucositis [n=1 each], attributable to BA). Both pts with DH were concurrently receiving NSAIDs. No treatment-related deaths occurred; one pt with DH died after refusing core standard medical management. Of 10 pts evaluable for response one CBR pt had a complete response (duration 15.3 months); partial responses were seen in two pts (one CBR). Overall response rate was 30.0% (95% CI 6.7-65.3%). Two pts were treated beyond progression without delayed response. Median overall survival was 7.4 months (95% CI, 2.9-26.8 months) for DEP and 12.5 months (95% CI, 9.6-inestimable) for CP. Post vaccination 14/16 (88%) pts developed T-cell responses to HPV-16 and/or HPV-18, with 6/6 in DEP and 8/10 in CP. **Conclusions:** PRGN-2009 is safe, well-tolerated, and induces HPV-specific T-cell immune responses. Further, PRGN-2009 combined with BA demonstrated clinical activity in pts with pretreated HPV-associated cancers, naive or resistant to checkpoint blockade. Clinical trial information: NCT04432597. Research Sponsor: U.S. National Institutes of Health; EMD Serono, Precigen Inc.

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Poster Session

Effect of personalized immunization with GNOS-PV02 of patients with hepatocellular carcinoma on TCR clonal expansion, tumor infiltration, and vaccine-specific reactivity. *First Author: Renzo Perales, Geneos Therapeutics, Plymouth Meeting, PA*

Background: Tumor-specific neoantigens can be identified from cancer biopsies and used to develop personalized therapeutic cancer vaccines (PTCV) to prime neoantigen-specific T cell responses. Here, we characterized the antitumor neoantigen-specific reactivity of tumor-infiltrating, high-frequency TCR clones in a patient treated with personalized therapeutic DNA cancer vaccine GNOS-PV02 in the ongoing GT-30 advanced hepatocellular carcinoma single-arm open-label multi-center phase Ib/IIa trial (NCT04251117). **Methods:** Paired blood and tumor biopsy samples from patient #8 enrolled in the GT-30 study were collected before and after treatment with GNOS-PV02 (1mg) + plasmid-encoded IL-12 (0.3mg) + Pembrolizumab (200mg). GNOS-PV02 and IL-12 were administered at Q3W for the first 4 doses, then, at Q9W. Pembrolizumab was administered Q3W. Neoantigen positivity was evaluated by IFN- γ -ELISpot. TCR β sequencing was performed on all 4 samples and single-cell TCR and transcriptome sequencing was performed from T cells isolated from the post-treatment blood sample. After vaccination, three newly identified TCRs in blood and tumor were inserted into a pMXs-IRES-GFP retroviral plasmid vector and used to generate engineered TCR T cells. Engineered T cells were tested against the neoantigens included in PTCV by flow cytometry. **Results:** The treatment resulted in a partial response with a decrease in tumor size of 44% by RECIST 1.1. Five vaccine-encoded responding neoantigens were identified. Differential abundance frame network analysis revealed that 27 of 42 (64.28%) significantly expanded peripheral TCR clones were also found enriched in the tumors post-treatment. Importantly, we observed an increase in cumulative frequency (from 0.4 to 7.7%), and absolute numbers (from 3 to 14) of significantly expanded vaccine-specific TCR clones in the tumor. Increased TCR clonality confirmed a focused tumor repertoire response. Single-cell sequencing data analysis revealed that the 6 most expanded clones in blood were activated CD8+CD69+ T cells (81.82%). Three full TCR sequences from T cell clones newly present in the tumor post-vaccination were selected, synthesized and cloned. TCR-engineered patient-specific T cells showed a dose-dependent CD8+ and CD4+ T cell activation (CD69+) upon stimulation with a pool of epitopes covering all the neoantigens in the patient's PTCV. **Conclusions:** PTCV treatment resulted in neoantigen-specific T cell responses, clonal expansion in the periphery and primary lesion, and tumor infiltration of T cells with an activated phenotype. TCR-engineered high-frequency T cells found in the tumor are reactive to PTCV-encoded neoantigens post-treatment. These results may account for the observed objective decrease in the primary tumor size. Research Sponsor: Geneos Therapeutics.

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Poster Session

Immunogenicity and clinical activity of tipapkinogen sovavivec (TG4001), an HPV-16 cancer vaccine: A randomized phase 2 study in advanced anogenital cancers. *First Author: Christophe Le Tourneau, Institut Curie, Paris, France*

Background: Human papillomavirus 16 (HPV-16) infection is associated with several cancer types with limited treatment options in the locally R/M settings. Furthermore, immune checkpoint inhibitors have limited activity against advanced HPV-cancers. TG4001 is a viral vector vaccine targeting HPV E6 and E7 antigens. We have previously shown in a single-arm, dose finding phase 1 study that TG4001 combined with PD-L1 blockade using avelumab was safe and associated with a response rate of 22%. Herein we report preliminary data on immunogenicity and clinical activity of TG4001 in a randomized phase 2 study comparing TG4001 plus avelumab versus avelumab alone. **Methods:** Eligibility criteria: R/M HPV16+ anogenital cancer including cervical, vulvar, vaginal, penile, and anal cancers; immunotherapy naive and with no more than one prior line of chemotherapy. HPV-16 positivity was required and centrally determined using a PCR based assay. Patients were randomly assigned 1:1 to receive either TG4001 plus avelumab (Vaccine arm) or avelumab alone. Randomization was stratified by tumor type (cervical, anal, genital). TG4001 was administered s.c at 5×10^7 pfu, Q1w for 5 weeks, then Q2w until month 6 followed by Q12w until progressive disease and avelumab i.v at 800 mg Q2w until progressive disease. PBMCs were collected at baseline, day 43 and day 85 to assess T-cell responses against E6 and E7 antigens using ex-vivo IFN γ ELISPOT and immunophenotyping of circulating T cells. Vaccine immune response (IR) was defined as onset of a new T-cell response against either antigen or amplification of a pre-existing response under treatment. Tumor response was assessed using RECIST 1.1. **Results:** 59 pts had been randomized by the time of data cut-off. IR was assessed in 24 pts in the vaccine arm and 16 pts in the avelumab arm. T cells against E6 or E7 antigens at baseline were rare with only 4 pts having a low intensity ELISPOT readout against either target prior to initiation of treatment. 11/24 pts in the vaccine arm had an IR, while none of the patients in the avelumab arm had an IR. Occurrence of IR was detected at day 43 and tended to gain in intensity at D85. In the vaccine arm, IR was associated with tumor response with 3 clinical responders among 11 pts with positive IR versus 1 response observed among the 13 patients without IR. Conversely, only 2 progressive disease pts among 11 positive IR compared favorably to the 6/13 vaccine arm pts with no IR. Remarkably, a complete clinical response was observed in a vaccine treated pt exhibiting the strongest E6 and E7 IR. **Conclusions:** TG4001 can induce a de novo immune response against HPV-16 antigens E6 and E7 in advanced HPV-16 cancers. The data suggest that these IRs are associated with anti-tumor response and that TG4001 vaccination in combination with ICI has the potential to drive clinical benefit in R/M anogenital cancers. Clinical trial information: NCT03260023. Research Sponsor: Transgene SA; Avelumab was provided by the healthcare business of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945), as part of an alliance between the healthcare business of Merck KGaA, Darmstadt, Germany and Pfizer.

ABSTRACT
WITHDRAWN

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Poster Session

Phase 1 dose escalation study of DSP107, a first-in-class CD47 and 4-1BB targeting fusion protein, in combination with atezolizumab in patients with advanced solid tumors. *First Author: Anwaar Saeed, University of Pittsburgh Medical Center, Pittsburgh, PA*

Background: DSP107 is a bi-functional fusion protein composed of sequences from the extracellular domain of SIRP α and 4-1BB ligand (4-1BBL). The SIRP α arm targets CD47 overexpressed on tumor cells, blocking the “don’t eat me” checkpoint and anchoring trimeric 4-1BBL to the tumor, which interacts with 4-1BB expressed on activated immune cells. This results in proliferation and conditional activation of effector cytotoxic T-cells in the tumor microenvironment. Thereby, DSP107 triggers both innate and adaptive immune responses. Phase 1 monotherapy dose escalation data demonstrated an excellent safety profile with no binding to red blood cells and no dose limiting toxicities (DLTs), hematological or hepato-toxicities. Here we describe data from the completed DSP107 plus atezolizumab combination dose escalation portion of study NCT04440735. **Methods:** Adult patients with advanced solid tumors were treated with weekly intravenous DSP107 infusions (1, 3 or 10 mg/kg; N = 6-7 patients/dose cohort) and atezolizumab (1200 mg) Q3W during 3-week treatment cycles. The primary objective was to determine the safety and tolerability of DSP107 in combination with atezolizumab. Restaging imaging was performed every two months and evaluated by RECIST v1.1 criteria. **Results:** In 19 patients, DSP107 with atezolizumab was well tolerated with no DLTs. Grade 1-2 treatment related adverse events (AEs) were observed in 68% of patients (13/19). The most frequent AEs included diarrhea (21%), fatigue (21%), infusion related reaction (IRR; 16%), nausea, decreased appetite, arthralgia, myalgia and Grade 1 anemia (11% each). IRRs were managed during subsequent infusions by reducing the infusion rate and administering IV fluids. Stable disease (SD) as best response was observed in 8/19 (42%) patients with treatment duration currently up to 10.5 months. At the highest dose of DSP107 (10 mg/kg), 3/7 patients had SD (1 microsatellite stable-colorectal cancer (MSS-CRC) patient with KRAS mutation had 16% target lesion shrinkage and no progression for 7 months). An additional 2 patients with advanced MSS-CRC (with BRAF and KRAS mutations, respectively) demonstrated deep and durable responses (-73 and -76% reduction in target lesions) including disappearance of pulmonary and hepatic target lesions in one patient. These patients currently continue to receive treatment after > 8 and > 6 months, respectively. **Conclusions:** DSP107 is a novel, CD47 and 4-1BB targeting fusion protein with a differentiated safety, binding and pharmacodynamic profile compared to other CD47 and 4-1BB targeting agents. These Phase 1 data suggest that the combination of DSP107 with PD(L)1 blockade may have anti-tumor activity in cold tumors such as MSS-CRC. Clinical trial information: NCT04440735. Research Sponsor: KAHN Medical Ltd.

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Poster Session

Using machine learning to characterize lung cancer microenvironment and the development of a model to predict the presence of similar microenvironment in other cancers. *First Author: Ahmad Charifa, Genomic Testing Cooperative, Irvine, CA*

Background: Poor response to immune checkpoint inhibitors (ICI) in colorectal cancer (CRC) is believed to be due to lack of immune suppressive tumor microenvironment (TME). In contrast, lung cancer TME is believed to be significantly more immunologically active and responsible for the relative success of ICI in lung cancer. We evaluated the TME in lung cancer and CRC using 43 immune biomarkers quantified using RNA sequencing and developed a model to classify TME into immunologically active (similar to lung cancer) vs inactive (similar to colorectal). These 43 immune biomarkers included B- and T-cell markers, cytokines and chemokines. **Methods:** RNA was extracted from FFPE samples from 707 patients with lung cancer, 227 patients with CRC, 131 patients with breast cancer, 111 patients with ovarian cancer, and 72 patients with pancreatic cancer. The expression levels of the 42 immunological markers were quantified using next generation sequencing (NGS) as a part of larger targeted RNA sequencing panel of 1408 genes. Using a machine learning algorithm, we first selected the relative genes that distinguish between two classes using two criteria: performance of each gene with K-fold cross-validation (K=12) and second based on stability measure using statistical significance tests. The selected genes were then used to predict one class from the other using random forest classifier. Samples were divided into a training set (67%) and testing set (33%). **Results:** A Bayesian-based algorithm selected the expression of 20 genes that were significantly relevant in differentiating between immunologically active and inactive TME. Using these 20 genes in Random Forest model, we can distinguish between lung and CRC with AUC of 0.997 (95% CI: 0.992-1.00) in the training set and AUC of 0.923 (95% CI: 0.880-0.966) in the testing set. Testing 131 breast cancer samples showed 23 (18%) with TME that can be classified as immunologically active. Of 111 ovarian samples 13 (12%) showed immunologically active TME and of 72 pancreatic samples, 17 (24%) showed microenvironment classified as active. The 20 genes that were adequate to distinguish between TME active vs inactive are: CD74, FCGBP, IL1R1, CD44, CD274, FCGR2B, IL21R, IL1RAP, IL7R, CD79A, CCL2, CYFIP2, CD19, IL2RA, CD8A, CD79B, ID1, CD22, FZD10, and IL1B, listed in order of their importance. **Conclusions:** This data shows that lung cancer TME is significantly different from that of CRC. Only 20 immune biomarkers adequate to distinguish between the two TME. The relevant biomarkers included CD274 (PD-L1) as well as one marker for T-cells (CD8A) but three markers for B-cells (CD19, CD22 and CD79B). This suggests that B-cells play a significant role in immunologically active TME and should be explored further as biomarkers for predicting response to ICI therapy. Research Sponsor: Genomic Testing Cooperative.

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Poster Session

A phase I study of nelmastobart (hSTC810), an anti-BTN1A1 antibody, in patients with advanced solid tumors. *First Author: Soohyeon Lee, Korea University Anam Hospital, Seoul, South Korea*

Background: Butyrophilin 1A1 (BTN1A1) is a novel immune checkpoint that is primarily expressed by tumor cells in a manner that is mutually exclusive with PD-(L)1. BTN1A1 can potentially be targeted to extend new immunotherapeutic treatment options to patients (pts) whose tumors are unresponsive to anti-PD-(L)1 therapy. This phase I study describes the safety and clinical activity of Nelmastobart (hSTC810), a humanized monoclonal antibody targeting BTN1A1, in pts with advanced solid tumors. **Methods:** Nelmastobart was administered intravenously every 2 weeks across 6 dose levels from 0.3 mg/kg to 15 mg/kg. The primary objectives were to determine the safety profile and maximum tolerated dose (MTD) and/or recommended phase 2 dose (RP2D). Using a 3+3 design, dose-escalation cohorts were evaluated for dose-limiting toxicities (DLT) during the first 2 cycles. Backfill cohorts were allowed once a dose was deemed safe. Response was assessed using RECIST 1.1 every 4 cycles (8 weeks). Pts were treated until disease progression or unacceptable toxicity. **Results:** As of January 30, 2023, enrollment in the dose-escalation cohorts is complete. A total of 39 pts with colon (n=14), lung (NSCLC n=3; SCLC n=2), urothelial (n=3), breast, cholangiocarcinoma, melanoma, ovarian, pancreatic (n=2) each, adrenocortical, anal, esophageal, H&N, PEComa, skin, and thymic (n=1) cancers each were treated in the dose-escalation and backfill cohorts. Median duration of therapy for all pts was 8 weeks (maximum 29 weeks). Most common treatment related adverse events (TRAEs) reported were grade 1-2 fatigue (6%), headache (5.9%), and nausea (4.4%); furthermore, there were no TRAEs $\geq$ 3. No pts was discontinued or required dose reduction due to TRAEs. There were no DLTs across all dose levels and the MTD was not reached. In evaluable pts, one confirmed partial response was observed in MSI-H colon cancer (3 mg/kg) and 13 pts (colon, H&N, lung, melanoma, ovarian, thymic carcinoma) had a best response of stable disease (SD) across multiple dose levels. Median duration of PR/SD pts on study was 17.5 weeks. Interim pharmacokinetics (PK) analysis demonstrated consistent exposure with linear PK. Pharmacodynamic analysis measuring cytokines and cell-based markers is pending and will be presented. Based on the safety, efficacy, and PK, we recommend 15 mg/kg Q2W as the RP2D. **Conclusions:** Nelmastobart is well-tolerated without DLTs up to the final dose of 15 mg/kg. Current data show evidence of anti-tumor activity and durable SD. Clinical development planning for a phase Ib/II clinical trial is underway to further characterize the therapeutic dose and efficacy in select solid tumors. Clinical trial information: NCT05231746. Research Sponsor: STCube, Inc.

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Poster Session

Multisystem immune-related adverse events from dual agent immunotherapy use. *First Author: Yuchen Li, Department of Oncology, Juravinski Cancer Centre, Hamilton, Ontario, Hamilton, ON, Canada*

Background: Immune-related adverse events (irAEs) are commonly seen in cancer patients who undergo immunotherapy treatment. Increasingly, there has been recognition that multiple different irAEs can occur during or/and after a single course of immunotherapy treatment, known as multisystem irAEs, though much remains unknown. The primary objective of this study was to assess for rate of multisystem irAEs in patients who received dual agent ipilimumab and nivolumab for cancer treatment. **Methods:** A retrospective cohort review was completed that included all cancer patients seen at Juravinski Cancer Centre who received at least one dose of ipilimumab and nivolumab from January 1, 2018 to May 31, 2022. Patient characteristics, cancer types, and number and types of irAEs were recorded. Multivariate logistic regressions were also completed comparing those who developed multisystem irAEs, single irAE, and no irAE. **Results:** A total of 123 patients were included in this study. Median age was 59 years old, with 69% male. 72 out of 123 patients (59%) had melanoma, 50/123 (41%) had renal cell carcinoma (RCC), and 1/123 (1%) had breast cancer. At least one irAE was seen in 72% of patients who were treated with ipilimumab and nivolumab, and most irAEs occurred during the combination phase (89% of first irAE, 59% of second irAE, 75% of third irAE, and 50% of fourth irAE). Multisystem irAEs were seen in 40% of the overall cohort. The most common irAE type was dermatitis (22%), followed by colitis (19%), hepatitis (17%), and thyroiditis (15%). 30 out of 89 patients (34%) who experienced irAE(s) required hospital admission for inpatient treatment of irAE(s). Patients who experienced multisystem irAEs had significantly higher rates of response to immunotherapy irAE ($p < 0.001$) and improved overall survival (OS) than those who experienced single or no irAE. **Conclusions:** From our single-centre cohort study, there appeared to be a higher than previously quoted number of patients who experienced irAEs after receiving ipilimumab and nivolumab, with majority of them developing multisystem irAEs. Many patients experienced debilitating associated symptoms and hospital admission relating to irAEs. It is important for both the counselling and consent of patients, and for patient education, to discuss the possibility of multiple irAEs prior to dual immunotherapy initiation. Research Sponsor: None.

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Poster Session

Cardiotoxicity surveillance among patients with cancer treated with immunotherapy. *First Author: Juliana Goes Martins Fagundes, Oncoclinicas Paraiba (Centro Paraibano de Oncologia), Joao Pessoa, Brazil*

Background: With the advancements of immunotherapy procedures and, more specifically, immunological checkpoint inhibitors (ICIs), the scenario of cancer treatment, whether in its early or advanced stages, have changed. With the expansion of ICIs usage, cardiovascular toxicities have been reported, but more robust data are needed to guide the follow-up of patients and toxicity prevention. **Methods:** This research is a single-centered, prospective observational cohort study that evaluated patients treated with ICIs regardless of indication, with or without chemotherapy combination. Patients underwent echocardiography evaluation with global longitudinal strain (GLS) and myocardial work, electrocardiogram, and collection of biomarkers before the start of treatment, in the second month after treatment started, and every 3 months, subsequently. Evaluations stopped once treatment completed one year, or the medication was discontinued either due to toxicity or disease progression. Cardiotoxicity (CT) was defined by $\geq 10\%$ reduction in left ventricular ejection fraction (LVEF) by less than 50%, troponin elevation by ≥ 0.30 ng/ml, or reduction in relative GLS by $\geq 15\%$. Frequencies were compared using Fisher's comparative test, as appropriate, and Mann-Whitney test for numerical variables. Statistical significance will be considered as $p < 0.05$ for two-tailed tests. **Results:** Out of the 98 patients scheduled for treatment, 39 patients underwent at least 2 evaluations and had their exams analyzed. There was a 26% incidence of overall CT, with half of these patients by LVEF reduction criteria and, considering only patients with lung cancer, there was an incidence of 35% with CT. Dividing the total sample into CT and non-CT groups, a higher number of men, smokers and patients with lung cancer was observed, as well as a lower LVEF baseline (67% vs 62.50, $p = 0.014$) in the CT group. Concomitant chemotherapy or higher baseline coronary calcium scores did not appear to increase the risk of CT among patients, but the use of beta-blockers was restricted to patients who did not develop an event. There was a reduction in myocardial work parameters in the 2nd month assessment: global index (GWI) 1833 vs 2334, $p = 0.006$, constructive work (GCW) 2299 vs 2683, $p = 0.040$, and work efficiency (GWE) 83 vs 95, $p = 0.025$ and tendency towards increased myocardial work loss (GWW) 286 vs 116, $p = 0.064$, in the comparison between groups. Those who met CT criteria had a longer overall survival, as did those who developed other immune-mediated adverse events and metformin users. **Conclusions:** This was the first study that carried out cardiotoxicity surveillance in patients undergoing immunotherapy, with a surprising finding of events in a small but high-risk sample. The development of immune-mediated toxicities seems to be related with therapeutic response. Also, the use of metformin seems to contribute to this response, as already demonstrated in preclinical studies. Research Sponsor: None.

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Poster Session

Comparing the impact of steroid sparing immunosuppression vs. steroid monotherapy for immune-related adverse events in non-small cell lung cancer and melanoma. *First Author: Sharjeel Syed, University of Chicago Medical Center, Department of Medicine, Chicago, IL*

Background: The effect of steroid-sparing immunosuppressive agents (SSiAs) for immune-related adverse events (irAEs) on immune checkpoint inhibitor (ICI) antitumor activity is not well-known. We compared tumor outcomes of patients who received corticosteroid monotherapy versus those who received an addition of SSiA for irAE treatment. **Methods:** We conducted a retrospective case-control study of patients age ≥ 18 years with melanoma or non-small cell lung cancer (NSCLC) who were treated with ≥ 1 ICI at a quaternary care center between 1/1/2016-11/1/2021. Patients must have received systemic corticosteroids or an SSiA for irAE treatment at least 1 week prior to death. Patients were divided into two cohorts: only corticosteroids (CS cohort) or steroids+SSiA (SSiA cohort). We used propensity score nearest-neighbor matching to match on tumor type, stage, and prior lines of therapy. Primary outcomes were progression-free survival (PFS) and overall survival (OS). Secondary outcomes included time from start of irAE treatment to irAE resolution. Hazard ratios (HR) for PFS and OS were calculated using the Cox proportional hazard regression method with time to steroid and SSiA as a time-varying covariate. **Results:** After matching, 48 patients were included, 24 in each cohort. Median age was 65. 41.7% of patients had NSCLC and 58.3% melanoma, 79.2% had stage 4 disease. 62.5% received ICIs as first line therapy, 33.3% as second-line, and 4.2% as third-line or higher. There was no significant demographic difference between the cohorts. Colitis was the most common irAE (39.6%). After adjusting for age, tumor type, tumor stage, and weeks from ICI start to steroid start, patients in the SSiA cohort had a shorter OS (HR 2.31, $p = 0.037$). We did not find a statistically significant difference for PFS (unadjusted HR 0.52, $p = 0.20$; adjusted HR 0.62, $p = 0.34$). Time from irAE treatment to resolution was longer in the SSiA cohort (8.1 weeks) compared to the CS cohort (4.9 weeks), but this did not reach statistical significance ($p = 0.07$). **Conclusions:** We found an association between decreased OS and use of SSiAs for irAE treatment compared to CS monotherapy, but no significant difference in PFS between the two cohorts. Large, prospective, randomized controlled trials are needed to separate the effects of SSiAs from high-dose CS in order to guide optimal treatment of irAEs. Research Sponsor: University of Chicago Institute of Translational Medicine Clinical and Translational Science Award K12/KL2 Grant 5K12TR002387-05; COVID-19 Funds to Retain Clinical Scientists by the SECURED (Supporting Early Career University Researchers to Excel through Disruptions) Steering Committee.

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Poster Session

A phase II randomized trial of talimogene laherparepvec (T-VEC) oncolytic immunotherapy with or without radiotherapy for patients with cutaneous metastases from solid tumors. *First Author: Christopher A. Barker, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Talimogene laherparepvec (T-VEC) is an oncolytic immunotherapy made from a modified herpes virus expressing granulocyte-macrophage colony-stimulating factor and is FDA approved for the treatment of advanced melanoma. Laboratory studies suggest radiotherapy (RT) may interact with oncolytic immunotherapy to facilitate an immune-mediated anticancer response. We hypothesized that the combination of T-VEC+RT would produce tumor responses in distant (non-irradiated and non-injected) metastases. **Methods:** A prospective phase II, randomized, Simon two-stage clinical trial of T-VEC with or without RT was conducted with the primary objective of determining if the response rate of the largest non-injected and non-irradiated metastasis was $\geq 27\%$. Eligible patients had ≥ 1 cutaneous metastasis from a solid tumor amenable to T-VEC and RT and 1 measurable metastasis that would not be treated with T-VEC or RT. Using type I and II error probabilities of 10% and 20%, it was calculated that 9 patients would be enrolled in each arm, and if at least 1 of 9 patients subjects exhibited a response, then 6 additional patients would be enrolled in the second stage. Tumor and overall response was assessed using modified World Health Organization (mWHO) and immune related response criteria (irRC). Treatment-emergent and treatment-related adverse events (TEAEs and TRAEs) were characterized using CTCAE v4.0. **Results:** 19 patients were enrolled and randomized to receive T-VEC alone (n=9) or T-VEC+RT (n=10). One patient in each arm demonstrated a complete response in the largest non-irradiated and non-injected metastasis but progressed in new metastases. The composite response rate in target tumors not injected or irradiated was 13% and 0% in the T-VEC alone and T-VEC+RT arms, respectively. The composite response rate in target tumors treated with T-VEC alone or T-VEC+RT was 7% and 22%, respectively. Because no patient exhibited an overall mWHO or irRC defined response and due to slow accrual, the trial was closed after the first stage of enrollment despite meeting the prespecified response rate to continue enrollment in the second stage. Grade 3-4 TEAEs and TRAEs occurred in 9 and 2 patients, with similar frequencies between study arms. The most common AE was fever and occurred in 47% of patients. Peripheral blood-based immunologic analyses will be presented. **Conclusions:** The response rate in the largest non-injected or non-irradiated metastasis following T-VEC with or without RT given to a cutaneous metastasis from solid tumor could be $\geq 27\%$ but was not determined in this trial due to premature closure, in part due to slow accrual rate and no observed mWHO defined overall responses. Cutaneous metastases responded more often after TVEC+RT than T-VEC alone, but the response in non-injected and non-irradiated tumors was more frequent after T-VEC alone. Clinical trial information: NCT02819843. Research Sponsor: Amgen.

ABSTRACT
WITHDRAWN

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Poster Session

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Poster Session

A phase I/IIa study to assess the safety, tolerability, PK, and PD of T3011, a genetically modified oncolytic virus (OVs) administered intravenously (IV) in patients with advanced solid tumors. *First Author: Ziming Li, Lung Cancer Center, Shanghai Chest Hospital, Shanghai JiaoTong University, Shanghai, China*

Background: T3011 is a genetically modified, next-generation oncolytic HSV-1 with 2 exogenous genes encoding the active heterodimer human IL-12 and the Fab fragment of an anti-human PD-1 antibody. T3011 intratumoral injection (IT) was reported to be well tolerated in patients (pts). IV therapy of OVs is rare and provides an attractive option to many pts with advanced cancers that are not candidates for IT therapy. **Methods:** It is a phase I/IIa multi-center, open label, single ascending dose (SAD)/multiple ascending dose (MAD) study to evaluate T3011 IV therapy. The primary objective is to evaluate the safety and tolerability. Dose cohort and regimen are shown in Table. PK and PD profiles are tested in samples of blood, saliva, urine, and tumor tissue. **Results:** As of 16 Dec 2022, 15 pts with stage IV disease were enrolled, 9 pts had received at least 3 lines of prior therapy. The median follow-up time is 1.58 months. Treatment-emergent adverse event (TEAE) occurred in 15 (100%) pts and treatment-related adverse event (TRAЕ) occurred in 10 (66.7%) pts. G3 TEAE in 3 (20%) pts (hypertriglyceridemia, dyspnea, lymphopenia) and G3 TRAЕ in 1 (6.7%) pt (lymphopenia), no ≥ G4 AE reported. Dyspnea, the only reported SAE (1, 6.7%), is drug-unrelated. TRAЕs were lymphopenia (5, 33.3%), anemia (1, 6.7%), diarrhea (1, 6.7%), malaise (1, 6.7%), urticaria (1, 6.7%), rash (1, 6.7%), constipation (1, 6.7%), flu like symptoms (1, 6.7%), headache (1, 6.7%) and abnormal laboratory test results (incidence were all 6.7%), most of them are mild and manageable. No AEs led to drug withdrawal. No DLT occurred; MTD was not reached. 11/15 pts achieved stable disease (SD) by RECIST v1.1. DCR was 73.3%. 1 pt with colorectal cancer who experienced irinotecan-based chemotherapy, anti-VEGF and radiotherapy in Cohort 1 had a long-term SD for over 4 months. In SAD part, T3011 DNA in blood at 2 hours post-dose was detected in 0% (0/3), 0% (0/4), 66.7% (2/3) and 100% (2/2) pts in Cohort 1, 2, 3 and 4 respectively. The DNA copies in pts of Cohort 4 are significantly higher than those of Cohort 3 (Mean viral DNA copies/ul 49.6 vs. 5.7). In cohort 2 of MAD part, T3011 DNA in blood at 2 hours post-dose was detected in 0% (0/3), 66.7% (2/3) and 100% (3/3) pts at C1D1, C1D4 and C1D8 respectively. T3011 DNA was not detected in saliva or urine samples. Pre-existing HSV-1 IgG was shown to hardly affect T3011 activity. **Conclusions:** T3011 IV is safe and well tolerated, and unlikely to spread to close contacts. Preliminary efficacy is encouraging. T3011 DNA in blood is in a dose-dependent manner with additive effect from repeated doses supporting continued recruitment of pts to higher dose cohorts. Clinical trial information: NCT05598268. Research Sponsor: ImmVira Co., Limited.

	Cohort 1 1 × 10 ⁶ PFU	Cohort 2 1 × 10 ⁶ PFU	Cohort 3 1 × 10 ⁶ PFU	Cohort 4 3 × 10 ⁶ PFU
Pts (n)				
SAD	3	4	3	2
D1 of each 21-day cycle)				
MAD	1	4	recruiting	recruiting
(D1,4,8 of each 21-day cycle)	(1 crossed over from SAD)	(1 crossed over from SAD)		

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Poster Session

The study of immune-related adverse events in a community-based centre. *First Author: Sandhya Cautha, Bronxcare Health System, Bronx, NY*

Background: The effectiveness of immunotherapy is often hindered by the development of immune-related adverse events (irAE). Racial minorities were under-represented in the key clinical trials that led to the approval of different immune checkpoint inhibitors (ICI). In this study, we explore the side effect profile of immune checkpoint inhibitors in our patient population that comprises almost entirely of minorities, mostly African Americans (AA) and Hispanics. We hypothesize that due to race-based differences in immune milieu of the body and disease susceptibility, the timing and severity of immunotherapy-related irAE would be different in AA and Hispanics compared to Caucasians. This can translate into a difference in clinical outcomes as well. There have been some suggestions of a positive association of the development of irAE with cancer survival, although the data is limited and heterogeneous. The purpose of our study is to study the frequency and severity of irAEs in racial minority groups, compare them with previous clinical trials population, and add valuable real-world data in this underrepresented group of patients. **Methods:** A retrospective chart review was performed on adult patients with solid malignancies treated with any ICI between January 1, 2015 and April 30, 2022. Patients were classified according to age (greater/equal to 65y or younger), sex, race (self-identified), primary cancer, and type of immunotherapy received. Outcome data using type and severity of irAE, time to development of irAE, and any association with clinical outcomes was collected and analyzed using descriptive statistics as well as univariate analysis. **Results:** A total of 78 patients were included in the final analysis. The mean age was 68 years; 51% were males; 42.3% were Hispanics, 37% were AA, 19.7% were others, and 1% were Whites. Most common malignancy was lung cancer (65.5%). Most common ICI agent used was Pembrolizumab (n = 52) and 2 patients were treated with combination therapy using Ipilimumab and Nivolumab. 41 (52.5%) patients had irAE of any grade while 9 (11.5%) patients experienced grade 3 side effects. None of the patients experienced grade 4 side effects. Most common irAE of any grade was hypothyroidism (n = 14) while most common grade 3 side effect was colitis (n = 6). 31 patients were less than 65y of age. There was no significant difference in irAE in patients less than 65 years of age vs ≥ 65 years (51.6% vs 53.1%) or grade 3 irAE (9.6% vs 12.7%). **Conclusions:** In our study population consisting mostly of AA and Hispanics, the rate of irAE of any grade as well as grade 3 or 4 irAE with ICI therapy was comparable to what was seen in clinical trials involving these drugs. This data and its potential effects on survival outcomes need to be analyzed in prospective studies involving a larger number of patients. Research Sponsor: None.

The incidence of thyroid-related adverse events in solid tumors receiving immune checkpoint blockade with curative intent: A meta-analysis. *First Author: Susu Zhou, Department of Medicine, Icahn School of Medicine at Mount Sinai, Mount Sinai Beth Israel., New York, NY*

Background: Adjuvant/neoadjuvant treatments with immune checkpoint blockade (ICB) improve survival outcomes in patients with several types of cancer. However, immune-related adverse events (irAEs) which frequently involve the thyroid gland may lead to delays in curative treatments such as surgery and radiotherapy. Thus, it is essential to report the incidence of thyroid-related adverse events (AEs) associated with the addition of ICB to conventional therapy with curative intent through a meta-analysis of randomized controls trials (RCTs). **Methods:** We performed a systematic search of PubMed, Embase, Web of Science, and Cochrane library for RCTs evaluating ICB-containing treatment of solid tumors with curative intent. We calculated the odds ratio (OR) of all-grade and grade 3-5 thyroid-related AEs including thyroiditis, hyperthyroidism, and hypothyroidism. We performed a meta-analysis using the random-effect model to compare the incidence of thyroid-related AEs in patients who received therapy with and without the addition of ICB. Subgroup analysis based on the type of ICB (anti-PD-1, anti-PD-L1, and anti-CTLA-4) was conducted. **Results:** 24 RCTs comprising 12,199 patients were analyzed. The addition of ICB was associated with higher incidence of all-grade thyroiditis (OR=3.53, 95%CI:1.88-6.64, p<0.0001), hyperthyroidism (OR=7.18, 95%CI:4.30-12.01, p<0.00001), and hypothyroidism (OR=5.39, 95%CI:3.68-7.90, p<0.00001). In subgroup analysis, PD-1 and PD-L1 inhibitors were particularly associated with higher incidence of hyperthyroidism and hypothyroidism. The incidence of grade 3-5 thyroid-related AEs in patients who received therapy with the addition of ICB was 0.13% (thyroiditis, N=4/3135), 0.20% (hyperthyroidism, N=12/5877), and 0.19% (hypothyroidism, N=12/6369). **Conclusions:** The addition of ICB to conventional therapy with curative intent was associated with an increased risk of all-grade thyroid-related AEs, but the incidence of grade 3-5 AEs was low. These results suggest ICB may be added safely as an adjunct to curative treatments such as surgery and radiotherapy. Clinicians should monitor patients' thyroid function and maintain vigilance for symptoms and signs of thyroid disease. OR (95% CI) and number of studies (N) for thyroid-related AEs with subgroup analysis. Research Sponsor: None.

		All		Anti-CTLA-4		Anti-PD-1		Anti-PD-L1	
		OR	N	OR	N	OR	N	OR	N
Thyroiditis	All	3.53 (1.88-6.64)	8	9.87 (0.52-187.9)	1	3.23 (1.64-6.35)	5	5.13 (0.60-44.2)	2
	G3-5	3.57 (0.42-30.6)	2		0	3.57 (0.42-30.6)	2	-	0
Hyperthyroidism	All	7.18 (4.30-12.0)	22	1.99 (0.54-7.33)	4	11.2 (5.89-21.3)	10	6.25 (2.69-14.5)	8
	G3-5	3.93 (1.21-12.8)	7	6.29 (0.70-56.7)	2	2.83 (0.46-17.4)	3	3.97 (0.44-36.0)	2
Hypothyroidism	All	5.39 (3.68-7.90)	24	1.70 (0.51-5.68)	6	5.72 (4.21-7.77)	10	8.02 (3.11-20.7)	8
	G3-5	3.63 (1.18-11.1)	7	3.03 (0.12-74.5)	1	4.30 (0.90-20.6)	4	3.03 (0.48-19.3)	2

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Poster Session

Association between physical activity, immune-related adverse events, and mortality in patients undergoing immune checkpoint inhibition. *First Author: Rik Jasper Verheijden, University Medical Center Utrecht, Utrecht, Netherlands*

Background: Immune checkpoint inhibitors (ICIs) have improved prospects for some, but not all patients with cancer and frequently induce severe immune-related adverse events (irAEs). While physical activity (PA) has been associated with prolonged survival and diminished toxicity of chemotherapy, its association with ICI efficacy and toxicity is currently unknown. Hence, here we study the association between PA in patients undergoing ICI, and survival and severe irAE occurrence. **Methods:** Patients with advanced cancer receiving anti-PD-L1 based immunotherapy at our academic center were enrolled in the UNICIT cohort. All participants who completed the PA questionnaire (SQUASH) at ICI initiation between 10-2019 and 01-2022 were included in this study. PA was quantified by calculating Metabolic Equivalent Task (MET) hours per week and moderate to vigorous sport and leisure time activity. Association of PA with overall survival (OS) was assessed using Cox proportional hazard regression. Association of PA with occurrence of a severe irAE (grade 3 or higher) within one year was assessed using logistic regression in patients with at least one year follow-up. All analyses were adjusted for sex, age, tumor type, treatment intent and ICI type. **Results:** In total, 251 patients were included, with a median follow-up of 20 months and a median age of 64 years. The majority (153 patients) had melanoma. Median OS was not reached. Compared to low levels of total PA, intermediate and high levels of total MET-hours were associated with prolonged survival (adjusted hazard ratios: 0.56 (95%CI 0.31-1.02) and 0.47 (95%CI 0.26-0.86), respectively; table). Thirty eight out of 209 patients with at least one year of follow-up developed severe irAEs within the first year. Compared to patients with low total PA levels, patients with intermediate or high levels of total PA have a lower odds of developing severe irAEs (adjusted odds ratios: 0.35 (95%CI 0.12-0.90) and 0.19 (95%CI 0.06-0.56), respectively). Similar trends of prolonged OS and reduced odds of severe irAE occurrence were observed in patients who performed more moderate to vigorous sport and leisure time activity. **Conclusions:** Higher physical activity levels at start of ICI treatment are associated with prolonged survival and lower risk of severe irAEs. Future research needs to elucidate whether inactive patients benefit from increasing PA levels after diagnosis. Research Sponsor: None.

Total physical activity (MET hours/week)	HR _{adj} (95%CI) of death	OR _{adj} (95%CI) of severe irAE
Low [0 to 51]	ref	ref
Intermediate (51 to 101]	0.56 (0.31-1.02)	0.35 (0.12-0.90)
High (101 to 371]	0.47 (0.26-0.86)	0.19 (0.06-0.56)
Moderate to vigorous sport and leisure time (hours/week)	HR _{adj} (95%CI) of death	OR _{adj} (95%CI) of severe irAE
Low [0 to 1.5]	ref	ref
Intermediate (1.5 to 6.5]	0.69 (0.40-1.20)	0.41 (0.15-1.03)
High (6.5 to 38.5]	0.57 (0.30-1.09)	0.11 (0.03-0.36)

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Poster Session

Development of a novel immune-related toxicity grading system for predicting outcomes in patients with solid tumours treated with immune checkpoint inhibitors (ICI). *First Author: Matthaios Kapiris, King's College London, London, United Kingdom*

Background: Adoption of ICI in clinical practice has led to improved outcomes in many tumour types. Their use is associated with immune related adverse events (irAEs), with unpredictable onset targeting multiple organs and for which conventional CTCAE toxicity grading has significant limitations. In addition, the correlation of irAEs to efficacy of ICI is becoming increasingly recognised. Here we present a novel toxicity assessment tool and describe its relationship with cancer outcomes. **Methods:** Data were collected from the Pathobiology of Adverse Immune Reactions (PAIR) prospective cohort study at Guy's Hospital from February 2018 until end of May 2022. Solid tumour patients with advanced disease naïve to ICI who received at least 1 dose were included. Minimum 6 months of follow-up was required. irAEs were captured based on the OST score which evaluates the number of affected Organs (O), number of Severe CTCAE (G3) toxicities (S) and sum of all grade Toxicities (T). OST was calculated at death or end of follow-up. Patients were divided in high and low toxicity groups, defined by the median value for each parameter. Descriptive statistics and crude and multivariate survival Cox Proportional Hazards regression analyses were performed accounting for age, tumour type and treatment. **Results:** A total of 123 patients were included. Median age was 68 years (range 23-87 yrs); 67 (54%) were male; 104 (85%) were White Caucasian. Most common tumour types were melanoma (33%), non-small cell lung (24%) and renal cell carcinoma (22%). Forty-six patients (37%) received Ipilimumab-Nivolumab, 37 (30%) Pembrolizumab and 24 (20%) Nivolumab. Twenty-two (18%) had autoimmune disease at baseline. Hypothyroidism (6%) and psoriasis (2%) were most common. Median number of affected organs was 2 (range 0-7), 32 (26%) had ≥ 1 G3 toxicity and the median T score was 3 (range 0-15). Survival data were available for 120 patients. After median follow-up of 39 months, 66 deaths (53.7%) occurred. Median OS was 16.9 months (95% CI: 9.9-24.1). High toxicity groups presented reduced risk of death compared to low-toxicity groups when evaluated for individual OST parameters [HR for Organ tox group (95% CI): 0.359 (0.198-0.649), HR for Severity group (95% CI): 0.402 (0.200-0.808), HR for Toxicity score group (95% CI): 0.353 (0.190-0.657)]. Of the three parameters, the number of Organs (O) was most strongly associated with reduced risk of death when analysed as a continuous variable [HR (95% CI): 0.683 (0.577-0.808)]. **Conclusions:** We have developed a novel immune toxicity grading system which can potentially predict survival outcomes for patients treated with ICI. Further prospective evaluation and correlation to translational secondary endpoints with immunological phenotyping is ongoing. External validation is warranted to support further use of OST in routine clinical practice. Research Sponsor: Biomedical Research Centre at Guy's and St Thomas' NHS Foundation Trust and King's College London.

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Poster Session

Sex differences in burden of adverse events in patients receiving immunotherapy. *First Author: Rosalba Miceli, Unit of Biostatistics for Clinical Research, Department of Epidemiology and Data Science, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy*

Background: The association between sex and the occurrence of immune-related adverse events (irAEs) in cancer patients who receive immune checkpoint inhibitors (ICIs) is an area of growing interest. Despite the collection of irAEs data in registration studies, the impact of sex differentiation is rarely published, and comparative analyses using meta-analytic approaches of retrospective data has produced contrasting results. G-DEFINER is a multicentre project evaluating the irAEs inequalities between female (F) and male (M) cancer patients treated with ICIs. The project explored the sex and gender differences spanning from clinical to personal and lifestyle traits (including diet and quality of life). Gene-expression profiling for immune assessment, SNPs, cytokines (blood samples) and microbiota analyses (faecal samples) are also being performed to identify the features associated with irAEs development. **Methods:** irAE burden (B) was estimated as the sum of the average and worst grade of irAEs occurring at each time. The cumulative sum of time-specific Bs was used as irAE burden index (BI). Median BI (mBI) was modelled using quantile regression models. A univariable analysis (UA), 1st G ≥ 2 irAE crude incidence curves (CCI) were estimated in a competing risks setting (competing event: deaths without irAE), and event-free survival (EFS) curves were estimated with the Kaplan-Meier method and compared with the log-rank test. Multivariable analysis (MA) of CCI and EFS was performed using Fine&Gray and Cox models, respectively. **Results:** At closing date (31st January 2023) the study has enrolled 256 patients. Our subgroup analysis includes 204 patients (86 F, 118 M) with median follow-up of 13 months; IQR: 6.1-20 months). Patients' age, previous oncologic treatments, cancer type (lung, melanoma, head&neck, colorectal MSI high, urogenital), PS ECOG, ICI type, concomitant chemotherapy (about 20%), and disease setting were well balanced in the two sex groups. F temporarily interrupted ICI administration more frequently than M (44 vs 29%, $p=0.034$) mainly due to irAEs (27 vs 11%); 83% F vs 71% M ($p=0.069$) contributed with 204 vs 240 any grade irAEs (significant differences: 36 vs 21% endocrine, $p=0.016$; 20% vs 9% hepatic, $p=0.040$). F more frequently developed G1 (64 vs 53%), G2 (49 vs 40%), G3 (24 vs 17%), G4 (6% vs 2%) irAEs. mBI was significantly higher in F both at UA ($p=0.024$) and MA ($p=0.048$). First G ≥ 2 irAE6- (12) month estimates in F vs M were 55% vs 45% (65% vs 53%) ($p=0.073$ UA and 0.140 MA). EFS between group difference was not significant both at UA ($p=0.206$) and MA ($p=0.729$). **Conclusions:** F experience a higher irAE burden and require close monitoring in order to avoid ICI interruption. The results also underline the need of using a measure of irAE cumulative load to gain insights into between groups differences. Clinical trial information: NCT04435964. Research Sponsor: European Union's Horizon 2020 research and innovation programme under grant agreement No 741874.

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Poster Session

Effect of fecal transplantation on patients' reported outcome after immune checkpoint inhibitor colitis. *First Author: Yinghong Wang, MD Anderson Cancer Center, Houston, TX*

Background: The use of fecal microbiota transplantation (FMT) has traditionally been reserved for the treatment of recurrent *Clostridioides difficile* infections (CDI). As the gut microbiome has been increasingly acknowledged to play a role in a variety of bodily processes, FMT has seen its application extended to other gastrointestinal disorders. Immune-mediated colitis (IMC) is a similar entity to inflammatory bowel disease and arises as a side effect of immune checkpoint inhibitor therapy to stimulate the immune response. Treatment of IMC is mostly limited to immunosuppressants e.g. corticosteroids, infliximab, and vedolizumab. Cases refractory to such medications pose a significant challenge. FMT has been shown to be a successful treatment in refractory IMC in small case series, further large studies are needed to determine its efficacy. **Methods:** We measured the efficacy of FMT for refractory IMC among 47 patients via chart review and clinical assessment and patients' reported outcome (PRO) via established MD Anderson Symptom Inventory (MDASI). Among them, 9 patients had concurrent CDI as well at the time of diagnosis. **Results:** Forty-seven patients were included in our study. Most patients had a peak diarrhea grade ≥ 3 (93.6%) and colitis grade ≥ 2 (91.5%). Ulcerous (23, 49.0%) and non-ulcerous (12, 25.5%) inflammation were the predominant endoscopic findings. 45 (95.7%) patients received corticosteroids, and 43 patients (91.5%) received add-on infliximab or vedolizumab. IMC symptom response was 85.1% after FMT with median time to response of 4.5 days. The transient complications rate is 34.0% at 7 days and 17.0% at 30 days. Response rate among the 38 patients without concurrent CDI was 86.8%. Forty-one (87.2%) patients demonstrated clinical remission by the end of the study period. On the PRO analysis, we observed a favorable trend of significant patient-reported symptom reduction on diarrhea during 12 weeks after FMT, along with improved daily physical functioning on working. **Conclusions:** FMT may serve as a potential treatment option in IMC refractory to standard treatment to avoid long-term steroid dependency and immunosuppression. It is effective to maintain IMC remission with a low complication rate. The role of the gut microbiome in cancer and the implications for FMT remain uncertain and need further elucidation. Clinical trial information: NCT03819296. Research Sponsor: Moonshot, Gateway, Sabin Fellowship, HESI.

FMT outcome on colitis.

Symptom improvement after FMT, all patients – no (%)	40 (85.1%)
Median time from FMT to symptom improvement– days (IQR)	4.5 (2-10)
FMT-related complications within 30 days–no (%)	8 (17.0%)
Clinical remission – no (%)	41 (87.2%)

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Poster Session

Timing of immunotherapy-induced pneumonitis in patients with primary lung malignancy. *First Author: Megan Winter, Albert Einstein Medical Center, Philadelphia, PA*

Background: Pneumonitis is a widely recognized side effect of immunotherapy with increased incidence in non-small cell lung cancers as compared to other solid organ malignancies. A review of the literature demonstrates an incidence of 5% in patients receiving PD-1/PD-L1 inhibitors. While biopsy provides definitive diagnosis of immunotherapy-induced pneumonitis, clinical symptoms and radiologic features are most utilized with treatment guided by the grade of toxicity. The ability to predict the timing, which patients, and to what extent pneumonitis will present has been a significant challenge. Our study aims to look at the timing of onset of immunotherapy-induced pneumonitis in patients treated with checkpoint inhibitors for primary lung cancer to elicit patterns which may assist in diagnosis and appropriate treatment. **Methods:** This is a single-institution, retrospective study reviewing patients with primary lung cancer who received checkpoint inhibitors between January 2018 and January 2023. The focus was on the date of initiation of therapy and the date of onset of pneumonitis. Immunotherapy-induced pneumonitis was defined as development of abnormal imaging findings with or without respiratory symptoms following initiation of immunotherapy and graded by the Common Terminology Criteria for Adverse Events (CTCAE). Additional patient demographics were collected to assess secondary patterns. **Results:** A total of 117 patients met the specified search criteria. Of these, 10 patients (8.5%) met the criteria for immunotherapy-induced pneumonitis. The average time between receiving the first dose of immunotherapy and the development of immunotherapy-induced pneumonitis was 66.5 days (range of 1 to 163 days). The average number of cycles received before diagnosis was 3.7, with most cases occurring after less than 5 cycles provided (7 out of 10). The grade of pneumonitis ranged from 1 to 5. All patients had non-small cell lung cancer, with the most prevalent histology being squamous cell carcinoma, ranging from stage III to stage IV. Durvalumab was the most prevalent immunotherapy (6 of the 10). **Conclusions:** The timing of immunotherapy-induced pneumonitis, while variable, occurred after receiving less than 5 cycles in majority of our cases, with most occurring after just 1 cycle. Interestingly, durvalumab was the most common immunotherapy in these cases. While our study is limited by the number of patients, the incidence of pneumonitis in our study was close to that of the national average and may, also, be reflective of the timing of immunotherapy-induced pneumonitis. Additional studies with larger numbers of patients are needed. Research Sponsor: None.

Risk of immune-related adverse events (irAE) with immune checkpoint inhibitors (ICI) in patients (pts) with family history (FH) of autoimmune disease (AID). *First Author: Piyush Grover, Melanoma Institute Australia, The University of Sydney, Sydney, Australia*

Background: Pts with personal history (PH) of AID are at increased risk of irAE following ICI. Risk of irAE in pts with FH of AID is unknown. **Methods:** In this retrospective cohort study, consecutive pts were recruited from 2 Australian melanoma cancer centers. Pts who received anti-PD-1 (PD1) based ICI with FH of AID were eligible. Pts with PH of AID were excluded. Toxicity data (CTCAE v5.0) was obtained and stratified by FH of AID (first/second/third degree relative). Descriptive statistics and Fisher's Exact test were used for analysis. **Results:** 396 melanoma cases were screened, of which 44 (11.1%) were eligible for inclusion. Baseline characteristics are summarized. 57 irAE occurred in 44 pts. The most common irAE were dermatological (n=11; 19.3%), colitis (n=8; 14.0%), endocrinopathies (n=8; 14.0%), hepatitis (n=7; 12.3%) and arthritis (n=7; 12.3%). Among 57 irAE, frequency of Grade 1,2,3 and 4 irAE was 16 (28.1%), 26 (45.6%), 12 (21.0%) and 3 (5.3%) respectively. Corticosteroids were used for 31 (54.4%) irAE. Hospital admission for management of irAE occurred in 11 pts (25.0%). ICI was discontinued in 20 pts (45.5%) due to irAE. In pts with irAE, FH of that irAE/AID was present in 6 pts (13.6%) (n=2 x arthritis, n= 2 x psoriasis, n= 1 x Crohn's disease, n= 1 x Grave's disease), and 4 of these patients had a first-degree relative with an AID. 3/6 pts had ICI ceased due to an irAE (peak toxicity Grade was 3) and 4/6 pts had RECIST response. There was no association in development of irAE between patients with FH of AID in a first-degree relative and those with FH of AID in second or third degree relative (p=0.17). Rate of irAE in pts with FH of AID was not statistically higher to that reported in registration trials of similar regimens (p=0.40). **Conclusions:** FH of AID is common in melanoma pts and was not associated with higher rate or morbidity of irAE. FH AID should be routinely collected, and larger scale studies need to be performed. Research Sponsor: None.

Baseline characteristics.	
	N = 44
Age, median (years) (IQR)	60.5 (45.7-69.0)
Sex, n (%)	
Male	18 (40.9)
Female	26 (59.1)
Melanoma sub-type, n (%)	
Cutaneous	35 (79.5)
Acral/mucosal	4 (9.1)
Unknown	5 (11.4)
Treatment setting, n (%)	
Adjuvant	24 (54.5)
Advanced	20 (45.5)
ECOG PS, n (%)	
0-1	44 (100)
LDH pre-ICI, n (%)	
Normal	32 (72.7)
Elevated	10 (22.7)
Unknown	2 (4.6)
Mutation, n (%)	
Triple wildtype	21 (47.7)
BRAF V600	11 (25.0)
Other	12 (27.3)
FH AID, n (%)	
First degree only	27 (61.4)
Second degree only	8 (18.2)
Third degree only	1 (2.3)
First + second degree	5 (11.3)
Second + third degree	2 (4.5)
First, second and third degree	1 (2.3)
Type of AID, n (%)	
Rheumatoid arthritis	16 (36.4)
Other multi system rheumatological	5 (11.3)
Psoriasis	3 (6.8)
Inflammatory bowel disease	8 (18.2)
Celiac disease	8 (18.2)
Type 1 diabetes mellitus	6 (13.6)
Gout's disease	8 (18.2)
Other	2 (4.5)
ICI, n (%)	
PD1 monotherapy	12 (27.3)
PD1 + Ipilimumab	12 (27.3)
PD1 + other ICI	20 (45.4)

Immune related adverse events (irAEs) in patients with solid tumors and advanced chronic kidney disease (CKD) receiving checkpoint inhibitors (CPIs). *First Author: Dalia Kaakour, University of California Irvine Department of Medicine, Orange, CA*

Background: Randomized controlled trials evaluating CPIs in the management of solid tumors have typically excluded patients with advanced CKD and end-stage renal disease (ESRD). Limited available data evaluating the safety of CPI use in this patient population demonstrated a similar incidence of irAEs in patients with advanced CKD compared to those with normal or mildly impaired renal function, with majority of irAEs being grade 1 or 2. CPIs are not modified by dialysis due to their molecular size and, as such, do not require renal dosing. **Methods:** We performed a retrospective analysis of patients over 18 years of age with solid tumors and advanced CKD, who received CPIs at the University of California Irvine from 1/2015 to 6/2021. Advanced CKD was defined as glomerular filtration rate (GFR) less than 60 ml/min. Patients must have received at least one dose of a PD-1/PD-L1 or CTLA-4 inhibitor as a single-agent or in combination with another therapy. Patients were stratified by severity of CKD, including CKD3 (GFR of 30-59 ml/min), CKD4 (GFR of 15-29 ml/min), and CKD 5/ESRD (GFR less than 15 ml/min). **Results:** A total of 32 patients were included, 24 (75.00%) with CKD3, 6 (18.25%) with CKD4, and 2 (6.25%) with CKD5/ESRD. 10 (31.25%) patients were female and 22 (68.75%) were male. Median age was 73.5 years [range: 26 to 98]. 22 (68.75%) received CPI monotherapy and 10 (31.25%) received a combination of CPI with another agent. After initiation of CPI therapy, 16 (50.00%) patients experienced an irAE, with a total of 23 unique irAEs due to some patients experiencing multiple irAEs. In patients with irAEs, 13 (81.25%) received CPI monotherapy and 3 (18.75%) received CPI combined with another agent. In patients with CKD3, CKD4, and CKD5/ESRD, 14 (87.50%), 2 (12.60%), and 0 (0.00%) experienced irAEs, respectively. Types of irAEs observed are listed, with the most common being colitis in 6 (26.1%) patients, endocrinopathies in 4 (17.39%) patients, and dermatologic in 4 (17.39%) patients. 18 (78.26%) of unique irAEs were grade 1 or 2, while 5 (21.74%) were grade 3 or higher. 10 (43.48%) of irAEs were managed with steroids as per physician discretion, 8 (80.00%) with CKD3 and 2 (20.00%) with CKD4. **Conclusions:** The safety of CPIs in patients with solid tumors and advanced CKD has not been rigorously evaluated. Recognizing the small sample size and retrospective nature of this dataset, the incidence and type of irAEs in patients with advanced CKD appears similar to that of patients with normal renal function or mild renal impairment. More prospective data in this population is needed, particularly in patients with CKD5/ESRD. Types of irAEs in patients with advanced CKD. Research Sponsor: None.

irAE	Frequency
Colitis	6
Endocrinopathy	4
Dermatologic	4
Arthritis	2
Renal (acute kidney injury and acute interstitial nephritis)	2
Thrombocytopenia	1
Peripheral neuropathy	1
Myasthenia gravis	1
Pulmonary	1
Fatigue	1

Edema and serositis as an adverse event in patients with cancer receiving immune checkpoint blockade: Systematic review to evaluate this immune-related adverse event and associated treatment strategies. *First Author: Evelyn Elias, Mount Sinai Beth Israel, New York, NY*

Background: Immune checkpoint blockade (ICB) is a standard therapeutic option for certain patients with solid tumors, often leading to durable responses. Immune-related adverse events (irAEs) can impact treatment duration and patients' quality of life. The mechanism of irAEs is proposed to be an inflammatory response triggered by blocking immune checkpoints, and nonspecific symptoms like edema and fluid accumulation can occur. We performed a systematic review to summarize reported studies evaluating edema and serositis to explore edema and serositis as an irAE and management strategies. **Methods:** We performed a database search in Medline, Embase, and Web of Science for studies reporting the incidence and outcome of immune-related generalized edema (irGE) including peripheral edema, capillary leak syndrome, serositis, pleural/peritoneal/pericardial effusion, and anasarca as an irAE among patients with solid tumors treated with ICB. Two independent reviewers analyzed the eligibility of each article. Those that did not report outcomes related to irGE were excluded. The number of patients, cancer type, name and type of ICB, type of irGE, treatment of irGE, and treatment outcome for irGE were extracted from each article to summarize the characteristics of irGE. **Results:** 662 articles were identified, and 80 studies were included (65 case reports/series, 8 cohort studies, 3 phase 1/2 clinical trials) that described clinical characteristics and treatment outcomes for AEs from 196 patients, and 259 irGE incidences reported. The median age was 62 (Interquartile range: 55-68). 35.9% of cases were female (n=28/78). Commonly reported irGEs were pericardial effusion (n=115, 44.4%), pleural effusion (n=58, 22.4%), peripheral edema (n=40, 15.4%), and ascites (n=19, 7.3%). PD-1 blockade was utilized in 75.8% of cases, followed by PD-L1 blockade (14.9%) and dual ICB (CTLA4 and PD-1 blockade, 4.6%). Common cancers where irGE occurred were: lung cancer (63.9%), malignant melanoma (17.0%), and urothelial carcinoma (3.1%). We classified irGEs into primary irGE (n=84, 42.9%), secondary to other irAEs (n=41, 20.9%), secondary to pseudoprogression (n=14, 7.1%), and cancer progression (n=13, 6.6%). Glucocorticoid was used to manage irGEs in 91 patients (46.4%); 48 cases (24.5%) required the prednisone-equivalent dose of > 1 mg/kg/day. ICB discontinuation was confirmed in 96 cases (49.0%) among which 53 (27.0%) permanently stopped ICB use due to irGEs. **Conclusions:** irGE is an important irAE among patients with solid tumors receiving ICB. Most cases required glucocorticoid therapy along with discontinuation of ICB, which could result in poorer quality of life and potentially impact outcomes. The pathophysiology, incidence and clinical outcomes of irGE need to be accurately described in further studies. Research Sponsor: None.

Real-world data: Clinical characteristics and outcomes of patients with advanced hepatocellular carcinoma treated with atezolizumab plus bevacizumab in Veteran Health Administration. *First Author: Munaf Alkadimi, University of Texas Health Science Center at San Antonio, San Anonio, TX*

Background: Advanced Hepatocellular carcinoma (HCC) is an aggressive tumor, and most patients have a poor prognosis. Recent clinical trials have demonstrated improved survival with molecularly targeted treatment and immunotherapy. Atezolizumab plus Bevacizumab (A+B) is the recommended first-line treatment for advanced HCC based on the phase 3 IMbrave 150 trial. However, in a real-life setting, many patients do not meet the inclusion criteria of this landmark trial. This study proposes a retrospective review of outcomes of advanced HCC patients receiving A + B in Veterans Health Administration (VHA). **Methods:** Patients with advanced HCC receiving 1st line systemic therapy with A+ B at the VHA between Dec 1, 2019, to Mar 1, 2022, were selected from the electronic medical records (EMR) using ICD-9 and ICD-10 codes. Abstractors reviewed EMR and followed from their index date of A+B initiation until death or their last VHA visit, with the study period ending on Jan 31, 2023. The Chi-Squared test was used to compare rates, and the Mann-Whitney test was used to compare medians. **Results:** A total of 332 patients met the study criteria. The median age was 67 yrs., 99% were males, 63% non-Hispanic White, 26% were Black, 66 % had ECOG $\geq$ 1, 84% had CPS class A, 16% had CPS class B and C, 62% had grade 2 ALBI score, 56% had viral hepatitis-caused HCC, 80 % had cirrhosis, and 67% had prior local therapies. The outcomes are shown. **Conclusions:** In our real world, despite having similar PFS as the phase 3 IMbrave 150 trial, our OS at 12 months was lower (52% vs. 67%), given that we had more elderly patients with moderate liver dysfunction and 40% were non-white. This study provides actual outcomes in clinical practice where patients do not match the study population of the pivotal trial. Research Sponsor: None.

End points for VA HCC patients given AB as 1st line.	
Characteristic of Interest	All Patients
N ($\geq$ 6 mo from initiation to abstraction)	332
N($\geq$ 12 mo from initiation to abstraction)	304
Number of A + B doses, median (IQR)	6 (3 – 13)
Range: (min, max)	(1, 34)
Overall Survival Time, months	11.4 (5.4 – 18.7)
OS: 6 mo	243 (73.2%)
OS: 1 yr	158 (52.0%)
Response to AB at first scan: CR	5 (1.6%)
PR	91 (28.4%)
SD	100 (31.3%)
PD	82 (25.6%)
Death	42 (13.1%)
Objective Response Rate (CR + PR)	96 (30.0%)
Disease Control Rate (CR + PR + SD)	196 (61.3%)
Progression-Free Survival, months	7.6 (3.0 – 14.9)
PFS: 6 mo	187 (58.8%)
PFS: 1 yr	105 (36.3%)
Duration of Response (CR,PR,SD), months	9.8 (4.9 – 15.6)

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Poster Session

Frequency of delayed immune-related adverse events (irAEs) in hospitalized patients treated with immune checkpoint inhibitors (ICIs). *First Author: Sienna Durbin, Massachusetts General Hospital, Boston, MA*

Background: Across cancer types and indications, the use of ICIs is increasing. Guidelines indicate that most irAEs occur in the months immediately following receipt of ICI. Little is known about the frequency of delayed irAEs following ICI administration. **Methods:** Patients who received ICIs and were hospitalized following ICI initiation between January 2011 and October 2022 were identified using pharmacy and hospital admission databases. Patient demographics, and oncologic and irAE history were extracted from the medical record. All admissions were reviewed by two physicians to evaluate for irAEs, which were defined as suspected or confirmed using published disease-specific criteria. We examined the number of irAEs hospitalizations at < 6 months, 6-12 months, 1-2 years, 2-5 years, and >5 years from the first dose of the most recent line of ICI to date of admission. **Results:** Among the 930 patients hospitalized with irAEs, average age was 66.0 years (range 18.3 - 96.2) and 61.2% were male. Most common tumor types were melanoma (42.0%), lung (24.1%), and gastrointestinal (12.7%). Median time from start of last line of ICI to hospitalization was 98 days (IQR 37-244.3). One hundred sixty-six patients (19.4%) had been treated with >1 prior line of ICI and 102 (11.0%) were diagnosed with multiple irAEs during the same admission. Of all patients admitted, 147 (15.7%) presented 6 months - 1 year after start of ICI line, 79 (8.4%) presented after 1-2 years, 35 (3.7%) presented after 2-5 years, and 2 (0.2%) presented after >5 years. Rates of irAEs by time from start of ICI line are demonstrated. **Conclusions:** Although irAEs occur in a time-dependent fashion, delayed, serious irAEs in hospitalized patients are common (28% at 6+ months), with a subset presenting two years or more after start of ICI. Providers must remain vigilant for potential irAEs regardless of elapsed time from ICI, especially as patients live longer and ICIs become widely used in different settings. Future work is needed to define potential triggers of and patients at risk for delayed irAEs. Research Sponsor: None.

	<6mos	6mos - 1yr	1-2yrs	2-5yrs	5+ yrs	Total
All irAEs, N (%)	710 (100)	147 (100)	79 (100)	35 (100)	2 (100)	937 (100)
Gastrointestinal	180 (25.3)	24 (23.1)	17 (21.5)	8 (22.8)	0 (0)	39 (24.6)
Lung	105 (14.8)	26 (17.7)	19 (24.1)	9 (25.7)	1 (50)	160 (16.4)
Liver	96 (13.5)	15 (10.2)	8 (10.1)	2 (5.7)	0 (0)	121 (12.4)
Endocrine	91 (12.8)	17 (11.6)	3 (3.8)	3 (8.6)	0 (0)	114 (11.7)
Cardiac	66 (9.3)	13 (8.8)	6 (7.6)	3 (8.6)	0 (0)	88 (9.0)
Renal	37 (5.2)	10 (6.8)	5 (6.3)	2 (5.7)	0 (0)	54 (5.5)
Dermatologic	41 (5.8)	11 (6.8)	2 (2.5)	2 (5.7)	0 (0)	53 (5.4)
Neurologic (Peripheral)	30 (4.2)	12 (6.8)	3 (3.8)	0 (0)	0 (0)	38 (3.9)
Hematologic	20 (2.8)	13 (6.8)	8 (10.1)	2 (5.7)	0 (0)	35 (3.6)
Rheumatologic	18 (2.5)	14 (8.8)	1 (1.3)	2 (5.7)	1 (50)	27 (2.8)
Neurologic (Central)	14 (2.0)	15 (8.8)	5 (6.3)	0 (0)	0 (0)	25 (2.6)
Other	12 (1.7)	16 (6.8)	2 (2.5)	0 (0)	0 (0)	19 (2.0)

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Poster Session

Pan tumor outcomes to immune checkpoint inhibitors in patients of Native American origin in the United States: The multicenter POINT-US study. *First Author: Minh Duc Phan, Stephenson Cancer Center, University of Oklahoma Health Sciences Center, Oklahoma City, OK*

Background: Despite receiving identical standard-of-care therapies, epidemiological data indicate that Native American (NA) patients (pts) with cancer have worse outcomes vs. White pts. ICIs have revolutionized the treatment of certain tumors, however pts from certain racial and ethnic groups, including NA pts, are underrepresented in ICI trials. **Methods:** This is an ongoing multi-center retrospective study across four U.S. academic cancer centers that serve a high volume of NA pts. We included pts with self-reported race as NA in electronic medical records. We evaluated clinical outcomes and immune-related adverse events (irAEs) of 71 NA pts age ≥ 18 years with various solid tumors treated with ICI-based therapies between 2015 to 2021. irAEs were defined based on the Common Terminology Criteria for Adverse Events (version 5.0) or RECIST 1.1, as available, was used to determine objective response rate (ORR). Kaplan Meier log-rank method was used to generate median progression free survival (mPFS) and median overall survival (mOS). **Results:** Median age (range) at ICI initiation was 62 (24-81) years; 43 (60%) were males, with 26 (37%) females, 2 pts with missing gender data. 55 (77%) of pts had ECOG performance status 0. The distribution of top six tumor types included (number of pts [%]): non-small cell lung cancer (NSCLC) 22 (31%), renal cell carcinoma (RCC) 16 (23%), melanoma 7 (10%), small cell lung cancer (SCLC) 4 (6%), hepatocellular carcinoma 4 (6%); colorectal adenocarcinoma, head and neck squamous cell carcinoma, cervical squamous cell carcinoma each had 3 pts (4%). Most pts (51 [72%]) received single agent ICI, 12 (17%) had dual ICI, 4 (6%) had chemotherapy+ ICI, and remaining had either ICI + tyrosine kinase inhibitor or ICI + study drug (4 [6%]). 55% of pts with NSCLC underwent tumor next-generation sequencing (NGS) while <30% of patients with renal cell carcinoma or melanoma had tumor NGS performed. Among 71 pts, 17 (24%) had any grade (G) irAE, 4 (6%) were reported to be ≥ 3 . The median time to irAE onset was 18 weeks and 3 (4%) pts discontinued ICI due to irAEs. The mPFS, mOS and ORR for the most frequent tumors (N ≥ 5) are shown. **Conclusions:** Although limited by sample size, our emerging data provides new insights into ICI efficacy and irAEs in NA pts that have been unknown to date. To our knowledge, this is the first and only attempt to date evaluating ICI outcomes in NA pts. Updated clinical data and tumor genomics will be presented at the meeting. Research Sponsor: FDA.

Tumor	Number of pts	Median PFS (months) [95% confidence interval]	Median OS (months)	Objective response rate (partial or complete response) (%)
			[95% confidence interval]	
NSCLC	22	7 [0-14.2]	19 [1.2-36.8]	33
RCC	16	5 [1.1-8.9]	23 [7.6-38.2]	19
Melanoma	7	30 [0-62]	not reached	29

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Poster Session

Safety and efficacy of immune checkpoint inhibitors (ICIs) in patients (pts) with cardiac metastases (mets) from solid tumors. *First Author: Amin Nassar, Yale Cancer Center, New Haven, CT*

Background: Given underlying differences in the tumor microenvironment across metastatic sites, ICIs demonstrate variable efficacy depending on sites of met involvement. Data on the safety and outcomes of pts on ICIs with cardiac mets are limited. **Methods:** In an international multi-center retrospective study, pts with solid tumors and baseline mets to the heart who had received ≥ 1 cycle of ICIs were included. Immune-related adverse events (irAEs) were graded per CTCAE v5.0. Objective response rates (ORR) were evaluated by RECIST1.1 when available. Median overall survival (mOS) and median progression-free survival (mPFS) were calculated from time of ICI initiation using the Kaplan-Meier method. **Results:** 110 pts across 20 institutions were identified with a median follow-up of 36 (95% CI 26-51) months. Melanoma (38%, n=42) and non-small cell lung cancer (NSCLC, 24%, n=26) were the most common cancers. Median age at ICI initiation was 65 (IQR: 59-75) years and 29% (n=26) received combination ICI therapy with anti-PD1 and anti-CTLA4. Overall, 62% (n=68) received ICIs as 1st line. The mets were mostly located in the atria (37%, n=41) and ventricles (35%, n=39). At ICI initiation, 21% (n=23) had a cardiac thrombus. Of 78 pts with available echocardiographic data at time of ICI initiation, the mean ejection fraction was 61 $\pm$ 7.1%. Cardiology referrals and cardiac MRIs since time of cancer diagnosis were completed on 53% (n=58) and 47% (n=52) of pts, respectively. Overall, 36.4% (n=40) of pts had cardiac complications from the mets, including arrhythmias (13%, n=14), arterial/venous emboli (3.6%, n=4), and cardiac tamponade (2.7%, n=3). For NSCLC, ORR, mPFS (95% CI), and mOS (95% CI) were 23%, 4.4 months (3.0-7.5), and 9.9 months (5.9-14.7), respectively. For melanoma, ORR, mPFS, and mOS were 35.7%, 9.1 months (5.2-20), and 29 months (14-58), respectively. Cardiac met ORRs for NSCLC and melanoma were 27% and 43%, respectively. 74% (N=71/96) of pts with evaluable response data had concordant response in the burden of overall disease and cardiac disease. irAEs are shown. **Conclusions:** Although cardiac mets are frequently associated with cardiac complications, ICIs demonstrate meaningful efficacy with no overtly concerning safety signals. Close to three-quarter of pts have concordant response in the overall disease and cardiac disease burden. Multi-disciplinary approach involving cardiologists and oncologists need to be implemented to appropriately manage pts with cardiac mets. Research Sponsor: None.

irAE leading to discontinuation	26 (29%)	
Systemic corticosteroids	36 (71%)	
Any irAE*	Any grade	Grade ≥ 3
Colitis/Diarrhea	53 (48%)	22 (20%)
Dermatitis	16 (15%)	8 (7.3%)
Hepatitis	13 (12%)	3 (2.7%)
Thyroid	9 (8.2%)	3 (2.7%)
Pneumonitis	8 (7.3%)	3 (2.7%)
Cardiac	2 (1.8%)	0 (0.0%)
Other	17 (15%)	10 (9.1%)

*Sum of individual irAEs does not add up to total as a subset of pts had more than one irAE.

2655

Poster Session

Incidence and characterization of neurological adverse events among a retrospective cohort of patients receiving immune checkpoint inhibitors. *First Author: John Hunting, Wake Forest Baptist Medical Center, Winston-Salem, NC*

Background: The rising usage of immune checkpoint inhibitors (ICIs) has increased the incidence of rare adverse events in routine practice. Neurological adverse events (nAEs) are a heterogeneous group of outcomes that are infrequent and typically diagnosed by exclusion. They more often involve the peripheral (e.g., neuropathy, myasthenia gravis) than the central nervous system (e.g., encephalitis, hypophysitis). Evidence remains extremely limited with no large cohorts and incidence reported through small case series. This study aimed to analyze data from all clinically significant nAEs to characterize their risk factors, incidence, severity, and management. **Methods:** We created a retrospective registry of all patients who received at least one dose of an ICI for any indication between 2/1/2011 and 4/7/2022 at a comprehensive cancer center and its outreach clinics. Study personnel reviewed clinical documentation from all patients to collect data on treatment-emergent adverse events; attribution and severity were estimated using National Cancer Institute guidelines and the Common Terminology Criteria for Adverse Events. The investigators created a secure, cloud-based registry (REDCap), validated it with data quality rules, and resolved all discrepancies; clinical research specialists at Vasta Global captured most of the data. Categorical variables were compared using Fisher's exact test. Statistical significance defined as p < 0.05. The study had institutional IRB approval. **Results:** In the total cohort of 3,137 patients, there were 47 nAEs (1.49%). The majority of these nAEs were peripheral (31, 0.99%; grade 3/4 in 14 patients, 0.45%) as opposed to central (16, 0.50%; grade 3/4 in 8, 0.25%). Pre-existing neurological comorbidities were present in five patients who had central nAEs (stroke = 3, dementia = 2) and in one patient with a peripheral nAE (stroke = 1). All high-grade (3-4) central nAEs occurred among renal (4, 50%), melanoma (3, 38%), or lung (1, 12.5%) primaries which was statistically significant when compared to other grade 3/4 adverse events (p < 0.0001) or no adverse events (p < 0.0001). Median days from first ICI to nAE was 55 [IQR [22-175] and average treatment with prednisone equivalent was 2.5 mg/kg, std 4.6. **Conclusions:** The incidence of nAEs (1-2%) appeared higher than prior estimates in this retrospective patient registry which included patients who did not have neurology consultation or specific billing codes. All high-grade nAEs occurred in a tumor type known to favor metastases to the brain. With similar patterns among low grade events, an underlying mechanism of molecular mimicry seems more likely. Both time to presentation and treatment remained highly heterogeneous. Further research is needed on treatment-emergent nAEs to determine if they are potentiated by neurologic comorbidities or subclinical brain metastases. Research Sponsor: None.

2656

Poster Session

A comprehensive pan-cancer analysis of PD-L1 expression using clone E1L3N in Chinese patients with cancer. *First Author: Huangbin Lu, Department of Research and Development, Amoy Diagnostics Co., Ltd., Xiamen, China*

Background: Immune checkpoint inhibitors (ICIs) benefit patients with multiple cancer types, and the expression of programmed death ligand 1 (PD-L1) protein assessed by immunohistochemistry (IHC) has been correlated with response and survival benefit from anti-PD-1/PD-L1 ICI therapies in several cancer types. IHC assay with E1L3N clone is currently approved by the NMPA for PD-L1 detection in non-small cell lung cancer (NSCLC), but its performance in other cancer types needs to be further validated. Thus, we performed this study to examine the prevalence of PD-L1 expression in a wide variety of tumor types in Chinese pan-cancer patients using the E1L3N antibody clone. **Methods:** From 2019 to 2022, a total of 13,647 patient across multiple tumor types were analyzed. Tumor tissue samples were subjected to IHC. PD-L1 expression was tested using the E1L3N PD-L1 IHC assay (Amoy Diagnostics, Xiamen, China), and scored with the tumor proportion score (TPS) and combined positive score (CPS). PD-L1 expression status was identified as positive and negative according to TPS or CPS. For NSCLC: negative (TPS < 1%), low expression (TPS 1-49%), and high expression (TPS ≥ 50%). For gastric/gastroesophageal junction carcinoma (GC/GJC): negative (CPS < 1), low expression (CPS 1-5), and high expression (CPS ≥ 5). For other cancer: negative (CPS < 1), low expression (CPS 1-10), and high expression (CPS ≥ 10). **Results:** In total, 14 cancer types were enrolled in the present study, including 68.2% NSCLC, 6.9% colorectal carcinoma (CRC), and 3.8% GC/GJC, and the remaining 21.1% include esophageal cancer (EC), breast cancer, cervical cancer (CC), biliary tract cancer (BTC), pancreatic cancer (PC), ovarian cancer, renal cancer, small cell lung cancer, urothelial carcinoma (UC), bladder cancer, head and neck squamous cell carcinoma (HNSCC), etc. PD-L1 positivity by TPS was observed in 52.5% NSCLC patients, similar to the frequency of PD-L1 expression in Chinese NSCLC patients detected using 22C3 clone. 76.0% and 36.7% of GC/GJC patients with PD-L1-positive tumors at a CPS cutoff of ≥ 1 and ≥ 5, respectively. PD-L1 positive expression frequency was higher than that in western GC/GJC patients detected using 22C3 and 28-8 clone (as reported from previous research: PD-L1 positivity with CPS ≥ 1 was 45.5% using the 22C3 assay and 49.1% using the 28-8 assay). 73.6% and 17.5% of CRC patients with PD-L1-positive tumors at a CPS cutoff of ≥ 1 and ≥ 10, respectively. In addition, 8 tumors (EC, CC, breast cancer, PC, BTC, UC, HNSCC, and bladder cancer) had the prevalence of PD-L1 CPS ≥ 1 greater than 50%. **Conclusions:** E1L3N can be used as a reliable alternative antibody clone to evaluate PD-L1 expression status not only in NSCLC patients but also in other cancer types. Research Sponsor: None.

2658

Poster Session

Factors associated with severe immune checkpoint inhibitor-induced pneumonitis. *First Author: Hamzah Abu-Sbeih, The Ohio State University, Columbus, OH*

Background: Immune checkpoint inhibitor (ICI) induced pneumonitis (ICIp) can be severe and even fatal, but risk factors for severe ICIp remain poorly characterized. In this abstract, we characterize ICIp and assess factors associated with severe disease. **Methods:** This is a retrospective study of consecutive patients who received ICI therapy and developed ICIp at the Ohio State University (2013-2020). Patients with ICIp were identified from a pharmacy database using ICD-10 codes followed by chart review to confirm diagnosis. ICIp was graded based on the CTCAE v5.0 criteria. Laboratory values were collected at the onset of ICIp. A thoracic radiologist reviewed chest imaging for pattern and severity. Survival probabilities were estimated with Kaplan-Meier curve and compared with log rank test. **Results:** Of 2963 patients who received ICI, we identified 119 patients (4%) with ICIp: 75 (63%) were males; 79 (66%) received PD-1 inhibitor monotherapy; and 71 (60%) had lung cancer. ICIp was severe (grade 1-2) in 69 patients (58%) and mild (grade 3-5) in 50 (42%). 74 patients (62%) were hospitalized. 63 patients (53%) needed oxygen supplementation. ICI therapy was held in all patients except one. ICI was rechallenged in 26 patients; 6 of them (23%) had recurrence of ICIp symptoms. All but 2 patients received steroids for the treatment of ICIp. 10 patients received non-steroidal medications (7 IVIG, 2 infliximab, 1 rituximab, 1 abatacept, 1 cyclophosphamide). Steroids were tapered in 6 patients of those who received non-steroidal medications. 3 of the patients who received IVIG had improvement of symptoms. Factors associated with severe ICIp. 21 patients (18%) died while hospitalized for ICIp are shown. Patients with severe ICIp had shorter overall survival than those with mild ICIp (P < 0.001). **Conclusions:** ICIp is a serious adverse event that limits ICI treatment and can lead to hospitalization and death. Factors associated with severe ICIp in our study include lower lymphocyte and eosinophil counts, lower albumin levels, finding of consolidation or bronchiectasis on imaging, and lower predicted FVC and TLC. Prospective studies are merited to validate our findings and to investigate the appropriate treatment of ICIp. Research Sponsor: None.

	Mild	Severe	P-value
Male, no. (%)	26 (52)	49 (71)	0.054
Lung cancer, no. (%)	36 (72)	35 (51)	0.032
ICI type, no. (%)			0.012
Anti-PD-1	30 (60)	49 (71)	
Anti-CTLA-4	0 (0)	2 (3)	
Anti-PD-L1	19 (38)	11 (16)	
Combination	1 (2)	7 (10)	
Lung parenchymal radiation, no. (%)	17 (34)	7 (10)	0.003
Laboratory, median (IQR)			
Lymphocyte counts (cells/uL)	870 [530-1470]	640 [82-942]	0.011
Eosinophil counts (cells/uL)	140 [21-430]	50 [0-200]	0.007
Albumin, mean (SD; g/dL)	3.67 (0.4)	3.25 (0.5)	<0.001
Chest imaging findings, mean (SD)			
Consolidation	0 (0)	0.11 (0.3)	0.019
Bronchiectasis	0 (0)	0.09 (0.3)	0.031
Pulmonary function test, mean (SD), n =38			
Forced vital capacity	84.8 (15.7)	67.3 (24.6)	0.012
Total lung capacity	99.4 (17.9)	85.4 (12.5)	0.020

2657

Poster Session

Fecal microbiota transplantation for refractory immune-checkpoint-inhibitor colitis. *First Author: Arielle Elkrief, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Immune-related colitis (irColitis) is associated with significant morbidity and mortality among patients treated with immune checkpoint inhibition (ICI). The gut microbiota has been implicated in the pathophysiology of irColitis. We hypothesized that abnormal fecal microbiome features would be present at the time of irColitis onset, and that restoring the microbiome to a healthy state would mitigate disease severity. **Methods:** We present fecal microbiota profiles from N = 18 patients with irColitis and describe our clinical experience of N = 5 patients treated with healthy donor fecal microbial transplantation (FMT). Recipients of ICI between May 2019 and June 2021 at Memorial Sloan Kettering Cancer Center whose stool samples were investigated for diarrhea were included in our dataset (N = 100). N = 18 patients with a diagnosis of irColitis were identified. Patients that had other causes of diarrhea were classified as part of the “no-colitis” comparator group (N = 32). All patients with infectious causes of diarrhea (*C. difficile*, other GI pathogen) were excluded from the analysis. Stool samples were profiled by whole metagenomic shotgun sequencing. FMT products from individual healthy donors were procured from the OpenBiome fecal bank and delivered via colonoscopy. **Results:** There was no difference in alpha diversity between the irColitis and no-colitis groups. Patients in the irColitis group had significantly higher relative abundance of *Proteobacteria* at the time of symptom onset compared to the no-colitis group (p = 0.04). *Escherichia spp.* and *Klebsiella spp.* were associated with irColitis, also described in multivariate analyses. Five patients with irColitis refractory to steroids and biologics received healthy-donor FMT, with initial clinical improvement in irColitis symptoms observed in four of five (80%) patients. Two out of five subsequently exhibited recurrence of irColitis symptoms following a course of antibiotics for pneumonia and urinary tract infection, respectively. Both received a second “salvage” FMT that was, again, followed by clinical improvement of irColitis. In these two cases, fecal profiles demonstrated dysbiotic shifts in the gut microbiome post-antibiotics characterized by *Proteobacteria* expansion, which was salvaged post salvage FMT, mirroring clinical resolution of irColitis symptoms. **Conclusions:** We observed that *Proteobacteria* expansion is characteristic of irColitis at time of symptom onset. FMT was followed by clinical improvements in several cases of refractory irColitis. Strategies to restore or prevent microbiome injury—with a particular focus on salvage FMT after antibiotic injury—in the context of immunotherapy toxicities could be further explored in prospective clinical trials. Research Sponsor: None.

2659

Poster Session

Immune-related adrenal insufficiency: A single center retrospective analysis. *First Author: Natalya Polshina, Moscow Clinical Scientific Center Named after Loginov A.F., Moscow, Russian Federation*

Background: Immune checkpoint inhibitors (ICI) became widely used for treatment of various malignancies. They may cause different immune-related adverse events (irAEs), including adrenal insufficiency (irAI). irAI was reported to be comparatively uncommon but potentially life threatening. We conducted a retrospective single center study to identify and describe the incidence and characteristics of AI associated with ICI. **Methods:** We reviewed the medical records of patients treated at an oncological department at Loginov Moscow Clinical Scientific Center between Sep'2019 and Jan'2023 with immunotherapy under direct cortisol monitoring every 6-8 weeks. The main criteria for AI was low serum cortisol in the absence of glucocorticoid intake. **Results:** A total 101 patients (pts) treated by ICI or ICI in combination with chemotherapy or targeted therapy for various malignancies were included in our retrospective analysis. 16 patients (15.8%) were diagnosed with AI: 7 pts with renal cell carcinoma (RCC), 6 pts with melanoma (2 in adjuvant setting), 1 with non-small-cell lung cancer (NSCLC), 1 with small-cell lung cancer (SCLC), 1 with MSI-high colorectal cancer (CRC). Median age was 65 (range 46-79), the majority (10 pts, 62.5%) were male. The median time of irAI onset from ICI start was 5 months (range 2-15). Assessment of serum cortisol was performed every 6-8 weeks routinely and off-schedule in patients who had new onset AI-like symptoms. The most frequent symptoms were unspecific and included fatigue and weakness (100%), loss of appetite/anorexia (69%), hypotension (50%), weight loss (44%), insomnia (38%), chills (31%), nausea/vomiting (31%), muscle pain or cramps (31% and 25% respectively), dizziness (25%), dry mouth (25%), headache (13%), fever (6%). Remarkably, laboratory detected serum cortisol decline preceded any AI symptoms in 7 patients (43.7%). Other 7 patients (43.7%) had concurrent secondary hypothyroidism which suggested panhypopituitarism. Hydrocortisone replacement led to rapid symptoms recovery in 15/16 patients. Additional treatment with fludrocortisone was required for only one patient who had primary/mixed AI due to bilateral metastases of RCC in adrenal glands. All patients resumed immunotherapy after symptoms resolved. Only 1 patient needed treatment modification (ipilimumab cessation). By 12th February 2023 median follow-up from irAI onset is 7 months (range 0.5-37), 12 patients are alive, they all remain on permanent hydrocortisone replacement therapy. **Conclusions:** Routine cortisol assessment during immunotherapy allowed us to detect irAI in 15.8% of patents that is higher than usually reported. Detection of irAI before clinical presentation let us prevent severe consequences including life threatening. We consider that routine cortisol assessment during immunotherapy should be implemented in clinical practice. Research Sponsor: None.

2660

Poster Session

Impact of obesity on the risk of immune-related adverse events (irAEs) among patients receiving immune-checkpoint inhibitors (ICI) treatment: A retrospective cohort study. *First Author: Mohamed I. Elsaid, The Ohio State University College of Medicine, Columbus, OH*

Background: Recent studies suggest that obesity is linked to improved progression-free and overall survivals in patients treated with Immune-Checkpoint Inhibitors (ICI). Studies have also shown that irAEs occurrence following ICI infusion is associated with improved survival. Current evidence on the relationship between obesity and the risk of irAEs has been inconclusive. We aimed to assess the impact of obesity on the risk of irAEs after ICI infusion using data from a large retrospective cohort. **Methods:** The study included newly diagnosed stage I-VI cancer patients treated with ICIs between 2012 and 2021 at the Ohio State University Comprehensive Cancer Center. Patients' body mass index (BMI) data at or before ICI infusion were classified into normal <25.0 Kg/M², 25 to <30 Kg/M² overweight and obese ≥ 30 Kg/M². An incident irAE was defined as any gastrointestinal, pulmonary, dermatological, endocrine or hepatobiliary irAEs following ICI infusion. Cox proportional hazard models were fitted to test the associations between obesity and 1) any irAEs and 2) organ-specific irAEs. We evaluated the dose-response association between BMI and irAEs using a three-knot restricted cubic spline in the adjusted Cox proportional models. **Results:** A total of 4,761 patients were included in the study with a median age of 62 years, 59.2% males and 89% White non-Hispanics. An estimated 34.7%, 31.5% and 33.8% of patients had normal, overweight, and obese BMIs. The median time to incident irAEs was 4.3 months. An estimated 2,791 (58.6%) experienced an irAE, with 28.8% having gastrointestinal, 17.7% pulmonary, 23.7% dermatological, 21.8% endocrine, and 4.4% hepatobiliary irAEs. BMI was a significant predictor of increased risk of irAEs, adjusted hazard ratio (aHR) 1.08 (95% CI: 0.98 to 1.19) overweight vs. normal BMI and aHR 1.17 (95% CI: 1.06 to 1.28) obese vs. normal BMI. In the organ-specific irAEs models, obese vs. normal BMI patients had higher risks of gastrointestinal aHR 1.23 (95% CI: 1.07 to 1.41), dermatological aHR 1.25 (95% CI: 1.07 to 1.28), and hepatobiliary aHR 1.61 (95% CI: 1.11 to 2.36) irAEs. A dose-response was observed in the relationship between BMI and the risk of irAEs whereby patients with BMIs lower than 22 Kg/M² (median normal BMI range 18.5-24.9 Kg/M²) had lower risks of irAEs [BMI 18.5 Kg/M² vs. 22 Kg/M², aHR 0.93 (95% CI, 0.88 to 0.97)] and those with BMIs higher than 22 Kg/M² had higher risks of irAEs [BMI 30 Kg/M² vs. 22 Kg/M², aHR 1.19 (95% CI, 1.09 to 1.29)] and [BMI 40 Kg/M² vs. 22 Kg/M², aHR 1.22 (95% CI, 1.11 to 1.34)]. **Conclusions:** Among patients treated with ICIs, higher BMI was significantly associated with an increased risk of irAEs. Patients with obesity should be monitored for symptom management following ICIs infusion. Our findings help to explain the previously reported benefits of increased BMI and higher irAEs rates on improved survival. Research Sponsor: None.

2662

Poster Session

Incidence, risk factors, and outcomes of immune-related adverse events (irAEs) in a prospective, pan-tumor population. *First Author: Aanika Balaji, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD*

Background: irAEs associated with immune checkpoint inhibitors (ICIs) can result in morbidity and mortality. The incidence, spectrum, and risk factors for irAEs are usually reported from retrospective studies and clinical trials, which typically exclude patients (pts) with pre-existing autoimmune disease (AD). The prevalence and risk factors for irAEs in a diverse, pan-tumor, real-world setting is not well understood. **Methods:** From 06/2021 to 2/2023, we prospectively enrolled pts receiving ICIs (alone or in combination as standard-of-care) at a tertiary care center in this iMCore network study. Univariate and multivariate logistic regressions and survival curves were used to interrogate risk factors for irAE development and the relationship between irAEs, graded using CTCAE v5.0, and clinical response by RECIST 1.1. **Results:** 132 pts with prior ICI therapy were prospectively followed. Median age was 65 years (IQR 56-72), 35% were female, 69% were white, and 24% were black. Most common tumor histologies were: hepatocellular, renal cell, bladder, non-small cell lung, and head and neck carcinoma. 23% (n=30/132) received dual ICI (nivolumab+ipilimumab). In the whole cohort, 36.4% (n=48/132) of pts developed any-grade irAE and 10.6% (n=14/132) developed a severe irAE (grades 3-5). There were 2 fatal irAEs (n=1 hepatitis, n=1 myocarditis) representing 1.5% of the total cohort. The median time to first irAE was 1.8 months (mos; IQR 1.2-3.1) for anti-PDL1 monotherapy, 1.2 mos (IQR 0.7-2.2) for dual ICI, 4.4 mos (0.2-8.7) for PDL1+chemotherapy, and 2.1 mos (1.3-3.1) for PDL1+other. A subgroup of pts (10.6%; n=14/132) had pre-existing AD and 50% (n=7/14) had ever received immunosuppression for their AD. Among pts with AD, the incidence of irAEs was 57% (n=8/14) vs 33.9% (n=40/118) among those without AD. Antitumor response for pts with AD was 27.3% vs 25.8% those without AD. Receipt of dual ICI therapy was associated with increased risk of any-grade irAE (OR 2.87 p=0.02) and severe irAE (OR 40.9 p=0.004). Pts with any grade irAEs were significantly more likely to experience a partial/complete response vs pts without irAEs (OR 4.14 p=0.02) and this relationship was preserved after adjustment for single vs dual ICI. Pts who did not develop irAEs had an overall response rate (ORR) of 18.2%, mPFS of 3.5 mos (IQR 1.6-7.3), and mOS 7.3 mos (IQR 3.8-9.9) vs pts who developed any grade irAE who had an ORR of 37.8%, mPFS of 5.9 mos (IQR 3.3-8.8), and mOS 8.6 mos (IQR 4.9-11.4). **Conclusions:** In this pan-tumor, prospective cohort study of pts receiving ICI therapy in a real world setting, we identified that pts with pre-existing AD and those on dual ICI had increased risk of irAE development. This signals the need for closer monitoring, early recognition, and management of irAEs in these pts. In addition, pts who developed irAEs were more likely to experience partial or complete response in a diverse tumor cohort. Research Sponsor: Genentech.

2661

Poster Session

Discontinuation of immunotherapy over 2 years for patients with non-small cell lung cancer (NSCLC): A search for predictors. *First Author: Priscilla Cascetta, Institut Gustave Roussy, Villejuif, Paris, France*

Background: In advanced NSCLC, treatment completion at 24 months emerged in trials evaluating immune checkpoint inhibitors (ICI). Nevertheless, in clinical practice the question of the optimal treatment duration is under debate. **Methods:** We performed a retrospective study on advanced NSCLC treated with ICI (alone or with chemotherapy) at Gustave Roussy before 2021. Among patients still receiving ICI at 12 months, we analyzed the reasons for ICI discontinuation at 18 and 24 months. **Results:** Of the 682 patients treated with ICI (first-line for n=230, 33.7%), 159 (23.3%) received ICI for ≥ 12 months and 122 (17.9%) for ≥ 18 months. Between 18-24 months, 20 (57.1%) patients interrupted ICI for progressive disease (PD), 8 (22.8%) for toxicity and 7 (20.0%) after discussion with the patient. Out of the 88 (12.9%) patients who completed 2-years of ICI (median duration of treatment: 31.46 months, first-line for n=51), 22 (25.0%) patients discontinued ICI for PD and 40 (45.5%) without PD: 14 (15.9%) for toxicities, patient request or unknown causes and 26 (29.5%) for clinical decision before (n=16, 61.5%) or after (n=10, 38.5%) 30 months of treatment. Discontinuation according to phase III clinical trial design was supported by complete response (CR) by PET imaging +/- tissue biopsy of metabolically active lesions +/- ctDNA in 17 (65.4%) cases just before therapy discontinuation. After a median follow-up of 45.6 months since treatment discontinuation for these 26 patients, only two experienced PD at 4 and 6 months from ICI interruption, in both cases with no proof of CR at ICI discontinuation (p=0.111). The remaining 26 (29.5%) patients who continued ICI after 2 years, are on treatment based either on absence of CR at PET-CT +/- tissue biopsy of metabolically active lesions (n=20, 76.9%) or after discussion with the patients (n=6, 23.1%). After a median follow-up of 40.17 months from the 24-months landmark, the median progression-free survival was unchanged in both continuation and discontinuation groups. **Conclusions:** The patients who completed 2-years of ICI treatment usually continue to experience long-term response after discontinuation. Considering that a subgroup of patients could still benefit from maintained ICI administration, PET imaging was considered to guide ICI cessation or continuation. Prospective studies specifically designed to investigate biomarkers of maintained responses or residual disease (imaging, ctDNA, multi-omics including microbiome) are required to establish the indication for ICI continuation or stop for each patient. Research Sponsor: None.

TPS2663

Poster Session

Phase 1 study of LB1410, a bivalent TIM-3/PD-1 bispecific antibody, in patients with advanced solid tumors or lymphoma. *First Author: Jiajian Liu, Shanghai, China*

Background: Cancer immunotherapies targeting PD-1 or PD-L1 have been proven effective in causing durable antitumor immune responses with less toxicity in many types of tumors. However, the response rate of anti-PD-1/PD-L1 treatments is far from satisfactory and most patients show primary or acquired resistance to the treatments. Tim-3, one of the next generation of immune checkpoint targets, co-expressed on exhausted T cells with PD-1. It is also expressed by innate immune populations, including NK and DC. Dual blocking PD-1 and Tim-3 not only on T cells but also on DC, NK cells may achieve better clinical benefit. LB1410 is a recombinant humanized anti-PD-1/TIM-3 bispecific antibody (BsAb) developed by L&L Biopharma Co., Ltd. for the patients who are resistant to or refractory from PD-1/PD-L1 treatments. It blocked the immune checkpoint PD-1 and TIM-3-mediated immunosuppressive signal pathways simultaneously, showed better T/DC cell activity and in vivo anti-tumor efficacy compared to Tim-3 and PD-1 antibody combination in preclinical studies. **Methods:** This is a FIH, multicenter, non-randomized, open label, phase 1 study of LB1410 in Participants With Advanced Solid Tumor or Lymphoma (Keyplus-001). The planned sample size is approximately 100 patients in two parts: part 1 dose escalation will evaluate safety, tolerability, pharmacokinetics (PK), pharmacodynamics, and determine the maximum tolerated dose (MTD) and/or the recommended phase 2 dose (RP2D), and Part 2 dose expansion will further characterize the safety profile and preliminary tumor response in several cohorts including NSCLC, CRC, EC etc. Enrollment criteria include adults with life expectancy of > 3 months, ECOG performance status 0-1, histologically or cytologically confirmed advanced and/or metastatic solid tumor malignancies or lymphoma for which standard treatment fails, or no standard treatment is available, or standard treatment is not applicable at this stage. Exclusion criteria include pregnancy, lactation, or breastfeeding, ongoing or recent evidence of significant autoimmune disease that required treatment with systemic immunosuppressive treatments. The primary endpoints are incidence of dose limiting toxicities and adverse events, MTD, and recommended phase 2 dose. Secondary objectives will evaluate PK parameters, preliminary antitumor activity, and immunogenicity of LB1410. Besides, the pharmacodynamics (PD) biomarkers related to LB1410 treatment, clinical activity will be explored. This clinical trial is in progress; cohorts 1 to 5 in dose escalation part have been completed. Clinical trial information: NCT05357651. Research Sponsor: L&L Biopharma Co., LTD., Shanghai, China.

TPS2664

Poster Session

A phase 1 first-in-human clinical trial of HMBD-002, an IgG4 monoclonal antibody targeting VISTA, in advanced solid tumors. *First Author: Jordi Rodon Ahnert, Department of Investigational Cancer Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: V-domain Ig Suppressor of T-cell Activation (VISTA), is an immune checkpoint regulator found on tumor, myeloid, and other immune cells. Its presence has been shown to enhance tumor growth, create an immunosuppressive microenvironment, and may potentially contribute to developing resistance to anti-CTLA-4 and anti-PD-1/PD-L1 therapies. Therefore, VISTA represents a promising therapeutic target. HMBD-002, a non-depleting, high-affinity IgG4 monoclonal antibody against VISTA, has demonstrated significant inhibition of tumor growth in preclinical studies, both as a monotherapy and in combination with pembrolizumab. HMBD-002 acts by increasing T-cell activity and reprogramming the suppressive tumor microenvironment to a proinflammatory antitumor phenotype. Cancer types including triple-negative breast cancer (TNBC) and non-small cell lung cancer (NSCLC), which exhibit high expression levels of VISTA in the TME, provide a rational basis for exploring these indications in clinical studies. **Methods:** This phase 1/2, open-label, multi-center trial is being conducted in two parts to evaluate the safety, pharmacokinetics, and antitumor activity of HMBD-002, an IgG4 monoclonal antibody targeting VISTA, as a monotherapy and in combination with pembrolizumab. The dose-escalation stage (Part 1) will follow a standard 3 + 3 study design with weekly dosing and adaptive dose-escalation increments to determine the recommended phase 2 dose (RP2D) for subsequent disease-directed studies. Monotherapy escalation cohorts 1-4 have been completed without dose-limiting toxicities (DLTs). The dose-expansion stage (Part 2) will evaluate the antitumor activity of HMBD-002 alone and combined with pembrolizumab in patients with TNBC and NSCLC, as well as a wide range of VISTA-expressing malignancies. Exploratory analyses will be conducted to assess treatment-induced immunological changes both systemically and within the tumor microenvironment. Longitudinal blood samples will be evaluated using single-cell mass cytometry (CYTOF) and multiplex cytokine analysis. Pre and on-treatment tumor tissue samples will be assessed for VISTA & PD-L1 expression using IHC. Additionally, tumor tissues will be evaluated using multiplex immunofluorescence, and gene-expression profiling. Biomarker correlations with clinical outcomes may lead to the identification of predictive markers of response to HMBD-002. Clinical trial information: NCT05082610. Research Sponsor: Hummingbird Bioscience Inc., Houston, TX, USA & Singapore; Cancer Prevention and Research Institute of Texas (CPRIT) Grant DP190027.

TPS2666

Poster Session

A phase 1, first-in-human (FIH) study of autologous macrophages engineered to express an anti-HER2 chimeric antigen receptor (CAR) in participants (pts) with HER2-overexpressing solid tumors. *First Author: Yara Abdou, University of North Carolina at Chapel Hill, Chapel Hill, NC*

Background: Macrophages are abundant in the solid tumor microenvironment (stME) and can promote tumor growth (M2) or enhance anti-tumor immunity (M1). CAR expression can redirect macrophage function to selectively target and phagocytose antigen overexpressing cancer cells. CAR-M can reprogram the stME and present neoantigens to T cells, leading to epitope spreading and anti-tumor immunity. CT-0508 is comprised of autologous monocyte-derived proinflammatory macrophages expressing an anti-HER2 CAR. Pre-clinical studies showed that CT-0508 induced targeted cancer cell phagocytosis while sparing normal cells, decreased tumor burden, prolonged survival, and was safe. Notably, anti-HER2 CAR-M treatment led to activation of the stME, with infiltration of CD8+ and CD4+ T cells, NK cells, dendritic cells, and increased activated CD8+ tumor infiltrating lymphocytes. In a pre-clinical anti-PD1 resistant solid tumor model, mice that received anti-HER2 CAR-M and anti-PD1 demonstrated improved tumor control, overall survival, and TME activation compared to single treatment alone, indicating synergy and capacity for CAR-M to sensitize solid tumors to checkpoint blockade. **Methods:** This Phase 1, First in Human study evaluates the safety, tolerability, cell manufacturing feasibility, trafficking, TME activation, and preliminary evidence of efficacy of investigational product CT-0508 in 18 participants (pts) with locally advanced (unresectable) /metastatic solid tumors overexpressing HER2. Pts previously treated with anti-HER2 therapies are eligible. Filgrastim mobilized autologous CD14+ monocytes are collected by apheresis, followed by manufacturing and cryopreservation. Group 1 pts (n = 9; enrollment complete) received fractionated doses of CT-0508 over Days 1, 3, and 5. Group 2 pts (n = 9) receive CT-0508 as a single infusion on D1. Additional cohorts include: CT-0508 co-administered with pembrolizumab and CT-0508 monotherapy administered intraperitoneally in pts with peritoneal predominant disease. Correlative assessments include pre- and post-treatment biopsies and blood samples for safety (immunogenicity), trafficking (PCR, RNA scope), CT-0508 persistence in blood and tumor, target antigen engagement, TME modulation (single cell RNA sequencing), immune response (TCR sequencing) and others. Clinical trial information: NCT04660929. Research Sponsor: Carisma Therapeutics.

TPS2665

Poster Session

A phase 1 trial of umbilical cord blood-derived tumor-reactive PD-L1+ natural killer cells engineered to express soluble IL-15 (TRACK-NK) in patients with non-small-cell lung cancer (NSCLC) refractory to PD-1/PD-L1 inhibitors. *First Author: Miguel Angel Villalona-Calero, Department of Medical Oncology and Therapeutics Research, City of Hope National Medical Center, Duarte, CA*

Background: The mechanism by which patients with PD-L1 – tumors can respond favorably to anti-PD-L1 monoclonal antibody therapy has been shown to involve the PD-L1+ NK cell in the tumor microenvironment (TME). PD-L1 is induced on the cell surface when NK cells recognize tumors, leading to enhanced NK-cell function without exhaustion. The PD-L1 + NK cell is capable of trafficking to the lung TME, recognizing and killing tumor cells as well as inducing activation of endogenous T cells via potent cytokine secretion, all without the expression of a chimeric antigen receptor (CAR). TRACK-NK cells are PD-L1+ NK cells derived from cord blood (CB) and engineered to express soluble IL-15 (sIL-15). The TRACK-NK cells express high levels of tumor reactive receptors that recognize "tumor stress" including DNAM-1, NKP30 and NKG2D. TRACK-NK cells induced significant reduction in tumor volume in mice injected with human A549 NSCLC cells compared to mock-transduced NK cells, or NK cells expressing sIL-15 (sIL-15-NK) but without *ex vivo* activation. Survival was also prolonged in the H460 NSCLC model compared to vehicle alone. We hypothesized that TRACK-NK cells can be safely administered, and will provide meaningful clinical benefit in patients with NSCLC. **Methods:** NCT05334329 is a first-in-human, phase 1 dose finding study of allogeneic, off-the shelf frozen and thawed TRACK-NK cells in patients with NSCLC progressing on treatment with PD-1/PD-L1 inhibitors. TRACK-NK cells (CB NK cells engineered with retroviral transduction to express sIL-15 and *ex vivo* expanded and activated to express PD-L1) are administered in four weekly intravenous infusions per cycle following lymphocyte depletion (Fludarabine/Cyclophosphamide x 3 days) in the outpatient setting. Patients not experiencing disease progression (per RECIST v1.1) following cycle 1 may receive a second cycle. Primary endpoints include: 1. Toxicity/adverse events as per NCI-CTCA version 5.0, and ASTCT Consensus Grading for Cytokine Release Syndrome (CRS) and Neurotoxicity; and 2. Magnitude/duration of TRACK-NK cell persistence in peripheral blood via droplet digital PCR. We are employing a Utility Based-Bayesian Optimal Interval design to direct optimal dose determination. Dose limiting toxicity is defined as any ≥ grade 3 non-hematologic toxicity; any grade 3 CRS that does not resolve to ≤ grade 1 within 7 days; any ≥ grade 4 CRS; any ≥ grade 2 neurotoxicity that does not resolve to grade 1 within 72 hours; any ≥ grade 3 autoimmune, hypersensitivity, and acute graft-versus-host reactions. Correlatives also include cytokines levels, quantity and activation of CD4 and CD8 cells in peripheral blood, and NK and T cell trafficking and TME changes in paired tumor biopsies using quantitative immunofluorescence and gene expression analysis. Clinical trial information: NCT05334329. Research Sponsor: U.S. National Institutes of Health; Cytoimmune.

TPS2667

Poster Session

Phase I study of NEROFE and doxorubicin in KRAS-mutated ST2-positive solid tumors. *First Author: Benjamin Adam Weinberg, Ruesch Center for the Cure of Gastrointestinal Cancers, Lombardi Comprehensive Cancer Center, Georgetown University, Washington, DC*

Background: KRAS-mutated tumors are notoriously difficult to treat clinically with targeted therapies. Recent advances targeting KRAS G12C with sotorasib and adagrasib are encouraging but limited to a small subset of patients. NEROFE is a 14 amino acid peptide which inhibits suppression of tumorigenicity 2 (ST2; member of the interleukin 1 [IL-1] receptor family and IL-33 receptor), a novel immune checkpoint present on tumor cells and tumor-associated macrophages. ST2 blockade with NEROFE has been shown to transform an immunosuppressive tumor microenvironment into an immune-stimulatory microenvironment. NEROFE also has been shown to induce microRNA miR-217 which downregulates KRAS and MAPK1/2 gene expression in preclinical models. When combined with low-dose doxorubicin, NEROFE has a synergistic effect on inducing apoptosis in KRAS-mutated, ST2-positive cell lines and xenograft models. **Methods:** This is a phase I trial of NEROFE given at 48 mg/m² (dose level [DL] -1), 96 mg/m² (DL1), 192 mg/m² (DL2), or 288 mg/m² (DL3) IV weekly with doxorubicin 8 mg/m² IV weekly. A standard 3+3 dose escalation/de-escalation is used. The primary objective is to determine the recommended phase II dose. Patients are eligible if they have an advanced solid tumor with a KRAS mutation and ST2-positivity (via immunohistochemistry [IHC], centrally confirmed with pre-screening allowed). Patients must have measurable disease amenable to serial biopsy. Patients must have had progression or intolerance to all standard therapies or must decline available standard therapy. Pharmacokinetic profiles will be analyzed from serial blood draws pre- and 1, 2, 4, 6, and 24 hours post-infusion on cycle 1 day 1 and cycle 2 day 1. Pre- and on-treatment tumor biopsies are mandatory. Correlative studies include IHC for ST2 expression, immune cell infiltration and blood-based analyses of KRAS mRNA, miR-217, and cytokines. Enrollment to DL1 began in Q1 2023 (NCT05661201). Clinical trial information: NCT05661201. Research Sponsor: Immune System Key Ltd; Ruesch Center for the Cure of Gastrointestinal Cancers.

TPS2668

Poster Session

GNC-038, a tetra-specific antibody, in patients with R/R non-Hodgkin lymphoma or acute lymphoblastic leukemia: A phase 1 study design and rationale. *First Author: Jianxiang Wang, Institute of Hematology, Chinese Academy of Medical Sciences, Tianjin, China*

Background: Bispecific T cell engagers can mediate single antigen-specific cell cytotoxicity, but cannot preempt clonal relapse, or modify the immunosuppressive cancer cell surface. The first-in-class octavalent, CD19xCD3x4-1BBxPD-L1 tetra-specific antibody, GNC-038, functions as a CD19-specific T cell engager by mediating direct antitumor activity, but further, GNC-038 overcomes inhibition of T cells by PD-L1 based on its 4 binding sites. The antitumor activity of GNC-038 is mediated by activating CD3 and 4-1BB signaling on T cells and targeting high expression of CD19 or PD-L1 on tumor cells. Preclinical studies showed GNC-038 has robust antitumor activity. Considering its favorable tolerance and pharmacokinetics in cynomolgus monkeys, we developed a phase I study to investigate GNC-038 for the treatment of relapsed/refractory non-Hodgkin lymphoma (NHL) and relapsed/refractory acute lymphoblastic leukemia (ALL). **Methods:** Patients diagnosed with relapsed/refractory non-Hodgkin lymphoma or acute lymphoblastic leukemia are currently being enrolled in this phase I study to evaluate the safety, tolerability and pharmacokinetics of GNC-038. This study will be conducted in two phases, dose-escalation (Ia) and dose-expansion (Ib). During the dose escalation phase, R/R-NHL patients will receive GNC-038 (0.016-6 µg/kg/d) as continuous intravenous (cIV) infusion for 8 weeks. Further escalation will be conducted with step-up dosing: cIV infusion of 3.6 µg/kg/d GNC-038 will be administered during week 1 followed by higher doses on subsequent weeks (9, 13.5, 20.25 or 30 µg/kg/d). R/R-ALL patients will receive GNC-038 by cIV infusion for 8 weeks (0.016-16 µg/kg/d). During the dose-expansion phase, one or more dosages will be chosen for further investigation in specific indications. The primary endpoints are dose limiting toxicity (DLT), maximum tolerated dose (MTD), treatment emergent adverse events (TEAE) and recommended phase 2 dose (RP2D). Secondary endpoints are adverse events (AEs), pharmacokinetics, objective response rate (ORR), duration of response (DOR), progression free survival (PFS) and overall survival (OS). Exploratory endpoints are biomarker assessment, anti-drug antibody (ADA) and pharmacodynamics. The dose expansion phase (Ib) has been initiated. Clinical trial information: NCT04606433. Research Sponsor: Sichuan Baili Pharmaceutical Co., Ltd.

TPS2670

Poster Session

A phase I/II dose escalation and expansion trial to evaluate safety and preliminary efficacy of BNT141 in patients with claudin-18.2-positive solid tumors. *First Author: Kyriakos P. Papadopoulos, START San Antonio, San Antonio, TX*

Background: Claudin-18.2 (CLDN18.2), whose expression is normally restricted to short-loop gastric epithelial cells, is ectopically expressed in tumors with unmet needs such as gastric, gastroesophageal junction (GEJ), pancreatic, ovarian, and biliary tract tumors. CLDN18.2 has thus emerged as a promising target for therapeutic antibody development. BNT141 is a novel RNA-based therapeutic that comprises two pseudouridine-modified mRNAs encapsulated in lipid nanoparticles. Upon intravenous injection, BNT141 is preferentially taken up by the liver where RNAs are translated and released into the circulation as fully assembled anti-CLDN18.2 antibodies. The resulting antibody is sequence identical to IMAB362, a CLDN18.2-targeted antibody that provided clinical benefit as an add-on to chemotherapy in the Phase III SPOTLIGHT trial (Shitara *et al. J Clin Oncol.* 2023). RNA-encoded antibodies can be developed more rapidly compared with recombinant antibodies and have the potential for favorable PK/PD properties and improved tolerability. **Methods:** This is a Phase I/II, open-label, multisite, dose escalation and expansion trial to examine safety, efficacy, and PK/PD of BNT141 in patients with CLDN18.2+ tumors (NCT04683939). The trial comprises 3 parts: dose escalation with BNT141 as monotherapy, dose escalation with BNT141 in combination with nab-paclitaxel and gemcitabine, and dose expansion. For monotherapy dose escalation, patients with CLDN18.2+ gastric, GEJ, pancreatic, mucinous ovarian, and biliary tract cancers who have exhausted or are ineligible for the current standard of care are eligible. CLDN18.2 positivity is defined as intermediate/strong staining intensity in ≥50% of tumor cells evaluated using a validated immunohistochemistry assay. Doses of BNT141 are escalated in up to 8 planned dose levels (DLs) until the maximum tolerated dose (MTD) is reached. For combination dose escalation, patients with advanced CLDN18.2+ pancreatic adenocarcinoma or cholangiocarcinoma who are eligible for treatment with nab-paclitaxel/gemcitabine will be included. Combination therapy will start at the first safe DL where the target antibody concentration is reached during monotherapy. Combination dose escalation will continue in parallel with the monotherapy part and will define the recommended Phase II dose (RP2D). For both parts, up to 10 additional patients may be enrolled at the MTD level to collect further safety and PK/PD data. For dose expansion, 2 cohorts of patients with CLDN18.2+ pancreatic adenocarcinoma or cholangiocarcinoma will receive combination therapy (nab-paclitaxel/gemcitabine) together with BNT141 at the defined RP2D. The study was initiated in January 2022 and recruitment is ongoing in the USA and Canada. Sites in Spain, Portugal, Germany, Denmark, Netherlands and the UK will be opened in 2023. Clinical trial information: NCT04683939. Research Sponsor: BioNTech SE.

TPS2669

Poster Session

A phase I/II dose escalation trial with expansion cohorts to evaluate safety and preliminary efficacy of BNT142 in patients with prospectively confirmed claudin 6-positive solid tumors. *First Author: Timothy A. Yap, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Claudin 6 (CLDN6), an oncofetal antigen that is expressed on the cell surface of several solid cancers, including testicular (95% of cases) and ovarian cancers (55% of cases), is a suitable target for cancer immunotherapy (Reinhard *et al. Science.* 2020; Haanen *et al. AACR* 2022). BNT142 comprises lipid nanoparticle-encapsulated RNAs that encode for a T-cell-engaging bispecific antibody against CLDN6 and the T cell receptor-associated molecule CD3. The resulting tribody is produced from two RNA molecules coding for CLDN6-recognizing single-chain variable fragments connected by a CD3-binding fragment antigen-binding region. After intravenous administration, BNT142 is directed to the liver where both RNAs are translated, assembled, and secreted as antibodies into the circulation. While classical recombinant protein antibody formats are affected by issues with stability and a lengthy manufacturing process, novel RNA-encoded antibodies can be developed quickly and will potentially provide more favorable exposure profiles. A previous preclinical study examining the therapeutic effect of RNA-encoded bispecific CLDN6xCD3 antibodies showed tumor regression in xenograft animal models with CLDN6+ tumors (Stadler *et al. Nat Med.* 2017). **Methods:** This is a first-in-human, Phase I/II, open-label, multicenter, dose escalation trial with expansion cohorts to evaluate the safety, efficacy, PK and PD of BNT142 in patients with CLDN6+ advanced solid tumors (NCT05262530). Patients with advanced/metastatic CLDN6+ testicular, ovarian, endometrial, and non-squamous non-small-cell lung cancer (NSCLC) are eligible for inclusion and are prospectively selected for trial entry using a CLDN6 immunohistochemistry assay in a central laboratory. Patients must have exhausted standard therapies available likely to confer a clinical benefit or not be a candidate for such available therapies. The trial design consists of a dose escalation and dose expansion part. In the dose escalation part, the treatment dose will be escalated in up to 8 dose levels (DLs) until the maximum administered and tolerated dose has been reached. Once a DL has been declared safe, the DL cohort may be backfilled to determine safety, PK/PD, and anti-tumor activity. Patients with rare or not otherwise specified CLDN6+ tumors not included in the eligible tumor types can be included in the dose escalation part. The recommended Phase II dose (RP2D) will be determined by data collected at all DLs. In the dose expansion part, CLDN6+ patients with testicular cancer, ovarian cancer, and non-squamous NSCLC who have received at least 1 systemic therapy will be treated at the RP2D. The trial was initiated in March 2022 and recruitment is ongoing at global locations in Europe and the USA. Additional sites will be opened in Europe, USA, and Asia in 2023. Clinical trial information: NCT05262530. Research Sponsor: BioNTech SE.

TPS2671

Poster Session

Trial START-001: A phase 1/2 study of STAR0602, a first-in-class, selective T cell receptor (TCR)-targeting, bifunctional antibody-fusion molecule, as monotherapy in patients with antigen-rich tumors post checkpoint inhibitor (CPI) treatment. *First Author: Ryan J. Sullivan, Massachusetts General Hospital, Boston, MA*

Background: Many patients do not respond to CPI-based therapies and most responders eventually develop resistance. Thus, the development of more effective therapies for CPI treatment resistance is a significant unmet medical need. STAR0602, a first-in-class, TCR β chain-targeting bifunctional antibody fused to a costimulatory molecule, binds the germline Vβ6/Vβ10 TCRs of human alpha/beta (αβ) T cells, and promotes the selective activation and expansion of CD8⁺ and CD4⁺ Vβ6/Vβ10 effector memory T cells by simultaneously engaging direct TCR activation with IL-2 receptor binding and activation in *cis*. Preclinical studies with STAR0602 and its murine surrogate showed potent single-agent anti-tumor activity in multiple CPI-refractory human organoid and murine syngeneic tumor models, and acceptable tolerability and limited cytokine release in monkeys and mice. Durable anti-tumor responses, with long-term protection from tumor re-challenge, was associated with *de novo* expansion and tumor infiltration of targeted Vβ T cell subsets with a novel effector memory gene signature and striking increase in TCR repertoire diversity. These data provide strong scientific rationale to investigate the safety and efficacy of STAR0602 in patients with CPI-resistant cancers. **Methods:** Using a 3+3 trial design, Phase 1 of START-001 is a dose escalation through eight provisional dose levels of STAR0602, administered via an intravenous infusion once every two weeks, to determine a recommended Phase 2 dose (RP2D), based on safety and tolerability, pharmacokinetics, pharmacodynamics, and preliminary anti-tumor activity. Subjects must have one of the following, histologically confirmed solid tumors that are unresectable, locally advanced or metastatic and for which standard curative therapies do not exist or are no longer effective: 1) high mutational burden solid tumors (TMB-H); 2) MSI-H/mismatch repair-deficient (dMMR) cancers; 3) Virally associated tumors including Merkel cell carcinoma, cervical, oropharyngeal, anal, penile, vaginal, and vulvar cancers. After an RP2D is selected, Phase 2 (dose expansion at this RP2D) will begin to further investigate the safety and preliminary anti-tumor activity of STAR0602 in 10 provisional cohorts of patients who have the following solid tumors: TMB-H, CPI experienced; TMB-H, no prior CPI experience; MSI-H/dMMR; virally associated tumors; K-RAS wild-type and MSI-L/MMR proficient colorectal cancer (CRC); K-Ras mutant CRC; metastatic triple-negative breast cancer; relapsed and refractory epithelial ovarian cancer; metastatic castration-resistant prostate cancer; primary stage IV or recurrent non-small cell lung cancer. Phase 1 enrollment has begun since January 2023. Clinical trial information: NCT05592626. Research Sponsor: Marengo Therapeutics, INC.

TPS2672

Poster Session

A first-in-human study of XTX301, a masked, tumor-activated interleukin-12 (IL-12), in patients with advanced solid tumors. *First Author: John George Knecht, Clear Lake Oncology, Webster, TX*

Background: Interleukin-12 (IL-12) is a proinflammatory cytokine that has shown promise as an immunotherapy for cancer. Although it has demonstrated potent antitumor activity in mouse models of cancer, development of IL-12 in the clinical setting has been limited by severe toxicities with systemic administration. XTX301 is a half-life extended, masked and tumor-activated IL-12. XTX301 is designed to be pharmacologically inactive in non-tumor tissue when circulating systemically, and unmasked by matrix metalloproteases (MMPs) preferentially active in the tumor microenvironment (TME). The masking domain is engineered to be removed via cleavage at a protease cleavage site in the XTX301 linker by MMPs. XTX301 is designed to produce a localized anti-tumor immune response while limiting exposure of the active form of XTX301 in non-tumor tissue, and thereby improving the therapeutic index of IL-12. Using a murine analog of XTX301 (mXTX301), tumor growth inhibition was demonstrated *in vivo* in murine models with a single dose of mXTX301. In mouse tumors, mXTX301 stimulated the infiltration of cytotoxic CD8+ T cells and induced pro-inflammatory gene expression signatures. Preclinical data have demonstrated tumor-selective activity of mXTX301 in mice with limited and reversible peripheral toxicities of XTX301 in non-human primates [Malkova et al., AACR 2023]; these data are supportive of further clinical development. **Methods:** XTX301-01 trial (NCT05684965) is a first-in human, multicenter, Phase 1, open label study to establish the safety and tolerability of monotherapy XTX301, and to determine a recommended phase 2 dose (RP2D). Additional objectives include assessment of pharmacokinetics (PK), pharmacodynamics (PD), immunogenicity and anti-tumor activity of XTX301. The study will enroll patients with solid tumors, including lymphoma, that have locally advanced or metastatic disease and have failed standard therapy, standard therapy does not confer survival benefit, or standard therapy is not available. Patients in part 1A will receive XTX301 monotherapy every 3 weeks via intravenous infusion in an outpatient setting, using a 3+3 dose escalation design. The starting dose for XTX301 is 5 ug/kg. Part 1B will further examine multiple doses of XTX301 as monotherapy in patients with select advanced solid tumors to further characterize PK, PD and dose response relationships. Part 1B will require mandatory fresh tumor biopsies before and after initiation of study drug administration to fully characterize the PD profile and PK of XTX301 in the tumor. Enrollment to the study is planned to begin in the first quarter of 2023. Clinical trial information: NCT05684965. Research Sponsor: Xilio Development, Inc.

TPS2673

Poster Session

A phase II study of durvalumab re-treatment +/- prednisone in patients who discontinued prior checkpoint therapy due to immune related toxicity (CCTG IND.238A). *First Author: Peter Michael Ellis, Juravinski Cancer Inst, Hamilton, ON, Canada*

Background: Up to 18% of patients permanently discontinue immune checkpoint blockade (ICB) therapy following G3/G4 immune-related adverse events (irAEs) even if reversible / easily managed with replacement therapy or steroids. Safety concerns exist with ICB re-treatment. Given the potential benefit of ICB and evidence that patients with irAEs may exhibit greater efficacy, there is interest in ICB rechallenge following successful management of G3/G4 irAEs in patients who have had benefit, and trials to prospectively investigate ways to prevent irAE recurrence are needed. Durvalumab is a human monoclonal antibody of IgG1κ subclass that binds to PD-L1. Canadian Cancer Trials Group (CCTG) IND.238A is a phase 2, open label, multi-centre study of durvalumab +/- prednisone rechallenge in patients who were benefitting from prior ICB but discontinued due to irAEs. **Methods:** Eligible patients have received prior anti-PD-(L)1 ICB alone or in combination with anti-CTLA-4 ICB, with or without chemotherapy/targeted therapy, and experienced either: 1) G3 or selected G4 irAEs (i.e. endocrinopathies manageable with replacement therapy; hematologic toxicity) that required drug discontinuation; 2) prolonged G2 irAEs where therapy was discontinued due to poor tolerability. Prior irAE must have resolved to ≤G1, patients must have completed steroid therapy and have documented RECIST 1.1 CR, PR, or prolonged SD (≥8 weeks) to initial ICB. Patients with prior (neo)adjuvant/consolidation ICB are eligible provided there has been ≥6-month treatment free interval before enrollment. Based on prior irAE, patients are allocated into either: 1) the High Risk cohort, receiving durvalumab (1500mg IV Q4W in all cohorts) + prednisone 0.5mg/kg/day for C1-2, or; 2) the Standard Risk cohort, where they are randomized to receive either durvalumab + prednisone 10mg/day for C1-2 (Cohort 2A) or durvalumab alone (Cohort 2B). Three to 6 patients are enrolled into each cohort initially, then each cohort expands up to a total of 60 evaluable patients (20 per cohort). Safety review takes place following enrollment of the 1st, 3rd, 6th and 10th patient in each cohort. Safety review occurs 4 weeks after the 1st patient treated on each cohort and subsequently once the last patient has been followed for at least 4 weeks. The primary endpoint is the incidence of treatment-related AEs (CTCAE v5.0), estimated as percentages of patients with each AE (90% exact CI will be calculated). Secondary objectives are ORR (RECIST 1.1 and iRECIST) and efficacy of corticosteroids in preventing recurrent or new ≥G2 irAEs (90% exact CI will be calculated). Exploratory endpoints include PFS / iPFS by Kaplan-Meier method, exploration of blood- and stool-based irAE biomarkers and PD-L1 expression. As of January 30, 2023, 12 of planned 60 patients have been enrolled. Clinical trial information: NCT03847649. Research Sponsor: AstraZeneca Canada Inc.; Canadian Cancer Society.

TPS2675

Poster Session

High-dose vitamin C to enhance neoadjuvant immune checkpoint therapy in mismatch repair proficient colon cancer: The ALFEO pilot study. *First Author: Andrea Sartore-Bianchi, Department of Oncology and Hemato-Oncology, Università degli Studi di Milano, Milan, Italy & Department of Hematology, Oncology, and Molecular Medicine, Grande Ospedale Metropolitano Niguarda, Milan, Italy*

Background: Most colon cancer (CC) patients can be treated with upfront curative surgery; however, relapse often occurs and the disease becomes deadly. Neoadjuvant chemotherapy does not jeopardize timing or quality of surgery and enhances relapse-free outcomes in proficient mismatch-repair (pMMR) CC (Morton et al, J Clin Oncol 2023). In the same setting, the use of immune checkpoint inhibitors (ICIs) with a single dose of ipilimumab (Ipi) and two doses of nivolumab (Nivo) proved to be feasible without delaying surgery and resulting in 23% major pathological responses (mPR) (Chalabi et al, ASCO 2022). We have previously shown that high dose vitamin C (HDVitC) triggers tumor infiltration and activation of CD8+ T cells in mouse tumors, enhancing efficacy of ICIs in pMMR CC preclinical models (Magri et al, Sci Transl Med 2020). **Methods:** ALFEO is an open-label pilot trial of neoadjuvant CC treatment to test whether HDVitC can enhance the efficacy of ICIs in this setting. Main inclusion criteria are pMMR CC stage cT4N0/TxN1-2/[cM1 liver-limited disease with favorable oncological criteria candidate for upfront surgery on both T and M after multidisciplinary team evaluation]. Patients will receive Nivo i.v. 3 mg/kg D1 and D15, Ipi i.v. 1 mg/kg D 1 and VitC 70 g/ m² D1-3 and 15-17. Tumor assessment will be performed at D21-28, followed by surgery within D28. Primary objective is activity of Nivo/Ipi + HDVitC; secondary objective is safety; exploratory objectives are correlation between efficacy and pharmacodynamic including tumor microenvironment changes. Primary endpoint is mPR rate. Considering the proof-of-principle nature of the trial, a design with a boundary for early stopping (both futility/utility and toxicity) and a fixed maximum sample size of 24 patients has been chosen. mPR for the Ipi/Nivo has been set at 23% (H₀), while H₁ at 75%. A Bayesian hypothesis test-based design (Zhou et al, Pharm Stat 2021) will be used for decision-making. Su. Clinical trial information: ECTR2022-502101-15-00. Research Sponsor: PNRR-MAD-2022-12376593; Fondazione Oncologia Niguarda.

ABSTRACT
WITHDRAWN

TPS2676

Poster Session

Phase 1/2 study of mRNA-4359 administered alone and in combination with immune checkpoint blockade in adult participants with advanced solid tumors. *First Author: John D. Powderly, Carolina BioOncology Institute, Huntersville, NC*

Background: mRNA-4359 is a lipid nanoparticle encapsulated mRNA-based cancer vaccine encoding for concatemeric program death-ligand 1 (PD-L1) and indoleamine 2,3-dioxygenase 1 (IDO1) antigens given as an intramuscular injection. These proteins are found across a wide range of cancer types. PD-L1 is a cell surface receptor expressed on both tumor and regulatory immune cells and functions as a checkpoint to inhibit T cell function, while IDO1 is an L-tryptophan metabolizing enzyme involved in T cell suppression and immune tolerance. Both are thought to impart an inhibitory tumor microenvironment which allows tumor cells to escape immune monitoring and clearance. T cells that can target PD-L1 and IDO1 are known to pre-exist in cancer patients and a recent study leveraging a peptide-based vaccine approach demonstrated they can be induced to elicit clinically meaningful and durable tumor responses in patients with metastatic melanoma when combined with PD-1 inhibition. mRNA-4359 encodes immunogenic peptides proposed to generate anti-PD-L1/IDO1-specific T-cells to kill immunosuppressive regulatory cells as well as cancer cells which express those antigens and thus tip the balance towards an inflammatory and/or immune permissive tumor microenvironment. Additionally, combination with checkpoint inhibition may further amplify this anti-tumor immunostimulatory effect, resulting in superior clinical outcomes. **Methods:** The primary objective of this first in human, open label Phase 1/2 study is to assess safety and tolerability, with secondary objectives to measure T cell profile changes and initial anti-tumor activity. Arm 1a entails dose escalation of mRNA-4359 monotherapy with dose levels guided by a modified continual reassessment method in participants with locally advanced/metastatic cancers, including cutaneous melanoma, non-small cell lung cancer (NSCLC), non-muscle invasive bladder cancer, head/neck squamous cell carcinoma, microsatellite stable colorectal cancer, basal cell carcinoma or triple negative breast cancer. Arm 1b will be dose confirmatory and will run concurrently with a pharmacodynamic arm; both will assess mRNA-4359 in combination with pembrolizumab in patients with primary/secondary checkpoint inhibitor refractory locally advanced/metastatic melanoma or NSCLC. The totality of available data from these arms will be used to support determination of a recommended phase 2 dose. Arm 2 includes two single arm expansion cohorts evaluating mRNA-4359 in combination with pembrolizumab therapy in patients who have not received any prior therapy for their cancer in this setting of locally advanced/metastatic melanoma (Cohort 1) or locally advanced/metastatic NSCLC with PD-L1 TPS of $\geq 1\%$ (Cohort 2). Study enrollment into Arm 1a has commenced in the United States and Australia with plans to open sites in Europe later in 2023. Clinical trial information: NCT05533697. Research Sponsor: Moderna Therapeutics, Inc.

TPS2678

Poster Session

A phase I trial of diphencyprone for cutaneous neurofibromas in adult patients with neurofibromatosis type 1. *First Author: Dina Poplasky, Department of Dermatology, Icahn School of Medicine at Mount Sinai, New York, NY*

Background: Neurofibromatosis type 1 (NF1) is an autosomal dominant genetic tumor predisposition syndrome affecting about 1 in 2500 people. Affected patients develop a variety of skin findings including café-au-lait macules, axillary freckling, and cutaneous neurofibromas (cNFs). These patients also have an increased risk of malignant tumors including gliomas and soft tissue sarcomas. However, the cNFs, of which a patient can have thousands, are often cited as the most burdensome sign. Despite their benign nature, these tumors can be physically bothersome and cause significant emotional distress. To date, there are no effective pharmacotherapies for these tumors. This is a single-center, phase I, open label trial to evaluate the safety, tolerability, and efficacy of diphencyprone (DPCP), a topical hapten that induces a delayed-type hypersensitivity skin reaction, for the treatment of cNFs in adults with NF1. **Methods:** This trial is enrolling NF1 patients aged 18 and older with at least four cNFs greater than 4mm. Subjects taking systemic immunosuppressants, those with underlying immunodeficiency or uncontrolled intercurrent illnesses, and those who are pregnant or nursing are excluded from the study. DPCP 0.04% ointment is administered topically once weekly to up to 20 cNFs in a localized area for 10 weeks. The primary endpoint is to determine the safety and tolerability of DPCP ointment in the treatment of cNFs. Adverse events are graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. To assess subjective tolerability, subjects score their symptoms, including pain, stinging, burning, and pruritus from 0 (none) to 3 (severe). Efficacy and tumor regression are assessed using the Response Evaluation Criteria in Solid Tumors guidelines in conjunction with photographs and manual tri-axial tumor measurements. Additionally, qualitative assessments are made by the study team using 3D whole-body photography. One treated tumor is tracked throughout the study with optical coherence tomography (OCT) imaging. Skin biopsies of a cNF and surrounding tissue are collected at baseline, on Day 17 after treatment initiation, and four weeks post-treatment for exploratory endpoints. Quantitative RT-PCR and single-cell RNA sequencing studies will assess gene expression changes in immune and tumor cell-related genes pre- and post-treatment with DPCP. Immunohistochemistry and proteomic profiling will be performed to characterize changes in the tumor microenvironment. Genetic testing for the NF1 germline mutation will be correlated with treatment response. Enrollment is ongoing with a target of 20 participants. Since September 2022, the study has enrolled 12 patients and five have completed the study. Clinical trial information: NCT05438290. Research Sponsor: The Friedman Brain Institute, Icahn School of Medicine at Mount Sinai.

TPS2677

Poster Session

Phase 2 trial of epidermal growth factor (EGF) vaccine CIMAvax in combination with pembrolizumab in first line and maintenance setting in advanced non-small cell lung cancer patients. *First Author: Prantesh Jain, Roswell Park Comprehensive Cancer Center, Buffalo, NY*

Background: CIMAvax-EGF is a novel growth-factor depleting immunotherapy consisting of human recombinant EGF conjugated to recombinant P64k derived from *Neisseria meningitidis*, that elicits an anti-EGF antibody response, resulting in reduction of circulating EGF levels. A randomized phase 3 study of CIMAvax-EGF administered as switch maintenance therapy after first-line platinum-based chemotherapy in patients with advanced NSCLC demonstrated overall survival (OS) advantage in comparison to best supportive care alone, particularly in patients with high baseline serum EGF levels. A phase 1 trial combining CIMAvax-EGF with nivolumab, an anti-PD1 immune checkpoint inhibitor, showed that the combination is safe and appears to induce higher rate of good anti-EGF antibody response within the first 8 weeks of therapy compared to historical comparison group receiving CIMAvax-EGF alone. CIMAvax-EGF is currently being investigated in combination with pembrolizumab in a multi-arm phase II trial as 1L therapy in combination with pembrolizumab for patients with EGFR/ALK wildtype NSCLC and PD-L1 $> 50\%$ (Cohort C) and as maintenance therapy after completing 1L chemoimmunotherapy for patients with PD-L1 $< 50\%$ (Cohorts D and E). Accrual to this trial is ongoing (NCT02955290). **Methods:** This is an open-label, non-randomized, multi-site, phase 2 basket trial. CIMAvax-EGF (2.4 mg IM every 2 weeks x 4 doses, then every 4 weeks thereafter) is being tested as first-line therapy in combination with pembrolizumab (200 mg IV every 4 weeks) in patients with advanced NSCLC with PD-L1 $\geq 50\%$ (Cohort C), using a Simon two stage design (n up to 41). A safety lead-in consisting of the first 6 NSCLC patients was completed. There were no G3 or higher adverse events attributed to the combination within the first 4 weeks of protocol treatment. Patients with advanced squamous NSCLC (Cohort D, n=50) and non-squamous NSCLC (without EGFR/ALK/ROS-1/KRAS mutations; Cohort E, n=45) with PD-L1 expression $< 50\%$ and no evidence of progression of disease by RECIST 1.1 criteria after at least 4 cycles of induction platinum-based doublet with pembrolizumab, prior to initiation of standard of care maintenance therapy will be enrolled to receive protocol treatment with pembrolizumab in combination with CIMAvax-EGF as maintenance therapy. The primary endpoint is to evaluate objective response rate (Cohort C), and 12-month PFS in Cohorts D and E. Secondary endpoints include 12-month overall survival in all cohorts. Exploratory objectives include characterizing tissue-based immune and EGFR signaling profile as well as serum EGF levels, anti-EGF antibody levels and other blood-based biomarkers in relation to clinical outcomes. Clinical trial information: NCT02955290. Research Sponsor: Roswell Park Cancer Institute.

TPS2679

Poster Session

A prospective observational study investigating the impact of immune checkpoint inhibitors for cancer on fertility in males and females of child-bearing age (immuno-fertility). *First Author: Rachel J Keogh, Beaumont RCSI Cancer Centre, Dublin 9, Ireland*

Background: Anti-PD-1/PD-L1/CTLA4 agents have revolutionized the treatment landscape of many cancer types, resulting in durable responses. With recent approvals in the adjuvant setting, the long-term consequences of immune checkpoint inhibitors (ICIs) such as the impact on fertility are of increasing clinical relevance. The impact of ICI therapy on fertility is poorly understood. Based on published data, we hypothesize that patient fertility may be affected by ICIs via several mechanisms, including: endocrine dysfunction, direct impact on gametogenesis, or autoantibody formation. **Methods:** We designed a prospective, multi-center translational study that aims to identify the effects of ICIs on fertility. We aim to recruit 88 patients over 3-4 years. Participants of child-bearing age as defined by study protocol who are due to start ICIs for any solid tumour malignancy, will be eligible. The primary endpoint of the study is a change in anti-Müllerian hormone level and antral follicle count in females, and a change in sperm concentration, motility, morphology in males measured before and serially during ICI therapy (up to 24 months). Secondary endpoints include analysis of FSH, LH, testosterone levels, the proportion of patients with a persistent change in any one reproductive parameter as assessed at follow-up visits, frequency of oligo/amenorrhoea in females and immunologic changes in seminal fluid in males. **Conclusions:** ICIs have led to a significant improvement in the long-term survival in selected patients with cancer. This study will elucidate the effects of ICIs on both male and female fertility over time, and provide useful information to guide patients and their care teams regarding long-term effects of ICIs on fertility. Recruitment is ongoing. Research Sponsor: Irish Cancer Society.

TPS2680

Poster Session

Abatacept for immune checkpoint inhibitor associated myocarditis (ATRIUM): Phase 3, investigator-initiated, randomized, placebo-controlled study to evaluate the efficacy and safety of abatacept compared to placebo in hospitalized patients with immune checkpoint inhibitor associated myocarditis. *First Author: Kerry Lynn Reynolds, Division of Oncology, Department of Medicine, Massachusetts General Hospital, Boston, MA*

Background: Patients with myocarditis secondary to treatment with an immune checkpoint inhibitor (ICI) represent a poor prognosis population with a critical unmet clinical need. Data have shown that the rate of major adverse cardiac events (MACE) with ICI myocarditis despite administration of corticosteroids ranges from 25-50%. Abatacept is a selective co-stimulation modulator that inhibits T cell activation by binding to CD80 and CD86, thereby blocking its interaction with CD28. In preclinical animal models of ICI myocarditis, the administration of abatacept led to a reduction in cardiac immune activation and an increase in survival. **Methods:** The abatacept for immune checkpoint inhibitor associated myocarditis (ATRIUM) trial is designed as a phase 3, investigator-initiated, randomized, placebo-controlled study to evaluate the efficacy and safety of abatacept compared to placebo in hospitalized participants with ICI associated myocarditis. Hospitalized participants diagnosed with ICI-related myocarditis, as defined by the International Cardio-Oncology Society, ≥ 18 , with serum evidence of ongoing myocardial injury (troponin ≥ 5 times the upper limit normal), and treated, or with intent to treat, with 1000 mg of solumedrol/day are eligible. In the randomized protocol, participants receive either abatacept (10 mg/kg) or placebo given IV followed by study drug infusion/placebo again at 24 hours and on day 14. Of note, there is an optional 4th dose on day 28. The primary aim is to test whether abatacept, as compared to placebo, is associated with a reduction in MACE among participants hospitalized with myocarditis secondary to an ICI. The primary outcome, MACE, is a composite of first occurrence of cardiovascular death, non-fatal sudden cardiac arrest, cardiogenic shock, significant ventricular arrhythmias, significant bradyarrhythmias, or incident heart failure. Each component of the primary composite end point will be evaluated individually as a secondary endpoint, as are troponin levels, rates of deep venous thrombosis and pulmonary embolism, and incidence rates of treatment-related adverse events. Exploratory outcomes focus on cancer outcomes, healthcare utilization, quality of life, and correlative studies. Recently, the trial has been amended to allow eligible participants who have achieved an ATRIUM primary end-point prior to randomization to be eligible for inclusion in the RESCUE arm of the protocol where they will be given open-label Abatacept on day 1, 2, 14, with optional dose at 28. The study is open at 20 sites across the US with a plan for a total of 50 locations across US and Canada. This study is recruiting at time of submission. Target enrollment is 390 patients. Clinical trial information: NCT05335928. Research Sponsor: Bristol Myers Squibb.

LBA3000

Oral Abstract Session

Efficacy and safety of trastuzumab deruxtecan (T-DXd) in patients (pts) with HER2-expressing solid tumors: DESTINY-PanTumor02 (DP-02) interim results. *First Author: Funda Meric-Bernstam, University of Texas MD Anderson Cancer Center, Houston, TX*

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2023, issue of the *Journal of Clinical Oncology*.

3001

Oral Abstract Session

BL-B01D1, a first-in-class EGFRxHER3 bispecific antibody-drug conjugate (ADC), in patients with locally advanced or metastatic solid tumor: Results from a first-in-human phase 1 study. *First Author: Li Zhang, Department of Medical Oncology, State Key Laboratory of Oncology in South China; Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University Cancer Center, Guangzhou, Guangdong, China*

Background: BL-B01D1 is a first-in-class novel ADC consisting of an EGFRxHER3 bispecific antibody linked to a novel TOP-1 inhibitor payload via a cleavable linker. We now present safety/efficacy results from a FIH phase I study of BL-B01D1. **Methods:** This study included patients (pts) with locally advanced or metastatic solid tumors. For dose escalation (D-ESC, i3+3), BL-B01D1 was administered intravenously at doses of 0.27, 1.5, 3.0 mg/kg QW, 2.5, 3.0, 3.5 mg/kg D1D8 Q3W or 4.5, 5.0, 6.0 mg/kg D1 Q3W. A subset of pts were enrolled into dose-expansion (D-EXP) at Q3W regimens. **Results:** As of Dec 31, 2022, 150 pts were enrolled and received at least one dose (D-ESC, n=25; D-EXP, n=125). DLTs were neutropenia, febrile neutropenia and thrombocytopenia at 3.0 mg/kg QW and 3.5 mg/kg D1D8 Q3W. The MTDs were determined to be 3.0 mg/kg D1D8 Q3W and 6.0 mg/kg D1 Q3W. D-EXP was carried out at 2.5, 3.0 mg/kg D1D8 Q3W and 4.5, 5.0, 6.0 mg/kg D1 Q3W. 144 pts were enrolled across all Q3W dose levels (D-ESC and D-EXP), including 89 NSCLC, 7 SCLC, 27 nasopharyngeal cancer (NPC), 19 HNSCC and 2 others. Most common TRAEs (>10%, all grade / ≥ G3) were leukopenia (60%/30%), neutropenia (51%/34%), anemia (45%/15%), thrombocytopenia (44%/19%), alopecia (30%/0%), nausea (29%/<1%), vomiting (28%/0%), asthenia (21%/<1%), decreased appetite (22%/<1%), asthenia (21%/<1%), hypophagia (16%/0%), diarrhoea (15%/2%), mouth ulceration (15%/<1%), rash (13%/0%). No ILD was observed. 122 pts were evaluable for efficacy (at least 1 tumor assessment). PK and other details will be updated in the meeting. **Conclusions:** BL-B01D1 demonstrated encouraging efficacy in heavily pretreated metastatic/locally advanced solid tumors, especially in pts with EGFRm NSCLC. The safety profile showed adequate safety and tolerability. Clinical trial information: NCT05194982. Research Sponsor: Sichuan Baili Pharmaceutical Co., Ltd.

	NSCLC (EGFRmut) (n=34) ¹	NSCLC (EGFRwt) (n=42) ²	(SCLC) (n=7)	(NPC) (n=24)	HNSCC (n=13)
Median prior treatment line (range)	4 (1-7)	2 (1-8)	2 (1-2)	3 (1-9)	3 (1-7)
Best overall response, n ³					
cPR	15	7	1	3	/
PR ⁴	6	10	0	8	1
SD (n with shrinkage)	10 (10)	23 (16)	5 (4)	13 (12)	9 (8)
PD	3	2	1	/	3
ORR ⁵ , %	61.8	40.5	14.3	45.8	7.7
(95% CI)	(43.6-77.8)	(25.6-56.7)	(0.4-57.9)	(25.6-67.2)	(0.2-36.0)
DCR, %	91.2	95.2	85.7%	100%	76.9%
(95% CI)	(76.3-98.1)	(83.8-99.4)	(42.1-99.6)	(85.8-100)	(46.2-95.0)

¹All had prior EGFR TKI, 88% (30/34) had prior 3rd gen EGFR TKI and 68% (23/34) had prior platinum-based chemotherapy (PBC). ²All had prior PBC, 88% (37/42) had prior PD-1/L1 and PBC. ³Only 49 pts had 1 tumor assessment, including 8 EGFRmut NSCLC, 19 EGFRwt NSCLC, 10 NPC, 8 HNSCC and 4 SCLC. ⁴Including pts whose PRs were not yet confirmed but still under treatment. ⁵During 12/2022–01/2023, treatment delay of 26 pts (11 NSCLC, 3 HNSCC, 10 NPC, 2 SCLC) due to COVID-19 had a significant negative effect on their 1st and/or 2nd tumor assessment(s).

3002

Oral Abstract Session

First-in-human study of ABBV-011, a seizure-related homolog protein 6 (SEZ6)-targeting antibody-drug conjugate, in patients with small cell lung cancer. *First Author: Daniel Morgensztern, Washington University School of Medicine, St. Louis, MO*

Background: Small cell lung cancer (SCLC) has a dismal prognosis and new therapies are urgently needed. SEZ6 is a transmembrane protein expressed in SCLC tumors that may be used as a therapeutic target. ABBV-011 is an antibody-drug conjugate (ADC) targeting SEZ6 with a calicheamicin payload, which has shown antitumor activity in preclinical models of SCLC. Preliminary results from the monotherapy dose-escalation and -expansion cohorts of the first-in-human ABBV-011 study are presented. **Methods:** Phase 1, open-label, multicenter study (NCT03639194) of ABBV-011 alone or in combination with budigalimab, a programmed cell death 1 inhibitor. Primary objectives were to assess the safety and tolerability and to determine the maximum tolerated dose (MTD) and/or recommended phase 2 dose of ABBV-011. Adults (≥18 years) with relapsed/refractory SCLC (1–3 lines of prior therapy) were enrolled. Dose escalation was guided by Bayesian continual reassessment method. ABBV-011 was administered intravenously at doses from 0.3 to 2.0 mg/kg once every 3 weeks. Dose expansion was conducted in SEZ6-selected patients. **Results:** At data cutoff on August 22, 2022, 99 patients were treated with ABBV-011 monotherapy. Median age was 63 years (range, 41–79), 50% of patients were male, and 68% had received ≥2 prior therapies. ABBV-011 ADC pharmacokinetics were approximately dose-proportional with an elimination half-life of 4.6 days across the dose range of 0.3–2.0 mg/kg. In dose escalation (n=26), 1 patient had a dose-limiting toxicity of grade (G) 3 fatigue at 2.0 mg/kg. We report safety and efficacy results for 40 patients in the dose-expansion 1.0-mg/kg ABBV-011 cohort. Median duration of treatment was 12 weeks (range, 1.9–63.3). Treatment-emergent adverse events (TEAEs) occurred in 39 (98%) patients, the most frequent being fatigue (48%), nausea (45%), anorexia (38%), thrombocytopenia (38%), and vomiting (35%). G3 TEAEs occurred in 18 (45%) patients, the most frequent being fatigue, thrombocytopenia, and neutropenia (10% each); 1 G4 TEAE of dyspnea was reported. Seven patients died due to malignant neoplasm/disease progression (n=6) or respiratory distress (n=1); none were related to ABBV-011. Hepatotoxicity was observed, including G≥2 TEAEs of hyperbilirubinemia (18%), increased gamma-glutamyltransferase (8%), ascites (5%), veno-occlusive liver disease (3%), and portal hypertension (3%). Confirmed objective response rate was 25% (10 partial responses [PR]), with median duration of response of 4.2 months (95% CI: 2.6, 6.7). Clinical benefit rate (CBR) was 65% (10 PR and 16 stable disease) and CBR lasting >12 weeks was 43%. The median progression-free survival was 3.5 months. **Conclusions:** The MTD was not reached and ABBV-011 was well tolerated at 1.0 mg/kg with promising antitumor activity observed. Further evaluation of ABBV-011 is ongoing. Clinical trial information: NCT03639194. Research Sponsor: AbbVie.

3003

Oral Abstract Session

Detection of peritoneal metastases during cytoreductive surgery using pegsitacianine, a pH sensitive imaging agent: Final results from a phase 2 study. *First Author: Patrick Wagner, Allegheny Health Network Cancer Institute, Pittsburgh, PA*

Background: For patients with peritoneal metastatic disease, extent of cytoreductive surgery (CRS) is a major prognostic factor for long-term survival, regardless of primary tumor type. Pegsitacianine is a systemically delivered pH-sensitive polymeric micellar fluorescent nanoprobe developed to intraoperatively identify residual disease and augment the completeness of CRS following standard of care radiographic imaging, visualization, palpation, and intended resection. **Methods:** NCT04950166 was a Phase 2, non-randomized, open-label, multi-center U.S. study. Patients eligible for CRS were administered a single intravenous dose of pegsitacianine at 1 mg/kg within 24–72 hours prior to surgery. After completion of intended CRS, the peritoneal cavity was systematically re-examined under near-infrared (NIR) illumination to evaluate for fluorescent tissue. Post-standard of care fluorescent tissue detected by pegsitacianine guidance was excised and sent for evaluation for presence of residual tumor by histopathology. Clinically significant events (CSE) were defined as detection of histologically confirmed residual disease excised under pegsitacianine guidance following standard CRS, resulting in additional excision or a change in the assessment of completeness of CRS. Treatment-related and treatment-emergent adverse events were coded by CTCAE (v5.01). **Results:** A total of 40 patients were enrolled and evaluable for CSE. Evaluable patients were defined as patients who completed pegsitacianine dosing, underwent CRS with post-SOC evaluation of the peritoneal cavity, and had evidence of disease upon histopathological evaluation of surgical specimens. These 40 patients represented 6 different primary tumor types (appendiceal, colorectal, endometrial, mesothelioma, ovarian, pancreatic). At the patient level, CSEs were detected in 20 of 40 (50%) patients. Patient-level false positive rate – wherein all pegsitacianine-guided fluorescent tissue specimens resected post-CRS were determined to be negative for cancer by histopathology – occurred in 12.5% of patients. Pegsitacianine was well tolerated with no SAEs. Treatment-related, non-anaphylactic infusion reactions occurred in 26% of patients and were transient, with a median duration of 9 minutes. **Conclusions:** Pegsitacianine received Breakthrough Therapy Designation from the U.S. Food and Drug Administration as a result of data collected in this trial. Pegsitacianine is well-tolerated and facilitates the recognition of occult residual disease following CRS. The high rate of residual disease detection suggests pegsitacianine has the potential to augment surgeon performance during CRS, leading to improved completeness of cytoreduction and patient outcomes. Clinical trial information: NCT04950166. Research Sponsor: Cancer Prevention and Research Institute of Texas; OncoNano Medicine.

3004

Oral Abstract Session

Methylated DNA biomarkers and incident cancer in the American Cancer Society (ACS) Cancer Prevention Study-3 (CPS-3) cohort. *First Author: Alpa Patel, American Cancer Society, Kennesaw, GA*

Background: Multi-cancer early detection (MCED) tests are being developed to complement current single-cancer screening, and are based on next-generation sequencing of cell-free DNA in blood plasma with subsequent analysis of genomic features by machine-learning algorithms. To evaluate the detectability of cancer signals in individuals without known cancer at the time of blood draw, we assessed pre-diagnostic signals using a previously validated locked, methylation-based assay in plasma samples from the ACS CPS-3 cohort. **Methods:** CPS-3 is a prospective cohort study of cancer incidence and mortality. Participants (N=294,000) donated a blood sample (36 mL) at enrollment (2006-2013) and are followed for cancer outcomes via routine linkages with population-based cancer and death registries. Selected participants diagnosed with cancer within 3 years (Y) of blood donation and an equivalent number of matched non-cancer participants were chosen for processing. Despite differences in sample collection (tube, protocol) and long storage time in freezer, standard requirements for MCED sample quality were applied. Primary outcome: demonstrate that cancer signal was detectable via the MCED test up to 3Y prior to conventional diagnosis. Secondary outcomes: assess detectability based on time from blood draw and other clinical factors. Sampling weights were considered in the statistical analyses. **Results:** Of 268,726 CPS-3 participants, 2,850 were selected and assayed by cohort sampling, and 2,754 were included in the primary analysis set. CPS-3 cohort demographics and cancer incidence patterns compared to Surveillance, Epidemiology, and End Results suggested that this cohort is younger and healthier than the U.S. population. The test negative rate was 100% among non-cancers. The test positive rate (TPR) stratified by time between blood draw and clinical diagnosis was 2.3% (3Y), 6.0% (2Y), 15.2% (1Y). For eventually fatal cancers, TPR was 5.1% (3Y), 21.6% (2Y), 55.1% (1Y) vs 1.8%, 4.1%, 10.2% for non-fatal cancers. By stage, within 1Y, TPR was 73.7% for Distant at 4-6 months (M) and 94.1% at 1-3M vs 26.7% for Regional at 4-6M and 71.0% at 1-3M. The overall accuracy of predicting cancer signal origin was 95% (1Y). Many cancers were detected 3Y prior to clinical diagnosis: for example, a case of colon/rectum cancer at Regional stage was detected at 991 days. **Conclusions:** The ACS CPS-3 cohort includes persons at lower-than-average risk of cancer but offered a bio-specimen repository with sufficient plasma samples to assess the preclinical detectability of cancer signals by retrospective evaluation. Rapid changes in detectability over time underscore the short preclinical time scales for aggressive cancers to develop, and therefore to be detected. These insights into cancer biology reinforce the importance of pre-diagnostic samples in the study of cancer signals for early detection. Research Sponsor: GRAIL, LLC, a subsidiary of Illumina, Inc., currently held separate from Illumina Inc., under the terms of the Interim Measures Order of the European Commission dated 29 October 2021.

3006

Oral Abstract Session

Safety and efficacy of the novel BRAF inhibitor FORE8394 in patients with advanced solid and CNS tumors: Results from a phase 1/2a study. *First Author: Macarena Ines De La Fuente, Sylvester Comprehensive Cancer Center, University of Miami, Miami, FL*

Background: FORE8394 is an investigational inhibitor (i) of class 1 (V600) and 2 (activating non-V600) BRAF-altered tumors. FORE8394 did not have paradoxical activation of the MAPK pathway in nonclinical studies. **Methods:** In a phase 1/2a study, patients (pts) aged ≥ 3 years with BRAF-altered, advanced solid or CNS tumors received FORE8394 (900-3600 mg/day or mg/m² dosing) with or without a pharmacokinetic booster (cobocistat 150 mg/day). CNS metastases and prior treatment with other BRAFi were allowed. Besides standard safety assessments, skin and eye exams were required. Objective response was assessed by RECIST v1.1 or RANO criteria. Efficacy was evaluated in pts with class 1/2 BRAF alterations and ≥ 1 post-baseline assessment, with mg/m² dosing (n=4) reported separately. **Results:** On 21Nov2022, 110 pts had received ≥ 1 dose of FORE8394. 85% completed ≥ 1 4-week cycle. 10 (9%) and 3 (3%) received FORE8394 ≥ 2 and ≥ 6 years, respectively; 14 (13%) are ongoing. Pts included 61 (55%) class 1 mutations, 19 (17%) class 2 mutations (excluding fusions), and 17 (15%) BRAF fusions. 64 pts (58%) had ≥ 2 prior lines of systemic therapy; 28 (25%) received prior MAPKi. Increased ALT (39%), increased AST (35%), fatigue (34%), nausea (27%), diarrhea (22%), and vomiting (20%) were the most frequently reported treatment-emergent adverse events (TEAEs); most were grade (G) 1/2. G3+ TEAEs were reported in 49% (54/110), the most common being increased ALT (9%), increased blood bilirubin (6%), and hyponatremia (5%). Transient G1 pyrexia was observed in 8 (7%) pts. All rashes were G1; none required a dose change. No TEAE of hyperkeratosis, papilloma, uveitis, retinal detachment, or LVEF reduction were reported. 1 pt discontinued due to FORE8394-related TEAE. Antitumor activity was observed in pts with MAPKi-naïve, V600 mutant tumors (excluding colorectal cancer [CRC]), 39% (9/23) having a PR (median duration of response [DoR]: 32 months). In 17 pts with V600 mutated tumors (excluding CRC) treated with prior MAPKi, 3 (18%) had PR and 5 (29%) had SD. In V600 mutated tumors, PRs occurred in 6 (55%) gliomas, 3 (100%) ovarian cancers, and 1 each in CRC (7%), small bowel (50%), papillary thyroid (13%) and anaplastic thyroid (25%) cancers. Of pts with BRAF-fusions, a pt with AGK-BRAF-fused melanoma had CR (DoR 51.8+ months); 46% (6/13) had SD. Of note, 1 child with V600E mutated Langerhans cell histiocytosis had SD with improvement in neurodegenerative changes and a progression-free survival of 55.8+ months. **Conclusions:** As single agent anticancer therapy, FORE8394 had antitumor activity in various tumors with BRAF alterations, including pts previously treated with MAPKi and pts with BRAF fusions. Durable tolerability was observed, and TEAEs indicative of paradoxical MAPK activation were not observed, consistent with the novel mechanism of action of FORE8394. These results support further evaluation of FORE8394. Clinical trial information: NCT02428712. Research Sponsor: FORE Biotherapeutics; Plexikon.

3005

Oral Abstract Session

Tumor fraction to improve patient selection for oncology early phase clinical trials: Analysis of two precision medicine studies. *First Author: Sophie Cousin, Early Phase Clinical Trials Unit and Thoracic Unit, Institut Bergonié, Bordeaux, France*

Background: Typical entry criteria in early phase studies include expected life expectancy greater than 3 months. However, this evaluation is quite subjective and more objective and reproducible tools are needed to improve patients (pts) selection. The quantification of ctDNA shed by measuring tumor fraction (TF) has been associated with prognosis in solid tumors pts. However, prognostic implications of TF quantification have been evaluated primarily in retrospective studies and in a limited number of cancer types. We report here the first prospective evaluation of the prognostic impact of TF in 2 independent precision medicine studies enrolling pts referred to consider their eligibility to early phase trials. **Methods:** All consecutive adult pts with an advanced solid tumor included between December 2020 and December 2021 in 2 precision medicine studies: BIP (NCT02534649, sponsor: Institut Bergonié, Bordeaux, France) and STING (NCT04932525, sponsor: Institut Gustave Roussy, Villejuif, France). All pts underwent comprehensive genomic profiling with the 324-gene FoundationOne. TF was analyzed as a binary variable, indicating whether a specimen had TF $\geq 10\%$ or TF $<10\%$. Multivariate analysis included previously validated prognostic scores: the Royal Marsden Hospital (albumin, LDH, number of metastatic sites) and the GRIM (LDH, neutrophil/lymphocyte ratio (NLR), albumin) scores as well as their individual components. **Results:** 1912 pts: N=965 in BIP and N=947 in STING were included. Their characteristics are described. High TF was associated with significantly worse overall survival (OS) in both BIP and STING studies. On multivariate analysis, TF was associated with worse OS (HR:2.49 [CI95%: 2.11 - 2.95, p<0.001] and HR:2.52 [CI95%: 2.06 - 3.08, p<0.001] in BIP and STING studies respectively) independently of the RMH and GRIM scores as well as their individual components. **Conclusions:** This is the first prospective analysis confirming that TF is a strong prognostic factor in pts with advanced solid tumors and represent an helpful tool in the process of patient selection for phase I trial entry. Research Sponsor: None.

	BIP (N=965)	STING (N=947)
Median Age (years) (Range)	66 21 - 93	63 (19 - 91)
Sex		
Women	466 (48.3%)	417 (44%)
Men	494 (51.2%)	514 (54.3%)
NA	5 (0.5%)	16 (1.7%)
Median OS (months)	11.5	11.8
CI95%	10.5 - 12.7	10.3 - 14.8
Albumin		
<3.5 g/dL	41 (4.2%)	59 (6.2%)
>3.5 g/dL	919 (95.2%)	869 (91.8%)
NA	5 (0.5%)	19 (2%)
LDH		
>ULN	700 (72.5%)	649 (68.5%)
< ULN	215 (22.3%)	244 (25.8%)
NA	50 (5.2%)	54 (5.7%)
NLR		
< 6	713 (73.9%)	310 (32.7%)
> 6	248 (25.7%)	142 (15%)
NA	4 (0.4%)	495 (52.3%)
Metastatic sites		
> 2	243 (25.2%)	367 (38.8%)
< 2	715 (74.1%)	580 (61.2%)
NA	7 (0.7%)	0
RMH score		
0	161 (16.7%)	114 (12%)
1	533 (55.2%)	326 (34.4%)
2	207 (21.5%)	407 (43%)
3	7 (0.7%)	27 (2.9%)
NA	57 (5.9%)	73 (7.7%)
GRIM score		
0	174 (18%)	74 (7.8%)
1	520 (53.9%)	220 (23.2%)
2	202 (20.9%)	102 (10.8%)
3	16 (1.7%)	8 (0.8%)
NA	53 (5.5%)	543 (57.3%)

3007

Oral Abstract Session

A phase I study of KL590586, a next-generation selective RET inhibitor, in patients with RET-altered solid tumors. *First Author: Qing Zhou, Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, Guangzhou, China*

Background: KL590586 (A400/EP0031) is a potent next-generation selective RET inhibitor (SRI) with activity against acquired resistance mutations to first-generation SRIs, and brain metastases (mets). Here we present preliminary data of the phase I part from a phase I/II study (KL400-I/II-01, NCT05265091) in patients (pts) with RET-altered advanced tumors to define safety, pharmacokinetics (PK) and efficacy. **Methods:** The phase I of KL400-I/II-01 consisted of dose-escalation (Bayesian Optimal Interval design) and dose-expansion. Primary endpoints were to determine the maximum tolerated dose (MTD) and/or Recommended Phase II Dose. Secondary endpoints included safety, PK, objective response rate (ORR), disease control rate (DCR), and duration of response (DoR) as per RECIST 1.1. **Results:** As of Dec. 30, 2022, 87 pts with RET-altered tumors were treated at 6 doses levels (10 to 120 mg QD). No DLTs were observed, and MTD was not reached. Incidence of treatment-related adverse events (TRAEs, any grade) was 93.1% (81/87), most (74.7%) were grade 1-2, reversible and included (>25%): AST increase (50.6%), ALT increase (48.3%), creatinine increase (33.3%), bilirubin increase (32.2%), constipation (32.2%) and headache (31%). 24.1% of pts had grade ≥ 3 TRAEs, the most common (occurring in >2% of pts) were ALP increase (2.3%), GGT increase (2.3%), ileus (2.3%). TRAEs led to dose reduction or treatment discontinuation in 4.6% and 6.9% of pts, respectively. Hypertension, QT interval prolongation, platelets decrease and lymphocytes decrease (leading to 1st gen SRI dose delays and modifications frequently) were rare (<5%) and low-grade. The exposure increased dose-dependently and the mean half-life was found to be 34.1-99.8h. Clinical responses were observed from 40mg onwards. 69 pts treated at the 40-120mg dose levels (57 NSCLC, 10 MTC, 1 pancreatic cancer, 1 ovarian cancer) were evaluable for efficacy analysis, ORR was 64% (NSCLC, MTC and pancreatic cancer). Most pts (58/69) remained on treatment, with the longest >11 months. The ORR in pts with systemic pretreated NSCLC (median prior treatment: 2, range 1-9, 28% pretreated with anti-PD1/PD-L1 therapy) was 63%(20/32, 1 CR), DCR 91% with median DoR not reached. 9 pts received prior 1st gen SRI, 7 with tumor shrinkage of -10% to -69%, with 3 PR and 4 SD. 11 pts with brain mets (without radiotherapy):4/5 with measurable brain disease had 100%, 100%, 80%, and 47% shrinkage. Overall CNS DCR was 100%. The ORR in treatment naïve NSCLC was 76% (19/25, 1 CR), DCR 92% and median DoR not reached. 3/4 pts with brain mets (without radiotherapy) had complete or partial disappearance of baseline brain lesions. **Conclusions:** KL590586 was well-tolerated, and associated with robust clinical activity in RET-altered tumors regardless of tumor type, including NSCLC pts with resistance to 1st gen SRIs and with CNS mets. Pivotal studies are planned. Clinical trial information: NCT05265091. Research Sponsor: Sichuan Kelun-Biotech Biopharmaceutical Co., Ltd.

3008

Oral Abstract Session

A phase 1 study of the protein arginine methyltransferase 5 (PRMT5) brain-penetrant inhibitor PRT811 in patients (pts) with recurrent high-grade glioma or uveal melanoma (UM). *First Author: Varun Monga, University of Iowa, Iowa City, IA*

Background: PRMT5 catalyzes symmetric arginine dimethylation of protein substrates and is involved in histone modification, transcription, and spliceosome assembly. PRT811 is a potent, selective, brain-penetrant PRMT5 inhibitor being studied in a phase 1, multicenter, open-label, dose-escalation and -expansion study in pts with advanced solid tumors, central nervous system lymphoma, and recurrent high-grade glioma (NCT04089449). Results from the dose-escalation phase have been previously presented. We report on the safety and efficacy of PRT811 in the dose-expansion phase for pts with recurrent high-grade glioma or UM, who have limited treatment (tx) options. **Methods:** Eligible pts were aged ≥ 18 years, had an ECOG performance status (PS) of 0-1, adequate organ function, biopsy-confirmed recurrent high-grade glioma or UM, and were resistant, refractory, or ineligible to receive standard tx. Pts received 15-800 mg of PRT811 orally once daily (QD; 30 days = 1 cycle). The primary objectives were to evaluate the incidence of dose-limiting toxicities and determine the maximum tolerated/recommended phase 2 dose (RP2D) of PRT811. Key secondary objectives were to evaluate the safety, tolerability, and preliminary efficacy (per RECIST v1.1/RANO criteria) of PRT811. **Results:** As of January 13, 2023, 86 pts were enrolled; of the 61 pts with recurrent high-grade glioma (n=38) or metastatic UM (MUM; n=23), 57.4% were female, 24.6% were aged ≥ 65 years, 91.4% had an ECOG PS of 0-1, and 8.2% were systemic therapy naive. Most pts (n=42) received the predicted RP2D of 600 mg QD and 19 pts received between 15 to 800 mg PRT811 QD. Overall, 13% of pts remain on tx. Most pts discontinued tx primarily due to disease progression (83.0%), adverse events (AEs; 5.7%), or pt withdrawal (5.7%). The most common tx-related AEs (mainly grade 1/2) were nausea (49.2%), vomiting (39.3%), fatigue (27.9%), constipation (14.8%), and thrombocytopenia (14.8%). The most common grade 3 tx-related AEs were thrombocytopenia (9.8%; reversible on tx interruption), anemia, fatigue, and lymphopenia (all 3.3%). No tx-related grade 4/5 serious AEs (investigator assessed) were observed; 2 pt deaths were unrelated to tx. Among the 16 *IDH1/2*-mutated (*IDH+*) pts with glioma, we observed 2 complete responses (CR; 1 ongoing, duration: 111+ weeks; 1 discontinued, duration: 33 weeks), 1 unconfirmed partial response (PR), and 8 pts with stable disease (SD). Among the 10 pts with MUM and a splicing gene mutation (*SPLC+*), 1 pt had a confirmed PR (duration: 43 weeks), 1 pt had an unconfirmed PR (ongoing), and 4 pts had SD. No CRs/PRs were observed in the 22 *IDH-* pts with glioma or 13 *SPLC-* pts with MUM. Additional follow-up data, including efficacy plots, will be presented. **Conclusions:** PRT811 demonstrated an acceptable safety profile and clinical activity in pts with glioma and MUM. Clinical trial information: NCT04089449. Research Sponsor: Prelude Therapeutics Incorporated.

3010

Poster Discussion Session

First-in-human phase 1/2a study of a potent and novel CDK2-selective inhibitor PF-07104091 in patients (pts) with advanced solid tumors, enriched for CDK4/6 inhibitor resistant HR+/HER2- breast cancer. *First Author: Timothy A. Yap, Department of Investigational Cancer Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: PF-07104091 is a novel CDK2-selective inhibitor under investigation in pts with selected advanced or metastatic solid tumors. We present the first disclosure of data from the first-in-human, multicenter, phase 1 study of PF-07104091 monotherapy (NCT04553133). **Methods:** Pts with HR+/HER2- advanced/metastatic breast cancer (mBC) who received ≥ 2 lines of treatment for mBC including prior endocrine therapy (ET) + CDK4/6 inhibitors (CDK4/6i), and pts with other solid tumors, were included. Prior therapy with fulvestrant and chemotherapy was allowed for pts with mBC. PF-07104091 (75-500 mg) was given twice daily (BID) orally in 28-day cycles, following Bayesian design with overdose control, to determine the maximum tolerated dose (MTD)/recommended dose for expansion (RDE). Primary objective was to assess safety and tolerability. Secondary objectives included pharmacokinetics and preliminary anti-tumor activity. **Results:** At data cut off (Aug 23, 2022), 35 pts with advanced solid tumors (n = 29 mBC) with median age 62y (range 32-80y), median 4 lines of prior systemic therapy (range 1-12) and ECOG PS 0 (20% pts) or 1 were enrolled. Of 29 pts with mBC, all had prior CDK4/6i, 25 (86.2%) prior fulvestrant, and 21 (72.4%) prior chemotherapy. Treatment-emergent adverse events (TEAEs) were observed in 34 pts (97.1%; 20 [57.1%] grade [G] ≥ 3). The most frequent TEAEs (all G ≤ 3) were nausea (77.1%; 14.3% G3), diarrhea (48.6%; 8.6% G3), vomiting (48.6%; 2.9% G3), fatigue (45.7%; 20.0% G3) and anemia (45.7%; 8.6% G3). Dose-limiting toxicity occurred in 5 pts: 1 pt (G3 fatigue) at 300 mg BID; 2 pts (1 G3 nausea and G3 anorexia, 1 G3 nausea) at 375 mg BID, and 2 pts (1 G3 fatigue and 1 G3 diarrhea) at 500 mg BID. Steady-state PF-07104091 plasma exposures increased proportionally with dose. A trend of early decrease in ctDNA was observed. Further pharmacodynamic studies are ongoing. PF-07104091 300 mg BID was identified as the MTD and selected as the monotherapy RDE. Among 16 response evaluable mBC pts (all prior CDK4/6i+ET) with measurable disease at baseline, confirmed RECIST v1.1 partial responses were observed in 3 (18.8%) pts (2 pts with duration of response > 6 months and 1 ongoing at data cut off), and stable disease in 6 (37.5%) pts. Disease control rate was 61.5% in mBC pts (response evaluable set, 95% CI: 40.6, 79.8). **Conclusions:** Treatment with PF-07104091 monotherapy was generally well tolerated and showed antitumor activity in heavily pretreated HR+ HER2- mBC pts who progressed on prior CDK4/6i. Dose expansions of PF-07104091 are ongoing as monotherapy in pts with ovarian cancer and in combination with fulvestrant in pts with breast cancer. Clinical trial information: NCT04553133. Research Sponsor: Pfizer.

3009

Poster Discussion Session

First-in-human first-in-class phase 1/2a study of the next generation CDK4-selective inhibitor PF-07220060 in patients (pts) with advanced solid tumors, enriched for HR+ HER2- mBC who progressed on prior CDK4/6 inhibitors and endocrine therapy. *First Author: Timothy A. Yap, Department of Investigational Cancer Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: PF-07220060 is a novel potent oral CDK4-selective inhibitor with significant sparing of CDK6. We report the first disclosure of the first-in-human, multicenter trial of PF-07220060 alone or with endocrine therapy (ET). **Methods:** This Phase 1/2a study in advanced solid tumors was enriched for pts with HR+ HER2- advanced/metastatic breast cancer (HR+/HER2- mBC) who had received ≥ 2 lines of treatment including ET and CDK4/6 inhibitors (CDK4/6i). Prior fulvestrant and chemotherapy were allowed. Primary objective was to assess safety and tolerability of PF-07220060 alone and in combination with ET. Secondary/exploratory objectives included anti-tumor activity, pharmacokinetics (PK) and pharmacodynamics (PD). **Results:** At data cut off (Nov 1, 2022), 34 pts with advanced solid tumors received PF-07220060 in monotherapy dose escalation (Part 1A: 100-500 mg BID), and 26 pts with HR+/HER2- mBC in combination (300mg/400mg BID) with letrozole or fulvestrant (Parts 1B + 1C). For pts with HR+/HER2- mBC, median age was 61.5y (range 41-82y), ECOG PS was 0 (38.5% pts) or 1, and median prior lines of systemic therapy (advanced setting) 4.5 (range 1-11); all had prior CDK4/6i, 19 (73.1%) prior fulvestrant and 20 (76.9%) prior chemotherapy. Most frequent all causality treatment-emergent adverse events (TEAEs) with PF-07220060 + ET were diarrhea (50.0%; 0% G3), neutropenia (50.0%; 15.4% G3) and nausea (38.5%; 3.8% G3) with no >G3 TEAEs. A similar safety profile was seen in monotherapy. Dose-limiting toxicities occurred at PF-07220060 500 mg monotherapy BID (n=2 G3 thrombocytopenia) and at 400 mg BID + fulvestrant (n=1 G3 leukopenia/neutropenia). Preliminary PK analyses showed PF-07220060 is rapidly absorbed with dose-dependent increases in exposure. PF-07220060 300 mg BID was selected as the recommended dose for expansion. PD biomarker modulation was seen in tumor (pRb, Ki67 inhibition) and blood (TK1 inhibition). In pts with HR+/HER2- mBC with measurable disease who progressed on prior CDK4/6i+ET (n=21) treated with PF-07220060 (300/400 mg BID) + ET, confirmed RECIST v1.1 responses were observed in 6 (28.6%) pts (1 complete [CR], 5 partial [PR]). Clinical benefit response (CR, PR, or ≥ 24 wks stable disease) was seen in 11 (52.4%) pts. Median progression-free survival was 24.7 wks (95% CI: 23.1, 47.4). At data cutoff, 8/26 (30.8%) pts with mBC continued PF-07220060 + ET without progression for up to 60+ wks. Updated efficacy, PK, PD, and biomarker data will be presented. **Conclusions:** PF-07220060 + ET showed efficacy in pts with HR+/HER2- mBC who progressed on prior CDK4/6i+ET. Tolerability of PF-07220060 alone and in combination with ET was encouraging. Dose expansions with PF-07220060 + ET in pts with HR+/HER2- mBC post CDK4/6i and in CDK4/6i naive pts are ongoing. Clinical trial information: NCT04557449. Research Sponsor: Pfizer.

3011

Poster Discussion Session

FUTURE-SUPER: A randomized, subtyping-based umbrella phase II trial for first-line treatment of metastatic triple-negative breast cancer. *First Author: Shao Zhimin, Fudan University Shanghai Cancer Center, Shanghai, China*

Background: Triple-negative breast cancers (TNBCs) are heterogeneous in molecular drivers and immune traits. Our previous studies classified TNBCs into four subtypes (luminal androgen receptor, LAR; immunomodulatory, IM; basal-like immune-suppressed, BLIS; and mesenchymal-like, MES). The subtyping-based treatment strategy was proved clinically feasible, with promising efficacy (Cell Res 2021, NCT03805399) in patients with heavily pretreated metastatic TNBC (mTNBC). Here, we conducted FUTURE-SUPER, a multi-cohort, randomized trial to further evaluate the efficacy of subtyping-based therapy in the first-line treatment of mTNBC. **Methods:** Patients with untreated locally recurrent inoperable or mTNBC were enrolled. After categorization into 5 cohorts according to TNBC subtypes and genomic biomarkers, patients were randomly assigned (in a 1:1 ratio) to receive nab-paclitaxel (control group) or nab-paclitaxel plus subtyping-based treatment (subtyping-based group): pyrotinib (LAR-HER2^{mut}), everolimus (LAR-PI3K/AKT^{mut}), camrelizumab and famitinib (IM), bevacizumab (BLIS/MES-PI3K/AKT^{wt}), everolimus (MES-PI3K/AKT^{mut}). The primary endpoint was progression-free survival (PFS). Secondary endpoints included PFS in each subtyping-based cohort, objective response rate (ORR), overall survival (OS) and safety. **Results:** Between July 29, 2020, and October 17, 2022, 139 patients were enrolled and randomly assigned. With a median follow-up of 18.5 mo (range, 3.5 to 30.3), 101 (72.7%) events of disease progression or death occurred. Median PFS was significantly longer in the subtyping-based group than in the control (11.3 mo vs 5.8 mo; hazard ratio [HR], 0.38; 95% confidence interval [CI], 0.25 to 0.57; P<0.0001). Greater magnitude of PFS benefits were seen for the IM (median, 15.1 mo vs 6.5 mo; HR 0.37; 95% CI, 0.19 to 0.73), BLIS (median, 9.4 mo vs 3.9 mo; HR 0.41; 95% CI, 0.16 to 0.56) and LAR-PI3K/AKT^{mut} (median, 19.1 mo vs 8.4 mo; HR 0.42; 95% CI, 0.12 to 1.53) subtypes. The ORR (measurable-disease population) was higher in the subtyping-based group than in the control group (80.0% [48/60] vs. 44.8% [26/58]; odds ratio, 0.20; 95% CI, 0.09 to 0.46). OS data were not mature. Most adverse events were of grade 1 or 2. Grade 3 and 4 toxicities were as expected, with neutropenia more frequently reported in the subtyping-based group (56.5% vs 26.1%). No treatment-related deaths were recorded. Further high-throughput biomarker analyses are ongoing. **Conclusions:** Subtyping-based precision treatment significantly prolonged PFS versus nab-paclitaxel in the first-line treatment of advanced TNBC, with manageable toxicities. Our findings highlight the profound clinical benefits with treatment optimization according to molecular/immunological subtypes in TNBC, outlining a direction for further exploration. Clinical trial information: NCT04395989. Research Sponsor: None.

3012

Poster Discussion Session

Debio 0123-101: A phase 1 trial of Debio 0123 in combination with carboplatin in advanced solid tumors—Safety, pharmacokinetic, and preliminary antitumor activity data. *First Author: Hans Gelderblom, Leiden University Medical Center, Leiden, Netherlands*

Background: Cell cycle faults are typical in cancer, with tumor cells depending on G2 checkpoints to avoid excess DNA damage. WEE1, a DNA damage-activated kinase, governs G2 by phosphorylating cyclin-dependent kinase 1 (CDK1) to arrest the cell cycle and permit DNA repair. Via CDK1 inhibition, WEE1 also blocks replication initiation, limiting oncogene-induced replication stress. WEE1 inhibition, with accumulating DNA damage, can induce mitotic catastrophe and apoptosis. Debio 0123, an orally available, ATP-competitive WEE1 inhibitor, is being studied as monotherapy and in combination with carboplatin (CP) in patients (pts) with solid tumors. Here, we report safety, pharmacokinetic (PK), pharmacodynamic, and antitumor activity data for the combination. **Methods:** Debio 0123-101 (NCT03968653) is a two-arm dose-escalation study in pts with advanced solid tumors that recurred or progressed after receiving platinum-containing therapy, where no standard therapy of proven benefit is available. In Arm A, Debio 0123 was given as monotherapy in cycle (C) 1 (as a single dose on day [D] -3 and once daily over D1-3) and in combination with CP from C2 until end of treatment (EOT). In Arm B, Debio 0123 was given in combination with CP on D1-3 and D8-10, from C1 to EOT. CP was given on D1 of each 21-day cycle in both arms. Skin biopsies were taken at baseline and C1D3 to assess target engagement (TE). **Results:** Arm A data (cut-off 31.12.2022) is shown. Overall, 38 pts were treated (78.9% female, mean age 58.5 years), with two pts ongoing. Using a continual reassessment method-guided dose escalation, tested Debio 0123 doses ranged from 30–520 mg. The maximum tolerated dose was declared at 520 mg. At this dose level, 2/6 pts experienced a dose-limiting toxicity. The treatment was deemed well tolerated, with a manageable safety profile in line with that expected for CP monotherapy. Most Debio 0123-related toxicities were grade 1/2. Preliminary PK data indicate that Debio 0123 plasma levels rise proportionally with dose. TE was seen from the 150 mg dose, becoming more pronounced with increasing dose levels. Confirmed partial responses (PR) occurred in 5/30 evaluable pts; 4/12 pts with platinum-resistant ovarian cancer achieved a PR (one ongoing). **Conclusions:** Debio 0123, combined with CP, has a manageable safety profile and is well tolerated up to 520 mg; this combination led to observable antitumor activity in pts with platinum-resistant cancer. Further study of Debio 0123 as a therapeutic agent is warranted. Clinical trial information: NCT03968653. Research Sponsor: Debiopharm.

Summary of treatment-emergent adverse events (TEAEs) related to Debio 0123 as per CTCAE v5.0.

TEAE	Any grade n (%)	Grade ≥3 n (%)
Thrombocytopenia/platelet count decreased	12 (31.6)	3 (7.9)
Nausea	12 (31.6)	0
Anemia	8 (21.1)	1 (2.6)
Fatigue	7 (18.4)	0
Leukopenia	5 (13.2)	1 (2.6)
Vomiting	5 (13.2)	0
Neutropenia/neutrophil count decreased	4 (10.5)	1 (2.6)

3015

Poster Discussion Session

Dose escalation results from a first-in-human study of ABBV-400, a novel c-Met-targeting antibody-drug conjugate, in advanced solid tumors. *First Author: Manish Sharma, START Midwest, Grand Rapids, MI*

Background: c-Met overexpression is common in non-small cell lung cancer (NSCLC), gastroesophageal adenocarcinoma (GEA), and colorectal cancer (CRC). There is a need for effective therapies that target c-Met-overexpressing tumors, as there are currently no approved options available. The antibody-drug conjugate (ADC) ABBV-400 consists of the c-Met-targeting antibody telisotuzumab conjugated to a potent topoisomerase 1 inhibitor (Top1i) payload. ABBV-400 exhibited sustained antitumor activity in patient-derived xenograft models of c-Met-expressing NSCLC, GEA, and CRC. Herein, we present data from the dose escalation of the first-in-human study of ABBV-400 monotherapy. **Methods:** A phase 1 dose escalation/expansion study of ABBV-400 has been initiated in patients with advanced solid tumors (NCT05029882). Primary objectives are to evaluate safety, tolerability, and pharmacokinetics (PK) of ABBV-400, to determine the recommended phase 2 dose, and to assess preliminary efficacy. PK will be characterized for the conjugate, total antibody, and free payload. Adults (≥18 years) with an advanced solid tumor that progressed on standard therapies were enrolled during dose escalation, without restrictions on the basis of c-Met overexpression status. **Results:** As of January 2023, 47 patients had enrolled in dose escalation with a median follow-up of 6.5 months. Median age was 58 years (range, 34–79), 25 (53%) patients were male, and the most common cancer types were CRC (n=21), NSCLC (n=5), and GEA (n=5). The median number of prior treatment lines was 4 (1–13). Most common hematologic adverse events (AEs) were anemia (66%; grade [G]≥3: 38%), neutropenia (62%; G≥3: 43%), thrombocytopenia (43%; G≥3: 26%), and leukopenia (32%; G≥3: 19%). Nausea (60%, all grade 1–2), fatigue (49%; G≥3: 4%), and vomiting (38%, all grade 1–2) were the most frequent non-hematologic AEs. One patient experienced grade 1 interstitial lung disease. Neutropenia and thrombocytopenia were the dose-limiting toxicities (DLTs) and were dose and exposure dependent. Clinical activity was observed with ABBV-400, with an objective response rate of 24.4% (11/45; 95% CI: 12.9, 39.5). All responses were confirmed partial responses (PR). In addition, 23 patients (50.0%) had stable disease (SD) and 7 (15.2%) had progressive disease. Among patients with CRC, 4/21 (19.0%) had a PR and 13/21 (61.9%) had durable SD, with a disease control rate of 81.0% (95% CI: 58.1, 94.6). Outside of CRC, PRs were observed in patients with NSCLC (EGFR wildtype and mutant), uterine cancer, and acral melanoma. **Conclusions:** On the basis of DLTs, a maximum tolerated dose of ABBV-400 was identified. At this dose, safety results appear comparable with other Top1i ADCs. Promising antitumor activity was seen with ABBV-400 across tumor types, justifying further evaluation in the ongoing dose expansion in NSCLC, GEA, and CRC. Clinical trial information: NCT05029882. Research Sponsor: AbbVie Inc.

3014

Poster Discussion Session

Tissue-agnostic efficacy of trastuzumab deruxtecan (T-DXd) in advanced solid tumors with HER2 amplification identified by plasma cell-free DNA (cfDNA) testing: Results from a phase 2 basket trial (HERALD/EPOC1806). *First Author: Hiroya Taniguchi, Department of Clinical Oncology, Aichi Cancer Center Hospital, Nagoya, Japan*

Background: HER2 (ERBB2) gene amplification (amp) is a potential therapeutic target beyond breast and gastric cancers. HER2 amp can be detected in plasma cfDNA which may be an alternative to tissue biopsy. HERALD/EPOC1806 was a multicenter, investigator-initiated phase 2 trial of T-DXd for patients with HER2-amplified advanced solid tumors identified by cfDNA testing. **Methods:** We enrolled adults with advanced solid tumors harboring HER2 amp detected by next-generation sequencing of cfDNA (Guardant360) in the GOZILA study (UMIN000029315). We excluded breast or gastric cancer patients with HER2 overexpression (IHC 3+ or IHC 2+/ISH+). Patients received T-DXd 5.4 mg/kg every 3 weeks until disease progression or unacceptable toxicity. The primary endpoint was investigator-assessed objective response rate (ORR). **Results:** From December 2019 to January 2022, 4,734 patients were screened by cfDNA in the GOZILA study. Among 252 with HER2 amp, 62 with 16 cancer types were enrolled in HERALD. Median baseline plasma HER2 copy number (CN) was 8.55 (range, 2.4–73.9). All patients but 3 (all with salivary gland cancer) received prior anti-cancer therapy (median, 3 lines; range, 0–8). At a median follow-up of 8.9 months (data cut-off: July 17, 2022), the confirmed ORR was 56.5% (95% CI, 43.3–69.0%), statistically higher than the threshold value of 5%. Responses were observed for 13 cancer types, including KRAS-mutant colorectal (1/3), PIK3CA-mutant endometrial (5/6), and tissue HER2-negative gastric cancers (1/2). Plasma HER2 CN above vs. below the baseline median value did not impact response (ORR: 58.1% vs. 54.8%); however, the clearance vs. persistence of HER2 amp in cfDNA on Cycle 2 Day 1 corresponded to higher response (ORR: 88.0% vs. 22.7%). ORR by independent review was 58.1% (95% CI, 44.8–70.5%), and the disease control rate was 90.3% (95% CI, 80.1–96.4%). Median progression-free survival was 7.0 (95% CI, 4.9–9.7) months, and the median duration of response was 8.8 months (95% CI, 5.8–11.2). Most adverse events were mild to moderate. Interstitial lung diseases occurred in 16 patients (25.8%, G1/G2/ G3: 14/1/1). **Conclusions:** T-DXd achieved a high ORR, durable response with a manageable safety profile in patients with advanced solid tumors and HER2 amp detected in cfDNA. Clinical trial information: JapicCTI-194707. Research Sponsor: AMED.

Tumor type	ORR (%)	n	Tumor type	ORR (%)	n
Total	56.5%	(35/62)			
Esophageal (mainly SCC)	50.0%	(6/12)	Small intestine	100.0%	(2/2)
Colorectal	50.0%	(5/10)	Urothelial	50.0%	(1/2)
Salivary gland	100.0%	(7/7)	Gastric (tissue-HER2 neg)	50.0%	(1/2)
Endometrial	83.3%	(5/6)	NSCLC	0.0%	(0/2)
Cervical	40.0%	(2/5)	Melanoma	100.0%	(1/1)
Biliary tract	25.0%	(1/4)	Paget's disease	100.0%	(1/1)
Pancreatic	0.0%	(0/4)	Prostate	100.0%	(1/1)
Ovarian	100.0%	(2/2)	Unknown primary	0.0%	(0/1)

3016

Poster Discussion Session

First-in-human dose escalation and expansion study of SYSA1801, an antibody-drug conjugate targeting claudin 18.2 in patients with resistant/refractory solid tumors. *First Author: Yakun Wang, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Department of Gastrointestinal Oncology, Peking University Cancer Hospital & Institute, Beijing, China*

Background: SYSA1801 is a MMAE antibody-drug conjugate (ADC) targeting claudin 18.2 (CLDN18.2), a tight junction protein broadly expressed in gastric, pancreatic, and other solid tumors. CLDN18.2 has a highly selective cell surface expression profile that is limited to normal gastric mucosa, making it a promising ADC therapeutic target. SYSA1801 has shown significant *in vitro* and *in vivo* anti-tumor activity in multiple cell lines and patient-derived xenografts expressing CLDN18.2. **Methods:** This is an open-label, multi-center, phase I study to evaluate the safety, tolerability, pharmacokinetics and efficacy of SYSA1801 in patients (pts) with histologically confirmed resistant/refractory solid tumors that express CLDN18.2 who progressed on or were intolerant to standard treatment, or had no standard treatment. This study consists of two parts; part 1 is a modified 3+3 dose-escalation design with five dose levels of SYSA1801 (0.5, 1, 2, 2.5 and 3 mg/kg) administered intravenously (IV) every 3 weeks (Q3W), followed by dose expansion at effective doses. Part 2 is a cohort expansion at the optimal dose. Here, we present the preliminary results of SYSA1801 for part 1. **Results:** As of Nov 5, 2022, 33 pts with a median age of 59 yrs (range 22–71) were enrolled to receive up to SYSA1801 3 mg/kg in part 1. 26 pts (78.8%) had gastric cancer (GC) and 7 pts (21.2%) had pancreatic cancer. ECOG PS was 0 in 5 pts (15.2%) and 1 in 28 pts (84.8%). 11 pts (33.3%) had been heavily pretreated (≥3 prior lines). Treatment-related adverse events (TRAEs) of any grade occurred in 25 pts (75.8%), in which 8 (24.2%) were ≥ grade 3. No treatment related death was reported. The most common TRAEs (occurring in >20% of pts) were nausea (42.4%), vomiting (36.4%), dry eye syndrome (21.2%) and anemia (21.2%). Two DLTs (grade-3 nausea and vomiting) occurred at the 3 mg/kg dose. The optimal dose of SYSA1801 is being explored. Of 33 pts enrolled, 21 pts were evaluable for efficacy per RECIST v1.1. Objective response rate (ORR) was 38.1% (95% CI: 18.1–61.6%, 8 PRs) and disease control rate (DCR) was 57.1% (95% CI: 34.0–78.2%, 4 SDs). Among 17 evaluable pts with GC, ORR and DCR were 47.1% (95% CI: 23.0–72.2%, 8 PRs) and 64.7% (95% CI: 38.3–85.8%, 3 SDs). One pt with GC receiving SYSA1801 at 1 mg/kg IV Q3W tolerated treatment for 44 weeks with durable confirmed partial response ongoing at the time of analysis. Another pt with GC who failed previous anti-CLDN18.2 treatment achieved a confirmed PR on SYSA1801 2 mg/kg IV Q3W. **Conclusions:** SYSA1801 shows promising early signs of efficacy with a well-tolerated safety profile in pts with CLDN18.2-expressing resistant/refractory solid tumors, especially GC. Part 1 of the study is ongoing with part 2 to start when the optimized dose is determined in China; studies outside of Greater China including in the United States are being planned by Elevation Oncology. Clinical trial information: NCT05009966. Research Sponsor: CSPC Zhongqi Pharmaceutical Technology Co., Ltd.

3017

Poster Discussion Session

ARTEMIS-001: Phase 1 study of HS-20093, a B7-H3–targeting antibody-drug conjugate, in patients with advanced solid tumor. *First Author: Jie Wang, Cancer Hospital, Chinese Academy of Medical Sciences, Beijing, China*

Background: B7-H3, a member of the B7 superfamily, is highly expressed in various solid tumors, but has limited expression at low level in normal tissues. HS-20093 is a B7-H3-targeted antibody-drug conjugate. It could be an attractive therapeutic option for advanced solid tumors, especially the patients (pts) who have failed in multi-line therapy requiring novel and more effective treatment. **Methods:** This is a first-in-human, multicenter, open-label phase 1 study of HS-20093 in advanced solid tumors (NCT05276609). Dose escalation part assessed safety and tolerability of intravenous HS-20093 with doses ranging from 1.0 to 16.0 mg/kg. The dose escalation schedule utilized an accelerated titration and interval 3+3 design. Pts with advanced solid tumor were required to have received prior standard therapy. HS-20093 is administered intravenously every 3 weeks. **Results:** The study completed all planned dose cohorts (1.0 to 16.0 mg/kg) as of cutoff date (20 December 2022). In dose escalation study, 53 pts of multiple tumor types were enrolled and received ≥ 1 dose of HS-20093, which included 29 pts with non-small cell lung cancer, 11 pts with small cell lung cancer (SCLC), 9 pts with sarcoma and 4 pts with other advanced solid tumors. At baseline, 25 pts (47.2%) had received ≥ 3 prior lines therapy with a mean of 3.2 (range, 1-12) prior lines of therapy. Three pts experienced dose-limiting toxicities (1 pt at 12.0 mg/kg; 2 pts at 16.0 mg/kg). The maximum tolerated dose was determined to be 12.0 mg/kg. Treatment-emergent adverse events (TEAEs) occurred in 53 pts (100%). The most common TEAEs overall in $\geq 30\%$ of pts were leukopenia, neutropenia, anemia, pyrexia, nausea, thrombocytopenia, hyponatremia, vomiting, lymphopenia, infusion-related reaction and fatigue. No interstitial lung disease was reported. Of 40 response-evaluable pts, regardless of baseline B7-H3 expression level, 14 partial responses (PRs) were observed in pts treated with HS-20093 from 4.0 mg/kg to 12.0 mg/kg doses (response rate: 35.0%), including 9 confirmed PRs and 5 PRs awaiting confirmation. The disease control rate was 85.0% (34/40, 95% CI: 70.2-94.3). The patient with the longest treatment duration (349 days) remains on treatment. In the subset of 9 SCLC pts, 7 PRs were observed (response rate: 77.8%) with the median depth of response of 50.5%, including 3 confirmed PRs and 4 PRs awaiting confirmation. All responses of SCLC pts occurred at the first disease assessment; the median time to first response was 6 weeks. HS-20093 displayed anti-tumor activity in SCLC pts who have progressed on prior derivative of camptothecin treatment. **Conclusions:** The safety profile of HS-20093 was acceptable. HS-20093 demonstrated promising antitumor activity in several tumor types, especially in SCLC. The further dose expansion study on efficacy and safety of HS-20093 in selected tumor types is ongoing. Clinical trial information: NCT05276609. Research Sponsor: Hansoh Pharmaceutical Group Co, Ltd.

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Poster Discussion Session

Preliminary safety and efficacy of tinengotinib tablets as monotherapy and combination therapy in advanced solid tumors: A phase Ib/II clinical trial. *First Author: Sarina A. Pihl-Paul, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Tinengotinib is a spectrum-selective multi-kinase inhibitor that targets cell proliferation, angiogenesis, and immune-oncology pathways by inhibiting Aurora kinases A/B, Janus kinases (JAK), and receptor tyrosine kinases (FGFRs, VEGFRs). Tinengotinib has shown preliminary efficacy in prostate cancer (PC), hormone receptor positive (HR+)/human epidermal growth factor receptor 2 negative (HER2-) breast cancer (BC), triple-negative BC (TNBC) and cholangiocarcinoma (CCA) in Phase (Ph) 1 trial. Here we present the preliminary safety, pharmacokinetics (PK), and efficacy of tinengotinib in a Ph Ib/II trial. **Methods:** Eligible patients (pts) with advanced or metastatic solid tumors were assigned to: Arm A (tinengotinib 12 mg QD), Arm B (tinengotinib 8/10/12 mg QD in combination with 100 mg/m² Abiraterone, HER2- BC); Arm C PK Run-in (tinengotinib 5/8/10/12 mg QD, or 4/6 mg BID). Objectives include safety (CTCAE v5.0) and tolerability, PK profile, efficacy (RECIST v1.1) and exploratory biomarker(s). **Results:** As of 30 Jan 2023, 157 pts with solid tumors were enrolled and treated. In monotherapy (Arm A and Arm C, N=153), median age was 62.5 years (23-83), 56% were female, 69% had ≥ 3 prior lines of therapy. In combination (Arm B, N=4), median age was 40 years (25-46), 100% were female, 100% had ≥ 3 prior lines of therapy. The treatment-related AEs (TRAE) in monotherapy arms were reported in 110 (71.9%) pts. 53 (34.6%) were Grade (G) 1-2, 55 (35.9%) were G3, 2 (1.3%) were G4, no G5 was observed; the most common TRAEs were hypertension (29.4%), stomatitis (20.9%), diarrhea (16.3%), nausea (13.7%) and palmar-plantar erythrodysesthesia syndrome (12.4%). In the combination arm, 4 treated pts at dose level 1 experienced G3 TRAEs, and the most common TRAEs were neutropenia (75%), stomatitis (50%), hyponatremia (50%), hypokalemia (50%) and hypertension (50%). In 108 efficacy-evaluable pts of monotherapy arms, the overall response rate (ORR) and disease control rate (DCR) were 16% and 60%, respectively. The ORR in PC, HR+/HER2- BC, TNBC and CCA were 50% (5/10), 40% (2/5), 50% (3/6) and 20% (3/15), respectively. Preliminary PK analysis showed a linear increase on exposure in terms of geometric mean C_{max,ss} and AUC_{0-24h,ss} from 5 mg QD to 12 mg QD. No significant difference in exposure was observed in QD vs BID. **Conclusions:** Tinengotinib monotherapy was well-tolerated. The tolerability assessment in combination with chemotherapy is underway. The PK results may support dose recommendation for subsequent trials. Encouraging anticancer activity of tinengotinib monotherapy were observed in pts with heavily pre-treated solid tumors, including PC, HR+/HER2- BC, TNBC and CCA. The ongoing Ph II study of tinengotinib continues to evaluate clinical benefit and safety in pts with PC. Clinical trial information: NCT04742959. Research Sponsor: TransThera Sciences (Nanjing), Inc.

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Poster Discussion Session

Phase 1 trial evaluating TTI-101, a first-in-class, orally bioavailable, small molecule, inhibitor of STAT3, in patients with advanced solid tumors. *First Author: Apostolia Maria Tsimberidou, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Signal transducer and activator of transcription 3 (STAT3) is a transcription factor at the critical intersection of signaling pathways controlling gene networks integral to the survival and immune sequestration of cancer cells. Given the integral role of STAT3 in tumorigenesis and immune suppression, STAT3 signaling inhibition may have dual antitumor activity. TTI-101 is a first-in-class, orally bioavailable, selective small molecule that binds to STAT3 and prevents STAT3-mediated transcriptional activation. A first-in-human, Phase 1, dose escalation and expansion study of TTI-101 monotherapy was conducted in patients with advanced/refractory solid tumors (NCT03195699). **Methods:** Patients with advanced metastatic cancer who had failed standard therapy were treated with TTI-101 twice daily in 28-day cycles at dose levels (DL) 1-4: 3.2 (DL1), 6.4 (DL2), 12.8 (DL3), and 25.6 (DL4) mg/kg/d ("3+3" design). Three different formulations of TTI-101 were used stepwise, beginning with formulation 1 (F1). A second-generation formulation (F2) was introduced at DL3 during dose escalation and patients were stratified into two cohorts: hepatocellular carcinoma (HCC) and other solid tumors. A third-generation formulation (F3) was evaluated once the recommended phase 2 dose (RP2D) was determined. Treatment continued until disease progression, unacceptable toxicity, or study withdrawal. **Results:** Key patient characteristics included a median age of 63 years (range, 33-78), 52% male, and a median number of 3 (range, 1-9) prior systemic therapies. No dose limiting toxicities (DLTs), or fatal treatment-related adverse events (TRAEs) were observed. Diarrhea was the only TRAE observed in $\geq 30\%$ of the safety population (n=64) with events being mostly Grade 1/2. F3 was better tolerated than F1 and F2 with no events $\geq$ Grade 3. One patient experienced transient Grade 4 hyperglycemia which resolved with insulin and metformin. Five patients had serious TRAEs (all Grade 3), which resolved. TTI-101 showed linear pharmacokinetics from DL1-3 plateauing at DL3. The RP2D was determined to be 12.8mg/kg/d (DL3) for both the HCC and other solid tumor cohorts. Of the 39 patients evaluable for response, 5 (13%) patients had confirmed partial responses (cPR) and 16 (41%) stable disease (SD). Of the 15 patients with HCC, 3 (20%) had a cPR with a median duration of 10.5 months. The other two cPRs were in ovarian cancer (n=1) and gastric cancer (n=1). **Conclusions:** TTI-101 was well-tolerated and no DLTs were noted. cPRs were observed across tumor types. The antitumor activity of TTI-101 monotherapy in the relapsed/refractory setting is promising, particularly in HCC. Two Phase 2 oncology studies of TTI-101 in STAT3-driven cancers (HCC and metastatic breast cancer) are underway. Clinical trial information: NCT03195699. Research Sponsor: Tvardi Therapeutics, Inc.; V Foundation; U.S. National Institutes of Health; Cancer Prevention and Research Institute of Texas (CPRIT).

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Poster Discussion Session

A first-in-human, phase 1 study of the SHP2 inhibitor PF-07284892 as monotherapy and in combination with different targeted therapies in oncogene-driven, treatment-resistant solid tumors. *First Author: Alexander E. Drilon, Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY*

Background: Src homology region 2 domain-containing phosphatase-2 (SHP2) activation mediates targeted therapy resistance in various oncogene-driven cancers. In this phase 1 study (NCT04800822), the novel SHP2 inhibitor PF-07284892 (ARRY-558) was evaluated alone and in combination with different targeted therapies in patients (pts) with oncogene-driven tumors that progressed on prior targeted therapy. Unlike other phase I studies, the unique design of this trial allowed pts to receive combination therapy during dose escalation after a period of PF-07284892 monotherapy. This is critical given that monotherapy efficacy was deemed unlikely based on preclinical data. **Methods:** Eligible pts with advanced solid tumors were enrolled into escalating dose cohorts of PF-07284892 monotherapy. In the absence of dose limiting toxicity (DLT), matched targeted therapy (lorlatinib for ALK/ROS1 fusion+ cancers, encorafenib + cetuximab for BRAF^{V600E} colorectal cancers, and binimetinib for MAPK-mutant cancers) could be added after 6 weeks of monotherapy at the discretion of the investigator. Primary objectives were safety, tolerability, and recommended dose for further evaluation (RDE) determination. Secondary/exploratory objectives included analyses of pharmacokinetics (PK), circulating tumor DNA (ctDNA), and monotherapy/combination therapy objective response (RECIST v1.1). **Results:** As of 9/19/2022, 33 pts with oncogene-driven solid tumors were enrolled (20-80 mg, orally twice weekly, day 1 and 4 or day 1 and 2 schedule), of whom 18 received combination therapy (5 ALK/ROS1 fusion+ cancers, 4 BRAF^{V600E}+CRCs, 9 MAPK mutant cancers). The median age was 54.5 y (range 32-78). The most common treatment-related adverse events (TRAEs; $>15\%$) for monotherapy were anemia (21%), peripheral edema (18%), and increased AST (18%). Cycle 1 monotherapy DLTs occurred in 4 pts: G3 increased AST, ALT, and bilirubin (n=1); anemia (n=1); and increased AST and ALT, and thrombocytopenia (n=1); and G4 bilirubin (n=1). PF-07284892 PK was dose proportional. 40 mg twice weekly (day 1 and 2) was selected as the RDE. With combination therapy, confirmed RECIST v1.1 partial responses (PR) were observed in 3 treatment-refractory pts (2 lorlatinib and 1 binimetinib combination), and stable disease was observed in 6 treatment-refractory pts. $\geq 80\%$ ctDNA founder mutation reduction was observed post combination therapy initiation in 2 of the responding pts. **Conclusions:** PF-07284892 was generally well tolerated alone and in combination with rational targeted therapies. This study design enabled combination therapy rescue of disease progression on PF-07284892 monotherapy with 3 pts achieving confirmed PR. Clinical trial information: NCT04800822. Research Sponsor: Pfizer.

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Poster Session

A phase II study of tinostamustine in patients (pts) with advanced solid tumours. *First Author: Anna Tinker, BC Cancer - Vancouver, Vancouver, BC, Canada*

Background: The novel multi-action alkylating deacetylase inhibitor tinostamustine improves drug access to DNA strands within cancer cells, breaks them and counteracts damage repair. Tinostamustine was well tolerated with signals of efficacy during dose escalation in pts with advanced solid tumours (Mita et al. Cancer Res 2019;79[13 Suppl]:CT023). **Methods:** This was an open-label Phase I/II trial of single agent tinostamustine in pts with advanced solid tumours (NCT03345485). The Phase II primary endpoint was objective response rate (ORR: complete response + partial response (PR)) and the rate of stable disease ≥ 4 mo duration following the recommended Phase II dose (RP2D; 80 mg/m² over 1 h on Day 1 & 15 of each 4-wk treatment cycle). Secondary endpoints included progression-free (PFS) and overall survival (OS), and duration of response. Eligible pts were ≥ 18 y with life expectancy ≥ 3 mo, Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 2 , histologically confirmed diagnosis of advanced/metastatic soft tissue sarcoma (STS), small-cell lung (SCLC), triple-negative breast (TNBC), ovarian (OvCa) or endometrial cancer, progression following ≥ 1 prior line of therapy, with no other standard therapy with proven clinical benefit available or recommended. **Results:** 36 pts were enrolled and evaluable for response; mean $\pm$ SD age 59.6 $\pm$ 11.2 y, 83.3% female, 80.6% Caucasian, all ECOG PS ≤ 1 , median of 3 (range 1–9) lines of prior therapy. At data cut-off (30 November 2022) pts had received a median of 2 (range 1–8) cycles of tinostamustine. 19 pts (52.8%) discontinued treatment due to progressive disease. One pt with synovial sarcoma (STS cohort; n=10) and one pt with OvCa (n=12) achieved a PR. Overall, 14 pts (38.9%) had stable disease ≥ 4 mo (0/4 SCLC; 3/10 STS; 3/4 TNBC; 5/12 OvCa; 3/6 endometrial cancer); Clinical Benefit Rate, 44.4% (95% CI: 27.9%, 61.9%). Median PFS and OS for all treated pts were 2.2 mo (95% CI 1.8, 3.3 mo) and 5.5 mo (95% CI 4.1, 15.0 mo), respectively. All pts experienced ≥ 1 treatment-emergent adverse event (TEAE), with 56.7% of events considered related to tinostamustine. Serious tinostamustine-related AEs were reported in 30.6% of pts (13 haematological events); 10 (27.8%) pts discontinued treatment due to TEAEs (platelet count decreased: 5 events in 3 pts, including 2 Grade 3 and 1 Grade 4; all other events n=1). Two pts experienced fatal TEAEs; n=1 each of intra-abdominal haemorrhage (considered related to study drug), hypoxia/dyspnoea (not study drug related). **Conclusions:** Tinostamustine demonstrated modest signals of efficacy, with 2 pts achieving a PR, and manageable tolerability in pts with advanced solid tumours for whom no other standard therapy with proven clinical benefit was available or recommended. Further studies are needed to fully explore the benefits of tinostamustine in solid tumours. Clinical trial information: NCT03345485. Research Sponsor: Mundipharma Research Limited and Purdue Pharmaceuticals LP.

3023

Poster Session

Safety and efficacy of DB-1303 in patients with advanced/metastatic solid tumors: A multicenter, open-label, first-in-human, phase 1/2a study. *First Author: Kathleen N. Moore, Stephenson Cancer Center at the University of Oklahoma, Oklahoma City, OK*

Background: DB-1303 is an antibody-drug conjugate (ADC) consisting of a humanized anti-HER2 IgG1 monoclonal antibody, covalently linked to proprietary DNA topoisomerase I inhibitor (P1003) via a maleimide tetrapeptide-based cleavable linker, with a high drug-to-antibody ratio (~8). **Methods:** This is a global first-in-human, dose-escalation and -expansion study in patients (pts) with advanced/metastatic solid tumors. Pts (ECOG 0-1) with HER2 – (high or low) expressing or mutant cancers who failed previously systemic therapies were recruited and received DB-1303 intravenously Q3W as monotherapy. The objectives were safety, tolerability, maximum tolerated dose (MTD) or recommended phase 2 dose (RP2D), pharmacokinetics (PK), and preliminary antitumor activity. Here we report the results from dose-escalation. **Results:** As of Jan 13, 2023, 85 pts received DB-1303 at 6 dose levels (2.2, 4.4, 6.0, 7.0, 8.0, and 10.0 mg/kg) and received a median of 7 (range, 1-27) prior lines of therapy, including previous anti-HER2 ADC therapy in 32.9% of pts. The median duration of treatment was 63.0 (range, 21-211) days, and 68 pts (80.0%) remained on treatment. Treatment-emergent adverse events (TEAEs) and $\geq$ grade (G) 3 TEAEs occurred in 74 pts (87.1%) and 18 pts (21.2%), respectively; the most common TEAEs were nausea (51.8%, 3.5% $\geq$ G3), vomiting (43.5%, 1.2% $\geq$ G3), platelet count decreased (35.3%, 3.5% $\geq$ G3), and anemia (29.4%, 5.9% $\geq$ G3). Few pts experienced neutropenia (10 [11.8%]) and alopecia (3 [3.5%]). There was no DLT or TEAEs leading to death. Interstitial lung disease occurred in 2 pts (2.4%, G1), without any $\geq$ G2. The exposure parameters (C_{max} and AUC) of DB-1303 ADC increased with ascending doses from 2.2 to 10.0 mg/kg. The half-life of DB-1303 ADC is approximately 6-7 days for 6.0-8.0 mg/kg dose cohorts. The exposure of serum release payload was magnitudes lower than that of DB-1303 ADC, demonstrating stability of the ADC in systemic circulation. A total of 52 pts had undergone at least one post-baseline tumor scan. Twenty-three pts (44.2%, 23/52) had objective partial tumor response per RECIST 1.1: Thirteen HER2+ breast cancer (BC) (50.0%, 13/26, including 5 pts with brain metastases [55.6%, 5/9]), 5 HER2 low BC (38.5%, 5/13), 2 colorectal cancer (66.7%, 2/3), 1 endometrial carcinoma (33.3%, 1/3), 1 esophageal cancer (50.0%, 1/2), and 1 ovarian cancer (50.0%, 1/2). Among all the pts, the DCR was 88.5% (46/52); for pts with HER2+ BC and HER2-low BC, the DCRs were 96.2% (25/26) and 84.6% (11/13), respectively. **Conclusions:** DB-1303 was well tolerated with encouraging preliminary antitumor activity in heavily pretreated pts with advanced/metastatic solid tumors, especially in pts with HER2+ BC and brain metastasis as well as in HER2-low BC. Expansion is ongoing in selected tumor pts treated at the RP2D. Clinical trial information: NCT05150691. Research Sponsor: Duality Biologics.

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Poster Session

Phase 1 study of indenoisoquinoline LMP744 in adults with relapsed solid tumors and lymphomas. *First Author: Brian Ko, Developmental Therapeutics Clinic, Division of Cancer Treatment and Diagnosis, National Cancer Institute, National Institutes of Health, Bethesda, MD*

Background: Indenoisoquinolines (IIQ) are non-camptothecin inhibitors of topoisomerase 1 (TOP1) that have improved characteristics over camptothecin TOP1 inhibitors. IIQs demonstrate better chemical stability, produce more persistent DNA breaks induced by trapping DNA-TOP1 cleavage complexes, induce DNA breaks at different sites than camptothecins, and are not substrates for cellular export proteins. We present data from a trial of LMP744 (NSC 706744), which was the most efficacious IIQ in a canine lymphoma trial, designed to establish the safety, efficacy, and maximum tolerated dose (MTD) of LMP744. **Methods:** We conducted a multicenter phase 1 trial in adult patients (pts) with dose escalations following design 3 of the Simon accelerated titration designs. LMP744 was administered intravenously daily on d1-5 in 28-day cycles (C), starting at dose level (DL) 1 (6 mg/m²/d). Responses and adverse events (AEs) were defined by RECIST 1.1 and CTCAE v4.0, respectively. Plasma concentrations were determined by LC-MS/MS with a validated assay over a range of 1-3,000 ng/mL. Paired biopsies (baseline and C1D2) were analyzed for DNA damage response markers (γ H2AX, pNBS1, and Rad51) by IFA. **Results:** A total of 36 pts were enrolled, median age was 61 years (range 35-81), median prior lines of systemic treatment was 5 (range 2-10) and 26 pts (72%) had received prior TOP1 inhibitor therapy. One pt on DL6 (190 mg/m²/d) experienced a dose-limiting toxicity (DLT) of grade 3 hypokalemia during C1, reverting the study to a 3+3 design. MTD was established at DL6. Of 24 patients evaluable for response, 1 pt with small cell lung cancer on DL6 achieved a partial response (PR), remaining on treatment for 7C. 17 pts had stable disease (including 1 pt with an unconfirmed PR), and 6 had progressive disease. Median duration of response among pts with SD was 4.5C (range 1-28). A total of 6 pts on DL6 with colorectal cancer (n=4, all had received prior irinotecan), mesothelioma (n=1), and low-grade appendiceal mucinous neoplasm (n=1) remained on study for >6 C. Treatment-related grade 3/4 AEs included leukopenia (n=9), anemia (n=4), dehydration (n=2), neutropenia (n=2) and nausea (n=2). Pharmacokinetic (PK) data for the first 17 patients suggests dose-linear PK, best fit to a 2-compartment model. Approximate half-life, clearance, central and peripheral volume values were 30 h, 90 L/h, 200 L, and 2500 L, respectively. Induction of γ H2AX and Rad51 was measured in the pt with PR. **Conclusions:** The MTD of LMP744 was established at 190 mg/m²/d on d1-5 in a 28d C. The single agent activity of LMP744 in this heavily pretreated population was limited; however, 4 colorectal cancer pts had prolonged stabilization of disease with prior progression on irinotecan. Analyses of secondary and exploratory correlatives are ongoing. Clinical trial information: NCT03030417. Research Sponsor: U.S. National Institutes of Health.

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Poster Session

SGN-B6A, an integrin beta-6 (ITGB6)-targeted antibody-drug conjugate (ADC), in patients with advanced solid tumors: Updated results from a phase 1 study (SGNB6A-001). *First Author: Antoine Hollebecque, Institut Gustave Roussy, Villejuif, France*

Background: The receptor ITGB6 plays a role in tumor pathogenesis and invasiveness, and its overexpression is correlated with poor outcomes. Non-small cell lung cancer (NSCLC), head and neck (HNSCC), and esophageal cancer (EC) are among tumors with high ITGB6 expression (Lyon 2021). SGN-B6A is an ITGB6-directed vedotin ADC with a monomethyl auristatin E (MMAE) payload. SGN-B6A elicits antitumor activity via MMAE-mediated cytotoxicity, bystander effect, and immunogenic cell death. Here, we present updated results of an ongoing phase 1 study with a focus on NSCLC, HNSCC, and EC (Hollebecque SITC 2022). **Methods:** SGNB6A-001 (NCT04389632) is an open-label, multicenter, dose-escalation/expansion study evaluating the safety, pharmacokinetics, and antitumor activity of SGN-B6A (per RECIST v1.1) in patients (pts) with advanced solid tumors. Dose escalation (Part A) explored continuous weekly and intermittent dosing regimens. Dose was calculated using total body weight (TBW) or adjusted ideal body weight. Dose expansion (Part B) is enrolling pts with NSCLC, HNSCC, and EC. **Results:** As of 14 December 2022, 148 pts received SGN-B6A, 88 pts in Part A and 60 pts in Part B; enrollment for Part A is complete. In all cohorts (N=148), treatment-emergent adverse events (TEAEs) were observed in 88.5% of pts: 50.7% were Grade ≥ 3 (21.6% related), and 37.2% were serious (8.1% related); 6.1% of pts discontinued treatment due to TEAEs. 3 pts (2.0%) died due to TEAEs; none of the deaths were considered treatment-related. The most common TEAE was fatigue (35.1%); the most common Grade ≥ 3 TEAE was neutropenia (8.1%); the most common TEAEs leading to treatment discontinuation were peripheral sensory neuropathy and pneumonia (1.4% each). Prior lines of therapy and efficacy data for Part A (NSCLC, EC, and HNSCC) and Part B (HNSCC) subsets are summarized. **Conclusions:** SGN-B6A demonstrated a manageable safety profile, and showed encouraging preliminary antitumor activity and response durability in dose escalation in a heavily pretreated population. Part B dose expansion cohorts in NSCLC, esophageal squamous cell carcinoma (ESCC), and HNSCC are ongoing. Clinical trial information: NCT04389632. Research Sponsor: Seagen Inc.

Tumor Type, n (Total; TBW Dosing)	NSCLC(n=27)	EC(n=12)	HNSCC(n=15)	HNSCC Expansion(n=19)
Median Prior Lines of Therapy (Range)	3.5 (1 to 8)	3.0 (1 to 5)	3.0 (1 to 4)	3.0 (1 to 6)
Confirmed ^a Best Overall Response, n (%)				
CR	2 (7.4)	0	0	0
PR	7 (25.9)	4 (33.3)	3 (20.0)	6 (31.6)
SD	8 (29.6)	4 (33.3)	6 (40.0)	5 (26.3)
PD	9 (33.3)	4 (33.3)	4 (26.7)	6 (31.6)
NE	1 (3.7)	0	2 (13.3)	2 (10.5)
ORR, n (%) [95% CI]	9 (33.3) [16.5, 54.0]	4 (33.3) [9.9, 65.1]	3 (20.0) [4.3, 48.1]	6 (31.6) [12.6, 56.6]
Median DOR, Months (Range)	11.3 (2.5 to 11.3+)	5.6 (3.5 to 9.8)	5.5 (4.7 to 20.5+)	- (2.3+ to 7.8+)

^a Best overall response per RECIST v1.1. CR or PR was confirmed with repeat scan ≥ 28 days after initial response. + Censored. - Not estimable.

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Poster Session

Final analysis of multi-histology basket trial expansion of ado-trastuzumab emtansine in patients with *HER2* amplified cancers. *First Author: Dazhi Liu, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Human epidermal growth factor receptor 2 (*HER2*, *ERBB2*) amplification occurs in 5% of non-breast non-gastric solid tumors. Ado-trastuzumab emtansine (T-DM1) showed preliminary efficacy in patients with *HER2* amplified lung, endometrial, salivary gland, biliary tract and ovarian cancers, but the extent of its differential effects across histologies is unknown. **Methods:** Patients with *HER2* amplified solid tumors were enrolled and received treatment 3.6mg/kg IV every 3 weeks. The primary endpoint was overall response rate (ORR) using RECIST v1.1 or PERCIST. A basket trial expansion used a Simon two stage optimal design applied to each of 5 histology cohorts with type I error rate under 2%, power of 90%, H0 10%, H1 40%, with family-wise error rate at 10%. After first stage, lung, salivary gland and endometrial cohorts were expanded to 23 patients. The null hypothesis was rejected for each cohort separately, if at least 6 responses were observed in each cohort. Secondary endpoints included duration of response (DOR), progression-free survival (PFS) and toxicity. *HER2* amplification was identified by fluorescence *in situ* hybridization (FISH), or next generation sequencing (NGS). Correlative studies were performed using tissue immunohistochemistry (IHC). Plasma cell-free DNA (cfDNA) was collected throughout study treatment. **Results:** 88 patients with 8 unique cancer types were treated across 5 cohorts of *HER2* amplified lung, salivary gland, colorectal, endometrial and other cancers. The median age was 66 (26-90). Median line of prior therapy was 2 (1-7). ORR was 33% (29/87 including 11 CRs, 95% CI 24-44%), including 47% (9/19) for lung cancers, 87% (13/15, 8 CRs) for salivary gland cancers, 22% (5/23, 3 CRs) for endometrial cancers, 12% (1/8) for biliary cancers, 14% (1/7) for ovarian cancers. Median DOR was 9.7 months (95% CI 4.8, 20.2), median PFS was 2.76 months (95% CI 2.53, 5.39). There were 8 (9%) G3 treatment related toxicities. *HER2* fold change corrected for purity and ploidy by FACETS algorithm correlated with response ($p=0.04$) and PFS ≥ 3 months ($p=0.0037$). *HER2* amplification by NGS correlated with *HER2*/CEP17 ≥ 2 by FISH (67/71 tested) and IHC3+ (54/68 tested). We observed persistent *HER2* amplification in plasma cfDNA during acquired resistance and progression on T-DM1 in patients with salivary gland cancers. **Conclusions:** Ado-trastuzumab emtansine showed promising efficacy in patients with *HER2* amplified lung and salivary gland cancers as identified by NGS, meeting the primary endpoint. However, its efficacy did not meet prespecified response rate in patients with *HER2* amplified endometrial, colorectal and other cancers. Histologic lineage differences in *HER2* amplified cancers affect response and translational research is critical for further drug development. Clinical trial information: NCT02675829. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology; U.S. National Institutes of Health.

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Poster Session

Mirzotamab clezutoclastax as monotherapy and in combination with taxane therapy in relapsed/refractory solid tumors: Dose expansion results. *First Author: Benedito A. Carneiro, Legorreta Cancer Center, Brown University, Providence, RI*

Background: Mirzotamab clezutoclastax (ABBV-155; Mirzo-C) is a first-in-class antibody-drug conjugate with three components: an anti-B7-H3 monoclonal antibody, a solubilizing linker, and a BCL-X_L inhibitor payload. By specific targeting of BCL-X_L, synergy with other anticancer agents was observed in preclinical models. When combined with a taxane, clinical antitumor activity was reported in relapsed and/or refractory (R/R) solid tumors during the dose escalation phase of an ongoing Phase 1, open-label study (NCT03595059). **Methods:** In the dose expansion phase of the Phase 1 study, patients were treated as follows: (i) R/R small cell lung cancer (SCLC) with Mirzo-C monotherapy, (ii) non-small cell lung cancer (NSCLC) with Mirzo-C + docetaxel, and (iii) hormone positive, Her2 negative, post-CDK4/6 inhibitor breast cancer (BrCa) with Mirzo-C + paclitaxel. Mirzo-C was administered at the recommended Phase 2 dose determined at dose escalation. Primary objectives were safety and overall response rate (ORR). **Results:** As of November 18, 2022, 78 patients were enrolled (NSCLC n=14; NSCLC n=36; BrCa n=28). The median (range) follow-up was 2.0 (0.6–9.1) months for the SCLC cohort, 4.9 (0.6–8.5) for NSCLC, and 10.4 (0.8–13.3) for BrCa. The median number of prior lines of systemic therapy was 2 in the SCLC cohort, 2 in NSCLC, and 6 in BrCa. Prior taxane therapy was received by 7% of patients in the SCLC cohort, 36% in NSCLC, and 64% in BrCa. The most common adverse events (AEs) in SCLC were fatigue, increased aspartate aminotransferase, diarrhea, and headache (21%, n=3 for each AE); fatigue was the most common AE in NSCLC (58%, n=21; Grade 3/4: 3%, n=1) and in BrCa (61%, n=17). Thrombocytopenia, a result of the systemic effects of BCL-X_L inhibitors, was not observed in the Mirzo-C monotherapy cohort. Neutropenia/decreased neutrophil count was not observed in the SCLC monotherapy cohort but was common with BrCa paclitaxel combo (64%, n=18; Grade 3/4: 29%, n=8) and NSCLC docetaxel combo (53%, n=19; Grade 3/4: 44%, n=16); 5 patients in the NSCLC cohort (14%) and 1 in BrCa (4%) had febrile neutropenia. Confirmed ORR was 0% in the SCLC cohort, 11% in NSCLC, and 18% in BrCa. **Conclusions:** Mirzo-C demonstrated a tolerable safety profile as monotherapy and with taxanes. No thrombocytopenia or neutropenia was observed with monotherapy. No single-agent activity of Mirzo-C was observed in SCLC. Combination treatments were active with high best overall response (BOR) and disease control rates in heavily pretreated NSCLC and BrCa patients, where Grade 3/4 neutropenia was observed. It is unknown if Mirzo-C exacerbated the neutropenia risk associated with taxanes. Clinical trial information: NCT03595059. Research Sponsor: AbbVie.

	SCLC, n (%)n=14	NSCLC, n (%)n=36	BrCa, n (%)n=28
PR	0	13 (36)	10 (36)
Confirmed PR	0	4 (11)	5 (18)
SD	1 (7)	16 (44)	10 (36)
Disease control (CR + PR + SD)	1 (7)	29 (81)	20 (71)
PD	9 (64)	2 (6)	6 (21)
Missing data	4 (29)	5 (14)	2 (7)

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Poster Session

A phase 1 dose escalation/expansion study of FID-007, a novel nanoparticle paclitaxel formulation, in patients with solid tumors. *First Author: Jacob Stephen Thomas, University of Southern California, Norris Comprehensive Cancer Center, Los Angeles, CA*

Background: FID-007 (FID) consists of paclitaxel encapsulated in a poly-ethyloxazoline (PEOX) polymer excipient designed to enhance PK, biodistribution, and tolerability. In addition to allowing the drug to remain in solution until it can enter a cancer cell, the PEOX nanoparticle preferentially delivers paclitaxel to the tumor through the leaky hyperpermeable vasculature. In xenograft studies, FID reduced or limited tumor growth in multiple tumor types including lung, gastric, breast, pancreatic, and ovarian cancer. Preclinically, FID was more effective at lower or comparable taxane doses, including nab-paclitaxel, with fewer side effects. We present the first-in-human trial of FID. **Methods:** The study is evaluating the safety, PK, and efficacy of FID in pts with advanced solid tumors. The primary objective is to determine the MTD and RP2D. Pts received FID in doses between 15mg/m² and 160mg/m² using a standard 3+3 dose escalation design. FID was given IV on Days 1, 8, and 15 of a 28-day cycle. Eligibility included ECOG 0-2, adequate organ function, and ≤ 3 prior lines of cytotoxic therapy for advanced disease. **Results:** Thirty-six patients were treated across 7 dose levels. Median age was 61 (39-65). ECOG PS was 2 in 1 patient, 1 in 69% of patients. Median number of prior therapies was 2 (1-5). Median number of cycles was 2.5 (1-30). There were 2 DLTs of grade 3 rash at 100 mg/m². Given the transient nature of the rash and response to topical therapy, DLT definition was modified to exclude grade 3 rash that lasts ≤ 7 days and 3 additional patients were treated at 100 mg/m² which was deemed tolerable. There was 1 DLT of grade 4 WBC decrease at 125 mg/m², and 1 DLT of G3 febrile neutropenia at 160 mg/m². There was no MTD. All grade treatment related adverse events (TRAEs) in $\geq 25\%$ of pts were rash (64%), alopecia (56%), leukopenia (47%), pruritus (44%), neutropenia (42%), anemia (42%), fatigue (39%), nausea (33%), anorexia (31%), dysgeusia (25%) and peripheral sensory neuropathy (25%). Grade 3/4 TRAEs occurring in > 1 pt were maculopapular rash (25%), anemia, neutropenia, and leukopenia (17% each). Of 36 evaluable patients, 7 (19%) had a partial response by RECIST 1.1 (pancreatic, biliary tract, and HNSCC) and 13 (36%) had stable disease. Three out of 4 HNSCC patients with PR had previously been treated with docetaxel. PK is linear and dose proportional. There is no paclitaxel accumulation after weekly dosing, and $t_{1/2}$ is between 18-26 hours. Based on overall tolerability and PK, the dose of 125mg/m² (dose level 6) has been chosen as RP2D. **Conclusions:** FID has a manageable safety profile and demonstrates preliminary evidence of anti-tumor activity in heavily pre-treated pts across different tumor types. No high-grade neuropathy has been noted to date. RP2D of FID is set at 125mg/m². PK is linear, dose proportional and comparable to that of nab-paclitaxel. Clinical trial information: NCT03537690. Research Sponsor: Fulgent Pharma.

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Poster Session

A novel genetic marker of fluoropyrimidine-induced cardiovascular toxicity. *First Author: Claire Palles, Institute of Cancer and Genomic Sciences, University of Birmingham, Birmingham, United Kingdom*

Background: Fluoropyrimidine (FP) based adjuvant chemotherapy (5-Fluorouracil and Capecitabine) increases survival of patients with colorectal and breast cancers. However, 1-5 % of patients experience cardiovascular toxicity, which is not explained by variants in the gene encoding dihydropyrimidine dehydrogenase. **Methods:** We sought genetic determinants of FP-induced cardiovascular toxicity by performing a genome wide association study of NCI-CTCAE graded cardiovascular toxicity using samples from the QUASAR 2 trial (n=759 patients with colorectal cancer (CRC)). Validation studies (n= 5438 patients with CRC and 1478 patients with breast cancer) were performed in the SCOT, COIN and TACT2 trials. The most commonly reported symptoms were chest pain, angina and arrhythmias with 6 patients experiencing myocardial infarctions. **Results:** rs4904753, mapping to an intron of *D-glutamate cyclase (DGLUCY)* was genome wide significant in QUASAR 2 ($P=4.38 \times 10^{-16}$) and validated in SCOT, COIN and TACT2 ($P<0.0002$ in all studies. rs4904753 was associated with levels of expression of *DGLUCY* in multiple tissues including the atrial appendage. Under a recessive model, 45.3% (61/137) of patients with cardiac toxicity as compared to 10.2% (691/6786) of controls carried both minor alleles (meta-analysis: OR=7.72, 95% CI 5.31-11.22, $P=1.03 \times 10^{-26}$). **Conclusions:** The sensitivity, specificity, positive predictive value and negative predictive values of testing for two copies of the toxicity associated allele of rs4904753 were 48%, 90%, 8% and 99% respectively. Clinical implementation of testing for this variant has the potential to identify almost half of those at risk of FP-induced cardiovascular toxicity with high specificity, thereby enabling changes to their clinical management. Research Sponsor: Cancer Research UK; University of Birmingham, Cardiff University School of Medicine.

rs4904753 is a novel marker of cardiovascular toxicity and has been validated in multiple independent clinical trials.

Study	Cancer type	Treatments	# cardiovascular toxicity cases	# controls	OR (95% CI)	P	OR (95% CI)	P
QUASAR 2	Stage III CRC	Capecitabine +/- Bevacizumab	24	735	19.19 (7.77-47.43)	4.38 x 10 ⁻¹⁶	41.99 (15.16-116.31)	4.00 x 10 ⁻¹⁶
SCOT	Stage III CRC	XELOX or FOLFOX	39	2900	3 (1.89-4.77)	2.42 x 10 ⁻⁴	6.07 (3.17-11.63)	7.54 x 10 ⁻⁷
COIN	Stage IV CRC	XELOX or FOLFOX	46	1694	3.01 (1.94-4.69)	7.08 x 10 ⁻⁷	5.95 (3.21-11.01)	2.54 x 10 ⁻⁷
TACT2	Breast cancer	CMF or Capecitabine	19	1462	3.36 (1.74-6.46)	2.00 x 10 ⁻⁴	5.6 (2.22-14.12)	8.11 x 10 ⁻⁴
Meta-analysis			137	6782	3.63 (2.76-4.78)	2.79 x 10 ⁻²⁰	7.72 (5.31-11.22)	1.03 x 10 ⁻²⁶

XELOX: Oxaliplatin and Capecitabine; OxMDG/FOLFOX: leucovorin, 5-FU, oxaliplatin; CMF: cyclophosphamide, methotrexate, 5-FU.

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Poster Session

A first-in-human, open label, multiple dose, dose escalation, and cohort expansion phase I study to investigate the safety, tolerability, pharmacokinetics and antitumor activity of BB-1701 in patients with locally advanced/metastatic HER2-expressing solid tumors. *First Author: Fei Ma, Cancer Hospital, Chinese Academy of Medical Sciences, Beijing, China*

Background: BB-1701 is an antibody-drug conjugate consisting of a humanized IgG1κ monoclonal antibody and eribulin. When BB-1701 targets HER2-expressing cancer cells and is internalized, free eribulin is cleaved from the ADC by cathepsin b and causes cytotoxicity to cancer cells. The neighboring cells were affected with bystander effects, like cytotoxicity on tumor cells and non-cytotoxic effects on microenvironment by free eribulin. Here, we report preliminary results from this phase 1 study (NCT04257110). **Methods:** This dose escalation study followed an accelerated titration and traditional "3 + 3" design with 6 dose levels from 0.4 to 2.6 mg/kg Q3W. Patients with confirmed advanced/metastatic HER2 overexpressing solid tumors, who had progressed on, or were intolerant to prior standard therapies, aged ≥ 18 years, with ECOG PS ≤ 2, and measurable disease, were enrolled. HER2 expressions were determined by IHC or next generation sequencing. Tumor imaging was conducted every 9 weeks. The primary objective is the assessment of safety and tolerability, and the secondary objective is the assessment of PK and preliminary anti-tumor activity. **Results:** A total of 29 patients were enrolled in this study. Tumor types were breast cancer, gastric/gastroesophageal junction cancer, colorectal cancer, gallbladder cancer, ovarian cancer and urothelial cancer. The medium prior lines of systemic therapy were 3 (range 1 – 6). During this study, no DLT was observed and the MTD was not reached. The most commonly reported (≥20%) treatment-related adverse events (TRAEs) were peripheral neuropathy, aspartate aminotransferase increased, neutrophil count decreased, white blood cell count decreased, alanine aminotransferase increased, hypertriglyceridemia, anemia, platelet count decreased. The most commonly reported ≥ grade 3 TRAEs (≥10 %) was peripheral neuropathy. There were two grade 4 adverse events: neurological symptom and sepsis. There was no interstitial lung disease observed during the study. Nine patients discontinued the study treatment due to peripheral neuropathy. Thirteen patients out of 26 patients evaluable for antitumor activity achieved partial response (PR), and 11 patients had stable diseases (SD). The best overall response rate (BOR) was 50.0% (13/26) and the disease control rate (DCR) was 92.3% (24/26). For 17 breast cancer patients in the study, 12 patients achieved PR, and 5 patients had SD. The BOR was 70.5% (12/17) and the DCR was 100% (17/17). For 5 gastric cancer patients in the study, all patients had SD. The duration of treatment ranged from 2 weeks to 66 weeks. **Conclusions:** BB-1701 was generally well tolerated up to 2.6 mg/kg dose levels and has shown promising antitumor activity in patients with HER2-overexpression solid tumors. Clinical trial information: NCT04257110. Research Sponsor: Bliss Biopharmaceutical (Hangzhou) Co., Ltd.

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Poster Session

Plasma lipidomic profiling of chemotherapy-induced peripheral neuropathy. *First Author: Nicole Yeung, Garvan Institute of Medical Research, Sydney, NSW, Australia*

Background: Chemotherapy-induced peripheral neuropathy (CIPN) is a dose-limiting side effect of cytotoxic cancer treatment. This may result in dose reduction (DR) or chemotherapy discontinuation (CD) and ultimately decrease the efficacy of therapy. There is a lack of studies examining the role of lipids in relation to CIPN, despite the association of obesity with worse CIPN, and hyperlipidaemia with diabetic neuropathy. The aim of this study is to determine if circulating lipids are associated with CIPN severity. **Methods:** Pre-chemotherapy plasma samples from 137 patients with CIPN from docetaxel or paclitaxel-based treatment underwent lipidomic analysis (788 lipids). CIPN severity was measured using the neurological grading scale Total Neuropathy Score-clinical version (TNSc score; John Hopkins University) and patient-reported outcome measure EORTC QLQ-CIPN20. The association of baseline lipid levels with severe CIPN, as defined by high TNSc and CIPN20 scores, was performed using linear modelling (LIMMA). Baseline lipids associated with shorter time to dose reduction (DR) or chemotherapy discontinuation (CD) due to CIPN was determined by Cox regression, with adjustment for body mass index (BMI), age and diabetes. Lipid profiles were identified using latent class analysis (LCA) of significant lipids from the Cox regression. **Results:** Higher TNSc or CIPN20 scores were associated with 107 and 43 lipid species respectively (LIMMA $p < 0.05$), of which only 3 species were in common. Triacylglycerols (TG) represented a significant proportion of lipids with elevated levels associated with higher TNSc (32.5%) or CIPN20 (9.1%) scores (Fisher's exact test $p < 0.001$). 70 lipid species were associated with shorter time to DR/CD (Cox regression $p < 0.05$), which included 15 TG with higher levels associated with shorter time to DR/CD. Unsupervised LCA identified a specific lipid profile associated with worse CIPN [Hazard ratio 2.61 (95% CI 1.40 – 4.84, $p = 0.002$)]. This lipid profile also had higher levels of TG (t-test $p < 0.05$). The high risk CIPN lipid profile was independently associated with shorter time to DR/CD when modelled with clinical factors (diabetes, age, BMI or prior numbness/tingling; Cox regression $p < 0.006$); however, these clinical factors were not associated with time to DR/CD in the multivariable models ($p > 0.08$). **Conclusions:** Higher levels of baseline plasma TG are associated with increased CIPN severity and shorter time to DR/CD in taxane-treated patients. These findings are consistent with other reports regarding the association of hyperlipidaemia with neuropathy. Further research is required to determine if TG-lowering medication can reduce the risk of CIPN development. Research Sponsor: Cancer Institute NSW Program Grant; National Health and Medical Research Council of Australia (NHMRC) Project Grant, NHMRC Career Development Fellowship.

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Poster Session

Changes in ctDNA levels as an early indicator of outcomes in advanced NSCLC treated with TKI: Initial findings from a retrospective aggregate analysis of 8 clinical trials. *First Author: Hillary Stires, Friends of Cancer Research, Washington, DC*

Background: To determine whether changes in circulating tumor DNA (ctDNA) levels reflect treatment outcome, Friends of Cancer Research created the ctDNA to Monitor Treatment Response (ctMoniTR) Project with collaborators from industry, government, academia, and advocacy. A prior ctMoniTR effort analyzing 5 clinical trials (CT) showed an association between decreases in ctDNA levels and improved outcomes in patients with advanced non-small cell lung cancer (aNSCLC) treated with an anti-PD-(L)1. The current study expands that work and focuses on CT investigating tyrosine kinase inhibitors (TKI) treatment in oncogene-driven aNSCLC. **Methods:** We performed a retrospective analysis of patient-level clinical and ctDNA data across 8 CT representing 1,015 patients with aNSCLC treated with TKI (i.e., anti-EGFR, ALK, RET, or MET). Patients included in the analysis had a baseline ctDNA measurement (T0), an on treatment ctDNA measurement within 10 weeks of treatment initiation (for those with multiple ctDNA measurements within 10 weeks, we used the lowest measurement within 10 weeks) (T1), and overall survival (OS) data ($n = 749$). CT used different ctDNA collection timepoints and assays. We randomly divided the dataset into training (2/3 of the data) and validation (1/3 of the data) datasets stratified by CT cohort (i.e., arm), age, tumor stage, and prior lines of therapy, then ran initial analyses on the training dataset ($n = 501$; reported herein). ctDNA change was calculated as the percent change in maximum variant allele frequency (VAF) between T0 and T1 using tumor-derived variants provided by sponsors for each unique patient sample. CT used either ddPCR or an NGS assay. ctDNA limits of detection were assay specific and varied across CT. Multivariate analyses are ongoing and validation dataset analyses will be conducted. **Results:** At T0, 141 patients had non-detected (ND) ctDNA and 360 patients had detected (D) ctDNA. Of these, 27% ($n = 136$) had ND ctDNA at both T0 and T1 ("ND/ND"), 52% ($n = 260$) had changes from D at T0 to ND at T1 ("D/ND"), 12% ($n = 60$) had at least a 50% decrease from T0 to T1 ("decrease") and 9% ($n = 45$) had an increase or a less pronounced decrease in ctDNA. In a univariate analysis, patients with ND/ND and D/ND were associated with improved OS compared to the decrease group. In addition to other characteristics, patients with max VAF ≤ 0.5% or ND at T0 ($n = 214$, 43%) had improved OS (HR = 0.44, $P < 0.001$) compared to those with max VAF > 0.5% at T0 ($n = 287$, 57%). **Conclusions:** In a retrospective aggregate analysis of 8 CT, ND ctDNA at T1 was associated with improved OS in patients with aNSCLC treated with TKI. Changes in ctDNA levels, particularly from D to ND, may provide an early indication of treatment benefit and predict long-term outcomes in this population. Additional ctMoniTR analyses are ongoing to validate the potential use of ctDNA as an early endpoint. Research Sponsor: Friends of Cancer Research.

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Poster Session

First report of ELUCIDATOR study: A prospective observational multicenter study on resistance mechanisms in patients with early disease progression during osimertinib. *First Author: Yasuyuki Mizumori, National Hospital Organization Himeji Medical Center, Himeji, Japan*

Background: Osimertinib (Osi) is the key standard therapy for patients (pts) with chemo-naïve advanced non-small cell lung cancer (NSCLC) harboring sensitizing epidermal growth factor receptor (EGFR) mutations. However, many of cases treated with Osi experience the disease progression (PD). Therefore, understanding first-line osimertinib resistance mechanisms is essential for future therapeutic strategies. Here, we addressed the underlying mechanisms of resistance to Osi using paired plasma DNA samples and particularly focused on early PD (PD within 6 months) cases. **Methods:** This trial is the multicenter prospective research, and we prospectively collected plasma DNA samples prior Osi treatment and at PD. Next-generation sequencing (NGS) implemented with the molecular barcoding method was performed to analyze gene mutations in 197 cancer-associated genes. Then using these ct-DNA, we analyzed the Osi resistance by ultra-sensitive NGS. In this interim analysis, we specially analyze the early PD (PD within 6 months) cases. **Results:** One hundred eighty-eight pts were enrolled between May 2019 and January 2021. Among these pts, 125 (66%) pts were female, 96 (51%) were EGFR exon 19 deletion mutation, and 109 (58%) were never smoker. Seventy-eight pts experienced PD and 36 pts experienced early PD at interim analysis. Baseline shedders, patients with plasma positivity for EGFR-activating mutation were more frequently observed in early PD pts than non-PD (86.1% vs 63.4%, $p = 0.009$). Early PD patients had significantly more co-occurring gene mutations along with EGFR mutations than non-early PD patients (2.89 ± 1.49 vs 1.97 ± 1.37 , $p = 0.002$). Most notably, 3 among 36 early PD pts and 8 among 78 PD pts had significant reduction of plasma EGFR mutant allele frequency at PD than that at baseline. Among those, 1 had germline BRCA1 mutation and 1 had BRINP3 mutation in 3 early PD pts, and 1 had germline BRCA2 mutation, and 1 had germline TP53 mutation in 5 PD pts excluding early PD pts. Co-occurring TP53 mutations were not relevant to early PD in this study cohort. **Conclusions:** Germline mutations in BRCA1/2, TP53 and BRINP3 may confer early and unprecedented resistance to Osi monotherapy. Plasma-based serial comprehensive gene profiling may help predict and identify patients unlikely to benefit from Osi treatment, though further study is warranted. Clinical trial information: jRCTS031180051. Research Sponsor: Japanese National Hospital Organization Multi-Center Clinical Research for Evidence-Based Medicine; AstraZeneca.

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Poster Session

Diagnostic value of hPG₈₀, as a new multi-cancer blood biomarker, in 16 different cancers: Results of the ONCOPRO prospective study. *First Author: Benoit You, Medical Oncology Department, Institut de Cancérologie des Hospices Civils de Lyon, CITOHL, Université Lyon 1, Lyon, France*

Background: hPG₈₀ (also called circulating progastrin) has been described as a promising multi-cancer blood biomarker. Indeed, hPG₈₀ is released from cancer cells to blood at the early steps of tumorigenesis due to WNT pathway activation (You et al *eBioMedicine* 2020). ONCOPRO study was designed to prospectively assess the hPG₈₀ diagnostic & clinical utility in patients with 16 types of cancers. **Methods:** ONCOPRO study (NCT03787056) was a large prospective case-control study led in Lyon University Hospital (France), designed to assess the diagnostic, and monitoring value of hPG₈₀ blood titers in 420 patients with 16 newly diagnosed cancers. hPG₈₀ was measured using kit DxPG80.Lab (Biodena care) at diagnosis, and then at each cycle/visit until recurrence for the curative cohorts, or for 3 treatment lines for the non-curative cohorts. The diagnostic value of hPG₈₀ (primary endpoint) was assessed by comparing the hPG₈₀ baseline titers measured in cancer patients to those of 330 healthy volunteers recruited in parallel (age & sex ratios matched with the cancer group), with a sample size calculated for precision of ± 0.23 for ROC AUC. **Results:** Out of 499 cancer patients enrolled between December 2018 and June 2022, 419 were assessable in 16 cancer cohorts (NSCLC & SCLC: n=70; Breast: n=50; Renal: n=50; Prostate: n=50; Liver: n=50; Head&Neck: n=49; Hepatocellular carcinoma (HCC): n=50; Colorectal: n=10; Thyroid: n=10; Pancreas: n=14; Ovarian: n=10; Glioblastoma: n=10; Endometrial: n=10; Bladder: n=10; Superficial oesophago-gastric: n=10; Lymphoma: n=10; Gastric: n=10). The median age of cancer patients was 66 [IQR: 58-73], with 60% men. hPG₈₀ concentration was significantly higher in cancer patients than in healthy subjects (median, 3.8 vs 2.0 pM, $P < 0.001$). It was not impacted by renal/liver, or CRP level, but slightly linked to age. hPG₈₀ titer was found stable on a 24h-hour period. The global diagnostic accuracy in cancer patients / control was ROC AUC, 0.63 [0.59-0.67] in the whole population. The highest diagnostic accuracy was seen in patients with lung cancer (AUC, 0.75 [0.68-0.82]; Sensitivity (Se)/Specificity (Sp) 0.49/0.90 for hPG₈₀ > 7.73 pM) and HCC (AUC, 0.75, 95% CI 0.66-0.83; Se/Sp 0.48/0.90 for hPG₈₀ > 7.73 pM). **Conclusions:** This large prospective study confirms that cancer patients have significantly higher blood concentration of hPG₈₀ than healthy subjects. The data about the different cohorts will guide the future development of hPG₈₀. Strong diagnostic accuracy was seen for lung cancers and HCC, with specificity > 90%. The screening programs of these cancers could be enriched by this simple blood hPG₈₀ ELISA assay, for complementing imaging limited specificity. Clinical trial information: NCT03787056. Research Sponsor: BiodenaCare.

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Poster Session

Early detection of lung cancer using small RNAs. *First Author: Amita Sharma, Massachusetts General Hospital, Boston, MA*

Background: Low-dose computed tomography (LDCT) screening can significantly reduce lung cancer mortality. However, annual screening is limited by low adherence in the USA and still not broadly implemented in Europe. As a result, <10% of lung cancers are detected through existing programs. Thus, there is great need for additional diagnostic modalities, such as a blood test that could be deployed in the primary care setting. **Methods:** We prospectively recruited 1,189 patients meeting the 2013 USPSTF screening criteria for lung cancer and collected stabilized whole blood. Ultra-deep small RNA sequencing was performed with a method to remove highly abundant erythroid RNAs, opening bandwidth for the detection of less abundant species originating from plasma or the immune cellular compartment. We utilized 100 random data splits to train and evaluate logistic regression classifiers using small RNA expression, discovered an 18-small RNA feature consensus signature (miLung), and validated this in an independent cohort (246 patients). Blood cell sorting and tumor tissue sequencing were performed to deconvolve small RNAs into their source of origin. **Results:** We generated diagnostic models and report a median ROC AUC of 0.86 (95% CI 0.84-0.86) in the discovery cohort, and generalized performance of 0.84 in the validation cohort. Diagnostic performance increased stage-dependently from 0.73 (95% CI 0.71-0.76) for Stage I to 0.90 (95% CI 0.89-0.90) for Stage IV. We identified a tumor-shed, plasma-bound ribosomal RNA fragment of the L1 stalk as a dominant predictor of lung cancer. The fragment is decreased following surgery with curative intent. In additional experiments, dried blood spot collection and sequencing revealed that small RNA analysis could potentially be conducted via home-sampling. **Conclusions:** These data suggest the potential of a small RNA-based blood test as a viable alternative to LDCT screening for early detection of smoking-associated lung cancer. Clinical trial information: NCT03452514. Research Sponsor: Hummingbird Diagnostics GmbH.

Patient characteristics.

	Discovery Cohort			Validation Cohort		
	Controls n = 498	Cancers n = 445	p-value	Controls n = 127	Cancers n = 119	p-value
Sex, n (%)						
Female	200 (40.2)	175 (39.3)	0.846	66 (52.0)	49 (41.2)	0.117
Male	298 (59.8)	270 (60.7)		61 (48.0)	70 (58.8)	
Age, Yr						
Mean $\pm$ SD	64.1 $\pm$ 5.4	64.7 $\pm$ 5.4	0.121	63.7 $\pm$ 5.8	65.8 $\pm$ 4.8	0.005
Median (range)	64.0 (55-75)	65.0 (55-75)		64.0 (55-74)	66.0 (55-74)	0.007
Smoking Status, n (%)						
Current	206 (41.4)	223 (50.1)	0.009	65 (51.2)	70 (58.8)	0.282
Former	292 (58.6)	222 (49.9)		62 (48.8)	49 (41.2)	
Pack Years, Mean $\pm$ SD	48.8 $\pm$ 20.0	53.7 $\pm$ 22.3	<0.001	49.1 $\pm$ 24.3	42.2 $\pm$ 20.4	0.035
Histological Subtype, n (%)						
NSCLC Adenocarcinoma		206 (46.3)	<0.001		68 (57.1)	<0.001
NSCLC Squamous		119 (26.7)			32 (26.9)	
NSCLC Other		38 (8.5)			1 (0.8)	
SCLC		57 (12.8)			13 (10.9)	
Other lung cancer		25 (5.6)			5 (4.2)	
Pathological Stage, n (%)						
Ia		69 (15.5)			18 (15.1)	
Ib		23 (5.2)			4 (3.4)	
Ila		14 (3.1)			3 (2.5)	
Ilb		46 (10.3)			7 (5.9)	
Illa		59 (13.3)			8 (6.7)	
Illb		55 (12.4)			8 (6.7)	
Illc		18 (4.0)			4 (3.4)	
III		5 (1.1)			4 (3.4)	
IV		156 (35.1)			64 (52.9)	

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Poster Session

First report of tumor-informed circulating tumor DNA in fibrolamellar carcinoma in adolescents and young adults: 51 patients. *First Author: Elise McKenna, Columbia University, New York, NY*

Background: Fibrolamellar Carcinoma (FLC) is an extremely rare form of primary liver cancer (50-200 cases/year), unrelated to hepatocellular carcinoma. The only established standard of care is surgery. However, recurrence is at least 80%, even with R0 surgery, suggesting that FLC is best thought of as a systemic disease instead of a surgical disease. Systemic therapies in retrospective studies of more than 25 show immunotherapy and chemotherapy combinations have promise. Circulating “tumor-informed” tumor DNA (ctDNA) is a tool for tracking microscopic systemic disease, serving as a marker of systemic involvement, has shown success in management of other cancers. FLC has never been studied using this technology. Our retrospective study of 51 patients over a 2.5-year period is the first attempt to understand if ctDNA can be helpful in the management of FLC. **Methods:** All patients consented to blood draws on a 1-3 monthly basis, according to the company (Signatera) protocol. All patients had regular imaging reviewed by the FibroFighters Foundation National Tumor Board. Complete response (CR), Partial response (PR) (> 30% decrease), Progressive Disease (PD) (> 20% increase), and Stable Disease (SD) (neither PD/PR/CR) were recorded according RECIST 1.1. The imaging closest in time to the blood draw was used for correlation purposes. “Negative” is defined as a value = 0.00. “Positive” is defined as a value > 0.00. **Results:** Fifty-one FLC patients (26M, 25F, median age 23, range 10-56), 92% stage (III/IV), consented to ctDNA “blood biopsies,” (n=226 samples, mean 4.4/patient, range 1-11). Negative values correlated with no evidence of disease (NED) on imaging 78% of the time, positive values with disease 94% [PPV/NPV/sens/spec of 0.78/0.94/0.93/0.81]. NPV and sens increased to almost 100% with a ctDNA threshold of > 1.0 at the expense of a lower PPV and spec. However, consecutive negative ctDNA values correlated with radiologic NED 86% [PPV/NPV/sens/spec = 0.86/0.84/0.77/0.91] without a single PD in this cohort (n=64). A “downward trend or slope” on consecutive values predicted Objective Response (CR+PR) and Disease Control (CR+PR+SD) at 68% and 96% [PPV/NPV/sens/spec of 0.68/0.49/0.36/0.78 and 0.96/0.26/0.36/0.94, respectively], while an “upward trend” performed less well to predict relapse [PPV/NPV/sens/spec = 0.54/0.98/0.94/0.81]. **Conclusions:** In this first exploration of 51 young FLC patients, and 226 tissue-informed cell free ctDNA data points, “Positive” and “Negative” values overall performed well for predicting RECIST 1.1 “disease” or “NED” respectively, especially for consecutive values of zero, where no progressions were observed in 64 distinct FLC scenarios. A downward trend or “slope” performed better than an upward trend to predict objective response (PR+CR) versus relapse (PD). Research Sponsor: FibroFighters Foundation.

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Poster Session

Longitudinal mutational analysis of TP53 in plasma circulating tumor DNA (ctDNA) in patients (pts) with solid tumors in a phase I study of BI 907828, an MDM2–p53 antagonist. *First Author: Alexander Peltzer, Boehringer Ingelheim Pharma GmbH & Co. KG, Department of Translational Medicine & Clinical Pharmacology, Biberach an der Riss, Germany*

Background: Inactivation of p53 can occur due to TP53 mutations or downregulation of wild-type p53 by its primary negative regulator, MDM2. Targeting the MDM2–p53 interaction may therefore restore p53 function. BI 907828, a highly potent MDM2–p53 antagonist, is being evaluated in a phase Ia/b study in pts with advanced solid tumors (NCT03449381). During dose escalation (phase Ia), BI 907828 demonstrated a manageable safety profile and early signs of efficacy. Here we present data from a longitudinal mutational analysis of TP53 using ctDNA. The objective of the analysis was to identify if mutations in TP53 can be associated with possible acquired resistance to BI 907828. **Methods:** Collection of blood samples for ctDNA analyses was optional and sampled longitudinally from pts at baseline and every cycle until end of treatment (EoT). ctDNA was purified from plasma and analyzed using tumor-specific next generation sequencing (NGS; custom-made 8-gene panel using KAPA HyperCap technology, including TP53) to identify tumor-derived somatic mutations that may be relevant to understanding resistance mechanisms to BI 907828. The limit of detection was determined to be 0.5% mutant allele frequency; common polymorphisms were filtered out. **Results:** Plasma samples for ctDNA analysis were available from 44/54 (81%) pts enrolled to phase Ia. Baseline plasma samples from 26/54 (48%) pts and EoT samples from 41/54 (76%) pts were analyzed. Mutations were found in 6/26 (23%) samples at baseline. In 2 pt samples, mutations were found in both tumor and ctDNA, but concordant results were limited to 1 pt. At EoT, no (0) mutations were found in 16/41 (39%) samples, 1 mutation in 11/41 (27%), 2 mutations in 6/41 (15%), 3 mutations in 2/41 (5%) and 4 mutations in 6/41 (15%). No sample had more than 4 mutations. The most frequent mutation at EoT (in 9/41 [22%] samples) was R175H, a known p53 loss of function (LOF) mutation, followed by R248Q/W LOF (in 6/41 [15%] samples). Mutations in non-TP53 genes were detectable independent of TP53 mutation status, suggesting ctDNA was present in all samples. No clear association of induction of mutations could be identified for any BI 907828 dose or dosing schedule, treatment duration, or tumor type. 9/20 (45%) pts with no detectable mutations at baseline maintained wild-type TP53 status at EoT. Signs of efficacy were observed in pts with acquired TP53 LOF mutations, suggesting that these mutations have no effect on efficacy. Analysis of TP53 mutational status at EoT in conjunction with correlative clinical efficacy will be presented. **Conclusions:** This mutation analysis represents one of the most comprehensive assessments of longitudinal ctDNA by NGS for TP53 from a clinical trial of an MDM2–p53 antagonist. Preliminary data suggest that BI 907828 does not systematically lead to broad acquisition of resistance by inducing alterations in TP53. Clinical trial information: NCT03449381. Research Sponsor: Boehringer Ingelheim.

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Poster Session

Long-term clinical outcomes of cancers diagnosed following detection by a blood-based multi-cancer early detection (MCED) test. *First Author: Adam H Buchanan, Geisinger, Danville, PA*

Background: Less than 20% of cancers are diagnosed as a result of standard-of-care (SOC) screening in the US. MCED tests may expand screening to more cancers, but the long-term outcomes of MCED test-detected cancers are unknown. DETECT-A was the first large prospective interventional clinical trial to evaluate an MCED blood test. The test used was an early version of CancerSEEK and was evaluated in 9,911 women without history of cancer (*Science* 369:6499, 2020). CancerSEEK, coupled with diagnostic PET-CT, safely identified cancers including those not detected by SOC screening, the majority of which were localized or regional. This follow-up observational study evaluated longitudinal clinical outcomes of cancers diagnosed as a result of an abnormal CancerSEEK test with a median follow up of 4.4 (IQR:4.1-4.6) years from initial CancerSEEK testing. **Methods:** Nine cancer types were diagnosed in 26 participants whose cancers were first detected by CancerSEEK. Information on cancer diagnosis, treatment, treatment response, remission status, recurrence, secondary cancer diagnoses, and mortality (cancer-related and all-cause) was extracted from electronic medical records through November 2022. Data collection for living participants took place a median of 3.7 years following cancer diagnosis (IQR: 3.3-3.9) and a median of 4.3 years (IQR: 4.1-4.7) following initial CancerSEEK screen. **Results:** Fourteen (53.8%) participants underwent surgery; 5 had surgery alone, 9 had surgery with adjuvant and/or neoadjuvant chemotherapy, radiation, or hormone therapy. Twelve of 14 (85.7%) surgically treated participants were in remission as of November 2022, including 10 with localized or regional disease at diagnosis. Among patients whose treatment was non-surgical (11) or unknown (1), 1 (8.3%) was in remission (stage I at diagnosis), 9 (75.0%) were deceased (all stage III or IV at diagnosis), and 2 (16.7%) were in surveillance or ongoing treatment (stage II and stage III at diagnosis). Overall, 13 of 26 (50%) participants were in remission [ovarian (4), thyroid (1), uterus (2), breast (1), colorectal (2), and lung (3)]; 7 of these 13 (54%) had cancers without recommended SOC screening modalities. Eleven of 17 (64.7%) participants with localized or regional disease (stage I, II, or III) were in remission, whereas 2 of 9 (22.2%) with stage IV disease at diagnosis were in remission. **Conclusions:** CancerSEEK detected cancers earlier in patients who, when treated subsequently with conventional methods, achieved long-term survival. Half of all patients with a CancerSEEK-detected cancer remain cancer-free after treatment >4 years (median) after their initial CancerSEEK test. This includes 7 patients with cancer types for which no SOC screening option exists. Additional biomarkers, new analytic methods and algorithms are being incorporated in the development of the next generation of the MCED test. Research Sponsor: Exact Sciences Corporation.

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Poster Session

Outcomes in participants with a false positive multi-cancer early detection (MCED) test: Results from >4 years follow-up from DETECT-A, the first large, prospective, interventional MCED study. *First Author: Anne Marie Lennon, Johns Hopkins University School of Medicine, Baltimore, MD*

Background: Recommended standard of care (SOC) early detection tests are solely available for four cancer types and fewer than 20% of incident cancers in the US are being diagnosed as a result of screening. Advances in detection of tumor-derived analytes in the blood are enabling the development of MCED tests that may expand early cancer detection. While MCED tests are being designed with high specificity, false positive (FP) results remain a concern for clinicians and patients alike, as no long-term outcomes of individuals with a FP MCED test have been reported. DETECT-A was the first prospective interventional clinical trial to evaluate an MCED blood test. The test used was an early version of CancerSEEK, evaluated in 9,911 women without history of cancer (*Science*, 369:6499, 2020). This prospectively planned analysis evaluates cancer incidence among DETECT-A participants with FP results, with the intention of providing key long-term data on test effectiveness. **Methods:** This analysis included 98 DETECT-A participants with FP results, where a FP was defined as a positive CancerSEEK result with subsequent PET-CT and clinical evaluation with no evidence of cancer within 1 year of the initial CancerSEEK test. Sixty-three of 98 participants had no follow-up procedure performed after imaging, and 35 subjects had noninvasive/minimally invasive follow-up procedures performed. Electronic medical records were analyzed from January 2020 through November 2022 for cancer diagnosis, treatment, remission, recurrence, and mortality. **Results:** Ninety-six of 98 participants with a FP result remained free of cancer with a median follow-up of 4.3 years (IQR: 3.9-4.9) from the initial CancerSEEK test. One stage I breast cancer and one stage III ovarian cancer were diagnosed 2.7 and 2.9 years respectively from the initial CancerSEEK test. **Conclusions:** Patients with a negative PET-CT and initial clinical evaluation after a positive CancerSEEK test had low (<1% per year) risk for cancer in the ensuing four years after the initial CancerSEEK test. If confirmed, this result should prove reassuring to clinicians and to patients who have no evidence of cancer on comprehensive imaging following a positive MCED test. Further, these results provide preliminary support for the recommendation that patients who participate in MCED testing and receive a FP result can safely return to routine care after comprehensive anatomic and functional imaging and clinical evaluation reveal no suspicion of cancer. Research Sponsor: Exact Sciences Corporation.

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Poster Session

A novel three-biomarker signature (CA-62, CEA, CYFRA 21-1) and early-stage NSC lung cancer detection. *First Author: Janneta Tcherkassova, UCM Technologies Inc., Toronto, ON, Canada*

Background: A double-blind clinical study was conducted on 304 clinically verified blood serum samples, including 141 non-small cell lung cancer (NSCLC), 133 healthy volunteers and 30 patients with chronic obstructive pulmonary disease (COPD). The objectives of the study were: The assessment of various cancer markers and their possible combinations for detection of early (I-II) stages of non-small cell lung cancer (NSCLC) and evaluation of the best cancer markers panel as a pre-screening tool for NSCLC before Low-Dose CT scan. **Methods:** Quantitative measurement of various tumor markers for serum samples was carried out using electrochemiluminescent immunoassays Elecsys CA-125, ELECSYS CA 19-9, ELECSYS CYFRA 21-1 and ELECSYS SCC (COBAS, Roche Diagnostics GmbH, Germany, EU), enzyme immunoassay CA15-3-ELISA-BEST, CEA-ELISA-BEST, NSE-ELISA-BEST (JSC "VECTOR-BEST", RF) and immunochemiluminescent analysis CLIA-CA-62 (LLC "JVS Diagnostics", RF). The results were compared to the literature data for other biomarkers and their panels. **Results:** Unlike other tumor markers, which are expressed proportionally to tumor size, the marker for epithelial carcinomas CA-62 is expressed from Stage I and demonstrated the highest diagnostic results in detecting early stages (I-II) of NSCLC. The biomarkers CYFRA 21-1 and SCC do not have sufficient sensitivity and specificity to diagnose asymptomatic lung cancer. However, the addition of cytokeratin 19 CYFRA 21-1 to glycoproteins CA-62 and CEA increases the specificity by eliminating false positive results, which significantly improves the diagnostic value of the cancer marker signature (CA-62, CEA and CYFRA 21-1): 100% Specificity, 93% Sensitivity, 100% PPV, 94% NPV and 94% test accuracy. **Conclusions:** The results of the study demonstrated that using the biomarkers signature (CA-62, CEA and CYFRA 21-1) allows increasing the specificity of CT scan for patients with suspicious abnormalities on the tomogram, improving the interpretation of visualized localized lesion, and improving the accuracy of differential diagnosis at detecting early stages of LC up to 94%. In the prospective, adding cancer markers panel signature (CA-62, CEA and CYFRA 21-1) to the current lung cancer risk assessment system as a pre-screening tool for LDCT may improve the quality of early-stage Lung cancer detection by significant increasing the sensitivity and by reducing the proportion of false positive results. Research Sponsor: UCM Technologies Inc.

Diagnostic characteristics obtained for different cancer markers and their panels.					
Cancer Marker	Sensitivity, %	Specificity, %	PPV, %	NPV, %	Accuracy, %
CEA	48.2	93.8	84.5	65.2	72.7
CA-62	96.4	97.0	96.4	96.0	96.7
NSE	9.2	96.0	68.4	26.7	55.6
SCC	18.4	98.0	89.6	58.2	61.2
CYFRA 21-1	44.0	96.0	91.2	66.4	72.0
CA 19-9	7.1	95.0	55.5	54.2	54.3
CA-125	22.0	97.0	86.1	58.9	62.2
CA 15-3	19.0	98.0	93.0	58.5	61.8
CA-62, CEA, CYFRA 21-1	93.0	100.0	100.0	94.0	94.0

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Poster Session

The detection of multiple cancer types with an extended set of methylation and protein markers. *First Author: Slava E. Katerov, Exact Sciences Corporation, Madison, WI*

Background: Cancer is the 2nd leading cause of mortality in the US, with an estimated 1.96M new cases expected in 2023. With guideline recommended screening unavailable for most cancers, multicancer early detection (MCED) tests in development may extend the reach of cancer screening. As part of an ongoing program examining multiple biomarker classes in cancer early detection, we examined the feasibility of combining blood DNA methylation and cancer protein markers for the detection of multiple cancer types. **Methods:** 236 samples from subjects with cancer (13 tumor organ types) were retrospectively collected and gender/age matched with 146 unscreened non-cancer control samples. Plasma and serum were used for cfDNA methylation analysis of 36 differentially methylated regions and 8 cancer-associated protein markers in a randomized, blinded fashion. Methylated DNA markers (MDMs) were assayed using target enrichment long-probe quantitative-amplified signal assays. Protein markers were assayed with commercial kits. Normalized methylation values/protein concentrations were used to develop a logistic regression model for cancer detection. The model was built with 5 random 0.7/0.3 training/validation splits, keeping case/control, cancer types, gender, and age distributions similar to the original data set. Models for MDMs and protein markers were created, and a combined model including both MDMs and protein markers was also evaluated for performance improvement. **Results:** A reduced subset of MDM and protein markers was identified to have robust detection of several cancer types. At 99% specificity, overall sensitivity for cancer detection was 68% (95% CI: 62%-74%) for MDMs, 43% (37%-50%) for proteins, and 75% (69%-80%) for MDMs and proteins combined. **Conclusions:** Building on promising results with mutation and protein biomarker analysis (*Science* 369:6499, 2020) this pilot study demonstrates the potential of combining DNA methylation and protein biomarkers and contributes to a larger scale effort to develop a multi-biomarker class MCED test (Ann Oncol 2022 Vol. 33:S575). Research Sponsor: Exact Sciences Corporation.

Sensitivity, % (95% CI).															
99% Specificity	Bladder	Breast	Cervical	Colorectal	Esophageal	Liver	Lung	Ovarian	Pancreatic	Prostate	Renal	Stomach	Uterine	All Cancers	
MDMs	50 (30-70)	64 (39-84)	100 (72-100)	65 (50-79)	100 (21-100)	62 (36-82)	85 (71-93)	75 (41-93)	67 (49-81)	20 (16-26)	45 (26-66)	52 (31-66)	82 (61-90)	68 (62-74)	68 (62-74)
Proteins	20 (8-35)	35 (20-51)	26 (15-42)	26 (15-42)	100 (21-100)	23 (8-52)	68 (52-80)	100 (86-100)	73 (56-86)	30 (11-60)	10 (3-30)	46 (27-65)	60 (43-73)	60 (31-83)	60 (31-83)
MDMs + Proteins	55 (33-70)	64 (39-84)	100 (72-100)	79 (64-89)	100 (21-100)	62 (36-82)	90 (77-96)	88 (63-98)	83 (66-93)	40 (17-69)	45 (26-66)	52 (31-66)	82 (61-90)	75 (69-80)	75 (69-80)
MDMs	54 (42-66)	62 (49-73)	100 (72-100)	81 (70-89)	100 (21-100)	62 (36-82)	88 (77-96)	88 (63-98)	83 (66-93)	40 (17-69)	45 (26-66)	52 (31-66)	82 (61-90)	75 (69-80)	75 (69-80)
Proteins	25 (16-37)	35 (20-51)	26 (15-42)	26 (15-42)	100 (21-100)	23 (8-52)	68 (52-80)	100 (86-100)	73 (56-86)	30 (11-60)	10 (3-30)	46 (27-65)	60 (43-73)	60 (31-83)	60 (31-83)
MDMs + Proteins	62 (50-73)	67 (54-78)	100 (72-100)	81 (69-93)	100 (21-100)	62 (36-82)	88 (77-96)	88 (63-98)	83 (66-93)	40 (17-69)	45 (26-66)	52 (31-66)	82 (61-90)	75 (69-80)	75 (69-80)

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Poster Session

Longitudinal circulating tumor DNA monitoring in patients with esophageal squamous cell carcinoma. *First Author: Shogo Takei, Department of gastroenterology and gastrointestinal oncology, National Cancer Center Hospital East, Kashiwa, Japan*

Background: The clinical utility of longitudinal monitoring with circulating tumor DNA (ctDNA) as a prognostic and a predictive biomarker was recently reported in patients with resectable colorectal cancer (Kotani D, et al. Nature Medicine 2023). Here we report a prospective, observational study of longitudinal ctDNA monitoring in patients with esophageal squamous cell carcinoma (ESCC) receiving neo-adjuvant chemotherapy (NAC) followed by surgery. **Methods:** Patients with ESCC planned for NAC followed by curative surgery, were prospectively enrolled in this study. As per the protocol, plasma samples were collected at 7 timepoints: pre-NAC, post-NAC, and 4, 12, 24, 36, and 48-weeks after surgery. CT scans were conducted every 3 months. Longitudinal ctDNA testing was performed using a personalized, tumor-informed ctDNA assay (Signatera, bespoke mPCR, NGS assay). In this initial report, ctDNA results at 3 time points (pre-NAC, post-NAC, and 4 weeks post-surgery) were analyzed and their association with clinical outcomes and tumor regression grade (TRG) scores were assessed. **Results:** So far, a total of 83 blood samples from 28 patients with ESCC were collected serially at pre-NAC (N=28), post-NAC (N=27), and post-surgical (N=28) time points. Pre-NAC ctDNA was detectable in 96.4% patients (27/28), and detection rates decreased at the post-NAC (37%; 10/27) and post-surgical (11%; 3/28) timepoints. ctDNA-positivity post-NAC and post-surgery was associated with a significantly shorter recurrence free survival (RFS) with HR of 7.0 (95% CI: 1.4-35.0; $p=0.02$) and HR of 14 (95% CI 3.0-62; $p<0.001$), respectively. Notably, patients who achieved ctDNA clearance with NAC had favorable RFS as compared to the patients who did not (HR=0.15, 95% CI: 0.03 – 0.75; $p=0.02$). Post-NAC ctDNA was also associated with tumor regression grade (TRG) score. None of the patients with TRG3 score (N=3) were ctDNA positive, whereas 7.7% (1/13) patients in the TRG2 category and 81.8% (9/11) in the TRG1 category were ctDNA-positive. **Conclusions:** Our study demonstrates a strong correlation between ctDNA status and clinical outcomes in ESCC patients. Assessment of ctDNA may be useful monitoring in patients with ESCC post NAC/surgery and may be used in the future to direct post-surgical management in this patient population. Clinical trial information: UMIN000042003. Research Sponsor: Department of gastroenterology and gastrointestinal oncology, National Cancer Center Hospital East.

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Poster Session

Distinguishing between cancer-related mutations and clonal hematopoiesis using cell-free RNA (cfRNA) expression levels in a machine learning model. *First Author: Maher Albitar, Genomic Testing Cooperative, Irvine, CA*

Background: Liquid biopsy is currently considered an important part of the clinical practice of oncology. However, proper interpretation of somatic mutations detected in liquid biopsy remains a challenge. Distinguishing cancer-related mutations from mutations resulting from clonal hematopoiesis of indeterminate potential (CHIP) can be difficult and a source of misinterpretation of liquid biopsy findings. We explored using cell-free RNA (cfRNA) profiling as a means for distinguishing between mutations detected as CHIP vs mutations detected as cancer. **Methods:** cfDNA and cfRNA from 102 patients with confirmed solid tumors, 93 patients with hematologic neoplasms and 40 patients with CHIP abnormalities were sequenced using a panel of 1501 gene for RNA and 284 genes for DNA. The solid tumors included lung, breast, ovarian, and colorectal. The hematologic neoplasms included lymphoid and myeloid neoplasms. Using a machine learning algorithm, we first selected the relative genes that distinguish between two classes using K-fold cross-validation ($K=12$). The selected genes were used to predict one class from the other using naïve Bayesian classifier, but we applied geometric mean naïve Bayesian (GMNB) to compensate for the expected underflow. **Results:** Using machine learning with cfRNA, we were able to distinguish between cases with confirmed cancer-related mutations and CHIP mutations with area under the curve (AUC) of 0.808 (95% CI: 0.720-0.895). Precision, recall and f1-score were 0.86, 0.422 and 0.566 for CHIP and 0.359, 0.825 and 0.500 for solid tumor, respectively. The machine learning required 70 genes for this classification. Leave-one-out (LOO) validation showed AUC of 0.766 (95% CI: 0.671-0.859). Distinguishing between hematologic neoplasms and CHIP was achievable using the expression of 30 genes. The AUC for this model was 0.787 (95% CI: 0.696-0.879). Precision, recall and f1-score were 0.906, 0.516, and 0.658 for CHIP and 0.438, 0.875, and 0.583 for hematologic neoplasms, respectively. Validation using LOO showed AUC of 0.736 (95% CI : 0.638-0.835). The top 10 genes that their expression was critical for distinguishing between CHIP and solid tumors were EIF4E, HNF1A, HOOK3, HIPK2, IL1RAP, BRAF, DNAJB1, GADD45B, H2AX, and HDAC6. The top 10 genes for distinguishing hematologic cancers from CHIP were PBX1, CAMTA1, PFDN5, PCBP1, SDC4, PRKACA, NT5C2, NBR1, RPS21, and AHCYL1. **Conclusions:** Analyzing cfRNA expression levels when used with machine learning may add another level of confidence to the ability of interpreting mutations detected in liquid biopsy testing, especially when these mutations are at low levels. This is particularly important in liquid biopsy testing for minimal residual disease (MRD) when a tissue baseline sample is not tested (tumor-agnostic). Research Sponsor: Genomic Testing Cooperative.

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Poster Session

A 5-hydroxymethylcytosine-based noninvasive model for ultrasensitive early detection of colorectal advanced adenoma and adenocarcinoma: The METHOD-2 study. *First Author: Jianmin Xu, Zhongshan Hospital, Fudan University, Shanghai, China*

Background: Detection of colorectal tumors at a time when there are more treatment options is associated with better outcomes. This prospective case-control study (NCT03676075) assessed the performance of 5-hydroxymethylcytosine (5hmC) biomarkers in circulating cell-free DNA (cfDNA) to detect advanced colorectal adenomas (ADA) or adenocarcinomas (CRC). **Methods:** This multi-center study enrolled 2,576 participants, including patients with newly diagnosed CRC ($n=1,074$), ADA ($n=356$), other solid tumors ($n=80$), and healthy individuals (HEA) ($n=1,066$), followed by genome-wide 5hmC profiling using the 5hmC-Seal, a highly sensitive chemical labeling approach. A weighted diagnostic model for CRC (stage I-III) and ADA was developed using the elastic net regularization in a training set of age-, sex-, region-matched samples and validated in independent samples. **Results:** Distribution of 5hmC in cfDNA reflected gene regulatory relevance and tissue of origin. In an independent validation set of 482 samples, a 96-gene model trained in stage I-III CRC, ADA, and HEA achieved an AUC (area under the curve) of 92.6% (95% CI [confidence interval], 90.7-94.5%) for distinguishing CRC from HEA, regardless of primary location or mutation. This model also showed high capacity for distinguishing ADA from HEA with an AUC of 87.9% as well as cancer-type specificity. Model performance was further confirmed in samples from multiple centers. Functionally, differential 5hmC features associated with CRC and ADA demonstrated relevance to CRC biology, including pathways such as calcium and MAPK signaling. **Conclusions:** Genome-wide mapping of 5hmC in cfDNA shows promise as a highly sensitive and specific approach to be integrated in a screening program for improving early detection of CRC and high-risk ADA. Clinical trial information: NCT03676075. Research Sponsor: the National Natural Science Foundation of China (82072653, 81602035); Clinical Research Plan of SHDC (SHDC2020CR5006);.

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Poster Session

FS-1502 in HER2-positive advanced breast cancer: Results from an open-label, phase 1 study. *First Author: Qiao Li, Department of Medical Oncology, Cancer Hospital Chinese Academy of Medical Sciences, Beijing, Chaoyang District, China*

Background: FS-1502 is an anti-HER2 antibody-drug conjugate that was well tolerated and showed good antitumor activity in patients (pts) with advanced HER2-expressing solid tumors in the dose-escalation stage of the current Phase 1 study. The results were presented at SABCS 2022. The recommend Phase 2 dose (RP2D) was 2.3 mg/kg IV once every 3 weeks. Here, we report the efficacy and safety of HER2-positive breast cancer (BC) pts treated with FS-1502 at the RP2D. **Methods:** This open-label Phase 1 trial was conducted at 9 hospitals in China. Heavily pretreated HER2-positive (IHC 3+ or 2+/FISH+) BC pts who had failed prior anti-HER2 therapy were recruited in the dose-expansion stage. All HER2-positive BC pts treated at the RP2D were pooled for analysis. Efficacy endpoints included objective response rate (ORR) and disease control rate (DCR) per RECIST v1.1. Safety endpoints included treatment-emergent adverse events (TEAEs) and the laboratory data. **Results:** As of cutoff date, December 24, 2022, the median study follow-up duration was 5.2 months. A total of 70 female HER2-positive BC pts, with a median age of 51.8 (range: 31-76) years, were enrolled and received at least one dose of FS-1502. The median prior therapy line was 3 (range: 1-16), and 91.4% (64/70) of pts had previously received at least 2 therapy lines. The most common metastasis organs were lung 55.7% (39/70), lymph node 54.3% (38/70) and bone 50% (35/70). 81.4% (57/70) of pts had at least 3 metastatic lesions. All pts had previously received anti-HER2 therapy, among which trastuzumab ± pertuzumab ($n=67$, 96%) and pyrotinib ($n=52$, 74%) were the most common. Among 68 efficacy-evaluable pts, the best ORR of 52.9% (36/68) (95% CI, 40.45-65.17) was achieved with 2 complete responses and 34 partial responses. DCR was 88.2% (60/68), median progression-free survival was 15.5 months (95% CI, 4.57-), and median duration of response was 12.9 months (95% CI, 5.72-). FS-1502 was well tolerated. No related interstitial lung disease occurred in any grade. Eye toxicity was mostly Grade 1 or 2 of dry eye and keratitis. Grade ≥ 3 study-related TEAEs were reported in 27 (38.6%) pts, in which the most common events (≥ 5%) were hypokalemia (18.6%), platelet count decreased (7.1%), and neutrophil count decreased (5.7%). One (1.4%) patient experienced adverse events leading to drug discontinuation (hemoptysis). Adverse events leading to death were reported in 2 (2.9%) pts (bacterial pneumonia and hemoptysis, respectively). Bacterial pneumonia was not related to FS-1502, while hemoptysis was possibly related to the drug. **Conclusions:** FS-1502 demonstrated very promising antitumor activity and was well tolerated in heavily pretreated HER2-positive BC, with mild eye toxicity and no related interstitial lung disease reported. A Phase 3 clinical trial is under planning to further confirm efficacy and safety of FS-1502 in pts with advanced HER2-positive BC. Clinical trial information: NCT03944499. Research Sponsor: Shanghai Fosun Pharmaceutical Industrial Development Co., Ltd.

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Poster Session

RAS testing of circulating cell-free DNA (cfDNA) from tissue RAS/BRAF wild-type metastatic colorectal carcinoma (mCRC) patients: Preliminary data from the Liquid Biopsy Monoclonal Antibodies in mCRC (LIBImAb) study. *First Author: Anna Maria Rachiglio, Cell Biology and Biotherapy Unit, Istituto Nazionale Tumori-IRCCS Fondazione G. Pascale, Naples, NA, Italy*

Background: In mCRC patients RAS/BRAF testing is usually performed on tissue biopsy in order to select patients for treatment with anti-EGFR monoclonal antibodies. Several studies described discordant RAS status between tissue and cfDNA testing from the same patients. In addition, up to 30% of patients with secondary resistance to anti-EGFR therapies become RAS mutant at progression. The LIBImAb study is a phase III, randomized, open-label, comparative, multi-centre trial to assess the superiority in terms of efficacy of bevacizumab versus cetuximab in combination with FOLFIRI chemotherapy in patients with mCRC, RAS/BRAF wild-type on tumor tissue and RAS mutant (RAS^{mut}) at liquid biopsy. This study is supported by the Italian Drug Agency (AIFA). We report preliminary data of liquid biopsy testing. **Methods:** Plasma samples from enrolled patients are analyzed for variants in exons 2, 3 and 4 of KRAS and NRAS genes and for codon 600 BRAF mutations using the fully automated Idylla system (Biocartis). Patients RAS^{mut} on liquid biopsy at baseline are randomized to receive FOLFIRI plus Cetuximab or FOLFIRI plus Bevacizumab. Patients RAS wild-type on cfDNA at baseline, are treated with FOLFIRI plus Cetuximab up to 8 cycles and, if not progressed, they are retested for RAS mutations on cfDNA. RAS^{mut} patients at re-screening are randomized to continue Cetuximab or to switch to Bevacizumab. **Results:** Plasma samples from 169 tissue RAS/BRAF wild-type mCRC patients at baseline and 75 patients at 8 cycles of treatment have been tested as of January 31, 2023. Analysis of baseline plasma samples detected 16 RAS mutations in 16/169 patients (9.5%). In particular, 12 KRAS variants (7.1%, 8 in exon 2 and 4 in exon 3) and 4 NRAS variants (2.3%, all in exon 2) were found. The Idylla test also detected 3 BRAF^{V600} mutations (1.8%) in 3 additional patients. The overall concordance between tissue and cfDNA testing for RAS/BRAF variants was 88.8%. RAS mutations were also detected in 6/75 (8%) plasma samples obtained at 8 cycles of FOLFIRI/cetuximab treatment. The cfDNA test revealed the presence of 5 KRAS (6.7%, 3 in exon 2 and 1 in exon 3) and 1 NRAS mutation (1.3%, exon 2). A BRAF^{V600} variant was detected in 1 additional patient (1.3%). The rate of RAS/BRAF mutant cases at 8 cycles of treatment was 9.3%. **Conclusions:** These preliminary data suggest that liquid biopsy might better recapitulate the heterogeneity of mCRC and might be useful in clinical practice to complement tissue testing. The clinical relevance of RAS variants detected in cfDNA will be determined in the LIBImAb trial. Research Sponsor: Italian Medicines Agency - AIFA.

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Poster Session

Construction of DNA methylation-based biomarkers for diagnosis of hepatocellular carcinoma. *First Author: Ximing Xu, Renmin Hospital of Wuhan University, Wuhan, China*

Background: Hepatocellular carcinoma is the most common malignant tumor in China. Most of the patients are found in the advanced stage, which causes its low survival rate. According to the latest epidemiological data, hepatocellular carcinoma is the second leading cause of cancer mortality. DNA methylation is closely related to tumor development. In this study, differentially expressed methylated genes related to tumorigenesis and development were screened from the database and the diagnostic model was constructed for early screening. **Methods:** Limma package was used to analyze the differences between TCGA _ LIHC liver cancer and GSE113409 normal blood methylation sites and differentially expressed methylation sites (logFC>1, p<0.05) were identified. The TCGA _ LIHC methylation database was used as the training set. Lasso method, and random forest method were used for screening the differentially expressed methylation sites for the construction of the diagnostic model. After that, the characteristic coefficient of methylation sites and ROC curve of the diagnostic model were obtained from the training set. According to the cd-score, HCC patients could be diagnosed in the early stage, thus improved their survival. **Results:** Limma package was used to analyze the differences between TCGA _ LIHC liver cancer and GSE113409 normal blood methylation sites and 7109 differentially expressed methylation sites (logFC>1, p<0.05) were identified. Then the top 1000 differentially expressed methylation sites were selected. The TCGA _ LIHC methylation database was used as the training set. 30 methylation sites were screened by lasso method, and 20 methylation sites were screened by random forest. Taking the intersection, a total of 6 methylation sites were obtained for diagnostic model: cg00346208, cg00084798, cg00458878, cg00006397, cg00325910, cg00399027. The characteristic coefficient of methylation sites were displayed in the table below and the AUC of the diagnostic model was 0.9991579. High cd-score tended to have hepatocellular carcinoma, and vice versa. **Conclusions:** We have identified several DNA methylation markers for the diagnosis of hepatocellular carcinoma from GEO and TCGA databases. This model can predict hepatocellular carcinoma and the AUC is higher than that of AFP, which means it may become a more sensitive indicator for the diagnosis of liver cancer. Research Sponsor: National natural Science Foundation of China(No.31971166).

Marker	Coefficients	SE	Z value	P value
Intercept	-3.941092	8.266537	-0.477	0.63354
cg00346208	-1.527868	6.673249	-0.229	0.81890
cg00084798	-7.257722	9.141976	-0.794	0.42726
cg00458878	34.516029	12.826257	2.691	0.00712**
cg00006397	-42.376880	14.546918	-2.913	0.00358**
cg00325910	0.005339	12.868925	0.000	0.99967
cg00399027	32.558860	10.268398	3.171	0.00152**

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Poster Session

Molecular profiling of ctDNA from NCI-MATCH patients enrolled for treatment with mTOR1/2 inhibitor sapanisertib (arm M) and the Hedgehog pathway inhibitor vismodegib (arm T). *First Author: Jennifer S. LoCoco, Illumina, Inc., San Diego, CA*

Background: The National Cancer Institute Molecular Analysis for Therapy Choice (NCI-MATCH) multi-arm phase II clinical trial tested biopsies from patients with advanced refractory cancer to assign treatment based on tumor molecular profile. Enrollment criteria for treatment with the mTOR1/2 inhibitor sapanisertib in Arm M, or the Hedgehog pathway inhibitor vismodegib in Arm T, included detection of mutations in TSC1/TSC2 or PTCH1/SMO in tissue, respectively. For a subset of patients enrolled on these two arms, matched plasma was also collected at time of enrollment or on treatment to evaluate ctDNA. **Methods:** Screening for NCI-MATCH was based on tissue sequencing that was initially performed centrally using the 143-gene OncoPrint Comprehensive Assay version 2 (OCAv2) and later referred to NCI-MATCH Designated Laboratory (DL) Network to perform sequencing for patient referral. Cell-free DNA (cfDNA) extracted from plasma collected in Streck tubes was input at 10 – 30 ng into a modified version of the Illumina TruSight Oncology 500 assay (TSO 500). Following error correction and read collapsing post-sequencing, variant calls were made and concordance between cfDNA libraries meeting prespecified QC criteria and tissue was evaluated. **Results:** Plasma, representing multiple collection timepoints, was available for 30/49 Arm M and 21/34 Arm T enrolled patients. A total of 95 cfDNA libraries, including replicates, were constructed and sequenced. Unique patient samples were tested across various timepoints (n = 35 pretreatment; n = 35 Cycle 2 Day 1; n = 8 at progression) plus replicates, with 90 (94.7%) libraries passing all prespecified QC criteria. Among Arm M patients there were 3 patients whose enrollment variant did not overlap with the TSO 500 gene panel. In total, 14 of 27 (51.8%) patients in Arm M and 18 of 21 (85.7%) patients in Arm T were concordant for enrollment mutation for at least one collection timepoint. In Arm T, 85.7% (n=38) of patient samples had at least one oncogenic or likely oncogenic (O/LO) mutation in the tumor sample at enrollment, with 73.6% (n = 28) of those also being detected by cfDNA. Interestingly, within Arm M and Arm T, a total of 7 patient samples were detected as MSI-H, with corresponding bTMB scores ranging from ~6 to > 100 Mut/Mb (median = 86.7). **Conclusions:** Detection of the enrollment mutations in treatment arms was observed in 51.8% - 85.7% of patients tested by ctDNA with overall variant concordance between tissue and ctDNA of at least 73.6%. These findings support the use of liquid biopsy as a tool for understanding genomic profiles of cancer patients both at diagnosis and progression, less invasively than standard tissue biopsies. In addition, 7 patients were identified as MSI-H, suggesting that blood-based testing could complement tissue testing for identifying patients who may benefit from targeted therapy. Research Sponsor: None.

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Poster Session

ctDNA-based genomic landscape analysis to evaluate molecular brake and gatekeeper mutations in FGFR2 alterations. *First Author: Paul Severson, Kinnate Biopharma, San Francisco, CA*

Background: FGFR2 and FGFR3 (FGFR2/3) gene alterations are oncogenic drivers found across various cancer types and have been successful targets of drug development. Several FGFR inhibitors (FGFRi) are approved for clinical use, and most are ATP-competitive, reversible inhibitors (1st-gen). Efficacy of the 1st-gen FGFRi can be limited by acquired resistance mutations in the FGFR kinase domain, typically molecular brake or gatekeeper mutations, which disrupt compounds binding through conformational changes or through direct steric hindrance, respectively. Irreversible (covalent) FGFRi, such as futibatinib, are in development to overcome kinase domain resistance mutations. However, preclinical evidence indicates that some of the known resistance mutations (eg. V564L) remain insensitive to futibatinib. **Methods:** To assess the landscape of FGFR-driven cancers and to better understand the prevalence of molecular brake and gatekeeper mutations, we analyzed the distribution of FGFR2/3 alterations in a large clinical genomic research database. This ctDNA-based genomic database was selected for the analysis given that liquid biopsy is a fit-for-purpose method to detect acquired resistance mutations. **Results:** We identified over 2,100 patients with FGFR2/3 alterations. Non-small cell lung cancer (NSCLC), breast, bladder, and cholangiocarcinoma (CCA) had the highest number of patients with FGFR2/3 alterations. 36% of all FGFR2 alterations across all cancer indications consisted of molecular brake or gatekeeper mutations. This finding was most enriched in CCA and breast cancer where 51% and 57%, respectively, of FGFR2 alterations were molecular brake or gatekeeper mutations. In breast cancer patients, molecular brake mutations were common and represent activating mutations in FGFRi-naïve patients. A small number of FGFR3 gene fusions were detected in CCA patients who had significantly shorter time on 1st-line treatment and trended toward shorter overall survival when compared to patients with FGFR2 fusions. We also identified CCA patients with FGFR2 fusions and one or more concurrent FGFR2 SNVs; primarily those in the kinase domain and associated with FGFRi resistance. Most of these putative cases of acquired resistance were polyclonal, with 2 or more (up to 8) FGFR2 SNVs coexisting with the fusion. Bladder cancer and NSCLC had the highest numbers of FGFR3 alterations. FGFR2/3 alterations were typically found without other driver mutations in CCA, bladder, and NSCLC patients. However, in breast there was a large overlap between FGFR2/3 alterations and other drivers. **Conclusions:** Herein, we identify a cohort of patients with FGFR2/3 molecular brake and gatekeeper mutations that may benefit from next-generation FGFR2/3-targeted therapies designed to inhibit a broad spectrum of both primary and secondary resistance mutations. Research Sponsor: Kinnate Biopharma.

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Poster Session

Association of tumor-informed minimal residual disease (MRD) with clinical outcomes for muscle invasive bladder cancer (MIBC): A multicenter retrospective real-world analysis. *First Author: Ajitha Kommalapati, University of Alabama at Birmingham, Birmingham, AL*

Background: Muscle invasive bladder cancer is associated with a significant elevated risk of mortality and morbidity due to micro metastatic spread at the time of diagnosis. Accurate biomarkers to guide treatment determination and evaluate response are needed. Previous studies using tumor informed ct-DNA have shown that MRD assessment may be informative in these scenarios. **Methods:** We conducted a retrospective multicenter analysis of real-world data obtained from commercial testing (Signatera; Natera, Inc.). This cohort of MIBC patients included those who underwent radical cystectomy with a minimum follow up of 90 days. Data were collected on patient demographics, clinical and pathological staging, histologic type, and treatments. Correlation of ct-DNA status with clinical outcomes was analyzed using Cox-regression analysis to evaluate utility of the assay for detecting residual disease post-surgery and radiological recurrence. **Results:** A total of 109 patients with 545 plasma samples were identified that fit the inclusion criteria. The majority of the patients [79, 72.5%] were male, with a median age of 70 (range: 32-88) years. Most patients had pure urothelial carcinoma [73.4%, 80/109]. Median follow-up was 13.63 (range: 3-89.04) months. On analyzing the first time point post-surgery (median 54 days), 91.55% (65/71) of ct-DNA negative patients at the first post-surgical test remained recurrence free while 65.79% (25/38) of positive patients had recurred at data cut-off. Therefore, ct-DNA positivity at the first post-surgical timepoint was associated with shorter disease-free survival (DFS) (HR=9.9, 95% CI: 4.1-24%, $p<0.001$). ct-DNA detected imaging recurrence with a median lead time of 61 days (range: 12-381). Similarly, on analyzing ct-DNA positivity at any time post-surgery, of those who remained ct-DNA negative (N=63), 96.83% (61/63) showed no evidence of recurrent disease. On the other hand, 63.04% (29/46) of pts with ct-DNA positivity at any time after cystectomy recurred and experienced reduced DFS (HR=25, 95%CI: 5.9-103%, $p<0.001$). The assay's sensitivity for predicting radiological recurrence at any time post-surgery was 93.55%. Notably, in the multivariate analysis, anytime ct-DNA positivity after cystectomy was found to be the only significant risk factor associated with shorter DFS (HR=23.07, 95%CI: 5.1-104.4, $p<0.001$). **Conclusions:** In this initial analysis of real-world data, MRD detection via tumor-informed ct-DNA testing was highly prognostic of patient outcomes post-surgery and may guide adjuvant treatment decisions. Future studies in this setting will explore the utility of ct-DNA testing as a predictive biomarker in response to systemic therapy. Research Sponsor: None.

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Poster Session

Development and evaluation of a multi-cancer screening (MCS) test for cancers common in Asia. *First Author: Michelle Pek, Lucence Diagnostics Pte. Ltd., Singapore, Singapore*

Background: The majority (78%) of cancer deaths in Asia arise from cancers with no existing screening recommendations. Earlier cancer detection is associated with improved outcomes. While single-cancer screening by liquid biopsy (notably plasma EBV DNA for nasopharyngeal cancer) is recognized in Asia, multi-cancer screening (MCS) liquid biopsy testing is a potential opportunity to address this key need. We developed a ctDNA mutation-based testing workflow based on targeted amplicon-based next generation sequencing testing of plasma and matched buffy coat as required to exclude clonal hematopoiesis, with a custom pipeline incorporating clinico-demographic factors for tissue-of-origin (TOO) calling. **Methods:** Primary objectives were to evaluate assay performance for detection of cancer-associated alterations, as well as TOO prediction accuracy. Validation was performed on a sample cohort of 476 untreated patients, each with 1 of 10 different cancers (lung, liver, breast, colorectal, prostate, nasopharyngeal, pancreas, bile duct, acute and chronic myeloid leukemia). 50 initial age-matched healthy controls were also used. A weighted sum model was used for TOO prediction, which was evaluated in an expanded 1478-sample cohort. Weights assigned to each cancer-associated alteration and its co-occurring combinations represent the importance or contribution of each alteration to each potential TOO. The impact of inclusion of clinico-demographic data (where available) on TOO prediction was also evaluated. **Results:** Overall sensitivity for detection of cancer-associated alterations was 72.7% (346/476). Sensitivity is higher in metastatic cases (82.5%) compared to localized cases (41.8%). Sample-level specificity for cancer-associated alterations/EBV detection was 96% (48/50), also comparable to previous series. Cancer-associated alterations/EBV were detected in approximately 50% of localized cases for 3 cancer types with no established screening recommendations in Asia (lung - 54.6%; bile duct - 50.0%; pancreas - 48.6%). In the expanded cohort, a high confidence call for TOO was obtained in 55.4% (818/1478) of samples with positive findings. Clinico-demographic data inclusion as a model variable improved overall TOO prediction accuracy in 10 cancer types to 93.8% (767/818), compared to an accuracy of 90.2% without factoring in clinico-demographic data. **Conclusions:** The MCS ctDNA assay shows reasonable sensitivity and specificity for detection of cancer-associated alterations, based on a retrospective study cohort. Tumor TOO can also be correctly classified in the majority of patients. Incorporation of clinico-demographic data to personalize TOO recommendations also improved accuracy of calls. Further prospective studies and the addition of multi-omic capabilities will continue to be helpful to determine MCS performance in an Asian multi-ethnic environment. Research Sponsor: None.

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Poster Session

Detection of early-stage cancers using circulating orphan non-coding RNAs in blood. *First Author: Mehran Karimzadeh, Exai Bio Inc., Palo Alto, CA*

Background: Orphan non-coding RNAs (oncRNAs) are a novel category of small RNAs (smRNAs) that are present in tumors and largely absent in healthy tissue. We investigated the utility of oncRNAs extracted from serum for early cancer detection across seven cancer types. **Methods:** We collected 2,882 serum samples from individuals with known cancers of the bladder ($n=152$), breast (220), colon and rectum (141), kidney (283), lung (281), pancreas (287), and stomach (280) as well as donors with no history of cancer (1,238). We used 0.5 mL serum aliquots to generate and sequence smRNA libraries at an average depth of 20 million 50-bp single-end reads. Samples were split into age-, sex-, and smoking status-matched training (1,232 cancer; 922 control) and validation (412 cancer; 316 control) cohorts. A large catalog of oncRNAs specific to each cancer was created using tumor and adjacent normal samples from The Cancer Genome Atlas (TCGA) smRNA-seq database. Using TCGA-derived oncRNAs, we trained a machine learning model to predict cancer presence and tissue of origin (TOO) in a 5-fold cross validation setup using our training cohort. For the validation cohort, we averaged the predictions from the five training cohort models. **Results:** The model ROC-AUC for detecting cancer was 0.95 (95% CI: 0.94-0.95 for training and 0.94-0.97 for validation cohorts). Sensitivities for detecting cancer at 95% specificity were 0.74 (0.70-0.76) for early stage (I/II) and 0.80 (0.76-0.84) for late stage (III/IV) cancers in the training cohort, and 0.77 (0.71-0.81) and 0.81 (0.73-0.87) in the validation cohort. Sensitivities of detection for each cancer type are shown. For samples with cancer and TOO predictions, our top 1 and top 2 TOO accuracy was 0.76 (0.68-0.84) and 0.83 (0.76-0.90) for the validation set. **Conclusions:** These results demonstrate that oncRNAs detected in serum can be used for accurate, early detection, and localization of multiple cancers. Research Sponsor: Exai Bio Inc.

	Training (N: sensitivity at 95% specificity (CI))		Validation (N: sensitivity at 95% specificity (CI))	
	Early stage (I/II)	Late stage (III/IV)	Early stage (I/II)	Late stage (III/IV)
All cancers	841: 0.73 (0.7-0.76)	391: 0.8 (0.76-0.84)	290: 0.77 (0.71-0.81)	122: 0.81 (0.73-0.88)
Bladder	68: 0.38 (0.27-0.51)	45: 0.8 (0.65-0.9)	27: 0.37 (0.19-0.58)	12: 1.0 (0.74-1)
Breast	119: 0.6 (0.5-0.69)	46: 0.72 (0.57-0.84)	42: 0.57 (0.41-0.72)	13: 0.77 (0.46-0.95)
Colorectal	51: 0.71 (0.56-0.83)	55: 0.78 (0.65-0.88)	16: 0.88 (0.62-0.98)	19: 0.68 (0.43-0.87)
Gastric	128: 0.8 (0.73-0.87)	83: 0.88 (0.79-0.94)	41: 0.83 (0.68-0.93)	28: 0.86 (0.67-0.96)
Kidney	154: 0.76 (0.68-0.82)	59: 0.73 (0.6-0.84)	53: 0.79 (0.66-0.89)	17: 0.76 (0.5-0.93)
Lung	149: 0.84 (0.77-0.89)	61: 0.87 (0.76-0.94)	49: 0.94 (0.83-0.99)	22: 0.86 (0.65-0.97)
Pancreas	172: 0.81 (0.75-0.87)	42: 0.79 (0.63-0.9)	62: 0.84 (0.72-0.92)	11: 0.73 (0.39-0.94)

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Poster Session

ctDNA NGS detection of fusions acquired as mechanisms of resistance in the post-EGFR setting across multiple solid tumors. *First Author: Arielle Yablonovitch, Guardant Health, Palo Alto, CA*

Background: Oncogenic fusions are rare but have targetable, FDA-approved therapies across all solid tumor types. These fusions have been associated with resistance to EGFR-TKI (EGFRi) in advanced non-small cell lung cancer (NSCLC) and anti-EGFR antibodies in colorectal cancer (CRC), but the prevalence of acquired fusions and their associated clinical outcomes have not been well-studied. We examined fusions in >5,000 patients with advanced NSCLC or CRC who had a history of EGFR-directed therapy in the GuardantINFORM clinical-genomic database. **Methods:** Fusions in *ALK*, *FGFR1-3*, *NTRK1-3*, *ROS1* and *RET* were examined in a cohort of 2,379 patients with NSCLC and 1,072 with CRC tested with Guardant360 or Guardant360 CDx (Guardant Health, Redwood City, CA) before approved EGFR-targeting therapies, and in 3,531 patients with NSCLC and 2,132 patients with CRC tested after EGFR therapy. Fusion clonality was calculated as the fusion variant allele fraction (VAF):max somatic VAF for each patient, with subclonal fusions defined as having clonality < 0.5. Clinical outcomes were compared between patients with and without fusions in the post-EGFR population, adjusting for age, gender, regimen/line of therapy, and max VAF. Comparisons of fusion prevalence pre- and post-EGFR therapy were performed using Fisher's exact test. **Results:** Fusions were detected more frequently in patients with NSCLC and CRC after EGFR therapy relative to pretreatment (NSCLC: 3.2% vs. pre-EGFR 0.5%, $p<0.05$; CRC: 6.4% vs. pre-EGFR 1.1%, $p<0.05$). Fusions in *RET* were most enriched in the post-EGFR NSCLC population (1.0% vs. pre-EGFR 0.1%, OR=11.6, $p<0.05$), while fusions in the *FGFR* family were most enriched in the post-EGFR CRC population (3.0% vs. pre-EGFR 0.3%, OR=10.8, $p<0.05$). The majority of fusions post-EGFR were subclonal in patients with NSCLC (86%) and CRC (96%), consistent with these fusions emerging as mechanisms of resistance. In patients with NSCLC, clinical outcomes (as measured by time-to-next-treatment (TTNT)) were significantly shorter in patients who acquired fusions compared to those without fusions (median 5.9 vs. 9.5 months, log-rank $p=0.01$, adjusted HR=1.7, adjusted $p=0.02$). Patients with CRC showed no significant difference in TTNT between those with and without acquired fusions. In patients with NSCLC who acquired fusions, 45% received an EGFRi in the next line and 23% received a TKI targeted to their fusion; TTNT on these therapies was not significantly different (median 5.3 months vs. 6.4 months, respectively). **Conclusions:** Fusions in patients with NSCLC and CRC were enriched post-EGFR therapy and were associated with inferior clinical outcomes in NSCLC. Recognition of the subclonal prevalence of acquired fusions provides important context as oncologists consider the next line of therapy. This work highlights the potential utility of genomic profiling in patients over the course of treatment. Research Sponsor: Guardant Health.

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Poster Session

Sequential monitoring of tumor macrophage fusion cells in the circulation of metastatic breast cancer and their prognostic value. *First Author: Kirby P Gardner, Creatv MicroTech, Inc., Monmouth Junction, NJ*

Background: Tumor Macrophage Fusion Cells (TMFCs) are hybrids fusions of tumor cells and macrophage/immune cells that have recently been identified in advanced solid tumors, such as metastatic Breast Cancer (mBC). Further, TMFCs are found in the blood of patients (pts) as a CD45+/CD14+ binucleated subtype of standard circulating tumor cells (CTCs), which are Cytokeratin+ (CK+) & CD45 negative, but distinct from highly hyperploidy cells known as cancer associated macrophage-like cells. However, no study has explored the clinical meaning of TMFCs in blood. To better elucidate the clinical meaning of TMFCs, we prospectively pooled 137 mBC pt samples prior to induction of new therapy, ie baseline (BL), and after therapy induction (FU). Both TMFCs or standard CTCs were identified and enumerated to analyze their prognostic value for progression-free survival (PFS) and overall survival (OS). **Methods:** In this prospective study, we collected 7.5 mL blood samples from n=137 mBC pts enrolled in prospective trials from multiple institutions before starting new treatment lines for newly progressive mBC. If possible, an optional FU sample was collected (n=73) after BL (median=4.9 weeks). TMFCs & CTCs were isolated using a CellSieve microfilter and differentiated by staining for CK, CD45, CD14, and DAPI. Cox proportional regression hazard ratios (HRs) with 95% Confidence Intervals (CI) for PFS & OS by univariate & multivariate analyses were based on RECIST v1.1, determined by local institutional pathologist over 24 months (M). **Results:** TMFCs were detected in 26.3% (n=36/137) at BL and associated with significantly worse PFS (HR=3.3, CI 1.9-5.7, p<0.001) & OS (HR=2.7, CI 1.4-5.1, p=0.005). TMFCs were also detected in 27.4% (n=20/73) at FU (n=73) and prognostic for PFS (HR=5.2, CI 2.3-11.9, p<0.001) & OS (HR=5.1, CI 1.8-14.2, p=0.004). Further, pts with increases in TMFCs between BL and FU had worse PFS (HR=4.3, CI 1.9-10.1, p=0.001) & OS (HR=4.5, CI 1.6-12.7, p=0.011). In contrast, pts with CTCs were found in 39.4% (n=54/137) at BL, which were prognostic for worse PFS (HR=2.0, CI 1.3-3.2, p=0.005) and not prognostic for OS (HR=1.7, CI 0.9-3.0, p=0.103). At FU, pts with CTCs were found in 38.4% (n=28/73), which were prognostic for worse PFS (HR=3.6, CI 1.8-7.3, p=0.001) & OS (HR=3.2, CI 1.3-8.0, p=0.021). Overall at BL, pts without CTCs or TMFCs had a 5.7 M mPFS & >24M mOS, CTCs alone had a 5.0 M mPFS & 20.3 M mOS, TMFCs had 2.0 M mPFS & 5.8 M mOS. At FU, pts without CTCs or TMFCs had a 5.8 M mPFS & 14.5 M mOS, CTCs alone had a 3.3 M mPFS & 14.6 M mOS, while TMFCs pts had a 1.7 M mPFS & 4.8 M mOS. **Conclusions:** TMFCs appear to represent a CTC subgroup with additional prognostic value to standard CTCs, that may correlate with significantly faster PFS and OS versus pts with CTCs alone, or without CTCs. Subtyping treatment regimens is ongoing to determine if the TMFC populations are responsive to specific therapy types in these mBC pts. Research Sponsor: U.S. National Institutes of Health; Creatv MicroTech.

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Poster Session

Clonal hematopoiesis (CH) associated mutations in patients with advanced solid tumors enrolled in phase I clinical trials. *First Author: Julieta Rodriguez, Drug Development Department, Gustave Roussy Cancer Campus, Villejuif, France*

Background: An increased number of CH associated mutations has been identified in patients (pts) with solid tumors. Their impact on pts outcomes remains unclear. This study aims to integrate molecular data and clinical characteristics of CH in pts enrolled phase I clinical trials. **Methods:** Data was collected retrospectively from medical records and molecular profile reports (Foundation One Liquid CDx Assay – 309 genes) performed before first study drug administration at the Drug Development department in Gustave Roussy (Villejuif, France) within the STING trial (NCT04932525). CH prevalence was assessed according to a variant allele frequency (VAF) threshold of 1% in epigenetic modifiers (*DNMT3A*, *TET2* and *ASXL1*). **Results:** From January 2021 to December 2022, 255 pts were enrolled in a phase I clinical trial and had a liquid biopsy. In total, 55% of patients were male with a median age of 62 years [24-86]. Most common tumor locations were gastrointestinal (27%), genitourinary (21%) and thorax (18%). Patients received a median of 2 prior lines of treatment before investigational study drug and CH assessment. At the end of the data cut off, 81% of pts discontinued phase I treatment mostly due to progression disease. Overall, 104 pts (41%) had at least 1 CH mutation in liquid biopsy at baseline with 55 pts (22%) at a VAF of $\geq 1\%$. Mutation frequency was *DNMT3A* in 42% (n= 23), *ASXL1* in 38% (n=21) and *TET2* in 31% (n=17). Co-mutations were present in 26 patients, with the most frequent being *DNMT3A* + *ASXL1*. Median PFS and OS were 3.7 months (m) for CH group vs 3.5m for no-CH (p=0.3) and 24m CH vs 15m no-CH (p=0.5), respectively. **Conclusions:** CH is commonly found in pts with solid tumors treated in phase I trials, with a prevalence in our cohort of 22%. Most frequent mutated gene was *DNMT3A*. Prognostic implications of the impact of these mutations in patient's outcomes remain to be elucidated and will be presented at the meeting. Research Sponsor: None.

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Poster Session

Pan-cancer detection and tissue-of-origin identification by whole-genome sequencing of plasma cell-free DNA. *First Author: Wei Guo, HaploX Biotechnology, Shenzhen, China*

Background: Despite notable advances in cancer therapeutics, much of the mortality of human cancers results from late diagnosis. The early detection of cancer remains an unmet need that can benefit the effective treatments and better prognosis. Cell-free DNA (cfDNA) in the circulation provides an emerging diagnostic method for non-invasive cancer screening. The fragmentation signatures of cfDNA originating from different cell types or malignancies display distinct patterns, suggesting the potential as cancer biomarkers. This study aims to investigate the fragmentation profiles of cfDNA in several cancer types, and to develop a new approach for pan-cancer detection and tissue-of-origin identification. **Methods:** Plasma samples from 739 patients with lung (N=577), colorectal (N=98), breast (N=51) and liver (N=13) cancers, as well as 716 healthy individuals were collected in this study. Cell-free DNA was isolated and used to generate the whole-genome sequencing data. We developed an approach called PatternWGS (Pan-cancer detection and tissue-of-origin identification by whole-genome sequencing) to analyze the DNA fragmentation patterns comprehensively. Fragmentation features integrating cfDNA fragment size distribution, frequency of end motif sequence, and copy number variation were utilized to construct the optimal prediction model. We presented a multi-cancer detection model for distinguishing individuals with and without cancer using Generalized Linear Models (glmnet), and further built a cancer-origin model to predict cancer types using Random Forest algorithm. Training and testing occurred on randomly selected sampling splits of 60% and 40% of the data, respectively. Features selection and model construction were performed by only training cohort, and the test set was solely used for performance evaluation. **Results:** A larger proportion of shorter cfDNA fragments in cancers was observed. We proposed a fragment score indicating the degree of short fragmentation, and this fragment score was significantly higher in cancers (p<0.001). Several end motifs were identified to be specifically enriched in cancer patients. The multi-cancer detection model reached an area under the curve (AUC) of 0.98, with the sensitivity of 93% at 95% specificity. The sensitivity of detecting lung, colorectal, breast, and liver cancers reached 94.2%, 87%, 100% and 100% respectively, at 95% specificity. The cancer-origin model demonstrated an overall accuracy of 81.7% for the identification of tissue of origin. **Conclusions:** Our prediction model demonstrated a superior performance for multi-cancer detection and cancer origin prediction, suggesting the potential of plasma cfDNA fragmentation signatures as non-invasive biomarkers for early cancer detection in clinical. The distinct fragmentation patterns in cancer provide new insight to understand the mechanism of tumorigenesis. Research Sponsor: None.

3057

Poster Session

NMR metabolomics in bladder cancer: Identification and monitoring of serum biomarkers during Pt-based treatment. *First Author: Roberta Giorgione, Clinical Oncology Unit, Careggi University Hospital, Florence, Italy. Department of Experimental and Clinical Medicine, University of Florence, Italy, Florence, Italy*

Background: To date, predictive and prognostic biomarkers for Bladder Cancer (BC) are lacking. Metabolomics, the study of small molecules involved in metabolism, aims to identify diagnostic, predictive and prognostic biomarkers. Overall, BC shows perturbations of various metabolic pathways, involved in biochemical reactions essential for energy production and for the maintenance of the REDOX balance, as well as in the metabolism of purines and pyrimidines. The main objective of this study is to characterize the serum metabolic profile of patients with BC undergoing platinum-based chemotherapy (Pt-CT), to identify the alterations induced by CT and evaluate the associated deregulated metabolic pathways, in order to identify potential biomarkers, prognostic and predictive of response to treatment. **Methods:** We enrolled patients with BC undergoing Pt-CT in different settings (neoadjuvant, adjuvant or metastatic). For each patient, a blood sample was collected before the start of each CT cycle (T0, T1, Tn). Metabolomic analysis was performed using the Bruker Avance 600 spectrometer. At baseline (T0), the metabolomic profiles of BC patients were compared with that of age- and sex-matched healthy controls. Major metabolites up- or down-regulated in patients with BC at baseline, were then monitored during CT (T1, Tn). **Results:** 14 patients were enrolled. When compared with age- and sex-matched healthy controls, patients with BC had elevated levels of acetate and acetone (ketone bodies), hypoxanthine, trimethylamine N-oxide (TMAO), glutamate, lactate, phenylalanine, and ornithine, and decreased levels of carnitine, choline, betaine, aspartate, threonine, 2-hydroxybutyrate, 2-aminobutyrate and histidine. When monitored during CT, hypoxanthine, glutamate, and aspartate levels increased; acetone, acetate and TMAO instead had a decreasing trend. **Conclusions:** The results of our pilot study confirm perturbations in several metabolic pathways: up-regulation of lactate, ketone bodies, hypoxanthine, phenylalanine, and glutamate levels in BC patients reflects altered glycolysis, fatty acid, purine, and amino acid metabolism, respectively. In addition, TMAO may play a role in the development of BC by promoting a pro-inflammatory and oxidative stress state. Furthermore, monitoring these metabolites could be a useful tool for predicting response to treatments. To our knowledge, there are no metabolomic studies that evaluated BC patients receiving CT and that included longitudinal monitoring to identify any changes in the metabolic profile induced by treatment. Research Sponsor: None.

3058

Poster Session

Diagnostic application of circulating CDH17 biomarker for screening GI malignancies. *First Author: Lui Ng, The University of Hong Kong, Pokfulam, Hong Kong*

Background: Colorectal cancer (CRC) is the most common and treatable gastrointestinal (GI) cancer, yet it remains the second leading cause of cancer associated deaths globally. Cadherin-17 (CDH17) is a biomarker for GI cancers characterized by its overexpression in stomach, liver, and colorectal cancers but controlled expression in normal tissues from healthy adults. Although an improvement in the detection strategy of CDH17 is essential to apply it for large scale CRC screening. We have developed a novel diagnostic immunoassay using a panel of highly specific antibodies (PCT/US2019/032752) that unveiled CDH17 as a potential diagnostic marker with high detection sensitivity and specificity in CRC. **Methods:** The study recruited 150 patients (Retrospective specimens - 50 colorectal adenomas and 100 colorectal cancer) and 50 asymptomatic 18-80 years old blood donors (prospective specimens). CDH17 expression levels were measured within the individual blood-plasma samples using an enzyme-linked immunoassay. **Results:** The novel CDH17 diagnostic assay showed a wide operating dynamic range extending from 90ng to a lower limit of detection at 123pg. Using the assay, we observed a progressive and a significant increase in the plasma CDH17 concentration from the asymptomatic individuals to the colorectal adenoma group, while the CRC patients showed the highest expression of the circulating protein (median: 2.5ng/mL vs 4.5ng/mL vs 8.0ng/mL, $P < 0.0001$). Within the CRC group, a higher CDH17 expression was associated with advanced tumor invasion, occurrence of nodal or distant metastases, as well as a clinical presentation of an advanced stage disease. The diagnostic power of the assay in terms of ROC AUC values was higher than 0.9 with an overall sensitivity of 82% that extended to 100% for metastatic CRC, while the specificity was at 94% for all stages combined ($P < 0.0001$). Plasma CDH17 outperformed the clinically applied CEA and CA19-9 markers in differentiating the CRC patients from the asymptomatic population. **Conclusions:** The CDH17 immunoassay is potentially a diagnostics tool aid for the detection of CDH17 within blood samples prompting the early diagnosis of CRC. **Research Sponsor:** Innovation Technology Fund: PSTS-SPC (Reference: SCT/005/21SP).

Plasma Biomarker	Cut-off	AUC	Sensitivity	Specificity
CDH17	5.5ng/mL	0.9324	82%	94%
CEA	5ng/mL	0.8501	76.09%	78.79%
CA19-9	37U/mL	0.5432	72%	18%

3060

Poster Session

Preclinical circulating tumor DNA (ctDNA) shedding duration and prognostic implications of modeling 3669 participants from American Cancer Society Cancer Prevention Study-3 (CPS-3) and Circulating Cell-free Genome Atlas substudy 3 (CCGA3). *First Author: Alpa Patel, American Cancer Society, Kennesaw, GA*

Background: Early detection of cancer occurs in the preclinical phase, when development of cancers is unobservable. Shedding of ctDNA has previously been associated with aggressive cancers, suggesting these tumors may develop rapidly before diagnosis. Assays of ctDNA in blood samples from prospective cohort studies at various lead times (interval between blood draw and diagnosis) may provide insight into the timescales of preclinical cancer development, as well as prognosis. **Methods:** We used a targeted methylation assay and the associated locked classifier for cancer signal detection (CSD) on samples from two large prospective biobank studies: 1) CPS-3, where blood draw at enrollment (2006-13) occurred ≤ 3 years (Ys) before clinical diagnosis ($n=1065$); 2) CCGA3 (NCT02889978), where blood draw (2016-19) was concurrent with clinical diagnosis ($n=2604$). We constructed a model for detectability including study, inherent shedding of ctDNA at clinical diagnosis, and effect of lead time by cancer type and stage. We additionally evaluated prognosis stratified by ctDNA status (CSD positivity), compared to expected cancer-specific survival (CSS) matched by age, cancer type, and stage for ≤ 9 Ys of follow-up, noting that ctDNA status may change during lead time. **Results:** Estimated inherent ctDNA detectability did not differ between CCGA3 and CPS-3 studies (95% confidence interval [CI] for difference is [-8.2%, 4.6%] and spans zero). Median [CI] detection timescales for exponential decay of detection by time were 0.75 [0.47, 1.3] Ys for localized stage, 0.89 [0.61, 1.33] Ys for regional, and 1.2 [0.84, 1.67] Ys for distant, consistent with a published model, and ranged by type from 0.49 [0.26, 0.88] Ys for pancreas to 2.45 [1.14, 4.87] for lymphoma. For CPS-3, estimated CSS at 9 Ys from blood draw was 54% for ctDNA+ and 79.5% for ctDNA- participants. Hazard ratios (HR) [CI] for ctDNA+ vs ctDNA- alone predicting CSS were 7 [4.2, 12.2], 4.2 [2.9, 6], and 3.5 [2.5, 4.7] for those diagnosed up to 1, 2, and 3 Ys after blood draw, respectively. Compared to synthetic controls for age, cancer type, stage, and lead time in Surveillance, Epidemiology, and End Results (SEER) data, CSS was better in each group: ctDNA+ HR 0.63 (CI: 0.54, 0.74); ctDNA- HR 0.45 (CI: 0.22, 0.74). **Conclusions:** These results provide estimates for the average detection window in tumors shedding ctDNA across multiple cancer sites and stages, including cancer types with no current screening paradigm. Taking lead time into account, preclinical ctDNA status selected clinically significant cancers, limiting potential for overdiagnosis. Additionally, long-term survival remained better than in SEER data, suggesting that ctDNA+ cancers can be survivable. Results require confirmation in future prospective analyses. **Research Sponsor:** GRAIL, LLC; American Cancer Society.

3059

Poster Session

Concordance of circulating and solid tumor DNA through comprehensive genomic profiling in a large integrated cancer network. *First Author: William LaFramboise, Allegheny Health Network Cancer Institute, Pittsburgh, PA*

Background: Comprehensive Genomic Profiling (CGP) of solid tumors is crucial in diagnosing and treating cancer patients. Circulating Tumor DNA (ctDNA) is a potential biomarker for detecting mutations when tissue samples are limited or unavailable. However, the sensitivity of ctDNA tests vary greatly, making concordance studies with tissue samples critical to validate clinical use. This study presents results of CGP in paired tumor tissue and plasma samples from representative cancer patients treated in a community-based, Integrated Network Cancer Program. **Methods:** Over 2000 cancer patients have provided solid tumor and/or blood samples to date including serial follow-up blood samples. To optimize ctDNA integrity, we collected blood using a membrane stabilizer (Streck), ensured courier transport in ≤ 72 hours, separated plasma via differential centrifugation $\times 3$, extracted cell free DNA with magnetic beads, and performed Next Generation Sequencing (NGS) using the ct-TSO500 assay (Illumina). In cases where patients provided both a solid tumor and concurrent blood sample, st-TSO500 NGS results from the solid tumor were compared to the ctDNA results for these matching specimens. Clinical actionability of variants was determined using the OncoKB database at levels 1, 2, and R1. **Results:** 146 matched blood and solid tumor specimens were analyzed to date. CGP studies revealed 1179 ± 102 unique variants across 20 different cancer types. Coding mutations from these specimens averaged 183 ± 25 variants. The ctDNA contained 96.5% of initial variants (1088 ± 95) and 95.1% of coding mutations (163 ± 20) found in the respective matched solid tumor. 76 patients had one or more oncogenic mutations detected only in the ctDNA and 28 (36.8%) of these included an actionable anticancer pharmacotherapy. Concordance by selective tumor type for clinical oncogenic variants was 95.8% (prostate), 95.0% (pancreas), 92.8% (lung and ovarian), 90.0% (endometrium), 84.3% (colon) and 82.4% for breast cancer. There was no difference in concordance between stage IV (91.0%) and stage I-III (86.5%) tumors ($p = 0.14$). An average of 6.2 ± 2.5 oncogenic variants were detected in both ctDNA and tissue. 99.3% of all patients contained an oncogenic biomarker in both ctDNA and tissue assays. **Conclusions:** We developed a prospective tissue and plasma repository of patients across a large integrated cancer network. These data demonstrate high concordance between circulating and solid tumor DNA using an "in-house" CGP assay. With no loss of concordance across cancer stages, ctDNA can identify actionable mutations not found in solid tumor analysis. This study is an important step toward incorporating "in-house" ctDNA CGP into routine cancer care. Future goals are to utilize these data for development of novel prognostic and predictive classifiers for use in a community-based hospital system across various disease sites. **Research Sponsor:** Highmark Health; Allegheny Health Network.

3061

Poster Session

Liquid biopsy identification of ERBB2 amplified and HER2 expressing metastatic breast cancer: Comparison and combination of cell and cell-free platforms. *First Author: Giuseppe Di Caro, Epic Sciences, San Diego, CA*

Background: Liquid biopsies are a non-invasive diagnostic approach for detecting circulating tumor cells (CTCs) or circulating tumor DNA (ctDNA) that may provide clinically actionable information for treatment decisions for metastatic breast cancer (MBC) patients when a conventional biopsy is otherwise infeasible. Here we report a comprehensive liquid biopsy platform including: 1) quantitative immunofluorescent HER2 and ER protein expression in CTCs (ctcIF), 2) determination of ERBB2 amplification and the number of Large-scale State transitions (LST) by single-cells CTC genomics (ctcDNA) and 3) alterations in plasma ctDNA. **Methods:** Blood samples from 457 progressing metastatic breast cancer patients and 25 healthy donors (HDs) as controls were collected for cell & cell-free DNA analysis. After plasma isolation, nucleated cells were plated, & slides were bio-banked for Immunofluorescent staining & subsequent imaging. CTCs were identified using Epic Sciences digital imaging & machine learning algorithms, and individual CTCs were sequenced for genomic quantification of LSTs and Copy Number Variants (CNV). Bio-banked plasma was analyzed to detect ctDNA alterations with high clinical relevance (Class IA). **Results:** Within this cohort of 457 MBC patients, the presence of CTCs, ctDNA (LST*) and ctDNA alterations were detected in 98%, 58%, and 42%, respectively, while no CTCs and no ctDNA alterations were detected in the HD cohort, suggesting high specificity. ctDNA genomics was more sensitive than ctDNA in detecting $ERBB2^{amp}$ in MBC patients (16%, and 2%, respectively). A mean variant allele frequency (VAF) of $< 25\%$, which is the threshold for detecting a two-fold $ERBB2$ amplification by ctDNA, was present in 20% and 80% of $ERBB2^{amp}$ MBC detected by the ctDNA and ctDNA platform, respectively, suggesting that the ctDNA platform can identify the majority of $ERBB2^{amp}$ among patients with a low ctDNA fraction. $HER2^{exp}$ or ER^{exp} expression by ctcIF were detected in 67% and 67% of MBC patients, respectively. A liquid biopsy classification of HER2 status by combining the three platforms (ctcIF, ctDNA, and ctDNA) identified that in the tested population, 16% were $ERBB2^{amp}$, 52% were HER2 expressing ($HER2^{exp}$ and $ERBB2^{nonamp}$), and 27% were $HER2^{neg}$ ($HER2^{-}$ and $ERBB2^{nonamp}$). To identify MBC patients that may potentially change treatment as a result of the test we identified a small cohort of MBC patients ($n=46$) with HER2- disease and tissue biopsy IHC=0, 74% of these patients had $HER2^{exp}$ CTC consistent with HER2 low expression which may aid therapeutic decisions in later line MBC. **Conclusions:** Here we report a comprehensive liquid biopsy profile combining ctcIF, ctDNA, and ctDNA platforms with high sensitivity and specificity in determining clinically actionable HER2 and ER biomarker status that may impact therapeutic decision-making in MBC patients. **Research Sponsor:** Epic Sciences.

3062

Poster Session

ctDNA analysis of NTRK fusion and mechanisms of acquired resistance to TRK inhibitors. *First Author: Karthigayini Sivaprakasam, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: The regulatory approval of TRK tyrosine kinase inhibitors (TKIs) represented a landmark in tissue-agnostic drug development. Adult and pediatric patients harboring *NTRK* fusions derive meaningful clinical benefits from the first-generation TRK TKIs larotrectinib and entrectinib. However, characterizing *NTRK* fusions and resistance mechanisms to TRK TKIs by circulating tumor DNA (ctDNA) remains to be studied. **Methods:** Patients with *NTRK*-fusion-positive tumors who received TRK TKIs and had ctDNA analyzed using next-generation sequencing (NGS) were retrospectively identified. Samples were collected at multiple time points, including pre-TRK TKI, on-treatment, and post-progression. Mechanisms of resistance to TRK TKIs were examined when post-progression ctDNA samples were available. **Results:** Twenty-seven patients, with a median age of 57 years (range 28-81) and 11 different cancer types were identified. Twenty-two patients (81%; 22/27) had at least one ctDNA-positive sample (tumor burden greater than 0). A total of 67 ctDNA samples were analyzed by MSKCC ACCESS ctDNA pipeline, of which 10 samples (15%; 10/67) were collected before any TRK TKI. Forty-two samples (63%; 42/67) had positive ctDNA and *NTRK* fusion was detected in 16 ctDNA samples (24%; 16/67), including 9 (56%) *NTRK1* fusions and 7 (44%) *NTRK3* fusions. Among the pre-TRK TKI samples (n=10), 2 samples (20%, 2/10) had *NTRK* fusions detected. A total of 8 patients had post-progression samples with a resistance mechanism identified, of which 5 patients received larotrectinib and 3 entrectinib. The ctDNA samples revealed 7 patients (88%; 7/8) with on-target resistance and 1 patient (12%; 1/8) with off-target resistance. Among on-target mutations identified, the most common involved the solvent front residue (86%, n=6/7: n=2 *NTRK3* G623R, n=2 *NTRK1* G595R, n=1 *NTRK3* G623E, n=1 *NTRK3* G623L) followed by the xDFG motif (14%, n=1/7: n=1 *NTRK1* G667C). Regarding off-target alterations, one patient developed a *BRAF*V600E mutation. **Conclusions:** The use of plasma ctDNA can improve the identification of *NTRK* fusions through non-invasive techniques and potentially identify subsequent resistance mechanisms after the administration of the TRK TKIs. Research Sponsor: U.S. National Institutes of Health.

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Poster Session

⁶⁸Ga-FAPI-46 PET for cancer imaging: A prospective single-arm clinical trial. *First Author: Wolfgang P. Fendler, Department of Nuclear Medicine, University of Duisburg-Essen and German Cancer Consortium (DKTK)-University Hospital Essen, Essen, Germany*

Background: Fibroblast activation protein (FAP) is expressed at high levels on tumor associated fibroblasts. FAP-directed radioligand positron-emission-tomography (FAP-PET) is a novel diagnostic tool for cancer. However, we currently do not understand the diagnostic performance of FAP-PET as compared to standard FDG-PET. Here we aim to compare tumor detection by FDG- vs. FAP-PET with independent validation of discrepant findings. **Methods:** Patients with (a) proven or suspected malignancy, (b) longest tumor diameter >1 cm, (c) intended surgery or biopsy, and (d) no prior external beam radiation or systemic tumor therapy within 3 months underwent FDG- and FAP-PET for tumor localization on subsequent days. Clinical reads were analyzed prospectively on a per-patient and per-region basis (local, locoregional nodal, distant organ or soft tissue, bone). Discrepant findings were validated as true vs. false positive by histopathology or image follow-up. Tracer uptake in tumor tissue was assessed by SUVmax. **Results:** In total n=100 patients (median 62 years, male/female n=68/32) underwent FDG- and FAP-PET. Five most frequent tumor entities and respective median FDG vs FAP uptake were RCC (n=19; SUVmax 8.4 vs. 7.1), sarcoma (n=18; 10.3 vs. 10.9), NSCLC (n=10; 12.4 vs. 13.7), lymphoma (n=9; 18.3 vs. 10.9), and PDAC (n=8; 4.1 vs. 7.3). On a per-patient basis, FDG- vs FAP-PET localized malignancy in n=93/94 patients. FDG- vs FAP-PET was concordant for the assessment of 362/400 (91%) regions. n=16/400 (4%) regions were negative on FDG- and positive on FAP-PET (88% true, 12% false positive). n=22/400 (6%) regions were negative on FAP- and positive on FDG-PET (57% true, 43% false positive). Two false positive FDG-PET findings were due to tracer uptake in reactive lymph nodes. There were no PET-related adverse events. **Conclusions:** In patients with various tumor entities, standard FDG- and novel FAP-PET localized tumor equally well. Additionally, FAP-PET was associated with a lower rate of false positive findings, especially in lymph node assessments. Clinical trial information: NCT05160051. Research Sponsor: SOFIE Bioscience; University Duisburg-Essen.

Tumor entity (n=100 patients)	n
RCC	19
Sarcoma	18
NSCLC	10
Lymphoma	9
PDAC	8
Bladder	7
Breast	4
Colorectal	4
Other	21

3063

Poster Session

Potential improvement in the diagnostic accuracy in detecting the estrogen receptor status in metastatic and recurrent breast cancer using 18F-FES PET/CT in the US. *First Author: Adolfo Fuentes-Alburo, GE Healthcare, Marlborough, MA*

Background: ER status helps classify BC for the most appropriate treatment pathway. Biopsy (Bx) and immunohistochemical (IHC) are established procedures to determine the ER status in metastatic BC (mBC, i.e., first occurrence of metastases) and recurrent BC (rBC, i.e., progression of mBC). In some cases, the accuracy of Bx/IHC to inform ER status may be challenged (e.g. difficult to access lesions; ER discordance within/across lesions and due to temporal heterogeneity; and when a Bx fails to obtain representative tissue). 16 α -18F-fluoro-17 β -fluoroestradiol (18F-FES) is a radiolabeled form of estrogen that binds to ER. For use with positron emission tomography /computed tomography imaging (PET/CT), it allows an assessment of whole-body ER+ status. In prospective trials and meta-analyses, 18F-FES PET/CT provided high diagnostic accuracy (DA) of ER+ disease. This study evaluated the potential increase in accuracy in determining ER+ status when 18F-FES PET/CT was added to IHC in mBC and rBC. **Methods:** An Excel based decision model was developed to estimate the impact on DA for ER+/HER2- US mBC and rBC patients over a five-year period by introducing 18F-FES PET/CT. The model assumed that 18F-FES PET/CT was added to Bx/IHC to classify ER status in three cases: (i) for mBC patients when Bx failed or was inconclusive, (ii) for mBC patients when Bx was not possible, or (iii) for all rBC patients. The DA between two scenarios was compared: scenario A, DA of Bx/IHC only and scenario B, 18F-FES PET/CT + Bx/IHC. **Results:** Scenario B, adding 18F-FES PET/CT, may lead to an increase in the initiation of appropriate endocrine- and chemotherapies, as defined by clinical practice guidelines, in all comparisons. The largest increase in DA was in rBC and, when Bx is not possible, in mBC patients. Also, results indicate that introducing 18F-FES PET/CT decreases the number of re-biopsies performed except when Bx was not possible (ii). **Conclusions:** Adding 18F-FES PET/CT to Bx/IHC is expected to improve the DA of a patients' ER status thereby increasing the information available to inform treatment, thus reducing the need for re-biopsies in mBC and rBC patients. By far the largest increase in DA of ER status using 18F-FES PET/CT was seen among patients with rBC (iii). Research Sponsor: GE Healthcare.

Modelled results in 3 cases (mBC population yr 1: n = 17,970 / yr 5: n = 72,150; rBC population yr 1: n = 8,750 / yr 5: n = 34,040).

Year	1			5		
Scenario	A	B	Δ (B vs A (%))	A	B	Δ (B vs A (%))
(i)						
Σ all appropriate therapies started	14,388	14,613	225 (1.6%)	21,243	21,516	273 (1.3%)
Re-biopsies	1,495	65	-1,430 (-95.6%)	1,765	106	-1,662 (-94.0%)
(ii)						
Σ all appropriate therapies started	14,388	15,128	741 (5.1%)	21,243	22,244	1,001 (4.7%)
Re-biopsies	1,495	1,496	1 (0.06%)	1,768	1,770	2 (0.13%)
(iii)						
Σ all appropriate therapies started	5,130	6,314	1,184 (23.1%)	6,478	7,972	1,494 (23.1%)
Re-biopsies	39	0	-39 (-100%)	47	0	-47 (-100%)

3065

Poster Session

Utility of artificial intelligence-based genomic classification of occult malignancies in clinical practice. *First Author: Sourat Darabi, Hoag Family Cancer Institute, Newport Beach, CA*

Background: Occult primary malignancies (OPM) are a significant clinical problem, representing 3 to 5% of advanced cancers. Patients with OPM have a worse prognosis and fewer treatment options than when the primary site of origin of cancer can be confidently identified. Novel artificial intelligence-based genomic classification of occult malignancies has been validated for clinical use by previous studies, but reports of clinical utility have not yet been published. We report our experience of consecutive cases where a commercial AI-based genomic classifier was used in routine practice at a high-volume community cancer center. **Methods:** Malignancies with uncertain pathological classification or site of origin were subjected to molecular profiling and AI-based genomic classification (GPSai) capable of recognizing a set of 115 distinct primary tumor sites and histology classes. Molecular profiling consisted of whole exome and whole transcriptome sequencing of FFPE tumor samples along with other predictive biomarkers assays performed by a commercial laboratory (Caris Life Sciences). The identification of targetable mutations was reported, but variants of unknown significance were excluded when reporting genomic alterations. **Results:** From 1,316 patients between October 2021-November 2022, we analyzed 70 (5.3%) patients with OPM, including 44 (62.9%) females and 26 (37.1%) males, with 34 (48.6%) being 65 or older. GPSai classification was ordered for 73 samples from 70 patients, which resulted in the classification of 33 (45.2%) tumors, inconclusive results in 36 (49.3%), and insufficient tissue quantity in 4 (5.5%). Of the 33 cases with a GPSai classification, the putative pathology diagnosis was concordant in 26 (78.8%) and discordant in 7 (21.2%) cases. We investigated discordance between the GPSai and pathological diagnoses in discordant cases. The pathological classification was favored over GPSai in all 7 discordant cases. Of the 36 cases that could not be confidently assigned a classification, 14 (38.9%) possessed potentially actionable alterations. 23 of the 36 had no presumptive site of origin. Of these, 10 of 23 (43.5%) were PD-L1 positive, 4 of 23 (17.4%) had a high TMB, and 1 of 23 (4.4%) had MMR deficiency. Additionally, based on molecular profile and examination of RNA expression levels, 2 cases were able to be classified with subsequent IHC confirmation. Based on the results from genomic testing, 55.7% of patients (39 of 70) had FDA-approved treatment options. **Conclusions:** Over a third of patients with OPM were able to be assigned a cancer diagnosis concordant with diagnoses by pathologists. Of those which could not be classified, targetable biomarkers were commonly found. AI-based genomic classification of occult primaries is useful in clinical practice to help discern the site of origin and identify treatment options. Research Sponsor: None.

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Poster Session

Tumor mutational burden as a predictive biomarker for molecularly matched therapy in two independent pan-cancer cohorts. *First Author: Damian Tobias Rieke, Charité – Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität Zu Berlin, Charité Comprehensive Cancer Center; German Cancer Consortium (DKTK), Berlin, Germany*

Background: Personalized cancer therapy based on molecular tumor aberrations has shown efficacy in a subset of tumors. Novel biomarkers are warranted to help extend this benefit to a larger patient population. Tumor mutational burden (TMB) is an established predictive biomarker for immune checkpoint inhibition. Its role for molecularly matched therapy is unknown. **Methods:** Comprehensive molecular profiling including whole-exome and RNA-sequencing was performed in 104 patients with advanced cancer within the DKTK MASTER program. 55 patients received a systemic therapy excluding immunotherapy. TMB and survival were analyzed in patients receiving molecularly matched therapy (n=34) or non-molecularly matched therapy (n=21) as well as in an independent published cohort of patients receiving molecularly matched (n=68) or non-molecularly matched (n=40) therapy (excluding immunotherapy). TMB and co-occurring driver mutations were analyzed in the DKTK MASTER cohort. **Results:** The median TMB of 1.68 mutations per megabase (mut/Mb) in the 34 patients receiving molecularly matched therapy was used to stratify patients into TMB-high and -low groups. Median overall survival (OS) and progression-free survival (PFS) were significantly shorter in the TMB-high than in the TMB-low group (OS: 4 months [95% CI, 3.3 to 7.6] versus 19 months [95%CI, 10.0 to not reached] p < 0.001, Hazard Ratio (HR) 4.4 [95%CI, 1.9 to 10.2], p<0.001; PFS 1.8 months [95%CI, 1.1 to 3.6] versus 8.5 months [95% CI, 2.8 to 17.0] p = 0.004, HR 2.9 [95%CI, 1.4 to 6.2], p=0.005). No significant differences were observed in patients receiving non-molecularly informed systemic therapy (OS HR 0.7 [95%CI, 0.2 to 2.6], p=0.635 and PFS HR 1.2 [95% CI, 0.4 to 3.5] p=0.701). In the validation cohort, shorter progression-free survival was also identified in the TMB-high group (median TMB cut-off of 4 mut/Mb; HR 2.2 [95%CI, 1.3 to 3.7] p=0.005) treated with molecularly matched therapy but not with non-molecularly informed therapy (HR 1.1 [95%CI, 0.5 to 2.2] p=0.848). TMB was associated with co-occurring driver mutations (n=104, r = 0.78 [95%CI, 0.68 to 0.85], p<0.001). **Conclusions:** High TMB was previously established as a positive predictive biomarker associated with efficacy of immune checkpoint inhibitor treatments. Our study reveals high TMB as a negative predictive biomarker associated with low efficacy of molecularly informed systemic therapy, potentially due to co-occurring driver mutations. Thus, TMB is a candidate predictive pan-cancer biomarker for combined precision oncology and immunotherapy programs. Research Sponsor: Deutsches Konsortium für Translationale Krebsforschung (DKTK).

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Poster Session

Deep neural networks to predict pathological invasiveness through surgical resection images: A computer vision based prospective clinical trial in pulmonary nodules. *First Author: Henian Yao, The First Clinical Medical College, Guangdong Medical University, Zhanjiang, China*

Background: Pathological subtypes associate with surgical strategies of pulmonary nodule, during which thoracic surgeons make surgical decision through intra-operative frozen resection diagnosis. However, frozen section is time-consuming, vague and maybe misleading due to the limited sample and subjective judgements from pathologists. This study developed a predictive deep neural network for pathological invasiveness of pulmonary nodules based on the surgical resection images of gross specimens. **Methods:** We prospectively collected the specimen image under standardized lighting conditions in operating theaters from patients with pulmonary nodules treated by surgery resection from June 2020 to September 2021 in Guangdong Provincial People's Hospital. Images were assigned into training cohort, validating cohort and test cohort as 8:1:1. With data augmentation, DenseNet was applied to classify the pulmonary nodules into high-risk and low-risk group. High-risk group was defined as grade 2 and grade 3 invasive pulmonary adenocarcinoma according to IASLC, while low-risk group was defined as adenocarcinoma in situ (AIS), minimally invasive adenocarcinoma (MIA) and grade 1 invasive pulmonary adenocarcinoma. Predictive efficiency was evaluated through area under the curve (AUC) of the receiver operating characteristic (ROC) curve, sensitivity, specificity, accuracy. Model performance would be compared with frozen section pathological diagnosis. **Results:** Among 1022 patients with pulmonary nodules enrolled, we have acquired 1080 images of the resected nodules in Guangdong Provincial People's Hospital, with a mean age of 56 years and 39.1% of male patients. The median age of patients were 57 years in training cohort and 56 years in validating cohort, with 38.1% male patients in training cohort and 42.5% male patients in test cohort. This study included 864 images in training cohort, 108 images in validating cohort and 108 images in test cohort. Mean diameter of the nodules were 14.6mm in training cohort and 17.2mm in test cohort. In terms of predictive performance, the AUC value of ROC curves was 96.0% in training cohort and 95.0% in test cohort. In training cohort, the sensitivity of model was 97.6%, with the accuracy of 97.5% and specificity of 97.6%. In test cohort, the sensitivity of model was 97.6%, with the specificity of 90.2% and accuracy of 95.4%. Compared with frozen resection in testing cohort, our deep neural network had higher accuracy in pathological prediction (95.4% vs 88.9%). **Conclusions:** This study developed and validated a predictive algorithm on pathological invasiveness of pulmonary nodules through computer vision technique with highly sensitivity and specificity, which could assist the rapid evaluation for pathological invasiveness and intraoperative surgical decisions. Research Sponsor: None.

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Poster Session

A panel of seven protein tumor markers for multi-cancer early detection by artificial intelligence. *First Author: Shichun Tu, Clinical Laboratories, Shenyao Bio, Zhengzhou, China*

Background: Early cancer detection is key to reducing cancer deaths. Unfortunately, many established cancer screening technologies are not suitable for use in low- and middle-income countries due to expenses, complexity, and dependency on extensive medical infrastructure. Therefore, a simple, affordable, efficient multi-cancer early detection test is a major unmet need. **Methods:** This study enrolled nearly 10,000 participants (1959 cancer cases and 7423 non-cancer cases) containing more than nine common cancer types. One tube of peripheral blood samples was collected from each participant and quantified a panel of seven selected protein tumor markers (PTMs) by a clinical common electrochemiluminescence immunoassay analyzer. A protein assay named OncoSeek was established using artificial intelligence to distinguish cancer from non-cancer cases by calculating the probability of cancer (POC) index based on the quantification results of 7 PTMs and clinical information including gender and age of the subjects. Then using another model to predict the possible affected tissue of origin (TOO) who has been detected with cancer signal. **Results:** In this study, we found that the conventional clinical method relied only on a single threshold for each protein tumor marker which would make a big problem that was when combining the result of those markers, the false positive rate would accumulate as the number of tests increased. Nevertheless, OncoSeek was empowered by artificial intelligence technology to significantly reduce the false positive rate, increasing the specificity from 56.9% (95% confidence interval (CI): 55.8% to 58.0%) to 92.9% (95% CI: 92.3% to 93.5%). In all cancer types sensitivity of the OncoSeek test was 51.7% (95% CI: 49.4% to 53.9%). The sensitivities ranged from 37.1% to 77.6% for the detection of the nine common cancer types (breast, colorectum, esophagus, liver, lung, lymphoma, ovary, pancreas, stomach), which account for ~59.2% of global cancer deaths annually. Furthermore, it has shown excellent sensitivity in several high-mortality cancer types for which there are a lack of routine screening tests in the clinic, such as the sensitivity of pancreatic cancer was 77.6% (95% CI: 69.3% to 84.6%). The overall accuracy of tissue of origin (TOO) prediction in true positives was 66.8%, which reduced the clinical diagnostic workup. **Conclusions:** In summary, this study supported that OncoSeek significantly outperforms the conventional clinical method, representing a novel blood-based test for multi-cancer early detection which is a non-invasive, easier, and efficient approach. Moreover, the accuracy of TOO of it which facilitates the follow-up diagnostic workup. As well as this method is affordable (the cost of the test is less than \$25) and requires nothing more than a blood draw at the screening sites, which makes it more practical in low- and middle-income countries. Research Sponsor: None.

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Poster Session

Systematic review and meta-analysis of the accuracy and applicability of blood-based multi-cancer early detection (MCED) in the general population. *First Author: Joo Hee Park, Northwestern University, Chicago, IL*

Background: Globally, cancer results in 10.08 million deaths per year. A single blood-based screening tool that detects multiple cancer types could significantly reduce cancer burden. We systematically reviewed and statistically examined both the accuracy and applicability of blood-based MCED tests to strategize their utilization in improving cancer detection. **Methods:** Original articles were searched from PubMed, Cochrane, and Embase for blood-based screening tests analyzing multiple cancer types and asymptomatic human subjects. We excluded studies with small sample sizes (n<30), hypothesis-generating/diagnostic tests, and non-blood-based tests. For cfDNA-based assays, measurements of diagnostic accuracy were pooled for meta-analysis. **Results:** Of 1,074 records identified and screened, 15 case-control and 4 cohort studies were analyzed, most of which utilized cfDNA-based diagnostic tests. Twelve cfDNA studies selected for meta-analysis had pooled sensitivity of 0.623 (95%CI 0.517 - 0.719) and specificity of 0.975 (0.942 - 0.990). Summary ROC curve shows variability in sensitivity and specificity between studies. However, sensitivity and specificity were not affected by study type, gender, or assay type. Sensitivity was higher for advanced staged cancers (III/IV 0.774 (0.697 - 0.837)) than early-stage cancers (I/II 0.503 (0.366 - 0.639)). Among cancer types, no significant differences were detected. Lastly, false positive and false negative rates were 0.025 (0.010 - 0.058) and 0.447 (0.438 - 0.456), respectively. **Conclusions:** Given high sensitivities and specificities, MCED tests show promise as additional screening tools. However, in the general population, misdiagnosis burden from false positive and negative rates is anticipated. Although multiple barriers exist to their application in the clinic, MCED tests may improve patient outcomes for cancers with no conventional screening tools and provide additional credibility when combined with existing tools. Future prospective studies with large and diverse populations are warranted. Research Sponsor: None.

Summarization of meta-analysis results on cfDNA-based multi cancer early detection tests.

	Sensitivity	Specificity	False Positive Rate	False Negative Rate
Events/Total	6414/11590	16093/16357	264/6678	5176/21269
Proportion (95% CI)	0.652 [0.537; 0.751]	0.978 [0.936; 0.992]	0.025 [0.010, 0.058]	0.447 [0.438; 0.456]

12 studies are included. CI = Confidence Interval.

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Poster Session

A machine learning-based multidimensional model integrating clinical, radiomics, and cell-free DNA methylation biomarkers for the classification of pulmonary nodules. *First Author: Wenhua Liang, Department of Thoracic Surgery/Esophageal Surgery, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, Guangdong, China*

Background: Patients with pulmonary nodules undergoing excessive invasive procedures is a pressing clinical problem. We sought to develop a noninvasive, machine learning-based multidimensional tool combining clinical, radiomic, and cell-free DNA (cfDNA) methylation biomarkers for improving accuracy of pulmonary nodules classification. **Methods:** This prospectively collected and retrospective blinded evaluation trial enrolled a total of 1,276 subjects at 24 hospitals in China. All patients with a 5-30 mm pulmonary nodule at high risk of lung cancer had undergone surgical resection with definitive pathological diagnosis. Clinical information, preoperative peripheral blood, and chest CT scans were collected. The regions of interest (ROIs) containing target nodule on the CT images were automatically segmented by a deep-learning based model. 2,153 radiomics features were extracted from ROIs using PyRadiomics. Based on clinical and radiomics features, four classification models were constructed using LightGBM, Lasso, Random Forest, and Logistic Regression algorithms. Subsequently, the predicted probabilities of the above four models were averaged to obtain a final score of the combined clinical and radiomic biomarkers model (CRBM) in a training set ($n=797$). Then we integrated CRBM model with our previously established cfDNA methylation model (PulmoSeek; DOI: 10.1172/JCI145973) to create a new combined model using logistic regression ($n=201$), PulmoSeek Plus V2.0, and verified it independently ($n=278$). The ROC curves were compared to evaluate the diagnostic performance among the CRBM, PulmoSeek, and PulmoSeek Plus V2.0 model, pathologic diagnosis as the gold standard. **Results:** The CRBM model achieved AUCs of 0.81(95%CI 0.73-0.90) and 0.80 (0.74-0.86) in the two validation sets ($n_1=201$, $n_2=278$), respectively. In the training set ($n=201$) and validation set ($n=278$), the PulmoSeek Plus V2.0 obtained AUCs of 0.93 (0.90-0.97) and 0.91 (0.88-0.95), and accuracies of 0.89 (0.84-0.93) and 0.84 (0.79-0.88), respectively. In the combined set ($n=479$), when compared with CRBM and PulmoSeek, PulmoSeek Plus V2.0 yielded improved AUCs of 11% and 6%, and accuracies of 6% and 3%, respectively. PulmoSeek Plus V2.0 model for rule-out at the fixed specificity of 50%, had an overall sensitivity of 0.98 (0.96-0.99), PPV of 0.86 (0.82-0.89), and NPV of 0.998 (0.988-1.000, at 5% prevalence). It maintains good diagnostic performance in early-stage lung cancer (0-I, $n=328$) and 5-10 mm nodules ($n=92$), with sensitivities of 0.98 (0.96-0.99) and 0.98 (0.92-0.99), respectively. **Conclusions:** PulmoSeek Plus V2.0, as a novel machine learning-based multidimensional model, improves the accuracy of pulmonary nodules classification, and potentially reduces the unnecessary invasive procedures among individuals with benign nodules. Clinical trial information: NCT03181490, NCT03651986. Research Sponsor: Funding China National Science Foundation (Grant No. 82022048, 81871893), Key Project of Guangzhou Scientific Research Project (Grant No. 201804020030).

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Poster Session

Liquid biopsy in combination with PET/CT versus PET/CT alone in diagnosis of lung cancer in small nodules. *First Author: Rajesh Shah, VA Palo Alto Health Care System, Palo Alto, CA*

Background: In the National Lung Screening Trial, almost two-thirds of patients that underwent an invasive procedure for diagnosis had benign findings, suggesting a significant number of patients were exposed to risk that could be avoided. Currently, to help distinguish malignant from benign nodules, Positron Emission Tomography/Computed Tomography (PET/CT) is used. However, PET/CT can be limited in its use for lesions less than 2 cm in size. The detection of circulating tumor DNA (ctDNA) and cell-free DNA (cfDNA) in the blood stream via liquid biopsy has demonstrated potential as a non-invasive approach in both screening and diagnostic tests. The purpose of this study is to assess whether combining liquid biopsy with PET/CT findings can better detect malignancy in small lung nodules 6-20 mm in size compared to PET/CT alone, possibly allowing earlier cancer detection and reduction in unneeded invasive diagnostic testing. **Methods:** This was a single-center prospective observational study for which the primary objective was to compare liquid biopsy plus PET/CT to PET/CT alone for detection of lung cancer in patients with newly discovered or newly growing solid lung nodules. Patients with nodules 6-20 mm in size who were scheduled to undergo 18F-Fluorodeoxyglucose PET/CT also underwent blood collection for plasma ctDNA/cfDNA testing using an amplicon-based next-generation sequencing assay incorporating molecular barcodes for error suppression. Tumor diagnosis was based on resolution of the nodule or tissue biopsy. For liquid biopsy, a multiomic model previously built using (1) cfDNA methylation frequencies, (2) ctDNA abundance, (3) somatic ctDNA mutations, and (4) cfDNA fragment size ratio was used to predict malignancy. For imaging, lesions with a maximum standardized uptake value of 2 or greater were considered malignant. **Results:** Between December 2021 and November 2022, 24 patients were enrolled. Of these, 13 had a definitive diagnosis and were included in the analysis with the remainder still undergoing serial imaging follow-up. Of the 13 patients, 9 were biopsy or surgically proven to be malignant, and 4 were benign based on biopsy or resolution. The median (IQR) nodule size was 14 mm (8-15). The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for PET/CT were 0.67, 1, 1, and 0.57, respectively. For multiomic liquid biopsy alone, these values were the same. However, combining multiomic liquid biopsy and PET/CT, the sensitivity, specificity, PPV, and NPV were 0.89, 1, 1, and 0.8, respectively. **Conclusions:** Combining multiomic liquid biopsy with PET/CT results in improved sensitivity for the detection of early-stage malignant solid lung nodules by 33% compared to PET/CT alone with no reduction in specificity. This could result in improved selection of patients requiring biopsy. Further evaluation with a larger cohort is needed to confirm the findings. Research Sponsor: Lucence Health, Inc.

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Poster Session

Large retrospective validation study of metabolomic biomarkers for resectable lung cancer detection and risk assessment. *First Author: Philippe Joubert, Quebec Heart and Lung Institute Research Center, Quebec, QC, Canada*

Background: Cancer can be regarded as a metabolic disease and many studies published aimed at identifying robust metabolites for lung cancer diagnosis using plasma samples. Regardless of the lung cancer staging, most of these studies were performed on relatively small sample sizes. The purpose of this study is to validate whether a panel of metabolomic biomarkers would improve risk assessment for lung cancer detection in 800 plasma samples from patients that underwent lung cancer resection, and to understand the potential role and intersection between lung cancer and other lung diseases. **Methods:** A blinded case-control study was performed using plasma samples from 586 patients with biopsy-confirmed lung cancer compared to 214 controls from the same institutional biorepository to evaluate the performance of a 5+ metabolites biomarker panel for lung cancer detection. The control group consists of 90 healthy individuals and 124 with other non-neoplastic lung diseases including asthma, COPD, bronchiectasis and COVID. The lung cancer subgroups include early-stage (Stage I & II) adenocarcinoma and squamous cells carcinoma, advanced stages (Stage III & IV) NSCLC and neuroendocrine tumors. In this study, plasma metabolic profiles were performed using different liquid chromatography methods coupled with a targeted and quantitative mass spectrometry approach. Metabolite concentrations, clinical data, and smoking history were used to develop logistic regression models to identify lung cancer at different stages using significant biomarkers. The area under the receiver operator characteristic curves (AUC), sensitivities and specificities at selected cut off points were calculated for each cancer stage. **Results:** Univariate and multivariate statistical analyses confirmed the performance of our 5+ metabolites panel (β -HBA, PC aa C38:0, PC ae C40:6, citric acid, tryptophan, and etc.) as being significantly different between controls and lung cancer cases. Linear regression model using metabolites alone yielded an AUC of 0.89 for lung cancer at all stages. When adding smoking status, the models achieved an AUC of 0.91 with sensitivity of 91% and specificity over 78% using a risk prediction threshold of 0.657. **Conclusions:** The blood-based metabolites panel validated on our current retrospective study exhibited robust performance for resectable lung cancer detection and risk assessment. This metabolomic panel assay demonstrates potential diagnostic applications and clinical utility for patient selection that require further follow-up and confirmation using LDCT or other lung imaging modalities. The inclusion of other lung diseases in the control group is more representative of a real clinical setting suggesting that this blood-based assay could be offered to the medical community. Further studies may also confirm its utility in the context of a lung cancer screening program. Research Sponsor: NRC-IRAP #980330; CIHR-IRSC grant # 0590008438; BioMark Diagnostics Inc.

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Poster Session

MYC amplification segment-size mutual exclusivity analysis with other oncogenic events in a pan-cancer sequencing cohort. *First Author: Matteo Repetto, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: MYC gene alterations resulting in increased copy number are recurrent oncogenic alterations across human malignancies. Presently no clear data exists to aid in interpreting MYC amplification characteristics for identifying MYC-dependent tumors. **Methods:** Analysis was conducted on a center-wide cohort of 68,920 tumor-normal matched samples from pediatric and adult patients sequenced with an FDA-authorized targeted sequencing panel (MSK-IMPACT). To ascertain tumor content, ploidy and allelic specific gene copy number, tumor-normal samples were analyzed with FACETS. Samples with tumor purity <20% were excluded. MYC amplification was defined as total copy number (TCN) minus ploidy ≥ 4 . All samples were queried for presence of concurrent oncogenic or likely-oncogenic alterations based on OncoKb annotation. Co-occurrence (Co) and mutual-exclusivity (Me) analysis between MYC amplification according to segment size and other oncogenic alterations was performed with DISCOVER (false discovery rate threshold of 0.01) for each tumor type. **Results:** After removing low-quality samples ($n=19,010/68,920$), 49,910 samples were included in the analysis. 3,219 (6.4%) samples harbored MYC amplification, with segment size ranging from less than 100Kb to more than 100Mb, with 38% samples displaying focal amplifications shorter than 10 Mb and 62% broad amplifications longer than 10 Mb. TCN was inversely correlated with segment size ($R = -0.34$, $p=2.2e^{-16}$). Triple-negative breast cancer (13.3%), hepatocellular carcinoma (8.7%), neuroendocrine tumors of the rectum (8.3%), high-grade serous ovarian cancer (7.6%) and large cell neuroendocrine carcinomas of the lung (6.7%) had the highest prevalence of MYC amplification without concurrent potentially driver oncogene mutations, amplifications or fusions. CoMe analysis demonstrated mutual exclusivity of MYC gene amplification regardless of segment size with most major tumor-type specific oncogenic events. All MYC amplifications were mutually exclusive with MET splice variants and mutations ($q < 0.001$) and KRAS mutations ($q < 0.001$) in lung adenocarcinoma (LUAD), FGFR3 mutations ($q < 0.001$) and fusions ($q < 0.001$) in bladder cancer, PTEN mutations ($q < 0.001$) in hormone receptor-positive breast cancer, KRAS mutations ($q < 0.001$) in colorectal cancer and CDK4 amplifications ($q < 0.001$) in sarcomas. Broad MYC amplifications were mutually exclusive with RET, ROS1 and ALK fusions in LUAD, while focal ones co-occurred with RET ($q=0.007$) and ALK fusions ($q < 0.001$) or secondary mutations ($q < 0.001$). **Conclusions:** This dataset defines a subgroup of MYC amplified cancers without co-occurring drivers and further subdivided by segment size, providing information that may help better identify patients for trials of novel MYC-directed therapies. Research Sponsor: None.

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Poster Session

Genomic characterization of *FGFR*-altered solid tumors using a clinically annotated pan-cancer repository. *First Author: Noura J. Choudhury, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Somatic mutations, gene fusions, and amplifications in *FGFR1/2/3* are found across solid tumors. *FGFR2/3* fusions and select mutations have matched FDA-approved therapies in intrahepatic cholangiocarcinoma (ICCA) and urothelial carcinoma (UC). Identification of *FGFR*-altered tumors may inform patient selection for future drug development. **Methods:** All solid tumors that underwent MSK-IMPACT, a DNA-based NGS panel with coverage of *FGFR1-4*, were queried for *FGFR1-4* alterations. *FGFR* structural variants (SV) were manually reviewed and compared to RNA sequencing data (RNAseq, Archer FusionPlex) when available. Alteration (alt) frequencies of ICCA and UC tumors with target *FGFR* alt (level 1 OncoKB evidence), non-target *FGFR* alt (lacking level 1 evidence) and no *FGFR* alt were compared using chi-squared tests and odds ratios. Euclidean distance was calculated between cohorts based on prevalence of frequently altered genes (>5%). Consensus clustering was used to identify optimal number of clusters and compare genomic profiles between clusters. **Results:** At data lock of June 1, 2022, 5695 tumors among 48,416 patients harbored an *FGFR* alteration (11.8%). *FGFR* SV were identified in 347 tumors on MSK-IMPACT. Of these 111/140 (79.2%) with RNAseq were positive. 98% (203/207) of SV without RNAseq were considered likely activating (canonical SV, n=125; in-frame inclusive of kinase domain, n=78). The most frequent fusion was *FGFR3-TACC3* (n=124), followed by fusions unique to a single patient (n=100). Fusions were discovered in >15 tumor types, most frequently in ICCA (n=93), UC (n=50) and high-grade glioma (n=44). Among 1176 ICCA tumors, 9.9% (n = 117) had a target *FGFR2* fusion. Target *FGFR* tumors were enriched for concurrent *BAP1* alt (18%) compared to tumors without *FGFR* alt (58/969, 5.9%) and with non-target *FGFR* alt (7/90, 7.8%). Both groups without target alt were enriched in *TP53*, *ARID1A* and *IDH1* alts compared to target group. Four optimal genomic clusters were identified, with *FGFR2* fusions enriching in cluster 4 (29% vs 3%, 7% and ≤1%); 21 non-target *FGFR* alt were also in cluster 4. Among 2720 UC tumors, 24.7% (n=672) had target *FGFR* alt (select *FGFR3* mutations and *FGFR2/3* fusions). Three genomic clusters were identified, with target *FGFR* enriched in cluster 3 (42% target *FGFR* vs cluster 1: 11%, cluster 2: 18%) and non-target *FGFR* alterations enriched in cluster 1 (13% vs. cluster 2: 9.4%, cluster 3: 7.0%); 68 non-target *FGFR* alt were in cluster 3. Tumors with non-target *FGFR* alterations and no *FGFR* alterations had close genomic association (Euclidean distance: 0.18). **Conclusions:** Activating *FGFR* fusions, which occur across tumor types with marked diversity in fusion partners, present opportunities for future drug development. Non-target *FGFR* alterations in ICCA and UC, particularly those that cluster with target *FGFR* alterations, may be candidates for future *FGFR*-targeted strategies. Research Sponsor: None.

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Poster Session

Aggregated analysis of 1,000 patients with cancer to assess the benefits of integrated whole exome and whole transcriptome sequencing. *First Author: Konstantin Chernyshov, BostonGene, Waltham, MA*

Background: As the field of precision medicine rapidly expands, clinical oncologists are turning to integrated whole transcriptome (WTS) and whole exome (WES) sequencing to identify the most effective treatment options. We performed a retrospective cohort analysis of WES and WTS data from 1,000 patients with 15 major cancer types to define meaningful relationships between transcriptomic-based tumor microenvironment (TME) subtypes and pan-cancer genomic biomarkers, such as tumor mutational burden (TMB) and microsatellite instability (MSI) status, that are prognostic for outcome and predictive for checkpoint inhibitor response. **Methods:** We retrospectively analyzed WES/WTS data from cancer patients for biomarkers using our internal bioinformatics workflow. Using transcriptome-based methods described by Bagaev et al., samples were classified into one of four TME subtypes prognostic of patient outcome (*Cancer Cell*, 2021). Statistical analysis consisted of Spearman's rank correlation. **Results:** Comprehensive WES and WTS analysis provided by the BostonGene Tumor Portrait Test identified biomarkers based on accepted guidelines specific to the patient's cancer type in 22.5% of cases. In addition, we revealed a correlation between WTS and IHC for cancer-relevant genes, including *CDX2* (R = 0.68), *KRT7* (R = 0.85), *KRT20* (R = 0.86), *NECTIN4* (R = 0.81), and *TACSTD2* (R = 0.81), indicating WTS may also be beneficial for estimating protein expression levels for cancer-specific biomarkers. Analysis of the TME showed that Fibrotic (F) and Immune Desert (D) were the most common subtypes. The F and D subtypes were linked to poor prognosis and were especially prevalent in liver and pancreatic cancers, respectively. TMB-high and MSI status were more prevalent in the immune-enriched subtypes, Immune-Enriched, Fibrotic (IE/F) and Immune-Enriched, Non-fibrotic (IE), over the less favorable F and D subtypes. The frequency of TMB-high and MSI status also differed in both IE subtypes associated with favorable prognosis, suggesting that TME subtyping provides additional prognostic power independent of TMB-high and MSI status. **Conclusions:** A deep interrogation of our integrated approach to genomic and transcriptomic profiling confirmed the advantages of a unified molecular analysis of tumor traits. We identified clinically significant biomarkers based on molecular features, demonstrated additional capabilities of TME analysis, and illustrated significant correlations between WTS and IHC data. These findings indicate that comprehensive WTS and WES analysis can assist clinicians in optimizing treatment plans as the landscape of personalized therapy continues to grow. Research Sponsor: None.

Frequency of pan-cancer biomarkers across conserved TME subtypes.

TME subtype	F, 34.0%	D, 30.7%	IE/F, 18.0%	IE, 17.3%	Total
TMB-high, %	5.8	8.4	7.5	12.1	8.0
MSI, %	0.7	1.6	0.7	4.3	1.6

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Poster Session

Detecting early stage breast cancer using low-depth cell-free DNA fragmentomics: A multi-center cohort study. *First Author: Jiaqi Liu, Cancer Hospital Chinese Academy of Medical Sciences, Beijing, China*

Background: Breast cancer (BC) has contributed to the most cancer-related mortalities among females in 2020. Early detection using breast imaging methods, such as mammography and ultrasound, has significantly improved patients' survival. However, these early-screening methods suffer from high false-positive rates, resulting in many unnecessary biopsies which add to patients' discomfort. Cell-free DNA (cfDNA) fragmentomics assays have recently illustrated prominent abilities for detecting various cancer. In this multi-center prospective cohort study, we aim to develop a non-invasive liquid biopsy assay utilizing cfDNA fragmentomics and machine learning for detecting early-stage BC patients. **Methods:** We recruited 402 female patients (234 with BC and 168 with benign nodules [BN]) from the Yantai Yuhuangding Hospital (training cohort, N = 193, 91 BC and 102 BN) and the Cancer Hospital of the Chinese Academy of Medical Sciences (independent validation cohort, N = 209, 143 BC and 66 BN). Surgical or core needle biopsies were performed for all 402 patients following positive breast imaging results by mammography and ultrasound. Each patient's malignant or benign status was then pathologically confirmed using the tissue specimen. Women with negative biopsy results were excluded from breast cancer through a 6-month follow-up. The fragmentomics profiles, which were generated using plasma cfDNA WGS data (~5X), were used by our machine-learning algorithm. An automated machine learning approach was deployed to optimize base models before being ensemble into the final predictive model. **Results:** Our predictive model showed excellent performance in discriminating BCs from BNs, reaching an Area Under the Curve (AUC) of 0.816 and 0.811 in the training cohort (5-fold cross-validation) and the independent validation cohort, respectively. It achieved 74.1% sensitivity (95% CI: 66.1-81.1%) at 81.8% specificity (95% CI: 70.4-90.2%) in the validation cohort. In a potential clinical setting, our model could detect 53.0% (95% CI: 40.3-65.4%) false positives from the breast imaging methods at a targeted 90% sensitivity (89.5%, 95% CI: 83.3-94.0%), which could theoretically reduce more than half of the unnecessary biopsies. Moreover, our model illustrated great predictive power (AUC = 0.830) among small nodules (≤ 1cm), which were difficult to distinguish by the traditional imaging methods (AUC = 0.690). Finally, our model maintained its predictive power during a down-sampling process, even using 2X WGS data in the independent validation cohort (mean AUC: 0.789, 0.781-0.798). **Conclusions:** Our non-invasive liquid biopsy assay, which utilized low-depth cfDNA fragmentomics profiling and machine learning, can distinguish malignant nodules from benign nodules. The highlight of our model is its ability to prevent unnecessary biopsies among patients with false positive breast imaging results. Research Sponsor: National Natural Science Foundation of China; CAMS Innovation Fund for Medical Sciences.

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Poster Session

Alternative allele frequency recalibration after NGS data analysis. *First Author: Maxim Ivanov, OncoAtlas LLC, Moscow, Russian Federation*

Background: With the spread of NGS in routine clinical practice data analysis methods actively evolve to increase and refine information yield. Not much attention is given to variant allele fraction (VAF) estimation though it impacts clinical insignificance of subclonal somatic variants and identification of variant origin. **Methods:** Real-world sequencing data of 2379 samples (including 781 tumor-only and 1598 blood-only sequencing datasets) obtained via amplicon-based sequencing was used for the retrospective analysis of variant allele frequency estimation of identified genetic variants employing different methods including ITVC, SiNVICT, Mutect2 and SGA. Original method (AODvAF) utilizing alignment-free algorithm based on wild-type and alternative genome subsequence abundance estimation was developed and compared with the original output from NGS data analysis software. Anticipated VAF estimation was based on analyte type and database annotation. **Results:** Across 3447 identified potentially germline variations (PGV) VAF estimations provided by ITVC, SiNVICT and SGA were highly correlated (Pearson correlation coefficient [PCC] 1.00), while Mutect2 and AODvAF demonstrated discordant results (Mutect2/AODvAF vs ITVC PCC 0.87/0.82). VAF miscalculation defined by absolute difference between estimated and anticipated VAF of 10% and more was noted for 25%, 26%, 22%, 15% and 7% for ITVC, SiNVICT, SGA, Mutect2 and AODvAF respectively. Across 308 pathogenic BRCA1, BRCA2, PALB2 mutations identified in blood-only sequencing 25, 15, 16, 10 and 5 were characterized by VAF of 30% and lower based on ITVC, SiNVICT, SGA, Mutect2 and AODvAF estimations respectively (54, 49, 33, 51 and 9 for VAF 40% and lower), which may lead to misinterpretation of these variants as post-zygotic. Automatic in-silico annotation of variant origin (germline vs somatic) based on ISOWN was correct for 89%, 91%, 94%, 93% and 98% of these variants. Variant origin for 55 pathogenic variants of genes associated with hereditary cancer syndromes identified in tumor-only sequencing was verified by Sanger sequencing. Cohen's kappa coefficient for variant origin discrimination (Sanger vs in-silico prediction) was 0.91, 0.90, 0.91, 0.94 and 0.97 based on VAF provided by ITVC, SiNVICT, SGA, Mutect2 and AODvAF respectively. **Conclusions:** Accurate VAF calculation allows precise variant origin identification and impacts interpretation of variants. Developed method allows correction of VAF after NGS data core analysis. Research Sponsor: The research was supported by the Russian Science Foundation (project No. 22-75-10154; <https://rscf.ru/project/22-75-10154/>).

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Poster Session

Multimodal machine learning analysis of more than 220,000 tumor profiles to diagnose molecular and morphological subtypes of cancer. *First Author: Jim Abraham, Caris Life Sciences, Phoenix, AZ*

Background: The diagnosis of a malignancy is typically informed by clinical presentation and tumor tissue features including cell morphology, immunohistochemistry, and molecular markers. Additionally, multi-omic approaches (Abraham 2021 Transl Oncol) and deep learning models using digital pathology (da Silva 2021 J Pathol) have augmented expert pathologists and led to improved diagnoses but are often not employed together on the same patient. The opportunity exists for a truly multimodal, multi-omic machine learning classifier that comprehensively assesses all aspects of a tumor from the molecular underpinnings to the morphological and histological phenotypic presentation to provide the most accurate diagnosis while at the same time providing predictive biomarker data from the same specimen. **Methods:** Whole transcriptome data from 220,246 tumor profiles, large panel and whole exome data from over 170,000 tumor profiles, and digital pathology features from over 50,000 tumors were used to construct a multi lineage classifier. The classifier was trained on 256 Oncotree classifications corresponding to established WHO diagnoses where a tumor of each class has been observed at least 30 times in our dataset. The dataset was split 50% for training and the other 50% for testing. UMAP was employed for dimensionality reduction, and ensemble models were used for making the final calls. The performance of the classifier was evaluated by comparing with traditional pathologist-directed diagnostic workup. **Results:** Tumor lineage classifiers predicted the correct classifications where the primary site was known with accuracies ranging between 97% and 100% when using the 32 highest level Oncotree categories corresponding to human tissues. Accuracy on the most granular Oncotree categories varied with many between 90 and 95%. When applied to Cancer of Unknown Primary (CUP) cases (n = 3589), an unequivocal Oncotree classification could be obtained over 90% of the time. **Conclusions:** Combining multi-omic and digital pathology information into a multimodal artificial intelligence platform can provide comprehensive information to pathologists to aid in diagnosis. This tool can be used to meet an unmet clinical need to define the lineage of CUP cases, which when coupled with biomarker data, will provide an opportunity to examine whether this information can be used to improve the outcomes of patient with CUP. Research Sponsor: None.

3080

Poster Session

Phase 1/1b study of SY-5609, a selective and potent CDK7 inhibitor, in advanced solid tumors and in 2L/3L pancreatic ductal adenocarcinoma (PDAC) in combination with gemcitabine +/- nab-paclitaxel. *First Author: Babar Bashir, Sarah Cannon Research Institute and Sidney Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA*

Background: SY-5609 is an oral, highly selective and potent noncovalent inhibitor of CDK7, a key regulator of cell cycle progression and transcription. In this Phase 1 FIH study (NCT04247126), the single agent (SA) continuous daily dosing (CDD) regimen maximum tolerated dose (MTD) was 3 mg/day. Subsequently, enhanced tolerability was demonstrated using an intermittent 7 day on/7 day off (7/7) schedule at higher dose levels (Sharma 2021). SY-5609 preclinical data and early clinical activity provided the rationale for evaluating SY-5609 + gemcitabine (gem) +/- nab-paclitaxel (np) in PDAC. Herein, we present data from the ongoing SA dose escalation and SY-5609 + gem +/- nab-paclitaxel (np) safety lead-ins (SLIs). **Methods:** The 7/7 schedule was used to further evaluate SA escalation in pts with select solid tumors. In the PDAC combination SLIs, SY-5609, starting with a dose of 4 mg, is escalated using the 7/7 schedule in combination with biweekly gem (1000 mg/m²) +/- np (125 mg/m²). Evaluations included safety, clinical activity (RECIST v1.1), PK, and induction of peripheral blood PD marker *POLR2A* (Papadopoulos 2020). **Results:** As of 13 Jan 2023, 87 pts have been enrolled (70 SA, 14 SY-5609 + gem, 3 SY-5609 + gem/np), including 30 pts across the 4, 5, 6, 7, and 10 mg SA 7/7 cohorts included in the safety summary. MTD for the 7/7 schedule has not been reached. The 15 mg SA cohort is now enrolling. Most SA 7/7 AEs were low-grade; AEs included (>20%) nausea, diarrhea, fatigue, anorexia, and thrombocytopenia. No new safety signals were observed in the SY-5609 4 mg and 5 mg + gem and SY-5609 4 mg + gem/np cohorts; 1 pt (SY-5609 5 mg + gem) had a DLT of Gr3 diarrhea. The 10 mg + gem cohort is now enrolling. Most SY-5609 + gem +/- np AEs were low grade. AEs in the SLIs were consistent with the safety profile of either SY-5609 or gem +/- np and included (>20%) fatigue, anorexia, nausea, abdominal pain, and constipation. In the SA cohorts (response-evaluable, n=29), 100% (3/3) of pts in the 10 mg 7/7 cohort had stable disease (SD) as the best response, compared to 19% (5/26) SD rate in 4 to 7 mg SA 7/7 cohorts. Disease control rate in the combination SLIs (response-evaluable, n=11) was 45% (5/11), including 1 confirmed partial response (4 mg + gem) in a patient with liver metastases who had a reduction in CA 19-9 from 60,357 U/mL to 968 U/mL, and SD in 4 pts (3 in 5 mg + gem, 1 in 4 mg + gem/np). SA and SLI PK data support an emerging exposure-activity relationship. *POLR2A* PD marker data from SA and SLI cohorts correlate with exposure. **Conclusions:** To date, intermittent dosing of SY-5609 on the 7/7 schedule has acceptable tolerability alone and in combination with gem +/- np. Encouraging preliminary clinical activity and the emerging exposure-activity relationship supports the ongoing escalation of SY-5609 in SA and combination SLI cohorts; updated results will be presented. Clinical trial information: NCT04247126. Research Sponsor: Syros Pharmaceuticals.

3079

Poster Session

In silico approaches to patient selection: Credentialing elraglusib as a novel treatment in metastatic melanoma resistant to checkpoint inhibitors. *First Author: Joseph McDermott, Lantern Pharma, Dallas, TX*

Background: Elraglusib (9-ING-41), a novel inhibitor of GSK-3 β , has been evaluated in >230 patients (pts) with advanced malignancies including metastatic melanoma in the 1801 phase 1/2 trial (NCT03678883). Pts with melanoma treated with single agent elraglusib demonstrated clinical benefit including a durable complete response despite multiple prior lines of therapy including checkpoint inhibitors (CPI). **Methods:** We collected data from numerous -omic modalities in the 1801 trial to characterize markers of elraglusib response with bioinformatics and machine learning (ML). Genomic panels were collected on 105 pts. The most frequent tumor types included colorectal cancer (n=35), pancreas (n=31), lung (n=15) and metastatic melanoma (n=12). Pts were treated with elraglusib as a single agent or in combination with chemotherapy. Pathway based features were generated by quantifying the percent of each Reactome pathway that was mutated. These pathway features were iteratively evaluated for their performance in shallow neural networks predicting patient RECIST with each model using 5-15 randomly selected features at a time. Publicly available genomic data from an anti-PD-1 trial in patients with metastatic melanoma (Hugo et al., 2017) was transformed into pathway-based features and input into the final model to predict elraglusib response in this population. **Results:** Our final pathway based genomic model for elraglusib response performed with a training accuracy of 93% and a test accuracy of 88% on the 1801 patients. We then tested the model on metastatic melanoma patients who were treated with anti-PD-1 therapy. We found that patients from Hugo et al. were predicted to respond to elraglusib (22/26). In addition, most patients with tumors resistant to anti-PD-1 therapy were also predicted to respond to elraglusib (10/12). Finally, we tested the model on metastatic melanoma patients treated with elraglusib in the 1801 study that had failed CPI and for whom -omic data was available. The model correctly identified 5/5 patients that demonstrated clinical benefit (1 CR, ongoing>1400 days; 4 prolonged OS of 107, 256, 357, and 556 days). **Conclusions:** We applied robust in-silico modeling developed using 1801 trial data to develop a rationale for the development of elraglusib in the treatment of metastatic melanoma including patients that failed or were refractory to anti-PD-1 treatment. This model correctly identified metastatic melanoma patients in 1801 with good clinical outcomes that had failed prior CPI treatment. Further, we present this in silico approach as a robust way to repurpose prior clinical study genomics and ML modeling for population enrichment during the clinical development of novel drugs. Clinical trial information: NCT03678883. Research Sponsor: Actuate Therapeutics Inc.

3081

Poster Session

Tolerability and preliminary activity of the potent, selective, oral CDK7 inhibitor SY-5609 in combination with fulvestrant in patients with advanced hormone receptor-positive (HR+), HER2- breast cancer (BC). *First Author: Dejan Juric, Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA*

Background: SY-5609 is an oral, reversible, potent, and selective inhibitor of CDK7, a key regulator of transcription and cell cycle, currently under investigation in a Phase 1 study in patients (pts) with select advanced solid tumors (NCT04247126). Single agent (SA) dose escalation is ongoing, using a 7 days on/7 days off (7/7) dosing schedule that optimized tolerability (Sharma 2021) and showed a correlation of antitumor activity with higher exposures. SY-5609 may address multiple CDK4/6 inhibitor resistance mechanisms and potentiates SERD activity in CDK4/6 inhibitor-resistant xenograft models (Johannessen 2019). In this Phase 1 study, it was combined with the SERD fulvestrant in advanced HR+, HER2- BC pts who are refractory to CDK4/6 inhibitor + hormonal therapy. **Methods:** Evaluation of SY-5609 + fulvestrant began with a SY-5609 dose that had cleared the SA dose-limiting toxicity (DLT) evaluation period. SY-5609 was dosed once daily at 3 mg or 4 mg on a 21 days on/7 days off (21/7), 5 days on/2 days off (5/2), or 7/7 schedule and was escalated using a 3+3 design, guided by safety and reports of Cycle 1 qualifying safety events (QSEs), which matched SA DLT criteria. Fulvestrant was dosed at the approved dose/schedule. Safety and tolerability of SY-5609 + fulvestrant and SY-5609 PK were secondary objectives. Exploratory objectives included preliminary antitumor activity (RECIST v1.1). **Results:** As of 12 Oct 2022, 14 pts (median age 63; range 46 - 83) received SY-5609 at 3 mg on a 21/7 schedule (n=8) or at 4 mg on a 5/2 (n=5) or 7/7 (n=1) schedule in combination with fulvestrant. Pts had advanced disease, including 79% with liver lesions, and a median of 5.5 (range 2 - 12) prior therapies; 100% had prior hormonal therapy, including 71% who received prior fulvestrant. The majority of adverse events (AEs) were low-grade and reversible. Related AEs ($\geq 10\%$) included nausea, diarrhea, fatigue, thrombocytopenia, and hot flush. Related $\geq$ Grade 3 AEs were reported in 3 pts (21%), including 1 QSE of Grade 3 thrombocytopenia at 4 mg 5/2. The highest tolerated dose in combination with fulvestrant was not reached. Stable disease (SD) was observed in 5/12 (42%) evaluable pts. SD with tumor shrinkage and/or SD >6 months was observed in 4 pts previously treated with fulvestrant and in pts with liver lesions and/or TP53 mutations. SY-5609 exposure in combination with fulvestrant appeared comparable to SA at Day 1. **Conclusions:** SY-5609 + fulvestrant has an acceptable safety profile consistent with SA SY-5609 or fulvestrant. The mechanistic rationale for CDK7 inhibition in HR+, HER2- BC and the tolerability and encouraging early activity in this heavily pretreated population support future investigation of SY-5609 in combination with SERDs, including defining the maximum tolerated combination dose using the 7/7 SY-5609 schedule. Clinical trial information: NCT04247126. Research Sponsor: Syros Pharmaceuticals.

3082

Poster Session

Initial results of dose finding in a first-in-human phase 1 study of a novel Claudin 6 (CLDN6) targeted antibody drug conjugate (ADC) TORL-1-23 in patients with advanced solid tumors. *First Author: Gottfried E. Konecny, University of California Los Angeles Medical Center, Santa Monica, CA*

Background: CLDN6, a member of the claudin family of tight junction proteins, is expressed at high levels in multiple human malignancies and has little to no expression in normal tissues. This expression profile makes CLDN6 an ideal target for development of new therapeutics. TORL-1-23 is first-in-class ADC targeting the tumor-specific antigen CLDN6. **Methods:** TORL123-001 (NCT05103683) is an ongoing, 2-part, first in human study to characterize the safety, tolerability, dose-limiting toxicities (DLTs), maximum tolerated dose (MTD), and recommended phase 2 dose (RP2D) of TORL-1-23 monotherapy in participants with advanced solid tumors. Serum pharmacokinetics (PK), immunogenicity and clinical efficacy are also assessed. TORL-1-23 is administered as a 30-minute IV infusion once every 3 weeks in 21-day cycles. During Part 1 (Dose Escalation), cohorts of 1 to 6 participants are evaluated at each dose level according to an accelerated titration design. In Part 2 (Dose Expansion), several cohorts of patients with CLDN6-expressing cancers will be evaluated to confirm the RP2D in ovarian cancer, NSCLC, and other CLDN6-expressing cancers using a CLDN6 IHC companion diagnostic. **Results:** As of 01FEB2023, 22 patients with ovarian (n=18), testicular (n=3), and endometrial (n=1) cancers were enrolled and treated across 8 dose levels ranging from 0.2 to 2.4 mg/kg IV every 3 weeks. 95% of pts had received ≥ 3 prior lines of treatment in the metastatic setting. The most common treatment-related adverse events were Gr1/2 fatigue (n=5), Gr1 peripheral neuropathy (n=4), and Gr1 nausea (n=3). No DLTs have been reported and no dose reductions have been required. Preliminary PK data demonstrate sustained exposure of TORL-1-23 ADC over the 21 day dosing interval and low levels of serum MMAE indicating low off-target MMAE exposure outside of tumor. Partial responses (PR) were observed in 4/17 efficacy evaluable participants with CLDN6+ disease (3 ovarian, 1 testicular). Dose escalation is ongoing and updated results will be presented. **Conclusions:** TORL-1-23 has a favorable safety/tolerability profile and PK characteristics with preliminary antitumor activity in pts with heavily-pretreated CLDN6-expressing ovarian and testicular cancers. Doses above the historic MTD for MMAE containing ADCs may be explored given the safety/tolerability and PK data observed up to 2.4 mg/kg. Dose finding is ongoing to identify the MTD and optimal doses for subsequent development. Clinical trial information: NCT05103683. Research Sponsor: TORL Biotherapeutics.

3084

Poster Session

First-in-human dose-escalation study of NBF-006, a novel investigational siRNA targeting GSTP, in patients with non-small cell lung, pancreatic, or colorectal cancer. *First Author: Anthony W. Tolcher, Texas Oncology-San Antonio Babcock NEXT Oncology, San Antonio, TX*

Background: Glutathione S-transferase Pi (GSTP) has an important role in detoxification and anti-oxidative damage response. Additionally, GSTP has a chaperone function which regulates key oncogenic pathways such as the KRAS and JNK pathways. Targeting multiple pathways could lead to more effective therapy than agents inhibiting single downstream kinase pathways (i.e., a MEK inhibitor), as alternative or redundant pathways could compensate for the inhibition of a single kinase. NBF-006 is a novel drug product containing a GSTP siRNA encapsulated within a lipid nanoparticle. It has been designed to deliver siRNA to tumors of the lung and common sites of metastatic spread (liver and marrow) which has been demonstrated in preclinical efficacy models. **Methods:** NBF-006-001 is a first-in-man (FIM) dose escalation study evaluating safety, tolerability, and PK of NBF-006 administered intravenously over 70 minutes, QW4 followed by a 2-week rest period in patients with advanced non-small cell lung (NSCLC), pancreatic (PANC), or colorectal cancer (CRC). **Results:** Twenty-one patients (11 NSCLC, 5 CRC, and 5 PANC) received treatment in a standard 3+3 dose escalation design (0.15 mg/kg [n=2], 0.3 mg/kg [n=3], 0.6 mg/kg [n=3], 1.2 mg/kg [n=6], and 1.6 mg/kg [n=7]). NBF-006 was well tolerated with no treatment-related grade 4-5 AEs, SAEs nor DLTs. Only one grade 3 event (WBC decrease) was assessed as possibly related. The most common NBF-006-related AEs were Grade 1 or 2 arthralgia, diarrhea, fatigue, and vomiting (11% each). There was no dose relationship in the number of AEs or any observed AEs. No meaningful complement activation, cytokine elevation nor ADA response has been observed to date (20 patients). One patient had 2 infusion related reactions (Grade 1 and 2). PK analysis indicated a terminal half-life ranging from 26 to 55 hours with no accumulation. Cmax and AUC demonstrated dose-proportionality up to 1.2 mg/kg and no additional increase in exposure at 1.6 mg/kg. NSCLC patients had an average and median number of prior lines of therapy of 4 and 3, respectively, with a range from 1-7 prior lines. One patient with NSCLC (treated at 1.6 mg/kg) experienced a durable partial response and progressed after ten months on the study. Four additional patients with NSCLC experienced stable disease, and two of these stayed on study treatment for >6 months (both treated at 1.2 mg/kg). One patient remains on treatment. CRC and PANC patients had an average/median of 4 and 3 prior lines, respectively. In CRC and PANC, stable disease for 24 weeks was the best response (n=1 each). **Conclusions:** This FIM study with NBF-006 demonstrated a favorable safety profile with early signs of antitumor activity in NSCLC. No DLTs or treatment-related SAEs were observed. Dose expansion in NSCLC is ongoing and will not be presented. Clinical trial information: NCT03819387. Research Sponsor: Nitto BioPharma, Inc., a subsidiary of Nitto Denko Corporation.

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Poster Session

A phase 1/2, first-in-human trial of ZB131, a novel antibody targeting cancer-specific plectin (CSP) in advanced solid tumors. *First Author: David Sommerhalder, NEXT Oncology, San Antonio, TX*

Background: Cancer-Specific Plectin (CSP) is a novel pro-tumorigenic target that is selectively expressed on the surface of tumors, while absent from benign tissue. CSP is highly expressed in many solid cancers, particularly pancreatic (PC), cholangiocarcinoma (CCA), and ovarian (OC). ZB131 (Zielbio), is a humanized anti-CSP IgG1 monoclonal antibody that binds specifically to CSP on the surface of tumor cells, rapidly internalizes and modulates key proliferative and cytoskeletal remodeling signaling pathways to decrease cancer cell growth and increase the recruitment of anti-tumor immune infiltrates. **Methods:** The dose escalation (3+3 design) and expansion are enrolling adult patients (pts) with advanced treatment-refractory solid tumors. ZB131 was administered IV over 60 minutes (without pre-medication) weekly. The starting dose of ZB131 is 0.3 mg/kg followed by 1, 3, 9, 15 and 30 mg/kg. Primary objectives are safety, tolerability, and maximum tolerated dose/determination of Phase 2 dose. Secondary objectives are preliminary efficacy (RECIST v1.1), Pharmacokinetic (PK) and pharmacodynamic parameters in blood and paired tumor biopsies. **Results:** As of 31 Jan 2023, 24 pts had enrolled (9 PC, 6 CCA, 4 OC, 5 other). The median age was 59.5 yr (range, 35 – 84) with a median of 4 prior lines of therapy. The median ZB131 treatment duration is 5.3 weeks (range, 1 – 33). No dose-limiting toxicities were observed up to the dose of 30 mg/kg which is currently enrolling. Treatment-related adverse events (TRAEs) were grade 1/2: nausea (n=6), fatigue (n=5), anemia (n=3), diarrhea (n=2), flu-like symptoms (n=2), and vomiting (n=2). Mild flu-like symptoms and nausea/vomiting were observed during or following infusion at doses of 9 mg/kg and above. Except for one episode of Gr 3 neutropenia at the 30 mg/kg dose, no other drug-related grade 3/4 TRAEs were reported. Five pts had stable disease range, 12 – 33 weeks (2 PC, 1 CCA, 2 OC), with a 43% decrease in CA-125 observed in one OC pt. The PKs are linear and dose-proportional for all dose levels evaluated (estimated $T_{1/2}$ of 6-9 days). No antidrug antibodies have been detected. **Conclusions:** Interim data from dose-escalation of this first-in-class, anti CSP antibody, demonstrates good tolerability with encouraging signs of activity and target engagement in heavily pretreated pts. Results support further clinical evaluation of ZB131 in dose-expansion cohorts including OC and including combination therapy with gemcitabine. Clinical trial information: NCT 05074472. Research Sponsor: Zielbio.

3085

Poster Session

Characterization of MCL-1 in patients with colorectal cancer (CRC): Expression, molecular profiles, and outcomes. *First Author: Pooja Mittal, Division of Medical Oncology, USC Norris Comprehensive Cancer Center, Keck School of Medicine, Los Angeles, CA*

Background: Myeloid cell leukemia 1 (MCL-1) is a member of the BCL-2 protein family and is anti-apoptotic/pro-survival in function. Dysregulation of MCL-1 expression has been reported in several solid tumors, including lung and breast cancer. In CRC, MCL-1 has been associated with resistance to chemotherapeutic drugs and multi-kinase inhibitor regorafenib. Our study aimed to characterize the molecular features associated with MCL-1 gene expression in CRC. **Methods:** 28,576 CRC samples were analyzed by Caris Life Sciences (Phoenix, AZ) with WTS (Illumina NovaSeq) and NextGen DNA sequencing (NextSeq, 592 Genes and NovaSeq, WES). MCL-1 expression was stratified by quartiles where top quartile transcripts per million (TPM) were considered high (Q4) and bottom quartile low (Q1). Cell infiltration (CI) in the tumor microenvironment (TME) was estimated by RNA deconvolution analysis using QuantiSeq. Interferon-gamma and T-cell inflamed signatures were also calculated from RNA data. X2 and Fisher-Exact tests were used, and statistical significance was determined as a P-value adjusted for multiple comparisons ($q < 0.05$). Real world survival was obtained from insurance claims data and Kaplan-Meier estimates were calculated for molecularly defined patients. **Results:** MCL-1 expression was significantly increased in rectal tumors compared to other primary tumor sites (median TPM [mTPM] 20.8 vs 18.9 vs 18.7, in rectal vs left-sided vs right-sided, respectively, $q < 0.0001$). MCL-1 high tumors were associated with increased rate of PD-L1 IHC levels (Q1 vs Q4: 4.2% vs 9.7% [all CRC]; 3.7% vs 8.9% [pMMR/MSS], $q < 0.0001$), while MCL-1-low showed marginally increased rates of TMB-high (8.0% vs 7.0% [all CRC]; 3.3% vs 2.6% [pMMR/MSS], $P < 0.05$). MCL-1-high expression was associated with a higher T-cell inflamed signature and IFN score ($q < 0.0001$). MCL-1 high was associated with higher mutation rates of CDKN2A, BRCA2, KRAS and GNAS, while lower mutation rates of TP53, PIK3CA, PTEN, BRAF, APC, FBXW7, AMER1, SOX9, and SMAD2 and copy number amplifications in several genes ($q < 0.05$). MCL-1 high TME had higher CI of M1 and M2 macrophages, monocytes, B cells, NK cells, and T-reg infiltration, while dendritic cells and CD4+ T-cell were lower ($q < 0.05$). Patients with high MCL-1 expressing CRC had longer survival (Q4 vs Q1: 33.5 vs 24.8 months, HR 0.72, 95% CI 0.67-0.77, $P < 0.0001$) and longer time-on-treatment with regorafenib although with limited clinical benefit (Q4 vs Q1: 2.03 vs 1.06 months, HR: 0.67, 95% CI: 0.50-0.89, $P = 0.005$). **Conclusions:** Our data show a strong correlation between distinct immune biomarkers, TME cell infiltration and MCL-1 expression in CRC. Furthermore, increased tumor MCL-1 expression improved patient prognosis and treatment outcomes. These findings suggest a key clinical role for MCL-1 as an important modulator of anti-tumor immunity and TME and a potential biomarker in CRC. Research Sponsor: National Cancer Institute, Gloria Borges WunderGlo, Dhont Family, San Pedro Peninsula Cancer Guild, Daniel Butler Research Fund, Victoria and Philip Wilson Research Fund, Fong research project, Ming Hsieh research fund.

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Poster Session

Intrapatent comparative efficacy of selective RET inhibitors using growth modulation index in patients with RET aberrant cancers. *First Author: Mohamed Alaa Gouda, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Selective RET inhibitors (RETi) have changed the paradigm for treatment of RET altered cancers. Current evidence on their efficacy comes from single-arm basket trials. In this study, we performed intrapatent efficacy comparison between approved selective RETi (selpercatinib and pralsetinib) and prior and/or subsequent therapies. We used growth modulation index (GMI) as a tool to compare efficacy, where a value of >1.33 is presumed a cutoff to establish superior efficacy. **Methods:** We included patients with RET-positive tumors who were treated at our institution as part of RETi clinical trials. We excluded patients with no other systemic therapy received before or after the RETi of interest. We also excluded patients who received both drugs to avoid overlapping efficacy bias, and patients who were treated for ≤ 30 days or had non-evaluable disease. Since some patients have been treated beyond progression or discontinued RETi due to intolerance, we used ratios for both time to treatment takeoff (TTT) and time to progression (TTP) to compare efficacy of RETi (at the RETi treatment line (n)) to prior therapy (n-1) and to subsequent therapy (n+1). GMI was defined as the ratio between TTT/TTT (n±1) or TTP to TTP (n±1). **Results:** We included 66 patients who received RETi and met our inclusion criteria [39 received selpercatinib and 27 received pralsetinib]. Most patients had GMI>1.33 using either TTT or TTP (61% (n=40) and 58% (n=38), respectively). The median GMI based on pre-RETi therapy was 2.1 and 1.6 (using TTT and TTP, respectively); while the median GMI based on post-RETi therapy was 4.9 and 4.4 (using TTT and TTP, respectively). Patients with GMI>1.33 were more likely to have PR as best response compared to patients with GMI<1.33 (85% vs 53%, p=0.005 using TTT; and 87% vs 54%, p=0.003 using TTP). GMI using TTT (n/n-1) was higher in patients with RET fusions compared to patients with RET mutations (3.7 vs 1.4, p=0.048). GMI using TTT and GMI using TTP(n/n+1) were lower in patients with WBCs <8 at baseline (2.6 vs 13.8, p=0.014; 2.6 vs 11.1, p=0.014, for TTT and TTP) and GI cancer diagnosis (0.4 vs 9.3, p=0.042; 0.4 vs 10.4, p=0.042, for TTT and TTP). **Conclusions:** Intrapatent efficacy comparisons are feasible using GMI calculations and provide a proof of concept on the favorability of selective RETi compared to other systemic therapies. Research Sponsor: N/A.

		n/n-1	n/n+1	n(n-1 OR n+1) *
All Patients	Number of patients	58	15	66
	GMI using TTT (median, IQR)	2.1 (4.3)	8.9 (12.7)	2.5 (6.2)
	GMI using TTP (median, IQR)	1.6 (4.4)	8 (29.5)	2.4 (5.5)
Pralsetinib	Number of patients	24	7	27
	GMI using TTT (median, IQR)	2.5 (7)	8.9 (13.9)	2.6 (8.6)
	GMI using TTP (median, IQR)	2.4 (4.3)	8 (10.8)	2.4 (7.2)
Selpercatinib	Number of patients	34	8	39
	GMI using TTT (median, IQR)	1.5 (4.4)	8.9 (16.8)	2.4 (5.8)
	GMI using TTP (median, IQR)	1.31 (4.5)	10.6 (16.3)	1.9 (5.2)

* Compared to whichever line had better TTT and TTP.

3088

Poster Session

Comprehensive CRISPR-enabled functional genomics profiling to identify targetable cancer genes in primary acute myeloid leukemia (AML). *First Author: Stephane Corbel, Function Oncology, San Diego, CA*

Background: Acute myeloid leukemia (AML) is a life-threatening hematopoietic malignancy affecting both older and younger patient populations. Despite the approval of multiple new therapeutics during the past decade, including new targeted agents, treatment outcomes for AML remain poor, with < 10% 5-year survival in patients over 60 years of age, and < 50% 5-year survival in younger patients. Also, comprehensive genomic profiling (CGP) for common molecular lesions (e.g., FLT3 mutation) incompletely stratifies the patient population, indicating that a more comprehensive approach to personalized medicine could be of significant clinical benefit. To this end we developed Fx Heme, an in vitro functional genomics platform using CRISPR/Cas9 technology in primary cancer patient samples. Previously, we have shown it to stratify clinical response in AML patients treated with a combination of the tyrosine kinase inhibitor sorafenib plus chemotherapy (e.g., GCLAM). Here we profile an expanded cohort to systematically characterize the AML functional genomics landscape and identify potential new targets for AML drug development. **Methods:** Unsourced primary tumor cells from patient samples were transduced with lentivirus harboring Cas9 enzyme and an sgRNA library which was designed to inhibit expression of genes encoding the targets of FDA-approved targeted oncology drugs, as well as internal negative references. Transduced cells were harvested at multiple timepoints, and sgRNA distribution was assessed by amplicon sequencing of DNA barcodes. Changes in barcode abundance were quantitated and aggregated for each gene to generate gene-level statistics, enabling identification of gene dependencies. **Results:** Comprehensive CRISPR/Cas9 functional genomics profiling was carried out retrospectively on pre-therapy samples from 59 AML patients. There were no false positives identified among negative controls. Functional dependencies on multiple genes were observed, with approximately half of patients (n=31; 52.5%) showing at least one gene dependency. We observed on average 6.7 dependencies per positive sample, with 5 of them revealing more than 10 dependencies. In addition to the targets of drugs approved to treat AML (FLT3, 10.2%; IDH1/2, 3.4%; SMO, 3.4%), a diversity of targetable genes for new therapeutic approaches to AML were identified across multiple known oncogenic signaling pathways. The prevalence of these recurrent gene dependencies ranged from 3.3% to 23.7% in our AML cohort. **Conclusions:** In summary, comprehensive functional genomic profiling using Fx Heme provides an effective platform to identify therapeutic opportunities in AML based on dependencies identified for targets of drugs not currently used to treat AML. These insights are now being utilized to develop additional treatment options and more effective personalization of treatment for AML. Research Sponsor: Function Oncology.

3087

Poster Session

CBX-12-101: A first-in-human study of CBX-12, an alphalex peptide drug conjugate (PDC) in patients (pts) with advanced or metastatic solid tumors. *First Author: Ildefonso I Rodriguez Rivera, NEXT Oncology, San Antonio, TX*

Background: Tumor-targeted drug delivery technologies are urgently needed to overcome conventional chemotherapy's lack of tumor selectivity. Alphalex conjugates, which contain a pH-low insertion peptide (pHLIP), a linker and a payload, are designed to overcome this lack of selectivity. Unlike antibody drug conjugates, alphalex PDCs target tumors in an antigen-agnostic manner. At pH ≥7.0, the peptide is unstructured. In the low-pH tumor microenvironment the peptide forms an alpha helix and inserts directionally into the tumor cell membrane delivering the linker and payload intracellularly where the linker is cleaved releasing the payload in the cytosol. CBX-12 consists of the pH-sensitive peptide, a self-immolating linker, and the topoisomerase 1 (TOP1) inhibitor exatecan. **Methods:** In this Phase 1 trial, cohorts of pts were treated with escalating doses of CBX-12 in a 3 + 3 design on three dosing schedules: daily x 5 every 3 weeks, daily x 3 every 3 weeks or once weekly. The primary objectives are safety, tolerability and to determine the MTD and/or RP2D. Secondary and exploratory objectives include evaluation of plasma PK of CBX-12 and exatecan, anti-tumor activity per RECIST v1.1, and measurement of anti-drug antibodies. **Results:** As of 26 Jan 2023, 42 pts have been treated on three schedules. The most frequent treatment-related AEs (TRAEs) were anaemia (42.9%), nausea (38.1%), fatigue (33.3%), ANC and WBC decreased (33.3% each), vomiting (26.2%), diarrhoea (23.8%) and thrombocytopenia (19.0%). The most frequent Gr3/4 TRAEs were ANC decreased (28.6%), anemia (23.8%), WBC decrease (16.7%), thrombocytopenia (14.3%). Dose limiting toxicity was observed in 6 pts: myelosuppression (6 pts) febrile neutropenia (2 pts), and sepsis (2 pts). Responses were observed in 2 of 9 pts with ovarian cancer and 2 of 8 with breast cancer. The MTD on the daily x 3 schedule is 45mg/m². Dose evaluation continues on the weekly schedule. **Conclusions:** In this FIH study of a pH-targeting alphalex PDC, CBX-12 demonstrated single-agent antitumor activity including 4 responses with the dominant toxicity of myelosuppression. Phase 2 expansion cohorts are planned in pts with platinum-resistant ovarian cancer and hormone-receptor positive, HER2 negative breast cancer. Clinical trial information: NCT04902872. Research Sponsor: Cybrexa.

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Poster Session

Sudocetaxel zendusortide (TH1902), a novel sortilin-receptor (SORT1)-targeting peptide-drug-conjugate (PDC) in patients (pts) with advanced solid tumors: Results from part 1 (dose-escalation) of a phase 1, open-label study. *First Author: Funda Meric-Bernstam, Department of Investigational Cancer Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: SORT1 is expressed in a variety of tumors when compared to most healthy tissue. TH1902 is a first-in-class PDC targeting SORT1, that consists of 2 molecules of docetaxel attached to the TH19P01 peptide via a cleavable succinyl linker. Conjugating the short peptide with various anti-cancer agents allows for targeted delivery of payloads to the tumor. Here we report results from Part 1 of a FIH, multicenter, phase 1 study, designed to explore the safety, pharmacokinetics (PK) and efficacy of TH1902 in advanced solid tumors. **Methods:** Part 1 used a modified rapid intrapatient dose escalation design. A starting dose of 30 mg/m² Q3W of TH1902 was used for the study based on the available pre-clinical data of TH1902 and the known safety profile of docetaxel. Eligibility criteria included pts with advanced solid tumors (all-comers) that have relapsed or are refractory to standard anticancer treatment. Pts had no limit on previous lines of therapy, and were required to have measurable disease by RECIST, expected survival of ≥3 months, ECOG 0-1, and adequate organ function. Pts were not required to be tested for SORT1 at entry. The primary objective of the study was to characterize the safety and tolerability of TH1902. The primary objective of Part 1 was to identify the maximum tolerated dose and the recommended dose for Part 2 (dose expansion). Additional objectives included the examination of the PK of TH1902 and free docetaxel, and outcomes as related to SORT1 expression. **Results:** As of April 2022, 18 pts were enrolled in Part 1 and included 6 ovarian, 1 endometrial, 1 cervical, 3 prostate, 3 ER+/Her2+ BC, 3 melanoma and 1 NSCLC. Pts received an average of 8 prior regimens (range: 3-20). All pts received at least 1 dose of study drug and were evaluated after the 1st cycle for a DLT. Dose levels between 30-420 mg/m² Q3W were studied. Following safety observations among the 6 patients enrolled at the 420 mg/m² dose level (Gr 3 neuropathy [n=2], Gr 4 neutropenia [n=2], Gr 3 ocular [n=1] and Gr 2 skin toxicities), the dose was reduced to 300 mg/m². At the at 300 mg/m² cohort, seven pts received a mean of 2.9 cycles. AEs (regardless of relatedness) occurred in all 7 (100%) pts, mostly Gr 1-2. One pt had Gr 3 worsening anemia (probably related) and Gr 3 abdominal pain/fistula (unrelated). AEs of interest were all Gr 1-2, and included: ocular (keratitis/dryness)=2 pts; GI (nausea/vomiting/diarrhea)=2 pts; neuropathy=2 pts; MSK (arthralgia/myalgia/extremity pain)=2 pts. In 15 evaluable pts in Part 1 clinical benefit was observed in 10 pts: 1 PR (prostate with 53% decrease in target lesion) and 9 SD. PK and SORT1 expression analyses are ongoing. **Conclusions:** Although biological activity has been observed, the optimal dosing regimen of TH1902 is currently under evaluation. Clinical trial information: NCT04706962. Research Sponsor: Theratechnologies.

3090

Poster Session

Pan-cancer landscape of FOXA1 alterations: Insights and clinical implications. *First Author: Edward Christopher Dee, Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Forkhead box A1 (FOXA1) is a pioneer transcription factor that regulates organogenesis and is associated with progression in breast and prostate cancers. To explore its role more broadly in oncogenesis, we characterize FOXA1 genomic alterations and clinical correlates in a large pan-cancer cohort from the American Association for Cancer Research project Genomics, Evidence, Neoplasia, Information, Exchange (AACR-GENIE) database. **Methods:** Using AACR-GENIE, FOXA1 mutations (in frame insertions/deletions (indel-inframe), frameshift insertions/deletions (indel truncating), point mutations (missense), fusions, and amplifications) were characterized across >30 cancer types for primary and metastatic tumors with patient characteristics and clinical outcomes. FOXA1 alterations were queried in the MSK-MET cohort, a subset of GENIE cohort, allowing the definition of hazard ratios (HRs) and overall survival estimates based on Cox proportional hazard models. **Results:** Among 120,625 samples queried from the AACR GENIE data, FOXA1 was profiled in 87,706 samples: 30,268 metastases, 49,228 primary tumors, and 8,210 not specified. FOXA1 mutations were present in 1,869 samples (2.1%), mostly in the forkhead DNA-binding domain. Prostate tumors were enriched with indel-inframe alterations whereas breast cancers were enriched with missense mutations. F266, R261, and D226 mutations in the Wing2 region were common in breast and prostate cancers. In the GENIE cohort, FOXA1 copy number profiles were collected for 74,715 samples, with amplification detected in 834 (1.1%) and deletion in 96 samples (0.1%). FOXA1-amplification was most common in non-small cell lung cancer (NSCLC, 3%, n=190, in primary; 6%, n=264, in metastatic), followed by small cell lung cancer (SCLC) (4.1%, n=10, in primary; 3.5%, n=10, in metastatic), breast (2%, n=80 in primary; 1.6%, n=73, in metastatic) and prostate cancers (2.2%, n=49, in primary; 1.6%, n=27 in metastatic). In the MSK-MET cohort, FOXA1 amplifications were associated with poorer outcomes in primary breast (HR: 3.04, 95% CI: 1.89-4.89, p=4e⁻⁶), primary NSCLC (HR: 1.45, 95% CI: 1.06-1.99, p=0.02), and prostate cancer (HR: 1.94, 95% CI: 1.03-3.68, p=0.04). FOXA1 amplifications were associated with wide-spread metastases in primary breast, NSCLC, and prostate cancer. **Conclusions:** In this observational study of pan-cancer FOXA1 mutant specimens from the GENIE database, we found that FOXA1 alterations in prostate cancer (primary and metastatic tumors) were predominantly indels versus missense in other cancers. We also observe a consistent association between FOXA1 amplification and enhanced metastatic potential regardless of tissue of origin. Our findings suggest that FOXA1 amplifications could serve as a potential prognostic and therapeutic target, particularly for breast, prostate, and non-small cell lung cancer. Research Sponsor: U.S. National Institutes of Health; Prostate Cancer Foundation.

3092

Poster Session

Hypersensitivity reaction to taxanes following COVID-19 vaccination. *First Author: Bennett Osantowski, Cleveland Clinic Foundation, Cleveland, OH*

Background: In oncology, many patients receive taxanes as part of their chemotherapy regimens to treat various types of cancers. The most commonly used taxanes, paclitaxel and docetaxel, are known to cause hypersensitivity reactions (HSRs) in 5-10% of cases. Providers at our institution perceived an increase in the frequency of HSR with taxanes after patients received vaccines against COVID-19. We aimed to compare the incidence of HSRs to taxanes among our oncology patients who have or have not received one or more COVID vaccine prior to initiation of either paclitaxel or docetaxel chemotherapy. **Methods:** Under an IRB-approved protocol, adult patients, ages ≥18, who had initial treatment with one or more infusions of paclitaxel or docetaxel for any type of cancer in 2020 or 2021 at a single cancer institute, were identified. Demographic, clinical and pathologic information was reviewed from electronic medical charts. The primary objective was to compare the rate of HSR reaction to taxanes among patients who had received any vaccine against COVID-19 prior to their initial taxane infusion versus patients who did not receive a COVID vaccine prior to the first taxane infusion. We also aimed to compare the different vaccine types and to describe, if an HSR occurred, if it was at the first or subsequent taxane infusion. **Results:** In this single-center retrospective cohort study, 355 patients that met the study criteria were analyzed. 204 patients received at least one COVID-19 vaccine prior to their first taxane infusion (58.8% Pfizer-BioNTech, 27.9% Moderna, 13.2% multiple vaccine types) and 151 patients received the vaccine either after their first taxane infusion or were unvaccinated (51.7% Pfizer-BioNTech, 23.8% Moderna, 2.6% Janssen, 21.9% unvaccinated). Of the patients vaccinated for COVID-19 prior to receiving their first taxane infusion, 11.8% had an HSR while 2.6% had an HSR in the post-taxane/unvaccinated group (p 0.003). Severity of HSR reactions was categorized as mild, moderate, or severe based on symptoms. If an HSR occurred, vaccinated patients were more likely to have a worse reaction (p 0.017). Of the 24 patients that had an HSR in the vaccinated group, 14 had a mild reaction, 8 had a moderate reaction, and 2 had a severe reaction. In the post-taxane/unvaccinated group, 3 had a mild reaction and 1 was moderate. 85.7% of HSR to taxanes occurred after the first cycle (24/28 reactions, p <0.001). There was no difference among the vaccine types, though very few patients received the Janssen vaccine. **Conclusions:** Vaccination for COVID19 prior to initiation of taxane containing chemotherapy was associated with a higher risk of taxane related HSR and a higher risk for more severe reactions. Since vaccination against COVID-19 is highly encouraged, particularly among patients with cancer, it is important for clinicians to be aware of this potential association so that they can better monitor for, and promptly treat these events. Research Sponsor: None.

3091

Poster Session

Proposition of a drug score to predict the clinical usefulness of therapeutic dose monitoring of oral molecularly targeted therapies. *First Author: Arthur Geraud, Gustave Roussy Institute, Villejuif, France*

Background: Therapeutic drug monitoring (TDM) consists in measuring and interpreting drug concentrations in biological fluids to personalize drug dosage. This method is widely used for drugs with a narrow therapeutic index (e.g., immunosuppressants or neuroleptics agents). In onco-hematology, current recommendations of TDM for oral molecularly targeted therapies (oMTT) differ among molecules, making it difficult to identify good TDM candidates. This study aims to propose a quantitative approach with a score to predict the clinical usefulness of TDM of oMTT. **Methods:** We selected the four key parameters needed for an oMTT to be a good candidate for TDM (e.g. interpatient pharmacokinetic variability, feasible dose-adaptation strategy, exposure-efficacy relationship, exposure-safety relationship). We collected each drug's pharmacokinetic (PK) and pharmacodynamics variables from drug labels, Center for Drug Evaluation and Research reports and early trials data. The score was defined from oMTT's exposition variability (variability score: coefficient of variation of drug exposition, the impact of food and proton pump inhibitors), technical complexity (PK linearity, active metabolite, half-life), efficacy (Exposure-response relationship (ERR)) and safety (maximum tolerated dose, Exposure-safety relationship (ESR)). The global score ranged from 0 to 100. To assess the relevance of the score, we evaluated molecules from other therapeutic classes with known strong recommendations of TDM (clozapine, everolimus, voriconazole). **Results:** In September 2021, we collected data from sixty-seven oMTTs. Scores were normally distributed (mean 48.3, standard deviation 15.6) and varies from 15 for acalabrutinib to 80 for sunitinib. Scores of drugs with strong recommendation of TDM were 68, 68 and 64 for clozapine, everolimus as an immunosuppressant, and voriconazole, respectively. We hypothesized that a score above 60 might be associated with relevant indications of TDM. Fifteen molecules had a score above 60 (sunitinib (80), cabozantinib (76.5), nilotinib (76), abemaciclib (76), axitinib (75), sorafenib (69.5) gefitinib (69.5), trametinib (67.5), talazoparib (67), crizotinib (66), pazopanib (65), sonidegib (63.5), neratinib (62.5), panobinostat (62) and imatinib (60.5)). **Conclusions:** We defined a score to identify good candidates for TDM in onco-hematology. Usefulness of TDM in oncology should be confirmed prospectively prioritizing these molecules. Research Sponsor: None.

3093

Poster Session

Bevacizumab exposure and tumor response in patients with platinum resistant epithelial ovarian cancer. *First Author: Judith Michels, Gustave Roussy, Département de Médecine Oncologique, Villejuif, France*

Background: There is a high unmet medical need for disease control in platinum resistant epithelial ovarian cancer patients (PROC). PemBOv trial (NCT03596281) showed promising results with the combination of pembrolizumab plus short-term flat dose bevacizumab with or without pegylated liposomal doxorubicin (PLD) based chemotherapy. However, overall, 20 % of pts showed trough levels for bevacizumab below the targeted threshold of plasma levels associated with efficacy. Based on the PemBOv data, the current analysis aimed to develop a pharmacometric model to characterize the tumor growth early kinetics and quantify the effect of treatment in the study cohorts. A focus was made on the association between bevacizumab exposure and tumor response. **Methods:** Tumor growth kinetic was studied to predict the clinical outcome. Population pharmacodynamic non-linear mixed-effects modeling approach was used to characterize tumor size evolution in patients. The Kkill parameter expressed as week⁻¹ was defined to best describe the shrinkage in tumor size depending on the treatments. In addition, Exposure-Response relationships was performed to evaluate whether bevacizumab plasma levels were associated with the previously determined Kkill parameter. The exposure to bevacizumab was defined by the trough level at the second treatment cycle (PreC2, µg/ml). **Results:** A strong difference in Kkill values was found between cohort A (pembrolizumab plus PLD, n=6, Kkill = 0.00091 week⁻¹) and either cohorts B (pembrolizumab + bevacizumab, n=19, Kkill = 0.002) and C (pembrolizumab + bevacizumab + PLD, n=19, Kkill = 0.02 week⁻¹) respectively, whereas little difference was observed between cohorts B and C. This difference indicates higher tumor shrinkage in cohorts B and C as compared to cohort A. No clear Exposure-Response relationship was evidenced between bevacizumab plasma levels and tumor shrinkage. Still, in patients treated with bevacizumab plus pembrolizumab (cohorts B and C), mean bevacizumab exposure was higher in patients with an ORR and Stable disease of at least 4 months as compared with patients with no clinical benefit (i.e., 69.4 VS. 48 µg/ml). Association between bevacizumab levels and clinical outcome deserves further investigations. Because Kkill can be estimated in an early fashion through *in silico* modeling, this could be evaluated as a surrogate marker to forecast clinical outcome. **Conclusions:** Bevacizumab exposure correlated with ORR and clinical benefit in PROC patients treated with bevacizumab plus pembrolizumab plus minus PLD, since higher plasma trough levels were associated with better clinical outcome. The early Kkill *in silico* modeling could pave the way for the development of prediction models for personalized treatments of PROC patients. Clinical trial information: NCT03596281. Research Sponsor: Merck; Fondation Cancer Luxembourg.

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Poster Session

EZH2/EZH1 inhibitor tulmimetostat (CPI-0209) in patients with advanced solid tumors or hematologic malignancies: Preliminary phase II results. *First Author: Charles Drescher, Swedish Cancer Institute, Seattle, WA*

Background: Many preclinical tumor models with mutations in *ARID1A* and *BAP1* are highly sensitive to EZH2 inhibition. Tulmimetostat (CPI-0209) is an investigational oral, next-generation, dual EZH2/EZH1 inhibitor with durable target coverage. Phase I dose escalation established a recommended Phase II dose of 350 mg (Lakhani et al. ASCO 2021). We report preliminary Phase II findings from the ongoing Phase I/II study (NCT04104776). **Methods:** Phase II is evaluating tulmimetostat 350 mg once daily in 28-day cycles in 6 disease-based cohorts (Table). The Simon 2-stage study design requires 1 response (complete [CR] or partial [PR]) in stage 1 (n = 10 patients [pts]) for expansion to stage 2 (plus n = 19) (except in M4, see table). Primary endpoint is objective response rate (ORR) based on disease-specific criteria; secondary objectives include safety. **Results:** As of Nov 08, 2022, 62 pts received ≥1 dose (safety evaluable); 48 had ≥1 postbaseline tumor assessment (efficacy evaluable). Pts had median 3.2 years (0.6–19.6) since diagnosis; 77.4% had ≥2 prior lines of therapy. Cohorts M2, M5 and M6 had completed stage 1 enrollment. At cut-off, best responses among evaluable patients (Table) show 4 cohorts have at least 1 confirmed response, including 2 CR and 1 PR in 7 pts with peripheral T-cell lymphoma (PTCL). 47 pts (75.8%) experienced TEAEs leading to dose modifications, 20 (32.3%) had serious TEAEs, and 5 (8.1%) discontinued treatment due to TEAEs. The most frequent TEAEs (≥15% of pts) (any Grade/Grade ≥3) considered at least possibly related to tulmimetostat were thrombocytopenia (51.6%/27.4%), diarrhea (45.2%/12.9%), nausea (37.1%/0%), anemia (30.6%/16.1%), fatigue (29.0%/0%), alopecia (25.8%/1.6%), dysgeusia (24.2%/0%), vomiting (21.0%/0%), and neutropenia (17.7%/14.5%). **Conclusions:** Based on response criteria of ORR ≥1/10 pts, the ovarian (M2), endometrial (M3), and mesothelioma (M5) cohorts achieved eligibility for stage 2 expansion (not relevant in M4). The safety profile of tulmimetostat is consistent with EZH2 inhibition and previous data. These preliminary findings in heavily pretreated pts with multiple tumor types, including tumors with *ARID1A* alterations or *BAP1* loss, support ongoing investigation of tulmimetostat. Clinical trial information: NCT04104776. Research Sponsor: MorphoSys AG.

Best confirmed responses.

Cohort	M2		M3		M5		M6
	M1 Urothelial ^{1,2}	Ovarian clear cell carcinoma ¹	Endometrial carcinoma ¹	M4 Lymphoma ³	M5 Mesothelioma ⁴	Metastatic castration- resistant prostate cancer	
Efficacy evaluable, N	5	10	5	7	12	9	
Best response, n							
CR	0	0	0	2	0	0	
PR	0	1	2	1	1	0	
Stable disease	4	6	1	0	7	6	
Progressive disease	1	3	0	4	4	3	
Not evaluable	0	0	2 ¹	0	0	0	

¹Or other advanced/metastatic solid tumors. ²*ARID1A* mutant. ³PTCL (n = 10) or diffuse large B-cell lymphoma (DLBCL) including GCB-DLBCL with ≥1 EZH2 hotspot mutation (n = 10); 1-stage enrollment in M4. ⁴*BAP1* loss. ⁵1 pt only 1 post-baseline assessment, before 4 weeks; 1 non-evaluable assessment.

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Poster Session

Phase II trial of dabrafenib and trametinib in patients with BRAFV600E/R or non-BRAFV600 mutated advanced solid tumors: Results from the BELIEVE trial (NCCH1901). *First Author: Makoto Tahara, National Cancer Center Hospital East, Japan, Kashiwa-Shi, Japan*

Background: BRAF V600 mutations are prevalent in melanoma, thyroid cancer, non-small cell lung cancer, and other malignancies to a lesser degree. The BELIEVE study, a Japanese equivalent of the NCI-MATCH trial, assessed the efficacy of the selective BRAF inhibitor dabrafenib and the MEK1/2 inhibitor trametinib in patients with solid tumors harboring *BRAFV600E/R* or non-*BRAFV600* mutations. **Methods:** The BELIEVE study was a single-arm, open-label clinical trial. Eligible patients were those with solid tumors, with the exception of those with colorectal cancer who were subsequently excluded through amendment. Participants received dabrafenib 150 mg twice daily and trametinib 2 mg/day continuously until disease progression or intolerable toxicity occurred. The primary endpoint was objective response rate (ORR; investigator assessed, RECIST criteria, CR+PR) and secondary endpoints were progression-free survival (PFS), 6-month PFS, and overall survival. The clinical hypothesis was that patients would respond to the matched drug. Bayesian analysis using a prior distribution with an expected response rate of 30% [Beta(0.6, 1.4)] was carried out. If the posterior distribution provided unexpectedly high probability (i.e. > 95%) of response rate exceeding 60% or being inferior to 20%, early termination would be considered during the trial. Otherwise, the efficacy of the drug would be concluded as promising in terms of the clinical hypothesis. **Results:** Fifty patients who had target lesions were included as primary endpoints. The median age was 56.5 years. The three most prevalent primary sites among the main cohort were the thyroid, the central nervous system and biliary tract. The confirmed ORR was 28.0% (95% CI, 16.2% to 42.5%), which met the pre-determined hypothesis, and disease control rate (DCR; CR+PR+SD) was 84.0% (95% CI, 70.9% to 92.8%); PFS was 6.5 months (95% CI, 4.2 to 7.2 months) and responses were observed across seven different types of tumors; the PFS rate at 6 months was 87.8%. Data regarding overall survival was premature, with a median of 9.7 months at the time of analysis. Furthermore, the median PFS was 4.5 months (95% CI, 0.8 to 8.6 months) for the seven patients without target lesions in the exploratory analysis. Adverse events reported among 57 safety analysis population were consistent with those previously reported for dabrafenib and trametinib. Patients who had grade ≥3 adverse events were 45.6%. The most frequent AEs were pyrexia (26.3%), anemia (12.3%), anorexia (8.8%), aspartate aminotransferase elevation (8.8%) and hypoalbuminemia (8.8%). **Conclusions:** The study met its primary endpoint with an ORR of 28.0% in this mixed histology pre-treatment cohort, furthermore, the DCR was 84.0%, which is encouraging for efficacy in *BRAFV600*-mutant tumors across solid tumors. Clinical trial information: jRCTs031190104. Research Sponsor: Health and Labour Sciences Research Grants, Japan Agency for Medical Research and Development.

3095

Poster Session

BLU-222, an oral, potent, and selective CDK2 inhibitor, in patients with advanced solid tumors: Phase 1 monotherapy dose escalation. *First Author: Manish R. Patel, Florida Cancer Specialists and Sarah Cannon Research Institute, Sarasota, FL*

Background: Cell growth regulation and proliferation is dependent on cyclins and CDKs. Cyclin E1 (*CCNE1*) is a cell cycle regulator that activates CDK2. A broad range of aggressive cancers overexpress cyclin E and/or harbor *CCNE1* gene amplifications. Inhibition or loss of CDK2 impairs the growth of *CCNE1*-amplified cell lines and cyclin E overexpression represents one of several CDK4/6 inhibitor resistance mechanisms, including in hormone receptor-positive/human epidermal growth factor receptor-2-negative (HR+/HER2-) breast cancer, making CDK2 inhibition a promising novel therapeutic approach. BLU-222 is an investigational, oral, potent, and selective CDK2 inhibitor in early clinical development with best-in-class potential. **Methods:** VELA (NCT05252416) is an international, open-label, phase 1/2 study evaluating the safety, PK, pharmacodynamics, and efficacy of BLU-222. In monotherapy dose-escalation, adult patients (pts) enrolled regardless of *CCNE1* status, but *CCNE1* amplification or progression after a CDK4/6 inhibitor were of specific interest. Pts with ECOG PS 0–2 and confirmed nonresectable tumors who had progressed following standard of care for advanced relapsed/recurrent disease were enrolled. BLU-222 was administered BID in continuous 28-day cycles, with dose escalation employing a Bayesian Optimal Interval design to identify the maximum tolerated dose. Blood samples were collected for PK and circulating biomarker analysis. **Results:** By Jan 29, 2023, 27 pts were enrolled in 6 escalating BID dose cohorts and included in the safety population. Median age was 64 y (range, 29–85); 85% were female. The most frequent cancer types were breast (44%, 12/27), endometrial (15%, 4/27), ovarian (11%, 3/27), and prostate (11%, 3/27). No pts discontinued treatment due to AEs. The most common (≥15%) AEs (all-cause AE; treatment-related AE) were nausea (33%; 26%), vomiting (22%; 11%), anemia (22%; 19%), diarrhea (22%; 22%), and fatigue (18%; 15%). Transient visual AEs (including blurred vision, photophobia, vision change) were seen in 5 pts (19%). These visual symptoms were mild except in 1 pt with Grade (Gr) 3 blurred vision/photophobia; all had fully resolved by/after the data cut-off. There were 2 dose limiting toxicities reported at the 2 highest dose levels: nausea (Gr 3; n=1) and blurred vision/photophobia (Gr 3; n=1). Translational pharmacodynamic data has shown early evidence of pathway modulation. One partial response was seen in a pt with HR+/HER2- metastatic breast cancer previously treated with 5 lines of therapy, including palbociclib, abemaciclib, and capecitabine. **Conclusions:** As of the cutoff date, BLU-222 monotherapy was generally well tolerated in pts at the BID doses tested. Dose escalation is ongoing to determine the recommended phase 2 dose. Preliminary evidence of cell cycle pathway modulation and clinical activity have been observed. Clinical trial information: NCT05252416. Research Sponsor: Blueprint Medicines.

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Poster Session

Safety, pharmacokinetics and anti-tumor activity of RP12146, a PARP1/2 inhibitor, in patients with locally advanced or metastatic solid tumors. *First Author: Piotr Jan Wysocki, Jagiellonian University Hospital, Kraków, Poland*

Background: RP12146 is an orally bioavailable, potent small-molecule inhibitor of poly (ADP-ribose) polymerase (PARP) 1 and PARP 2. Pre-clinically, RP1246 demonstrated anti-proliferative activity in both *BRCA* and non-*BRCA* mutant cancer cell lines of different tumor types as well as in xenograft models. The first-in-human of RP12146 as a single agent is underway to determine the safety, pharmacokinetics and anti-tumor activity. **Methods:** The phase I/Ib study was designed as two-part study. Phase I was a dose escalation, 3+3 design, MTD determination study and would enroll pts who have tumors which are known to harbour DNA repair deficiencies. Phase Ib is dose expansion at the MTD/ optimal dose and would enroll thirty-six pts (12 pts each of advanced/metastatic ovarian cancer (OC), breast cancer (BC), and castration-resistant Prostate cancer (mCRPC) having a confirmed deleterious HRR mutation. RP12146 was administered orally in a 28-days cycles until disease progression. Safety were the primary outcome and the investigator-assessed ORR, CBR and PFS assessed using RECIST v1.1, are the secondary outcomes. Predictive biomarker analysis included inhibition of PARP enzyme as measured by gH2AX levels in PMBCs. **Results:** As of 31-Jan-2023, 9 pts in the dose escalation at 3 dose levels (100 mg QD, 200mg BID and 400 mg BID) and 13 pts (with 5 CHEK2, 4 BRCA2, 2 ATM, 1 CDK12, and 1 RAD51C mutations) in dose expansion have been enrolled. No DLTs were reported in dose escalation. The dose of 400mg BID was considered for dose expansion. Out of 22 pts enrolled, 13 pts had PC, 3 pts had OC, and 2 pts had BC. Most of the related AEs reported were mild in severity except one event of Grade 3 anaemia which resolved, and patient continues to be on therapy. None of the pts developed related SAEs or discontinued due to an AE. Eleven patients (50%) in the expansion group continue to be on RP12146 treatment. RP12146 exhibited rapid absorption achieving maximum concentrations in 1 hr, with an elimination half-life of ~ 4 hrs. Out of the 7 efficacy evaluable PC patients, 5pts showed stable disease and 2pts showed progressive disease. Out of 3 OC pts, 2 pts showed stable disease, and one pt had progressive disease. Among two BC pts, one showed stable disease and the other had progressive disease. Overall, out of 16 efficacy evaluable patients, 8 patients (50%) showed stable disease. **Conclusions:** RP12146 showed a differentiated safety profile so far with limited hematological toxicities reported as compared to the first-generation PARP inhibitors. Updated safety and efficacy data will be provided at the time of presentation. Clinical trial information: NCT05002868. Research Sponsor: Rhizen Pharmaceuticals AG.

3098

Poster Session

A phase 1, multicenter, open-label study of a new BRAF inhibitor ABM-1310 in adult patients (pts) with *BRAF*V600-mutated solid tumors. *First Author: Sarina A. Piha-Paul, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: ABM-1310 is a novel small-molecule BRAF inhibitor with high water solubility, cell permeability, and blood-brain barrier penetration as demonstrated in preclinical studies. Here we report preliminary findings from a first-in-patient phase 1 study of ABM-1310. **Methods:** This US multicenter, open-label, dose-escalation with cohort expansion trial includes adult pts with advanced *BRAF*V600-mutated solid tumors, including those with active brain metastasis from solid tumors or primary malignant brain tumors. Previous BRAF/MEK inhibitor treatment is permitted. In dose escalation Part A, ABM-1310 monotherapy is given orally twice a day (25–250 mg bid). In dose escalation Part B, ABM-1310 (100 and 200 mg bid) is given in combination with the MEK inhibitor cobimetinib (60 mg QD d1–21 q4w). Primary objectives: determine maximum tolerated dose and recommended phase 2 dose of ABM-1310 ± cobimetinib. Secondary objectives: safety/tolerability; pharmacokinetics; preliminary efficacy. Dose-limiting toxicities (DLTs) are assessed during cycle 1 by a 3+3 design. **Results:** As of November 28, 2022, 20 pts (65% male; median age 57.5 years) have been treated with ABM-1310 monotherapy across six dose levels in Part A: 25 mg bid (n=3); 50 mg bid (n=3); 100 mg bid (n=4); 150 mg bid (n=4); 200 mg bid (n=4); 250 mg bid (n=2). All pts experienced adverse events (AEs), most frequently skin rash (40%) and QT prolongation (20%). Three pts had drug-related grade ≥3 AEs (nausea/vomiting, QT prolongation and rash) and two had drug-related serious AEs (SAEs) (nausea/vomiting and creatinine increase). Among 16 efficacy evaluable pts, two (pleomorphic xanthoastrocytoma and glioblastoma) had a partial response (PR) and eight had stable disease (SD) as their best response (per RECIST or RANO). In Part B, two ABM-1310 dose levels were assessed in combination with cobimetinib: 100 mg bid (n=3) and 200 mg bid (n=3). Four pts had AEs and drug-related AEs (rash and QT prolongation). There were no SAEs. Among three evaluable pts, one (melanoma) had a PR and one had SD as their best response. There were no confirmed DLTs in either dose-escalation Part A or B, although a few pts had ABM-1310 treatment interruption and subsequent dose reduction. No pts discontinued prematurely for any safety or tolerability reason and there were no drug-related deaths. Preliminary assessment of ABM-1310 drug exposure vs dosage showed a linear dose-proportional relationship. This trial is ongoing. **Conclusions:** ABM-1310 at the currently tested doses up to 200 mg bid, either alone or in combination with cobimetinib, was generally well tolerated, with no new safety signals. Preliminary efficacy data demonstrate favorable activity of ABM-1310 in pts with *BRAF*V600-mutated solid tumors, including primary CNS tumors, and pts previously refractory to other BRAF/MEK inhibitors and I/O therapies. Clinical trial information: NCT04190628. Research Sponsor: ABM Therapeutics.

3100

Poster Session

First-in-human phase 1 study of pimicotinib (ABSK021), a CSF-1R inhibitor, in patients with advanced solid tumors. *First Author: Gerald Steven Falchook, Sarah Cannon Research Institute at HealthONE, Denver, CO*

Background: Colony-stimulating factor 1 (CSF-1) pathway is involved in the development of various types of cancer. Pimicotinib is an orally available, selective, potent small molecule CSF-1R inhibitor with significant pre-clinical anti-tumor activity. Here we present the results of the phase 1 trial. **Methods:** The escalation part employed a 3+3 design with a starting dose of 25 mg QD (28-day/ cycle) to determine the maximum tolerated dose (MTD) and the recommended dose for expansion (RDE). Additional pts with selected tumor types including pancreatic carcinoma, triple-negative breast cancer, lung cancer, and sarcoma were treated at RDE in the expansion part for further evaluation. Tenosynovial giant cell tumor (TGCT) cohorts were analyzed and reported separately. **Results:** As of December 31, 2022, 74 pts received at least one dose of pimicotinib at 25 mg (n=6), 50 mg (n=58), 75 mg (n=8), or 100 mg (n=2) QD, respectively. Median age was 59 y; 68.9% were female; 47.3% were white, 33.8% were Asian and 18.9% were African American. 74.3% were ECOG PS 1; 85.1% had metastasis; 67.6% had ≥3 lines of prior systemic anti-tumor therapies. Median duration of treatment was 49.5 days (range 4–377). Treatment-related adverse events (TRAEs), Grade ≥3 TRAEs, and serious TRAEs occurred in 74.3%, 21.6%, and 4.1% of pts, respectively. The most common TRAEs (≥20%) were serum enzyme elevations, including CPK, AST and LDH, which were all believed to be pimicotinib MOA related, with CPK increase (14.9%) being the only Grade ≥3 TRAE reported in ≥10% of pts. 3 pts (4.1%) reported serious TRAEs of ascites, blood bilirubin increase, and vaginal hemorrhage. After single and multiple dosing, pimicotinib plasma exposure increased slightly less than dose proportion. The rapid oral absorption (median t_{max} of 0.87–1.52 hrs) with moderate terminal $t_{1/2}$ (mean $t_{1/2}$ ranges: 43.6–63.5 hrs) suggested sustained drug exposure was achieved with a once daily dosing schedule. No dose adjustment was needed based on tested covariates including weight, age and race. Pimicotinib treatment led to a more than 85% reduction of non-classical monocytes (NCM) across all dose levels. Plasma CSF-1 levels were significantly increased from 25mg QD to 50mg QD and reached a plateau at 50mg QD, with ~40-fold maximal induction. Reduced CD163+ macrophages in skin and tumor tissues were seen at 50mg QD. All tested doses showed adequate inhibition of NCM, and CSF-1 change showed a positive correlation with plasma pimicotinib concentration. The MTD and RDE were determined as 75 mg QD and 50 mg QD. **Conclusions:** Tolerable safety profile and favorable PK/PD properties supported pimicotinib to be further evaluated in advanced solid tumors, including combinations. Clinical trial information: NCT04192344. Research Sponsor: Abbisko Therapeutics Co., Ltd.

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Poster Session

Phase 1 results of CYT-0851, a monocarboxylate transporter (MCT) inhibitor, in combination with capecitabine (cape) or gemcitabine (gem) in advanced solid tumors. *First Author: Ryan C. Lynch, University of Washington/Fred Hutchinson Cancer Research Center, Seattle, WA*

Background: The MCT inhibitor CYT-0851 blocks lactate transport resulting in glycolytic cancer cell death. Monotherapy clinical activity has been previously reported in lymphoma and solid tumors. Preclinical studies assessing CYT-0851 with chemotherapy identified enhanced growth inhibition when combined with 5-FU or gem supporting clinical evaluation. **Methods:** Patients (pts) with solid tumors were treated with CYT-0851 + standard dosing of cape or gem in 21- and 28-day cycles, respectively, following a 3+3 design. The primary objective was to determine the MTD. Secondary objectives included: safety, PK, and anti-tumor activity by RECIST. **Results:** As of Feb 1, 2023, 14 pts (pancreatic n=9; ovarian n=5) were treated in 4 cohorts (100–400 mg QD) with cape. No DLTs occurred, and 400 mg QD was selected as the RP2D. 8 pts (57%) experienced a treatment-related adverse event (TRAE), including 2 (14%) with a G3/4 AE. The most common related AEs were primarily G1/2 and included fatigue (21%), nausea, decreased appetite, dry skin, mucosal inflammation and maculopapular rash (all 14%). 10 pts (sarcoma n=6; HNSCC n=1; ovarian n=1; pancreatic n=2) were treated in 2 cohorts (100, 200 mg QD) with gem. No DLTs occurred. Escalation is ongoing with up to 2 further cohorts. 9 pts (90%) experienced a TRAE, including 5 (50%) with a G3/4 AE which were primarily cytopenias. The most common TRAEs were fatigue (50%), anemia (50%), neutropenia (40%), thrombocytopenia (30%), nausea, pruritus, ALT/AST increased, neutrophil decreased and WBC decreased (all 20%). CYT-0851 exposure was similar between combination therapy and monotherapy. 8 pts in the cape cohorts were response-evaluable, including 3 with ovarian cancer. 1 pt with platinum-resistant ovarian cancer had a confirmed PR with treatment ongoing at 174 days. 7 pts had SD. 6 pts in the gem cohorts were response-evaluable. 1 pt with sarcoma had a confirmed PR, 4 pts had SD and 1 had PD. **Conclusions:** 400 mg QD was selected as the RP2D in combination with cape as no MTD was identified. Escalation of gem + CYT-0851 is ongoing to identify the MTD. Both combinations have demonstrated an acceptable safety and tolerability profile with no unanticipated toxicities at clinically active doses. Encouraging antitumor activity has been observed in heavily pre-treated pts with both regimens including pts with ovarian cancer in the cape combo. The cape cohort is being expanded with additional pts with ovarian cancer and will be presented. Clinical trial information: NCT03997968. Research Sponsor: Cyteir Therapeutics.

3101

Poster Session

Clinical activity of palbociclib and ribociclib monotherapy in advanced cancers with cyclin D-CDK4/6 pathway alterations in the Dutch DRUP and Australian MoST trials. *First Author: Laurien Joanna Zevenin, Department of Molecular Oncology & Immunology, Netherlands Cancer Institute, Amsterdam, Netherlands*

Background: The Dutch Drug Rediscovery Protocol (DRUP, NCT02925234) and the Australian Cancer Molecular Screening and Therapeutic (MoST, ACTRN12616000931471) Program are similar non-randomized, multi-drug, pan-cancer trial platforms that aim to identify signals of clinical activity of molecularly matched targeted therapies or immunotherapies outside their approved indications. Here, we report results for advanced or metastatic pre-treated cancer patients with tumors harboring Cyclin D-CDK4/6 pathway alterations that were treated with CDK4/6 inhibitors palbociclib or ribociclib as monotherapy. **Methods:** Eligible adult patients had therapy-refractory solid malignancies with one of the following alterations: amplifications of *CDK4*, *CDK6*, *CCND1*, *CCND2* or *CCND3*, or complete loss of *CDKN2A* or *SMARCA4*. Within MoST, all patients were treated with palbociclib, whereas in DRUP, palbociclib and ribociclib were assigned to different cohorts (defined by tumor type and alteration). The primary endpoints for this combined analysis were clinical benefit, defined as confirmed objective response or stable disease (SD) ≥16 weeks, and safety. **Results:** Among 139 enrolled patients 33 tumor types were represented, with glioblastoma multiforme (18%), sarcoma (13%), non-small cell lung cancer (9%) and pancreatic cancers (9%) being most common; 116 patients received palbociclib and 23 received ribociclib. In 112 evaluable patients, the objective response rate was 0% and clinical benefit rate at 16 weeks was 15% (17 cases of SD ≥16 weeks). Median progression-free survival was 4 months (95% CI 3–5 months) and median overall survival 5 months (95% CI 4–6 months). No unexpected toxicity was observed for either drug. Additional driver alterations were identified in 98% and 77% of patients based on whole genome sequencing (WGS) and sequencing next generation sequencing (NGS) analysis at baseline, respectively (Most common in WGS: *TP53* (45%), *KRAS* (25%), *PTEN* (15%), *SMAD4* (15%). Most common in NGS: *TP53* (21%), *EGFR* (17%), *TERT* promoter (15%), *KRAS* (11%). **Conclusions:** Results show minimal clinical activity of palbociclib and ribociclib monotherapy in patients with pre-treated cancers harboring cyclin D-CDK4/6 pathway alterations. Our findings indicate that single agent use of palbociclib or ribociclib is not recommended. Furthermore, we demonstrate that merging data from similar precision oncology trials is feasible. This finding is especially relevant in the context of precision oncology, with rare molecular subsets and/or cancer histologies. Clinical trial information: NCT02925234. Research Sponsor: The Dutch Cancer Society (KWF); pfizer/novartis.

3102

Poster Session

Efficacy and safety of futibatinib for refractory advanced solid malignancies with *FGFR* alterations identified in circulating tumor DNA: TiFFANY, A GOZILA-affiliated Trial. First Author: Tomoko Jogo, Department of Surgery, Munakata Medical Association Hospital, Munakata, Japan

Background: *FGFR* alterations are observed in approximately 7% of advanced solid malignancies and are associated with poor prognosis and resistance to traditional anti-cancer therapy. Despite this, optimal therapeutic strategies with *FGFR* inhibitors for most of *FGFR*-altered solid malignancies are yet to be defined. Circulating tumor DNA (ctDNA) analysis has the potential to accurately detect *FGFR* alterations by assessing spatial and temporal intratumoral heterogeneity. **Methods:** We conducted a multicenter, investigator-initiated, phase II basket-type trial, TiFFANY, to evaluate the efficacy and safety of futibatinib, a highly selective covalent pan-*FGFR* inhibitor, in patients (pts) with advanced solid malignancies with *FGFR* alterations identified by ctDNA analysis who were refractory or intolerant to standard-of-care treatment. ctDNA analysis was performed in the GOZILA study. Enrolled pts received futibatinib at a dose of 20 mg once daily in a 21 day-cycle. The primary endpoint was investigator-assessed objective response rate (ORR). We set the threshold ORR of 5% and expected one of 25%. Planned sample size was 26 with one-sided alpha of 2.5% and power of 80%. Blood and tissue samples collected before treatment (baseline), at week 3, and after disease progression were analyzed for biomarkers and resistance mechanisms. **Results:** Twenty-six pts with *FGFR* alterations (mutation, 9; amplification, 13; fusion, 4) in ctDNA were enrolled between August 2019 and March 2021. The primary endpoint was met with five (19.2%; 95% CI, 6.6–39.4%) achieving a confirmed partial response (PR) in various cancer types (biliary tract, gastric, urothelial, and urachal cancer). Median progression-free survival and overall survival were 2.6 and 8.9 months. The most common treatment-associated adverse events were hyperphosphatemia (100%), eye toxicity (46.2%) and diarrhea (42.3%), all of which were manageable. The median proportional change in ctDNA fraction from baseline to 3 weeks after treatment initiation in pts who achieved PR was significantly less than in pts with stable or progressive disease (0.11 vs. 1.0 vs. 1.6, respectively). Pts with no concurrent RTK/RAS/PI3K and cell cycle alterations in ctDNA were significantly more likely to respond to futibatinib than those with at least one of these alterations (ORR 50% vs. 0%; $P=0.0038$). Acquired gene alterations in ctDNA after progression tended to be more common in pts with *FGFR* amplification (83.3%) than in those with *FGFR* mutation or fusion (60% or 66.7%). **Conclusions:** Futibatinib demonstrated promising efficacy in refractory advanced solid malignancies with *FGFR* alterations in ctDNA with an acceptable toxicity profile. Oncogenic co-alterations detected by ctDNA genotyping may predict primary resistance. Clinical trial information: JapicCTI-194624. Research Sponsor: Japan Agency for Medical Research and Development.

3104

Poster Session

A phase 2 study of the WEE1 inhibitor AZD1775 in *SETD2*-deficient advanced solid tumor malignancies. First Author: Edward Maldonado, University of California San Francisco, San Francisco, CA

Background: AZD1775 is an inhibitor of the WEE1 kinase, leading to loss of genome integrity. Pathogenic *SETD2* mutations lead to genome-wide loss of histone H3K36 trimethylation (H3K36me3) and hypersensitivity to WEE1 inhibition with a synthetic lethal effect. AZD1775 was studied in 2 cohorts of patients: A) Patients (pts) with locally advanced/metastatic solid tumor malignancy other than clear cell renal cell carcinoma (ccRCC) and B) pts with locally advanced/metastatic ccRCC. **Methods:** Eligible pts had a locally advanced/metastatic cancer with progression on ≥ 1 prior systemic therapy (including prior tyrosine kinase inhibitor or checkpoint inhibitor for cohort B), and a pathogenic *SETD2* mutation by CLIA-certified next generation sequencing panel. Pts received AZD1775 at a starting dose of 300 mg PO daily on days 1-5, 8-12 of each 21-day cycle. The primary objective was to determine the objective response rate (ORR) by RECIST 1.1 criteria in each cohort. Planned sample size was 9 pts in each cohort in stage 1 of a Simon two-stage design. Secondary objectives were to determine the clinical benefit rate (CBR) (defined as partial response or stable disease [SD] > 4 months), duration of response (DOR), and safety. Correlative assays include the evaluation of H3K36me3 mark by immunohistochemistry (IHC) in archival tumor tissue. **Results:** Between 05/2019 and 10/2021, 18 pts whose tumor harbored a pathogenic mutation in *SETD2* were enrolled (9/ cohort). The median age was 60 years (range 45–74), ECOG PS 0 in 8 (44.4%). One patient remains on treatment; 17 have discontinued (disease progression, $n = 9$; adverse event, $n = 4$; patient withdrawal, $n = 2$; patient death, $n = 1$). The median duration of treatment was 1.89 months (range 0.75–13.5). There were no confirmed objective responses and therefore enrollment was halted following accrual to stage 1. Tumor regression of any magnitude was observed in 5/17 (29%) evaluable pts. Stable disease was the best overall response in 10/17 (59%) evaluable pts, including 3 pts with SD for > 4 months. One patient with RCC remains on treatment with SD for 14+ months duration. The most common adverse events of any grade were nausea (59%), anemia (41%), diarrhea (41%), and neutropenia (41%). Twelve pts (67%) experienced a Grade ≥ 3 adverse event. Evaluation of H3K36me3 using IHC as an exploratory biomarker is underway. **Conclusions:** AZD1775 given as monotherapy failed to achieve an objective response in *SETD2*-altered RCC and other solid tumor malignancies. However, a subset of pts derived clinical benefit as manifested by tumor regressions and/or durable stable disease. Evaluation of AZD1775 in combination with other DNA damage-inducing agents that cause replication stress may be warranted, potentially with the integration of the H3K36me3 mark as a biomarker for patient selection. Clinical trial information: NCT03284385. Research Sponsor: U.S. National Institutes of Health.

3103

Poster Session

A multicenter, open-label, single-arm, phase 1 dose-escalation and phase 2 dose-expansion study to evaluate the safety, tolerability, and anti-tumor activity of FCN-159 in adults with neurofibromatosis type 1. First Author: Xiaojie Hu, Department of Plastic and Reconstructive Surgery, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University, School of Medicine, Shanghai, China

Background: Neurofibromatosis type 1 (NF1) is a common autosomal dominant genetic disease characterized by elevated RAS-mitogen activated protein kinase (MAPK) signaling that causes tumors to grow along the nerves. There is currently no medical cure for adult patients (pts). Plexiform neurofibromas (PN) is present in 20–50% of NF1 pts and may cause serious complications. FCN-159 is a highly potent anti-tumorigenic agent that functions via selective inhibition of MEK1/2. This study assessed the safety and efficacy of FCN-159 in adult NF1 pts with PN. **Methods:** This was a multi-center, open-label, single-arm phase 1 dose-escalation (data have been published in ASCO 2022, abstract no. 3011) and phase 2 dose-expansion study. Participants with NF1-related PN that was not completely resectable or not suitable for surgery were enrolled in the study to receive FCN-159 monotherapy continuously on a 28-day cycles. Herein, we report the safety and clinical efficacy of adult participants in both phase 1 and phase 2. **Results:** As of November 21, 2022, 82 pts were enrolled, including 19 pts in phase 1 and 63 pts in phase 2. The median follow-up was 10.2 months (range 9.4–11.0 months) at the data cut-off. All pts received more than one dose of FCN-159 and 78 had at least one tumor assessment based on REINS criteria. A total of 26 (33%) pts had achieved partial response (PR) as best response, 51 (65%) pts had stable disease (SD), and only one pt was not evaluable for not meeting the minimum SD requirement of at least 16 weeks. The overall response rate (ORR) was 31.7% (95% CI: 21.9–42.9%). After 6–8 cycles of treatment, 68.2% (15/22) of pts with definite tumor pain (NRS-11 score ≥ 2 points) at baseline had a decrease in pain intensity of at least 2 points at C7/C9 assessment. Pain scores decreased by an average of 2.7 points across all 22 pts. A total of 82 (100%) pts experienced treatment emergent adverse events (TEAEs). The most common TEAEs ($\geq 20\%$) included folliculitis (69.5%), mouth ulcer (47.6%), diarrhea (41.5%), paronychia (41.5%), alopecia (32.9%), elevated lactate dehydrogenase (30.5%), elevated alkaline phosphatase (29.3%), tricuspid insufficiency (26.8%), and mitral insufficiency (26.8%). The most common grade ≥ 3 TEAEs were folliculitis (25.6%), paronychia (4.9%). There were no grade ≥ 4 treatment-related adverse events. One pt (1.2%) experienced a serious adverse event (duodenal ulcer) considered related to the study drug. 9.8% reported TEAEs leading to dose reductions, and 12.2% reported TEAEs leading to discontinuation. No death occurred during the study. **Conclusions:** Overall, FCN-159 has a manageable safety profile and demonstrated evidence of anti-tumor activity in the adult population with NF1-related PN. These promising findings warrant further investigation with long-time follow-up. Clinical trial information: NCT04954001. Research Sponsor: Shanghai Fosun Pharmaceutical Industrial Development Co., Ltd.

3105

Poster Session

RAF-inhibitor rechallenge therapy in BRAF aberrated pan-cancers: RE-RAFFLE study. First Author: Blessie Elizabeth Nelson, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Prior studies have demonstrated clinical benefit with rechallenging the RAF pathway in melanoma with prior exposure to BRAF inhibitors. Purpose of this study was to explore antitumor activity and outcomes of BRAF aberrated solid tumors retreated with RAF inhibitors (RAFI). **Methods:** Between January 2010 and November 2022, 44 pts with BRAF alterations [V600E (42); V600K (1); K601Q (1)] who received RAFI as monotherapy or in combination were rechallenged with a second RAFI with or without other therapies at a single tertiary cancer center. All received therapy as part of standard of care or investigational (INV) regimens. Primary objectives: objective response rate (ORR), overall survival (OS) and progression-free survival (PFS) on rechallenge. **Results:** Median age: 54.5 (25–76) with predominantly Caucasian pts (36; 82%) and males (26; 59%). Tumor types: melanoma (16; 36%), colon (10; 23%), thyroid (4; 9%), brain (4; 9%) and others (10; 23%). Median treatment duration was 7 months (m) for first RAFI (RAF1i) and 2.8m with second RAFI (RAF2i) while median time to RAF2i was 3.3m. Best ORR to rechallenge with RAF2i was partial response (PR) (8; 18.1%), stable disease (SD) (16; 36%) and progressive disease (PD) (20; 45.4%) with 5 PR + 6 SD > 6 m. PRs were seen in thyroid (1 anaplastic; 2 papillary), 1 ovarian, 2 melanoma, 1 cholangiocarcinoma and 1 anaplastic astrocytoma with median duration of response for 2.5m. Of the 36 pts who discontinued RAF1i due to PD, 14% responded (6 PR) to RAF2i. Among 16 pts who had CR or PR on RAF1i, 5 pts had PR with RAF2i. In RAF2i group, of all pts achieving PR ($n = 8$), 5 pts had other intervening therapies prior to RAF2i (immunotherapy [IO]; kinase inhibitors; chemotherapy; INV) while 3 had no interim therapies and both factors did not have significant impact on survival for RAF2i ($p=0.2$). 5 responders received combination with MEKi, while 1 had MEKi + IO and 2 had monotherapy. ORR did not significantly differ between combination and monotherapy group in RAF2i ($p=0.056$). At median follow up of 20m, median OS and PFS from rechallenge was 15.5m and 2.7m. 9 pts had genomic testing post RAF1i (3 tumor; 7 blood) with no new acquired aberrations and persistence of BRAF V600E mutation. Independent prognostic factors for survival at rechallenge compared to RAF1i included inferior outcomes with male gender (HR: 3.05; $p=0.0089$), presence of metastatic sites (HR: 3.12; $p=0.036$), ECOG (1 vs. 0 or 2; HR: 3.50; $p<0.001$) while rechallenge with combination RAF2i had a worse survival impact compared to RAF2i monotherapy (PFS: 11.6m vs 2.7m; HR: 3.6; $p=0.00145$). These findings need to be cautiously inferred due to small sample size. **Conclusions:** Rechallenge with RAFI(s) resulted in a clinically meaningful benefit in $> 50\%$ pts on efficacy (> 6 m in 25%) and survival outcomes. Further prospective studies are warranted to validate these findings and expand re-challenging targeted therapy options in tumor-agnostic BRAF-aberrated cancers. Research Sponsor: None.

3106

Poster Session

Dose optimization of novel BRAF inhibitor FORE8394 based on PK and efficacy results. *First Author: Eric Jeffrey Sherman, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: FORE8394 is a selective inhibitor of class 1 (V600) and 2 (activating non-V600) BRAF alterations that avoids paradoxical MAPK pathway activation. Consistent with the paradigm shift to optimal dosing vs identifying the maximal tolerated dose, integrated pharmacokinetic (PK), genomics, safety, and efficacy data, and exposure-response modeling were used to identify the recommended dose (RD). **Methods:** In a single arm phase 1/2a study, patients (pts) age ≥ 3 years with advanced solid or CNS tumors with BRAF alterations received FORE8394 900-3600 mg/day with or without the PK enhancer cobicistat (cobi) until progression. Efficacy pts had class 1 or 2 BRAF alterations & ≥ 1 post-baseline assessment (mITT); the BRAF V600 MAPKi naïve, non CRC subset provided a homogenous subset to also inform dose selection. PK was evaluated after single and repeated dosing. **Results:** To date, 110 pts (age range 4-86 years) received ≥ 1 dose of FORE8394; 58% had ≥ 2 prior lines of therapy, 25% had prior MAPKi. PK was independent of age or weight. Cobi increased FORE8394 exposure 2-3-fold. Exposure increased with dose, with less than proportional increase at doses > 900 mg BID. Higher Cmax and trough levels were achieved with QD vs BID/TID. Objective (confirmed) responses were observed at all doses; however, objective response rate (ORR) was greatest (50%) at 900mg QD + cobi, with no further increases in ORR at higher doses. Dose-limiting toxicities were only observed at doses ≥ 1500 mg/day + cobi: 1500-1800 mg/day (4) and 2700-3600 mg/day (1). Similarly, treatment-emergent adverse events (TEAEs) $\geq$ Grade 3 (G3) increased at the higher doses. Only 1 pt discontinued FORE8394 due to treatment-related AE (G3 bilirubin; 3600 mg/day). **Conclusions:** Based on the entirety of safety, PK, and efficacy data, the optimal RD of FORE8394 in Phase 2 is 900 mg QD + cobi in pts ≥ 10 years old. This achieved targeted efficacious exposures with robust antitumor activity and favorable safety. This dose optimization is consistent with current guidelines, avoids higher exposure that may lead to higher toxicity and compromise dose intensity. QD dosing also allows for a convenient dosing regimen. A Phase 2 study at the RD is ongoing in pts with recurrent V600E BRAF-mutated primary CNS tumors and advanced solid or CNS tumors with BRAF fusions. Clinical trial information: NCT02428712. Research Sponsor: FORE Biotherapeutics and Plexikon.

Assigned Regimen	Safety	Efficacy (mITT)	Efficacy MAPKi naïve V600, except CRC
Total daily dose FORE8394 (mg) QD to TID ¹	$\geq$ G3 TEAE	ORR	ORR
900-1800	8/18 (44%)	1/13 (8%)	1/3 (33%)
900 + cobi	9/30 (30%)	7/25 (28%)	5/9 (56%)
450 mg BID	4/11 (36%)	4/10 (40%)	2/4 (50%)
900 mg QD	3/8 (38%)	3/6 (50%)	3/3 (100%)
Titration ²	2/11 (18%)	0/9 (0%)	0/2 (0%)
1200-1800 + cobi	28/49 (57%)	4/36 (11%)	2/8 (25%)
2700-3600 + cobi	6/9 (67%)	2/8 (25%)	1/3 (33%)

BID, twice daily; CRC, colorectal cancer; N, total number of pts; QD, once daily; TID, thrice daily. ¹ Does not include 4 pts ≤ 17 years with mg/m² dosing. ² FORE8394 was gradually increased from 450 mg BID based on individual tolerability.

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Poster Session

Phase II study of crizotinib in patients with MET amplification and MET exon 14 deletion: Results from NCI-MATCH ECOG-ACRIN trial (EAY131) sub-protocols C1 and C2. *First Author: Niamh Coleman, St. James's Hospital, Dublin, Ireland*

Background: The NCI-Molecular Analysis for Therapy Choice (MATCH) platform trial enrolled patients with solid tumors, lymphomas, or multiple myeloma to trials of targeted therapies based on matching genomic alterations. Subprotocols C1 and C2 evaluated MET tyrosine kinase inhibitor crizotinib in pts with MET amplification (METamp; C1) or MET exon 14 mutation/deletion (METex14; C2). **Methods:** Pts whose tumors had METamp or METex14 were eligible for C1 and C2, respectively. Results were confirmed by MATCH Oncomine assay if possible; C2 explored METex14 quantification at DNA level retrospectively using cases with sufficient tissue for analysis of DNA mutations surrounding MET exon 14 and control samples with a variable amount of MET exon 14 counts using Anchored Multiplex PCR. Pts in C1 and C2 received crizotinib orally BD daily in 28-day cycles until progression or unacceptable toxicity. Tumor assessment occurred every 2 cycles. Primary endpoint was ORR; PFS; secondary endpoints: 6-month PFS, OS, and predictive biomarkers. **Results:** C1 enrolled 44 pts, of which 28, representing a variety of histologies, were eligible, received treatment, and included in the primary efficacy analysis as prespecified by protocol; GI (n=17) and lung (n=7) were most common. Median age: 67 (range 28-82), 9 pts were women. Median MET copy number was 16.8 (min 7.1, max 78.0). Of 28 pts, 4 had PR; 10 had SD, 13 had PD as best response; disease control rate (DCR) 50% (14/28); one pt was unevaluable. ORR was 14% (4/28, 90% CI: 5.0%-29.8%). Median PFS was 3.4 mo (90% CI: 1.8-3.7); median OS 7.1 mo (90% CI: 5.0-11.5). 4 pts with confirmed PR were lung (n=2), GI (n=1), melanoma (n=1); 1 pt had SD > 6 mo (NSCLC). Most pts had ≥ 1 co-occurring gene alteration (n=27; 96%), TP53 co-mutation most frequently (n=23, 82%); 21 pts had ≥ 3 co-occurring mutations. C2 enrolled 20 pts, 14 evaluable received treatment: GI (n=5); lung (n=6); other (n=3). Median age for the 14 pts was 68 (range 57-78); 6 pts were women, 9 (64%) had ≥ 3 lines of prior therapy. Most pts had ≥ 1 co-occurring gene alteration (n=13; 93%, range 1-4); TP53 co-mutations were frequent (n=7, 50%). Of 14 pts, 2 had PR (both NSCLC); 4 had SD, 4 had PD as best response, and DCR was 43% (6/14). 2 pts had SD > 6 mo (1 lung, 1 bladder). ORR was 14% (2/14, 90% CI: 2.6%-38.5%). Median PFS 2.0 mo (90% CI: 1.4-4.1). On quantification by Met count $\geq 50,000$ mPFS 8.8 months (90% CI: 2.1-NA), MET count $< 50,000$ mPFS 1.7 mo (90% CI: 1.1-3.7). All lung cancer pts with confirmed PR/SD > 6 mo had documented MET count $> 50,000$. Most common reason for permanent treatment discontinuation was disease progression. No new toxicity signals were identified. **Conclusions:** We demonstrate clinical activity using crizotinib across tumors in patients with METamp and METex14. In METex14, differentiating true pathogenic variants from low-level splice variant transcripts may be clinically meaningful. Clinical trial information: NCT02465060. Research Sponsor: U.S. National Institutes of Health.

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Poster Session

A phase 1 study of TPST-1495 as a single agent and in combination with pembrolizumab in patients with advanced solid tumors. *First Author: Susanna Varkey Ulahannan, University of Oklahoma Health Sciences Center, Oklahoma City, OK*

Background: TPST-1495 is a novel oral therapy designed to be a selective dual antagonist of the prostanoid receptors, EP2 and EP4. Through these receptors, PGE2 stimulates tumor growth, suppresses immunity, and supports adaptive resistance to checkpoint inhibitors. In preclinical models, dual EP2/EP4 inhibition with TPST-1495 increased anti-tumor efficacy, reduced immune suppression, and activated immune effector response significantly better than single EP2 or EP4 antagonists and the COX-2 inhibitor celecoxib. **Methods:** In this Phase 1 study, subjects with advanced solid tumors received TPST-1495 in a modified 3+3 design optimizing dose and schedule as monotherapy and in combination with standard dose pembrolizumab. Study objectives included safety, PK/PD, recommended phase 2 dose (RP2D), anti-tumor activity and exploratory biomarkers. AEs were assessed per CTCAE v5 and efficacy per RECIST v1.1. **Results:** TPST-1495 monotherapy was dosed BID (n=11), QD (n=22) or QD days 1-5 every 7 days (n=17) and in combination was dosed QD only with pembrolizumab 200 mg IV q3 weeks (n=24). TPST-1495 doses ranged from 15 mg QD to 100 mg BID. Most subjects had CRC (61%) followed by endometrial (5.4%) and pancreatic (5.4%) cancer. Median prior lines of systemic therapy were 4 (2-10) in monotherapy; 3 (1-8) in combination. The most common treatment related AEs (TRAEs) were diarrhea (22%), abdominal pain (20%), fatigue, and nausea (18% each) for monotherapy and nausea (29%), fatigue (21%) and diarrhea (17%) for combination therapy. The most common Gr 3 TRAEs were anemia (6.0%) in monotherapy, and ALT/AST increased and fatigue (4.2% each) in combination. No Gr 4/5 TRAEs were reported. For mono vs combo cohorts, the median time on study was 1.9 mo (0.2-10.2) vs 2.7 mo (0.5-10.4) and the disease control rate was 43% (19/44) vs 43% (9/21) with 1 PR in a combination subject with MSS CRC. Pharmacodynamic activities included on-treatment increases in urine PGE2 metabolites and drug-dependent TNF- α rescue in an ex-vivo whole blood PGE2 challenge assay. The RP2D is 50 mg QD for mono and in evaluation for combo therapy. In a subject with endometrial cancer with 22% tumor shrinkage and 222+ days on combination therapy paired biopsies showed high COX-2 expression in the TME at baseline and increased CD8+ and CD8+GrB T cell infiltration on treatment. **Conclusions:** PGE2 is an important target for cancer and immunotherapy but remains ineffectively drugged. TPST-1495 is a novel oral therapy that inhibits signaling only at the tumor promoting EP2/EP4 receptors. In patients with heavily treated solid tumors, primarily MSS CRC, TPST-1495 had pharmacodynamic activity, a manageable safety profile, and a potential signal of activity consistent with the preclinical data and IO combination mechanism. A combination therapy cohort in endometrial cancer is underway. Updated results and biomarker work will be presented. Clinical trial information: NCT04344795. Research Sponsor: Tempest Therapeutics.

3109

Poster Session

First-in-human phase 1 trial of the safety, tolerability, pharmacokinetics, and preliminary anti-tumor activity of WSD0922-Fu: Initial report from dose escalation cohort. *First Author: Sani Haider Kizilbash, Mayo Clinic, Rochester, MN*

Background: WSD0922-Fu is an oral, central nervous system (CNS)-penetrant, small molecule, ATP non-competitive, reversible EGFR inhibitor which potently inhibits EGFR aberrations specific to non-small cell lung cancer (NSCLC) and high-grade astrocytoma (HGA). We report initial results of a first-in-human phase 1 dose-escalation trial (NCT04197934) in patients with EGFR aberrant recurrent HGA and NSCLC. **Methods:** Adult patients with either recurrent EGFR mutant NSCLC with CNS metastases or recurrent EGFR mutant and/or EGFR amplified HGA were enrolled. WSD0922-Fu was orally administered, and dose escalated in cohorts based on a standard 3+3 design to determine the maximum tolerated dose (MTD). Toxicities were graded per CTCAE v5.0 and preliminary efficacy was based on modified RANO criteria or RECIST 1.1 as appropriate. **Results:** 25 patients (17 HGA, 8 NSCLC) were enrolled and treated in six cohorts (40 mg once daily to 320 mg twice daily, 28-day cycles). The median age was 57 years (range 39-75 years). 24% were female and 36% were ECOG 0. For patients with HGA, all patients were previously treated with radiation and temozolomide; the median number of prior lines of systemic therapy was 1 (range 1-4). For patients with NSCLC, all patients were previously treated with an EGFR inhibitor (prior osimertinib 88%); the median number of prior lines of systemic therapy was 1.5 (range 1-6). The median duration of exposure to WSD0922-Fu among all patients was 54 days (range 2-258 days). The most common ($\geq 25\%$) treatment-related adverse events included fatigue (68%), acneiform rash (68%), diarrhea (52%), nausea (48%) and pruritis (28%). The frequency of severe AEs was dose dependent. The most common Grade 3+ AEs ($\geq 10\%$) included lymphopenia (16%), acneiform rash (12%), headache (12%) and diarrhea (12%). The MTD was defined as 160 mg twice daily. At Cycle 1 Day 15 for patients treated at this dose level, the mean terminal elimination half-life (%CV) in the plasma was 31.6 h (102%) (median 14.5 h; range 6.2-78.7 h). The mean Cmax, Tmax, oral clearance at steady state, and AUC (0-12 h) (%CV) were 4513 ng/mL (50%), 2.0 hr (69%), 6.9 L/hr/m² (42%), and 28084 h*ng/mL (52%), respectively. Oral clearance at steady state was inversely related with dose, suggesting either inhibition or saturation of clearance processes. Among patients treated at MTD or higher dose levels and with available response data, 100% (5/5) of patients with NSCLC demonstrated clinical benefit (SD + PR) while 60% of patients had partial responses (intracranial and extracranial). Furthermore, prolonged stable disease (9 cycles) was observed in a patient with EGFRvIII mutant GBM. **Conclusions:** The MTD for WSD0922-Fu monotherapy is 160 mg BID. Preliminary efficacy was observed in patients with osimertinib-resistant NSCLC and EGFRvIII mutant HGA. Enrollment to expansion cohorts is ongoing. Clinical trial information: NCT04197934. Research Sponsor: Wayshine Biopharma; R01 FD-R-07288 (U.S. Food & Drug Administration (FDA) Office of Orphan Products Development (OOPD)).

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Poster Session

First-in-human (FIH) phase I dose escalation study (part A) of the first oral allosteric modulator of phosphoinositide 3-kinase inhibitor delta (PI3Kδ) rognolisib in patients with advanced cancer and dose confirmation in uveal melanoma (part B). *First Author: Anna Maria Di Giacomo, Center for Immuno-Oncology, University Hospital of Siena, Siena, Italy*

Background: The highly selective oral allosteric modulator of PI3Kδ, rognolisib (IOA-244), blocks the activity of PI3Kδ -dependent signalling, in both tumour cells and Tregs. **Methods:** Part A explored the continuous daily dosing of rognolisib at 10, 20, 40 and 80 mg in patients (pts) with solid tumours and Follicular Lymphoma (FL). Part B consists of dose confirmation cohorts, including uveal melanoma (UM) pts. Primary objective: safety of the anticipated biologically effective dose (BED), or the recommended phase 2 dose (RP2D). Secondary objectives: PK; PD (e.g., inhibition of CD63 expression on basophils, changes in immune cell subsets in peripheral blood); RECIST 1.1. or Lugano-based responses; PFS and OS. Exploratory studies: phenotypic changes in circulating immune cells by Cytometry by Time of Flight (CyTOF); response assessments by radiomics; analysis of circulating protein signatures via Olink proteomic. **Results:** Part A Solid Tumour (completed): Sixteen pts were treated in 4 cohorts, each with 4 pts. Pts characteristics: uveal melanoma (9/16; 56%), cutaneous melanoma (5/16; 31%) and pleural mesothelioma (2/16; 13%). Only Grade 1 and 2 AEs by CTCAE v5 were observed, including 2 cases of transient (lasting < 24 hrs) diarrhoea and 2 of AST/ALT elevation. Part A FL Cohort (completed): 8 pts were treated at 20 mg (n=4) and 80 mg (n=4). Grade 3 toxicities were transient and observed in 2/8 (25%) pts. 2/4 pts (50%) at the 80 mg had PR as per Lugano criteria. Neither in the solid tumour nor in the haematology pts treatment-emergent adverse events (TEAE) led to study drug discontinuation, immune related toxicity, or a Dose Limiting Toxicity. Subgroup evaluation: UM pts (Part A and Part B): 24 pts (Part A: 9 pts; Part B ongoing: 15 pts), of which 18 pts treated at 80 mg QD (RP2D). Mean time on treatment: 8.6 mo (range: 1.0-27.9 mo). ORR (RECIST 1.1): PR: 1/20 (5%); SD: 16/20 (80%). Median OS for Part A: 20.8 mo (5/9 with 4 pts alive); Part B: not determined; 1-year OS rate: Part A 66.7%; Part B: ongoing. Exploratory Investigations: Radiomics-based evaluation of CT images in pts with solid tumors assessed each metastatic organ, detecting mixed responses; peripheral proteomic evaluation detected changes in several cytokines and chemokines; CyTOF detected reduction in circulating Tregs associated with increased activated effector CD8⁺ T cells. **Conclusions:** Rognolisib is well tolerated at the 80 mg dose, shows signs of efficacy and induces phenotypic changes in the circulating immune cells. As best response at the RP2D, the most robust anti-tumour activity was observed in FL (50% PR) and UM pts (5% PR; 80% SD). Clinical trial information: NCT04328844. Research Sponsor: iOncura SA.

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Poster Session

Discovery of gene fusions in driver-negative NCI-MATCH screening samples. *First Author: Stefan T Kaluziak, Massachusetts General Hospital/Harvard Medical School, Boston, MA*

Background: NCI-MATCH aimed to determine the treatment efficacy of identifying actionable genetic alterations, irrespective of cancer histology, and to tailor treatment to the putative molecular drivers of tumors. Leveraging next-generation sequencing (NGS) and ThermoFisher's OncoPrint assay, this phase II trial genotyped 5,540 patient samples during active screening. Reviewing the genotyping statistics, we noted that NCI-MATCH identified fusions in 164 tumors, only 2.96%. This result is substantially lower than expected, given that clinical assays used at MGH's and Yale's diagnostic laboratories identified fusions in 8.5% of the 7,500 sequenced cases, 2.5% of which were novel. Notably, the OncoPrint assay, based on multiplexed PCR, is unable to detect driver fusion events when either of the gene partners are unknown, or a novel breakpoint is involved. Cross-referencing identified fusions from MGH's cohort with OncoPrint's primers, 5-30% of these fusions were potentially missed, suggesting that we could detect up to 30% more fusions than originally identified. Developed at MGH's Molecular Diagnostics Laboratory, Anchored Multiplex PCR (AMP) interrogates 138 known fusion partners, enabling unbiased fusion detection when only one partner is known. With a high likelihood of identifying novel fusion drivers using AMP technology, we sequenced 663 cases that had no identified mutations of interest (MOI) from the NCI-MATCH cohort. **Methods:** A total of 200ng of RNA per sample was shipped from ECOG-ACRIN's repository at MD Anderson Cancer Center to MGH (n = 319) and Yale (n = 349). Samples were processed with ArcherDX's FusionPlex Pan Solid Tumor v2 kit and sequenced on the NextSeq500 with 150 base pair (bp) Paired-End (PE) kits. Data analysis was completed with ArcherDX's analytics platform in conjunction with custom Python and R code. Reported fusions were manually verified on a case-by-case basis. All statistical tests were conducted in R. **Results:** Of the cases sequenced, most (663/693, 95.7%) were successfully processed with AMP. We identified 142 cases with at least one gene fusion out of 663 MOI-Negative cases (21%; 95% CI [18%, 25%]), with 90 as unique fusions, significantly more than the 8.5% observed at MGH (P < .001). Of the 142 fusion-positive cases, 36 have potentially actionable driver events, 27 contain novel fusions not previously described, and in 63 cases no drugs are available to target either component of the fusion. Additionally, we identified fusions in (12/34, 35%) Cholangiocarcinoma and (38/101, 37.6%) Sarcoma cases, 9 and 3 of which were potentially actionable respectively. **Conclusions:** As hypothesized, we identified fusions that the NCI-MATCH screening had missed, detailing sequencing technology improvement that could be broadly applicable to many clinical laboratories sequencing tumors. Clinical trial information: NCT02465060. Research Sponsor: U.S. National Institutes of Health.

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Poster Session

Comprehensive genomic profiling before the first-line setting versus after the completion of standard of care in patients with previously untreated advanced solid tumors: The prospective FIRST-Dx study. *First Author: Junichi Matsubara, Department of Therapeutic Oncology, Graduate School of Medicine, Kyoto University, Kyoto, Japan*

Background: Precision oncology using the comprehensive genomic profiling (CGP) test by next-generation sequencing has been introduced into clinical practice. In Japan, only 6.8% of patients accessed the precision treatment because it is only indicated after standard of care (SoC). FoundationOne CDx (F1CDx) is the software as a medical device for the detection of actionable and druggable genomic alterations in 324 genes. F1CDx has the function of both CGP test and companion diagnostics (CDx). Therefore, F1CDx could be ideally used in the early stages of treatments. In this study, we investigated the clinical utility of F1CDx in previously untreated patients with metastatic or recurrent solid tumors. **Methods:** We conducted a multi-institutional, prospective study in six hospitals in Japan (FIRST-Dx study). Chemotherapy-naïve adult patients with advanced solid tumor (GI, Lung, Breast, GYN, Melanoma) and ECOG performance status of 0-1 were enrolled. Primary endpoint was the ratio of patients with actionable mutation. Secondary endpoints were the ratio of patients with druggable mutation, molecular-based recommended therapy (MBRT), gene alteration with CDx, CGP success rate, and patients who actually received MBRT. **Results:** 183 patients were enrolled between May 2021 and February 2022, 180 patients with median (range) age 64 (23-88) years underwent F1CDx test (92 men, lung [n=28], colon/small intestine [n=27], pancreas [n=27], breast [n=25], biliary tract [n=20], gastric [n=19], uterus [n=12], esophagus [n=10], ovary [n=6], and skin melanoma [n=6]). 175 tests were successful (CGP success rate: 97%), and 172 patients were evaluable for endpoint analyses with follow-up through July 2022. Actionable and druggable cancer genomic alterations were found in 172 patients (100.0% [95% CI: 97.9-100.0%]) and 109 patients (63.4% [95% CI: 55.7-70.6%]), respectively. MBRT determined by molecular tumor board was found in 105 patients (61.0% [95% CI: 53.3-68.4%]). Genomic alterations included in the CDx list of F1CDx were found in 49 patients (28.5% [95%CI: 21.9-35.9%]) in the tumor-agnostic setting. After a median follow-up of 7.9 months, 34 patients (19.8% [95% CI: 14.1-26.5%]) actually received MBRTs. Twenty-six patients received evidence level A MBRT, two received evidence level B MBRT, and six received evidence level C MBRT. **Conclusions:** We showed that 61% of the patients with previously untreated advanced cancer had MBRTs found by F1CDx and 20% of them actually received MBRTs early in their disease course. CGP test before SoC for advanced solid tumors could provide better opportunities for receiving MBRTs than after completion of SoC. Our data would recommend expanded approval with respect to the timing of CGP test for patients with previously untreated advanced solid tumors. Clinical trial information: UMIN000042408. Research Sponsor: Chugai Pharmaceutical Co., Ltd.

3113

Poster Session

Impact of patient travel time on disparities in precision oncology clinical trials. *First Author: Yuji Uehara, Department of Experimental Therapeutics, National Cancer Center Hospital, Tokyo, Japan*

Background: Precision oncology revolutionizes cancer care, allowing personalized treatments to improve outcomes. Precision oncology often entails participation in genotype-matched clinical trials, resulting in referrals from institutions providing comprehensive genomic profiling (CGP) testing to those conducting these trials. It is still being determined whether there are regional disparities in precision oncology. **Methods:** We conducted a retrospective review of 1127 patients (pts) referred to National Cancer Center Hospital (NCCCH) for participation in genotype-matched clinical trials following CGP testing performed between June 2020 and June 2022. Travel distance and time were calculated utilizing Google Maps from the patient's residence to the NCCCH. A total of 23 covariates were preselected and dichotomized per previous research or expert consensus as follows: age, sex, performance status, body mass index, tumor type, number of lines of prior therapies, number of metastatic sites, liver metastases, brain metastases, pleural or peritoneal effusions, biopsiality, neutrophil, hemoglobin, platelet, albumin, creatinine, total bilirubin, LDH, AST, CRP, place of residence (urban vs. rural), referring hospitals, and household income. All independent variables associated with participation in genotype-matched trials (P < 0.20) were included in a multivariable model, and variable importance was calculated using a machine learning (ML) model (gradient-boosted decision tree). **Results:** A total of 127 (11%) of 1127 pts were enrolled in the genotype-matched trials. Of 127 pts, 82 (65%) and 45 (35%) participated in phase 1 trials and phase 2/3 trials, respectively. The overall median travel distance and time were 38 km (interquartile range [IQR] 21-107) and 55 minutes (IQR 35-110), respectively. In multivariable regression, travel distance (≥100km vs. <100km) was not associated with the proportion of genotype-matched trial participation (9% vs. 12%; odds ratio [OR], 0.68; 95% confidence interval [CI], 0.42-1.07; P = 0.11); however, in pts with travel time ≥120 minutes, the proportion of genotype-matched trial participation was significantly lower than those with travel time < 120 minutes (7% vs. 13%; OR, 0.54; 95% CI, 0.32-0.89; P = 0.019). The proportion of genotype-matched trial participation decreased as travel time increased from <40 minutes to 40-120 minutes to ≥120 minutes (13% vs. 12% vs. 7%, respectively; OR, 0.67; 95% CI, 0.50-0.88; P = 0.006). Travel time was also identified as an important factor in the ML model, whereas low-income and residence in rural areas were of minor importance. **Conclusions:** Patients with travel time ≥120 minutes were less likely to participate in genotype-matched clinical trials than those with travel time <120 minutes. Regional disparities may be creating inequities in precision oncology, which warrant immediate action, including decentralization of clinical trials. Research Sponsor: None.

3114

Poster Session

The relationship between the change with neoadjuvant chemotherapy in the tumor-infiltrating lymphocyte (TIL) expressions and pathological response in breast cancer patients. *First Author: Ahmet Bilici, Istanbul Medipol University, Medical Faculty, Department of Medical Oncology, Istanbul, Turkey*

Background: Many prognostic biomarkers for survival have been studied in the neoadjuvant setting for locally advanced breast cancer (LABC). Our study assessed the correlation between the change in tumour-infiltrating lymphocytes (TIL) before and after neoadjuvant chemotherapy (NAC) in breast tissue and its impact on survival in patients with LABC. **Methods:** Eighty-four LABC patients were retrospectively analysed in this study. TIL was assessed by means of immunohistochemistry (Eclipse Ni, Nikon, Japan) in paraffin-embedded blocks obtained by core-needle biopsy or surgical specimen with respect to the 'TIL working group' criteria. **Results:** TIL scores were grouped as 0%, <10%, 10-50%, and >50%, the median TIL percentage was 17.5% before NAC and 5% after NAC, and the difference was statistically significant ($p<0.001$). Postop-Ki-67 ($p=0.005$), molecular subtype ($p=0.027$), pre-NAC TIL score ($p=0.006$), post-NAC TIL score ($p<0.001$), postop-Ki-67 ($p=0.005$) and preoperative residual cancer burden tumour-infiltrating lymphocyte (RCB-TIL) ($p<0.001$) were significantly correlated with pCR. Higher TIL scores were significantly associated with higher PCR rates. Univariate analysis for disease-free survival (DFS) and overall survival (OS) revealed that postop-Ki-67 level and presence of pCR and postoperative Ki-67 score ($p=0.031$) were significant prognostic factors, respectively. The independent prognostic factor for DFS were postop-Ki-67 score ($p=0.012$, RR: 6.16, 95% CI: 1.48-9.12), post-NAC TIL score ($p=0.041$, RR: 0.42, 95% CI: 0.16-1.06) and the presence of pCR ($p=0.038$, RR: 0.10, 95% CI: 0.01-0.87). Logistic regression analysis showed that a preoperative Ki-67 score greater than 14% ($p=0.001$, OR: 4.55; 95% CI: 0.11-1.49), a postoperative Ki-67 score equal to or lower than 14% ($p=0.011$, OR: 1.10; 95% CI: 0.42-2.29), preop-grade 3 ($p=0.01$, OR: 2.65; 95% CI: 0.85-3.14), low postop-TIL score ($p<0.001$, OR: 3.14; 95% CI: 0.79-4.11) were significant predictive factors for pCR. **Conclusions:** Our study confirms the hypothesis that TIL expressions may be therapeutic targets, especially in specific molecular breast cancer subtypes. Research Sponsor: None.

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Poster Session

Molecular classification of cancer site of origin and lineage. *First Author: Nicholas Robert Rydzewski, National Institutes of Health, National Cancer Institute, Bethesda, MD*

Background: Histopathologic assessment has been the primary modality for the diagnosis of human cancers since the 19th century, and to this day remains the mainstay of diagnosis, risk stratification and staging. While the field has made significant advances, the "art of pathology" relies heavily on subjective visual inspection, with significant levels of inter-observer variability and sometimes uncertainty in diagnosis. Advances in next-generation sequencing have ushered in new molecular diagnostic frameworks that can improve accuracy, critical in deciding treatment. **Methods:** We utilized machine learning (XGBoost) and developed comprehensive molecular classifiers for cancer site of origin (22 classes i.e. breast, prostate, lung, etc.) and cancer lineage (8 classes i.e. adenocarcinoma, squamous cell carcinoma, etc.) to augment traditional histopathologic assessment. These models were trained on a total of 8,249 tumor samples. We then evaluated performance using a large independent validation cohort consisting of 10,376 samples. While 8,886 of these were primary tumors from 97 different datasets, uniquely we also assessed performance in 1,490 metastatic tumors from 17 datasets. Pathologic diagnosis of metastatic tumors can be more difficult due to de-differentiation, but metastatic samples for molecular profiling are difficult to obtain and were only rarely included in previous efforts. **Results:** After model training, we locked the site of origin and lineage expression-based models and next evaluated performance on our independent validation cohort. Overall accuracy was 92.5% for cancer site of origin and 97.2% for cancer lineage on validation. Accuracy among primary site samples was higher than for metastatic samples (93.4%, and 86.8% for cancer site of origin, respectively; 97.5% and 95.7% for cancer lineage, respectively). However, accuracy jumped to an astounding 98-99% for both site of origin and lineage in both primary and metastatic samples where the signatures were highly confident, encompassing the majority of cases. Our unique approach in evaluating site of origin and lineage separately allowed us to identify a lineage differentiation score that was associated with small cell lung and neuroendocrine prostate tumors (AUC 0.955 and 0.833, respectively), as well as worse survival across most evaluable tumor types. **Conclusions:** To our knowledge, this is the largest and most comprehensive validation of platform-independent site of origin/lineage classifiers to date. Our approach can be applied to any existing research or commercial RNA-seq assay, and provides an objective and quantifiable confidence measurement that is correlated with accuracy. This allows for nuanced interpretation of high vs. low confidence predictions, which can complement and potentially even help guide traditional histopathologic assessment in cancer research, clinical trial design, and ultimately clinical practice. Research Sponsor: U.S. National Institutes of Health; Doris Duke Charitable Foundation; Department of Defense; Shared research services at the UWCCC are supported by Cancer Center Support Grant P30 CA014520.

3115

Poster Session

Talazoparib (Tala) in patients (pts) with solid tumors with BRCA1/2 mutation (mut): Results from the Targeted Agent and Profiling Utilization Registry (TAPUR) study. *First Author: Gordan Srkalovic, Herbert-Herman Cancer Center, Michigan Cancer Research Consortium, Lansing, MI*

Background: TAPUR is a phase II basket study evaluating antitumor activity of commercially available targeted agents in pts with advanced cancers with specific genomic alterations. Results in a cohort of pts with solid tumors with *BRCA1/2* mut treated with Tala are reported. **Methods:** Eligible pts had measurable disease, ECOG performance status (PS) 0-2, adequate organ function, and no standard treatment (tx) options. Genomic testing was performed in CLIA-certified, CAP-accredited site selected labs. Pts received 1 mg of Tala orally daily until disease progression. Primary endpoint was disease control (DC) per investigator defined as complete (CR) or partial (PR) response or stable disease (SD) of at least 16+ weeks (wks) duration (SD16+) per RECIST v1.1. The hypothesized null DC rate of 15% was evaluated by a 1-sided exact binomial test (alpha 0.10; 82% power). Secondary endpoints were progression-free survival (PFS), overall survival (OS), duration of response (DOR) and SD, and safety. DOR is defined as time from pt's first documented objective response (OR) to progressive disease (PD). Duration of SD is defined as time from tx start to PD. **Results:** 28 pts with 16 solid tumors (6/28 pts had lung cancer) with *BRCA1* (n=9), *BRCA2* (n=16), or *BRCA1/2* (n=3) mut were enrolled from Dec 2019 to Sept 2021. All pts were included in efficacy analyses. Demographics and outcomes are shown. 1 CR, 9 PR and 6 SD16+ were observed for a DC rate of 57% (1-sided 90% CI: 43% to 100%) and an OR rate of 36% (95% CI: 19% to 56%); the null hypothesis of a 15% DC rate was rejected ($p<0.001$). 11/16 pts with OR or SD16+ had a *BRCA2* mut, 4 had *BRCA1* mut, and 1 had both. The pt with a CR (duration of 93 wks) had non-melanoma skin cancer, with *BRCA2* and *ATM* muts, and was microsatellite instability high with 41 muts per megabase. Pts with PR had various solid tumors; 6/9 pts had *BRCA2* mut, 2 had *BRCA1* mut, 1 had both. Of pts with DC, 11 had tumor types for which PARP inhibitors are not yet FDA approved. Median duration of PR was 20 wks (range, 11-80). 10/16 pts with DC had a co-alteration in the 24 homologous recombination-related genes examined, mainly *ATM* (3) or *ARID1A* (2). 13 pts had ≥ 1 grade 3 tx-related adverse or serious adverse events including: anemia, AST or bilirubin increase, hyponatremia, nausea, vomiting, neutrophil, platelet, or white blood cell decrease. **Conclusions:** Tala demonstrated antitumor activity in heavily pretreated pts with advanced solid tumors with *BRCA1/2* mut. Additional study is warranted to confirm the efficacy of Tala in non-breast, non-ovarian cancer pts with *BRCA1/2* mut. Clinical trial information: NCT02693535. Research Sponsor: Pfizer; AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly and Company, Genentech, Merck, Seagen.

Demographics and efficacy outcomes (N=28).		
Median (Med) age, years (range)	66 (32-80)	
ECOG PS, %	0	8 (29)
	1	19 (68)
	2	1 (4)
Prior systemic regimens, %	0-2	11 (39)
	≥ 3	17 (61)
DC rate, % (OR and SD16+) (1-sided 90% CI)	57 (43, 100)	
OR rate, % (95% CI)	36 (19, 56)	
Med PFS, wks (95% CI)	24 (8, 39)	
Med OS, wks (95% CI)	71 (32, inf)	

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Poster Session

Temsirolimus (T) in patients (pts) with solid tumors with PIK3CA mutation (mut): Results from the Targeted Agent and Profiling Utilization Registry (TAPUR) study. *First Author: Carmen Julia Calfa, Sylvester Comprehensive Cancer Center, University of Miami Miller School of Medicine, Miami, FL*

Background: TAPUR is a phase II basket study evaluating antitumor activity of commercially available targeted agents in pts with advanced cancers with genomic alterations. Results in cohorts of pts with breast cancer (BC) and other solid tumors with *PIK3CA* mut treated with T are reported. **Methods:** Eligible pts had BC or other solid tumors, measurable disease, ECOG performance status (PS) 0-2, adequate organ function, and no standard treatment (tx) options. Genomic testing was performed in CLIA-certified, CAP-accredited site selected labs. After antihistamine pre-tx, 25 mg of T was infused over 30-60 minutes once weekly until disease progression. Primary endpoint was disease control (DC), defined as complete or partial (PR) response, or stable disease of at least 16+ weeks (wks) duration (SD16+) per RECIST v1.1. For the BC cohort, Simon's optimal 2-stage design with null DC rate of 15% vs. 35% (power=0.85, $\alpha=0.10$) was used with stage 1 (n=10) stopping for futility if $< 2/10$ pts had DC. Low accruing histology-specific cohorts with *PIK3CA* and T tx were collapsed into 1 histology-pooled (HP) cohort. For the HP cohort, the hypothesized null DC rate of 15% was evaluated by a 1-sided exact binomial test with $\alpha=0.10$. Secondary endpoints were progression-free survival (PFS), overall survival (OS), and safety. **Results:** 12 pts with *PIK3CA* mut with BC and 29 pts with *PIK3CA* mut in other solid tumors (across 9 tumor types) were enrolled. 2 pts (1 in each cohort) were found to be ineligible after enrolling and were not included in efficacy analyses. Demographics and outcomes for each cohort are shown. At the end of stage 1 in the BC cohort, 1 PR was observed for DC and OR rates of 9%; the cohort was closed for futility ($p=0.83$). For the HP cohort, 3 PR and 5 SD16+ were observed for DC rate of 29% ($p=0.049$) and OR rate of 11%; the null hypothesis was rejected. Cancer types in pts with OR or SD16+ included cervical, ovarian and head/neck; most common muts were H1047R/L (3), E545K (2) and E542K (2). 1 pt with ovarian and H1047R has ongoing PR at 86 wks. 11/41 pts had ≥ 1 tx-related grade 3-4 adverse or serious adverse event, including anemia, headache, hyperglycemia, hypertension, hypertriglyceridemia, mucositis oral, lymphocyte, neutrophil or platelet count decrease, pneumonitis, and sepsis. **Conclusions:** Although T does not appear to have antitumor activity in pts with BC with *PIK3CA* mut, it does show antitumor activity in pts with other solid tumors with *PIK3CA* mut and warrants further study. Clinical trial information: NCT02693535. Research Sponsor: Pfizer; AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly and Company, Genentech, Merck, Seagen.

Demographics (N=29 HP; 12 BC) and efficacy outcomes (n=28 HP; 11 BC).			
	HP (n=29)	BC (n=12)	
ECOG PS, %	0	15 (52)	6 (50)
	1	13 (45)	6 (50)
	2	1 (3)	0 (0)
Prior systemic regimens, %	1-2	6 (21)	1 (8)
	≥ 3	23 (79)	11 (92)
DC rate, % (OR and SD16+) (90% CI)	29 (17, 100)		
OR rate, % (95% CI)	11 (2, 28)		
Median PFS, wks (95% CI)	8 (8, 16)		
Median OS, wks (95% CI)	27 (20, 45)		

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Poster Session

The genomic, transcriptomic, and immunological landscape of TROP2 in solid tumors. *First Author: Asaad Trabolsi, Jackson Memorial Hospital/ University of Miami, Miami, FL*

Background: TROP2 expression is associated with decreased overall survival in colorectal and pancreatic cancers. The antibody drug conjugate sacituzumab delivers a SN38 toxic payload to TROP2-expressing cells and is approved for the treatment of breast cancer and urothelial carcinoma. We aimed to explore the genomic and immunological landscape of *TACSTD2* (TROP2-encoding gene) in different solid tumors. **Methods:** Tumors from breast cancer (BC, N=11,246), colorectal carcinoma (CRC, N= 15,425), liver cancer (LC, N=433), pancreatic cancer (PC, N=5,488) and urothelial carcinoma (UC, N=5,488) were assessed at Caris Life Sciences (Phoenix, AZ) with NextGen Sequencing of DNA (592-gene or whole exome) and RNA (whole transcriptome). PD-L1 (SP142; Positive (+): $\geq 2+$, $\geq 5\%$) expression was assessed by IHC. When investigating the genomic landscape, mutation prevalence was calculated for pathogenic SNVs/indels. *TACSTD2*-High (H) and -Low (L) expression was defined as top and bottom quartile of *TACSTD2* transcripts per million, respectively. A transcriptomic signature predictive of response to immunotherapy was applied (T cell-inflamed score [Bao, 2020]). tests were applied as appropriate, with P-values adjusted for multiple comparisons ($p < .05$). Real-world overall survival data was obtained from insurance claims and Kaplan-Meier estimates were calculated for molecularly defined subpopulations of patients. **Results:** Compared to *TACSTD2*-L, *TACSTD2*-H tumors had a higher prevalence of *TP53* mutations in BC (*TACSTD2*-H 59% vs -L 48%), CRC (77% vs 71%), LC (43% vs 23%) and PC (83% vs 69%), whereas UC *TACSTD2*-H had a lower prevalence (54% vs 67%, $p < .05$ for all). *TACSTD2*-H tumors had a higher rate of *KRAS* mutations in CRC (55% vs 38%, $p < .05$) and PC (96% vs 78%, $p < .05$). In CRC, the percentage of *KRAS* mutations that were G12C was higher in *TACSTD2*-H (7.3% vs 6.4%, $p < .05$). *TACSTD2*-H tumors had a higher rate of *ARID1A* mutations in CRC (6.7% vs 10%, $p < .05$) and UC (29 vs 20%, $p < .05$). A higher prevalence of PD-L1+ tumors was observed in CRC *TACSTD2*-H (6.4 vs 3.9%, $p < .05$) and the opposite pattern was observed in UC (16% vs 37%, $p < .05$). *TACSTD2*-H tumors were more frequently T cell-inflamed across investigated cancers (BC: *TACSTD2*-H 36% vs -L 19%, CRC: 29% vs 14%, LC: 54% vs 10%, PC: 42% vs 20%, UC: 32% vs 28%, all $p < .05$). *TACSTD2*-H was associated with worse overall survival in PC (HR 1.31 [1.19-1.44], $p < .001$), BC (HR 1.13 [1.03-1.23], $p < .007$) and CRC (HR 1.33 [1.24-1.42], $p < .001$), while this association was not observed in UC (HR .98 [.86-1.12], $p = .75$) or LC (HR 1.14 [.82-1.57], $p = .44$). **Conclusions:** The association of *TACSTD2* expression with *KRAS*, *TP53* and *ARID1A* mutations and T cell-inflamed tumors (ICI responsive) should be considered as possible combination therapies with TROP2 targeting antibody drug conjugates are investigated. Research Sponsor: None.

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Poster Session

Pan-cancer diagnostic proteomic signature of tissue-of-origin (TOO) using data-independent acquisition mass spectrometry (DIA-MS) from 1289 human tissue samples. *First Author: Emma Boys, ProCan, Children's Medical Research Institute, Faculty of Medicine and Health, The University of Sydney, Westmead, Australia*

Background: Accurate tumour classification based upon tissue of origin (TOO) remains important to guide treatment selection and prognosis but can be challenging in patients with poorly differentiated malignancy, cancer of unknown primary (CUP) or those with prior malignancy. Data-independent acquisition mass spectrometry (DIA-MS)-based proteomics is emerging as a potential clinical diagnostic and prognostic tool. We aimed to develop a protein-based signature to identify histological subtype and adenocarcinoma TOO using DIA-MS data obtained from a pan-cancer study of human tissue samples as an adjunct to histopathological assessment in challenging clinical scenarios. **Methods:** We performed DIA-MS-based proteomic profiling of 795 fresh frozen tumour and 494 tumour-adjacent normal samples from the Victorian Cancer Biobank in a clinically orientated workflow. We filtered the cohort to include tumour types relevant to CUP. Protein quantification was derived from raw peptide intensity data. Random forest classifiers to identify histological subtype and adenocarcinoma TOO were subsequently trained and tested using 70% and 30% of the data respectively. Evaluation metrics included top-k accuracy (predicting how often the correct class is among the top k predicted classes) and area under the receiver operating curve (AUROC) (one-versus-rest) $\pm$ 95% confidence interval. **Results:** The final tumour cohort consisted of 427 tumour samples representing eight histological subtypes (adenocarcinoma, germ cell tumour, lymphoma, melanoma, renal cell carcinoma, sarcoma, squamous cell carcinoma, thyroid carcinoma) and seven adenocarcinoma TOO (breast, colorectal, liver, lung, ovary, pancreas, prostate). From 9,051 quantified proteins, 83 were identified with potential utility at identifying histological subtype and adenocarcinoma TOO for use in machine learning models. The histological subtype model identified cancer subtype in the test set with top-1 and top-2 accuracy of 0.95 $\pm$ 0.03 and 0.98 $\pm$ 0.02 respectively. Average test AUROC over all cancer types (n=8) was 0.98 $\pm$ 0.02. The adenocarcinoma TOO model identified tumour TOO in the test set with top-1 and top-2 accuracy of 0.88 $\pm$ 0.07 and 0.95 $\pm$ 0.04 respectively. Average test AUROC over all adenocarcinoma TOO (n=7) was 0.97 $\pm$ 0.02. **Conclusions:** Our clinically orientated DIA-MS-based proteomic workflow and supervised machine learning can identify protein signatures that classify histological subtype and TOO in tumour samples with high accuracy. This technology may assist diagnostic classification of cancer in challenging clinical scenarios, such as CUP. Research Sponsor: E.B. is supported by the ICPMR Jerry Koutts Scholarship and the Royal Australasian College of Physicians Arnott Research Entry Scholarship in Cancer Research; Royal Australasian College of Physicians; ICPMR Jerry Koutts Scholarship; ProCan is supported by the Australian Cancer Research Foundation, Cancer Institute New South Wales (NSW) (2017/TPG001, REG171150), NSW Ministry of Health (CMP-01), The University of Sydney, Cancer Council NSW (IG 18-01), Ian Potter Foundation, the Medical Research Futures Fund (MRFF-PD), National Health and Medical Research Council (NHMRC) of Australia European Union grant (GNT1170739, a companion grant to support the European Commission's Horizon 2020 Program, H2020-SC1-DTH-2018-1, 'iPC - individualizedPaediatricCure' [ref. 826121]), and National Breast Cancer Foundation (IIRS-18-164). Work at ProCan is done under the auspices of a Memorandum of Understanding between Children's Medical Research Institute and the U.S. National Cancer Institute's International Cancer Proteogenomics Consortium (ICPC), that encourages cooperation among institutions and nations in proteogenomic cancer research in which datasets are made available to the public.

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Poster Session

Novel deep learning-based prognostic prediction model for colorectal cancer using hematoxylin and eosin-stained whole slide images. *First Author: Teppei Konishi, Biomy Inc., Tokyo, Japan*

Background: Previous studies have shown that the presence or absence of genetic mutations is critical for colorectal cancer prognosis. However, genomic testing can be expensive and difficult to perform on all samples. In contrast, hematoxylin and eosin (H&E) staining is relatively inexpensive and can be performed on all tissue specimens. In this study, we designed a novel prognostic method using spatial image features extracted from H&E-stained whole slide images (WSIs) and genetic mutation prediction neural networks. **Methods:** We obtained H&E-stained WSIs and data on Microsatellite Instability (*MSI*), *BRAF*, *TTN* and *APC* gene mutations from a clinical cohort of 548 patients with The Cancer Genome Atlas (TCGA) Colon adenocarcinoma and rectum adenocarcinoma. We divided them into training (n=361), validation (n=90), and test (n=115) groups. Classification models were trained to predict the presence or absence of *MSI*, *BRAF*, *TTN*, and *APC* mutations. The model input comprised features of the H&E-stained WSIs, as obtained via a deep learning-based feature extractor. All resultant models were incorporated into a prognostic model (overall survival: > 60 months (low risk)/ < 60 months (high risk)). Our prognostic model's performance was evaluated against TCGA colorectal dataset, and a survival analysis was performed on the model using the Kaplan-Meier method. Finally, we compared our model's performance with the end-to-end prognostic prediction of a convolutional neural network (CNN) that also used H&E-stained WSIs as input and provided prognostic prediction as output. **Results:** Our deep learning-based prognostic prediction model achieved an AUC score of 0.834 with a 95% confidence interval (CI) of 0.734–1.000 alongside TCGA dataset; the survival analysis compared the survival distributions of low-risk and high-risk groups, as predicted by our model; a p -value < 0.01 was obtained. The model could classify low- and high-risk patients and accurately predict patient status as alive (low risk) or deceased (high risk) at 60 months. In contrast, the CNN-based model achieved an AUC score of only 0.502 (95% CI: 0.315–0.690) on the same TCGA dataset, and the p -value obtained for it under the Kaplan-Meier log-rank test was greater than 0.5. The CNN-based method was unable to distinguish between low- and high-risk patients, confirming that our method using spatial imaging features extracted from WSIs was a more effective approach. **Conclusions:** We developed a novel prognostic prediction method using spatial image features extracted from WSIs and genetic mutation prediction neural networks. Our results demonstrated the advantage of using image features over gene mutation data for prognostic prediction in colorectal cancer patients. Research Sponsor: Biomy Inc.

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Poster Session

Tumor agnostic efficacy and safety of erdafitinib (erda) in patients (pts) with advanced solid tumors with prespecified *FGFR* alterations (*FGFRalt*): RAG-NAR primary analysis. *First Author: Shubham Pant, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: *FGFRalt* are present across malignancies at various frequencies and may act as oncogenic drivers across tissue histology. Erda is an oral selective pan-*FGFR* tyrosine kinase inhibitor with activity and safety in pts with prespecified *FGFR*-altered locally advanced or metastatic urothelial carcinoma (UC) and cholangiocarcinoma. RAGNAR (NCT04083976) is an ongoing phase 2 open-label, single-arm tumor agnostic trial of erda in pretreated adult and pediatric pts with *FGFRalt* advanced solid tumors. Interim results showed erda clinical benefit, with an objective response rate (ORR) of 29.2%. Here we report results of the primary analysis. **Methods:** Pts aged ≥ 12 y with advanced or metastatic (non-UC) tumors of any histology with predefined *FGFR1-4alt* (mutations/fusions per local/central test), disease progression on ≥ 1 prior line of systemic therapy (tx), and no alternative standard tx received oral erda until disease progression or intolerable toxicity. The primary end point was ORR by independent review committee (IRC). Secondary end points included duration of response (DOR), disease control rate (DCR [CR + PR + SD]), clinical benefit rate (CBR [CR + PR + SD > 4 mo]), progression-free survival (PFS), overall survival (OS), and treatment-emergent adverse events (TEAEs). **Results:** At data cutoff, 217 pts were treated, median age was 57.0 y (range, 12-79), median prior systemic tx was 2 (46%; ≥ 3 lines of tx) with an ORR to last line prior to study entry of 10.1%. ORR to erda tx by IRC was 29.5% (95% CI, 23.5-36.0) with 6 CRs (2.8%) and 58 PRs (26.7%) in 16 distinct tumor types, including advanced CNS, thoracic, gastrointestinal, gynecologic, and rare tumors. ORR was comparable across *FGFR1-3* mutations (25.3% [95% CI, 16.0-36.7]) and fusions (32.6% [95% CI, 25.1-40.9]). Median DOR, PFS, and OS were 6.9 mo (95% CI, 4.4-7.1), 4.2 mo (95% CI, 4.1-5.5), and 10.7 mo (95% CI, 8.7-12.1), respectively; DCR was 73.7% and CBR was 45.6%. 99.5% of pts experienced TEAEs, including 70.0% with grade ≥ 3 . Treatment-related serious AEs occurred in 8.3% of pts with no treatment-related deaths. **Conclusions:** Primary analysis results from RAGNAR, the largest tumor agnostic trial of targeted tx to date, confirm efficacy of erda in heavily pretreated pts with *FGFRalt* advanced solid tumors. Erda activity was observed in adults and adolescents across tumor types, and across *FGFR1-3* gene mutations and fusions. Erda tolerability was consistent with its known safety profile. Clinical trial information: NCT04083976. Research Sponsor: Janssen Research & Development.

Tumor type	ORR n/N (%)		
Total	64/217 (29.5)		
Cholangiocarcinoma	16/31 (51.6)	Esophageal	1/8 (12.5)
High-grade glioma	3/30 (10.0)	Ovarian	2/8 (25.0)
Pancreatic	10/18 (55.6)	Unknown primary	2/8 (25.0)
Breast	5/16 (31.3)	Low-grade glioma	2/7 (28.6)
Squamous NSCLC	3/14 (21.4)	Salivary gland	5/5 (100.0)
Nonsquamous NSCLC	3/9 (33.3)	Duodenal	1/1 (100.0)
Endometrial	4/8 (50.0)	Thyroid	1/1 (100.0)

Characterizing telomerase reverse transcriptase (*TERT*) promoter mutations (mut) across sex, race, and cancer types. *First Author: Talal El Zarif, Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA*

Background: *TERT* promoter mut. have been evaluated as a predictive biomarker for patients (pts) receiving immune checkpoint inhibitors. Understanding the prevalence of *TERT* promoter mut. by sex, race, and cancer type is essential for optimizing its use. **Methods:** Pts who underwent next-generation sequencing at Dana-Farber Cancer Institute and Memorial Sloan Kettering Cancer Center were identified from the AACR Genomics Evidence Neoplasia Information Exchange (GENIE) registry v11.0. Self-reported race and sex data were extracted for ten cancer types with the highest prevalence of *TERT* promoter mut. The strength of associations with *TERT* promoter mut. was quantified by Odds ratios (ORs) and two-sided Fisher's exact tests, along with FDR-adjusted q-values using the Benjamini-Hochberg method. **Results:** We identified 31,925 pts – 87.6% (27,970) self-identified as White, 7.1% (2,273) Asian, and 5.3% (1,682) Black. *TERT* promoter mut. were present in 17% (5,470) tumors, including 56% (1,346/2,411) bladder cancers, 43% (966/2,243) melanomas, 41% (395/959) thyroid cancers, and 23% (183/782) head and neck cancers (HNC). *TERT* promoter mut. were significantly higher in males vs. females in melanoma, cancer of unknown primary (CUP), hepatobiliary (HPB), and thyroid cancers. In contrast, males harbored fewer mut. vs. females with HNC. Interestingly, *TERT* promoter mut. varied by race. Mut. frequency was significantly higher in White pts with melanoma (44%, n=964/2176) compared to Asian and Black pts (2.9%, n=2/67) (OR=25.8; 95% CI=6.9–217, p<0.0001). Asian males with HNC (37%, n=22/60) were enriched for *TERT* promoter mut. vs. White males (19%, n=93/489) (OR=2.5; 95% CI=1.4–4.4; q=0.03). Within HNC tumors, oral cavity (OC) tumors (44.3%, n=85/192) were associated with higher *TERT* promoter mut. vs. other HNC subtypes (16.6%, n=98/590) (OR=4.4; 95% CI=3.03–6.26; p<0.0001). Asian pts with OC (70%, n=14/20) harbored more mut. vs. White pts with OC (41.4%, n=70/169) (OR=3.3; 95% CI=1.2–9; p<0.05). **Conclusions:** Our study demonstrates differences in the distribution of *TERT* promoter mut. by sex, race, and cancer type. Considering these variations is crucial for future clinical trial design and biomarker studies. Research Sponsor: None.

Cancer	<i>TERT</i> promoter mut: males % (n)	<i>TERT</i> promoter mut: females % (n)	Male vs. female OR (95%CI)	p-value
HPB	17% (137/827)	5% (36/741)	3.89 (2.63–5.86)	<0.0001
CUP	11% (116/1056)	6% (64/1081)	1.96 (1.42–2.74)	<0.0001
Melanoma	49% (638/1298)	35% (328/945)	1.95 (1.63–2.32)	<0.0001
HNC	21% (118/575)	31% (65/207)	0.56 (0.39–0.82)	0.0021
Thyroid	46% (213/468)	37% (182/491)	1.42 (1.09–1.85)	0.009
Soft Tissue Sarcoma	8% (101/1238)	6% (75/1228)	1.37 (0.99–1.89)	0.05
Non-Small Cell Lung Cancer	5% (180/3797)	4% (222/5637)	1.21 (0.99–1.49)	0.06
Colorectal Cancer	4% (125/3390)	4% (121/2921)	0.89 (0.68–1.15)	0.36
Bladder Cancer	56% (1003/1781)	54% (343/630)	1.08 (0.90–1.30)	0.43

Caveat emptor: A descriptive analysis of guideline-recommended biomarker inclusion in targeted NGS panels for metastatic non-small cell lung cancer (mNSCLC). *First Author: John Leonard Fox, Illumina, San Diego, CA*

Background: Next generation sequencing (NGS)-based panels are routinely used in the diagnosis of mNSCLC, guidelines recommending assessing 12 genes for small variants (SV), (EGFR, BRAF, KRAS, MET, ERBB2); fusions (F), (ALK, ROS1, RET, NTRK1, NTRK2, NTRK3); and copy number variants (CNV), (MET) to assess eligibility for targeted drug therapies. Reimbursement is often limited to targeted panels; yet, a comprehensive review of targeted panels' ability to capture all recommended biomarkers has not been reported. **Methods:** Targeted panels were classified as ≤50 and 51-100 genes. We searched the DEX Diagnostics Exchange Registry for NGS-based lung cancer and solid tumor targeted panels. Each panel was compared against the 12 recommended genetic variants. If the type of genetic analysis (SV/F/CNV) was unclear, labs were contacted for clarification. Fusion assays by PCR or FISH with reflex testing to NGS were included. **Results:** 30 targeted NGS panels from 21 commercial labs were identified; 13 (43%) were specific to lung cancer. Six of 13 panels assessing fusions used FISH or PCR not NGS alone. 12 panels reported only SV, 8 small SV/F, 5 SV/CNS, and 5 all three variant types. Only 1 of the 30 panels (51-100 genes) captured all 12 biomarkers with correct variant types. Of 20 panels reporting ALK, RET, and ROS1, only 11 (55%) reported fusions. Of the 5 reporting all three variant types, NTRK fusions were most commonly absent. On average, solid tumor panels sequenced twice as many genes (51 vs. 24) but were no more likely to capture all recommended biomarkers ((1/17 (6%) vs. 0/13 (0%), (p>0.05)). The average biomarkers captured in lung vs. solid tumor panels were 7.9 and 6.6, respectively (p>0.05), while in ≤50 gene panels vs. 51-100 gene panels, 7.0 and 7.6, respectively (p>0.05). **Conclusions:** Of 30 commercially available NGS panels with <100 genes, only one captured all recommended gene variant types for mNSCLC. Failure to capture all biomarkers was independent of panel size or specificity to lung cancer. NGS panels including small variants, fusions, and copy number variants assessed more biomarkers. Medical oncologists and clinical pathologists ordering targeted NGS panels for the management of patients with mNSCLC must ensure they assess all biomarkers relevant to targeted therapies. Insurers reimbursing targeted panels should acknowledge the inadequacy of <100 gene panels alone to provide guideline-concordant molecular diagnostic testing. Research Sponsor: Illumina.

Guideline-recommended biomarker capture count by panel type and gene variant class.				
≤50 genes	SV	1	9	
	SV/CNV		2	1
	SV/F		1	3
	SV/F/CNV		2	1
51-100 genes	SV	2		
	SV/CNV		2	
	SV/F		1	
	SV/F/CNV		1	1

Homologous recombination deficiency (HRD) in non-small cell lung cancer: Genomic analysis using an RNA-based HRD algorithm. *First Author: Stephanie Thiede, Tempus Labs, Inc., Chicago, IL*

Background: Recent evidence has suggested that some patients with non-small cell lung cancer (NSCLC) harbor a HRD signature that represents a distinct genomic subtype that could be targeted by PARP inhibitors (PARPi). However, there is little data on HRD prevalence in NSCLC or its genomic associations. Here, we evaluated the co-occurrence of driver mutations and established immune biomarkers with an RNA-based HRD signature in a large, real-world NSCLC cohort. **Methods:** We analyzed data from 5119 NSCLC patients that underwent sequencing via the Tempus xT test (DNA-seq of 648 genes; RNA-seq with whole exome capture). HRD status was predicted by the Tempus HRD-RNA test, a pan-cancer logistic regression classifier that uses an RNA gene expression signature optimized to distinguish between BRCA-biallelic loss and homologous recombination repair (HRR)-WT samples (Leibowitz et al, 2022). Cohort samples were excluded from model training. All comparisons were tested via chi-squared or Fisher's exact tests. **Results:** An RNA-derived signature of HRD (HRD-RNA+) was observed in 3.53% (n=181/5119) of patients. HRD-RNA+ prevalence was higher in squamous cell carcinoma (84/1331, 6.3%) relative to adenocarcinoma (68/3015, 2.3%; p<0.001). The prevalence of select alterations by HRD-RNA status are shown in Table. Alterations in *BRCA1/2* and HRR genes (inclusive of *BRCA1/2*) were enriched in HRD-RNA+ vs. HRD-RNA- cases (8.8% vs. 2.5%; p<0.001; 22% vs. 15%, p=0.008 respectively). Notably, 141 (78%) HRD-RNA+ patients had no alterations in HRR genes. Of all NCCN targetable driver mutations assessed, *KRAS* G12C and *ALK* fusions were the only targetable drivers with significantly different prevalence in HRD-RNA+ vs. HRD-RNA- patients. Across the entire cohort, NCCN driver mutations were depleted in HRD RNA+ patients (18% in HRD-RNA+ vs. 30% in HRD-RNA-, p<0.001). Immune biomarkers (TMB, PD-L1) did not vary by HRD-RNA status. **Conclusions:** Compared to HRD-RNA- NSCLC, HRD-RNA+ NSCLC represents a unique, molecularly defined subset that has a decreased prevalence of NCCN-driver mutations and is not enriched for TMB-H or PD-L1 expression. Further, this signature increases the number of patients classified as HRD-RNA+ compared to HRR gene alterations alone. Functional characterization (e.g. RAD51 foci immunofluorescence assay) and clinical benefit of targeted HRD therapies such as PARPi should be explored in this HRD-RNA+ population. Research Sponsor: Tempus Labs.

	HRD-RNA+, N = 181	HRD-RNA-, N = 4,938	p-value
<i>BRCA1/2</i> loss or mutation, n (%)	16 (8.8%)	122 (2.5%)	<0.001
HRR gene(s) loss or mutation, n (%)	40 (22%)	736 (15%)	0.008
<i>KRAS</i> G12C, n (%)	8 (4.4%)	529 (11%)	0.007
<i>ALK</i> Fusion, n (%)	0 (0%)	112 (2.3%)	0.034
<i>BRAF</i> V600E, n (%)	0 (0%)	60 (1.2%)	0.3
EGFR mutation, n (%)	22 (12%)	761 (15%)	0.2
<i>ROS1/NTRK1/2/3/RET</i> Fusion, n (%)	1 (0.6%)	45 (0.9%)	>0.9
MET Exon 14 skipping, n (%)	1 (0.6%)	47 (1.0%)	>0.9
NCCN Driver(s), n (%)	33 (18%)	1,617 (33%)	<0.001

Clinical activity of mitogen-activated protein kinase (MAPK) inhibitors in patients with MAP2K1 (MEK1)-mutated metastatic cancers: A systematic review and meta-analysis. *First Author: Matthew Dankner, McGill University, Montréal, QC, Canada*

Background: MAP2K1 (MEK1) mutations are potentially actionable driver mutations in cancer. MAP2K1 mutations can be classified into 3 classes according to molecular characteristics. The efficacy of MAPK inhibitors (MAPKi) for the treatment of MAP2K1 mutant tumors is not well understood. We sought to characterize the genomic and clinical landscape of MAP2K1 mutant tumors, and to evaluate the relationship between MAP2K1 mutation class and clinical activity of MAPKi in patients with MAP2K1 mutant metastatic solid tumors. **Methods:** We interrogated AACR GENIE (v13) to identify all tumors with Class 1/2/3 MAP2K1 mutant solid tumors. We performed a systematic review and meta-analysis of individual patient data from patients with MAP2K1 mutant cancer published between 2010-22. Key inclusion criteria were: MAP2K1 mutation, solid tumor, metastatic disease, treatment with MAPKi and available treatment response data. The primary endpoint was progression-free survival (PFS) and the secondary endpoints were overall response rate (RR) and duration of response (DOR). Chi-squared and Log-Rank tests were used to evaluate statistical significance of differences between groups. **Results:** MAP2K1 driver mutations were present in 917/167,423 (0.5%) tumors in the AACR GENIE dataset. MAP2K1 mutants were most commonly identified in melanoma, colorectal (CRC) and non-small cell lung cancer (NSCLC). In solid tumors, Class 2 mutations were the most prevalent (n=310, 63%) followed by Class 1 (n=119, 24%) and Class 3 (n=66, 13%). Co-occurring MAPK pathway activating mutations (*KRAS*, *NRAS*, *HRAS*, *NF1*, *BRAF*, *RAF1*, or *EGFR*) were significantly more likely (P<0.0001) to occur in Class 1 (82.3%), versus Class 2 (30.9%) or Class 3 (10.6%) MAP2K1 mutant tumors. We identified 55 patients with MAP2K1 mutant tumors who received MAPKi (n=16/30/6/3 for Class 1/2/3/unclassified, respectively). Of these, (n=22, 18, 12, 3) had melanoma, CRC, NSCLC, or other cancers, respectively. Patients were treated with BRAFi (n=12), MEKi (n=24), BRAF+MEKi (n=2), ERKi (n=1) or EGFRi (n=16). Co-occurring MAPK pathway mutations were present in 51% of tumors. In the entire cohort, the RR was 24% and median PFS was 3.3 months. The RR did not differ according to mutation class, cancer type or MAPKi regimen. However, patients with Class 2 mutations experienced longer PFS (4.0 months) and DOR (23.8 months) compared to patients with Class 1, 3 or unclassified MAP2K1 mutations (PFS 3.0 months, P=0.035; DOR 4.2 months, P=0.04). **Conclusions:** Class 2 MAP2K1 mutations are RAF-regulated oncogenic mutations with a relatively low incidence of co-occurring MAPK pathway activating mutations. Some patients with Class 2 MAP2K1 mutations may derive durable therapeutic benefit from MAPKi. Prospective clinical studies with MAPK inhibitors are warranted in patients with MAP2K1-mutated metastatic cancer. Research Sponsor: None.

3126

Poster Session

Genetic heterogeneity between paired primary and metastatic solid tumors and implications for neoantigen-based personalized cancer vaccines. *First Author: Timothy I Shaw, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL*

Background: Neoantigen-based personalized cancer vaccines carry significant promise in treating solid malignancies. For the purpose of neoantigen prediction, questions remain on the suitability of the primary versus the metastatic tumor of an individual patient (pt). Here we performed an in-depth analysis of somatic variants of 45 pts with paired primary and metastatic solid tumors. **Methods:** Pts were enrolled in the Total Cancer Care protocol across the Oncology Research Information Exchange Network (ORIEN). Whole-exome sequencing (WES) of primary and metastatic tumor pairs was performed for 45 pts. These included head and neck (n = 8), renal cell carcinoma (n = 7), non-small cell lung cancer (n = 6), melanoma (n = 5), bladder (n = 3), sarcoma (n = 3), ovary (n = 3), esophageal (n = 2), colorectal (n = 2) and other singletons (n = 5). The data was analyzed through the ORIEN AVATAR Molecular Analysis Pipeline, which consisted of adapter trimming, single sample variant detection, somatic mutation detection and filtering, variant annotation, and filtering of variants from a panel of normal samples. In this analysis, we focused on somatic events that result in an in-frame alteration (such as missense, in-frame insertion/deletion) and out-of-frame protein-altering mutations (such as frameshifts, de novo start and nonstop gain). To assign the clones based on the variant allele frequency, we performed complete linkage clustering. Each cluster was then assigned based on the identified oncogenic driver variant. **Results:** For in-frame events, we noticed that bladder cancer, melanoma, and gynecological cancers shared close to 75% of the mutations between paired primary and metastatic cases. In contrast, esophageal, brain, and endometrial cancers had a low overlap (< 25%) of variants. For out-of-frame events, we found that these events tend to have a lower proportion of shared somatic variants between primary and metastasis than in-frame variants. Through a closer evaluation of the variant allele frequency in variants shared between primary and metastatic disease, we were able to track several cancer drivers, such as oncogenic drivers of BRAF V600E, RB1 R358*, NRAS G13R, KRAS G12A, and TP53 loss-of-function that were consistently present in paired primary and metastatic tumors. Here, we were able to assign the putative clone based on the driver event in 39 out of 45 pts. **Conclusions:** Our analysis demonstrates genetic variations that exist when comparing paired primary and metastatic tumors that appear to vary by histology. Variants are potentially undergoing negative selection supported by the preferential loss of out-of-frame events in metastatic tumors. Understanding the clonal structure will be key to neoantigen prediction for effective neoantigen-based vaccines. Additional steps in variant prioritization are ongoing and will be reported at the meeting. Research Sponsor: M2GEN ORIEN NOVA Grant; American Cancer Society.

3128

Poster Session

Multi-omic characterization of RCC1 expression and its association with molecular alterations, immune phenotypes, and cancer outcomes. *First Author: Brian Warnecke, University of California Irvine School of Medicine, Orange, CA*

Background: Regulator of Chromosome Condensation 1 (RCC1) is the only identified guanine nucleotide exchange factor for the Ras-related nuclear protein Ran and it functions in nuclear transport, cell cycle and DNA damage response. Overexpressed in several cancer types, RCC1 is associated with poor outcomes. We aim to investigate the role of aberrant RCC1 co-alterations and association with immune phenotypes and cancer outcomes. **Methods:** DNA (592-gene or whole exome)/RNA (whole transcriptome) sequencing was performed at Caris Life Sciences (Phoenix, AZ). Samples were stratified by RCC1 expression quartile thresholds (Q1:low, Q4:high) for small cell lung (SCLC, n=876), non-small cell lung (NSCLC, n=21603), gastric (GC, n=1908), pancreatic (PC, n=5071) and colorectal (CRC, n=14892) cancers. PD-L1+ expression was tested by IHC (22c3: 31%; SP142: 32+5%). TMB-High was defined as ≥ 10 mutations/MB. Overall survival (OS) was calculated using Kaplan-Meier estimate. Statistical significance was determined using chi-square and Wilcoxon rank sum test and adjusted for multiple comparisons (* $P < 0.05$). **Results:** Median RCC1 expression was highest in SCLC (14.3 transcript per million [TPM]), followed by GC (9.9), NSCLC (9.9), CRC (9.8), and PC (6.9). TMB-high rates increased progressively with RCC1 expression in NSCLC (Q1-Q4 range: 31-41%*), GC (7-22%*) and CRC (3-13%*), consistent with dMMR/MSI-high rates in GC (5-18%*) and CRC (3-13%*). Similar trends were observed for PD-L1+ rates in PC (Q1-Q4 range: 13-20%*), CRC (2-5%*) and NSCLC (55-58%*). In NSCLC, TP53 (Q1-Q4 range: 57-77%*), RB1 (7-13%*), and EGFR (10-15%*) mutations were seen more with higher RCC1 expression, while STK11 (15-10%*) and KRAS (33-21%*) mutations were seen less. In PC, TP53 mutations (Q1-Q4 range: 70-85%*) and MYC amplifications (1-4%*) were seen more with RCC1 expression, whereas ATM mutations were seen less (6-3%). In CRC, TP53 (Q1-Q4 range: 70-81%*) and APC (72-81%*) mutations were seen more with RCC1 expression, while GNAS mutations were seen less (4-2%*). In both SCLC and NSCLC, high RCC1 expression was associated with increased dendritic cell (5-6%* and 8-1.3%*, respectively) and NK cell fractions (5-6%* and 2.5-3.2%*) and decreased Treg fractions (1.8-1.3%* and 3.0-2.6%*). In pMMR/MSS CRC, high RCC1 expression was associated with increased dendritic cell (6-9%*), NK cell (3-4%*), neutrophil (6-8%*) and CD4 T cell fractions (1.1-1.2%*) and decreased CD8 T cell (5-4%*) and Treg fractions (1.9-1.7%*). High RCC1 expression was associated with worse OS in NSCLC (HR 1.3*), PC (HR 1.5*) and CRC (HR 1.3*), with a similar but not significant effect in SCLC (HR 1.2) and GC (HR 1.2). **Conclusions:** RCC1 expression is a negative prognostic marker in NSCLC, PC, and CRC. Further studies to investigate this at the molecular level may be a potential opportunity for novel targeted drug development. Research Sponsor: None.

3127

Poster Session

Trastuzumab emtansine (T-DM1) in advanced cancers with HER2 mutations or amplification: Results from the Molecular Screening and Therapeutics (MoST) Program substudy. *First Author: Subotheni Thavaneswaran, NHMRC Clinical Trials Centre, The University of Sydney, Sydney, NSW, Australia*

Background: The antibody-drug conjugate T-DM1 is widely used for the treatment of HER2-positive metastatic breast cancer. Its activity in other advanced solid tumors harboring HER2 alterations identified by comprehensive genomic profiling (CGP) needs further characterization. **Methods:** The MoST program provides a precision oncology framework for screening patients (pts) by CGP to identify genomic alterations with potential to match to biomarker-directed clinical trials. This multi-center, single-arm phase 2 trial (ACTRN12619001265167) enrolled adult pts with refractory solid tumors (excluding breast and gastroesophageal cancers) with HER2 alterations. This trial recruited 2 groups of 16 pts (group 1: mutations, group 2: genomic amplification, defined as copy number ≥ 6 copies). The primary composite endpoint was objective tumor response (OTR) assessed by RECIST 1.1 and time-to-progression (TTP) ratio (defined as TTP on T-DM1: TTP1 on prior line of systemic therapy). Anti-tumor activity of T-DM1 was confirmed if ≥ 3 of each 16 pt group achieved an OTR. Key secondary endpoints were progression-free and overall survival (PFS and OS) and safety as assessed by CTCAE 5.0. **Results:** 32 pts had a median age of 64 years (interquartile range [IQR] 53 to 69); 94% an ECOG PS ≤ 1 ; 53% female; and median 2 (IQR 1 to 3.5) prior lines of systemic therapy. The cohort included non-small cell lung cancer (NSCLC, n=12), colorectal (CRC, n=5), salivary gland (SGC, n=5), ovarian (n=3), uterine (n=2), gallbladder (n=2), and 1 each of bladder, pancreas and cervix cancers. After a median follow-up of 17 months (mo), the primary endpoint was met with 7 pts (22%) achieving an OTR, including 3 pts (19%) in group 1 (2 NSCLC and 1 SGC) and 4 pts (25%) in group 2 (3 SGC, and 1 uterine serous carcinoma [USC]). Fourteen of 29 TTP-evaluable pts (48%) achieved a TTP ratio ≥ 1.3 , including 10 pts without an OTR: equating to 53% (n=17) deriving clinical benefit. The median PFS and OS were 4.5 (95% CI 2.1 to 7.0) and 18.23 mo (95% CI 8.11 to not reached) respectively and 6 mo PFS rate 44% (95% CI 26 to 60%). The (NSCLC) responders in group 1 harbored exon 20 insertions (Y772_A775dup and G778_P780dup) and the SGC, a L755S mutation. None of the S310Y/F mutations (n=5, including 2 NSCLCs) had an OTR. The USC was ERBB2 amplified (18 copies) on CGP, discordant with in situ hybridisation (ISH) testing results. Overall, 4 pts had CGP-amplified, ISH negative tumors, of whom 2 achieved an OTR. No responses were seen in CRC pts (all RAS/BRAF-wildtype and IHC 2-3+). No new safety concerns for T-DM1 were reported. **Conclusions:** T-DM1 has anti-tumor activity across a heavily treated, diverse range of cancer types with HER2 alterations identified by CGP, including several unidentified by standard ISH testing. We await results from our partner trial in the first line advanced NSCLC setting to corroborate the group 1 findings. Clinical trial information: ACTRN12619001265167. Research Sponsor: Australian Government - Medical Research Future Fund; Roche Products Pty. Limited (Australia).

3129

Poster Session

A 19-protein signature to predict outcomes in a cohort of stage II and III CRC. *First Author: Rosemary Habib, The Westmead Institute for Medical Research, Faculty of Medicine, The University of Sydney, Westmead, NSW, Australia*

Background: Colorectal cancer (CRC) is the second leading cause of cancer-related deaths worldwide and remains an area of unmet clinical need. Despite advances in treating stage II and III disease, 30-50% of patients relapse. Additionally, variable survival outcomes are seen in patients with similar disease stages, making it difficult to predict relapses. Here we outline some of the proteomic pathways of early-stage CRC along with the identification of a proteomic-based prognostic signature that predicts relapse in stage II/III CRC. **Methods:** Archival formalin fixed paraffin embedded tumour (TUM) specimens and matched normal adjacent tissues (NAT) from a cohort of 495 CRC patients (with upfront resected stage II and III CRC) were prepared for proteomic analyses using data-independent acquisition mass spectrometry (DIA-MS). TUM samples with $< 20\%$ tumour were excluded from the analysis. Differential expression analyses were performed to identify the top differentially expressed proteins (DEP) within TUM. DEP were subjected to crosstalk and pathway enrichment analysis (PEA). Survival analysis based on initial univariate and subsequent 100 runs of multivariate Cox regression with Least Absolute Shrinkage and Selection Operator (LASSO) was performed to obtain a reduced list of candidate proteins associated with recurrence-free survival (RFS). The proteins that appeared in greater than 95% of the LASSO runs were used in a multivariate Cox model with recursive feature selection to yield the final list of 19 proteins. A risk score was calculated as the sum of the intensities of each of the 19 proteins multiplied by the corresponding regression coefficients. The median of the risk scores was used as the threshold to dichotomise patients into either a low- or a high-risk group. **Results:** 399 TUM and 381 NAT were analysed, showing 799 DEP, with 529 upregulated and 270 downregulated in TUM vs NAT, respectively. PEA of the upregulated proteins showed enrichment of pathways related to extracellular matrix organisation, tRNA processing and collagen formation. PEA of the downregulated DEPs revealed pathways related to smooth muscle contraction, focal adhesion and oxidation. The 19-protein signature dichotomised patients into low- and high-risk groups with a C-index of 0.829. The signature was prognostic for RFS (hazard ratio (HR) 2.7, 95% confidence interval (CI): [2.24 – 3.18]) and for overall survival (OS) (HR 1.6, 95% CI [1.40, 1.76]). The prognostic significance of the signature was maintained after adjusting for other clinical variables for both RFS and OS (both $p < 0.001$) using multivariate Cox regression. **Conclusions:** Our findings show that CRC disrupts the extracellular matrix and upregulates collagen formation, making these potential targets for novel therapies. We have also identified a 19-protein signature that is associated with survival in our cohort independent of other clinical variables. Research Sponsor: Sydney West Translational Research Centre.

3130

Poster Session

Predictive biomarker for cisplatin in prospective phase 2 of liposomal cisplatin in metastatic breast cancer. *First Author: Dorte Nielsen, Herlev, Copenhagen, Denmark*

Background: Heavily pretreated late-stage breast cancer patients of any subtype represent a huge treatment challenge. Cisplatin may work in selected patients but is often disqualified because of toxicity. LiPlaCis is a liposomal formulation of cisplatin in development utilizing the sPLA₂-triggered targeted release of cisplatin. The prediction of cisplatin efficacy with a 205 mRNA profile has previously been demonstrated in a retrospective study in two NSCLC cancer patient cohorts receiving adjuvant cisplatin¹.

Methods: The dose-escalation part of a phase 1/2 study, of 20 patients with a variety of locally advanced or metastatic solid tumors, suggested a phase 2 dose of LiPlaCis to be 75mg on day 1 and 8 q 3 wks. In this phase 2 part, the cisplatin drug response predictor (DRP) was used to select metastatic breast cancer (mBC) patients with response likelihood scores from FFPE diagnostic or later biopsies. Patients were treated until progression or unacceptable toxicity. Halfway through phase 2 part, the dosing was changed to a per body surface schedule (40 mg/m²) after a fatal event with the flat dosing (in effect 51 mg/m² for this patient). Among the 52 patients included in the phase 2 part, we here report data from the 37 patients with mBC platinum naïve, with DRP scores 34-100%, and with RECIST-defined response outcomes. Within this subgroup, we conducted a post hoc analysis of possible DRP cut-off values that could identify patients with a clinically meaningful response to treatment. **Results:** mBC patients had received a median of 7 previous treatment lines. A DRP score ≥80% (DRP80+) discriminated well between responders and non-responders to liposomal cisplatin. All 4 partial remissions in the study were in the DRP80+ group, and other key efficacy endpoints were in favor of the DRP80+ vs the lower scores (DRP80-). LiPlaCis was generally well tolerated, with a mean of 4.4 treatment cycles administered per patient. Only 1 SAE (pyelonephritis) was reported and considered related to treatment. One patient died whilst on treatment, but due to disease progression. From a total of 164 treatment cycles, 18 of the patients reported 1 grade 4 and 41 grade 3 AEs considered possibly related to treatment. **Conclusions:** LiPlaCis shows efficacy in heavily pretreated mBC patients, especially when using the DRP method as a companion diagnostic. Further, this is the first clinical study to prospectively validate DRP as a method to identify responders to chemotherapy cisplatin. 1) Buhl et al PLOS One doi: 10.1371/journal.pone.0194609. Clinical trial information: NCT01861496. Research Sponsor: CHOSA Oncology; EUROSARS.

		Total	DRP80-	DRP80+	p-value ²
N		37	21	16	
Tumor response	ORR	4 (10.8%)	0 (0%)	4 (25.0%)	0.0276
	CBR	8 (21.6%)	2 (9.5%)	6 (37.5%)	0.0554
PFS (in weeks)	median [95%CI]	15 [7,24]	8 [6,23]	19 [13,30]	0.155
	median [95%CI]	50 [33,60]	44 [21,60]	56 [17,62]	0.554

²DRP80+ vs DRP80-.

3132

Poster Session

NRG1 fusions in solid tumors. *First Author: Brinda Gupta, Lombardi Comprehensive Cancer Center, Georgetown University, Washington, DC*

Background: *NRG1* fusions are rare but actionable genomic drivers that occur across a growing number of tumor types. *NRG1* has an EGF-like domain that serves as a ligand for ErbB (HER3) receptors, thereby inducing heterodimerization, usually with HER2, and subsequent activation of relevant downstream signaling pathways. Agents targeting the HER2/HER3 pathway have shown early clinical promise in *NRG1* fusion-positive cancers: currently zenocutuzumab has FDA Fast Track Designation for tumors harboring *NRG1*-fusions. Here, we update the incidence and characterization of *NRG1* fusions across tumor types. **Methods:** Samples were submitted for clinical molecular profiling at Caris Life Sciences via Caris MI Tumor Seek (Phoenix, AZ). Gene fusion detection was performed on mRNA isolated from a formalin-fixed paraffin-embedded tumor sample using the Illumina NovaSeq platform (Illumina, Inc., San Diego, CA) and Agilent SureSelect Human All Exon V7 bait panel (Agilent Technologies, Santa Clara, CA). All *NRG1* fusions with ≥ 3 junction reads were identified for manual review and for characterization of fusion class, intact functional domains, domain prediction, breakpoints, frame retention and co-occurring alterations by next-generation sequencing. **Results:** In an analysis of 169,273 tumor specimens, 261 unique tumors with an *NRG1* fusion were identified for an overall incidence of 0.154% across tumors. *NRG1* fusions were most frequently detected in NSCLC, breast cancer, ovarian cancer, pancreatic ductal adenocarcinoma, colorectal cancer, cholangiocarcinoma, prostate cancer, bladder and urothelial cancers, esophagogastric cancers and less commonly, prostate cancer, soft tissue sarcoma, anal cancer, salivary gland cancers, head and neck cancer, small intestine cancer, small cell lung cancer, endometrial cancer, thyroid cancer, neuroendocrine cancer, high grade glioma, and melanoma. The highest incidence was in breast cancer (0.301%), followed by cholangiocarcinoma (0.263%), NSCLC (0.232%), carcinoma of unknown primary (0.215%), pancreatic ductal adenocarcinoma (0.190%), ovarian cancer (0.174%), bladder cancer (0.148%), esophageal cancer (0.145%) and vulvar cancers (0.145%). There were 153 unique *NRG1* fusion partners. The most common fusion partner was CD74 (12.37%), followed by SLC3A2 (8.13%), ATP1B1 (4.59%), and RBPMS (4.24%). **Conclusions:** *NRG1* fusions are rare but actionable genomic events with significant heterogeneity of tumor type and fusion partner. Research Sponsor: Caris Life Sciences.

3131

Poster Session

Patient access to precision medicine: Identifying barriers to biomarker testing in non-small cell lung cancer. *First Author: Ayse Levent, Ipsos, New York, NY*

Background: The growing number of targeted therapies approved to treat non-small cell lung cancer (NSCLC) has anchored biomarker testing in clinical practice. Despite general concordance across international guidelines recommending advanced NSCLC patients be tested for oncogenic alterations and immune biomarkers, this is not always the case. This study uses real-world data to explore the barriers to testing across US, Japan, Germany and China. **Methods:** Ipsos' Biomarker Testing Rate Monitor is a multi-stakeholder, physician-reported syndicated patient record database. 206 cancer-treating physicians (US=69, Japan=37, Germany=41, China=59) were screened for seniority and caseload and submitted data on 990 NSCLC patients (aggregate) in which biomarker testing had not taken place. Data were collected online January – December 2022. **Results:** Analyzing physician cited barriers why patients were not tested, choosing not to test at patient's current stage was highest in the reported US patient cohort, guidelines not calling for testing at this point was more frequently cited in the Japan (27%) and Germany (25%) patient cohort and patient's co-pay was more frequently cited in the China cohort (34%). The Japan cohort had higher mentions of tissue not being available. Country disparities in the reported metastatic (IIIB-IV) cohort included lack of tissue in Japan (48%) and Germany (25%), deferring testing to a later point in the US (21%) and high co-pay in China (50%). The top cited reasons are shown. **Conclusions:** Results from this study indicate that, despite guidelines, not all oncology patients receive biomarker testing. While reimbursement structures are difficult to overcome, a concerted effort is needed to raise awareness of the clinical utility of biomarker testing and of the importance of collecting sufficient tissue during the biopsy to allow patients the chance of benefiting from precision medicines. Similarly, calls for earlier testing would support efforts that ensure the best available treatment options are available to patients throughout their journey. Further investigation using comparator cohort is warranted. Research Sponsor: Ipsos-Insight, LLC.

	US (n=249)	JP (n=274)	DE (n=182)	CH (n=305)	US (n=182)	JP (n=161)	DE (n=101)	CH (n=183)	US (n=67)	JP (n=113)	DE (n=61)	CH (n=122)
Patient's insurance doesn't cover testing	15%	8%	14%	27%	15%	11%	11%	21%	15%	4%	18%	35%
Patient's co-pay for testing is too high	15%	5%	11%	34%	14%	4%	7%	23%	16%	6%	18%	50%
Will not test at this stage (may test at a later point in time)	21%	26%	19%	26%	20%	37%	21%	34%	21%	12%	15%	14%
Tissue not available for testing	12%	25%	13%	14%	11%	9%	6%	13%	16%	48%	25%	16%
Standard of Care guidance does not call for testing at this point of care	14%	27%	25%	7%	13%	37%	37%	4%	18%	12%	5%	10%

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Poster Session

The genomic, transcriptomic, and immunologic landscape in solid tumors expressing leukocyte immunoglobulin-like receptor B2 (LILRB2). *First Author: Sandra Jones, University of Miami Miller School of Medicine/ Jackson Memorial Hospital, Miami, FL*

Background: *LILRB2* is primarily expressed on myeloid cells and provides negative feedback during inflammatory response. A blocking antibody targeting *LILRB2* in myeloid cells is in clinical trials. Various solid tumors are also enriched with these receptors. Here we investigate differences between *LILRB2* expression in the local versus metastatic setting, influences on the tumor microenvironment, and effects on clinical outcomes for a group of solid tumors. **Methods:** Liver cancer (LC, N=532), urothelial carcinoma (UC, N=4125), pancreatic cancer (PC, N=5488), prostate adenocarcinoma (PA, N=5500) and non-small cell lung cancer (NSCLC, N=21604) tumors were tested at Caris Life Sciences (Phoenix, AZ) with NextGen sequencing of DNA (592-gene or whole exome) and RNA (whole transcriptome). Primary and metastatic sites were defined based on the biopsy site relative to known primary site. *LILRB2*-High (H) and -Low (L) expression was defined as top and bottom quartile of *LILRB2* transcripts/million, respectively. PD-L1 (SP142; Positive (+): ≥2, ≥5%) expression was tested by IHC. Gene expression profiles were analyzed for transcriptomic signatures predictive of response to immunotherapy (T-cell inflamed score). Immune cell fractions were estimated with RNA deconvolution using quanTIseq. Mann-Whitney U and χ^2 tests were applied as appropriate with P-values adjusted for multiple comparisons. Overall survival data was obtained from insurance claims, and Kaplan-Meier estimates were calculated for molecularly defined subpopulations of patients. **Results:** Median expression of *LILRB2* was increased in metastatic versus primary UC (1.23-fold, $p<0.001$), while similar expression was observed in PC (1.1, $p=0.02$), LC (0.87, $p=0.68$), PA (1.0, $p=0.69$), and NSCLC (0.96, $p=0.003$). Compared to *LILRB2*^L, *LILRB2*^H tumors had an increased prevalence of TP53 mutations in LC (*LILRB2*^H 53 vs 22%, $p<0.05$) and UC (64 vs 53, $p<0.05$). *LILRB2*^H tumors had an increased rate of PD-L1+ in PC (20 vs 11%), NSCLC (32 vs 11%), and UC (40 vs 11, all $p<0.05$). Across all tumors, *LILRB2*^H have an increased amount of M1 (UC: 6.34-fold, PC: 1.50, LC: 3.30, PA: -H 0.5% vs -L 0.0, NSCLC: 2.08) and M2 macrophages (UC: 1.40, PC: 1.78, LC: 1.61, PA: 1.07, NSCLC: 1.47) as compared to *LILRB2*^L ($p<0.05$, all). *LILRB2*^H tumors were more frequently T cell-inflamed across investigated cancers (NSCLC: 66.4 vs 2.8%, PC: 60 vs 4.3, LC: 61 vs 3.0, PA: 69 vs 4.8, UC: 70 vs 2.6, all $p<0.05$). *LILRB2*^H PC tumors had decreased overall survival (HR 1.21 [1.0-1.2]). In NSCLC, *LILRB2*^H tumors had longer time on pembrolizumab (HR 0.87 [0.78-0.97]). **Conclusions:** *LILRB2* expression was associated with biomarkers of response to immunotherapy such as PD-L1+ and an increased proportion of T cell-inflamed tumors. These data suggest that PC, NSCLC and UC tumors could benefit from a combination of ICI and *LILRB2*-blocking antibodies. Research Sponsor: Caris Life Sciences.

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Poster Session

Characterizing the landscape of RING-type E3 ubiquitin transferase-altered (RNF43 alt) colorectal cancer (CRC) and defining unique subsets with potential therapeutic vulnerabilities in microsatellite instability-high (MSI-H) CRC. *First Author: Abdul Rafeh Naqash, Stephenson Cancer Center, University of Oklahoma Health Sciences, Oklahoma City, OK*

Background: RNF43 is a tumor suppressor gene that represses the WNT/ β -catenin pathway. Emerging data show that RNF43 alt are commonly present in MSI-H CRC with improved outcomes to immune checkpoint inhibitors (ICI). We evaluated whether genomic and transcriptomic analysis of MSI-H RNF43 alt CRC defines distinct subsets with potential therapeutic vulnerabilities. **Methods:** We analyzed CRC tumors (any stage/ subtype) sequenced with Tempus xT assay (DNA-seq of 648 genes at 500x coverage, full transcriptome RNA-seq). RNF43 alt were defined as pathogenic/likely pathogenic per OncoKB, or copy number aberrations (CNA); deep deletions, or amplifications ($>8x$). RNF43 alt vs. wildtype (wt) were compared using Chi-squared/Fisher's Exact tests or Wilcoxon rank-sum tests to evaluate differences in biomarkers. Gene Set Variation Analysis (GSVA) was applied to gene expression data to derive single-sample pathway enrichment scores. ICI-treated MSI-H CRC from the MSKCC cohort (n = 74), publicly available in AACR GENIE v13, was used to assess the overall survival (OS) using the Kaplan-Meier method. **Results:** RNF43 alt was identified in 5.2% (635 of 12,243) CRC tumors. CNA accounted for 6% of RNF43 alt CRC. RNF43 alt vs. RNF43 wt CRC was associated with older age (median 69 vs. 59 years, $p < 0.001$), more prevalent in females (56% vs 43%; $p < 0.001$). A detailed comparison of RNF43 alt vs. RNF43 wt CRC with $p < 0.001$ are shown (Table). Of MSI-H CRC (n = 714), 51% were RNF43 alt, with 80% being RNF43 p.GLY659fs. Among MSI-H RNF43 alt CRC, BRAF alt was co-mutated in 59%, with BRAF^{V600E} constituting 99%. Median TMB was higher for MSI-H RNF43 alt vs. MSI-H RNF43 wt (40 vs. 31 mut/MB, $p < 0.001$). Among MSI-H CRC, GSVA identified significant downregulation of Cetuximab benefit pathway and upregulation of IGF1R and PI3K/AKT pathways in RNF43 alt vs RNF43 wt. Among ICI-treated MSI-H CRC (n = 74) from the MSKCC cohort, no significant OS difference (HR 0.81 [95%CI: 0.34 – 1.97]; $p = 0.65$) was noted for RNF43 alt (n = 42) vs. wt (n = 32). **Conclusions:** RNF43 alt are common in MSI-H CRC and associated with potentially actionable genomic and transcriptomic signatures. Functional characterization of interplay between the WNT signaling and therapeutically relevant pathways (PI3K/AKT, BRAF, IGF1R, Cetuximab benefit) to better define optimal ICI combination approaches in MSI-H RNF43 alt CRC is ongoing. Research Sponsor: Tempus Labs.

	RNF43 altered, Total = 635	RNF43 WT, Total = 11608
Sidedness*		
Left	77/230 (33%)	3474/4381 (79%)
Transverse	35/230 (15%)	189/4381 (4%)
Right	118/230 (51%)	718/4381 (16%)
TMB Median (mut/MB)	27	3
TMB > 10 MB	375/632 (59%)	441/10740 (4%)
PDL1 positivity (IHC)*	21/187 (11%)	180/4169 (4%)
MSI-H and/or dMMR	364/633 (58%)	350/11345 (3%)

*Of tumors with known sidedness, *of tumors with internal IHC. Bold denominators reflect non-missing data.

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Poster Session

Use of a systems-biology informed machine learning model to predict drug response using clinically available NGS data. *First Author: Maayan Baron, Zephyr AI, Mclean, VA*

Background: Tremendous progress towards understanding the molecular underpinnings of cancer has ushered in an era of precision medicine, where actionable biomarkers inform rational design of novel drugs, repurposing of existing medications or new combination therapies, agnostic of tumor type. However less than 20% of cancer patients match to therapies using existing predictive biomarkers. There is therefore an acute need for new methods to expand the population of patients who could benefit from existing drugs and improve patient selection and design of clinical trials evaluating new or repurposed drugs. **Methods:** We developed systems biology-informed AI methods trained on vast multi-omics and multi-modal datasets from DepMap, TCGA and other publicly available sources, to uncover latent vulnerabilities existing in tumors. These vulnerabilities map to pharmacological sensitivities and can be assigned to individual patients using clinically available molecular data. To evaluate our model, we focused on predicting sensitivities to a third-generation tyrosine kinase inhibitor (TKI), which we assessed in non-small cell lung cancer (NSCLC) cell lines, patient derived xenografts (PDXs) and a clinicogenomics cohort from AACR Project GENIE (n=2004 patients, n=273 patients treated with TKI of interest). Where applicable, whole exome data used as input for validation model predictions were filtered to ~300 genes included on commercial NGS panels to reflect data available in RWD cohorts. **Results:** Our model accurately predicts response to the TKI across diverse cancer cell lines with high accuracy ($r^2 = 0.768$; $\rho = 0.83$; mean absolute error = 0.065). Using NSCLC cancer cell lines and PDX model systems heterogeneous for this TKI's current FDA molecular label (but within the scope of the drug's current cancer indication), we were able to further validate our model's predictions, show they were not dependent on obvious molecular confounders, and demonstrate a potential label expansion opportunity for this drug beyond the current narrow molecular label. While all NSCLC patients from AACR Project GENIE treated with this TKI were "on label", NSCLC patients our model predicted to be sensitive to the TKI had a 4-month increased median PFS compared to patients predicted to be less sensitive (Log-rank test p -value < 0.05 ; HR = 1.64; 1.23-2.22, 95% CI). The PFS partition was not due to obvious clinical confounders such as stage ($p = 0.91$), age ($p = 0.86$), sex ($p = 0.63$), smoking status ($p = 0.57$) or on-target mutations ($p = 0.70$). Biological networks associated with each prediction provide rich context and highlight a putative rational drug combination strategy for this drug. **Conclusions:** We have developed an ML model that uses clinically obtainable NGS data to accurately predict increased sensitivity to a third-generation TKI validated in NSCLC cell lines, PDX models and a RWD patient cohort. Research Sponsor: Zephyr AI.

3135

Poster Session

Exploring expression levels of HER2, HER3, MET, Claudin18.2, and MUC16 across 16 cancer types using an artificial intelligence-powered immunohistochemistry analyzer. *First Author: Seunghwan Shin, Oncology, Lunit, Seoul, Korea, Republic of (South)*

Background: Quantifying tumor-associated antigen (TAA) expression levels on tumor cells (TC) from immunohistochemistry (IHC) stained slides has been widely used to predict response to novel anti-tumor agents. However, obtaining the precise quantification of TAA expression levels from various cancer types is still challenging. To quantify five targets of interest, we applied an artificial intelligence (AI)-powered analyzer to 16 cancer types. **Methods:** AI-powered whole slide image (WSI) analyzers were developed using IHC positive or negative tumor cells (TC) from PD-L1 22C3 pharmDx and HER2 4B5 datasets, annotated by pathologists. The universal model was trained by IHC-positive or negative TCs from all datasets, while the second model was trained by the intensity of positive (from 1+ to 3+) or negative TCs from the HER2 dataset. Both AI models were applied to the pan-cancer tissue microarray dataset (n = 1,370) with MUC16, CLDN18.2, MET, HER3, and HER2 IHC staining, respectively. The expression levels of those TAAs were calculated with tumor proportion score (TPS) or ASCO/CAP scoring criteria for HER2 in 16 cancer types including biliary tract, breast, colorectum, esophagus, head and neck, kidney, liver, lung, ovary, bladder, pancreas, prostate, stomach, thyroid, cervical, and endometrial cancer. **Results:** Based on the TPS of 1% or more, the positivity of MUC16 and CLDN18.2 were most frequently observed in ovary (51.6%) and kidney (24.2%), respectively, and MET and HER3 in colorectum (63.8%; 40.5%). The five most highly expressed tumors and their frequency of TPS $\geq 1\%$ are shown. HER2 3+ tumor cells were most highly expressed in the breast, followed by the bladder. **Conclusions:** This study describes the TAA expression levels in various tumors using an AI-powered IHC analyzer. This method could be useful for exploring target cancer types and predicting response to novel TAA targeted agents. Research Sponsor: None.

Order of expression levels	Positivity in all types (%)				
	First (%)	Second (%)	Third (%)	Fourth (%)	Fifth (%)
MUC16	Ovary (52.8)	Biliary tract (33.3)	Endometrium (25.0)	Cervical (18.6)	Breast (17.1)
CLDN18.2	Kidney (24.2)	Prostate (26.1)	Stomach (22.8)	Pancreas (20.0)	Bladder (16.7)
MET	Colorectum (63.8)	Thyroid (59.7)	Pancreas (40.0)	Kidney (38.2)	Lung (35.4)
HER3	Colorectum (40.5)	Bladder (24.4)	Stomach (18.8)	Kidney (13.2)	Liver (4.2)
HER2	Breast (3+ (21.4), 2+ (3.6), 1+ (14.3))	Bladder (3+ (11.1), 2+ (8.9), 1+ (16.7))	Stomach (3+ (5.1), 2+ (0.6), 1+ (7.7))	Biliary tract (3+ (0), 2+ (7.4), 1+ (7.4))	Endometrium (3+ (0), 2+ (7.4), 1+ (7.0))

3137

Poster Session

Impact of HER2 assay sensitivity on the ability to detect tumors with low to ultra-low HER2 expression: A TMA study on more than 10,000 tumors from more than 100 tumor entities. *First Author: Maximilian Lennartz, University Medical Center Hamburg-Eppendorf, Hamburg, Germany*

Background: Detection of low level HER2 expression (HER2 low) is a prerequisite for therapy with new HER2 inhibitors in advanced breast cancer. Currently, tumors with immunohistochemical 1+ expression, and possibly also those with lower expression, are considered HER2 low. Therefore, the question of optimal sensitivity of HER2 assays is of increasing importance for clinical HER2 testing. In addition, there is hope that tumor types other than those with typical 3+ positivity may also benefit from these therapies. The aim of this study was to systematically investigate the influence of HER2 immunohistochemistry assay parameters on the detection rate of tumors with HER2 low expression in different tumor types. **Methods:** A tissue microarray containing $>10,000$ tissue samples from more than 100 different tumor types and subtypes was analyzed for immunohistochemical expression of HER2 using different immunohistochemistry protocols and anti-HER2 antibodies, including the HercepTest and laboratory developed tests designed for high sensitivity. HER2 IHC evaluation included the recording of HER2 low (1+), ultralow (any staining, less than 1+), and 0 (completely negative). **Results:** Irrespective of the assay sensitivity all assays showed the expected/tolerable association with HER2 fluorescence in situ data in a cohort of 356 breast cancers. For the HercepTest, HER2 amplification was seen in 93% of 28 3+ cases, 55% of 11 2+ cases and in 1.5% of 274 0 and 1+ cases. For the most sensitive assay, amplification was seen in 90% of 30 3+ cases, 19% of 37 2+ cases and in 0.8% of 249 0 and 1+ cases. In non-breast cancers, the use of different assays resulted in highly variable results regarding the range of tumors with low or ultra-low HER2 expression in different tumor entities. For example, low (1+) and ultra-low (+) expression was observed in 7-24% (1+) and 11-28% (+) of serous ovarian cancers, 6.2-24% (1+) and 3.4-19% (+) of endometrioid endometrial cancers, 5.5-14% (1+) and 7.7-13% (+) of intestinal gastric cancers, 1.8-9.2% (1+) and 4.5-11% (+) of ductal adenocarcinomas of the pancreas, 1.9-33% (1+) and 5.5-11% (+) of muscle invasive urinary bladder cancers, 2.9-16% (1+) and 4.3-12% (+) of adenocarcinomas of the colon, 0-7.7% (1+) and 2.4-4.6% (+) of clear cell renal cell carcinomas, 4.8-6.5% (1+) and 6.0-8.6% (+) squamous cell carcinomas (SQCC) of the larynx, 6.3-7.1% (1+) and 2.4-6.3% (+) SQCC of the esophagus, 0.8-26% (1+) and 2.4-12% (+) SQCC of the cervix, as well as 1.5-5.1% (1+) and 1.5-2.2% (+) SQCC of the vulva. **Conclusions:** Low level HER2 expression occurs commonly in many cancer types. The rate of identifiable tumors with HER2 low or HER2 ultra-low expression greatly varies depending on assay parameters that can easily be modified. Clinical trials are needed to identify the HER2 expression thresholds to identify patients who may benefit from anti-HER2-low therapies. Research Sponsor: None.

3138

Poster Session

Pathway enrichment analysis in tumors with high mutation burdens and interferon- γ signature expression: A pancancer analysis. *First Author: Xuanyi Li, Vanderbilt University Medical Center, Nashville, TN*

Background: Tumor mutation burden (TMB) correlates with immunotherapy response, but outcomes still vary in high TMB cancers, and many high TMB tumors lack T cell infiltration. Here, we assessed gene expression signatures of high TMB, including both inflamed and non-inflamed tumors (defined by interferon- γ [IFN- γ] gene signatures). **Methods:** Gene set enrichment analysis (GSEA) was assessed from RNA-sequencing data in tumors in TCGA. TMB and IFN- γ signature score were assessed by previously published methods. We performed GSEA on high vs low TMB tumors, and further stratified by high vs low IFN- γ signature expression within high TMB tumors. We validated results in Tempus RNA-sequencing data from 264 patients at Vanderbilt. **Results:** 4020 TCGA cases in non-small cell lung, melanoma, bladder, head and neck, kidney, and colorectal cancer were included. Major signatures upregulated in the high TMB group included cell cycle signaling, nuclear protein/mRNA export, cholesterol biosynthetics, and ubiquitin signaling. High TMB/high IFN- γ signature tumors were enriched in immune-related pathways (neutrophil and monocyte chemotaxis, T cell activation and proliferation, and interleukin-1 secretion), and non-immune pathways including cAMP metabolic process and phosphatidylinositol signaling. High TMB/low IFN- γ signature tumors had enriched pathways in nonsense mediated decay, electron transport chain/oxidative phosphorylation, and mitochondrial translational disassembly. 264 tumors from Vanderbilt were used for validation; pathways including cholesterol biosynthetics also correlated with immunotherapy response. **Conclusions:** High TMB tumors were enriched in pathways such as ubiquitin signaling, which could regulate immune cell function in antitumor immunity. Within high TMB cancers, tumors with higher IFN- γ signatures have enriched immune-related, and metabolic pathways, which could suggest novel therapeutic targets to make high TMB/ low IFN- γ tumors more immunogenic. Research Sponsor: None.

3139

Poster Session

Evolution of HER2 scores after neoadjuvant systemic therapy in breast cancer. *First Author: Esther G Chong, Loma Linda University Medical Center, Loma Linda, CA*

Background: Breast cancer (BC) is a malignancy with a wide array of histopathological characteristics and tumor heterogeneity leading to major clinical implications for management. With the recent approval of antibody-drug conjugates (ADCs) for human epidermal growth factor receptor 2 (HER2)-low advanced BC, there is increased significance for characterizing the spectrum of HER2 expression in the curative setting. **Methods:** We conducted a single institution retrospective review of patients with BC who received neoadjuvant systemic therapy (NAST) followed by definitive surgical resection from 2008 to 2022. The initial tumor biopsies were tested for estrogen receptor (ER), progesterone receptor (PR), and HER2 status per ASCO/CAP guidelines and repeated on the residual tumor tissue after NAST. HER2 status was categorized into HER2-negative (IHC 0), HER2-low (IHC 1 or IHC 2/ Fluorescence in situ hybridization [FISH] negative), and HER2-positive (IHC 2/ FISH positive or IHC 3). Concordance and discordance with HER2 status in the pre and post NAST tumor samples were analyzed using descriptive statistics. **Results:** Of 340 patients with BC who received NAST, 55 patients with residual disease had pre and post treatment biomarker data available for analysis. Prevalence of HER2-low was 70.9% (39/55) in the pretreatment tumors while it was 58.2% (32/55) in the post treatment tumors. 40% of tumors (22/55) had HER2 discordance while 60% (33/55) demonstrated concordance with HER2 expression after NAST. Among the changes in HER2 status, a shift from HER2-low to HER2-negative status occurred most frequently in 18.2% of tumors (10/55). In tumors with HER2 discordance, 36.4% (8/22) were also noted to have changes in ER or PR status while this was seen in 48.5% (16/33) of tumors with HER2 concordance. For rates of recurrence, 22.7% (5/22) of patients in the HER2 discordant group had relapsed compared to 18.2% (6/33) patients in the HER2 concordant group. **Conclusions:** Dynamics of HER2 expression is increasingly important in the rapidly changing therapeutic landscape of BC. Our study shows high prevalence of HER2-low expression in tumors with residual disease after NAST and frequent conversion of HER2-low to HER2-negative status with NAST. Further studies are warranted to determine the clinical and therapeutic relevance of biomarker evolution and tumor heterogeneity in the curative setting. Research Sponsor: None.

HER2 discordance and concordance rates.

	N= 55	100 %
Low to neg	10	18.2%
Low to positive	4	7.3%
Negative to low	3	5.5%
Negative to positive	1	1.8%
Positive to neg	0	0.0%
Positive to low	4	7.3%
Positive to positive	4	7.3%
Low to low	25	45.5%
Negative to negative	4	7.3%

3140

Poster Session

A four-tier classification system for studying homologous recombination repair gene reversion mutations as a mechanism of resistance to PARP inhibitors and platinum chemotherapy. *First Author: Qiuxiang Ou, Geneseeq Research Institute, Nanjing Geneseeq Technology Inc., Nanjing, China*

Background: Pathogenic mutations in homologous recombination repair (HRR) genes are highly associated with the oncogenesis of multiple cancers and represent favorable biomarkers for platinum (Pt)-based chemotherapy and poly ADP ribose polymerase inhibitors (PARPi). While the development of drug resistance by restoring protein function via secondary mutation is commonly observed, a thorough analysis of the landscape of HRR gene reversion mutation is lacking. **Methods:** A real-world database with ~13,000 pan-cancer patients who underwent targeted next-generation sequencing and contained a primary germline or somatic pathogenic mutation of 25 pre-defined HRR genes, including *ATM*, *ATR*, *BARD1*, *BLM*, *BRCA1*, *BRCA2*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *ERCC3*, *FANCA*, *FANCC*, *FANCD2*, *FANCI*, *FANCL*, *MRE11A*, *NBN*, *PALB2*, *RAD51*, *RAD51C*, *RAD51B*, *RAD51D*, *RAD54L*, and *WRN*, was used to identify HRR secondary mutations, which were further classified into four tiers by mutation type and intended reversion mechanism. Patient's clinical data and treatment history were retrospectively reviewed. **Results:** The potential mechanism of HRR gene reversion was categorized into four tiers, including Tier 1 (single nucleotide variation, SNV), Tier 2 (frameshift), Tier 3 (deletion), and Tier 4 of other mutation types that were not further discussed in this study. A total of 42 patients were identified with Tier 1/2/3 secondary HRR gene mutations in the presence of a primary pathogenic germline (N = 32) or somatic (N = 10) mutation. *BRCA1* (15/42, 35.7%) and *BRCA2* (23/42, 54.8%) were most frequently observed in this cohort with significant enrichment of exon 11 aberrations of both genes. The other HRR genes identified of Tier 1/2/3 reversion mutations included *PALB2* (N = 3, Tier 3) and *RAD51D* (N = 1, Tier 1). More specifically, a majority of *BRCA1* reversion mutations (8/15) were Tier 1 SNV, while the most prevalent reversion mechanism for *BRCA2* was Tier 3 deletion, which accounted for 60.9% (14/23) of all *BRCA2* cases with a median deleted length of 1164 bp (range: 153–6745 bp). Furthermore, we reported the treatment history data of three cancer patients (pancreatic, prostate, and lung, respectively) demonstrated the acquisition of *BRCA2* reversion mutations (Tier 2 and Tier 3) at post-Pt/Olaparib in the presence of a primary germline *BRCA2* pathogenic mutation, strongly suggestive of the role of reversion mutations in driving resistance to Olaparib or Pt-chemotherapy. **Conclusions:** Owing to a large-scale real-world dataset, we retrospectively investigated the landscape of the reversion mechanism of HRR genes and established a four-tier classification system for secondary HRR mutations in the presence of primary germline/somatic pathogenic HRR mutations. This study is of great clinical value in studying mechanisms of drug resistance to Pt-chemotherapy and PARPi. Research Sponsor: None.

3141

Poster Session

Larotrectinib long-term efficacy and safety in adult patients (pts) with tropomyosin receptor kinase (TRK) fusion cancer. *First Author: David S. Hong, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Neurotrophic tyrosine receptor kinase (*NTRK*) gene fusions are oncogenic drivers in a broad array of tumor types. Larotrectinib is a first-in-class, highly selective, central nervous system (CNS)-active TRK inhibitor approved for tumor-agnostic use in pts with TRK fusion cancer based on a rapid, robust, and durable objective response rate (ORR) in both adult and pediatric pts with various non-primary CNS cancers. Here, we report data on an expanded cohort of adult pts with TRK fusion cancer treated with larotrectinib. **Methods:** Adults with non-primary CNS TRK fusion cancer treated in three larotrectinib clinical trials (NCT02576431, NCT02122913, and NCT02637687) were included. Larotrectinib was administered at 100 mg twice daily in most pts. Responses were assessed per Independent Review Committee (IRC) using RECIST v1.1. Data cut-off: July 2022. **Results:** As of July 2022, there were 194 adult pts enrolled, with 180 eligible for efficacy analyses by IRC; 22 pts had known brain metastases at baseline. There were 24 different tumor types; the most common were lung (n=30; 15%), soft tissue sarcoma (n=30; 15%), thyroid (n=28; 14%), salivary gland (n=25; 13%), and colon (n=23; 12%). Median age was 57 years (range 19–90). The gene fusions involved *NTRK1* (n=90; 46%), *NTRK2* (n=7; 4%), or *NTRK3* (n=97; 50%). Pts had previously received a median of one systemic therapy (range 0–10). ORR was 57% (95% CI 50–65): 29 (16%) complete response (including one pathological complete response), 74 (41%) partial response, 39 (22%) stable disease, 23 (13%) progressive disease, and 15 (8%) not evaluable. ORR in 22 evaluable pts with baseline CNS metastases was 68% (95% CI 45–86). Median time to response was 1.8 months, and median duration of response was 43.3 months (95% CI 29.2–not estimable [NE]) at a median follow-up of 32.3 months. Median progression-free survival was 24.6 months (95% CI 11.3–34.5) at a median follow-up of 28.5 months. Median overall survival was 48.7 months (95% CI 38.5–NE) at a median follow-up of 33.8 months. At data cut-off, 39 of the 73 pts who had disease progression continued treatment post-progression for ≥ 4 weeks. Treatment-related adverse events (TRAEs) were predominantly Grade 1/2. Grade 3/4 TRAEs occurred in 27 (14%) pts. Treatment discontinuation due to TRAEs was reported in one pt (increased alanine aminotransferase and aspartate aminotransferase). **Conclusions:** In this expanded dataset with extended follow-up, larotrectinib continues to demonstrate rapid and durable responses, extended survival, and a favorable safety profile in adults with TRK fusion cancer, including those with CNS metastases. These results support the wider adoption of next-generation sequencing panels that include *NTRK* gene fusions when testing pts with solid tumors; this ensures that pts are offered the right medicine for their disease as soon as possible. Clinical trial information: NCT02576431, NCT02122913, NCT02637687. Research Sponsor: These studies were funded by Bayer HealthCare Pharmaceuticals, Inc.

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Poster Session

Treatment of chronic hepatitis C virus infection to increase access to cancer clinical trials in patients with hematologic malignancies: A prospective observational study. *First Author: Khalis Mustafayev, Departments of Infectious Diseases, Infection Control and Employee Health. The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Most cancer patients with chronic hepatitis C virus (HCV) infection are excluded from cancer clinical trials (CCTs). The use of direct-acting antivirals (DAAs) to eradicate HCV and allow access to CCTs in HCV-infected cancer patients has not been studied. We aimed to evaluate the efficacy and safety of DAA treatment to increase access to CCTs in patients with chronic HCV infection and hematologic malignancies (HM). **Methods:** HCV-infected patients with HM seen at MD Anderson Cancer Center between 01/01/2016 and 01/31/2023 were enrolled in a prospective observational study. Those initially excluded from CCTs and then treated with DAAs to allow that cancer treatment were further analyzed (cases). HCV-infected cancer patients treated with DAAs but never enrolled in CCTs were used as controls. The 1:1 matching between cases and controls was based on the cancer type and stage, history of > 3 types of chemotherapy, and presence of cirrhosis. The primary outcomes were the efficacy and safety of DAAs. The secondary outcomes were overall survival (OS) and progression-free survival (PFS). **Results:** Twenty-four patients with HM initially excluded from CCTs because of HCV were enrolled. Twelve of them (50%) received DAAs to have access to CCTs and they were matched to 12 controls. Most of the cases were men (10; 83%), white (6; 50%), non-cirrhotic (10; 83%), and with HCV genotype 1 (9; 75%). Most patients in the control group were men (7; 58%), white (9; 75%), non-cirrhotic (8; 67%), and with HCV genotype 1 (9; 75%). Among the entire study group, adverse events occurred in 6 of the 24 patients (25%), and all were grade 1-2. No HCV-associated liver failure or death occurred. The overall sustained virologic response (microbiologic cure) after completion of antiviral therapy was 92%. Median OS was 74 months in the cases vs 52 months in the controls, median PFS was 30 months in the cases vs 33 months in the controls. When compared to controls in multivariate analysis, cases had significantly better OS (hazard ratio = 0.23, 95% CI = 0.06 to 0.85, $p = 0.027$). No significant differences were noted in PFS ($p = 0.13$). Death due to progressive HM occurred in all 12 controls (100%) but only in 4 cases (33%) ($p = 0.001$). **Conclusions:** DAA treatment increases access to CCTs and improves OS in patients with chronic HCV infection and HM. HCV infection should not be considered a contraindication to investigational cancer treatment. The use of DAAs to facilitate access CCTs could become one of the most common indications for DAAs in HCV-infected cancer patients. Research Sponsor: The University of Texas MD Anderson Cancer Center Institutional Research Grant on Clinical/Translational Research.

3144

Poster Session

Novel LTK fusions based on NGS sequencing data in Chinese patients with solid tumors. *First Author: Hui Chen, Shanghai Origimed Co., Ltd, Shanghai, China*

Background: Leukocyte receptor tyrosine kinase (*LTK*) gene has the same kinase domain (PTKc-ALK-*LTK*) as *ALK*, and could functionally respond to *ALK* inhibitors such as lorlatinib. Previous study reported that *CLIP1-LTK* fusion was a novel oncogenic driver mutation in lung cancer (occur in 0.4% of non-small cell lung cancer), which was sensitive to the *ALK* tyrosine kinase inhibitor lorlatinib. So far, *LTK* fusion has been rarely reported. **Methods:** A total of 11 Chinese solid tumor patients were reviewed, including 6 cases of *LTK* positive rearrangements in DNA and 5 cases of *LTK* positive fusion in RNA. FFPE samples were collected for NGS-based 450 cancer gene panel detection in both DNA and RNA level, and matched blood samples were used as normal control to filter out germline mutations. *LTK* fusions were analyzed by Origifus algorithm. **Results:** We found 6 patients with *LTK* rearrangements by DNA-based NGS detection, including lung adenocarcinoma, colorectal cancer, stomach cancer, spindle cell sarcoma of small intestine, adenocarcinoma of the pancreas, and cancer of unknown primary, and 5 soft tissue sarcoma patients with *RPAP1 E25-LTK E2* fusions by RNA-based NGS detection. We analyzed the patterns of partner genes and breakpoints of the 6 *LTK* rearrangements. The partner genes included *NUSAP1* ($n=2$), *NDUFAF1* ($n=1$), *LOC105370802* ($n=1$), *EHD4* ($n=1$), and *AGBL1* ($n=1$). All these partner genes were located on the same chromosome as *LTK*, rather than *CLIP1*, which was identified as a translocation. The breakpoints on *LTK* included exon20 ($n=2$), intron1 ($n=2$), exon6 ($n=1$), and exon10 ($n=1$). Five of the 6 fusions consisted of a complete PTKc-ALK-*LTK* domain. Among the 6 *LTK* rearrangements, *LTK E20-NUSAP1 E2* was predicted as a fusion. Interestingly, this clinical real-world sample also harbored a classic *NTRK1* fusion, *LMNA E2-NTRK1 E11*. The other *NUSAP1-LTK* was predicted to have a transcript of 3'-3', but one of the breakpoints was observed at *LTK* exon6, which could be located at the kinase domain, so the possibility of eventual fusion cannot be excluded. The two *NUSAP1-LTK* fusions were found in a stomach tumor and a soft tissue sarcoma, respectively. One non-small-cell lung cancer (NSCLC) patient had a breakpoint detected on *LTK* exon10, which is the same as the exon of *CLIP1-LTK* reported. **Conclusions:** This study revealed novel *LTK* fusions/rearrangements and their cancer distribution in Chinese patients with solid tumors. We gave the details of these fusions/rearrangements which enrich our understanding of the *LTK* fusion. Although the small number of cases, our analysis promoted the attention on *LTK* and its potential value of drug research and clinical treatment in pan-cancer. Research Sponsor: None.

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Poster Session

Dupilumab for the treatment of dermatologic adverse events associated with MEK and EGFR inhibitors. *First Author: Stephanie Gu, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Mitogen activated protein kinase kinase inhibitors (MEKi) and epidermal growth factor receptor inhibitors (EGFRi) are targeted therapies used in the treatment of various cancers. Dermatologic adverse events (dAEs) are common with these medications. Dupilumab, a human monoclonal antibody that targets IL-4, is an FDA approved therapy for the treatment of atopic dermatitis. It has also shown utility in the treatment of many other skin disorders, including toxicities associated with anticancer therapies. In our study, we aim to evaluate the efficacy and safety of dupilumab for the treatment of MEKi/EGFRi associated dAEs. **Methods:** Patients who received dupilumab for the treatment of a dAE attributed to MEKi or EGFRi from 3/1/2017 to 10/1/2022 were identified at Memorial Sloan Kettering Cancer Center. Severity of dAEs was graded at baseline and follow up using Common Terminology Criteria for Adverse Events (CTCAE) v5.0. Patient response to dupilumab was categorized into complete response (CR) (reduction to grade 0), partial response (PR) (reduction to grade 1), or no response (NR) (including change from grade 3/2 to grade ≥ 2). **Results:** A total of 17 patients (median age 62 years [5 – 87], 58.8% female) who received dupilumab for MEKi (70.6%) or EGFRi (29.4%) related dAEs were identified. Two patients on MEKi were also on concomitant BRAF inhibitors. Patients were white (88.2%), black (5.9%), and Asian (5.9%) and were all undergoing treatment for solid tumors. All dAEs had an eczematous phenotype; 16 were grade 2 (88.2%) and one (5.9%) was grade 3. The median time from dAE development to initiation of dupilumab was 121 days (5 – 1330). Following treatment, 15 patients (88.2%) experienced improvement, with 46.7% and 53.3% achieving CR and PR, respectively. Patients were on dupilumab for a median of 89 days (0-2556), with CR and PR patients exhibiting initial documented response after a median of 30 days (6 – 173). The median CTCAE grade decreased from 2 to 1, and the number of patients on topical and systemic steroids following addition of dupilumab decreased from 17 (100%) to 7 (41.2%) and 5 (29.4%) to 1 (5.9%), respectively. As a result of intolerable anti-cancer therapy-associated dAEs, 4 patients (all on MEKi) initially discontinued their antineoplastic. Three patients (75%) were successfully rechallenged with their original MEKi, while 1 (25%) was switched to another MEKi without subsequent dAE recurrence. No patients reported adverse events to dupilumab treatment. **Conclusions:** Patients may experience eczematous eruptions while undergoing treatment with MEKi or EGFRi. Dupilumab may be a safe and effective steroid sparing therapeutic option for the management of these dAEs. Research Sponsor: None.

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Poster Session

Immune modulation and the oral live biotherapeutic product, MRx0518, in treatment-naïve patients with cancer: Updated safety data. *First Author: Mark Lythgoe, Imperial College, London, London, United Kingdom*

Background: Live biotherapeutic products (LBPs) are emerging novel anti-cancer therapies. MRx0518 is a gut microbiome-derived oral LBP, consisting of a single strain of *Enterococcus gallinarum*, which has demonstrated potent anti-tumorigenic efficacy pre-clinically. We have previously shown MRx0518 monotherapy is associated with significant genomic, immune, microbiome, and metabolomic changes, consistent with anti-cancer efficacy in treatment-naïve patients. Here, we report long-term subject follow-up, and further signals of immune modulatory changes from flow cytometry analysis. **Methods:** NCT03934827 is a Phase 1B single-centre study in treatment-naïve patients with confirmed cancer, planned for surgical resection. 17 patients (8 breast, 4 prostate, 3 uterine, 1 bladder & 1 melanoma) received MRx0518 (1×10^{10} – 1×10^{11} CFU) BID monotherapy for 7-28 days from inclusion until surgery. Safety data was collected from dosing until 1-year following cessation. Exploratory analysis included evaluation of pre- and post-treatment peripheral blood mononuclear cells (PBMCs) by multiparametric flow cytometry for leucocyte activation, indicative of anti-cancer efficacy. **Results:** A total of 29 adverse events (AEs), all CTCAE grade 1 (96%) and grade 2 (4%), were reported. Only 8 (28%) were deemed related to MRx0518. No grade 3/4 toxicities or serious AEs were recorded. At 30-days, and 1-year follow-up no further serious AEs occurred. At a median follow-up of 41 months, 13 (76%) patients remain cancer-free, with 2 (11%) reoccurrences and 2 (11%) lost to follow-up. Analysis of pre- and post-treatment PBMCs identified statistically significant increases in CD3⁺CD56⁺ ($p < 0.0005$), natural killer cells ($p < 0.005$), natural killer T-cells ($p < 0.01$), CD8⁺CD62L⁺ ($p < 0.001$), and CD4⁺CD62L⁺ ($p < 0.0001$) subsets following MRx0518 therapy. A positive trend was also seen in CD3⁺CD8⁺ cells. Furthermore, we observed a significant increase in both subsets of T-regulatory lymphocytes (nTreg ($p < 0.05$) and eTreg ($p < 0.05$)) and a decrease in both CD4⁺ ($p < 0.05$) and CD8⁺ ($p < 0.005$) central memory cells. Sub-analysis of the breast cancer patient group showed a significantly higher increase in CD3⁺CD56⁺ cells ($p < 0.0001$) and intermediate monocytes ($p < 0.01$). **Conclusions:** This study demonstrates the long-term safety profile of MRx0518 therapy in treatment-naïve cancer patients. Analysis of PBMCs reveals clear evidence of immune modulation, consistent with significant anti-cancer efficacy. This is concordant with prior findings from this study. Notably, significant changes in CD3⁺CD56⁺ have also been demonstrated in other studies of microbiome modulation (e.g., NCT03341143), and may be important determinant of anti-cancer efficacy. Despite the limitations of a small sample size, this effect is particularly prominent in the breast cancer subgroup, warranting further evaluation. Clinical trial information: NCT03934827. Research Sponsor: Imperial College London.

3146

Poster Session

Tumor-agnostic genomic and clinical analysis of solid tumors with *BRAF* fusions. *First Author: Monica F Chen, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Approximately 15% of cancers harbor *BRAF* alterations, of which ~5% are *BRAF* fusions. *BRAF* fusions are class II alterations that have worse outcomes than class I V600E alterations. While prior investigational therapies for *BRAF* fusions had disappointing outcomes, novel therapies are in clinical trials, underscoring the need to better characterize these tumors. **Methods:** Data from adult and pediatric patients with *BRAF* fusion+ cancers identified between January 2014 and November 2022 utilizing a center-wide next generation sequencing (NGS) program of >99,000 sequenced samples were analyzed. DNA-based hybrid capture tumor NGS (MSK-IMPACT), ctDNA targeted NGS (MSK-ACCESS), and/or RNA anchored multiplex PCR tumor NGS (MSK-Fusion) were used. Fusions were manually reviewed and considered to have oncogenic potential if they had an in-frame protein fusion involving a non-*BRAF* partner gene and an intact *BRAF* kinase domain (exons 11-18). Fusions not previously reported in OncoKB, COSMIC, TCGA, NIH gene, Fusion GDB2, and PubMed were classified as novel. All cases underwent clinical data curation including baseline demographic, tumor characteristics, and treatment histories. **Results:** 212 patients (0.2%) with *BRAF*-fusion positive solid tumors were identified. 194 were identified by DNA-based tumor NGS (96 had sufficient tissue for confirmatory RNA-based NGS, all of which were positive). Six were identified by ctDNA NGS and 12 by RNA-based tumor NGS only (5 had insufficient tissue for DNA-based tumor NGS). 83 unique 5' fusion partners were found, of which 42 were novel. The most frequent tumor types were pilocytic astrocytoma (n=30, 14%), prostate CA (n=28, 13%), melanoma (n=24, 11%), lung CA (n=21, 10%), and colon CA (n=15, 7%). 44% of patients with pilocytic astrocytoma had *BRAF* fusions, of which 90% were *BRAF-KIAA1549*. Concomitant alterations ($\geq 10\%$ frequency) included *TP53* (24%), *TERT* (18%), *CDKN2A* deletions (13%), and *CDKN2B* deletions (12%). 20% (n=43) were treated with MAPK-pathway directed therapies spanning multiple histologies and lines of therapies. Of the 212 patients, 17 had acquired *BRAF* fusions after targeted therapy for another oncogene (*EGFR* mutation (n=11), *BRAF*V600E (n=4), *FGFR* fusion (n=1), *NTRK* fusion (n=1)). The majority of patients with acquired *BRAF* fusions had *EGFR*-mutant lung adenocarcinoma (n=11, 76%); the median time from *EGFR* targeted therapy initiation to *BRAF* fusion detection was 25 months (range 16-38 months). **Conclusions:** A wide variety of adult and pediatric solid tumors harbored de novo *BRAF* fusions. Complementary RNA sequencing optimized fusion identification in many cases. Multiple novel fusion partners were found. Acquired *BRAF* fusions were identified after targeted therapy for a variety of distinct oncogenes, the majority of which were *EGFR* mutations. Research Sponsor: T32.

3149

Poster Session

Reporting and impact of subsequent cycle toxicities in oncology phase I clinical trials. *First Author: Avina Rami, Harvard Medical School, Boston, MA*

Background: In recent years, the landscape of clinical trial development has evolved to include immunotherapy and targeted therapies, which have different lengths of administration and toxicity profiles compared to standard chemotherapy. As treatments have evolved, the classic assumptions of toxicity associated with cytotoxic agents may be less relevant, requiring new strategies for design of trials intended to inform dosing strategies for agents that may be administered beyond a set number of defined cycles. We aimed to describe the overall incidence of dose-limiting toxicities (DLTs) during and after cycle 1, the frequency of reporting subsequent cycle toxicities, and the impact of post-cycle 1 DLTs on conclusions drawn from oncology phase I clinical trials. **Methods:** We conducted a systematic review of subsequent cycle toxicities in oncology phase I clinical trials published in the *Journal of Clinical Oncology* from 2000 to 2020. Only trials that included more than one cycle of therapy were included. Data elements captured included: year of publication, study design, trial sponsor type, intervention type, number of anti-cancer therapies involved, primary diagnosis, incidence and type of cycle 1 DLT, incidence of dose modification in cycle 1, incidence and type of post-cycle 1 DLTs, incidence of dose modification in post-cycle 1, presence of a recommended phase 2 dose (RP2D) and impact of subsequent cycle toxicity on RP2D. **Results:** From 2000 to 2020, we identified 489 full-text articles reporting on therapeutic phase I clinical trials. Of these, 421 (86%) reported data regarding cycle 1 DLTs and 170 (35%) reported cycle 1 dose modifications. The overall median cycle 1 DLT rate was 8.89%. Only 47 (9.6%) publications reported whether or not there were post-cycle 1 DLTs and only 92 (19%) reported whether or not there were dose modifications beyond cycle 1. The overall median post-cycle 1 DLT rate among trials that reported post-cycle 1 data was 14.8%. A RP2D was reported in 76% (371 of 489) trials. Among these 371 studies, 89% did not report whether post-cycle 1 toxicities impacted the RP2D. Independent predictors of reporting toxicity data beyond cycle 1 included year of publication, investigational agent type, novelty, disease type, trial size, and sponsor. **Conclusions:** Reporting of subsequent cycle DLTs and dose modification is uncommon in oncology phase I clinical trial publications. As newer oncology treatments trend towards longer duration of treatment, there will be an increased need to understand toxicities occurring post-cycle 1. Guidelines for reporting of phase I clinical trials should expand to include toxicity data beyond the first cycle. Research Sponsor: Alex's Lemonade Stand Foundation.

3148

Poster Session

Phase 1 studies of D07001-F4 and D07001-softgel capsule: Oral metronomic gemcitabine in subjects with advanced solid tumors. *First Author: Chia-Chi Lin, National Taiwan University Hospital, Taipei, Taiwan*

Background: Metronomic chemotherapy with frequent, low dose administration may not only retain the anticancer feature of conventional, periodic maximum tolerated dose (MTD)-based, parenteral chemotherapy, but also possess other novel properties such as immune enhancement and angiogenesis suppression. D07001 is an absorption, enhanced oral gemcitabine originally developed as liquid form (D07001-F4), then further refined into D07001-softgel capsule to enhance therapeutical applicability. Herein, we report the results of two phase I studies that evaluated the dose-limiting toxicity (DLT), pharmacokinetics (PK), bioavailability (BA) and maximum tolerated dose (MTD) of D07001-F4 and D07001-softgel capsules in subjects with refractory, advanced solid tumors. **Methods:** Both studies applied 3+3 dose escalation design. Referring to a similar trial by Eli Lilly, in the first Phase I study (NCT01800630), eligible subjects received a bolus intravenous injection of 5 mg gemcitabine in run-in period then D07001-F4 thrice per week for 2 weeks followed by 1 week rest with escalating doses from 2 to 80 mg. Since no dose-limiting toxicity (DLT) was observed even at maximum 80mg dose-level (DL) in this study, another Ib study (NCT03531320) with the uses of refined D07001-softgel capsule and a modified regimen without the resting period was conducted in subjects with refractory gastrointestinal malignancies to investigating the DLT, maximum tolerated dose (MTD) and PK. The test dose of this Ib study was from 40 to 120 mg (40, 60, 80, 120), in which the bridging dose of 40 mg was employed based on its equivalence to the dose of 80 mg in the first Phase I study. **Results:** A total of 53 eligible patients were enrolled, 34 (10 DL) and 19 (5+1 DL) in the Phase I and Ib studies, respectively. Comparing to parenteral gemcitabine, the mean oral bioavailability of D07001-F4 was about 39%. No DLT was observed in all planned DL, until the 120 mg DL of D07001-softgel capsules, in which 2/6 patients had DLTs (grade 3 hepatotoxicity and grade 3 anorexia, respectively). An addition 100 mg DL was tested (without DLT in a 3 patient cohort) and determined as MTD. Cmax and AUC_(0-48h) of gemcitabine metabolite (dFdU) on C1D1 were largely dose-dependent and comparable for two formulations at bridging dose levels. Despite similar trend for dFdC, more inter-individual variation was observed. The mean dFdC Cmax at MTD of D07001-softgel capsules was 24 ng/mL (0.09 mM) and half-life of 5 hours. Grade >3 anorexia (10.5%) and diarrhea (10.5%) were observed in Phase Ib extension study. **Conclusions:** The results suggest the feasibility of oral gemcitabine treatment with D07001-softgel capsules, which is well-tolerated for continuous dosing and deserves further clinical investigation. Clinical trial information: NCT01800630, NCT03531320. Research Sponsor: Innopharm Inc.

3150

Poster Session

The characteristics of metabolic related pathways under different anoikis activities revealed by pan-cancer analyses. *First Author: Shanshan Xiao, Hangzhou Repugene Technology Co., Ltd., Hangzhou, China*

Background: Anoikis is usually activated to eliminate extracellular matrix-detached cells. Cancers develop several mechanisms to escape from this cellular death signaling pathway which was associated with metabolic reprogramming in tumor development and progression. Comprehensively understanding the characteristics of anoikis activities in pan cancers facilitating better clinical treatment strategies. **Methods:** RNA-Seq data and related patient information were collected from 33 cancer types in TCGA database. We also obtained anoikis related genes (ARGs) from Harmonizome database. The related pathways of epithelial-mesenchymal transition (EMT) and reactive oxygen species (ROS) genes were collected from MSigDB. Autophagy genes were from HADB and metabolic intermediates were from published literatures. Firstly, pathway scores of anoikis and the related pathways were computed through single sample gene set enrichment analysis (ssGSEA). Then, survival analyses based on the anoikis scores were performed to achieve the threshold between the high anoikis (HA) or low anoikis (LA) sample groups. To study the drug efficacy, cell line transcriptome and IC50 data were obtained from GDSC database. Pearson correlations were computed between anoikis and other related pathways or immune cell infiltrations in each sample group. **Results:** Most ARGs were up-regulated in tumors, the same as the HA sample group. Differentially expressed genes between HA and LA were mostly involved in metabolic super-pathways, including metabolic intermediates (TCA cycle, carbohydrate, lipid, nucleotide, vitamin cofactor, and amino acid, etc.) and promoting anoikis-resistance pathways including EMT, inflammation and autophagy. Higher scores of anoikis related pathways were identified in HA across various cancers. Kaplan-Meier survival analysis revealed that HA in KIRC, KIRP, LAML, LGG, LUAD, PAAD, STAD, THYM, and UVM cancers had significantly worse clinical outcomes ($p < 0.05$). Functional enrichment analysis of ARGs through GSEA suggested that anoikis resistance was promoted, whereas anoikis was retarded in those cancers. However, patients in HA of several cancers had longer survives than LA, which may owe to the higher infiltrating levels of anti-tumor immune cells including CD8+ T, CD4+ memory activated T cells, particularly in BRCA, MESO, SARC, and UCEC cancers. Drug efficacy analysis revealed that *BCL2* gene was significantly associated with sensitive drug response on Venetoclax, ABT737, and Tozasertib. And *TLE1* and *CAV1* were associated with Tozasertib resistance and AZD5991 resistance, respectively. **Conclusions:** The characteristics of anoikis activities and metabolic related pathways during tumor progression were comprehensively studied and the prognosis value of anoikis was further assessed by drug efficacy. Research Sponsor: Hangzhou Repugene Technology Co., Ltd.

3151

Poster Session

Development of bifunctional CRBN-SOS1 degraders for treatment of mutant KRAS cancers. *First Author: Kyle Begovich, Biotheryx, Inc, San Diego, CA*

Background: KRAS, a GTPase that regulates cellular growth, is the most frequently mutated oncogene in non-small cell lung, pancreatic and colorectal cancers. Hyperactivation of KRAS in mutant alleles result in upregulated signaling within the MAPK pathway leading to aberrant cell proliferation. In addition to the pan- and mutant-specific KRAS inhibitors, its upstream GEF activator, SOS1, has emerged as an attractive therapeutic target given its ability to regulate the active, GTP-loaded state of KRAS and mitigate MAPK pathway feedback. **Methods:** Utilizing our PRODEGY platform, we developed bifunctional CRBN-SOS1 degraders for the treatment of patients with KRAS-mutated cancers, independent of mutation type. **Results:** Our degraders display CRBN- and proteasome-mediated SOS1 degradation with $DC_{50s} < 15nM$ in high-throughput (HiBit) and traditional Western Blot assays in multiple mutant KRAS cell lines. SOS1 degradation resulted in the reduction of active KRAS, HRAS and MRAS levels when assayed by RAF-RBD pull-downs in MIA PaCa-2 (KRAS G12C) cells. Other downstream signaling markers (pERK and pS6) were also decreased upon SOS1 degradation in KRAS G12C, G12V, G12S and G13D cell lines in 3D Western Blot assays. Notably, the observed pERK and pS6 inhibition was driven by SOS1 degradation and not inhibition as decreases in signaling was no longer observed when SOS1 degraders were outcompeted with CRBN competitors. To assess the antiproliferative effects of our SOS1 degraders, we developed 3D proliferation assays in various KRAS mutant (G12A, G12C, G12D, G12V, G12S, G13C and G13D) as well as KRAS amplified cell lines and observed IC_{50s} ranging from 0.5 - 70nM. Treatment of CRBN KO and SOS1 KO H358 and MIA PaCa-2 cell lines with our SOS1 degraders resulted in 100- to 400-fold IC_{50} values, validating that the functional activity observed is dependent on its targets. Consistent with our *in vitro* data, treatment of SOS1 degraders in MIA PaCa-2 xenografts resulted in > 90% degradation and led to significant tumor growth inhibition. Given the diversity of mutations and tumors as well as acquired drug resistance to allele-specific KRAS inhibitors, we sought to determine if coupling SOS1 degradation with other EGFR-RAS-MAPK inhibitors could produce more potent responses to maximize patient benefit. Strong synergistic antiproliferative effects were observed when SOS1 degraders were co-treated with KRAS inhibitors AMG510 (G12C) and MRTX1133 (G12D) in respective KRAS-mutant cell lines as well as with MEK inhibition and EGFR inhibition. Lastly, combination of AMG510 or Trametinib with SOS1 degraders yielded strong synergy and a greater anti-tumor response in MIA PaCa-2 xenografts relative to the individual agents themselves. **Conclusions:** Together, these results highlight the potential of SOS1 degraders alone and in combination as therapeutic options for a variety of KRAS-driven cancers. Research Sponsor: Biotheryx.

TPS3153

Poster Session

TROPION-PanTumor03: Phase 2, multicenter study of datopotamab deruxtecan (Dato-DXd) as monotherapy and in combination with anticancer agents in patients (pts) with advanced/metastatic solid tumors. *First Author: Yelena Y. Janjigian, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Pts with metastatic epithelial tumors who progress after initial therapy have a poor prognosis; new therapeutic agents could potentially improve outcomes. Trophoblast cell surface protein 2 (TROP2) is a transmembrane glycoprotein that is over-expressed on the cell surface of many epithelial cancers representing a promising target for surface-directed therapeutic modalities. Dato-DXd is an antibody-drug conjugate consisting of a humanized anti-TROP2 IgG1 monoclonal antibody covalently linked to a highly potent topoisomerase I inhibitor payload via a stable, tumor-selective, tetrapeptide-based cleavable linker. Dato-DXd monotherapy demonstrated encouraging efficacy and safety in pts with lung and breast cancer (TROPION-PanTumor01 study; NCT03401385). **Methods:** The phase 2, multicenter, open-label TROPION-PanTumor03 study (NCT05489211) is exploring safety and efficacy of Dato-DXd as monotherapy and in combination with various anticancer agents (e.g. durvalumab, AZD5305, nivolumab, bevacizumab, chemotherapies) that may be active in the tumor types being evaluated. TROPION-PanTumor03 is a master trial comprising independent substudies to enable simultaneous evaluation of the recommended phase 2 dose (RP2D), safety, and preliminary efficacy of Dato-DXd across several tumor types and treatment combinations. Pts with endometrial, gastric, metastatic castration-resistant prostate (mCRPC), ovarian, and colorectal (CRC) cancer are being enrolled. Eligible pts: age ≥ 18 years, histologically/cytologically documented advanced or metastatic disease, ≥ 1 measurable target lesion (RECIST 1.1) not previously irradiated (mCRPC substudy: non-measurable bone metastatic disease permitted), and adequate bone marrow and organ function. An FFPE tumor sample must be available for all pts. Prospective selection for TROP2 expression is required in pts with CRC; in all other cohorts, TROP2 expression will be analyzed retrospectively. In all monotherapy cohorts, pts will receive Dato-DXd 6 mg/kg IV infusion Q3W; in the combination cohorts, Dato-DXd 4 or 6 mg/kg Q3W, as appropriate for each combination. Pts will receive treatment until disease progression, unacceptable toxicity, or withdrawal. Primary endpoints: objective response rate, PSA50 response (mCRPC substudy only), and safety/tolerability. Secondary endpoints: progression-free survival, duration of response, disease control rate, best % change in tumor size, pharmacokinetics, and immunogenicity (anti-drug antibodies). Exploratory endpoints incl. overall survival, pt-reported outcomes, and biomarker analysis (incl. TROP2 and PD-L1 expression, tumor mutational profiling, proteomics and ctDNA profiling). Recruitment is ongoing as of Feb 2023. ©2023 American Association for Cancer Research. Reused with permission. Clinical trial information: NCT05489211. Research Sponsor: AstraZeneca in collaboration with Daichi-Sankyo.

3152

Poster Session

A powerful drug combination strategy targeting BRAF-mutant melanoma. *First Author: Luke Daniel Rothermel, University Hospitals, Seidman Cancer Center and Department of Surgery, Cleveland, OH*

Background: BRAF inhibitors, such as vemurafenib and dabrafenib, are effective in treating patients with melanoma harboring (V600E) BRAF mutations. These drugs block the activity of the mutated BRAF protein, which impacts the development and progression of melanoma. Despite initial efficacy, drug resistance reliably occurs leading to disease relapse. Here we show how BRAF inhibitors cause metabolic reprogramming in melanoma cells to achieve drug resistance and promote cell survival. Previously we demonstrated that wild-type isocitrate dehydrogenase 1 (wtIDH1) supports mitochondrial function and maintains redox homeostasis in melanoma, and that an FDA-approved mutant IDH1 inhibitor, ivosidenib (AG-120), is actually a potent wtIDH1 inhibitor. Thus, we hypothesized that wtIDH1 inhibition would synergize with BRAF inhibition. **Methods:** Metabolomic profiling using LC-MS determined the impact of BRAF inhibition on cellular metabolism. Cell viability was assessed by PicoGreen in drug combination assays. Synergism was calculated using the Bliss-Independence dose-response model for drug interaction. *In vivo* modeling of AG-120 in combination with BRAF inhibition used melanoma cell xenografts in athymic nude mice for tumor volume analyses, and survival studies were performed in both immunocompetent C57BL/6J mice (murine YUMM1.7 cells) and immunocompromised athymic nude mice (human A375 cells). **Results:** Metabolomics data suggest that BRAF-mutated melanoma cells treated with BRAF inhibitors increased oxidative metabolism and mitochondrial dependence (i.e., survival adaptations). These alterations suggest an opportunity for mitochondrial inhibitors to improve drug efficacy. Targeting wtIDH1 with AG-120 in combination with dabrafenib significantly reduced melanoma cell viability. A positive synergy score and Bliss score greater than 1 indicate that the combined treatment was more effective in reducing cell viability than either treatment alone. Further, the combination of AG-120 and dabrafenib was the most effective *in vivo*, reducing tumor growth in the BRAF-mutated melanoma xenograft model, and improving mouse survival compared to monotherapy controls. Mice tolerated combination therapy with no reduction in body weight observed. **Conclusions:** Our findings indicate that dual inhibition of mutated BRAF and wild-type IDH1 represents a novel treatment strategy for BRAF-mutated melanomas, with potential for application to other BRAF-mutated cancers (e.g., colon, hepatobiliary, thyroid, etc.). Research Sponsor: U.S. National Institutes of Health.

TPS3154

Poster Session

XMT-1660: A phase 1b trial of a B7-H4 targeted antibody drug conjugate (ADC) in breast, endometrial, and ovarian cancers. *First Author: Erika P. Hamilton, Sarah Cannon Research Institute, Tennessee Oncology, Nashville, TN*

Background: Breast cancer (BC) is the most commonly diagnosed cancer and one of the leading causes of cancer death in women. Despite significant therapeutic advances, the majority of patients with unresectable or recurrent/metastatic disease eventually develop resistance to available standard of care (SOC) therapies. High B7-H4 expression has been observed in several cancers including breast, endometrial, and ovarian, with limited expression in normal tissue. As a member of the CD28/B7 family of cell surface proteins, it promotes tumorigenesis by suppressing anti-tumor immunity. XMT-1660 is a B7-H4-directed Dolasynthen antibody drug conjugate designed with a precise, optimized drug-to-antibody ratio and a DolaLock microtubule inhibitor payload with controlled bystander effect. In the preclinical setting, XMT-1660 has demonstrated anti-tumor activity in TNBC and ER+/HER2- patient-derived xenograft mouse models, which included tumors from heavily pre-treated patients (Collins et al, AACR 2022). Increased anti-tumor activity tended to be more frequent in preclinical models with higher B7-H4 expression, providing rationale for a Ph1 clinical trial. **Methods:** The Ph1 trial includes a first-in-human open-label dose escalation (DES) portion followed by dose expansion (EXP) evaluating XMT-1660 in patients with BC, EC, and OC following progression on SOC as applicable (i.e., CDK4/6i + ET; platinum-based chemotherapy). In the DES, Bayesian Optimal Interval (BOIN) design will be used to determine the MTD. Patients will receive XMT-1660 IV Q3 weeks. Primary endpoints in DES are to assess safety and determine a recommended phase 2 dose (RP2D) and assessment of preliminary efficacy as a secondary endpoint. In parallel with DES, optional backfill cohorts will enroll patients into tumor-type specific cohorts (TNBC, HR+/HER2- BC, EC, or OC) at a selected dose level from DES and can be initiated at multiple dose levels simultaneously. In the EXP portion, cohorts enrolling TNBC, ER+/HER2- BC, EC/OC are planned and additional patients may be enrolled based on emerging data. The primary endpoint of EXP is to assess safety and tolerability, overall response rate, disease control rate, and duration of response. Secondary endpoints include pharmacokinetic analysis and assessment of antidrug antibodies. Patients are not selected by B7-H4 status, but baseline tumors samples are collected for retrospective tumor tissue evaluation. The trial is currently enrolling patients. NCT05377996. Clinical trial information: NCT05377996. Research Sponsor: Mersana Therapeutics.

TPS3156

Poster Session

EGRET: A first-in-human study of the novel antibody-drug conjugate (ADC) AZD9592 as monotherapy or combined with other anticancer agents in patients (pts) with advanced solid tumors. *First Author: Charu Aggarwal, Perelman Center for Advanced Medicine, Philadelphia, PA*

Background: The epidermal growth factor receptor (EGFR) and mesenchymal-epidermal transition tyrosine kinase receptor (c-MET) are expressed in diverse solid tumors, and function as driver genes in some types. Clinical benefit of bispecific monoclonal antibodies (Ab) targeting these receptors was demonstrated in pts with EGFR mutated (EGFRm) non-small-cell lung cancer (NSCLC), but an ADC targeting these receptors has not been developed. AZD9592 is an ADC with a bispecific Ab targeting EGFR and c-MET. When internalized, AZD9592 releases a topoisomerase 1 inhibitor (TOP1i) warhead that traps TOP1 on DNA, causing double-strand breaks and induction of apoptotic cell death. Preclinical data have demonstrated promising efficacy and safety of AZD9592 in tumors expressing EGFR and c-MET, including but not limited to adenocarcinoma and squamous NSCLC and head and neck squamous cell carcinoma (HNSCC). **Methods:** EGRET is a phase 1, open-label, multicenter, modular study in pts with advanced solid tumors (NCT05647122). Module 1 will evaluate AZD9592 monotherapy in pts with metastatic NSCLC (mNSCLC) with EGFRm (sensitizing L858R mutation or exon 19 deletions) or EGFR wild-type, or recurrent or metastatic HNSCC. Module 2 will evaluate AZD9592 in combination with osimertinib in pts with EGFRm mNSCLC. Each module will include dose escalation (Part A) and dose expansion (Part B) cohorts. Key inclusion criteria are age ≥ 18 years, ECOG performance status 0–1, life expectancy ≥ 12 weeks, measurable disease per RECIST v1.1, and adequate organ and bone marrow function. Key exclusion criteria for both modules include unresolved toxicities of Grade ≥ 2 (NCI CTCAE v5.0) from prior therapy, uncontrolled intercurrent illness, cardiovascular disorders, history of drug-induced interstitial lung disease or pneumonitis, and previous treatment with a TOP1i ADC or an EGFR- or MET-targeted ADC. Treatment continues until disease progression, initiation of alternative anticancer therapy or unacceptable toxicity. The primary objectives of Part A are to assess safety and tolerability, and to determine the maximum tolerated dose and/or the recommended phase 2 dose of AZD9592 as monotherapy or in combination with osimertinib. The primary objectives for Part B are to evaluate safety and tolerability, and antitumor activity by investigator-assessed objective response rate (ORR) according to RECIST v1.1. Secondary objectives for both Part A and B include assessing AZD9592, as monotherapy and in combination with osimertinib, for efficacy (by ORR, disease control rate, duration of response, and progression-free and overall survival), pharmacokinetics, and immunogenicity. Descriptive statistics will be used for all variables. The study will include sites across the EU, USA, and Asia Pacific; sites in USA and Australia are currently open for enrollment. Clinical trial information: NCT05647122. Research Sponsor: AstraZeneca.

TPS3158

Poster Session

TROPION-Lung04: Phase 1b, multicenter study of datopotamab deruxatecan (Dato-DXd) in combination with immunotherapy $\pm$ carboplatin in advanced/metastatic non-small cell lung cancer (mNSCLC). *First Author: Hossein Borghaei, Fox Chase Cancer Center, Philadelphia, PA*

Background: Datopotamab deruxatecan (Dato-DXd) is a TROP2-directed antibody drug conjugate that has shown encouraging preliminary activity and safety in patients (pts) with lung or breast cancers. The TROPION-Lung04 study was designed to assess the safety, tolerability, and antitumor activity of Dato-DXd in combination with immunotherapy $\pm$ carboplatin in pts with advanced or metastatic NSCLC. **Methods:** TROPION-Lung04 (NCT04612751) is a Phase 1b, multicenter, open-label, 2-part, dose escalation/confirmation and expansion study in ≈ 232 pts without actionable genomic alterations. In Part 1 (dose escalation/confirmation), pts will be enrolled to 1 of up to 11 cohorts. Details of cohorts 1–4 (Dato-DXd [4 or 6 mg/kg] + durvalumab [1120 mg Q3W] $\pm$ up to 4 cycles of carboplatin [AUC 5] Q3W) were previously described (Borghaei H, *et al.* JTO 2021;16(10):S1098-S1099). Cohorts 5–11 were recently added to evaluate Dato-DXd in combination with bispecific immunotherapies AZD2936 (anti-PD-1/TIGIT) and MEDI5752 (anti-PD-1/CTLA-4) in treatment-naïve pts. Pts in cohorts 5–8 will receive Dato-DXd (4 or 6 mg/kg) + AZD2936 $\pm$ carboplatin; pts in cohorts 9–11 will receive Dato-DXd + MEDI5752 $\pm$ carboplatin. Cohorts 5 and 6 will recruit pts with PD-L1 tumor proportion score (TPS) $\geq 50\%$ in Parts 1 and 2A, and PD-L1 TPS 1–49% in Part 2B. Cohorts 7–11 will recruit pts with PD-L1 TPS $< 50\%$ only. Dose confirmation in Cohorts 5–11 will be guided by an mTP1-2 design where a minimum of 6 and a maximum of 9 pts will be assessed for dose-limiting toxicities (DLTs) during Cycle 1; if the DLT incidence meets pre-specified toxicity criteria, Part 2 dose expansions may be opened. Pts may continue Dato-DXd or immunotherapy treatment until disease progression (per RECIST v1.1) or unacceptable toxicity. Study endpoints are shown in the table. Enrollment across all combination cohorts is ongoing. Clinical trial information: NCT04612751. Research Sponsor: AstraZeneca in collaboration with Daiichi-Sankyo.

Study endpoints.

Primary endpoint	Assessment of safety and tolerability through the incidence of DLTs, treatment-emergent adverse events (AEs), serious AEs, AEs of special interest, ECOG performance status, vital signs and standard clinical/laboratory parameters
Secondary efficacy endpoints	Objective response rate Duration of response Disease control rate Progression-free survival Time to treatment response Best percentage change in the sum of diameters of measurable tumors Overall survival
Additional secondary endpoints	Pharmacokinetics Immunogenicity (anti-drug antibodies)

TPS3157

Poster Session

Phase 1/2 study of PRO1184, a novel folate receptor alpha-directed antibody-drug conjugate, in patients with locally advanced and/or metastatic solid tumors. *First Author: Justin A Call, START Mountain Region, West Valley City, UT*

Background: PRO1184 is an antibody-drug conjugate (ADC) directed to folate receptor alpha (FR α), a cell surface antigen overexpressed in multiple cancers including ovarian, endometrial, lung, mesothelioma, and breast cancer. PRO1184 consists of a human monoclonal antibody that selectively binds FR α , a novel cleavable hydrophilic linker, and a topoisomerase 1 inhibitor payload, exatecan. Previous studies demonstrated that the hydrophilic linker confers excellent physicochemical properties and pharmacokinetic (PK) profiles across a range of payload mechanisms and is superior to conventional linkers on these critical parameters for ADCs. In addition, exatecan is broadly active in many tumor types, is membrane permeable, and is not a substrate of multidrug resistance efflux pumps. It may thus lend a robust bystander effect and induce deeper or more durable responses in refractory tumors. Preclinical studies further established that PRO1184 exerts potent antitumor activity in mouse xenograft models with high, moderate, and low FR α expression, consistent with the inherent potency and expected bystander activity of the exatecan payload. PRO1184 is stable in plasma and retains the excellent PK properties and bioactivity of the unconjugated parent antibody. The preliminary safety profile of PRO1184 was more favorable than a benchmarking deruxatecan-based ADC in cynomolgus monkeys. PRO1184 is thus a promising development candidate with a potentially large therapeutic index to benefit a broad population of patients with FR α -expressing solid tumors. **Methods:** PRO1184-001 is an ongoing, phase 1/2, open-label dose escalation and expansion study. Eligible patients are adults with metastatic or unresectable solid tumors, including ovarian, endometrial, non-small cell lung, breast cancer, or mesothelioma. Patients must have measurable disease per the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, or mRECIST 1.1 for pleural mesothelioma. Patients must also have previously received therapies known to confer clinical benefit unless considered ineligible, refused by the patient, or not available in the region. PRO1184 is given by intravenous infusion on Day 1 of a 21-day cycle and treatment may continue until disease progression, unacceptable toxicity, or other reason for discontinuation. The primary objectives are to evaluate the safety and tolerability of PRO1184 and to identify the maximum tolerated dose, if reached, and recommended phase 2 dose (RP2D). Part A of the study consists of a dose escalation phase and Part B consists of 4 FR α -expressing tumor specific expansion cohorts treated at the RP2D. PK, immunogenicity, and antitumor activity will also be evaluated. The study is currently enrolling at sites in the US, with future enrollment in China planned (NCT05579366). Clinical trial information: NCT05579366. Research Sponsor: Profound Bio US Co.

TPS3159

Poster Session

Phase 1 trial of a novel C'Dot drug conjugate (CDC), ELU001, in patients with solid tumors known to overexpress folate receptor alpha (FR α). *First Author: Wen Wee Ma, Division of Medical Oncology, Mayo Clinic, Rochester, MN*

Background: ELU001 is a novel first-in-class nanoparticle drug conjugate that consists of ~ 13 folic acid targeting moieties and a payload of ~ 22 molecules of the topoisomerase-1 inhibitor, exatecan. Folic acid and exatecan are covalently bound by non-cleavable and cathepsin-B cleavable linkers, respectively, to short polyethylene glycol chains which surround the C'Dot's silica core. CDCs are very small (~ 6 nm), allowing for more efficient penetration into solid tumors compared to ADCs and a rapid elimination by the kidneys, which is expected to lead to less toxicity than ADCs that have a longer half-life in circulation. ELU001's high avidity is designed to promote binding to FR α on the surface of cancer cells that express any level of antigen (low to high). ELU001 then internalizes into the tumor cell and traffics to the lysosome where enzymatic cleavage releases the exatecan payload. ELU001 has demonstrated efficacy in preclinical models with low, moderate and high levels of FR α . The first-in-human trial, ELU-FR α -1, is currently recruiting patients with ovarian, endometrial, colorectal, gastric, gastroesophageal junction, triple negative breast, or non-small cell lung cancers, or cholangiocarcinoma cancers, and, in the opinion of the Investigator, have no meaningful life-prolonging therapy option available. **Methods:** This is a Phase 1/2 multicenter, open label clinical trial with two parts: Part 1 Dose Escalation and Part 2 Tumor Group Expansion Cohort(s). In Part 1, patients with cancer types with a high likelihood of having FR α overexpressing tumors, (ovarian, endometrial, colorectal, gastric, gastroesophageal junction, triple negative breast, or non-small cell lung cancers, or cholangiocarcinoma) will be enrolled. FR α expression is determined retrospectively. ELU001 is administered either weekly (QW) (once a week for 3 weeks, 1 week rest), every other week (Q2W, with no rest between cycles), or every three weeks (Q3W). Initial Part 2 expansion cohorts are planned in ovarian cancer with high FR α expression, ovarian cancer with moderate or low FR α expression, and endometrial cancer with any positive FR α expression. Here, FR α will be prospectively determined. Other cancer types may be assessed in the future. The primary objective for Part 1 is to identify the MTD/RP2D. The primary objective for Part 2 is to determine the ORR. Secondary objectives include DOR, PFS, TFST, PFS2, OS, frequency, severity and tolerability of adverse events, PK, ADA, and FR α expression assessments. Part 1 Dose Escalation will recruit about 2-5 patients at each dose for each regimen (QW; Q2W; Q3W). Part 2 Stage 1 will recruit about 15 patients per tumor group expansion cohort and is expected to begin recruitment in the second half of 2023. The study is enrolling in Part 1 Q2W Cohort 301 and Q3W Cohort A in the US. Clinical trial information: NCT05001282. Research Sponsor: Elucida Oncology.

TPS3160

Poster Session

First-in-human clinical trial design of a first-in-class theranostic approach with a peptide-based radioligand targeting CA IX-expressing tumors. *First Author: Darren R. Feldman, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Expression of carbonic anhydrase IX (CA IX), a cell surface glycoprotein, can be induced by a state of hypoxia or by mutation of the Von Hippel-Lindau tumor suppressor gene. CAIX expression in tumors is often associated with progressive disease and overall poor outcomes in various solid cancers. Notably, high CA IX expression has been observed in 83%, 40%, and 29% of clear cell renal cell carcinoma (ccRCC), pancreatic ductal adenocarcinoma (PDAC), and colorectal cancer (CRC) specimens, respectively¹. CA IX may therefore represent a valuable therapeutic target. DPI-4452 is a first-in-class cyclic peptide that binds with high affinity to CA IX. Radiolabeling DPI-4452 with gallium-68 (⁶⁸Ga)[Ga-DPI-4452] or lutetium-177 (¹⁷⁷Lu)[Lu-DPI-4452] is an innovative theranostic approach for identifying and treating patients (pts) with CA IX-expressing tumors. Pre-clinical data has shown that [¹⁷⁷Lu]Lu-DPI-4452 is taken up by tumors and induces dose-dependent growth inhibition in ccRCC and CRC xenograft mouse models^{1,2}. **Methods:** We present the design of a Phase I/II study (NCT05706129) of [⁶⁸Ga]Ga-DPI-4452 and [¹⁷⁷Lu]Lu-DPI-4452 in pts with unresectable locally advanced or metastatic ccRCC, CRC or PDAC. The study is comprised of three phases: imaging (Part A), dose-escalation (Part B), and expansion (Part C). In Part A, pts will receive a single intravenous (IV) 185 MBq dose of [⁶⁸Ga]Ga-DPI-4452. Safety, tolerability, pharmacokinetics (PK), dosimetry and imaging characteristics of [⁶⁸Ga]Ga-DPI-4452 will be evaluated using positron emission tomography/computed tomography (CT) at four timepoints on Day 1. All pts will be followed for seven days post-injection for safety observations. In Part B, based on [⁶⁸Ga]Ga-DPI-4452 uptake, pts will receive sequential, escalating doses of IV [¹⁷⁷Lu]Lu-DPI-4452 on Day 1 of each 28-day cycle for up to eight cycles. During Cycle 1, each pt will undergo up to four whole-body planar imaging and single photon emission CT/CT analyses for dosimetry over seven days. In Part B, the recommended Phase 2 dose of [¹⁷⁷Lu]Lu-DPI-4452 will be determined, guided by a Bayesian Logistic Regression model. Safety, PK, and dosimetry will be assessed to minimize any radiation-induced toxicity and to optimize absorbed radiation dose in the tumor. Upon completion of Part B, Part C will enroll up to three cohorts of pts with CA IX-positive ccRCC, CRC or PDAC to assess preliminary efficacy of [¹⁷⁷Lu]Lu-DPI-4452, with a primary endpoint of objective response rate, as measured by RECIST v1.1. References Wiedemann N et al. *J Nucl Med* 2022;63(Suppl 2): 4048. Attinger A et al. *Eur J Nucl Med Mol Imaging* 2022;49(Suppl 1):S1–S751. Clinical trial information: NCT05706129. Research Sponsor: Debiopharm.

TPS3162

Poster Session

Phase 1 trial of GD2-SADA: ¹⁷⁷Lu-DOTA drug complex in patients with recurrent or refractory metastatic solid tumors known to express GD2 including small cell lung cancer (SCLC), sarcoma, and malignant melanoma. *First Author: Taofeek K. Owonikoko, UPMC Hillman Cancer Center, Pittsburgh, PA*

Background: GD2 is a disialoganglioside with high expression in small cell lung cancers (SCLC), sarcomas and melanomas and limited expression in normal tissues. The SADA platform represents a 2-step pretargeted radioimmunotherapy approach developed to optimize tumor targeting and reduce normal tissue irradiation. The GD2-SADA molecule is composed of a non-radioactive, bispecific antibody (anti-GD2 x anti-DOTA) linked to a tetramerization sequence from the p53 protein. In the first step, the GD2-SADA molecule is administered in a tetrameric form with a high affinity to the GD2 tumor target. In preclinical research, any unbound GD2-SADA molecule will disassemble to monomers and has shown to clear via the kidneys. In the second step, the radioactive payload ¹⁷⁷Lu-DOTA is administered, which binds to the anti-DOTA part of the GD2-SADA and leads to radiation-induced damage at the target and has shown limited exposure to non-target tissues in preclinical research. This pre-targeting approach supports the concept of highly focused irradiation of the tumor target with the potential of administering higher radioactivity doses. **Methods:** Trial 1001 (NCT05130255) is a first-in-human, dose-escalation, single-arm, open-label, non-randomized, multicenter phase 1 trial with the purpose of evaluating safety and tolerability of GD2-SADA: ¹⁷⁷Lu-DOTA. The trial is composed of 3 parts: Part A is dose escalation of the GD2-SADA dose and testing of different intervals between GD2-SADA and ¹⁷⁷Lu-DOTA. Part B is dose escalation of the ¹⁷⁷Lu-DOTA radioactivity dose to establish its maximum tolerated dose (MTD). Part C involves repeated dosing to assess the safety profile and determine the Recommended Phase 2 Dose (RP2D). Parts B and C may only begin upon completion of dose-limiting toxicity (DLT) observation period of Parts A and B, respectively. Escalation is based on classical 3+3 design. Parts A, B, and C will include 18, 12, and 32 patients, respectively. Patients can only be assigned to one part of the trial. The trial will include adult/adolescent patients with either SCLC, sarcoma, or melanoma with radiographical relapse/progression on standard therapies. The patients must be in ECOG performance status 0-1 and have adequate hematological, renal, and liver function. The patients must have measurable disease according to RECIST 1.1. Patients with active CNS metastases are ineligible. Safety endpoints (DLTs and adverse events) will be summarized by trial part and cohort. Objective response according to RECIST 1.1 and disease control rates at 6, 12 and 24 months will be presented with exact 95% CI. PFS, OS, and duration of response will be estimated using Kaplan-Meier methods. Additional objectives include dosimetry, PK, and immunogenicity data. The study is actively enrolling at US sites. Clinical trial information: NCT05130255. Research Sponsor: Y-mAbs Therapeutics, Inc.

TPS3161

Poster Session

FRONTIER: FAPi radioligand open-label, phase 1 study to evaluate safety, tolerability and dosimetry of [Lu-177]-PNT6555—A dose escalation study for treatment of patients with select solid tumors. *First Author: Lisa Bodei, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Fibroblast activation protein alpha (FAP) is a 170 kDa transmembrane glycoprotein expressed during development, active tissue remodeling, and cancer. Overexpression on cancer-associated fibroblasts in the tumor microenvironment, and on some cancer cells of mesenchymal origin, leads to the presence of FAP in > 90% of epithelial tumors, making FAP a compelling anti-cancer target. PNT6555, a potent FAP-targeting compound with rapid clearance from normal tissues and prolonged tumor retention in preclinical models¹, is a radioligand consisting of a DOTA chelator (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid) and a FAP-targeting moiety (Bz-D-Ala-boroPro) connected via an aminomethyl linker. The corresponding gallium-68 and lutetium-177 chelates constitute the imaging and therapeutic theranostic pair of PNT6555 under evaluation in this phase I study. **Methods:** FRONTIER (NCT05432193) is a multicenter, open-label, multi-dose phase I study of PNT6555 in participants with pancreatic ductal adenocarcinoma, esophageal cancer, colorectal cancer, melanoma skin cancer, cholangiocarcinoma, or soft tissue sarcoma solid tumors with FAP over-expression. The primary aim is to evaluate the safety and tolerability of [Lu-177]-PNT6555 in order to determine a recommended phase II dose (RP2D). Dosimetry, pharmacokinetics, and tumor and immune responses will also be assessed for [Lu-177]-PNT6555, as well as safety, tolerability, and diagnostic performance of [Ga-68]-PNT6555 PET/CT. Key eligibility criteria include being refractory to prior treatment with no alternative available therapeutic options, having adequate organ function, and being FAP-positive on [Ga-68]-PNT6555 PET/CT scan, defined as ≥50% of lesions with an SUV_{max} of ≥1.5x the liver SUV_{mean}. [Ga-68]-PNT6555 will be dosed at 120–220 MBq (3.2–5.9 mCi), with PET/CT initiated 90 (±30) min later. FAP-positive participants will receive [Lu-177]-PNT6555 once every 6 weeks for up to 6 cycles. Starting at 4 GBq (108 mCi) ± 10%, [Lu-177]-PNT6555 may be escalated by 4 GBq, with a maximum planned dose of 12 GBq. De-escalation by 2 GBq may also occur. Dose finding will be guided by the modified toxicity probability interval (mTPI-2) statistical design with a targeted toxicity rate of 30%. The planned total sample size is 30, with targets of 3–12 DLT evaluable patients per dose level. Cohort 1 has been completed without a DLT. Enrollment to cohort 2 began in January 2023. 1. Hallet R, et al. *Pre-clinical characterization of the novel fibroblast activation protein (FAP) targeting ligand PNT6555 for the imaging and therapy of cancer. Presented at SNMMI Annual Meeting April 2022; Vancouver, BC, Canada.* Clinical trial information: NCT05432193. Research Sponsor: POINT Biopharma.

TPS3163

Poster Session

A phase 1/2 study of CFT1946, a novel, bifunctional degradation activating compound (BIDAC) degrader, of mutant BRAF V600 as monotherapy and in combination with trametinib, in mutant BRAF V600 solid tumors. *First Author: Meredith McKean, Sarah Cannon Research Institute, Tennessee Oncology, PLLC, Nashville, TN*

Background: BRAF is a protein kinase that acts as a signal transducer in the MAPK pathway. Mutant BRAF V600 is capable of uncontrolled signaling and is constitutively active and signals as a monomer, leading to hyperactivation of MEK, ERK, and dysregulation of cellular proliferation. Mutant BRAF V600 is a clinically-validated target in a variety of cancers including melanoma, colorectal cancer (CRC), non-small cell lung cancer (NSCLC), and anaplastic thyroid carcinoma (ATC). Currently approved BRAF inhibitors (BRAFi) result in paradoxical RAF activation as the mutant BRAF protein is still able to dimerize with WT BRAF, resulting in a dimeric signaling complex. CFT1946 is a novel, orally bioavailable BIDAC degrader that inhibits and degrades mutant BRAF V600 protein. Distinct from approved BRAFi, CFT1946 avoids paradoxical RAF activation as the degraded BRAF V600 mutant protein can no longer incorporate into a dimeric signaling complex. CFT1946 is selective for the mutant protein and spares WT BRAF V600. CFT1946 has demonstrated preclinical activity in BRAF V600 mutant in vitro and in vivo models, including models resistant to BRAFi. These preclinical data provide rationale for a first-in-human (FIH) study to evaluate CFT1946 in BRAF V600 mutant solid tumors. **Methods:** This is a FIH, open-label, multicenter, Phase 1/2 clinical trial to characterize the initial safety, tolerability, and preliminary efficacy of CFT1946 and CFT1946+trametinib in BRAF V600 mutant melanoma, NSCLC, CRC, ATC, and other non-CNS BRAF V600 mutant solid tumors. This study includes 2 phases: dose escalation Phase 1 comprising CFT1946 (Arm A) with a starting oral dose of 20 mg twice daily and CFT1946+trametinib (Arm B) as well as dose expansion Phase 2 comprising CFT1946 (Arm A1) and CFT1946+trametinib (Arms B1 and B2). Arm A1 and B1 will include BRAF V600 mutant melanoma and NSCLC with prior BRAFi therapy while Arm B2 will enroll BRAF V600 mutant NSCLC who are BRAFi-naïve. Phase 2 will be initiated once the RP2D has been identified. Eligible subjects are ≥18yo with documented BRAF V600 mutant cancers who have received ≥1 prior therapy. CFT1946 will be administered orally in 28-day cycles until disease progression or intolerable toxicity. Primary objectives include safety, tolerability, RP2D and preliminary antitumor activity of CFT1946 monotherapy and in combination with trametinib. Secondary objectives include assessment of pharmacokinetics and pharmacodynamics. Key inclusion criteria include documented evidence of a BRAF V600 mutation obtained from tumor tissue or liquid biopsy; at least 1 prior line of standard-of-care therapy for locally advanced or metastatic disease. The study is anticipated to enroll 101–122 patients across 11 participating US and European sites and is currently open to enrollment (NCT05668585). Clinical trial information: NCT05668585. Research Sponsor: C4 Therapeutics.

TPS3164

Poster Session

A phase 1, open-label, dose escalation and dose expansion study to evaluate the safety, tolerability, pharmacokinetics, and antitumor activity of PF-07799933 (ARRY-440) as a single agent and in combination therapy in participants 16 years and older with advanced solid tumors with BRAF alterations. *First Author: J. Thaddeus Thaddeus Beck, Highlands Oncology Group, Springdale, AR*

Background: Approved BRAF inhibitors (BRAFi) are inactive against RAF dimers. Accordingly, the acquisition of BRAF dimers (e.g., through drug-acquired splice variants or BRAF amplification) may lead to therapy resistance. Non-V600 (class II and III) BRAF alterations that occur *de novo* in diverse tumor types also signal as dimers and therefore have no approved targeted therapeutic options. Additional liabilities of approved BRAFi include toxicity from paradoxical activation of wild-type (WT) RAF and limited brain penetration, a common primary and metastatic site for BRAF-altered cancers. In contrast to approved agents, investigational BRAFi inhibit WT and mutant RAF proteins (A, B, and C-RAF, monomers, dimers), and therefore may be limited by on-target toxicity from “pan-RAF” inhibition. PF-07799933 is an oral selective ATP-competitive small-molecule RAF kinase inhibitor that suppresses BRAF signaling in BRAF V600-mutant and non-V600-BRAF mutant tumors. It displays significantly less paradoxical activation than approved BRAFi and is not “pan RAF” as it spares non-BRAF-containing RAF dimers. We describe here the Phase 1 study of PF-07799933 as monotherapy or in combination with binimetinib or cetuximab in participants with BRAF-altered advanced solid tumors.

Methods: The purpose of this first-in-human study is to investigate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics, and potential clinical benefits of PF-07799933 administered as a single agent and in combination in participants with BRAF Class I, II and III mutated solid tumors with or without brain involvement. Part 1 (monotherapy dose escalation) and Part 2 (combination dose escalation) will enroll participants with BRAF V600 mutation who have progressed on a approved BRAFi or with *de novo* Class II or III alterations who have progressed on standard of care therapy. The primary objective of Part 1 is to determine monotherapy MTD/RDE of PF-07799933. Participants in Part 1 will be allowed to add on rational combination with either binimetinib or cetuximab at the time of disease progression. Once PK measurements indicate the potential for significant BRAF inhibition in the brain, participants with untreated and symptomatic brain metastases will be allowed to enroll. The primary objective of Part 2 is combination MTD/RDE of PF-07799933 with binimetinib or cetuximab. The primary objective of Part 3 is efficacy in defined cohorts (total ~120 participants): Cohort 1-2: BRAF V600 mutant melanoma; Cohort 3: BRAF Class II altered melanoma; Cohorts 4-5: BRAF V600 and Class II altered CRC; Cohort 6: other BRAF V600, Class I/III altered solid tumor not qualifying for Cohorts 1-5. Clinical trial information: NCT05355701. Research Sponsor: Pfizer.

TPS3166

Poster Session

SPARK, studying pathways of resistance in KRAS-driven cancers: A remote plasma ctDNA participation study to identify mechanisms of resistance to KRAS inhibitors. *First Author: Biagio Ricciuti, Dana-Farber Cancer Institute, Lowe Center for Thoracic Oncology, Boston, MA*

Background: KRAS mutations account for a significant proportion of oncogenic mutations in cancers of the lung, colon, pancreas, and other organs. Cancers with KRAS^{G12C} mutations are now targetable with direct KRAS^{G12C} inhibitors, and other allele-specific and pan-KRAS inhibitors are in clinical development. Recent work has shown that complex resistance mechanisms can arise after treatment with KRAS^{G12C} inhibitors, including polyclonal KRAS alterations, acquired bypass mechanisms, and acquired fusions. The SPARK protocol is a remote participation ctDNA collection study that will evaluate mechanisms of resistance to RAS inhibitors and combination therapies. **Methods:** SPARK (NCT05272423) is a non-interventional, single coordinating center, decentralized biospecimen collection study, with a planned accrual of up to 250 patients with a diagnosis of KRAS-mutant cancer who are experiencing disease progression on a specific KRAS inhibitor or combination of inhibitors. The study will enable a web-based remote consent (<https://alcmi.net/research/spark/>) and subjects will be sent blood collection kits with the necessary materials for local phlebotomy for the FoundationOne Liquid CDx (F1LCDx) Biopsy Assay. Plasma NGS results will be returned to the treating physician and the study team. Patients will initially be enrolled into two cohorts: Cohort 1A will be restricted to KRAS G12C mutant cancers who progressed after being treated with KRAS G12C inhibitors. Cohort 1B will enroll patients with KRAS mutant cancers whose tumors progressed on any KRAS inhibitor (other than a direct KRAS G12C inhibitor). Cohort 2 will enroll KRAS mutant patients that have progressed on KRAS inhibitors and who have already had a sequencing assay performed to determine the resistance mechanism to KRAS inhibitors. These patients will be invited to share their data and medical history with the study team. Plasma for F1LCDx analysis will be optional for Cohort 2. Mechanisms of acquired resistance will be summarized with descriptive statistics, and compared across drugs (e.g., sotorasib vs adagrasib), between tumor types (e.g., NSCLC vs CRC), and by regimen (e.g. monotherapy vs combination therapy) to determine if different resistance mutations arise in these settings. Progression-free survival (PFS), and overall survival (OS) with KRAS inhibitors will be analyzed depending on the resistance mechanism (e.g. on-target vs off-target). Kaplan-Meier method will be used estimate median survival, and log-rank test will be used to compare groups of interests. Cox-regression model will be used to estimate univariable and multivariable hazard ratios. Outcomes from subsequent treatment after the development of acquired resistance will also be explored with descriptive statistics. No interim analysis is planned. The study activated on November 1st 2022. Clinical trial information: NCT05272423. Research Sponsor: AMGEN.

TPS3165

Poster Session

A phase 1, open-label, first-in-human study of TAS2940 in patients with advanced solid tumors. *First Author: Jordi Rodon Ahnert, Department of Investigational Cancer Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Aberrant expression and signaling of the ERBB family of receptor tyrosine kinases, including epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor 2 (HER2), has a role in the pathogenesis of solid tumors such as breast cancer (BC), non-small cell lung cancer (NSCLC), and glioblastoma (GBM). Although therapies that target HER2 are effective in early and advanced HER2-overexpressing BC, many patients develop resistance despite tumor dependence on HER2 at the time of progression. Approximately 4% of patients with NSCLC have HER2 mutations, mostly presenting as exon 20 insertions (ex20ins); however, approved HER2/EGFR tyrosine kinase inhibitors (TKIs) have limited efficacy in patients with NSCLC and HER2 ex20ins. Many patients with NSCLC or BC develop brain metastases, and EGFR alterations, including EGFRvIII mutations, are common in GBM. There is therefore a need for a brain-penetrable TKI with activity against tumors harboring HER2/EGFR alterations. TAS2940 is a potent, selective, and orally bioavailable pan-ERBB inhibitor that has shown promising preclinical efficacy against cancers with a variety of HER2/EGFR mutations and amplifications. Further, TAS2940 inhibited tumor growth and induced tumor regression in a dose-dependent manner in nude mice intracranially implanted with NCI-N87, a HER2-overexpressing human gastric cancer cell line. **Methods:** TAS2940-101 (NCT04982926) is an open-label, phase 1, first-in-human trial to evaluate the safety, tolerability, pharmacokinetics (PK), and preliminary antitumor activity of TAS2940 in patients with advanced solid tumors and HER2/EGFR aberrations. Eligible patients are aged ≥18 years, have non-measurable (Part 1) or measurable (Part 1 and 2) disease per RECIST 1.1 or RANO criteria, ECOG performance status 0/1, and adequate organ function. Patients with non-stable brain metastases are excluded. Part 1 (dose escalation) will use a Bayesian optimal interval design with a starting dose of 15 mg/kg orally QD (planned dose levels: 15, 30, 60, 120, 240 and 480 mg). Once the recommended phase 2 dose is determined, Part 2 (dose expansion) will enroll patients with NSCLC (Cohort A), HER2+ BC (Cohort B), recurrent/refractory GBM (Cohort C), or other solid tumors with EGFR/HER2 aberrations (Cohort D). The primary objectives are the maximum tolerated dose of TAS2940 in Part 1 and antitumor activity in Part 2. Secondary objectives include antitumor activity in Part 1. The safety and PK profile of TAS2940 will be assessed in both parts. Approximately 142 patients will be enrolled, comprising ~42 in Part 1 and ~100 in Part 2. As of January 24, 2023, 15 patients have been enrolled. No dose-limiting toxicities have been reported with dose escalation up to 240 mg QD. Recruitment is ongoing. Clinical trial information: NCT04982926. Research Sponsor: Taiho Oncology, Inc.

TPS3167

Poster Session

BRUOG 387: Phase Ib investigator-initiated trial of a heat shock protein 90 inhibitor (HSP90i) combined with a CDK4/6i in advanced breast cancer progressing on CDK4/6i and in solid tumors with retinoblastoma (Rb)-deficiency (IND163592). *First Author: Wafik S. El-Deiry, Legorreta Cancer Center at Brown University, Providence, RI*

Background: Cyclin-dependent kinases 4/6 (CDK4/6) promote cell-cycle progression and cancer growth. CDK4/6 inhibitors (CDK4/6i), in combination with hormonal therapy, increase progression-free and overall survival (PFS and OS) in breast cancer but resistance to CDK4/6i is associated with genomic abnormalities including Rb-deficiency. Combined CDK4/6i/HSP90i has been shown to inhibit HIF1- α including in tumor cells with Rb-deficiency. Synergy between multiple CDK4/6i's and HSP90i's has suggested a drug class effect for combination. In CDK4/6i-treated cells, E3-ubiquitin ligase Smurf2 associates with and targets degradation of HIF1- α independent of VHL or hypoxia. BRUOG 387 investigates whether dual targeting of CDK4/6 and HSP90, through HIF1- α in patients with ER/PR+ Her2-advanced breast cancer progressing on CDK4/6i and patients with refractory Rb-deficient tumors is safe and reasonably tolerated. **Methods:** A phase Ib open-label single-arm dose de-escalation study is evaluating safety, tolerability as primary outcomes, recommended doses for cohort expansion and preliminary efficacy of CDK4/6i and HSP90i (IND163592; NCT05655598; the only HSP90i combination study in US). Patients with ER/PR+ Her2- advanced breast cancer progressing on CDK4/6i, and in cohort expansion, patients with Rb-deficient solid tumors (SCLC, soft tissue sarcoma, endometrial and bladder cancer) are included. CDK4/6i (palbociclib at dose previously tolerated up to 125 mg daily PO D1-21 of 28 day cycle) in combination with HSP90i (TAS-116/pimipitesib starting at 120 mg 5 days on 2 days off, for D1-28 of cycle) is used in 3+3 dose-de-escalation design. The study includes PK analysis, and PD analysis will include HIF1/2, Smurf2, Rb, HIF targets VEGF, erythropoietin, Glut1, proliferation, cell death, cancer stem cells, NK, T-cells, RNA-seq and angiogenesis in pre- and post-treatment biopsies. Biostatistical design and analysis includes 3 dose levels of TAS-116 + palbociclib (level 0: TAS-116 120 mg, palbociclib 125 mg; level -1: TAS-116 80 mg, palbociclib 125 mg); level -2: TAS-116 40 mg, palbociclib 125 mg). Limiting Toxicities will include grade 4 neutropenia lasting > 7 days, neutropenic fever, grade 4 thrombocytopenia or Grade 3 non-hematologic toxicity not controlled with medical management. The study will enroll a total of approximately 15-27 patients (6-18 patients in dose de-escalation portion of the study and 9 additional patients in the cohort expansion phase). Secondary outcome analyses include response rate (CR, PR) measured by RECIST v.1.1 with exact two-sided 95% confidence intervals. OS, PFS, TTP, and DOR will be summarized using methods of Kaplan and Meier. Clinical trial information: NCT05655598. Research Sponsor: Brown University Oncology Research Group; Legorreta Cancer Center at Brown University.

TPS3168

Poster Session

Phase 2, multicenter, open-label basket trial of *nab*-sirolimus for patients with malignant solid tumors harboring pathogenic inactivating alterations in *TSC1* or *TSC2* genes (PRECISION I). *First Author: Gopa Iyer, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: *nab*-Sirolimus is a novel albumin-bound mTOR inhibitor (mTORi) approved in the US for adult patients with malignant PEComa. In an exploratory analysis of the pivotal AMPECT trial of *nab*-sirolimus in advanced malignant PEComa (NCT02494570), 8/9 (89%) and 1/5 (20%) patients with inactivating alterations in *TSC2* and *TSC1*, respectively, had confirmed response (Wagner, *J Clin Oncol*, 2021). *TSC1* and *TSC2* alterations have been observed in patients with a broad variety of cancers. Most treatment-related adverse events in AMPECT were grade 1/2 (none were grade ≥ 4) and were consistent with mTORi class adverse events. **Methods:** PRECISION I (NCT05103358) will evaluate efficacy and safety of *nab*-sirolimus in patients with *TSC1* (Arm A) and *TSC2* (Arm B) alterations. Eligible patients are ≥ 12 y old and mTORi-naïve, possess malignant solid tumors with *TSC1/TSC2* inactivating alterations (confirmed by central review of sequencing reports), and have received appropriate standard treatments, per investigator. *nab*-Sirolimus 100 mg/m² will be given weekly intravenously over 30 min on Days 1 and 8 of each 21-d cycle. The primary endpoint is overall response rate per independent radiographic review (IRR) using RECIST v1.1. Other endpoints include duration of response, time to response, progression-free survival by IRR, overall survival, patient-reported quality of life, and safety. Enrollment began March 2022. Collaboration with leading next-generation sequencing vendors will expedite the identification of patients with qualifying *TSC1/TSC2* mutations; study access will be facilitated through a just-in-time approach to trial location activation. Based on the prevalence of *TSC1/TSC2* inactivating alterations, the most frequent tumor types expected are bladder, hepatobiliary, endometrial, soft tissue sarcoma, ovarian, and esophagogastric (Table). Clinical trial information: NCT05103358. Research Sponsor: Aadi Bioscience, Inc.

Estimated frequency of definite impact *TSC1* or *TSC2* alterations.

Tumor type	TSC1 Mutations, % ^a	TSC2 Mutations, % ^a	TSC1/TSC2 Combined, %
Bladder	6.33	1.70	8.03
Hepatobiliary	1.27	3.31	4.58
Endometrial	2.10	1.22	3.32
Soft tissue sarcoma	1.28	1.71	2.99
Ovarian	1.85	0.92	2.77
Esophagogastric	0.65	1.46	2.11
Colorectal carcinoma	0.99	0.39	1.38
Pancreatic	0.57	-	0.57

^aThe proportion of patients with definite impact mutations (ie, mutations known to have a biological impact, including frameshift, nonsense, and splice-site mutations and deep deletions) derived from analysis of TCGA and cBioPortal by Gulati et al. Data on file.

3500

Oral Abstract Session

FOLFFOXIRI plus bevacizumab and atezolizumab as upfront treatment of unresectable metastatic colorectal cancer (mCRC): Updated and overall survival results of the phase II randomized AtezoTRIBE study. *First Author:* Carlotta Antoniotti, Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa & Unit of Medical Oncology 2, Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy

Background: AtezotRIE (NCT03721653) is a phase II randomized trial in which unresectable mCRC pts were randomized 1:2 to 1st-line FOLFOXIRI/bev [arm A] or FOLFOXIRI/bev/atezo [arm B]. Adding atezo to FOLFOXIRI/bev was safe and improved PFS (primary endpoint), with a modest benefit also among pts with pMMR tumors. Subgroup analyses suggest that TMB and Immunoscore IC (IS) IC - an IHC biomarker measuring CD8 and PD-L1 cell densities and their proximity - may identify pts with pMMR tumors deriving benefit from adding atezo to FOLFOXIRI/bev. **Methods:** The study had 85% power to detect a HR for PFS (time from randomization to 1st PD or death [PD1]) of .66 in favor of arm B with 1-sided α error of .10. Secondary endpoints included PFS2 (time from randomization to PD on any treatment given after PD1 or death [PD2]), 2nd PFS (time from PD1 to PD2), and OS. MMR, TMB, IS IC were correlated to clinical outcome. **Results:** 218 pts (arm A/B:73/145) were enrolled. Main pts' characteristics were right-sided 44%/45%, RAS mut 71%/74%, BRAF mut 14%/8%, dMMR 7%/6%, high TMB 10%/12%, high IS IC 32%/32%. At a median follow-up of 37.0 mos, 175 80% OS A/B: 64/111 PD1, 150 (69%, arm A/B: 53/97) PD2, and 118 (54%, arm A/B: 43/75) OS events were collected. Out of 175 pts with a PD1 event, 135 (77%, arm A/B:50/85) received a subsequent treatment; among them, 121 pts (arm A/B: 43/78) had a PD2 event. PFS, PFS2, 2nd PFS and OS results in the intention-to-treat (ITT) population and the pMMR group are listed in the Table. In the ITT population, significant interactions between treatment and MMR status (P_{int} .011), TMB (P_{int} .008), and IS IC (P_{int} .037) were reported in terms of PFS. Only IS IC was associated with a differential OS benefit (P_{int} .065), with pts bearing IS IC-high tumors deriving benefit from adding atezo (HR 0.43, 95%CI 0.19-1.00), differently than those with IS IC-low tumors (HR 1.09, 95%CI 0.65-1.83). In the pMMR group, significant interactions between treatment and TMB and IS IC were reported in terms of PFS (P_{int} .016 and .051, respectively) and OS (P_{int} .043 and .063, respectively). Pts bearing IS IC-high tumors derived higher OS benefit from adding atezo (HR 0.44, 95%CI 0.19-1.03), than those with IS IC-low tumors (HR 1.15, 95% CI 0.67-1.97).

Conclusions: Pts with IS IC-high and/or TMB high pMMR mCRC seem to derive a survival benefit from adding atezo to FOLFOXIRI/bev as upfront treatment. These findings deserve confirmation in a properly designed phase III trial. Clinical trial information: NCT03721653.

Research Sponsor: GONO Foundation; Roche.

mos	ITT (n = 218)				pMMR (n = 201)			
	Arm A	Arm B	HR (80% CI)	P	Arm A	Arm B	HR (80% CI)	P
mPFS	11.5	13.1	0.71 (0.58-0.87)	.015	11.5	13.0	0.79 (0.64-0.97)	.073
mPFS2	19.9	22.6	0.85 (0.68-1.05)	.164	19.9	21.0	0.90 (0.72-1.12)	.269
m2 nd PFS*	5.7	6.3	1.15 (0.90-1.48)	.228	5.7	6.3	1.13 (0.88-1.45)	.270
mOS	27.2	33.0	0.81 (0.63-1.04)	.136	26.9	30.8	0.83 (0.64-1.07)	.172

*assessed on 135 pts in ITT and 127 pts in pMMR populations

LBA3503

Oral Abstract Session

Phase III randomized clinical trial comparing the efficacy of neoadjuvant chemotherapy and standard treatment in patients with locally advanced colon cancer: The NeoCol trial. *First Author: Lars Henrik Jensen, Danish Colorectal Cancer Center South, University Hospital of Southern Denmark, Vejle Hospital, Vejle, Denmark*

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2023, issue of the *Journal of Clinical Oncology*.

3501

Oral Abstract Session

Trastuzumab deruxtecan (T-DXd) in patients (pts) with HER2-overexpressing/amplified (HER2+) metastatic colorectal cancer (mCRC): Primary results from the multicenter, randomized, phase 2 DESTINY-CRC02 study. *First Author: Kanwal Pratap Singh Raghav, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: T-DXd (6.4 mg/kg, every 3 weeks [Q3W]) demonstrated antitumor activity in pts with HER2+ mCRC in DESTINY-CRC01 (Siena et al. *Lancet Oncol.* 2021). We present primary results of DESTINY-CRC02 (NCT04744831), which assessed the efficacy and safety of T-DXd (5.4 and 6.4 mg/kg) in pts with HER2+ mCRC. **Methods:** This was a multicenter phase 2 study. Eligible pts had centrally confirmed HER2+ (immunohistochemistry [IHC] 3+ or IHC 2+ in situ hybridization [ISH]+) mCRC. Pts with RAS wild-type (wt) or mutant (m) mCRC were eligible. Pts had received prior standard therapy, unless contraindicated; prior anti-HER2 therapy was allowed. In stage 1, 80 pts were randomized 1:1 to 5.4 (n = 40) or 6.4 (n = 40) mg/kg T-DXd Q3W. In stage 2, an additional 42 pts received 5.4 mg/kg T-DXd. Primary endpoint was confirmed objective response rate (cORR) by blinded independent central review (BICR). Secondary endpoints included duration of response (DoR), progression-free survival (PFS), overall survival (OS), and safety. **Results:** At data cutoff (Nov 1, 2022), most pts in the 5.4 and 6.4 mg/kg T-DXd arms had HER2 IHC 3+ (78.0% and 85.0%), RAS wt tumors (82.9% and 85.0%), and a median of 3 and 4 prior lines of therapy, respectively. cORR was 37.8% (95% CI, 27.3-49.2%) in the 5.4 mg/kg arm and 27.5% (95% CI, 14.6-43.9%) in the 6.4 mg/kg arm (all partial responses in both arms). Key efficacy data are shown in the Table: Grade ≥3 treatment-emergent adverse events (AEs) were observed in 41/83 pts (49.4%) and 23/39 pts (59.0%) in the 5.4 and 6.4 mg/kg T-DXd arms, respectively. Serious AEs were observed in 20/83 pts (24.1%) and 12/39 pts (30.8%) in the 5.4 and 6.4 mg/kg arms, respectively. Independently adjudicated drug-related interstitial lung disease occurred in 7/83 pts (8.4%) with 5.4 mg/kg T-DXd and 5/39 pts (12.8%) with 6.4 mg/kg T-DXd, and most events were grade 1/2 (1 grade 5 in the 6.4 mg/kg arm). **Conclusions:** T-DXd showed promising antitumor activity in pts with HER2+ mCRC at both 5.4 and 6.4 mg/kg doses. Antitumor efficacy was observed irrespective of RAS mutation status at 5.4 mg/kg T-DXd, and in those with prior anti-HER2 therapy. Overall, safety was consistent with the known safety profile of T-DXd and favored the 5.4 mg/kg dose. Clinical trial information: NCT04744831. Research Sponsor: Daiichi Sankyo, Inc and AstraZeneca.

Efficacy summary.		5.4 mg/kg T-DXd n = 82	6.4 mg/kg T-DXd n = 40
Median follow-up, mo (range)		8.9 (0.5-17.1)	10.3 (0.7-16.4)
Median DoR by BICR		5.5 (4.2-8.1)	5.5 (3.7-non-evaluable)
Mo (95% CI)			
Median PFS, mo (95% CI)		5.8 (4.6-7.0)	5.5 (4.2-7.0)
Best overall response by BICR in subgroups, n/N (%) [95% CI]			
Prior anti-HER2 therapy		7/17 (41.2)	4/10 (40.0)
		(18.4-67.1)	(12.2-73.8)
HER2 IHC 3+		30/54 (46.9)	10/34 (29.4)
		(34.3-59.8)	(15.1-47.5)
HER2 IHC 2+/tISH+		1/18 (5.6)	1/6 (16.7)
		(0.1-27.3)	
RAS wt		27/68 (39.7)	11/34 (32.4)
		(28.0-52.3)	(17.4-50.5)
RA5m		4/14 (28.6)	0/6
		(8.4-58.1)	

*All RASm responders were IHC 3+.

LBA3504

Oral Abstract Session

Total neoadjuvant therapy with mFOLFIRINOX versus preoperative chemoradiation in patients with locally advanced rectal cancer: 7-year results of PRODIGE 23 phase III trial, a UNICANCER GI trial. *First Author: Thierry Conroy, Institut de Cancérologie de Lorraine, Vandoeuvre-Lès-Nancy, France*

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2023, issue of the *Journal of Clinical Oncology*.

3505

Oral Abstract Session

Long-term outcome of neoadjuvant mFOLFOX6 with or without radiation versus fluorouracil plus radiation for locally advanced rectal cancer: A multicenter, randomized phase III trial. *First Author: Jianwei Zhang, Sixth Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China*

Background: Previous results of phase III FOWARC trial demonstrated that mFOLFOX6, with or without radiation, did not significantly improve survival versus fluorouracil with radiation in patients with locally advanced rectal cancer at 3 years. Here, we presented the data of long-term disease free survival (DFS) and overall survival (OS). **Methods:** In this multicenter, phase III trial, patients with stage II/III rectal cancer were randomly assigned (1:1:1) to receive 5 cycles of infusional fluorouracil (leucovorin 400 mg/m², fluorouracil 400 mg/m², and fluorouracil 2.4 g/m² over 48 hours) plus radiotherapy (46.0 to 50.4 Gy delivered in 23 to 25 fractions during cycles 2 to 4) followed by surgery and seven cycles of infusional fluorouracil adjuvant treatment, mFOLFOX6 plus radiotherapy, or four to six cycles of mFOLFOX6 followed by surgery and six to eight cycles of mFOLFOX6. **Results:** Totally, 495 patients were enrolled, 165 patients in each group. 445 patients underwent surgery. After a median follow-up of 9.5 years, DFS events were observed in 56, 54, and 55 patients in fluorouracil plus radiotherapy, mFOLFOX6 plus radiotherapy, and mFOLFOX6 groups. The 10-year DFS rate were 55.5%, 63.0% and 62.8% (P = 0.934 by the log-rank test). OS events were reported in 39, 38, and 40 patients in the 3 groups. The 10-year OS rate was 66.2%, 73.2% and 73.0% (P = 0.919 by the log-rank test), respectively. **Conclusions:** With long-term follow up, no significant difference in was found in survival outcome between mFOLFOX6, with and without radiation. Comparing with fluorouracil plus radiation, mFOLFOX6 plus radiation also failed to improve long-term survival. Clinical trial information: NCT01211210. Research Sponsor: Supported by National Key Clinical Discipline, China National Natural Science Foundation.

3507

Oral Abstract Session

Phase III FIRE-4 study (AIO KRK-0114): Influence of baseline liquid biopsy results in first-line treatment efficacy of FOLFIRI/cetuximab in patients with tissue RAS-WT mCRC. *First Author: Sebastian Stintzing, Medical Department, Division of Hematology, Oncology, and Cancer Immunology (CCM), Charité Universitätsmedizin Berlin, Berlin, Germany*

Background: FIRE-4 (AIO KRK-0114) is performed in RAS wild-type (wt) mCRC patients. This randomized study tests the efficacy of early switch maintenance during 1st-line therapy (part 1) and re-challenge with cetuximab (part 2) in later-line treatment. In part 1, arm A patients continued FOLFIRI/Cet until progression or intolerable toxicity. In arm B, patients received FOLFIRI/Cet for 8-12 cycles, after which maintenance therapy with 5-FU/FA plus bevacizumab (5-FU/Bev) was applied. The first randomization evaluates the question if an early switch from cetuximab to bevacizumab may prolong PFS. Within the translational protocol, serial baseline liquid biopsy were taken to analyze RAS and BRAF mutations. **Methods:** Within this randomized, controlled, open-label phase-III study, patients received FOLFIRI (irinotecan plus 5-FU/FA) plus cetuximab at the standard dosing schedule. In arm A, FOLFIRI plus cetuximab was continued until progression or intolerable toxicity. In arm B, patients received 8 cycles of FOLFIRI plus cetuximab (in case of tumor response) or 12 cycles (in case of stable disease) followed by maintenance with 5-FU/FA plus bevacizumab (5mg/kg) until disease progression or intolerable toxicity. Overall survival after second randomization (part 2) is evaluated as a primary endpoint. Liquid Biopsies were analyzed by RAS BEAming and BRAF ddPCR technology. **Results:** From August 2015 to January 2021, 673 patients were randomized, and liquid biopsies of 540 patients were evaluable at baseline. Of those, 70 (13%) were RAS mutant and 38 (7%) BRAFV600E mutant at baseline. Patients with a detectable RASmut had a significant shorter PFS and OS when compared to RASwt patients (PFS: 9.0mo vs. 11.5mo; p < 0.001; OS: 22.1mo vs 33.6mo; p < 0.001). Whereas, for RASwt patients no difference for both arms with respect to PFS and OS could be observed, RASmut patients (n = 70) had a clear trend towards shorter survival in the standard FOLFIRI cetuximab arm (PFS: 6.4mo vs. 10.1mo, p = 0.54; OS: 24.9mo vs. 16.3mo, p = 0.10). Patients with a BRAF mutation in liquid biopsy had median survival times as expected for BRAF mutant patients (PFS = 5.5mo; OS = 12.0mo). In the standard arm, with a continuous administration of cetuximab, the conversion rate from RASwt to RASmut was significantly higher at progression than in the switch maintenance arm. **Conclusions:** Liquid biopsy detected RAS mutation in 13% of patients deemed RASwt based on tissue analyses. These patients show outcome characteristics expected for RAS mutant patients (median PFS of 9.0 months and median OS of 22 months). The study thus shows the clinical relevance of liquid biopsy in the verification of RAS mutational status. Clinical trial information: NCT02934529. Research Sponsor: Merck.

3506

Oral Abstract Session

NeoRAS wild-type metastatic colorectal cancer in the SCRUM-Japan GOZILA study. *First Author: Hiroki Osumi, Department of Gastroenterological Chemotherapy, Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, Japan*

Background: The "NeoRAS" phenomenon refers to RAS mutant (MT) metastatic colorectal cancer (mCRC) that becomes RAS wild-type (WT) following treatment. This NeoRAS WT population might represent a novel indication for EGFR inhibitors, which are less effective in RAS MT mCRC. The incidence and clinicopathological characteristics of NeoRAS WT mCRC using plasma cell-free DNA (cfDNA) next generation sequencing has not been defined. **Methods:** As part of a large-scale nationwide screening platform (SCRUM-Japan GOZILA), 478 patients with an initial diagnosis of RAS MT mCRC by tissue analysis (MEBGEN RASKET-B) who received systemic therapy underwent cfDNA testing (Guardant 360) prior to later lines of treatment. Based on the cfDNA results, we evaluated the clinicopathological characteristics of those with NeoRAS WT and RAS MT. NeoRAS WT was defined as no RAS MT (KRAS or NRAS) detected in plasma and was assessed in the overall cohort (Cohort A) and in the subgroup with at least one somatic alteration detected in plasma (Cohort B) to exclude those with insufficient tumor DNA shedding. **Results:** Median age at the time of blood sampling was 62.0 years old, and 257 (51.9%) were men. 160 (32.3%) and 319 (64.4%) had right-sided tumors and multi-organ metastases. The lungs were the most frequent site of metastasis (60.2%), followed by liver (57.4%), lymph nodes (28.9%), and peritoneum (28.5%). The prevalence of NeoRAS WT was 19.0% (91/478) in Cohort A and 9.8% (41/429) in Cohort B. The frequency of NeoRAS WT in tumors originally with KRAS exon 2 MT tended to be lower than in those with other RAS MT (18.1% vs 25.4%, P = 0.21 in Cohort A, 9.0% vs 15.4%, P = 0.14 in Cohort B). There were significant differences in the prevalence of NeoRAS WT between patients with single organ vs multi-organ metastases (P < 0.001 in Cohort A, P = 0.004 in Cohort B), absence vs presence of liver metastasis (P < 0.001 in both Cohort A and B), lymph node metastasis (P = 0.006 in Cohort A), peritoneal metastasis (P = 0.002 in group A), and bone metastasis (P = 0.029 in Cohort A), testing immediately prior to 2nd through to 4th line treatment vs later lines (P = 0.007 in Cohort A), immediate prior use of regorafenib (P = 0.027 in Cohort A) and any history of vascular endothelial growth factor inhibitors (P = 0.003 in Cohort A, P = 0.035 in Cohort B). In the logistic regression multivariate analysis, absence of liver metastasis (odds ratio [OR], 5.83; P < 0.001 in Cohort A, OR, 2.84; P = 0.005 in Cohort B), absence of lymph node metastasis (OR, 2.18; P = 0.034 in Cohort A) and tissue RASMT other than KRAS exon 2 (OR, 2.35; P = 0.049 in Cohort B) were significantly related to the emergence of NeoRAS WT. Among 6 NeoRAS WT patients treated with EGFR inhibitors, one had partial response and another one had stable disease for at least 6 months. **Conclusions:** Liver and lymph node metastasis and RASMT other than those in KRAS exon 2 are factors associated with the development of NeoRAS WT mCRC. EGFR inhibitors might be effective treatment. Research Sponsor: SCRUM-Japan Funds.

3508

Oral Abstract Session

Efficacy of panitumumab in patients with left-sided disease, MSS/MSI-L, and RAS/BRAF WT: A biomarker study of the phase III PARADIGM trial. *First Author: Kentaro Yamazaki, Division of Gastrointestinal Oncology, Shizuoka Cancer Center, Shizuoka, Japan*

Background: The PARADIGM trial (NCT02394795) showed longer median overall survival (OS) with first-line mFOLFOX6 plus panitumumab (PAN) vs bevacizumab (BEV) in patients (pts) with RAS wild type (WT) and left-sided metastatic colorectal cancer (mCRC; 37.9 vs 34.3 months, respectively; hazard ratio [HR], 0.82; P=0.031) and similar OS in right-sided pts (HR 1.09; Yoshino T, et al. ASCO 2022 LBA1). Based on current guideline recommendations regarding clinically relevant biomarkers, here we report clinical outcomes in left-sided mCRC pts with microsatellite stable or microsatellite instability low (MSS/MSI-L) and RAS (KRAS/NRAS)/BRAF (V600E) WT from PARADIGM. **Methods:** Baseline plasma circulating tumor DNA (ctDNA; >10 ng/mL and >10 nM DNA) from pts enrolled in the biomarker study (NCT02394834) was assessed using a custom panel (PlasmaSELECT-R 91, PGdx). The efficacy (OS, progression-free survival [PFS], response rate [RR], and curative resection rate [RO]) of PAN plus mFOLFOX6 compared with BEV plus mFOLFOX6 according to RAS, BRAF (V600E), and MSI status and primary tumor location was evaluated. **Results:** Among 802 pts in the full analysis set, 733 (91%) had evaluable pre-treatment samples for ctDNA analysis. Of these pts, 53 (7.2%) and 78 (10.6%) pts had RAS and BRAF (V600E) mutations, respectively, and 20 (2.7%) pts had MSI high (MSI-H) status. In left-sided mCRC pts with MSS/MSI-L and RAS/BRAF WT, OS tended to be longer with PAN vs BEV (40.6 [95% CI, 36.3-44.4] vs 34.8 [95% CI, 31.3-41.2] months, respectively; HR, 0.79 [95% CI, 0.64-0.97]). Although PFS was comparable between PAN (13.6 months [95% CI, 12.6-15.3]) and BEV (12.6 months [95% CI, 11.3-14.1]; HR, 0.95 [95% CI, 0.77-1.17]), RR and RO resection rates were higher with PAN (RR: 83.2% [95% CI, 78.0-87.6]; RO: 18.8% [95% CI: 14.2-24.1]) compared with BEV (RR: 66.4% [95% CI, 60.0-72.3]; RO: 10.0% [95% CI: 6.5-14.5]). OS was similar or inferior to PAN vs BEV regardless of the primary sidedness in pts with MSI-H or RAS/BRAF mutations (Table). **Conclusions:** These results support PAN + mFOLFOX6 as a first-line therapy for left-sided pts with MSS/MSI-L and RAS/BRAF WT. Clinical trial information: NCT02394795. Research Sponsor: Takeda Pharmaceutical Company Limited, Tokyo, Japan.

Population	MSS/MSI-L and RAS/BRAF WT			MSI-H or RAS/BRAF mutation		
	PAN + mFOLFOX6	BEV + mFOLFOX6	Difference; HR (95% CI)	PAN + mFOLFOX6	BEV + mFOLFOX6	Difference; HR (95% CI)
Left-sided, n	256	241		31	26	
Median OS, mo	40.6	34.8		15.4	25.2	-9.8;
(95% CI)	(36.3-44.4)	(31.3-41.2)	0.79 (0.64-0.97)	(9.6-20.9)	(17.0-30.9)	1.53 (0.84-2.76)
Right-sided, n	41	55		37	36	
Median OS, mo	37.9	30.9	7.0;	13.7	17.9	-4.2;
(95% CI)	(22.0-42.2)	(23.2-35.4)	0.94 (0.60-1.48)	(11.3-18.7)	(11.6-22.4)	1.28 (0.78-2.11)
Overall, n	299	299		69	66	
Median OS, mo	39.0	34.1	4.9;	14.6	19.8	-5.2;
(95% CI)	(36.3-43.3)	(31.1-37.6)	0.79 (0.66-0.96)	(11.3-18.8)	(15.3-25.5)	1.27 (0.88-1.84)

3509

Clinical Science Symposium

Transcriptional metabolic profiling young onset colorectal cancer (CRC) patients. *First Author: Deepak Vadehra, Roswell Park Comprehensive Cancer Center, Buffalo, NY*

Background: Patients diagnosed with colorectal cancer (CRC) at age < 50 years typically present with more advanced disease, resulting in poor therapeutic response and clinical outcomes. Therefore, there is an unmet need to understand the differences in transcriptional profiles between younger (<50) and older (> 50) CRC patients. **Methods:** Using TCGA (n = 397; > 50 = 349; < 50 = 48) and Oncology Research Information Exchange network (ORIEN) CRC datasets (n = 460; > 50 = 364; < 50 = 96), patients were separated into younger and older populations. Baseline characteristics of the patients in this analysis are provided in the accompanying table. Subsequently, their transcriptional profiles were compared and assessed via differential gene expression analysis (DESeq2), gene set enrichment analysis (GSEA), immune deconvolution (TIMER2.0), and metabolic pathway analysis (MetaPhOR). These pathways were then mapped to assess transcriptional dysregulation, and patterns of predicted metabolic flux. **Results:** Comparisons of older and younger groups revealed a large number of significantly differentially expressed transcripts (n = 2629), enrichment in younger groups of metabolic pathways (amino acids and lipids), oncogenes (MYC targets and NRAS targets), and cellular processes. In the older group we found enrichment of methylation and histone modification, immune response, and other metabolic pathways, like androgens. Metabolic pathway analysis revealed consistent alterations in steroid hormone metabolism and kynurenine metabolism, which were largely upregulated in the over 50 group. Additionally, pathways associated with response to both CTLA4 and PDL1 treatment were largely upregulated in the over 50 group. This transcriptional signature may be associated with a pre-disposition to different clinical outcomes and therapeutic response for agents targeting these pathways. **Conclusions:** Overall, this study has revealed differences in transcriptional metabolic profiles and other drivers of disease, as well as immune profiles, between younger and older CRC populations. This biology should be explored in the future, as new avenues for treatment in younger CRC populations. Research Sponsor: None.

	TCGA		P	ORIEN CRC		P
	> 50 n = 349 (88%)	≤ 50 n = 48 (12%)		> 50 n = 364 (79%)	≤ 50 n = 96 (21%)	
Race			0.371			0.621
White	165(47)	26(54)		313(86)	80(83)	
Non-white	50(14)	12(25)		51(14)	16(17)	
Not reported	134(38)	10(21)		0(0)	0(0)	
Gender			0.215			0.801
Female	159(46)	27(56)		163(45)	45(47)	
Male	190(54)	21(44)		201(55)	51(53)	
Tumor stage			0.088			0.009
IIA/IB	67(19)	4(8)		21(5)	3(3)	
IIIA/IBC	111(32)	13(27)		90(24)	10(10)	
IIIIIA/BC	162(46)	29(60)		104(29)	34(35)	
IIIV/ABC	0(0)	0(0)		87(24)	31(32)	
Not reported	9(3)	2(4)		62(17)	18(18)	
BMI			0.169			0.624
BMI < 18	0(0)	0(0)		4(1)	1(1)	
BMI 18-24.9	55(15)	10(20)		70(19)	24(25)	
BMI 24.9-30	15(3)	15(31)		11(3)	25(26)	
BMI > 30	66(18)	7(14)		109(30)	28(29)	
Not reported	171(48)	16(33)		70(19)	18(18)	

3511

Clinical Science Symposium

Evaluation of genomic alterations in early-onset versus late-onset colorectal cancer. *First Author: Eric Michael Lander, Division of Hematology/Oncology, Vanderbilt University Medical Center, Nashville, TN*

Background: The etiology of the rising incidence of early-onset colorectal cancer (EOCRC), defined as CRC in patients aged < 50, remains unknown. In this study, we evaluated tumor genomic differences in patients with EOCRC versus average-onset CRC (AOCRC, age > 60). **Methods:** The cohort included 13,262 patients diagnosed with stages I-III colon or rectal cancer who had whole exome sequencing as part of their ctDNA testing (Signatera, bespoke mPCR NGS assay). Tumor mutational burden (TMB) and microsatellite instability (MSI) status were derived from tumor whole exome sequencing analysis. The prevalence of somatic variants and mutations in known oncogenic pathways was compared between EOCRC and AOCRC groups, stratified by TMB and MSI status. Fisher's exact test was used to test significance between the groups and p-values were adjusted using the FDR method for multiple test correction. **Results:** A total of 3,093 patients with EOCRC (70.8% colon, 27.4% rectal, 1.9% unknown) and 10,169 patients with AOCRC (79.9% colon, 18.3% rectal, 1.7% unknown) were included, where 9.0%/37.3%/53.7% were AJCC stages I, II, and III, respectively. Early-onset patients compared to average-onset patients had fewer cases of stage II CRC (30.7% vs. 39.3%, $p < 0.01$) and more cases of stage III CRC (60.9% vs. 51.6%, $p < 0.01$). Patients with EOCRC were less commonly MSI-H compared to patients with AOCRC (10% vs. 17%, $p < 0.01$), or have high tumor mutational burden (15% vs. 19%, $p < 0.01$). The BRAFV600E mutation and truncated RNF43 mutations were less prevalent in EOCRC (3% vs. 15% and 2% vs. 9%, $p < 0.01$), regardless of TMB and MSI status. Molecular alterations of the RTK-RAS pathway were less prevalent in the EOCRC cohort ($p < 0.01$), while TP53 pathway alterations were more frequent in the EOCRC cohort ($p < 0.01$). In the TMB-low/MSS group, TP53 mutations were more common in EOCRC (8% vs. 5%, $p < 0.01$), but APC gene mutations were less common in EOCRC (56% vs. 66%, $p < 0.01$). In the TMB-H/MSI-H group, BRAFV600E (4% vs. 60%), RNF43G659V (16% vs. 45%), and WNT1 G619A (6% vs. 20%) mutations were less prevalent in EOCRC ($p < 0.01$ for all mutations); however, patients with EOCRC had more PIK3CA H1047R (22% vs. 9%), APC R1468* (11% vs. 3%), and KRAS A146T (7% vs. 2%) variants ($p < 0.01$ for all mutations). In the TMB-H/MSS group, EOCRC patients were more likely to have driver mutations in the PI3K pathway (74% vs. 56%, $p < 0.01$). The POLE P286R mutation was more common in TMB-H/MSS patients with EOCRC (38% vs. 13%, $p < 0.01$), whereas ACVR2A K437R was less common (11% vs. 30%, $p < 0.01$). Prevalence of somatic variants and mutated oncogenic pathways did not vary significantly by tumor stage. **Conclusions:** Patients with AOCRC harbored more somatic variants and mutations in established pathways of CRC carcinogenesis. Tumors in EOCRC cases carried unique genomic alterations that varied across the TMB and microsatellite subpopulations. BRAFV600E and RNF43 truncating mutations were more frequent in AOCRC. Research Sponsor: U.S. National Institutes of Health.

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Clinical Science Symposium

Metabolomic differences in young-onset versus average-onset colorectal adenocarcinoma. *First Author: Thejus Jayakrishnan, Taussig Cancer Institute, Cleveland, OH*

Background: Novel deleterious effects of environmental exposures may play a role in the rising incidence of young-onset colorectal cancer (yoCRC). We used metabolomics to assess differences between yoCRC and average-onset CRC (aoCRC), in comparison to healthy controls, which may provide insight into the pathogenesis and suggest any exposure risks. **Methods:** Patients with stage I-IV CRC and healthy controls were identified from prospective biobanks and categorized based on age < 50 years (yoCRC or young controls) or age > 60 years (aoCRC or older controls). Plasma metabolites were profiled using GC-TOF mass spectrometry. Differential abundance of metabolites was investigated using unadjusted and adjusted logistic regression. Metabolic pathway analysis was performed using Metaboanalyst 5.0. All p-values were adjusted for multiple testing (false-discovery rate, FDR $p < 0.20$ considered significant). **Results:** The study population comprised 170 CRC patients (66 yoCRC and 104 aoCRC) and 49 healthy controls (34 young and 15 old). Association analyses revealed four differentially abundant metabolites: citrate (FDR $p = 0.04$), cholesterol (0.14), and two unidentified metabolites (UM). Metabolic pathways significantly altered in yoCRC vs. aoCRC included: carbohydrate metabolism (citrate cycle, FDR $p = 0.04$), carbohydrate biosynthesis (glyoxylate and dicarboxylate metabolism, FDR $p = 0.004$), amino-acid metabolism (alanine, aspartate, and glutamate metabolism, FDR $p = 0.01$, arginine biosynthesis, FDR $p = 0.02$, and amino-acid t-RNA biosynthesis, FDR $p = 0.03$). There were no significant metabolomic differences between young and old controls. Significant associations on survival analysis included: adipic acid with aoCRC (HR = 3.1, 95% CI = 1.7-5.6, FDR $p = 0.13$, unadjusted analysis) suggesting worse survival with higher levels and 4-hydroxyhippuric acid with the whole cohort (HR = 0.4, 95% CI = 0.3-0.7, FDR $p = 0.05$, adjusted analyses) indicating better survival with higher levels. **Conclusions:** We identified significant differences in the citrate cycle - a core pathway of cellular metabolism associated with colorectal cancer. Metabolomic differences in pathways of carcinogenic significance (aspartate) and environmental exposures (arginine and dietary red meat) were also noted, suggesting potential relationships with younger age of CRC onset. Research Sponsor: Sondra and Stephen Hardis Chair in Oncology Research.

Differentially Abundant Metabolite	OR (95% CI)	FDR p
Citrate	14.54 (4.26-56.35)	0.04
Cholesterol	0.01 (0.001-0.10)	0.14
Altered Pathway	Pathway Impact Factor	FDR p
Glyoxylate and dicarboxylate metabolism	0.23	0.005
Citrate (TCA) cycle	0.14	0.04
Alanine, aspartate and glutamate metabolism	0.28	0.01
Glycine, serine and threonine metabolism	0.28	0.14
Aminoacyl-tRNA biosynthesis	0.17	0.01
Arginine biosynthesis	0.13	0.02

*Results for unknown metabolites are not included. Odds Ratio (OR) > 1 indicates higher abundance of metabolites in aoCRC vs. yoCRC.

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Poster Discussion Session

Overall survival results for trifluridine/tipiracil plus bevacizumab vs capecitabine plus bevacizumab: Results from the phase 3 SOLSTICE study. *First Author: Thierry Andre, Hôpital Saint-Antoine, Paris, France*

Background: SOLSTICE, a phase 3 study, tested trifluridine/tipiracil+bevacizumab (FTD/TPI+bev) vs capecitabine+bevacizumab (cape+bev) in first-line for patients with unresectable metastatic CRC who were eligible for intensive chemotherapy (full-dose doublet/triplet). As previously reported, the study did not meet the primary endpoint (progression-free survival (PFS): 9.4 months [95% CI, 9.1-10.9] for FTD/TPI+bev vs 9.3 months [95% CI: 8.9-9.8] for cape+bev, HR 0.87 [95% CI: 0.75-1.02]). Here we report on the key secondary endpoint – overall survival (OS) and an update of the safety data. **Methods:** From 21 Mar 2019 to 14 Sep 2020, 856 patients were randomized (1:1) to either FTD/TPI+bev or cape+bev. Stratification factors were: ECOG performance status (0 vs 1 vs 2), reason for non-eligibility for intensive therapy (clinical condition vs non-clinical condition) and tumor localization (right vs left). The primary endpoint was PFS based on investigator assessment according to RECIST 1.1 criteria. The key secondary endpoint was OS, defined as the time from randomization to death from any cause. Other secondary endpoints included overall response rate, disease control rate, quality of life, and safety. OS was analyzed after 578 events to detect a hazard ratio of 0.79 with 80.0% power at one-sided 2.5% level of significance. **Results:** 426 patients were randomly assigned to FTD/TPI+bev and 430 to cape+bev. The median OS was 19.74 months with FTD/TPI+bev and 18.59 months with cape+bev (HR, 1.06; 95% CI, 0.90, 1.25) with survival probabilities for FTD/TPI+bev vs cape+bev comparable at different time-points. In the multivariate analysis, factors significantly associated with higher OS in the whole population were age < 70 years, left location of the primary disease, surgical resection of the primary tumor, number of metastatic sites (1-2 vs ≥ 3 sites), absence of liver metastasis, neutrophils lymphocyte ratio < 3, Charlson score 0 vs 1-2, and ECOG PS 1 vs 2. No significant treatment effect was observed after adjustment for the prognosis factors (HR, 1.08; 95% CI, 0.92, 1.28), which is consistent with the main OS analysis. The updated safety data was consistent with those communicated at the time of the primary PFS analysis. No new safety signal was identified. As previously reported, the most common severe emergent adverse events were neutropenia 54% vs 1%, neutrophil count decreased 19% vs 1%, anemia 16% vs 4%, hand-foot syndrome 0% vs 15%, and hypertension 9% vs 11% in FTD/TPI+bev vs cape+bev, respectively. **Conclusions:** This was the largest phase 3 study that explored two treatment regimens in a population ineligible for intensive therapy. FTD/TPI+bev was not superior to cape+bev in terms of PFS and OS. The risk of death was similar in both treatment arms. With a different and manageable safety profile, FTD/TPI+bev represents a feasible alternative to cape+bev in this population. Clinical trial information: NCT03869892. Research Sponsor: Institut de Recherches Internationales Servier.

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Poster Discussion Session

Sotorasib (Soto) plus panitumumab (Pmab) and FOLFIRI for previously treated KRAS G12C-mutated metastatic colorectal cancer (mCRC): Code-Break 101 phase 1b safety and efficacy. *First Author: David S. Hong, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Soto, a KRAS^{G12C} inhibitor, had a 9.7% objective response rate (ORR) as monotherapy for chemorefractory patients (pts) with KRAS G12C-mutated mCRC. When combined with Pmab, a monoclonal anti-EGFR antibody, ORR increased to 30%, supporting the model that the doublet mitigates Soto-related feedback reactivation of the RAS-MAPK pathway and accumulation of activated EGFR. We hypothesize that Soto plus Pmab and FOLFIRI will further enhance Soto efficacy while maintaining a manageable safety profile. We report the first results for a KRAS^{G12C} inhibitor combined with an EGFR inhibitor and chemotherapy in pts with prior mCRC treatment. **Methods:** Pts included dose exploration and expansion cohorts from CodeBreak 101 subprotocol H (NCT04185883) who received Soto (960 mg PO daily) plus Pmab (6 mg/kg IV Q2W) and standard-dose FOLFIRI (IV Q2W). Key eligibility criteria were KRAS G12C-mutated mCRC and ≥ 1 prior treatment for metastatic disease. Pts in dose expansion were KRAS^{G12C} inhibitor-naïve. The primary endpoint was safety. Secondary endpoints included efficacy and pharmacokinetics (PK). **Results:** As of November 30, 2022, 33 pts (median age: 53 years; 48% female) were treated (6 in dose exploration, 27 in dose expansion). Median prior lines of systemic therapy was 2 (range: 1-6), with 33% and 67% of pts receiving 1 or ≥ 2 prior lines, respectively; 97% had prior fluoropyrimidine and 73% had prior irinotecan. Two pts in dose exploration received prior Soto. None of the 6 pts in dose level 1 of dose exploration had dose limiting toxicities (DLTs) during DLT evaluation (first 28 days), and Soto (960 mg PO daily) plus Pmab (6 mg/kg IV Q2W) and FOLFIRI (IV Q2W) was the recommended phase 2 dose. Treatment-related adverse events (TRAEs) of any grade occurred in 32 (97.0%) pts; 1 pt discontinued the full regimen due to grade 3 ALT increase. Fifteen (45.5%) had grade ≥ 3 TRAEs (most commonly dermatologic; n = 5). There were no fatal TRAEs. Safety findings were consistent with known profiles of Soto, Pmab, and FOLFIRI. No clinically meaningful PK interaction was observed between Soto and irinotecan. Of 31 pts evaluable for response, confirmed ORR (all partial responses) was 58.1% (95% CI: 39.1, 75.5). The 2 pts with prior Soto achieved partial response (n = 1) and stable disease (n = 1). Disease control rate was 93.5% (95% CI: 78.6, 99.2). With median follow-up of 5.7 and 7.4 months, respectively, progression-free and overall survival data are not yet mature. Fully enrolled data will be presented. **Conclusions:** In the first ever data set for this novel combination, Soto plus Pmab and FOLFIRI showed promising safety and efficacy in pre-treated KRAS G12C-mutated mCRC, with a confirmed ORR of 58.1%. Adverse events were manageable and consistent with the expected safety profile of the drugs used, and there was no clinically meaningful Soto and irinotecan PK interaction. Clinical trial information: NCT04185883. Research Sponsor: Amgen, Inc.

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Poster Discussion Session

Postoperative hepatic arterial chemotherapy after resection of colorectal liver metastases in patients at high risk of hepatic recurrence: A multicenter randomized phase II trial (PRODIGE 43 - PACHA-01). *First Author: Maximiliano Gelli, Gustave Roussy, Villejuif, France*

Background: Hepatic arterial infusion (HAI) of chemotherapy (CTx) has been proposed as a potential treatment to decrease the risk of hepatic recurrence after resection of colorectal liver metastases (CRLM). Randomized controlled trials (RCTs) led to controversial results and meta-analyses are inconclusive. We conducted a comparative phase II RCT to assess the efficacy of adjuvant HAI oxaliplatin with concomitant intravenous (IV) CTx in pts at high risk of hepatic recurrence (≥ 4 resected CRLM). **Methods:** Pts who underwent curative-intent surgery of at least 4 CRLM after preoperative IV CTx were randomly assigned (1:1) to receive adjuvant IV fluorouracil/leucovorin (LV5FU2) combined with oxaliplatin (85mg/m²) by HAI (HAI-IV arm) or IV route (IV arm) every 2 weeks, for at least 3 months to achieve a minimal duration of perioperative CTx of 6 months. The primary endpoint was the hepatic recurrence free survival (h-RFS). Secondary endpoints included the feasibility of delivering at least 4 CTx cycles, toxicity (NCI-CTCAE 4.0) including HAI catheter-related complications, RFS, overall survival (OS) and recurrence pattern. 108 randomized pts were required to detect a gain in 18-month h-RFS from 30% to 50% with a one-sided α risk of 10% and 95% power. The primary endpoint was analyzed with a Cox regression model, with adjustment for stratification factors (tumor response to preoperative CTx and number of resected CRLM). The study was prematurely stopped after randomization of 99 pts due to recruitment issues and HAI catheters market withdrawal. **Results:** Between Jun 2015 and Dec 2020, 99 pts (median age, 62; median number of CRLM, 5) were randomly assigned in HAI-IV arm (50 pts) or IV arm (49 pts). After a median follow-up of 56 months, the intent-to-treat analysis showed a significantly longer h-RFS in the HAI-IV arm compared to the IV arm (median 25 [16-37] vs 12 months [8-21]; HR 0.598 [95%CI 0.379-0.944], p = 0.027). 5-year h-RFS was 32% [19-45] in the HAI-IV arm vs 13% [4-27] in the IV arm, respectively. Median and 5-year OS were 74 months [51-74] and 60% [43-74] in the HAI-IV arm vs 54 months [37-69] and 46% [29-61] in the IV arm (HR 0.551 [0.299-1.015], p = 0.056). The median number of postoperative CTx cycles was 6 in both groups with 86% and 78% of patients having received at least 4 cycles in HAI-IV and IV arms (p = 0.7), respectively. Grade 3-4 toxicity rate was 58% in the HAI-IV arm vs 31% in the IV arm (p = 0.01). Overall, nine pts (18%) experienced HAI-related complications. No toxic death occurred in both arms. **Conclusions:** Despite a higher but acceptable toxicity, combination of HAI oxaliplatin with IV LV5FU2 significantly improved h-RFS after curative resection of CRLM in high-risk patients. This combined treatment should be considered as a valid option for these patients. Clinical trial information: NCT02494973. Research Sponsor: Institut National du Cancer, Programme Hospitalier de Recherche Clinique du Cancer, Ligue Contre le Cancer.

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Poster Discussion Session

Phase 1 study of WNT pathway Porcupine inhibitor CGX1321 and phase 1b study of CGX1321 + pembrolizumab (pembro) in patients (pts) with advanced gastrointestinal (GI) tumors. *First Author: Marios Giannakis, Dana-Farber Cancer Institute, Boston, MA*

Background: Despite the fundamental role of WNT signaling in GI cancers, especially colorectal cancer (CRC), no drug targeting WNT signaling has been successfully developed. CGX1321, a highly-potent and selective inhibitor of O-acyltransferase Porcupine, blocks WNT ligand secretion. Preclinical studies show that CGX1321 inhibits WNT signaling and growth of tumors with *RSP0* fusions or inactivating *RNF43* mutations. Activation of WNT signaling has been associated with cancer immune-suppression and resistance to immunotherapy. **Methods:** The first-in-human trials (NCT02675946 in U.S., NCT03507998 in China) include phase 1 CGX1321 dose escalation (3 – 18 mg, once daily) and dose expansion (18 mg), and phase 1b CGX1321 + pembro combination (Keynote 596). The primary objectives were safety, tolerability and identification of recommended doses and schedules for further evaluation. Secondary objectives were characterization of the PK profile and PD response and anti-tumor activity. CGX1321 was dosed once daily, orally, for 21 days out of 28-day cycles as single-agent, or for 14 days out of 21-day cycles in combination with pembro. **Results:** As of January 1, 2023, 77 pts were enrolled, including 38 pts with solid tumors in the CGX1321 dose escalation, 17 pts with CRC or small bowel cancer (SBC) carrying *RSP0* or *RNF43* alterations in the CGX1321 expansion, 17 pts with microsatellite stable (MSS) CRC in the CGX1321 + pembro dose escalation and 5 pts with MSS CRC in the CGX1321 + pembro expansion. Six of the 17 pts with MSS CRC or SBC from the CGX1321 single-agent expansion were rolled over to CGX1321 + pembro upon disease progression. Across all cohorts, treatment was well tolerated with the majority of AEs being Grade 1/2 and not related to CGX1321, while Grade > 3 AEs related to CGX1321 were infrequent ($\sim 6\%$). Dysgeusia, a common AE observed with other WNT inhibitors, was mild (mostly Grade 1). Bone resorption, the main on-target AE, was manageable and preventable by prophylactic administration of denosumab or zoledronic acid. PK and PD analyses showed adequate drug exposure and significant inhibition of WNT signaling as measured by reduced hair follicle axin2 expression from 12 mg dose. Twelve of 17 pts (71%) with confirmed tumor genetic alterations in *RSP0* or *RNF43* had SD with median time to progression of 112 days (range: 56 – 392). Of the 6 pts in the roll-over cohort, 3 pts with *RSP03* fusion tumors achieved PR during CGX1321 + pembro combination therapy. **Conclusions:** CGX1321 has demonstrated potent inhibition of the WNT pathway with manageable side effects. Promising efficacy signals have been observed in pts whose tumors harbor *RSP0* fusion, supporting further development of CGX1321 monotherapy and CGX1321 + anti-PD-1/L1 in a defined patient population that is historically known to be refractory to standard therapies and immune checkpoint inhibitors. Clinical trial information: NCT02675946, NCT03507998. Research Sponsor: Curegenix.

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Poster Discussion Session

Adjuvant systemic chemotherapy with or without hepatic arterial infusion of floxuridine in patients following colorectal cancer liver metastases resection (HARVEST): A prospective, randomized controlled trial. *First Author: Yu-hong Li, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University, Guangzhou, China*

Background: Several retrospective studies have previously demonstrated that a combination of adjuvant systemic chemotherapy and hepatic arterial infusion (HAI) could benefit patients following colorectal cancer liver metastases (CRLM) resection. This prospective clinical study aimed to determine whether adding HAI to adjuvant systemic chemotherapy could reduce the risk of recurrence following CRLM resection. **Methods:** The HARVEST study is an investigator-initiated, prospective, randomized controlled trial investigating the efficacy and safety of adjuvant intravenous chemotherapy with or without HAI floxuridine (FUDR) in CRLM patients that underwent liver metastasectomy. Patients in the systemic chemotherapy plus HAIC arm (HAI group) received systemic FOLFOX (q2w) plus HAI (FUDR, d1-14, q4w) for up to 6 months, while the systemic chemotherapy group without HAI (non-HAI group) received intravenous FOLFOX only. The primary study endpoint is the relapse-free survival in the modified intention-to-treat (mITT) population. Blood samples at different time points were also collected and circulating tumor DNA (ctDNA) was tested for NPY and SEPT9 methylation. **Results:** The study was prematurely terminated due to FUDR production halt in China. Ninety-two patients were randomized and seventy-seven patients (38 in the HAI group and 39 in the non-HAI group) were eventually included in our mITT analysis. After a median follow-up of 35.8 months, there were 22 (57.9%) and 25 (64.1%) recurrences in the HAI and non-HAI groups, respectively. The median relapse-free survival was 20.0 months in the HAI group and 11.7 months in the non-HAI group (p = 0.14; HR 0.65; 95% confidence interval [CI] 0.37 to 1.16). No significant difference was found in terms of overall survival between the two groups (p = 0.461). Our subgroup analysis revealed that patients with multiple liver metastases (p < 0.01) and RAS/BRAF mutation (p < 0.01) could benefit from adjuvant HAI treatment. Based on ctDNA status, patients with positive postoperative ctDNA methylation benefited from adjuvant HAI treatment (p < 0.01), while those with negative postoperative ctDNA methylation status (p = 0.95) did not. Chemotherapy-related adverse events were comparable between the two groups. **Conclusions:** Adjuvant chemotherapy intensification using HAI did not significantly reduce recurrence following CRLM resection. However, patients with multiple liver metastases, RAS/BRAF mutation and those with positive postoperative ctDNA might benefit from adjuvant HAI treatment. Clinical trial information: NCT03500874. Research Sponsor: None.

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Poster Discussion Session

Upfront palliative resection of primary tumor versus no resection in patients with synchronous metastatic colorectal cancer: The randomized phase 3 CAIRO4 study of the Dutch Colorectal Cancer Group (DCCG). *First Author: Miriam Koopman, Department of Medical Oncology, University Medical Center Utrecht, Utrecht University, Utrecht, Netherlands*

Background: Primary tumor resection (PTR) in patients with synchronous metastatic colorectal cancer (CRC) has been associated with a survival benefit in comparative cohort studies. In the CAIRO4 phase III randomized trial, the potential benefit of upfront PTR followed by systemic therapy versus systemic therapy alone was investigated. **Methods:** Main eligibility criteria included histologically confirmed CRC, unresectable metastases, resectable primary tumor in situ without related severe symptoms, and WHO performance status (PS) 0-2. Eligible patients were randomized to first-line fluoropyrimidine-based chemotherapy plus bevacizumab with or without upfront PTR strategy. Randomization was stratified for number of metastatic sites (1 versus more), institution, WHO PS (0-1 versus 2), serum LDH (normal versus > ULN), and location of the primary tumor (left versus right-sided). The primary endpoint was overall survival (OS), which was analyzed by intention-to-treat (ITT) using the Max-Combo test. The original sample size of 306 patients was amended to 206 participants due to slow accrual. With final primary analysis based on 181 events, the study had 71% power to detect the OS difference of 19 versus 13 months deemed clinically relevant in the original sample size calculation. The trial is registered as NCT01606098. **Results:** Between August 2012 and February 2021, 206 patients were randomized: 103 patients to each arm. Two patients in the upfront PTR arm were excluded due to ineligibility. A total of 204 patients (57% male, median age 65 [IQR 59-71] years, 50% right-sided CRC and 98% WHO PS 0-1) were included with a median follow-up of 63.6 months. In the upfront PTR arm 5% of patients did not undergo PTR and 13% did not receive subsequent systemic therapy. In the arm without upfront PTR, 1% of patients did not receive systemic therapy. The median number of cycles was 9 [IQR 4-15] in the upfront PTR arm versus 11 [6-16] in the arm without upfront PTR. Median OS was 22.2 (95% CI 17.5-25.7) months in the upfront PTR arm and 19.5 (95% CI 16.1-22.7) months in the arm without upfront PTR ($p = 0.269$). Median PFS was 10.1 (95% CI 8.7-11.7) months in the upfront PTR arm and 10.1 (95% CI 8.6-11.8) months in the arm without upfront PTR ($p = 0.805$). At a later point in their disease course, 1.9% of patients in the arm without upfront PTR underwent a colectomy and 16.5% required PTR for symptom palliation. **Conclusions:** In patients with synchronous metastatic CRC amenable to palliative systemic therapy without severe symptoms related to the primary tumor, upfront PTR did not result in a significant median OS difference compared to immediate start with systemic treatment. Funding: This work was funded by the Dutch Cancer Society (grant KUN 2012-5697) and Hoffmann-La Roche Ltd. Clinical trial information: NCT01606098. Research Sponsor: Hoffmann-La Roche Ltd.; Dutch Cancer Society (grant KUN 2012-5697).

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Poster Discussion Session

Neoadjuvant chemotherapy (NAC) followed by total mesorectal excision (TME) and adjuvant chemotherapy versus TME followed by adjuvant chemotherapy in very low-lying clinical (c) T3 rectal cancer (NAIR): A multi-center, randomized, open-label, phase 2/3 trial. *First Author: Yuichiro Tsukada, Department of Colorectal Surgery, National Cancer Center Hospital East, Kashiwa, Japan*

Background: Chemoradiotherapy and total neoadjuvant therapy are the standard treatments for locally advanced rectal cancer (LARC). Although radiotherapy (RT) is an integral part of treatment, it negatively impacts anal function after TME for cases of very low-lying LARCs. This trial examined the efficacy, safety, and influence on postoperative anal function of NAC without RT in patients (pts) with very low-lying cT3 LARCs. **Methods:** Pts with cT3NO-2M0 adenocarcinomas located within 5 cm from the anal verge, whose anuses were expected to be preserved, were randomly assigned (1:1) to either the NAC group (preoperative chemotherapy with six cycles of mFOLFOX6 or four cycles of CAPOX followed by TME; then, postoperative identical regimen) or the TME group (upfront TME followed by postoperative chemotherapy with 12 cycles of mFOLFOX6 or 8 cycles of CAPOX), stratified by cN stage, center, and sex. The primary endpoint was the 3-year recurrence-free survival (RFS), which was compared between groups using a stratified log-rank test at a one-sided alpha level of 20%. **Results:** Between February 2013 and March 2019, 130 pts were enrolled and randomly assigned to a treatment group. A total of 127 pts were evaluable (65 in the NAC group and 62 in the TME group). All but one patient with early progression completed preoperative chemotherapy in the NAC group, and all pts in both groups underwent TME. After a median follow-up of 37.4 months (IQR 36.5-40.5), the 3-year RFS was 75.5% (95% CI 62.5-84.5) in the NAC group vs. 70.9% (95% CI 57.2-80.9) in the TME group (hazard ratio 0.67, 95% CI 0.34-1.32; $P = 0.098$), and the primary endpoint was met. There were no differences in the occurrence of grade 3 or higher postoperative complications (20% in the NAC group vs. 21% in the TME group [$P = 1.000$]), chemo-associated grade 3 or higher adverse events (28% in the NAC group vs. 23% in the TME group [$P = 0.551$]), or any grade of peripheral sensory neuropathy lasting for 3 years (22.7% in the NAC group vs. 38.5% in the TME group in pts treated with mFOLFOX6 [$P = 0.3163$], 7.1% in the NAC group vs. 33.3% in the TME group in pts treated with CAPOX [$P = 0.1038$]), between the groups. No treatment-related deaths occurred in either of the groups. At 3 years after randomization, 61 pts in the NAC group (93.8%) and 52 pts in the TME group (83.9%) could defecate via their anuses ($P = 0.092$). The median Wexner incontinence score was 11.0 in the NAC group and 10.0 in the TME group ($P = 0.3405$). **Conclusions:** For pts with very low-lying cT3 LARC, NAC followed by TME and adjuvant chemotherapy achieved significantly better RFS and anus-preserving rates compared to upfront TME followed by adjuvant chemotherapy, without deteriorating postoperative complications or postoperative anal function. Clinical trial information: UMIN000009510. Research Sponsor: National Cancer Center Research and Development Fund (23-A-26).

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Poster Discussion Session

15-month safety and efficacy data after intraperitoneal treatment with ²²⁴Radium-labelled microparticles after CRS-HIPEC for peritoneal metastasis from colorectal cancer. *First Author: Stein G Larsen, Norwegian Radium Hospital, Oslo, Norway*

Background: Peritoneal metastasis (PM) from colorectal cancer carries a dismal prognosis. Improved survival can be achieved by extensive cytoreductive surgery (CRS), frequently used together with hyperthermic intraperitoneal chemotherapy (HIPEC), with median time to recurrence around 12 months. Radspherin is a novel treatment principle based on the delivery of short range and cytotoxic alpha particles emitted during the decay of ²²⁴Ra. Alpha particles have high linear energy transfer and a radiation range less than 100 μ m (3-10 cell diameters), generating highly localized and effective radiation with non-repairable double-strand DNA breaks in affected cells. Our hypothesis is that Radspherin produces an alpha-particle radiation field exclusively to the surfaces and liquid volumes of the peritoneum, delivering lethal doses to remaining micrometastasis in the peritoneal linings and eradicate free-floating tumor cells after surgical resection, thus assumingly prolonging time to recurrence and potentially overall survival. **Methods:** A phase 1/2a study (EudraCT 2018-002803-33) is ongoing to evaluate safety, tolerability and signal of efficacy of Radspherin injected intraperitoneally two days after CRS-HIPEC. After completion of dose escalation (1-2-4-7 MBq), an activity-dose of 7 MBq was recommended. Assessment of safety and efficacy (diagnostic imaging) was performed every three months. Safety data and progression-free survival (PFS) at 15 months are presented. **Results:** Twenty-three patients (pts) were enrolled across cohorts (safety population), of these 12 pts received the recommended dose of 7MBq, 9 pts single dose and 3 pts split dose (3,5 MBq x2). Twelve pts had synchronous PM and 11 metachronous PM. Median age was 64 years (28-78), 70 % were female and median peritoneal cancer index was 7 (3-19). To date, 271 adverse events (AE) were reported, whereof only 7 (all grade 1-2) were deemed related to Radspherin. Fourteen serious adverse events (SAEs) in 8 pts have been reported, none considered related to Radspherin. At 15 months, 9 out of 23 pts (39 %) had recurred, whereof 4 pts recurred in the peritoneum. In the expansion cohort (7MBq), 3 out of 12 pts (25 %) had recurred and none of these pts had peritoneal recurrences. Median PFS was not reached in the two populations. **Conclusions:** Radspherin was well tolerated with no related SAEs reported. At 15 months median PFS has not been reached and none of the patients at recommended dose had peritoneal recurrences. The results are encouraging and warrant further exploration of Radspherin as a novel treatment principle in clinical trials. Clinical trial information: NCT03732781. Research Sponsor: Oncoinvent AS; Innovation Norway.

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Poster Discussion Session

Sustained organ preservation in patients with rectal cancer treated with total neoadjuvant therapy: Long-term results of the OPRA trial. *First Author: Floris S Verheij, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: The preliminary results of the OPRA trial demonstrated that a substantial number of patients with locally advanced rectal cancer treated with total neoadjuvant therapy (TNT) could achieve organ preservation. Although most tumor regrowths seem to occur within the first 3 years, longer follow-up is needed to assess the ongoing risk of regrowth. Here, we report the long-term organ preservation rate and oncologic outcomes of the OPRA trial. **Methods:** A prospective, multi-institutional phase II trial, in which patients with stage II or III rectal cancer were randomized to receive either induction chemotherapy followed by chemoradiation (INCT-CRT) or chemoradiation followed by consolidation chemotherapy (CRT-CNCT). Patients underwent reassessment for treatment response 8-12 weeks after TNT. Patients who achieved a complete or near-complete response after finishing TNT were offered a watch and wait approach (WW). Those with incomplete response were recommended total mesorectal excision (TME). We report 5-year disease-free survival (DFS), organ preservation (defined as TME-free survival), local recurrence-free survival (LRFS), distant metastasis-free survival (DMFS) and overall survival (OS) for each treatment group. We also compared DFS between patients who underwent upfront TME after restaging and patients who underwent TME after tumor regrowth. All analyses followed the intention-to-treat principle and groups were compared using the log-rank test. **Results:** Of the 324 patients randomized, 158 were assigned to the INCT-CRT group and 166 to the CRT-CNCT group. Median follow-up was 56 months; 85 DFS events were observed. The rates of 3- and 5-year DFS, TME-free survival, LRFS, DMFS and OS are listed in the Table. In total, 80 of the 225 (36%) patients who started WW developed a regrowth; 94% occurred within 2 years and 99% occurred within 3 years. The rate of TME-free survival at 5 years was significantly higher for CRT-CNCT (54%) than in INCT-CRT (39%). 5-year DFS was similar for patients who underwent TME after restaging (61%) compared to patients who underwent TME after regrowth (62%, $p = 0.86$). **Conclusions:** In patients with rectal cancer treated with TNT and WW, the majority of tumor regrowths occur in the first 2 years, and regrowth after 3 years is vanishingly rare. Salvage TME for tumor regrowth during WW appears to offer similar outcome to immediate TME after incomplete response to TNT. Distant metastases remain the most frequent cause of treatment failure, with similar rates in the two treatment groups. Clinical trial information: NCT02008656. Research Sponsor: U.S. National Institutes of Health.

3- and 5-year rates with 95% CI.

	Induction		Consolidation		P
	3-year, %	5-year, %	3-year, %	5-year, %	
DFS	77 (70-84)	72 (65-80)	76 (70-83)	71 (63-78)	0.60
TME-free survival	41 (34-50)	39 (32-48)	55 (48-63)	54 (47-63)	0.01
LRFS	95 (91-99)	94 (90-98)	94 (90-98)	90 (85-95)	0.27
DMFS	83 (78-90)	82 (75-89)	83 (77-89)	79 (72-86)	0.66
OS	95 (92-99)	88 (82-94)	94 (91-98)	88 (82-94)	0.73

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Poster Discussion Session

Circulating tumor DNA dynamics as an early predictor of recurrence in patients with radically resected colorectal cancer: Updated results from GALAXY study in the CIRCULATE-Japan. *First Author: Eiji Oki, Kyushu University, Fukuoka-Shi Higashi-Ku, Japan*

Background: Postoperative circulating tumor DNA (ctDNA)-based molecular residual disease (MRD) is reported to be associated with a high risk of recurrence. Here, we present an updated analysis and the lead time interval (LTI) of ctDNA positivity to radiographic recurrence in patients (pts) with radically resected colorectal cancer (CRC), stage II-IV in the observational GALAXY study. **Methods:** Serial ctDNA was analyzed using personalized tumor-informed assay (Signatera bespoke multiplex-PCR NGS assay) at 1 (4-week MRD time point), 3, 6, 9, 12, 18, and 24 months after surgery until recurrence, and CT scans were conducted every 6 months. The primary endpoint was disease-free survival (DFS), defined as the time between the date of surgery and date of diagnosis with relapse or death due to any cause. The LTI was defined from the first ctDNA positive date at post-surgery to radiographic recurrence. **Results:** Among 3,615 CRC pts who were enrolled between May 2020 and April 2022 in GALAXY study, 2,083 pts that met the inclusion criteria were analyzed in this report. The median follow-up period was 16.3 months. Of 2,083 pts analyzed, 286 (14%) were ctDNA-positive at 4-weeks MRD time point and 1,797 (86%) were ctDNA-negative. Pts with ctDNA-positivity at 4-weeks MRD timepoint demonstrated an inferior DFS and were 12 times more likely to recur, compared to ctDNA-negative pts (HR:12, 95CI: 9.1-15%; $p < 0.0001$). We further combined ctDNA status with BRAF V600E status at 4-week MRD time point and observed that pts with ctDNA-positivity and BRAF V600E mutation showed significantly shorter DFS compared to ctDNA-positive pts with BRAF wild-type ($p < 0.001$). Whereas, in pts with ctDNA-negativity no significant difference in DFS was observed ($p = 0.306$). On performing ctDNA dynamics analysis between 4-weeks to 12 weeks, compared to pts who remained ctDNA-negative ($N = 1529$), a significantly shorter DFS was observed for pts who converted from ctDNA-negative to positive ($N = 112$, HR: 14.5, 95%CI: 8.8-23.8%, $p < 0.0001$) or who remained positive ($N = 124$, HR: 25.4, 95%CI: 18.3-35.3; $p < 0.0001$). Radiographic recurrence was observed in 186 pts (46%). Of these, 121 pts (65%) had CT imaging performed every 6 months, as per the protocol. The median LTI was 142 days (IQR, 43-189 days). **Conclusions:** Our study builds on the existing evidence from the recently published, prospective GALAXY study. ctDNA status at MRD time point post-surgery is prognostic of patient outcomes and is the most significant risk factor regardless of BRAF V600E status. ctDNA positivity predicted radiologic recurrence several months ahead of clinical recurrence. Pts with positive postoperative ctDNA should be examined carefully due to a high risk of recurrence. ctDNA-guided adjuvant strategy will further be established by ongoing randomized VEGA and ALTAIR studies in the CIRCULATE-Japan. Clinical trial information: UMIN000039205. Research Sponsor: Japan Agency for Medical Research and Development (AMED).

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Poster Discussion Session

Predictive models of recurrence from transcriptomic signatures of the tumor microenvironment and cell cycle in stage III colon cancer from PETACC-8 and IDEA France trials. *First Author: Claire Gallois, Institut du Cancer Paris CARPEM, APHP, Digestive Oncology Department, APHP.Centre - Université Paris Cité, Hôpital Européen G. Pompidou, Paris, France*

Background: The objective of this work was to establish predictive models of the risk of recurrence in stage III colon cancer (CC) based on transcriptomic signatures of the tumor microenvironment (TME) and cell cycle from the PETACC-8 (training set) and IDEA-France (validation set) trials. **Methods:** 3'RNAseq was performed in 1733 patients from the PETACC-8 trial (85%) and 1263 patients from the IDEA-France trial (63%). 4 transcriptomic signatures were analyzed: a signature reflecting T-cells infiltration named "Immunoscore-Like", a signature reflecting M2 macrophage infiltration named "M2-like", the expression of CXCL13 (reflecting B cells infiltration) and a score based on the Oncotype DX® Colon Cancer RS using the same formula from the stromal score and the cell cycle score, named "Oncotype DX Like". In the 1st multivariate model, we analyzed the 4 signatures separately with a dichotomization into "high" and "low" with the best cut point value for the prediction of time to recurrence (TTR) in PETACC-8 trial. In the 2nd multivariate model, we defined a score named "IPS" (Immune Proliferative Stromal), corresponding to the number of deleterious signatures ("high" or "low" depending on the signatures), ranging from 0 to 4. **Results:** The 1st multivariate model, built from PETACC-8 trial, showed that these 4 signatures were significantly associated with TTR with a protective effect of Immunoscore Like and CXCL13 "high" (HR: 0.66, $p = 0.003$ and 0.60, $p < 0.001$ respectively) and a deleterious effect of M2 Like and Oncotype Like "high" (HR: 1.28, $p = 0.05$ and HR: 1.37, $p = 0.01$, respectively), independently of known prognostic factors, with a C-index of 0.73. This model was applied to the IDEA-France cohort by calculating a predictive score for each patient, with TTR significantly different depending on the quartile of this score with a 3-year TTR ranging from 55% for the lowest quartile to 90% for the highest quartile ($p < 0.001$). In the 2nd model, in the 2 cohorts, IPS score was independently associated with TTR with a HR increasing with the IPS score, independently of T and N stage and intra-tumoral CMS heterogeneity (Table). **Conclusions:** Using transcriptomic data of patients with stage III CC from 2 large-scale adjuvant trials, two predictive models based on signatures of the TME and the cell cycle, provide important information in addition to known prognostic factors for patient stratification on risk of recurrence. Beyond T and N stage, for the decision of adjuvant chemotherapy in stage III CC, the combination of these different variables could be exploited in the future for personalized care (de-escalation, intensification). Research Sponsor: ARCAD.

	PETACC-8		IDEA-France	
	HR	p	HR	p
T4	2.0	< 0.01	1.6	< 0.01
N2	2.2	< 0.01	2.4	< 0.01
IPS				
1	1.8	0.2	2.3	0.2
2	3.4	< 0.01	3.9	0.058
3	4.4	< 0.01	4.6	0.03
4	6.7	< 0.01	5.7	0.02
Dismal CMS combination	1.6	< 0.01	1.1	0.5
Treatment duration 3 months			1.5	< 0.01

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Poster Discussion Session

Association of positive ctDNA-based minimal residual disease assays during surveillance and undiagnosed concomitant radiographic recurrences in colorectal cancer (CRC): Results from the MD Anderson INTERCEPT program. *First Author: Arvind Dasari, Department of Gastrointestinal Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Observational cohorts have shown that detection of circulating tumor DNA (ctDNA)-defined minimal residual disease (MRD) following curative intent therapy has very high specificity and positive predictive value for future radiographic recurrence with a lead time of over 9 months. However, such data have not incorporated rigorous clinical evaluation for concomitant recurrence, nor have they established the clinical utility of MRD monitoring after completion of curative intent therapy. **Methods:** Pts with stages II-IV CRC (6/1/19 - 12/31/22, data cutoff) treated with curative intent at MD Anderson Cancer Center were evaluated with a tumor-informed MRD assay (Signatera, Natera), as part of the institutional INTERCEPT program that aims to integrate MRD-based testing into CRC clinical care. Surveillance visits including scans and tumor markers were performed per established guidelines. ctDNA was recommended post-operatively and q3m with each surveillance visit. Pts and providers were informed of the results and subsequent clinical courses including additional radiologic testing for ctDNA+ MRD tests were tracked. **Results:** 1259 pts were included in the INTERCEPT program (median 57y, [21-93]; 55% male; stage% I-III/IV 69/31; colon/rectum% 61/39), with 1049 pts tested after curative intent surgery. Of these, 159/1049 pts (15%) had ctDNA+; distribution of pts, % (+ve/total) from time of such surgery in m was: 0-3 (54.6/43.8); 3-6 (21.3/30); 6-12 (24/33.2). Of the pts with ctDNA+ after surgery, 49 pts (32%) were ctDNA+ prior to or during adjuvant therapy and 86 (57%) during surveillance. Of the 86 pts who were ctDNA+ during surveillance, imaging revealed concomitant new metastases in 46 (53%); i.e. only 40 (47%) were true MRD+. A total of 191 imaging studies were done (range 1-4) within 90d of the initial ctDNA+ including 99 as routine surveillance concurrent with ctDNA testing and 92 as additional follow up based on results. Of 40 pts with true MRD, majority (27 pts, 67.5%) were enrolled onto ongoing MRD trials (<https://crcmrmd.com/>). **Conclusions:** Our experience provides support for the feasibility of incorporation of MRD testing as part of routine surveillance. ctDNA+ results trigger a high rate of reflex imaging and, as a result, 53% of ctDNA+ patients have concomitant new radiographic findings. While clinical trials are feasible in true MRD+ pts, eligibility criteria for these trials need to be carefully specified about adequate radiographic evaluation. Research Sponsor: None.

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Poster Session

Circulating tumor DNA (ctDNA) to assess response in patients with anal cancer treated with definitive chemoradiation. *First Author: Janet Alvarez, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: We hypothesize that circulating tumor DNA (ctDNA) dynamics can provide an early response indicator in patients with anal squamous cell carcinoma (ASCC) undergoing definitive chemoradiotherapy (CRT). **Methods:** Since 2021, patients with ASCC undergoing CRT at 2 institutions were offered ctDNA monitoring with the Natera Signatera assay, a commercial tumor-bespoke, multiplex PCR assay. All patients provided written informed consent for ctDNA testing. Patients were clinically restaged 3-4 months after CRT by clinical exam, endoscopy, and/or MRI, as well as annually with a chest, abdomen, and pelvis CT. Complete clinical response (cCR) was defined as having no tumor observed by digital exam, endoscopy, and/or MRI. Molecular ctDNA response was described according to cCR, tumor recurrence, and survival. **Results:** From January 2021 to October 2022, 41 patients with ASCC treated with CRT underwent ctDNA response assessment. Most patients (66%) had stage III disease. Patients were treated to a median radiation dose of 54 Gy in 27 fractions — with combinatorial mitomycin and fluoropyrimidine-based chemotherapy in 88% of patients, and fluoropyrimidine-based chemotherapy alone in 12%. The median follow-up was 22 weeks (range 0-89 weeks). ctDNA testing was performed in 36 patients at baseline, 31 patients during CRT, 27 patients within 40 days after CRT, 23 patients 3-6 months post-CRT, 23 patients 6-12 months post CRT, and 10 patients > 12 months post CRT. At baseline, 89% of patients had detectable ctDNA. Patients with stage III, as compared to stage I-II, disease had numerically higher baseline ctDNA levels (29 vs. 2.9 mean tumor molecules per milliliter (MTM/mL), $p = 0.04$). ctDNA levels decreased with treatment (24 vs. 2.1 MTM/mL, $p = 0.005$) among the 24 patients with detectable baseline ctDNA and ctDNA tested during CRT. Fifty eight percent of patients converted from ctDNA positive to ctDNA negative during CRT. Similarly, post-CRT ctDNA levels decreased (23 vs. 0.01 MTM/mL, $p = 0.01$), with 95% of patients converting from ctDNA positive to ctDNA negative. The time to ctDNA clearance was significantly shorter than the time to cCR (median 31 vs. 131 days, $p < 0.0001$). In follow up 2 patients reverted from ctDNA negative to ctDNA positive at 113 -155 days post-CRT. Currently all patients are clinically and radiographically without evidence of disease. **Conclusions:** Surveillance ctDNA monitoring provides an earlier response assessment for patients with ASCC undergoing CRT. However, longer term follow-up is required to determine if ctDNA response correlates with long-term recurrence free survival. Prospective trials are needed to assess the clinical utility of integrating molecular ctDNA response into therapeutic response surveillance. Research Sponsor: U.S. National Institutes of Health.

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Poster Session

HPV integration as a prognostic biomarker for metastatic anal cancer: A next-generation sequencing ctDNA-based approach. *First Author: Benny Johnson, Department of Gastrointestinal Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Anal cancer is an HPV-associated malignancy with increasing prevalence in the United States. Immune checkpoint blockade demonstrates limited efficacy in patients with metastatic squamous cell cancer of the anal canal (mSCCA), and no prognostic or predictive biomarkers have demonstrated clinical utility in this population. Available circulating tumor DNA (ctDNA) assays have utilized ddPCR methodologies to report only the most common HPV types (HPV-16 and HPV-18) and HPV copy numbers. To extend the utility of an HPV ctDNA assay, we created a novel next-generation sequencing HPV ctDNA assay to analyze HPV integration as a prognostic biomarker for patients with mSCCA. **Methods:** Using an IRB-approved protocol, ctDNA isolated from the plasma of patients with mSCCA was sequenced using a 1.4Mb hybrid-capture target-enrichment panel covering the whole genome sequences of all 193 HPV types. HPV type, HPV copy number, and HPV integration status/locus were determined using a bioinformatic pipeline developed in-house. A Fisher's exact test was used to compare radiographic and ctDNA changes in response to systemic treatment. Unpaired t-tests were used to compare demographics between patients with HPV integration (I) or no integration (NI) status in the ctDNA. Median survival was estimated (Kaplan Meier) and compared according to integration status using a log-rank test. **Results:** 68 plasma samples from 27 patients with mSCCA were analyzed. While HPV-16 was detected in ctDNA of all 27 patients, five patients had additional oncogenic HPV types [HPV-18 (2), HPV-45 (2), HPV-73 (1)]. Radiographic changes in metastatic disease volume were concordant with HPV copy number changes in the ctDNA (odds ratio 12.2, 95% confidence interval (CI) 2.0-75; $p = .007$). HPV integration events were detected in the ctDNA for 16 (59%) patients (median 2, range 1-7 unique events per patient). For the 23 patients with mSCCA who received anti-PD1 immunotherapy (15 I, 8 NI), there were no differences in age (60 vs 59 years, $p = .88$) or prior lines of treatment (3.0 vs 3.5, $p = .72$). There was a trend towards improved median progression-free survival for NI ctDNA status (5.8 vs 3.2 months, hazard ratio (HR) 1.8, 95% CI .71-4.5). Relative to NI status, I status was associated with worse overall survival rates (OS) (22.5 vs 44.9 months, HR 5.0, 95% CI 1.5-17, $p = .005$). **Conclusions:** Detection of HPV integration status for all HPV types is feasible using a ctDNA-based approach for patients with SCCA. HPV integration was prognostic for worse OS in patients with mSCCA. Identification of HPV integration as a novel prognostic biomarker for survival outcomes in mSCCA warrants further evaluation in larger clinical trials. Research Sponsor: MD Anderson HPV Moonshot; Anonymous donor.

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Poster Session

Pathological analysis of tumor microenvironmental features using deep learning to predict survival of colon carcinomas. *First Author: Frank A. Sinicrope, Mayo Clinic College of Medicine, Rochester, MN*

Background: Advances in deep learning may improve the ability to evaluate and quantify pathological features in solid tumors to improve prediction of patient disease-free survival (DFS). We used an artificial intelligence (AI) algorithm to quantify morphological features in the tumor microenvironment of stage III colon cancers. **Methods:** We analyzed digitized stage III colon carcinomas (N = 402; 382 met QC) from participants in a phase III trial of FOLFOX-based adjuvant chemotherapy that included all available tumors with dMMR and a randomly selected cohort of pMMR tumors (median follow-up 60 months) [NCCTG N0147; Alliance for Clinical Trials in Oncology]. Fifteen morphological features were extracted using the QuantCRC algorithm that segments images into carcinoma (low-grade, high-grade, signet ring cell), stroma (immature, mature, and inflammatory), mucin, tumor/stroma ratio, tumor budding/poorly differentiated clusters (TB/PDC), necrosis, smooth muscle, fat, and tumor-infiltrating lymphocytes (TILs) and tumor area (mucin, epithelium and TB/PDC). Analysis of AI-derived features with clinical variables, molecular alterations (BRAF/KRAS), and DFS were examined using Kaplan-Meier methodology and multivariable Cox regression. **Results:** Among the 15 AI-derived morphological features, the following differed significantly between dMMR (n = 191) and pMMR (n = 189) whereby dMMR tumors had lower mature stroma, but higher inflammatory stroma and tumor, higher tumor grade and increased mucin, TB/PDCs, signet ring cells, and TILs (all $p < 0.05$). Among dMMR tumors, multivariable analysis revealed that tumor area [mucin, epithelium and TB/PDC] (HR_{adj} 0.45, 95%CI (0.24, 0.84), $p < 0.01$, [Q2/3 vs Q1]) and N stage were the only significant and independent prognostic variables. Among pMMR tumors, multivariable analysis identified that tumor budding/poorly differentiated clusters (TB/PDCs) (HR_{adj} 0.20, 95%CI (0.06, 0.61), $p < 0.01$, [Q1 vs Q4]) was the strongest prognostic variable and the only morphological feature that was significantly associated with DFS along with age, N stage and T stage. **Conclusions:** Using AI, we can extract and quantify distinct morphological features in tumor sections that differ between dMMR and pMMR and multivariately, can significantly and robustly enhance prognostication within each MMR group. Among pMMR tumors, tumor budding/poorly differentiated clusters was the strongest predictor of DFS. Support: NIH U10CA180821, U10CA180882, U24CA196171, R01 CA210509 (to FAS). Study NCCTG N0147 received funds from Sanofi https://acknowledgments.alliancefound.org. ClinicalTrials.gov Identifier: NCT00079274 Key words Artificial Intelligence; Tumor Microenvironment; Colonic Neoplasms; Disease-free survival. Research Sponsor: U.S. National Institutes of Health; Sanofi; NIH U10CA180821, U10CA180882, U24CA196171, R01 CA210509 (to FAS).

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Poster Session

Variation in FOLFOX, FOLFIRI, and FOLFOXIRI effects on CD8+ T cell and PDL1 levels in MSS CRC patients. *First Author: Lindsey Carlsen, Brown University, Providence, RI*

Background: Colorectal cancer (CRC) is a heterogeneous disease treated with FOLFOX, FOLFIRI, and FOLFOXIRI chemotherapy regimens. About 85% of CRC patients have microsatellite stable (MSS) tumors that resist immune checkpoint blockade (ICB). Some studies suggest that chemotherapy modulates the MSS CRC tumor microenvironment (TME) to enhance CD8+ T cell infiltration, but ICB remains ineffective. We evaluated the TME of MSS CRC patients to investigate chemotherapy impact on immune markers. **Methods:** CRC patient samples (n = 16,827) underwent DNA (592-gene or whole exome)/RNA (whole transcriptome) sequencing at Caris Life Sciences. Immune cell fractions within TMEs were estimated from RNA deconvolution (quanTseq; Finotello, 2019; n = 11,109). PDL1 expression was assessed by IHC (SP142; $\geq 2+$ /5%). Patients who received FOLFOX (n = 425), FOLFIRI (n = 88), or FOLFOXIRI (n = 19) < 1 year prior to tumor collection or who didn't receive these treatments > 4000 days before tumor collection (untreated, n = 6,608) were analyzed. Statistical significance was determined using chi-square, Fisher's exact, and Mann-Whitney U tests, where appropriate. **Results:** FOLFOX-treated CRC (n = 213) had a higher CD8+ T cell fraction vs untreated (n = 3,449, FC = 1.9, $p < 0.01$) CRC and there was no difference among FOLFIRI-treated (n = 37, FC = 1.1, $p = 0.13$) or FOLFOXIRI-treated (n = 9, FC = 2.2, $p = 0.49$) CRC. Survival outcomes were similar in FOLFOX-treated CD8+ T cell-high (n = 82) vs low (n = 161, HR = 1.3, $p = 0.12$) and in FOLFOX-treated PDL1+ (n = 13) vs PDL1- (n = 338) CRC (HR = 1.6, $p = 0.14$). The CD8+ T cell fraction was similar in untreated KRAS wild-type (WT, n = 1714) vs untreated KRAS-mutated (mut, n = 1718) CRC (FC = 1.3, $p < 0.01$). FOLFOX-treated KRAS-mut CRC had a higher CD8+ T cell fraction (n = 1718 untreated, 96 treated, FC = 2.3, $p < 0.01$) and CD69 expression (n = 1724 untreated, 97 treated, FC = 1.7, $p < 0.01$) vs untreated KRAS-mut CRC. This FOLFOX-dependent effect on CD8+ T cells was lower in WT KRAS CRC (n = 114 FOLFOX-treated, n = 1714 untreated, FC = 1.6, $p < 0.01$) but survival outcomes were similar in FOLFOX-treated WT (n = 210) vs KRAS-mut CRC (n = 210) CRC (HR = 1.0, $p = 0.82$). The CD8+ T cell fraction was similar in untreated right- (R; n = 803) vs left-sided CRC (L; n = 927, FC = 1.3, $p < 0.01$) but PDL1+ IHC rates were significantly higher in R-CRC (n = 1340 L, 1124 R, FC = 2.2, $p < 0.01$). The CD8+ T cell fraction was similar in untreated WT (n = 3144) vs BRAF-mut CRC (n = 248, FC = 0.8, $p < 0.01$), but BRAF-mut were more frequently PDL1+ (n = 4622 WT, 340 mut, FC = 4.2, $p < 0.01$). PDL1+ rates were similar in untreated (n = 1124) vs FOLFIRI-treated R-CRC (n = 12, FC = 2.0, $p = 0.46$) but were higher in FOLFIRI-treated (n = 9) vs untreated (n = 1340) L-CRC (n = 9, FC = 6.0, $p = 0.04$). **Conclusions:** We describe an association between FOLFOX and subsequent infiltration by CD8+ T-cells and high PDL1+ rates in R-CRC, BRAF-mut CRC, and FOLFIRI-treated L-CRC. The findings provide insights for future therapeutic strategies. Research Sponsor: U.S. National Institutes of Health.

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Poster Session

HER2 testing in the MOUNTAINEER trial: Analysis of treatment response based on central HER2 assessment using IHC/ISH and NGS. *First Author: John H Strickler, Duke University Medical Center, Durham, NC*

Background: Tucatinib (TUC) is a highly selective HER2-directed TKI approved by the FDA in combination w/trastuzumab (Tras) for treatment (tx) of pts w/ RAS wild-type HER2+ unresectable or metastatic colorectal cancer (mCRC) that has progressed following tx w/ fluoropyrimidine, oxaliplatin-, and irinotecan-based chemotherapy. There are currently no established best practices for HER2 testing/interpretation in mCRC. Here we present results of central HER2 testing across multiple platforms and response to tx for MOUNTAINEER pts treated w/ TUC + Tras based on central HER2 status. **Methods:** MOUNTAINEER (NCT03043313) enrolled pts w/ local HER2+ mCRC using ≥ 1 method: IHC, ISH, and/or NGS testing; retrospective central assessment of HER2 status was performed on multiple platforms. Pts in cohorts A+B were treated w/ TUC + Tras; pts in cohort C were treated w/ TUC monotherapy. Confirmed objective response rates (cORRs) using RECIST v1.1 per BICR, DOR, and PFS were calculated for pts treated w/ TUC + Tras based on each central testing method. **Results:** 114 pts were enrolled in cohorts A (n = 45), B (n = 39), and C (n = 30) w/ HER2+ tumors per ≥ 1 local testing method. Of samples submitted for central testing for Cohorts A and B, 70 per IHC/FISH, 50 per tissue NGS, and 71 per blood NGS had evaluable results. In all cohorts, there was 81.0% (95% CI, 68.6-90.1) agreement between blood and tissue NGS, 92.6% (95% CI, 83.7-97.6) between IHC/FISH and tissue NGS, and 79.5% (95% CI, 69.2-87.6) between IHC/FISH and blood NGS. In cohorts A and B, pts w/ HER2+ tumors by central IHC/ISH had a mDOR of 16.4 months (95% CI: 10.6-25.5) and mPFS of 10.1 months (95% CI: 4.2-15.2). cORR was 41.1% to 47.7% for the 3 assays. Detailed HER2 results are presented in the Table. **Conclusions:** Percent agreement of HER2 status was highest w/ tissue-based platforms. Detection of HER2 amplification by ctDNA NGS is useful; however, pts w/o HER2 amplification should be confirmed w/ a tissue-based assay. HER2 status by all 3 platforms predicted tx response to TUC + Tras. cORR in IHC2+/ISH+ was numerically lower but remained clinically relevant. These data support use of the above methods to identify HER2+ mCRC patients that may benefit from TUC + Tras. Clinical trial information: NCT03043313. Research Sponsor: Seagen Inc.

Response	Central IHC + FISH (n = 70)			PGdx tissue NGS (n = 50)		Guardant ctDNA (n = 71)	
	Positive (IHC3+) (n = 45)	Positive (IHC2+/ ISH+) (n = 15)	Negative (n = 10)	Positive (n = 44)	Negative (n = 6)	Positive (n = 56)	Negative (n = 15)
CR	3	0	0	1	0	1	1
PR	18	3	1	20	0	22	2
SD*	17	5	4	16	2	18	7
PD	7	6	5	7	4	14	4
NA	0	1	0	0	0	1	1
cORR, n, (%)	21, (46.7%) (31.7-62.1)	3, (20.0%) (4.3-48.1)	1, (10.0%) (0.3-44.5)	21, (47.7%) (32.5-63.3)	0, (0%) (0-45.9)	23, (41.1%) (28.1-55)	3, (20.0%) (4.3-48.1)
mDOR, months (95% CI)	16.4 (10.6, 25.5)	-	-	15.3 (8.9, 25.5)	-	12.4 (6.2, 38.3)	-
mPFS, months (95% CI)	10.1 (4.2, 15.2)	-	2.8 (1.2, 6.3)	10.1 (7.0, 20.7)	2.1 (1.3, -)	8.1 (3.1, 10.2)	10.9 (2.0, 18.4)

*Includes non-CR/non-PD.

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Poster Session

A prospective, cross-sectional, multicentre study to evaluate the clinical performance of the ColoSTAT in vitro diagnostic for the detection of biomarkers associated with colorectal cancer. *First Author: Emily He, Concord Repatriation General Hospital, Camperdown, Australia*

Background: Colorectal cancer (CRC) survival rates could be improved if more cancers were detected early. The ColoSTAT blood test and algorithm combines concentrations of 5 protein biomarkers with age and sex to provide an alternative to current CRC screening methods like the faecal immunochemical test (FIT). We compared the performance of ColoSTAT to colonoscopy in detecting CRC. **Methods:** Patients in this Australian study were either recently diagnosed with CRC using colonoscopy and progressing to surgery or neoadjuvant treatment (Cohort 1) or had no CRC history and were scheduled for colonoscopy (Cohort 2). Due to COVID-19 pandemic-related recruitment delays, the samples from Cohort 1 were supplemented with bio-banked blood samples (BBS) from patients with clinically confirmed CRC. Patients provided a 17 mL blood sample and were followed until start of cancer treatment or colonoscopy. All blood samples were de-identified prior to testing by an independent laboratory. The primary endpoints were ColoSTAT sensitivity of $\geq 73\%$ (lower 95% confidence limit [LCL] $> 60\%$), and specificity $\geq 90\%$ (LCL $> 80\%$). Sensitivity by TNM stage was an exploratory endpoint (ACTRN12619000301167). **Results:** Cohort 1 enrolled 29 patients, Cohort 2 enrolled 768 patients and 192 BBS were included. Patient demographic characteristics were similar in Cohorts 1, 2 and BBS. Overall, the median age of the patients ($n = 989$) was 64 years (range 40 to 88) and 53.4% were female. Definitive ColoSTAT results were obtained for 22 patients in Cohort 1, 554 in Cohort 2 and 81 in BBS. Overall, the estimated sensitivity of ColoSTAT for detection of CRC compared with colonoscopy was 81.3% (95%CL 73.0%-87.4%) and estimated specificity 91.0% (95%CL 87.7%-93.5%) (Table). **Conclusions:** The ColoSTAT test met the primary endpoints of performance based on sensitivity and specificity in detecting CRC compared to colonoscopy. ColoSTAT sensitivity and specificity for CRC were comparable with published performance parameters for FIT which range from 74-93% (sensitivity) and 85-96% (specificity).¹ Clinical trial information: ACTRN12619000301167. Research Sponsor: This study was solely funded by Vision Tech Bio Pty Ltd (subsidiary of Rhythm Biosciences Limited). S. Gibb, WriteSource Medical Pty Ltd provided medical writing services funded by Rhythm Biosciences.

Sensitivity and specificity of ColoSTAT vs colonoscopy.	
All participants/BBS (N = 989)	
Definitive ColoSTAT result (indeterminant, invalid, no test)	657 (97, 208, 27)
Colonoscopy result available (no colonoscopy)	911 (78)
Definitive ColoSTAT and colonoscopy	603
ColoSTAT True +ve (A), False +ve (B), False -ve (C), True -ve (D)	91, 35*, 21, 354*,
Sensitivity (95%CI) (A/(A+C))	81.3% (73.0%-87.4%)
Specificity (95%CI) (D/(B+D))	91.0% (87.7%-93.5%)
ColoSTAT sensitivity by CRC stage (I, II, III, IV)*	I: 87.5% (64.0%-96.5%), II: 91.3% (73.2%-97.6%), III: 92.3% (66.7%-98.6%), IV: 100% (87.9%-100%)

*Specificity calculated using the prospective cohorts ^aExploratory endpoint; staging data available for BBS only ^bSwitalski J et al, Cancers 2022, 14, 4391.

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Poster Session

Chemotherapeutic sensitivity in colorectal cancer expressing low RNA of wild type homologous recombination genes. *First Author: Daniel Walden, Mayo Clinic Arizona, Phoenix, AZ*

Background: Homologous recombination deficient (HRD) colorectal cancer (CRC) has improved overall survival (OS) when exposed to DNA damaging agents (DDA) oxaliplatin (OX) and irinotecan (IR). However, this OS benefit is only observed in HRD mutated CRC. Low expression of wild type (WT) *BRCA1* RNA displays prolonged OS in ovarian cancer; this finding has not been investigated in CRC or outside *BRCA*. We investigate if low expression of WT HR genes is associated with prolonged OS in response to DDA. **Methods:** A total of 12,860 CRC patients tumor biopsies were analyzed by next-generation sequencing (592, NextSeq; WES, WTS NovaSeq). Patients with HRD mutations and MSI-H were excluded ($N = 935$). 11,925 patients were included in the analysis. A total of 11 core (*BARD1*, *BLM*, *BRCA1*, *BRCA2*, *BRIP1*, *MRE11*, *NBN*, *PALB2*, *RAD50*, *RAD51*, *RAD51B*) and 7 related (*BAP1*, *WRN*, *DNMT3A*, *ERCC1*, *FANCA*, *FANCF*, *RECQL4*) HR genes were analyzed. Samples were classified by RNA expression percentiles within the studied cohort. Real world OS was extracted from insurance claims and calculated using Kaplan-Meier estimates for molecularly defined cohorts from first of OX or IR to last contact. **Results:** OS benefit is seen in low RNA expression (bottom 10%) compared to high expression (top 10%) of all core WT HR genes except *RAD51B*, *BARD1* and *BRCA2* in response to IR. We observe a progressively longer OS with lower associated RNA expression in response to DDA. OS of nearly 7 years was observed in low expressing *BRCA1* and *RAD51* following IR exposure and 4.5-year OS benefit when compared to high expression of these genes. OS benefit in response to OX was less robust but significantly prolonged in *BRCA1* and *BRIP1* (Table). Patients harboring HRD mutations had similar OS to WT HR RNA low (bottom 10%) in response to OX (HR = 0.75; $p = 0.1$) and IR (HR = 0.82; $p = 0.36$). **Conclusions:** Here we report a novel subclass of CRC defined as patients with low RNA expressing WT HR genes that exhibit differential sensitivity to DDA. Significantly longer survival is noted in CRC with low expression *BRCA1*, *RAD51* and *BLM*, while post-OX survival was significantly prolonged with low expression of *BRCA1*, *BRIP1* and *FANCA*. Further characterization of sensitive HR genes will better predict DDA sensitivity and impact treatment sequencing. Research Sponsor: None.

Gene – DDA	HR	Top 10% RNA	Bottom 10% RNA	p-val	Gene-DDA	HR	Top 10% RNA	Bottom 10% RNA	p-val
<i>BRCA1</i> -IR	0.62	25.9 m (N = 232)	80.5 m (N = 197)	0.009	<i>BRCA1</i> -OX	0.66	40.3 m (N = 362)	61.5 m (N = 358)	0.005
<i>RAD51</i> -IR	0.55	26.1 m (N = 255)	80.5 m (N = 231)	< 0.001	<i>RAD51</i> -OX	0.69	61.8 m (N = 406)	64.7 m (N = 420)	0.008
<i>BLM</i> -IR	0.50	26.6 m (N = 232)	53.3 m (N = 205)	0.001	<i>BLM</i> -OX	0.66	50.5 m (N = 348)	61.8 m (N = 389)	0.008
<i>BRIP1</i> -IR	0.60	26.6 m (N = 234)	45.0 m (N = 211)	0.007	<i>BRIP1</i> -OX	0.67	47.3 m (N = 336)	74.9 m (N = 381)	0.009
<i>FANCA</i> -IR	0.63	25.0 m (N = 224)	35.3 m (N = 194)	0.01	<i>FANCA</i> -OX	0.64	41.4 m (N = 327)	60.9 m (N = 357)	0.004

3530

Poster Session

Comprehensive study of the intratumoral microbiome in early- vs. late-onset colorectal cancer: Final analysis of COSMO CRC. *First Author: Benjamin Adam Weinberg, Ruesch Center for the Cure of Gastrointestinal Cancers, Lombardi Comprehensive Cancer Center, Georgetown University, Washington, DC*

Background: Although colorectal cancer (CRC) incidence has declined overall, CRC in individuals under age 45 (early-onset CRC, EOCRC) has risen dramatically. Obesity and diabetes may partially explain this epidemiologic shift; however, many patients (pts) with EOCRC are neither obese nor diabetic. Certain bacteria disrupt colonic luminal integrity and promote inflammation, leading to oncogenic mutations in colonic epithelial cells. *Fusobacterium nucleatum* (*F. nuc*) promotes CRC by suppressing immune response within the tumor microenvironment, activating the β -catenin pathway, and causing chemoresistance due to autophagy. The intratumoral microbiome (MB) in pts with EOCRC may differ from pts with late-onset CRC (LOCRC). **Methods:** We compared the intratumoral MB in pts with CRC diagnosed before age 45 (EOCRC) and after age 65 (LOCRC) in a prospective/retrospective study between 2017 and 2022. Primary and metastatic tumors were included. DNA was extracted from tumors and analyzed using 16S ribosomal gene sequencing. We compared the frequency of *F. nuc* and other bacterial and fungal DNA in tumors EOCRC vs. LOCRC pts. Next-generation tumor sequencing and diet questionnaire data were available for some pts. **Results:** Tumors from 36 EOCRC pts (median age 38 years) and 27 LOCRC pts (median age 72 years) were analyzed. In total, 917 unique bacterial and fungal species were detected. *F. nuc* was found in 30.6% of EOCRC and 29.6% of LOCRC ($p = 0.94$). *Cladosporium* sp. was seen more commonly in EOCRC (30.6% vs. 11%, $p = 0.04$), whereas *Pseudomonas luteola* (2.8% vs. 22.2%), *Ralstonia* sp. (22.2% vs. 48.1%), and *Moraxella osloensis* (19.4% vs. 44.4%) were seen more commonly in LOCRC ($p < 0.05$). *Clostridium perfringens* (11.1%), *Escherichia coli* (11.1%), *Leptotrichia hofstadii* (11.1%), *Mycosphaerella* sp. (11.1%), *Neodevriesia modesta* (11.1%), *Penicillium* sp. (11.1%), and *Leptosphaeria* sp. (11.1%) were seen exclusively in LOCRC ($p < 0.05$). There was no significant difference in median MB diversity in EOCRC vs. LOCRC (43 vs. 45 organisms per pt). Median follow up from time of diagnosis was 39.6 months (mo). Twenty-three EOCRC pts (64%) and 19 LOCRC pts (70%) are alive. Median overall survival (mOS) was 75.5 mo (95% CI: 40 - NA) in EOCRC and 60 mo (95% CI: 50.5 - NA) in LOCRC. There was no significant difference in OS in LOCRC vs. EOCRC (Log-rank test $p = 0.85$). Pts with *F. nuc* positive tumors ($N = 17$) had a mOS of 75.5 mo (95% CI: 23 - NA), whereas pts with *F. nuc* negative tumors ($N = 46$) had a mOS of 60 mo (95% CI: 50.5 - NA). There was no significant difference in OS in *F. nuc* positive vs. *F. nuc* negative groups (Log-rank test $p = 0.87$). **Conclusions:** There are significant differences in the intratumoral microbiome in EOCRC and LOCRC. These findings warrant larger, prospective studies to elucidate the role the intratumoral microbiome plays in the carcinogenesis, the tumor immune microenvironment, and responsiveness to specific therapies. Research Sponsor: Colorectal Cancer Alliance; Victoria Casey and Peter Teeley Foundation.

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Poster Session

Circulating tumor DNA in plasma as an early predictor for pathological lymph node involvement and (neo-)adjuvant chemotherapy in patients with colon cancer. *First Author: Louise Raunkilde, Department of Oncology, Danish Colorectal Cancer Center South, Vejle Hospital, University Hospital of Southern Denmark, Institute of Regional Health Research, University of Southern Denmark, Vejle, Denmark*

Background: Postoperative chemotherapy is standard for colon cancer patients with pathological lymph node involvement (pN+). If the presence of pN+ could be accurately predicted prior to surgery, the initiation of neoadjuvant chemotherapy could potentially reduce the presence of micrometastasis and enhance survival. The objective of this study was to assess the utility of preoperative methylated circulating tumor DNA (meth-ctDNA) as a predictive marker for pN+ and its clinical value as a marker for the initiation of neoadjuvant chemotherapy. **Methods:** The clinical data of 203 colon cancer patients (stage I-III) was collected from the Colorectal Cancer Database established at Danish Colorectal Cancer Center South, Vejle Hospital, Denmark. Patients were randomized into a discovery and a validation cohort. Plasma collected preoperatively was analyzed for three different meth-ctDNAs (Neuropeptide Y, Galactose-3-O-Sulfotransferase 3, and KN Motif and Ankyrin Repeat Domains 1) by droplet digital PCR (ddPCR). **Results:** Based on analysis of the discovery cohort, samples were considered positive if two or more of the three methylation markers had at least three positive droplets in the ddPCR analysis. 40% of patients in the discovery cohort and 46% of patients in the validation cohort were considered positive. When using meth-ctDNA as a diagnostic tool to predict pN+, the sensitivity and specificity in the discovery cohort were 42% and 61% respectively. In the validation cohort the values were 54% and 59%, respectively. AUC was $< 60\%$ in both cohorts. Meth-ctDNA was associated to clinical tumor (T-) and node (N-) category in both cohorts ($p \leq 0.01$). Four-year disease free survival (DFS) in patients with and without detectable meth-ctDNA was 60% and 90% in the discovery cohort ($p = 0.01$), and 62% and 78% in the validation cohort ($p = 0.04$). Meth-ctDNA remained the strongest prognostic factor of DFS in the multivariate analysis compared to clinical T- or N-category, gender and age ($p = 0.065$, HR 2.46, 95% CI 1.03-5.88), however not statistically significant. Four-year overall survival (OS) in patients with and without detectable meth-ctDNA was 75% and 95% in the discovery cohort ($p = 0.006$), and 78% and 91% in the validation cohort ($p = 0.02$). In the multivariate analysis, meth-ctDNA was the strongest prognostic factor of OS compared to clinical T- or N-category, gender and age ($p = 0.016$, HR 4.54, 95% CI 1.32-15.6). **Conclusions:** The preoperative measurement of meth-ctDNA was not found to be a clinically significant predictor of pN+ or a reliable indicator for the initiation of neoadjuvant chemotherapy. Nonetheless, the results showed that preoperative ctDNA is a powerful prognostic indicator, suggesting that randomized controlled trials should be conducted to determine the efficacy of neoadjuvant chemotherapy in colon cancer patients with preoperative detectable ctDNA. Research Sponsor: Moltum, Grønbeck-Olsen and Højmoesgaard.

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Poster Session

Correlation of single-cell cytokine secretion with clinical outcome in patients (pts) with metastatic colorectal cancer (mCRC) treated with capecitabine (C), bevacizumab (B), ± atezolizumab (A). *First Author: Niharika B. Mettu, Duke University Medical Center, Durham, NC*

Background: The BACCI trial (NCT02873195) randomized 133 mCRC pts to C+B+A (investigational) or C+B+placebo. Longer progression free survival (PFS) was observed in the investigational vs placebo arm. To investigate T-cell functional heterogeneity, we performed single-cell proteomic analyses on pts with either long or short PFS and evaluated T-cell function as a prognostic and predictive biomarker. **Methods:** Isolated CD8+ and CD4+ cells were analyzed at baseline and first restaging from pts with long (> 6 mo, N = 14) or short (< 2 mo, N = 13) PFS. Single-cell, functional proteomic analyses were conducted using the IsoLight system (Isoplexis), which assessed secretion of 32 cytokines from an average of 786 cells per sample. The cumulative readout was poly-functional strength index (PSI), a composite score of frequency and magnitude of secreted cytokines. Cytokines are organized into effector (E), stimulatory, chemoattractive (CA), regulatory, and inflammatory (I) clusters. Differential expression analyses were done using Wilcoxon rank-sum tests. Potential predictive effects were assessed using logistic regressions with interaction between treatment and biomarkers. No multiple comparison control was done due to the exploratory nature of analyses. **Results:** Baseline CD8+ and CD4+ cells were stimulated *ex vivo* and single-cell cytokine analyses performed. Prognostic analyses indicated that CD8+ cells from pts with long PFS had ~3-fold higher PSI compared to pts with short PFS (p = 0.005). Further analysis identified that the E (p = 0.005) and CA clusters (p = 0.005) most impacted PSI, significant individual cytokines are listed in the table. Baseline CD8+ cell function was not predictive of outcome. Baseline CD4+ cell function was not prognostic or predictive of outcome. Analysis of CD8+ cells after treatment identified that changes in CA cluster was prognostic of long PFS (p = 0.024). Cytokine changes from CD4+ cells were not prognostic; however, early changes in the CD4+ CA cluster were predictive of outcome (p-int = 0.055). Similarly, early changes in the CD8+ I cluster were predictive of outcome (p-int = 0.073). **Conclusions:** These results reveal pts with long PFS had more functional CD8+ T-cells with a higher PSI than pts with short PFS. Predictive analyses suggested that early changes in the CD4+ CA and CD8+ I clusters were associated with benefit from immunotherapy. These preliminary results highlight the importance of single-cell functional proteomic analyses. Research Sponsor: Mario Family Foundation.

Effect	Cell-type	Timepoint	Cytokine (p-value) - Cluster
Prognostic	CD8+	Baseline	TNF-α (p = 0.033) - E IFN-γ (p = 0.036) - E MIP-1α (p = 0.014) - E MIP-1β (p = 0.005) - CA MIP-1α (p = 0.007) - E MIP-1β (p = 0.027) - CA
Prognostic	CD8+	On-study change	MIP-1α (p = 0.033) - E MIP-1β (p = 0.029) - CA TNF-α (p = 0.084) - E
Predictive	CD4+	On-study change	
Predictive	CD8+	On-study change	

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Poster Session

Consensus molecular subtyping of colorectal cancer to demonstrate cetuximab benefit in right-sided CMS2 tumors, and pembrolizumab benefit in MSS CMS1 tumors. *First Author: John Paul Y.C. Shen, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Consensus Molecular Subtypes (CMS) of colorectal cancer (CRC) were first developed in 2015 using microarray-based assays but are not widely used clinically. We developed a Caris CMS classifier on whole transcriptome sequencing data (WTS) with high concordance with the previously established CMS pipeline (Guinney et al 2015), and applied to a large clinic-genomic database of CRC to investigate the utility of CMS classification in identifying patients that may respond well to therapies commonly used in CRC. **Methods:** Next-generation sequencing (NGS) of DNA (592-gene or whole exome) and WTS was tested on CRC patient samples (n = 12,788) at a CLIA-certified lab (Caris Life Sciences, Phoenix, AZ). Caris CMS classifier was trained against the original CMS datasets using a classic SVM model and cross-validated for optimization of the SVM parameters. Possible over-training was evaluated by predicting CMS from an independent blinded dataset (TCGA, N = 512) with an accuracy of 88.3%. Real-world overall survival was obtained from insurance claims and calculated from tissue collection to last contact (OS); time on treatment (TOT) was from first to last of treatment time. Kaplan-Meier estimates were calculated for molecularly defined cohorts. Significance was determined as p of < 0.05. **Results:** Among all patients, CMS1 was seen in 16%, CMS2 in 32%, CMS3 in 17% and CMS4 in 35%. MSI-H/MMRd (31%) and BRAF mut (33%) were most prevalent in CMS1 with KRAS mt the highest in CMS3 (66%). CMS2 was associated with the longest mOS (33m; 95% CI: 31m-35m), followed by CMS4 (29m; 28-31m), CMS3 (27m; 25-29m) and CMS1 (22m; 20-23m). In the microsatellite stable (MSS) tumors treated with pembrolizumab, CMS1 (N = 22, mTOT: 4.2m; 2.8-9.1m) had longer TOT than CMS2 (N = 45, mTOT: 2.1m; 1.4-3.1m), CMS3 (N = 21, 2.1m; 1.4m-3.0m) and CMS4 (N = 40; 2.1m; 1.4m-2.8m); CMS1 vs. CMS2-4 in MSS (HR: 0.58; CI: 0.34-0.97, p = 0.035). When investigating cetuximab, CMS2 had the longest mTOT (N = 189, mTOT: 6.3m; 5.4m-7.7m) among the four groups. Interestingly, although among all Ras WT tumors left-sided CRC showed longer mTOT on cetuximab (n = 457, mTOT: 5.4m; 4.7m-6.3m) than right-sided (n = 151, mTOT: 3.8m; 3.3m-4.5m), CMS2 showed similar mTOT from the left (n = 128) and the right (n = 16, mTOT: 6.3m vs. 5.6m, HR = 0.896, 95% CI: 0.501-1.604, p = 0.722). Notably, CMS2 comprises 49% of left- and 15% of right-sided tumors, potentially underlying the TOT difference seen between left and right. **Conclusions:** A WTS based CMS classifier allows for investigation in a large real-world clinic-genomic database. We found that MSS CMS1 CRC's may derive benefit from immunotherapy. Additionally, CMS2 subgroup of right-sided tumors may derive benefit from cetuximab. Routine CMS subgrouping of CRC provides important treatment associations that should be further investigated. Research Sponsor: None.

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Poster Session

Gut microbiome composition as predictor of the efficacy of adding atezolizumab to first-line FOLFOXIRI plus bevacizumab in metastatic colorectal cancer: A translational analysis of the AtezoTRIBE study. *First Author: Federica Marmorino, Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa & Unit of Medical Oncology 2, Azienda Ospedaliera Universitaria Pisana, Pisa, Italy*

Background: Gut microbiome has emerged as a biomarker of clinical benefit to immune-checkpoint inhibitors (ICI) but no data are available in metastatic colorectal cancer (mCRC). The AtezoTRIBE study demonstrated that the addition of atezolizumab (atezo) to FOLFOXIRI plus bevacizumab (bev) prolongs progression-free survival (PFS), but this benefit is limited for patients with proficient mismatch repair (pMMR) tumors. Here, we aimed at investigating the potential predictive role of microbiome in identifying mCRC patients able to achieve benefit from ICI. **Methods:** AtezoTRIBE was a phase II trial in which 218 mCRC patients, unselected for MMR status, were randomized 1:2 to receive first-line FOLFOXIRI/bev (arm A) or FOLFOXIRI/bev/atezo (arm B). Stools were prospectively collected. Metagenomic (MG) data from whole genome sequencing (WGS) at level of species genome bins (SGBs) were analysed by linear models corrected for clinical and tumor-related parameters and fold-ratios. We defined as responders (R) those patients who experienced a PFS ≥ 12 months. **Results:** Stool samples were collected at baseline for 171 (78%) patients (55 in arm A and 116 in arm B) but only 163 were available for MG. Patients with deficient MMR (dMMR) tumors (N = 10) showed significantly lower MG diversity than pMMR ones (N = 148) harboring oral bacteria and pathobionts whose intrinsic immunogenicity has not been demonstrated. Regarding pMMR mCRC patients, baseline microbiome composition was not significantly different according to the treatment arm. The microbiome diversity was not significantly different between R and not-R in both arms, but specific immunogenic SGBs (Lachnospiraceae family members) were over-represented in R treated in arm B. Veillonellaceae and pathobionts were associated with poor prognosis and/or differential benefit from the addition of atezo. Fusobacterium nucleatum was associated with a poor prognosis, also in arm B. **Conclusions:** This is the largest prospective analysis showing that SGBs may be useful as a biomarker of potential benefit or detrimental effect from atezo in pMMR mCRC patients. Our results prompt the design of microbiota-centered diagnostic tests to identify pMMR mCRC patients more likely to benefit from ICI-based therapeutic strategies. Clinical trial information: NCT03721653. Research Sponsor: GONO Foundation.

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Poster Session

Genomic landscapes of early-onset versus average-onset colorectal cancer populations. *First Author: Michael H. Storandt, Mayo Clinic, Rochester, MN*

Background: Early-onset colorectal cancer (eoCRC, initial CRC diagnosis at age < 50 years) has been increasing in the past two decades especially in Western countries. This study evaluates somatic and germline profiles in eoCRC compared to average-onset CRC (aoCRC, initial CRC diagnosis at age ≥ 50 years). **Methods:** This is a retrospective, cross-sectional study utilizing data from de-identified records of colorectal cancer patients tested with the Tempus xT assay from 2017 to 2022. Briefly, the assay is a targeted panel that detects single nucleotide variants, insertions and/or deletions, and copy number variants in 598-648 genes, as well as chromosomal rearrangements in 22 genes with high sensitivity and specificity. Baseline characteristics and immunologic markers were compared between eoCRC and aoCRC by Wilcoxon Rank Sum or Chi-squared test (reporting p-values). Somatic and germline mutations were compared between two age groups with false discovery rate adjustments (reporting q-values). **Results:** In this study, 2,379 eoCRC and 8,627 aoCRC patients were included, with the majority diagnosed with stage IV disease. Additionally, germline alterations were assessed on a subset of 6,311 patients with tumor/normal match testing (eoCRC = 1,413 and aoCRC = 4,898). Left-sided primaries were more common in eoCRC (85% left/rectum in eoCRC vs. 75% left/rectum in aoCRC (p < 0.001), and rates of microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) were lower compared to aoCRC (4.2% vs. 6.8%, p < 0.001). eoCRC has a unique somatic mutation profile compared to aoCRC. A higher prevalence of germline mutations was observed in eoCRC overall (6.9% vs. 5%, p = 0.006); however, no statistically significant differences were observed in individual germline genes compared to aoCRC, likely due to relatively small numbers. **Conclusions:** eoCRC has a unique mutational profile and presence of germline mutations in 6.9% of eoCRC, indicating a potential role for universal germline testing in CRC. Research Sponsor: TEMPUS Labs.

	eoCRC (n = 2,379)	aoCRC (n = 8,627)	p-value/q-value
Baseline characteristics			
Median age at diagnosis (IGR)	43 (38, 47)	64 (57, 72)	< 0.001
Gender: male	1,275 (54%)	4,967 (58%)	< 0.001
Stage IV	1,389 (58%)	5,278 (60%)	0.030
Left sided/rectal primary *	840 (35%)	2,530 (29%)	< 0.001
Immunologic markers			
TMB ≥ 10	124 (5.7%)	614 (7.6%)	0.002
MSI-H	97 (4.2%)	564 (6.7%)	< 0.001
dMMR	25 (2.6%)	253 (6.9%)	< 0.001
Somatic mutations profiles **			
BRAF	111 (4.7%)	845 (9.8%)	< 0.001
BRAF ^{V600E} /MSI-H	1 (1.0%)	262 (46%)	
RNF43	68 (2.9%)	515 (6.0%)	< 0.001
AMER1	83 (3.5%)	503 (5.8%)	< 0.001
ZNF93	24 (1.0%)	192 (2.2%)	0.008
Germline mutation profiles **			
eoCRC (N = 1,413)		aoCRC (N = 4,898)	
Overall prevalence	6.9%	5.0%	0.006
TP53	5 (0.4%)	2 (< 0.1%)	0.2
APC	9 (0.6%)	11 (0.2%)	0.4
ATM	11 (0.8%)	19 (0.4%)	0.4
RAD51C	4 (0.3%)	3 (< 0.1%)	0.4

* Include patients with CRC tissue sequenced. ** list first 4 mutations based on the lowest q values in order of prevalence.

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Poster Session

Deep learning tumor heterogeneity metric from histopathology images vs next generation sequencing-derived scores for colon cancer prognostication.
First Author: Hatim Amiji, Frank H. Netter MD School of Medicine at Quinnipiac University, North Haven, CT

Background: Tumor heterogeneity is as an important determinant of clinical behavior in many cancer types, with increased heterogeneity thought to confer inferior clinical outcome. Sequencing based assessment of colon cancer has been used to quantify tumor heterogeneity and correlate it with survival, but is sensitive to the mutation calling algorithm utilized. Digitization of histopathology slides allows application of deep learning methods for image analysis. Automated slide annotation and feature extraction provides numeric representations of underlying phenotype from which tumor heterogeneity can be estimated. Here we compare the ability of a deep-learning tumor heterogeneity score (THS) to estimate overall survival in colon cancer patients to estimates produced by bulk sequencing derived mutant-allele tumor heterogeneity (MATH) and copy number variation (CNV) event scores. **Methods:** Digitized whole slide images (WSIs) from The Cancer Genome Atlas (TCGA) colon adenocarcinoma dataset are processed in a computational pipeline for tissue detection, numerical feature extraction, and cell type classification. WSIs are tiled and local THS calculated from imaging features. Corresponding MATH and CNV derived heterogeneity metrics are calculated from published sequencing data. Kaplan Meier curves are used to compare patient survival stratified by tumor heterogeneity as calculated by the three independent methods. Automated regional annotation identifies intra-tumoral and tumor-stromal boundary tiles and tumor THS is correlated to distance from the boundary. **Results:** Images from 379 patients (209 right-sided, 152 left-sided tumors) yielded 575,762 tiles. Automated annotation resulted in 272,791 intra-tumoral and 11,340 tumor-stromal boundary tiles. Stratification by imaging derived THS provided significant separation of overall survival curves ($p < .01$) in contrast to MATH and CNV methods ($p > .05$ for both). THS significantly separated the curves in right- but not left-sided cancers ($p = .03$ and $.44$, respectively). Evaluating THS as a function of distance from the tumor-stromal boundary, right-sided tumors showed significant decrease in THS with increasing distance from tumor edge. **Conclusions:** Our novel pipeline produced spatially resolved imaging data informed by underlying tumor phenotype without need for pathologist annotation. The resultant THS correlated with outcome and outperformed sequencing-based prognostication methods. The spatial information identified higher heterogeneity at the tumor edge than interior regions of right-sided, but not left-sided tumors, capturing known but poorly understood differences in colon tumors by location. Deep learning image analysis provided reproducible and cost-effective data with great potential both in clinical biomarker discovery and as a research tool. Research Sponsor: The Jackson Laboratory for Genomic Medicine; Hartford Healthcare.

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Poster Session

Prognostic and predictive significance of pre- and post-operative plasma tumor markers in patients with appendiceal adenocarcinoma undergoing cytoreductive surgery: Insights from a single-center study.
First Author: Abdelrahman M.G. Yousef, University of Texas MD Anderson Cancer Center, Houston, TX

Background: Appendiceal adenocarcinomas (AA) are both rare and heterogeneous diseases. Cytoreductive (CRS) surgery followed by heated intraperitoneal chemotherapy (HIPEC) remains the best treatment for AA patients with peritoneal metastasis. This study seeks to investigate the clinical utility of pre- and post-operative plasma tumor markers (TM, CEA, CA19-9, CA-125) by association with survival outcomes. **Methods:** Under an approved IRB protocol the Palantir Foundry software system was used to query MD Anderson internal database to identify patients with AA who underwent CRS between 2016 to 2022. Elevation of TM was defined as above the laboratory upper limit of normal (CEA > 3 ng/mL, CA 19-9 > 37 U/mL, and CA-125 > 37 U/mL). Relationship between normal and elevated serum TM and progression-free survival (PFS) and overall survival (OS) was evaluated using univariate and multivariate Cox-proportional hazards regression analysis, considering multiple clinicopathologic variables. **Results:** 296 patients were identified; preoperative CEA, CA19-9 and CA125 was elevated in 60%, 29% and 28% of patients, respectively. Preoperative elevation of any TM was associated with higher PFS (22 vs. 15, $p < 0.0001$). Moreover, elevated preoperative TM was associated with incompleteness of cytoreduction (OR = 6.5, $p < 0.0001$). Compared to preoperative measurements, all TM levels dropped after surgery (Mean score 31 vs 11 for CEA, 136 vs 32 for CA19-9 and 36 vs 17 for CA125). Preoperative elevation of any TM (HR = 1.5, $p = 0.0288$) and post-op elevation of any TM were with poor PFS on univariate analysis, however only post-op elevated TM levels (HR = 2.3, $p = 0.0001$) were associated with poor PFS on multivariate analysis. Interestingly, elevated TM was not associated with OS. Post-op TM levels were analyzed to evaluate the positive and negative predictive value in prediction of relapse in 6 months from surgery, PPV was 45% and NPV was 84%. **Conclusions:** Preoperative elevation of TM can identify patients at higher risk for incomplete cytoreduction and relapse after surgery. Postoperative elevation of TM is a risk factor for relapse. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology; CCSI; Col. Daniel Connelly Memorial Fund; U.S. National Institutes of Health; Cancer Prevention & Research Institute of Texas.

Clinical Characteristics	Univariate Analysis			Multivariate Analysis		
	HR	P value	95 CI%	HR	P value	95 CI%
Black or African American	2.506	0.0039	1.34 4.68	1.7	0.13	0.9 3.5
Goblet/Signet Tumor Histopathology	1.69	0.0047	1.18 2.43	1.8	0.0059	1.2 2.8
High Grade Tumor	1.705	0.0026	1.20 2.41	1.3	0.28	0.8 2
Incomplete CRS (CCR 2/3)	3.912	1.78E-11	2.63 5.82	3.1	0.0001	1.8 5.5
Preop elevation of TM	1.513	0.0288	1.04 2.19	0.97	0.89	0.6 1.5
Postop elevation of TM	2.572	4.73E-08	1.83 3.61	2.3	0.0001	1.5 3.5
Utilization of Neoadjuvant	2.062	0.0001	1.47 2.90	1.3	0.22	0.9 2
Utilization of Adjuvant	2.835	1.75E-06	1.85 4.35	1.6	0.065	1.0 2.7
PCI score more than 25	1.684	0.0038	1.18 2.40	1	0.96	0.6 1.7

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Poster Session

Evaluation of microsatellite instability status, a definitive predictive biomarker for immune checkpoint inhibitors (ICI), in underrepresented minorities (URM) with gastrointestinal (GI) cancers.
First Author: Fiyinfolu Balogun, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Mismatch repair deficiency (dMMR) results in MSI-H state and is the first tumor type-agnostic biomarker predictive of ICI response. Among GI cancers, MSI-H is most frequent in colorectal cancer (CRC 15%), gastroesophageal (GEC, 5%) and other (small bowel, hepatopancreatobiliary; 1%). For CRC, MSI-H can be attributed to germline mutation (Lynch syndrome, 3%) or somatic inactivation (sporadic, 12%) of foundational MMR genes. Studies evaluating ICI efficacy in dMMR cancers focus primarily on non-Hispanic White (NHW) patients (pts). We present prevalence, tumor genomic features, and outcomes in pts from a large cohort at Memorial Sloan Kettering (MSK). **Methods:** Retrospective analysis of MSI-H GI cancers from MSK-IMPACT database. Pts were grouped by self-reported race and ethnicity into 4 study arms: NHW, Asian, non-Hispanic Black (NHB), and Hispanic. Age, tumor type, tumor mutation burden (TMB), and MMR genes were analyzed. Overall survival (OS) estimated with Kaplan-Meier. **Results:** Of 776 pts with MSI-H GI cancers: 623 (80.3%) NHW, 60 (7.7%) Hispanic, 50 Asian (6.5%), and 43 (5.5%) NHB. CRC (76%), GEC (14%), other cancers (10%). We present initial evaluation of CRC and GEC: Median age, TMB, and most frequently altered MMR genes (MMR gene FA) are in table. Median OS (mOS) in NHW/URM by receipt of ICI in MSI-H CRC were 38.5m/25.3m ($p < 0.07$) in no-ICI group, 34.2m/28.7m ($p < 0.64$) in +ICI group; MSI-H GEC 43.4m/30m ($p < 0.44$) in no-ICI group, 28.8m/26.7m in +ICI group. **Conclusions:** Number of URM MSI-H CRC/GEC pts is 7 to 15-fold less than NHW, with no such difference in % MSI-H/mSS between groups; reflecting significant underestimating in URM pts. In MSI-H CRC, median age (m-Age) at sequencing was younger in URM compared to NHW; pronounced in Asian and Hispanic patients, who were 10+ years younger than NHW. No such age difference seen in GEC. No difference in mOS detected between NHW and URM, however a non-significant trend towards worse mOS in URM was observed in the no-ICI group. Next steps include validation of clinico-genomics of MSI-H GI cancers in other large cohorts, including TEMPUS (N = 768) which is ongoing. Research Sponsor: None.

	NHW CRC	NHB CRC	Asian CRC	Hispanic CRC
MSI-H/mSS % (MSI-H, N)	13% (3679)	10% (349)	8% (430)	14% (331)
m-Age (range (p vs NHW))	67 19-60 (1)	61 28-78 (0.025)	57 26-89 (0.023)	55 25-87 (0.048)
m-TMB range (p vs NHW)	58 3-369 (1)	54 21-201 (0.43)	50 26-219 (0.06)	61 32-400 (0.95)
MMR gene FA (% I N)	MSH6 (27% 492)	MLH1 (26% 34)	MSH2 (26% 34)	MSH6 (36% 145)
	NHW GEC	NHB GEC	Asian GEC	Hispanic GEC
MSI-H/mSS % (MSI-H, N)	5% (1314)	7% (83)	5% (184)	7% (124)
m-Age (range (p vs NHW))	71 45-90 (1)	70 55-81 (0.3)	68 49-85 (0.55)	68 35-88 (0.53)
m-TMB range (p vs NHW)	50 2-172 (1)	75 30-87 (0.34)	49 18-72 (0.59)	44 31-62 (0.3)
MMR gene FA (% I N)	MSH6/MLH1 (13% 76)	MLH1 (33% 6)	MSH6 (30% 110)	MSH2/MSH6 (11% 9)

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Poster Session

Does serial circulating tumor DNA (ctDNA) monitoring identify additional acquired actionable alterations in metastatic colorectal cancer (mCRC)?
First Author: Jonathan M. Loree, BC Cancer Agency, Vancouver, BC, Canada

Background: Traditionally, biomarker ascertainment occurred once for patients (pts) with mCRC. An advantage of ctDNA is the ease of repeated assessments. However, real-world evidence about the value of serial ctDNA in revealing actionable alterations is needed. **Methods:** We retrospectively evaluated 3350 pts with mCRC and a Guardant360 ctDNA assay (Guardant Health) revealing ≥ 1 somatic alteration who underwent ≥ 1 subsequent Guardant360 test to compare detection of mutations (mut: single nucleotide variants (SNVs) and indels), amplifications (amps), fusions, microsatellite instability (MSI), and blood tumor mutational burden (bTMB). Variants were filtered to pt-specific levels of detection by limiting variants across assays to those above a 0.1% mutant allele frequency (MAF) threshold on the serial test with the lowest somatic MAF for that pt. Clonal muts were defined as those at $\geq 10\%$ of max MAF per sample. **Results:** A total of 9130 assays (mean of 2.7 assays/pt) occurring a median of 165 days apart were evaluated. Among 1476 pts initially with no alteration in MAPK pathway genes (*RAS* and *EGFR* SNV or indel, *BRAF* V600E SNV, or *ERBB2/MET* amplifications), 382 (25.8%) acquired a MAPK alteration on their second test. More gains were clonal than subclonal (231:151, 60.5%:39.5%). In pts with a subsequent assay after an acquisition (N = 80), 12 (15.0%) clonal and 15 (18.8%) subclonal acquisitions disappeared in the third assay, a median of 150 days later. Among alterations with a therapy, *KRAS* G12C/D, *BRAF* V600E, and *ERBB2* amps acquisitions occurred at any later assay in 84/1476 (5.7%), 29/1476 (2%), and 21/1476 (1.4%) pts without an initial MAPK alteration, respectively. Of these, 84/134 (62.6%) emerged without another concurrent MAPK alteration, 61/84 (72.6%) of which are subclonal. Of 92 fusions noted in 86 pts, 87/92 (94.5%) were subclonal and only 28/92 (30.4%) were initially present. The majority of fusions were acquired de-novo subclonal fusions (58/64, 90.6%) but 2 pre-existing subclonal fusions subsequently became clonal. Among pts evaluable for MSI, 56/3030 (1.8%) were initially MSI-H and 30 (1%) subsequently had MSI detected on a future assay. New MSI detection was more common in pts with DNA repair muts (*BRCA1/BRCA2/ATM/CHEK2/MLH1/RAD51D*) on an initial assay (OR 7.52, 95% CI 3.39-16.69, $p < 0.0001$). Among pts evaluable for bTMB, 60/1387 (4.3%) initially had bTMB ≥ 20 muts/Mb, and 256/1327 (19.3%) subsequently rose above 20 muts/Mb on a future assay, a median of 417 days after initial assay. Rising bTMB associated with rising max somatic MAF (Spearman rho = 0.50, $p < 0.0001$). Pts with DNA repair muts on an initial assay were more likely to have bTMB rise to ≥ 20 muts/Mb (OR 2.58, 95% CI 1.81-3.68, $p < 0.001$). **Conclusions:** In this large mCRC cohort, serial ctDNA appears to be a feasible approach to identify acquired alterations with therapeutic implications. Research Sponsor: Guardant Health.

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Poster Session

Racial and genetic ancestry associations with gene expression patterns in a real-world cohort of colorectal cancer patients. *First Author: David Hein, UT Southwestern Medical Center, Dallas, TX*

Background: There is a growing incidence of colorectal cancer (CRC) among young adults and persistent disparities in outcomes by race/ethnicity across all ages. Gene expression signatures, as well as consensus molecular subtypes (CMS) derived from these, have been proposed to predict prognosis and therapy response in CRC. However, it is unclear whether gene expression or CMS are associated with racial disparities observed in CRC. We assessed whether race or genetic ancestry are associated with CMS or gene expression patterns in a deidentified cohort of 1,768 CRC patients. **Methods:** Patients tumors underwent tumor profiling with the Tempus xT NGS 648-gene assay as well as full-transcriptome RNA sequencing. We used a set of 654 ancestry-informative markers to infer genetic ancestry likelihoods for Africa (AFR), America (AMR), East Asia (EAS), Europe (EUR), and South Asia (SAS). Race/ethnicity labels, often missing in real-world data, were imputed using ancestry proportions from the literature and adjusted based on observed metadata. Gene expression data was used to assign CMS to all patients (CMS1, 2, 3, 4 and indeterminate) using CMScaller, and multinomial logistic regression was used to assess associations with race/ethnicity imputed labels and ancestry proportions. We then assessed differential expression (DE) in the MSigDB hallmark and C2 BioCarta gene sets using four separate workflows. The first two workflows used limma-voom followed by ROAST to assess DE among the imputed labels and then among the ancestry proportions (isometric log ratio transformed). The second two workflows used GSVA followed by limma. **Results:** Among 1,768 patients, 240 were imputed non-Hispanic (NH) Black, 94 NH Asian, 261 Hispanic/Latino/Native American (HLN), and 1,173 NH White. NH Black patients had higher odds of CMS3 vs CMS1 (OR = 2.66, $p < 0.001$) and HLN patients had higher odds of indeterminate CMS vs CMS1 (OR = 1.90, $p = 0.020$), compared to NH White. AFR ancestry was significantly associated with CMS3 (OR = 1.05 per doubling in AFR proportion, $p = 0.047$) and indeterminate CMS (OR = 1.07, $p = 0.023$). In the gene set analysis, NH Black race/ethnicity was associated with over-expression of the BioCarta *WNT* pathway gene set. Both AFR ancestry and NH Black race/ethnicity were associated with under-expression of the MSigDB hallmark coagulation and BioCarta alternative complement gene sets and over-expression of the *PTX2* pathway gene set (all significant with both ROAST and GSVA). **Conclusions:** We found that NH Black patients and AFR ancestry were associated with higher rates of CMS3, which is associated with *KRAS* mutation and was previously reported to be more common among Black patients. Indeterminate CMS associations with AFR ancestry and HLN highlights the need to use diverse patient cohorts when training unsupervised learning models to improve prognosis prediction in non-White patients. Research Sponsor: Dedman Family Scholarship.

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Poster Session

A deep learning model for the prediction of microsatellite instability and pathogenic POLE mutations in colorectal cancer using histopathologic images. *First Author: Ting Xu, Department of GI Oncology, Department of Gastrointestinal Oncology, Peking University Cancer Hospital & Institute, Beijing, China*

Background: Immunotherapy has brought about a landmark change in anti-tumor treatment in the past years. High microsatellite instability (MSI-H) is now the only clinically approved biomarker predicting response to immunotherapy in CRC. Increasing evidence suggests that POLE mutations in the exonuclease domain could drive an ultra-mutational phenotype and improve the treatment outcomes of ICI in solid tumors. In this study, we set out to apply a deep learning model using H&E-stained, formalin-fixed, paraffin-embedded (FFPE) whole slide images (WSIs) of CRC primary tumors. **Methods:** The deep learning model is developed and validated through five-fold cross-validation using WSI of primary tumors from 506 CRC patients and externally validated using 52 WSIs from a prospective cohort. The microsatellite status, tumor mutation burden (TMB) and POLE genotype were determined by next-generation sequencing (NGS). Patients with MSS status and a low TMB (< 20 Mutations/Mb) were admitted to the MSS group, and CRCs with a POLE mutation which was defined as an oncogenic mutation referring to the POLE functional mutation list at OncoKB (POLE (oncoKB.org)) were admitted to the POLE mutant group. Clustering-constrained-attention multiple-instance learning (CLAM) model is employed as the base model, and we conduct the model ensemble by performing a large-scale hyper-parameter search, selecting five models with the highest value in one of the performance metrics, including the AUROC, accuracy, precision, recall, and f1 score, and finally averaging the predictions of the five models. **Results:** The internal dataset included 237 MSS, 142 MSI-H, and 127 POLE mutant CRC. The three groups had significant differences in primary location ($p < 0.0001$), histology ($p < 0.0001$), tumor differentiation ($p = 0.002$), tumor stage ($p < 0.0001$), Crohn's-like reaction ($p < 0.0001$) and tumor growth pattern ($p = 0.001$). The cross-validation performance of the ensemble model (M_e) in the internal dataset achieves an AUROC of 0.944 for three-way classification task (POLE vs. MSI-H vs. MSS) and 0.940 for two-way classification task (POLE & MSI-H vs. MSS) which were superior to the performance of each single CLAM model. To demonstrate the generalizability of the deep learning model, a domestic perspective cohort consisting of 20 MSS, 17 MSI-H, and 15 POLE mutant CRC H&E images were used to validate the external performance. And the M_e retained robust performance on the external dataset, with an AUROC of 0.904 for three-way classification task and 0.836 for two-way classification task. **Conclusions:** A CLAM-based deep learning model could directly predict the MSI-H and POLE mutation from histological images that could be used to stratify CRC patients for immunotherapy with faster turnaround time and lower costs compared with traditional sequencing methods. Research Sponsor: None.

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Poster Session

Artificial intelligence-derived immune phenotypes for prediction of prognosis in patients with stage III colon cancer (NCCTG N0147; Alliance). *First Author: Bahar Saberzadeh Ardestani, Mayo Clinic, Rochester, MN*

Background: Solid tumors can be characterized by distinct immune phenotypes based on the level of T cell infiltration in the tumor microenvironment (TME) which may provide prognostic information and also inform strategies to restore the anti-tumor immune response. Immune phenotypes were determined using an artificial intelligence (AI) algorithm in digitized whole-slide images (WSI) of tumors with deficient (d) mismatch repair (MMR) vs proficient (p) MMR. **Methods:** Stage III colon carcinomas (N = 401; 393 met QC) from participants in a phase III trial of FOLFOX-based adjuvant chemotherapy were analyzed including all available tumors with dMMR (n = 196) and a randomly selected cohort of pMMR tumors (n = 195). Using an AI algorithm (Lunit SCOPE) previously trained on solid tumors, digitized tumors were categorized into three immune phenotypes based on epithelial and stromal TIL data-driven cutpoints in dMMR and pMMR (inflamed: TIL high in epithelium ($> 25\%$); excluded: TIL high in stroma ($> 25\%$), low in epithelium; and desert: TIL low in epithelium and stroma). Phenotypes were then examined in relationship to disease-free survival (DFS) using Kaplan-Meier methodology. **Results:** Of the 3 immune phenotypes in dMMR tumors, 25% were inflamed, 50% were immune-excluded, and 25% were immune-desert. Based on univariate results, multivariable modeling was performed incorporating immune phenotype in addition to age, histological grade, N stage, T stage, performance status, treatment arm, *BRAF* and *KRAS* status and identified immune phenotypes and N stage to be significantly associated with DFS. Among dMMR tumors, immune desert phenotype was associated with the poorest DFS (Desert: HR_{adj} 1.95, 95%CI (1.01, 3.80); Excluded: HR_{adj} 0.89, 95%CI (0.47, 1.69); Inflamed: ref; $p < 0.01$). When compared to immune desert tumors, immune-excluded tumors had significantly better DFS (HR_{adj} 0.49, 95%CI (0.27, 0.88), $p < 0.01$). At a median follow-up of 60 months, 3-year DFS of patients with dMMR was 71.2% with Immune inflamed, 78.5% with Excluded, and 54.5% with Desert phenotypes. In contrast to dMMR, univariate analyses of data-driven cutpoints in pMMR tumors was not prognostic. Using a different data-driven cutpoint (15%), the revised immune phenotypes remained non-significant for DFS within pMMR tumors. **Conclusions:** Distinct AI-derived immune phenotypes in the TME were identified that were significantly prognostic in patients with dMMR, but not pMMR colon cancers. A data-driven immune-desert phenotype was identified in dMMR tumors that was associated with significantly poorer survival. Further investigation of the potential predictive utility of these phenotypes for immunotherapy are planned. Support: <https://acknowledgments.alliancefound.org>. ClinicalTrials.gov Identifier: NCT00079274. Research Sponsor: U.S. National Institutes of Health; Sanofi; U10CA180821, U10CA180882, U24CA196171, R01 CA210509 (to FAS).

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Poster Session

Prognostic role of TP53 variants in the phase III study of FOLFIRI/cetuximab versus FOLFIRI/cetuximab followed by cetuximab (Cet) alone in first-line therapy of patients with RAS and BRAF wild-type (wt) metastatic colorectal cancer (mCRC) (ERMES study). *First Author: Nicola Normanno, Cell Biology and Biopharmacy Unit, Istituto Nazionale Tumori-IRCCS Fondazione Pascale, Napoli, Italy*

Background: The ERMES study explored the optimal intensity of anti-EGFR-based first line therapy for RAS/BRAF wt mCRC once achieved disease control. Although the study did not demonstrate non-inferiority of maintenance with Cet alone versus standard treatment, preliminary results suggested that a strategy of de-escalation treatment with only Cet might be effective in selected patients. Conflicting results have been previously reported for the predictive and prognostic role of TP53 variants in mCRC patients receiving anti-EGFR monoclonal antibody therapy. Here we describe the role of TP53 mutations within the ERMES study. **Methods:** Patients with untreated RAS/BRAF wt mCRC were randomly assigned (1:1) to receive either FOLFIRI/Cet until PD/toxicity (arm A) or FOLFIRI/Cet for 8 cycles followed by Cet alone (arm B). Tumor tissue samples were tested using the OncoPrint Solid Tumor DNA kit covering hot spot mutations in 22 genes, including *KRAS*, *NRAS*, *BRAF* and *TP53*. Variant calling was performed using the Variant Caller Ion Torrent suite 5.16 software. The prognostic value of TP53 variants was assessed in the intention-to-treat (ITT) patients' population with available sequencing data. **Results:** Tumor tissue specimens were available for 418/593 (70.5%) patients of the ITT population. Testing failed in 29 cases, whereas *KRAS*/*NRAS*/*BRAF* V600E variants were found in 36/389 (9.2%) patients, who were enrolled on the basis of local testing. Progression free survival (PFS) data were not available for 4 cases. Therefore, the final population in analysis was 349 cases. TP53 variants were detected in 165/349 (47.3%) patients, of which 86/165 (52.1%) in arm A and 79/165 (47.9%) in arm B. The median PFS (mPFS) of TP53 wild type patients in the overall population was 9.4 months versus 10.4 months in the TP53 mutant subgroup (HR 0.8439; 95%CI, 0.673-1.058; $p = 0.142$). In arm A, the mPFS of TP53 wild type patients was 10.8 months versus 10.7 months in TP53 mutant patients, with an HR 1.053 (95%CI, 0.7582-1.462; $p = 0.76$). The mPFS of TP53 wild type patients in arm B was 8.3 months versus 10.2 months in the TP53 mutant cohort, with an HR 0.7 (95%CI, 0.5087-0.9657; $p = 0.0298$). No significant difference was observed for the overall response rate (ORR) in both arms between TP53 mutant and wild type patients. **Conclusions:** These preliminary data suggest a possible prognostic role of TP53 variants in RAS/BRAF wild type mCRC patients receiving first line FOLFIRI/cetuximab followed by Cet alone. Comprehensive genomic profiling is ongoing to identify genomic signatures associated with sensitivity to Cet. Research Sponsor: This study was financially supported by Merck Serono S.p.A., Rome, Italy, an affiliate of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945).

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Poster Session

Plasma arginine as a candidate predictive biomarker for response to immune checkpoint inhibition (ICI) in metastatic colorectal cancer (mCRC): Analysis of the CCTG CO.26 trial. *First Author: Lucy Xiaolu Ma, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada*

Background: Nutritional stress is one of the mechanisms used by tumour cells to evade the immune system. Arginine (ARG), an amino acid involved in several cellular functions including immunomodulation, is important in regulating T-lymphocyte cell activity and the anti-tumour response. ARG deficiency in the tumour microenvironment has been shown to impair T-cell response while ARG supplementation may promote anti-tumour immune activity. In this exploratory post-hoc analysis of the Phase II CO.26 trial (NCT02870920), we investigated the role of plasma ARG in predicting response to ICI in patients (pts) with refractory mCRC. **Methods:** CO.26 was a phase II trial which randomized pts with refractory mCRC to durvalumab plus tremelimumab (D+T) versus best supportive care (BSC). Plasma ARG concentrations were determined from blood samples pre-treatment using HPLC-tandem mass spectrometry. The median plasma ARG value was used as a cut-off stratifying pts into ARG-high (≥ 10650 ng/ml) versus ARG-low (< 10650 ng/ml) groups. Progression-free (PFS) and overall survival (OS) were estimated using the Kaplan-Meier method and compared between groups using the log-rank test. Cox proportional hazard models were used to analyze prognostic and predictive impacts of ARG on PFS and OS. **Results:** Of 180 pts enrolled in CO.26, 162 pts (N = 115 treated with D+T and 47 BSC) had pre-treatment blood samples for baseline ARG analysis. There were no significant differences in baseline characteristics between pts included in this analysis and the total study pts, or between ARG-high and ARG-low pts. In pts treated with D+T, ARG-high was associated with more favourable prognosis (ARG-high median OS 7.62 months vs. ARG-low 5.49 months, multivariable hazard ratio [HR] 0.60, 95% confidence interval [CI] 0.40-0.91, $p = 0.016$). In ARG-high pts, D+T significantly improved OS (median OS 7.62 months with D+T vs 3.61 months BSC; HR 0.61, 95% CI 0.37-0.99, $p = 0.04$). In ARG-low pts there was no OS benefit with D+T (median OS 5.49 months D+T vs 4.27 months BSC; HR 0.84, 95% CI 0.50-1.41, $p = 0.51$). Interaction $p = 0.037$. Baseline ARG values had no association with PFS or disease control rate. **Conclusions:** Baseline plasma ARG was prognostic in pts with mCRC treated with D+T, and high ARG was predictive of improved OS with ICI. Prospective studies should be done to validate ARG as a biomarker identifying mCRC pts likely to derive benefit from ICI. Therapeutic approaches targeting the ARG pathway should be investigated in future studies. Research Sponsor: The Canadian Cancer Trials Group (CCTG) is funded by the Canadian Cancer Society.; AstraZeneca provided durvalumab and tremelimumab and contributed partial funding for the CO.26 trial.

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Poster Session

A prospective study of FOLFIRI plus aflibercept as second-line treatment after failure of FOLFOXIRI plus bevacizumab in patients with unresectable/metastatic colorectal cancer (CRC): EFFORT study. *First Author: Hironaga Satake, Department of Medical Oncology, Kochi Medical School, Nankoku-City, Japan*

Background: FOLFOXIRI plus bevacizumab (BEV) is a first-line treatment option for patients with unresectable or metastatic CRC. However, there are no clear recommendations for second-line therapy after failure of FOLFOXIRI plus BEV. The EFFORT study investigated whether FOLFIRI plus aflibercept is active following FOLFOXIRI plus BEV in unresectable/metastatic CRC. **Methods:** EFFORT was an open-label, multicenter, single arm phase II study. Patients with unresectable/metastatic CRC who failed FOLFOXIRI plus BEV as a first-line therapy received aflibercept plus FOLFIRI (aflibercept 4 mg/kg, irinotecan 150 mg/m² IV over 90 min, with leucovorin 200 mg/m² IV over 2 hours, followed by fluorouracil 400 mg/m² bolus and fluorouracil 2400 mg/m² continuous infusion over 46 hours) every 2 weeks on day 1 of each cycle. The primary endpoint was progression-free survival (PFS) in the full analysis set (FAS). To achieve 80% power to show a significant benefit with a one-sided alpha level of 0.10, assuming a threshold PFS of 3 months and an expected value of at least 5.4 months, 32 patients needed to be enrolled. Major secondary endpoints included overall survival (OS), overall response rate (ORR) and safety. **Results:** From April 2019 to May 2021, 35 patients were enrolled and FAS included 34 patients (one patient who did not meet eligibility criteria was excluded). Of them, 18 were males, median age was 63 years (range: 32-78) and ECOG Performance Status was either 0 (n = 28) or 1 (n = 6). The primary tumor was left-sided in most patients (23/34) and 27 patients had liver metastases. And 23 patients had RAS mutation. The primary endpoint was met with a median PFS of 4.3 months [80% CI: 3.7-5.1]. The median OS was 15.2 months [95% CI: 8.9-22.7]. Objective tumor responses were CR (n = 1), PR (n = 4), SD (n = 21) or PD (n = 8). ORR was 14.7% (5/34) [95% CI: 5.0-31.1], and disease control rate was 76.5% (26/34) [95% CI: 58.8-89.3]. Main grade 3 or 4 adverse events were neutropenia (7/35, 20.0%), thrombocytopenia (3/35, 8.6%), leucopenia (2/35, 5.7%), and hypertension (3/35, 8.6%). No severe proteinuria and no treatment-related death were reported. **Conclusions:** Aflibercept plus FOLFIRI given after failure of FOLFOXIRI plus BEV is active and shows a manageable safety profile. This regimen maybe a useful as second-line treatment option in such patients. Clinical trial information: jRCTs071190003. Research Sponsor: Sanofi Pharmaceutical Co., Ltd.

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Poster Session

A phase 1 dose escalation study of GCC19CART: A novel coupled CAR therapy for patients with metastatic colorectal cancer. *First Author: Lei Xiao, Innovative Cellular Therapeutics Co., Ltd., Rockville, MD*

Background: GCC19CART, the first clinical candidate from the CoupledCAR solid tumor platform, is designed to overcome the limitations of conventional CAR T-cells in solid tumor malignancies by pairing solid tumor CAR T-cells with CD19 targeting CAR T-cells to amplify the proliferation and activation of the solid tumor CAR T component. GCC19CART targets guanylate cyclase-C (GCC), which is expressed in the metastatic lesions of 70%-80% of subjects with colorectal cancers and largely restricted to the intestinal tract. A Phase 1 investigator-initiated clinical trial is underway in China for patients with relapsed or refractory metastatic colorectal cancer who have received at least 2 prior lines of therapy. As of a data cutoff on Jan 28, 2023 21 subjects have been enrolled in 2 dose escalation groups at 5 hospitals in China. **Methods:** Subjects are screened for GCC expression by immunohistochemistry. Eligible subjects undergo leukapheresis, a single dose of lymphodepleting chemotherapy (fludarabine 30mg/m² and cyclophosphamide 300mg/m²) 3 days prior to infusion, and then administration of a single infusion of GCC19CART at one of two preassigned doses: 1×10^6 or 2×10^6 CAR T-cells/kg. All responses were confirmed by an independent third-party imaging contract research organization. **Results:** 13 subjects have been enrolled to dose level 1 (1×10^6 cells/kg) and 8 subjects have been enrolled to dose level 2 (2×10^6 cells/kg). The most common adverse events were cytokine release syndrome (CRS) in 21/21 subjects (Grade 1 19/21 (90.48%) or Grade 2 2/21 (9.52%)) and diarrhea in 21/21 subjects (Grade 1 6/21 (28.57%) Grade 2 5/21 (23.81%) Grade 3 9/21 (42.86%) or Grade 4 1/21 (4.76%)). All patients with grade 3 and higher side effects were well managed. Immune effector cell-associated neurotoxicity syndrome (ICANS) was observed in 2/21 (9.52%) subjects at Grade 3 or 4 and resolved with corticosteroids. The combined overall response rate (ORR) for both dose levels was 28.6% (6/21). For dose level 1, overall response rate (ORR) was 15.4% (2/13). Two subjects demonstrated a partial response (PR) while 3 additional subjects had partial metabolic response (PMR) on PET/CT with stable disease (SD) or progressive disease (PD) per RECIST 1.1. For dose level 2, The ORR was 50% (4/8). 4 subjects demonstrated a PR and 2 additional subjects had PMR on PET/CT with SD per RECIST 1.1. The median PFS was 1.9 months in the dose 1 group and 6.3 months in the dose 2 group. The median overall survival was 13.3 months in the dose 1 group and 18.3 months in the dose 2 group. **Conclusions:** Preliminary results demonstrate that GCC19CART has meaningful dose-dependent clinical activity and an acceptable safety profile in relapsed or refractory metastatic colorectal cancer. This trial is ongoing and updated data will be presented. A Phase 1 trial of GCC19CART in the US has opened for accrual and is expected to enroll patients in mid-2022. Clinical trial information: ChiCTR2000040645. Research Sponsor: Innovative Cellular Therapeutics.

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Poster Session

First-line (1L) nivolumab (NIVO) + ipilimumab (IPI) in patients (pts) with microsatellite instability-high/mismatch repair deficient (MSI-H/dMMR) metastatic colorectal cancer (mCRC): 64-month (mo) follow-up from CheckMate 142. *First Author: Heinz-Josef Lenz, University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA*

Background: NIVO + IPI demonstrated robust, durable clinical benefit, and was well tolerated as a 1L therapy in pts with MSI-H/dMMR mCRC in the phase 2 CheckMate 142 study (NCT02060188), leading to the inclusion of NIVO + IPI in the NCCN guidelines as an initial therapy option for these pts. At 52-mo median follow-up, 1L NIVO + IPI continued to demonstrate durable clinical benefit, and no new safety signals were identified. Here we report longer follow-up results. **Methods:** Pts with MSI-H/dMMR mCRC and no prior treatment for metastatic disease received NIVO 3 mg/kg Q2W + IPI 1 mg/kg Q6W until disease progression or unacceptable toxicity. The primary endpoint was objective response rate (ORR) by investigator assessment (INV) per RECIST v1.1. Other key endpoints were disease control rate (DCR), duration of response (DOR), progression-free survival (PFS), all by INV; overall survival (OS); and safety. **Results:** In total, 45 pts received 1L NIVO + IPI. With median follow-up of 64.2 mo (range, 59.4-68.9 mo), ORR by INV was 71% (95% CI, 56-84%). The proportion of pts with a best overall response of complete response (CR) was 20%, partial response (PR) was 51%, stable disease (SD) was 13%, and progressive disease was 16%. Median DOR (mDOR) was not reached, and the 60-mo DOR rate was 72%. Median PFS (mPFS) by INV and median OS (mOS) were not reached, with 60-mo PFS and OS rates of 55% and 67%, respectively (Table). Among pts alive at the data cutoff (n = 31), 30 remained treatment-free after initial study treatment without receiving any subsequent systemic therapy, with a median treatment-free interval of 34.7 mo (range, 1.6-61.4 mo). Exploratory analysis by tumor mutational burden status will be presented. Safety data are shown in the Table. **Conclusions:** At 64-mo follow-up, NIVO + IPI continued to demonstrate clinically meaningful survival and durable responses, with mPFS, mOS, and mDOR still not reached, suggesting the potential for long-term clinical benefit. Safety remained consistent with previous data. These findings further support current recommendations for NIVO + IPI as a 1L treatment for pts with MSI-H/dMMR mCRC. Clinical trial information: NCT02060188. Research Sponsor: Bristol Myers Squibb.

Efficacy	1L NIVO + IPI (N = 45)
ORR ^{a,b} (95% CI), %	71 (56-84)
DCR ^{a,c} (95% CI), %	84 (71-94)
mPFS ^a (95% CI), mo	NR (28.8-NE)
60-mo PFS rate (95% CI), %	55 (38-69)
mOS (95% CI), mo	NR (NE)
60-mo OS rate (95% CI), %	67 (51-79)
Safety, n (%)	
Any-grade/grade 3 or 4 TRAEs	36 (80)/9 (20)
Any-grade TRAEs leading to discontinuation	7 (16)

^aPer INV; ^bPts with CR or PR divided by the number of treated pts; ^cPts with CR, PR, or SD (for ≥ 12 weeks) divided by the number of treated pts. NE, not estimable; NR, not reached; TRAE, treatment-related adverse event.

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Poster Session

Impact of number and size of colorectal metastases (CRM) on survival in patients with RAS wild-type metastatic colorectal cancer treated within the PanaMa trial (AIO KRK 0212). *First Author: Greta Sommerhäuser, Department of Hematology, Oncology and Tumorimmunology, Charité-Universitätsmedizin Berlin, Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany*

Background: In this exploratory analysis, we aim to evaluate surrogates of metastatic burden, namely number of CRMs and size of largest CRM, for their prognostic and predictive value on efficacy of maintenance therapy with 5-fluorouracil/leucovorin (FU/FA) plus panitumumab (pmab) or FU/FA alone in RAS wildtype mCRC patients treated within the PanaMa trial. **Methods:** Number of CRMs and size of largest CRM at baseline were determined taking into account target and non-target lesions measured by central radiological review. Median number of metastases was set as threshold ($n \leq / > 10$) to assess the prognostic and predictive value of CRM count on PFS and OS of maintenance therapy. A threshold of $\leq / > 50$ mm was set to evaluate the impact of the largest CRM on the above time-to-event endpoints. PFS and OS were expressed by Kaplan-Meier method and compared by log-rank testing. Hazard ratios (HR) with 95% CIs were estimated using Cox regression models. **Results:** Out of 248 patients receiving maintenance therapy, CT and MRI scans of 211 patients were centrally evaluable (FU/FA+Pmab, $n=106$; FU/FA alone, $n=105$). At baseline, 50.1% of the patients were diagnosed with > 10 CRM. Median size of the largest CRM was 45 mm. Number of CRMs $n \leq 10$ was associated with favorable PFS, while both, number $n \leq 10$, and size of largest CRM ≤ 50 mm correlated with favorable OS compared to $n > 10$ and size of largest CRM > 50 mm, respectively. In patients with > 10 CRMs, and those with largest CRM sized > 50 mm, PFS of maintenance therapy was significantly superior with FU/FA+Pmab compared to FU/FA alone (Table). **Conclusions:** Metastatic burden was found to be prognostic for PFS and OS of maintenance therapy. Additionally, number and largest size of CRMs proved predictive of PFS of maintenance therapy with Pmab, the primary endpoint of the trial. Patients with high metastatic burden at baseline appear to benefit particularly from Pmab-containing maintenance therapy. Clinical trial information: NCT01991873. Research Sponsor: Amgen Inc.

Metastatic burden according to number and size of colorectal metastases (CRM) and treatment arms.

	≤ 10 CRMs		Largest CRM ≤ 50 mm	
	A (n = 52)	B (n = 52)	A (n = 64)	B (n = 60)
Median PFS, months	10.3	6.0	8.4	6.5
HR (95% CI), P(log-rank)	0.74 (0.49-1.13) P=0.164		0.90 (0.61-1.33) P=0.586	
	> 10 CRMs		Largest CRM > 50 mm	
	A (n = 54)	B (n = 53)	A (n = 42)	B (n = 45)
Median PFS, months	8.1	5.6	9.2	5.0
HR (95% CI), P(log-rank)	0.63 (0.42-0.95) P=0.028		0.48 (0.31-0.75) P=0.001	

[A] FU/FA+Pmab; [B] FU/FA alone.

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Poster Session

Size-related heterogeneity of colorectal liver metastases (CRLM) in patients with advanced RAS wild-type metastatic colorectal cancer (mCRC) treated in the PanaMa trial: Implication for treatment decisions. *First Author: Greta Sommerhäuser, Department of Hematology, Oncology and Tumorimmunology, Charité-Universitätsmedizin Berlin, Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany*

Background: In patients with mCRC, the liver represents the primary site of metastasis. In patients with primarily unresectable metastatic disease, primary tumor location and molecular subtypes mainly determine the therapeutic approach. In addition, image-based characterization of hepatic metastatic pattern may provide additional information concerning prognosis and treatment efficacy. Therefore, CRLM were characterized according to size-based heterogeneity in the PanaMa trial (maintenance therapy with 5-fluorouracil/leucovorin (FU/FA) plus panitumumab (Pmab) vs. FU/FA alone following induction therapy with six cycles of FU/FA, oxaliplatin and Pmab). **Methods:** Assessments were performed in patients with at least two lesions, considering target and non-target lesions, within a central radiological review of the trial. Variance in size expressed as ratio between the smallest and largest lesion measured ($\leq / >$ threefold difference in size) was evaluated for its prognostic and predictive impact on progression-free (PFS) and overall (OS) survival of maintenance therapy. Time-to-event endpoints were expressed by Kaplan-Meier method and compared by log-rank tests. Cox regressions were used to indicate Hazard ratios (HR) with 95% CIs. **Results:** Imaging data of 211/248 (85.1%) patients receiving maintenance therapy were evaluable for central radiological review (FU/FA+Pmab, $n=106$; FU/FA, $n=105$). Of those, 165/211 patients (78.2%) had at least two CRLM. Size of CRLM ranged between 5–180mm, with the smallest metastasis in the individual assessments measuring a median of 12mm and the largest a median of 53mm. Large heterogeneity with more than a threefold difference in size between the smallest and largest CRLM was observed in 49.7% of patients, particularly pronounced in patients with polymetastatic disease (> 5 lesions). Homogeneous metastasis in terms of lesion size ($\leq$ threefold difference) was associated with favorable OS (HR 0.63; 95% CI, 0.42–0.95; $P=0.027$) - irrespective of study arm compared to heterogeneous lesion disease. Maintenance therapy with FU/FA+Pmab compared with FU/FA alone seemed favourably active in both patients with heterogeneous metastases (HR 0.53; 95% CI, 0.34–0.85; $P=0.008$) as well as to a numerically lesser extent in patients with homogeneous metastases (HR 0.68; 95% CI, 0.43–1.10; $P=0.116$). **Conclusions:** Imaging-based characterization of CRLM focusing on size-related heterogeneity was associated with favorable prognosis potentially indicating more aggressive underlying tumor dynamics in case of heterogeneous lesion size. In addition, the efficacy of Pmab during maintenance was evident in both patient groups (homogeneous and heterogeneous disease lesions) with a numerically greater effect in patients with heterogeneous lesions. Clinical trial information: NCT01991873. Research Sponsor: Amgen Inc.

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Poster Session

Alternating short-course oxaliplatin-based chemotherapy and nivolumab as first-line treatment of patients with abdominal metastases from microsatellite-stable (MSS) colorectal cancer (CRC): A randomized phase 2 trial. *First Author: Anne Hansen Ree, Akershus University Hospital, Lørenskog, Norway*

Background: The CRC incidence increases sharply from the age of 60. Most patients harbor primarily non-immunogenic MSS disease and abdominal metastases are in particular considered unresponsive to immune checkpoint blockade (ICB). The METIMMOX trial explored if MSS-CRC can be transformed into an immunogenic malignancy by short-course oxaliplatin-based therapy and if followed by ICB (without concomitant chemotherapy that might compromise an invoked tumor-defeating immunity) may result in durable clinical response for patients with abdominal metastases. **Methods:** Patients had MSS-CRC with infradiaphragmatic metastases deemed unresectable, ECOG performance status 0-1, and were eligible for first-line oxaliplatin-based therapy. They were randomly assigned to FLOX (oxaliplatin 85 mg/m² day 1, bolus 5-fluorouracil 500 mg/m² and folic acid 100 mg days 1-2) Q2W (control arm) or alternating cycles of 2 FLOX Q2W and 2 nivolumab (240 mg) Q2W (experimental (exp) arm) with break periods at prespecified intervals. Response assessment per i/RECIST by blinded central review was done every 8 weeks with progression-free survival (PFS) as primary endpoint. Sample size of 40 in each arm with 1:1 randomization would detect exp arm doubling of median PFS. Associations between PFS and relevant patient and disease variables were estimated by Cox proportional-hazards regression models. Prespecified correlative analyses included circulating tumor DNA (ctDNA) by droplet digital PCR and circulating immune cell composition by high-dimensional single-cell mass cytometry. **Results:** Of 80 enrolled subjects (05/2018-10/2021), 76 intention-to-treat (ITT) cases were equally allocated to the study arms and followed to censoring at 10/2022 with identical median PFS of 9.3 months (95% CI, 6.4-12.9 (control arm) and 4.6-15.2 (exp arm)). The adjusted Cox model revealed interaction between age and study arm, as patients ≥ 60 years had significantly lowered risk of progression when receiving exp therapy (median PFS 13.6 months (95% CI, 8.5-18.8); $p=0.022$). No unexpected adverse events were recorded; specifically, no grade ≥ 4 immune-mediated adverse event occurred. Of note, 17% of exp arm patients had durable complete response, among whom all BRAF-mutant cases ($n=3$) with PFS 21-35 months and rapid clearance of baseline BRAF-mutant ctDNA (control arm BRAF-mutant cases ($n=10$), median PFS 3.6 months). Responding exp arm patients showed distinct subsets of circulating immune cells with more homogenous profiles than ICB-unresponsive subjects. **Conclusions:** With equal primary endpoint for the ITT cases, alternating short-course oxaliplatin-based therapy and nivolumab significantly improved PFS compared to standard first-line chemotherapy in MSS-CRC patients ≥ 60 years with abdominal metastases. Clinical trial information: NCT03388190. Research Sponsor: Norwegian Cancer Society, including its Umbrella Foundation for Cancer Research, Grants 182496 and 215613; Bristol-Myers Squibb.

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Poster Session

Prognostic value of liver metastases in colorectal cancer treated by systemic therapy: An ARCAD pooled analysis. *First Author: Romain Cohen, Sorbonne University, Department of Medical Oncology, Saint-Antoine Hospital, AP-HP, Paris, France*

Background: Approximately 30% of patients (pts) diagnosed with colorectal cancer (CRC) develop liver metastases (LM). Liver is the most common organ of metastasis of CRC. The ARCAD database contains individual patient data of randomized trials that included CRC pts with initially unresectable metastases treated with systemic therapy. The aim of this study was to assess the response and survival outcomes in non-LM (NLM) vs LM across different lines of treatment. **Methods:** We analyzed survival outcomes of mCRC pts with either single site (SS) or multiple sites (MS) according to LM status in the following treatment groups: A: chemotherapy (CT) alone, B: CT + VEGF-antibodies, C: CT + EGFR-antibodies in KRAS wild-type tumors, within first-line (1L) and second-line (2L) of therapy and D: pts enrolled on third line (≥ 3 L) trials treated with trifluridine/tipiracil or regorafenib and placebo. The primary and secondary endpoints were overall survival (OS) and progression-free survival (PFS) which were assessed using Kaplan-Meier estimates and adjusted Cox models on ECOG PS, age, and gender. **Results:** We included 26 trials with 17924 pts. 14066 pts had LM. Pts with LM had a higher rate of colon vs rectum as primary tumor (72 vs 62%; $P<.001$) and less SS (31 vs 47%; $P<.001$) than those with NLM. OS and PFS results in subgroups are reported in the table. In groups A and B, we found better OS and PFS outcomes in NLM pts as either SS or MS in 1L and 2L. In group C from 1L, we found better survival outcomes in pts with SS LM. In pts with MS, NLM superiority was observed in OS but not in PFS. However, these results were influenced by primary tumor sidedness. In group D, better OS and PFS was observed in pts without LM than those with LM whether in pts with SS or MS. Response rates were higher in LM than in NLM in most 1L and 2L subgroups. **Conclusions:** LM is a poor prognostic factor for mCRC increasing from the 1L to ≥ 3 L. Survival with CT alone and CT + anti-VEGF according to LM and NLM differs significantly in 1L and 2L but not with CT + anti-EGFR. This data justifies using LM as a stratification factor at least in ≥ 3 L trials. Research Sponsor: ARCAD Foundation.

NLM vs LM (Reference) HR (95% CI)	1L		2L		≥ 3 L	
	OS	PFS	OS	PFS	OS	PFS
Group A All pts	.76 (.68-.84)	.84 (.77-.92)	.64 (.58-.71)	.72 (.66-.79)	Group D - Trifluridine/tipiracil	.36 (.29-.44) .52 (.44-.60)
SS	.79 (.67-.94)	.93 (.80-1.1)	.58 (.48-.69)	.67 (.57-.78)		.33 (.21-.51) .43 (.31-.59)
MS	.76 (.67-.86)	.81 (.72-.91)	.71 (.63-.81)	.77 (.69-.87)		.39 (.30-.51) .58 (.48-.71)
Group B All pts	.81 (.74-.89)	.91 (.84-.98)	.62 (.55-.71)	.75 (.67-.84)	Group D - Placebo	.40 (.32-.52) .60 (.49-.73)
SS	.88 (.77-.96)	.99 (.89-1.1)	.55 (.44-.68)	.76 (.63-.91)		.14 (.07-.28) .43 (.25-.73)
MS	.84 (.73-.96)	.88 (.79-.99)	.81 (.68-.96)	.79 (.68-.91)		.51 (.39-.68) .62 (.50-.79)
Group C All pts	.97 (.86-1.1)	1.0 (.91-1.2)	1.1 (.84-1.5)	1.2 (.93-1.6)		
SS	1.2 (1.0-1.5)	1.1 (.95-1.3)	1.1 (.44-2.8)	1.9 (.88-3.9)		
MS	.85 (.72-1.0)	1.1 (.90-1.3)	1.1 (.80-1.5)	1.1 (.82-1.5)		

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Poster Session

A phase Ib/II study to evaluate surufatinib combined with camrelizumab and chemotherapy in the second-line treatment of advanced colorectal cancer: Phase Ib results. *First Author: Sheng Li, Department of Oncology, Jiangsu Cancer Hospital, Nanjing, China*

Background: Surufatinib is a novel small-molecule kinase inhibitor targeting VEGFR1-3, FGFR and CSF-1R with confirmed efficacy in epNET and pNET. Pre-clinical studies have demonstrated that surufatinib combined with immune checkpoint inhibitors (ICIs) have synergistic antitumor effects by modulating tumor immune microenvironment. Additionally, surufatinib plus toripalimab (anti-PD-1) has showed preliminary anti-tumor activity in multiple solid tumors, including colorectal cancer (CRC). This study aimed to evaluate the efficacy and safety of surufatinib plus camrelizumab (anti-PD-1), irinotecan and GM-CSF as second-line treatment in advanced CRC. Here we reported the results of the phase Ib study. **Methods:** This ongoing phase Ib/II, open-label trial (NCT04929652) enrolled patients (pts) aged 18-75 years old with pathologically confirmed locally advanced or metastatic CRC who have progressed on/been intolerant to the standard first-line therapy. In the Ib dose escalation/de-escalation phase, pts received surufatinib at 250mg once daily (QD) as starting dose, in combination with fixed dose of camrelizumab (200 mg, d1), irinotecan (200 mg/m², d1) and GM-CSF (5ug/kg, d2-d7), every 3 weeks (Q3W). Based on DLTs, the dose of surufatinib should escalate to 300 mg or de-escalate to 200 mg. The primary objective of the phase Ib study was to determine the safety and DLT in first treatment cycle defining the recommended phase 2 dose (RP2D). Additional 36 pts were enrolled in the phase II dose expansion stage using RP2D. Primary endpoint of phase II was ORR as per RECIST 1.1. Secondary endpoints included PFS, DCR, OS and safety. **Results:** Enrollment opened in Nov 2021 and data cutoff in Dec 2022. 12 pts (median age 54) were treated in Phase Ib study (surufatinib 250 mg: N = 6; surufatinib 300 mg: N = 6). 75% were male and 17% had ECOG PS 1. 11/12 (92%) pts were positive for KRAS, NRAS or BRAF mutations. No DLT was observed in the starting dose cohort (surufatinib 250 mg), and one patient in the surufatinib 300 mg cohort experienced DLT (Grade [G] 3 vomiting). Surufatinib 300 mg QD was defined as the RP2D. Other G3 treatment related adverse events (TRAEs) were hypertension (1/12; 8.3%) and diarrhea (1/12; 8.3%). All other TRAEs were grade 1-2, and the most common (≥40%) were diarrhea (75%), fatigue (58%), vomiting (58%), nausea (50%), hypertension (42%), proteinuria (42%) and alopecia (42%). Of the 12 pts evaluable for tumor response, 3 pts achieved PR, 9 pts achieved SD. The ORR was 25% (3/12), the DCR was 100% (12/12) and median PFS was 7.2 months (95%CI 3.7-10.7). **Conclusions:** Surufatinib plus camrelizumab, irinotecan and GM-CSF was well tolerated, with a manageable safety profile, and showed preliminary anti-tumor activity in patients with advanced CRC. The dose-expansion phase is ongoing. Clinical trial information: NCT04929652. Research Sponsor: None.

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Poster Session

Preliminary results from ERAS-007 plus encorafenib and cetuximab (EC) in patients (pts) with metastatic BRAF V600E mutated colorectal cancer (CRC) in HERKULES-3 study: A phase 1b/2 study of agents targeting the mitogen-activated protein kinase (MAPK) pathway in pts with advanced gastrointestinal malignancies (GI cancers). *First Author: Michael Sangmin Lee, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: The RAS/MAPK pathway (including BRAF) is dysregulated in a broad range of cancers including CRC, resulting in downstream activation of ERK1/2. Metastatic CRC with BRAF V600E mutation (BRAF V600E mCRC) has dramatically worse survival than non-BRAF V600E mutated CRCs, and novel therapies are needed. ERAS-007 is a novel, potent, and orally bioavailable inhibitor of ERK. The combination of a BRAF plus EGFR inhibitor (EC) is approved for the treatment of pts with BRAF V600E mCRC; however, only 20% of pts experience an objective response. ERAS-007 alone or in combination with EC showed promising in vitro and in vivo activity in BRAF V600E CRC models to support the combinatorial clinical benefit of ERAS-007+EC in BRAF V600E mCRC. **Methods:** HERKULES-3 is a Phase 1b/2 study to assess the safety, tolerability, PK, and preliminary clinical activity of ERAS-007 combinations targeting the MAPK pathway in pts with advanced GI cancers. Within this study, we are currently evaluating the safety and tolerability of escalating doses of ERAS-007 + EC in pts with BRAF V600E CRC. Prior BRAF inhibitor and EGFR inhibitor treatment is neither required nor excluded to be enrolled in this study. **Results:** As of 30 November 2022, 12 patients were dosed with ERAS-007 twice daily-once a week (BID-QW) (75 and 100 mg; n = 10) or once daily once a week (QW) (150 mg; n = 2) in combination with EC (300 mg oral daily + 500 mg/m² intravenous infusion once every 2 weeks). The treatment-emergent AEs (TEAEs) occurring in ≥20% of pts were fatigue (50%), headache (42%), constipation, diarrhea, nausea, dermatitis acneiform (33% each), and vomiting (25%). No TEAEs led to ERAS-007 discontinuation or death. Grade ≥3 TEAEs were reported in 3 pts (25%). Grade ≥3 treatment-related AEs reported in ≥ 2 patients (17%) include hypertension, headache, confusional state, and skin toxicity. Three pts (25%) died due to disease progression. No DLTs were reported. Out of 4 efficacy evaluable EC naive pts, one confirmed partial response (PR) and one unconfirmed PR were observed. Evaluation of PK is ongoing and preliminary data will be presented. **Conclusions:** ERAS-007+EC in pts with BRAF V600E CRC shows acceptable preliminary safety/tolerability and evidence of clinical activity. The highest dose of ERAS-007 evaluated and cleared by the safety review committee to date is 100 mg BID-QW when combined with EC. Observed PK, toxicity, and preliminary activity support continued evaluation of this combination in pts with BRAF V600E CRC. Clinical trial information: NCT05039177. Research Sponsor: Erasca; Lilly and Pfizer.

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Poster Session

Trifluridine/tipiracil (FTD/TPI) in extensively pre-treated metastatic colorectal cancer (mCRC) patients: Evaluation of prognostic subgroups of the TALLISUR study. *First Author: Meinolf Karthaus, Department of Hematology and Oncology, Munich Hospital Neuperlach, Munich, Germany*

Background: Compared to placebo, FTD/TPI significantly improved overall survival (OS) in patients (pts) with pre-treated mCRC in the pivotal phase III RECURSE trial. Subgroup analyses indicated that all subgroups benefitted from FTD/TPI. Of note, FTD/TPI prolonged survival even more in pts ≥ 65 years old. To evaluate these observations with data from daily clinical practice, we performed a subgroup analysis of the TALLISUR study. **Methods:** In this prospective, multi-center, German, open-label, phase IV study, pts with extensively pre-treated mCRC chose between best supportive care (BSC) or oral FTD/TPI (35 mg/m² bid on days 1–5 and 8–12 of each 28-day cycle). Duration of treatment and OS were analyzed for various subgroups. Based on a post-hoc analysis of the RECURSE trial, 3 subgroups were defined according to: best, good and poor prognostic characteristics (BPC, GPC, PPC). Pts with < 3 metastatic sites at inclusion and ≥ 18 months from diagnosis to inclusion were considered to have GPC. GPC pts without liver metastasis at inclusion were considered to have BPC. All remaining pts were considered to have PPC. **Results:** Of 195 eligible pts, 186 pts chose treatment with FTD/TPI, while 9 pts decided to receive BSC only. Median OS was 6.9 (95% CI 6.1–8.3) months. Mean duration of treatment with FTD/TPI was 14.6 (range 0.1–102.7) weeks. Results of the subgroup analysis are summarized in the table. Pts ≥ 65 years old presented a longer median OS (7.2 vs 6.2 months). **Conclusions:** When given the choice between treatment and BSC in late-stage CRC, the vast majority of pts opted for treatment. Low metastatic burden and indolent disease were factors of good prognosis for FTD/TPI therapy regarding OS. Independent of baseline characteristics such as age, sidedness, and time of onset of metastases, virtually all pts benefitted from therapy with FTD/TPI. Albeit not statistically significant, elderly pts tend to have improved survival with FTD/TPI, consistent with results from RECURSE. Clinical trial registration number: EudraCT No 2017-000292-83. Research Sponsor: Servier.

Subgroup analysis – survival and duration of treatment with FTD/TPI.

Subgroup	Median OS (95% CI) [months]	Mean duration of treatment (range) [weeks]
BPC (n = 20)	12.2 (6.0 – 18.2)	16.3 (0.4 – 83.7)
GPC (n = 65)	7.9 (6.2 – 13.3)	15.1 (0.4 – 102.7)
PPC (n = 121)	6.8 (5.4 – 8.1)	14.3 (0.1 – 102.7)
Age < 65 years (n = 74)	6.2 (4.8 – 8.6)	13.7 (0.1 – 102.7)
Age ≥ 65 years (n = 112)	7.2 (6.3 – 11.1)	15.2 (0.7 – 102.7)
Synchronous metastases (n = 102)	6.9 (6.2 – 10.1)	12.4 (0.1 – 72.7)
Metachronous metastases (n = 63)	7.3 (5.3 – 12.4)	16.8 (1.3 – 102.7)
Left sided tumor (n = 138)	6.8 (6.0 – 8.3)	13.9 (0.1 – 102.7)
Right sided tumor (n = 42)	8.1 (5.9 – 12.8)	16.9 (0.4 – 72.7)

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Poster Session

Preliminary results from ERAS-007 plus palbociclib (palbo) in patients (pts) with KRAS/NRAS mutant (m) colorectal cancer (CRC) or KRASm pancreatic ductal adenocarcinoma (PDAC) in HERKULES-3 study: A phase 1b/2 study of agents targeting the mitogen-activated protein kinase (MAPK) pathway in pts with advanced gastrointestinal malignancies (GI cancers). *First Author: Susanna Varkey Ulahannan, University of Oklahoma Health Sciences Center, Oklahoma City, OK*

Background: The RAS/MAPK pathway is dysregulated in a broad range of cancers including CRC and PDAC, resulting in downstream activation of ERK1/2. ERAS-007 is a novel, orally bioavailable inhibitor of ERK. Palbo is an oral CDK4/6 inhibitor that inhibits cellular proliferation, an essential feature of tumor growth. Both in vitro & in vivo data exploring the combination of ERAS-007 and palbo in a panel of CRC and pancreatic CDX and/or PDX models have shown promising activity to support the potential combinatorial clinical benefit in RASm CRC and PDAC pts. **Methods:** HERKULES-3 is a Phase 1b/2 study to assess safety, tolerability, PK, and preliminary clinical activity of ERAS-007 combinations targeting the MAPK pathway in pts with advanced GI cancers. Within this study, we are currently evaluating the safety, tolerability, and PK of escalating doses of ERAS-007 twice daily-once a week (BID-QW) (75, 100 mg) in combination with palbo once daily (QD) (75, 100, 125 mg) in pts with KRASm/NRASm CRC or KRASm PDAC. **Results:** As of 30 November 2022, 30 pts were dosed with the combination of palbo and ERAS-007. Treatment emergent AEs (TEAEs) occurring in ≥20% of pts were diarrhea (40%), nausea (40%), anemia (33%), vision blurred (27%), fatigue (23%), and neutrophil count decreased (20%). ERAS-007 treatment related AEs (TRAEs) were reported in 19 pts (63%), with the most frequently reported as diarrhea (40%), nausea (33%), and vision blurred (27%). Grade (Gr) ≥3 TEAEs were reported in 12 pts (40%), including 3 related to ERAS-007 (neutrophil count decreased, diarrhea and dermatitis acneiform). Neutrophil count decreased and anemia were the only Gr 3 events reported in ≥ 2 pts. No Gr 4 events were reported. Two Gr 5 events unrelated to any drugs (hemorrhage intracranial and malignant pleural effusion) and one Gr 5 event (anemia) related to palbo were reported. Two pts discontinued ERAS-007 due to TEAEs (Gr 5 malignant pleural effusion and Gr 2 neutrophil count decreased). Three pts reported 4 DLTs: 1 pt at 75mg ERAS-007 + 125mg palbo (Gr 3 maculopapular rash & Gr 4 sepsis), 1 pt at 100mg ERAS-007 + 100mg palbo (Gr 3 dermatitis acneiform), and 1 pt at 100mg ERAS-007 + 125mg palbo (Gr 3 thrombocytopenia). Based on preliminary PK, no clinically relevant PK interactions were identified between ERAS-007 and palbo. The evaluation of clinical activity is ongoing. **Conclusions:** ERAS-007 in combination with palbo in pts with KRASm/NRASm CRC or KRASm PDAC shows expected preliminary safety with reversible and manageable AEs. The highest dose evaluated and cleared by the safety review committee to date is ERAS-007 100 mg BID-QW in combination with the approved monotherapy dose of palbo 125 mg QD. Clinical trial information: NCT05039177. Research Sponsor: Erasca (Sponsor); Pfizer (collaborator).

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Poster Session

Novel GUCY2C targeting CAR-T therapy: Efficacy in advanced colorectal cancer. *First Author: Qianyu Zhang, Anhui Provincial Cancer Hospital, Hefei, China*

Background: Chimeric antigen receptor (CAR) T cells have shown remarkable success in treating patients with hematologic malignancies. However, the majority of CAR-T cell clinical trials in solid tumors have limited success which is partially attributed to the detrimental tumor microenvironment and the lack of ideal target. Recently, GUCY2C emerges as an ideal therapeutic target which is highly expressed in colorectal cancer (CRC). Here, a novel nanobody-based GUCY2C targeting CAR-T cell developed by us is applied to treat advanced colorectal cancer patients who failed third-line therapy. **Methods:** In this open-label, single-arm, investigator-initiated exploratory trial (ChiCTR2100044831), we primarily explore the safety and the low-dose efficacy of the autologous anti-GUCY2C CAR-T cells. All patients screened by IHC met our criteria for GUCY2C positivity. All enrolled patients had received at least 3 prior lines of therapy and had multiple metastases at baseline. Totally, 13 advanced CRC patients aged 18 to 65 years were infused with the anti-GUCY2C CAR-T cells at a dose range of 0.5-3 x10⁶/kg after standard Cy-Flu lymphodepletion. Adverse events (AE) were graded according to CTCAE 5.0, and objective tumor responses were assessed per RECIST 1.1 criteria. **Results:** Between November 2021 and December 2022, 13 subjects with refractory metastatic CRC (mCRC) were treated with the anti-GUCY2C-CAR-T cells infusions at a dose range of 0.5-3 x10⁶/kg. There were no dose-limiting toxicities, treatment-related death or any form of neurotoxicity occurred in this study. The most common TEAEs were diarrhea in 9/13 (69%) subjects (Grade 1: 2/13 (15.38%) Grade 2: 3/13 (23.07%) Grade 3: 4/13 (30.77%)). 8/13 (62%) mCRC subjects experienced grade 1 or grade 2 mouth ulcer generally appear as a single lesion lasting for a few days. All cytokine release syndromes (CRS) observed were grade 1. Totally 9 pts (69%) experienced grade 1 CRS and all resolved by supportive care without the need of tocilizumab. No grade 4 AEs except for decreased lymphocytes in 12/13 pts (92%), decreased white blood cells in 1/13 pts (7.7%) and decreased platelet in 1/13 pts (7.7%). Among 10 evaluable patients, 6 partial responses, 2 stable disease and 2 progressive disease were achieved. At all dose levels ORR and DCR were 60% and 80% respectively. Notably, all 3 patients infused at the dose level above 2x10⁶/kg reached partial responses. Among the 3 non-evaluable patients, 1 patient lost follow-up, 1 patient died of bone marrow failure and 1 patient died of COVID-19 related complications before the first efficacy evaluation. Additional data will be presented at the meeting. **Conclusions:** This clinical study indicated that the anti-GUCY2C CAR-T cell therapy was well tolerated and had promising efficacy in heavily pretreated mCRC patients. Clinical trial information: ChiCTR2100044831. Research Sponsor: None.

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Poster Session

Matching-adjusted indirect treatment comparisons (MAIC) of sotorasib vs trifluridine/tipiracil (T/T) and regorafenib as monotherapy in chemorefractory KRAS G12C-mutated metastatic colorectal cancer (mCRC). *First Author: Timothy Jay Price, Queen Elizabeth Hospital, University of Adelaide, Adelaide, Australia*

Background: In the single-arm phase 1/2 CodeBreak 100 study (NCT03600883) evaluating sotorasib monotherapy in KRAS G12C-mutated mCRC patients whose disease progressed on or after fluoropyrimidine, oxaliplatin, and irinotecan treatment, the overall response rate was 12%, and the median progression-free survival (PFS) and overall survival (OS) was 4.2 and 13.4 months, respectively (data cutoff March 2021, n = 91). To compare the efficacy and safety of sotorasib with standard of care (SOC) T/T and regorafenib as monotherapy treatments, MAICs were performed. **Methods:** Clinical outcomes and adverse events (AEs) were compared from representative studies in mCRC patients who received sotorasib 960 mg once daily in CodeBreak 100, T/T in the phase 3 RECURSE study (NCT01607957, n = 534), and regorafenib in the phase 3 CORRECT study (NCT01103323, n = 505). By weighting individual patient-level data from CodeBreak 100, differences in available baseline characteristics considered to be prognostic factors, including age, race, sex, type of cancer (colon vs. rectum), ECOG performance status, time from diagnosis of metastatic disease, number of metastatic sites, number of prior lines of therapy, and prior bevacizumab treatment, were adjusted with the MAIC. MAICs compared sotorasib with T/T and regorafenib separately. Odds ratios (ORs) were estimated for objective response rates, hazard ratios (HRs) were used for PFS and OS. AEs were compared descriptively. **Results:** The effective sample size of sotorasib with matched characteristics consisted of 29 and 56 patients in the T/T and regorafenib comparison, respectively. The MAIC results showed that treatment with sotorasib increases the likelihood of response to treatment, with an adjusted OR of 8.5 vs T/T and 16.1 vs regorafenib. Sotorasib decreased the risk of progression or death by 41% vs T/T and 45% vs regorafenib (Table). Grade 3+ treatment-emergent AEs occurred in 37%, 69%, and 78% of sotorasib-, T/T-, and regorafenib-treated patients, respectively. **Conclusions:** The analyses suggest that sotorasib monotherapy is associated with a statistically significant and clinically meaningful improvement in response rates, PFS and OS vs. T/T and regorafenib in heavily pretreated chemorefractory KRAS G12C-mutated mCRC patients. The analyses are limited by the decreased sample size for sotorasib, the lack of KRAS G12C-specific data in SOC studies, and the impact of differences in post-progression treatments on OS across studies. Research Sponsor: Amgen.

	Sotorasib vs T/T	Sotorasib vs regorafenib
Objective response, OR (95% CI)*	8.5 (3.2-22.1)	16.1 (5.5-46.6)
PFS, HR (95% CI)	0.59 (0.40-0.88)	0.55 (0.39-0.78)
OS, HR (95% CI)	0.32 (0.18-0.57)	0.42 (0.28-0.62)

* Per central review for sotorasib, per investigator assessment for comparators CI: confidence interval.

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Poster Session

Determinants of permanent liver limited disease (pLLD) in metastatic colorectal cancer (mCRC). *First Author: Francesc Salva, Vall d'Hebron Institute of Oncology (VHIO), Medical Oncology, Vall d'Hebron University Hospital (HUVH), Barcelona, Spain*

Background: CRC is a complex and heterogeneous disease, with the liver being the most frequent site of metastasis. Around 20% of patients will always progress exclusively in the liver. These patients may be candidates for more aggressive therapeutic procedures that will impact in their outcome. LIVERMET SURVEY Database (LMSD) is a prospective international database, focused on patients operated for CRC liver metastasis, whether resected or not, which purpose is to evaluate patient outcomes and prognostic factors for these resected patients. We propose to analyse all patients enrolled in the (LMSD) to better characterised those determinants that are associated with pLLD. **Methods:** We analyzed all patients included in the LMSD. Patients with relapse of their disease after the first liver surgery were selected. In order to test associations between hepatic only and extrahepatic metastasis, a univariate and multivariate logistic model was performed with the variables considered clinically more relevant. Imputation of missing data using the mice method (Multivariate Imputation via Chained Equations) was performed. All analyses were performed with R 4.1.1 software. **Results:** A total of 8715 patients out of 33581 (26%) included in the LMSD presented disease recurrence after a first liver surgery. During their oncological history, pLLD occurred in 1392 patients (16%), and extrahepatic relapse was presented in 7323 patients (84%). The characteristics of patients with pLLD were as follows: 58.4% patients presented synchronous disease, 20.2% had right sided primary tumor, 58.6% presented unilateral disease at time of first hepatic surgery and 20.4% of patients presented R1 surgery. In multivariate analysis, right sided and rectum (HR 0.82, p = 0.001), unilateral liver involvement (HR 0.74, p < 0.001) and > 3cm of diameter in greatest lesion with maximum of 3 lesions (HR 0.85, p = 0.02) were predictive determinants of extrahepatic disease. Only synchronous metastases (HR 1.29, p < 0.001) and male sex (HR 1.15, p = 0.028) were associated with pLLD. Molecular information according to RAS, BRAF and MSI status was not evaluable in a majority of patients since this item has been recently implemented in the questionnaire. **Conclusions:** This study confirms that about 16% of patients with LLD mCRC will be pLLD mCRC. Despite clinical determinants like synchronous metastatic disease, which is associated with pLLD, further analyses including molecular determinants are needed. Identifying those determinants of pLLD in a scenario where more extreme surgeries and liver transplantations are being considered is a great challenge that needs to be addressed. Research Sponsor: None.

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Poster Session

A phase II study of regorafenib plus sintilimab as salvage-line treatments in non-MSI-H metastatic colorectal cancer (mCRC). *First Author: Rui Liu, Department of Gastrointestinal Medical Oncology, Tianjin Medical University Cancer Institute & Hospital, National Clinical Research Center for Cancer, Key Laboratory of Cancer Prevention and Therapy, Tianjin's Clinical Research Center for Cancer, Tianjin, China*

Background: PD-1 blockade is particularly ineffective in patients with microsatellite stable (MSS) or mismatch repair (MMR)-proficient colorectal cancer (CRC). Regorafenib (R) has been shown to modulate anti-tumor immunity by different mechanisms including reduction of tumor-associated macrophages (TAMs) and the immunosuppressive cells. Synergy between Regorafenib and anti-PD-1/PD-L1 antibodies has been shown in pre-clinical models, as well as in several clinical studies, compared with either treatment alone. The purpose of this study was to evaluate the activity of regorafenib in combination with immune checkpoint inhibitors. **Methods:** This is a single-arm, open-label, phase II trial assessing the efficacy and safety of Regorafenib (80mg QD 3weeks/4) + Sintilimab (S) (200mg every 3 weeks) combination in non MSI-H mCRC patients (pts). The primary endpoint was the overall survival (OS). Secondary endpoints included progression free survival (PFS), objective response rate (ORR), disease control rate (DCR) and Safety. **Results:** As of February 1, 2023, a total of 103 patients with mCRC were enrolled and received R+S. Median age was 57 (range, 28-75). Male 59.2%, ECOG PS 0/1/2 20.4%/66.0%/13.6%, left-sided colon/right-sided colon/rectum 39.8%/15.5%/44.7%, RAS mutant 42.7%. The ORR was 21.4% and DCR was 63.1%, with complete response (cCR) in 1 (1.0%), partial response (PR) in 21 (20.4%) and stable disease (SD) in 43 (41.7%) patients. With a median follow up of 19.9 months (range, 0.1-41.4), the median PFS was 4.0 months (95% CI, 3.1-4.4 months) and median OS was 13.0 months (95% CI, 12.0-16.5 months). The patients who achieved ORR have significantly longer PFS (20.8 vs. 3.2 months, p < 0.001) and OS (not reach vs. 12.0 months, p < 0.001) than the non-ORR patients. The median PFS were similar regardless the KRAS mutation status, primary sidedness, or liver metastases. Multivariate analysis revealed that male, ECOG PS2, the number of metastatic sites ≥ 2, and RAS mutant were significantly associated with worse OS. The most common grade 3/4 adverse events were hand-foot syndrome (1.9%), stomatitis (1.9%), rash (1.0%), hypertension (1.0%), allergic reaction (1.0%), fatigue (1.0%) and fever (1.0%). 8(7.8%) patients experienced at least 1 dose modification or treatment interruption. No death was related to the treatment. **Conclusions:** In this study the R+S combination as salvage-line treatments in non-MSI-H mCRC achieved a promising clinical benefit, with a manageable safety profile. Female, ECOG PS0/1, single metastases, RAS wild type mCRC were associated with better OS. Clinical trial information: NCT04745130. Research Sponsor: None.

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Poster Session

Safety and efficacy of D-1553 in KRAS G12C-mutated colorectal cancer: Results from a phase I/II study. *First Author: Dan-yun Ruan, Department of Medical Oncology, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University, Guangzhou, China*

Background: KRAS G12C mutation is an oncogenic driver that occurs in 3-4% of colorectal cancer (CRC). D-1553 is a novel oral and potent KRAS^{G12C} inhibitor. This phase I/II open-label study (NCT04585035) is an international multicohort study evaluating the safety, tolerability, pharmacokinetics (PK) and efficacy of D-1553 in patients (pts) with KRAS G12C mutated locally advanced or metastatic solid tumors. The Phase I part was conducted to determine the recommended phase 2 dose (RP2D) of D-1553. The Phase II part enrolled multiple expansion cohorts of different cancer types. The endpoints of the study include clinical activity, safety and PK. Here we report preliminary data from pts with locally advanced unresectable or metastatic CRC receiving $\geq$ RP2D of D-1553 monotherapy. **Methods:** Pts with locally advanced unresectable or metastatic CRC with progression after standard treatment were enrolled in the Phase I and Phase II parts of the study. Pts were required to have KRAS G12C mutations in tumor or ctDNA samples and no prior KRAS G12C directed therapy. The current analysis includes CRC patients who were treated with D-1553 at RP2D (600 mg BID in Phase I and II) and above (800 mg BID in Phase I) as monotherapy. **Results:** As of 30 December 2022, 24 pts with previously heavily treated locally advanced or metastatic CRC (54.2% male; median age, 61.5 years [range 44, 74]; ECOG PS 0/1: 45.8%/54.2%) were enrolled and received D-1553 600 mg (n = 23) or 800 mg (n = 1) BID monotherapy. 95.8% of pts had stage IV disease. 66.7% had $\geq$ 2 prior lines of therapy (median: 2 [range, 1, 6]). Median treatment duration was 5.75 (range 1.51, 11.83) months (mo) with a median follow-up of 6.64 (range 2.46, 13.11) mo. Confirmed ORR was 20.8% (5/24) (95% CI: 7.1%-42.2%), and DCR was 95.8% (23/24). Median PFS was 7.62 mo (95% CI, 2.89 to 9.53 mo). At the data cutoff date, 37.5% (9/24) of pts remain on study treatment. Treatment-related adverse events (TRAEs) of any grade occurred in 50% (12/24), most were grade 1 or 2 in severity. Two pts had grade 3/4 TRAEs (alanine aminotransferase increased, diarrhea, hypertension and hypokalaemia). No TRAEs were fatal or resulted in D-1553 discontinuation. The most common ($\geq$ 5%) TRAEs (any grade) were increased alanine aminotransferase or aspartate aminotransferase, increased total bilirubin or conjugated bilirubin, diarrhea, hypothyroidism and nausea. **Conclusions:** D-1553 demonstrated a tolerable safety profile and promising monotherapy activity in pts with heavily pretreated locally advanced or metastatic CRC and KRAS G12C mutations. This study is ongoing to further evaluate the safety and efficacy of D-1553 as monotherapy and in combination with cetuximab or chemotherapy in pts with locally advanced or metastatic CRC. Clinical trial information: NCT04585035. Research Sponsor: InventisBio Co., Ltd.

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Poster Session

A multicenter randomized phase II trial comparing CAPOXIRI + bevacizumab with FOLFOXIRI + bevacizumab as first-line treatment in patients with metastatic colorectal cancer: Primary results of the QUATTRO-II study. *First Author: Hideaki Bando, Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan*

Background: FOLFOXIRI plus bevacizumab (Bev) is highly effective for treating patients (pts) with metastatic colorectal cancer (mCRC); however, high incidences of hematologic adverse events (AEs) and pump infusion of 5-FU q2wk can complicate treatment continuation. According to the safety lead-in (Step 1), CAPOXIRI plus Bev with 1600-mg/m² capecitabine (Cap), 130-mg/m² oxaliplatin (Ox), 200-mg/m² irinotecan (Iri), and 7.5-mg/kg Bev q3wk was the recommended phase 2 dose (Kotani D, et al., Invest New Drugs, 2021). Here, we report the results of the randomized phase II part (Step 2) of the QUATTRO-II study, which examined the efficacy and safety of CAPOXIRI + Bev versus FOLFOXIRI + Bev. **Methods:** Enrolled pts were ECOG PS 0 or 1, and had chemotherapy-naïve mCRC with wild-type or single heterozygous UGT1A1 *6/*28 genetic polymorphism. Pts were randomly allocated to FOLFOXIRI + Bev (Arm A) or CAPOXIRI + Bev (Arm B) in a 1:1 ratio. The induction treatment in Arm A/B was continued for 8/6 cycles (12/8 cycles at maximum if feasible), and the maintenance treatment was either 5-FU + leucovorin + Bev or Cap + Bev at the discretion of the investigators. The primary endpoint was progression-free survival (PFS), with the two groups deemed equivalent if the hazard ratio (HR) of the point estimate was 0.8 < HR < 1.25. Secondary endpoints were overall survival (OS), overall response rate (ORR), early tumor shrinkage (ETS), depth of response (DpR), and safety. **Results:** From June 2020 to June 2021, 103 pts (Arm A/B, 51/52 pts) were randomly assigned. Baseline characteristics, including age (median 60 years in both arms) and ECOG PS 0 (90%/94%), were well balanced between arms. At a median follow-up of 23.7 months, the median PFS (Arm A/B) was 10.6 months (95% CI 7.7–13.3)/10.9 months (95% CI 9.3–14.3; HR 1.119, P = 0.639), and the primary endpoint was met (HR: 0.8 < 1.119 < 1.25). The 2-year OS rate (Arm A/B) was 65.5% (95% CI 49.5–77.6)/74.3% (95% CI 59.8–84.2), with the median OS not reached. Moreover, the ORR was 76.5% (95% CI 62.5–87.2)/84.6% (95% CI 71.9–93.1). ETS was achieved in 71.4%/82.0% of pts, and the median DpR was 43.0%/54.2%. Incidences of major grade $\geq$ 3 AEs (Arm A/B) were as follows: neutropenia (68.6%/40.4%), febrile neutropenia (6.8%/11.5%), diarrhea (7.8%/17.3%), and appetite loss (7.8%/17.3%). No treatment-related deaths occurred. **Conclusions:** The efficacy of CAPOXIRI + Bev was comparable to that of FOLFOXIRI + Bev. Although CAPOXIRI + Bev was associated with increased incidences of certain nonhematologic AEs, it was well tolerated, with a decreased incidence of neutropenia and no unexpected safety signal. Good survival and response results suggest that CAPOXIRI + Bev could become a new first-line treatment option in pts with mCRC. Clinical trial information: NCT04097444. Research Sponsor: Chugai Pharmaceutical.

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Poster Session

Impact of sex on the efficacy of first-line mFOLFOX6 (plus or minus bevacizumab) versus mFOLFOX6 (plus or minus bevacizumab) plus Y90-radioembolization in patients with metastatic colorectal cancer: An exploratory, retrospective analysis of the phase III SIRFLOX trial. *First Author: Kathrin Heinrich, Department of Medicine III and Comprehensive Cancer Center (CCC Munich LMU), University Hospital, LMU Munich, Munich, Germany*

Background: Clinical trials in metastatic colorectal cancer (mCRC) investigating systemic and local treatment options are usually conducted irrespective of sex. However, sex-associated differences relating to safety and efficacy in the treatment of mCRC are of gaining interest. **Methods:** The SIRFLOX trial investigated the efficacy and safety of adding radioembolization using yttrium-90 resin microspheres (SIRT) to standard fluorouracil, leucovorin, and oxaliplatin (FOLFOX)-based chemotherapy in patients with previously untreated mCRC comparing it to standard treatment with FOLFOX-based chemotherapy. In this post-hoc analysis, the study population was stratified for sex (male versus female) using Propensity Score Matching (PSM) with baseline variables with difference (p-value < 0.20) in a gender specific comparison serving as matching covariates (age, BSA, sidedness, bilirubin). Groups were matched in a 1:1 ratio, with the nearest calculated propensity logit, with a caliper width of $\leq$ 0.20 of the SD of the propensity score logit. Evaluated efficacy endpoints were progression-free survival (PFS, primary endpoint of the trial) and overall survival (OS). **Results:** 356 (67.2%) male and 173 (32.6%) female patients were randomized and treated in the SIRFLOX trial. In the overall study population, there was no difference regarding PFS or OS between male and female patients. No difference in PFS and OS between male (n = 101) and female (n = 101) patients could be observed independently of treatment arm. After PSM, female patients showed significant benefit regarding PFS from SIRT + chemotherapy compared to chemotherapy alone (12.2 [9.9-17] vs. 9.9 [7.5-12.7], p = 0.047) that translated into a trend to longer OS (27.3 [25.6-36.5] vs. 23.7 [17.8-28.8] months, p = 0.094, HR 0.68 [0.43-1.10]) while male patients did not show a difference regarding PFS and OS between treatment arms (p = 0.170, HR 1.41 [0.87-2.10]). In the experimental arm, female patients had significantly longer OS compared to male patients (27.3 [25.6-36.5] vs. 21.0 [17.9-26.7] months, p = 0.031, HR 0.64 [0.42-0.96]). Sex did not impact on OS in the chemotherapy arm (p = 0.410, HR 1.22 [0.76-2.02]). **Conclusions:** In the SIRFLOX trial, female patients seem to benefit from the addition of SIRT to chemotherapy regarding PFS and OS. This was not observed in male patients. To our knowledge, this is the first analysis to show sex-differences in the application of SIRT in patients with mCRC. Our results support the development of specific protocols according to sex. Clinical trial information: NCT00724503. Research Sponsor: None.

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Poster Session

Associations between early tumor shrinkage (ETS)/depth of response (DpR) and overall and post-progression survivals (OS/PPS) from the Analysis and Research in Cancers of the Digestive System (ARCAD) database. *First Author: Hideaki Bando, Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan*

Background: According to the various types of clinical trials for metastatic colorectal cancer (mCRC), ETS and DpR are suggested as the surrogates of OS. Whereas associations between ETS/DpR and OS/PPS in the era of chemotherapy (chemo) +anti-EGFR antibody (ab)/bevacizumab (bev) in 1st line therapy have not been elucidated. **Methods:** From 40,889 Individual patient data (IPD) from 59 studies in ARCAD mCRC database, 2,138 treatment-naïve pts with RAS wild-type (wt) mCRC were selected from 7 randomized studies (PRIME, CAIRO2, CRYSTAL, OPUS, CALGB80495, WJOG4407G, ATOM) of chemo with/without anti-EGFR ab or bev. The ETS was defined as 20% $\geq$ tumor shrinkage at 8 $\pm$ 2wks (ETS+ $\geq$ 20%, ETS- < 20%). Multivariate Cox regression models for OS/PPS were performed to investigate associations between ETS+ and ETS- by primary tumor location (overall/left-sided/right-sided), adjusting for potential confounders. DpR was defined as tumor shrinkage at nadir. OS/PPS were evaluated across quartile limits of DpR by multivariate Cox regression models. **Results:** In pts with overall or left-sided RAS wt mCRC, adjusted hazard ratios (HRs) of OS/PPS between ETS- and ETS+ for chemo +anti-EGFR ab, chemo +bev, and chemo alone showed great improvement, respectively (Table). In pts with overall or left-sided RAS wt mCRC, HRs of ETS for OS/PPS are higher in pts treated with chemo +anti-EGFR ab compared to those treated with chemo +bev or chemo alone. Compared to the pts with highest quartile (defined as $\geq$ 75th percentile (Q3)) of DpR, HRs of OS/PPS for lower quartile groups showed upward trends in pts with RAS wt & overall (Table). **Conclusions:** ETS/DpR in pts with RAS wt mCRC might be a potential prognostic marker of OS/PPS regardless of targeted therapy and primary tumor location. Superior prognostic values of ETS+ are expected in pts treated with anti-EGFR ab. Research Sponsor: ARCAD foundation and ARCAD-Asia.

		OS, HR (95%CI) *1			PPS, HR (95%CI) *1		
		Chemo +Anti-EGFR (N=912)	Chemo +BEV (N=512)	Chemo alone (N=711)	Chemo +Anti-EGFR (N=581)	Chemo +BEV (N=426)	Chemo alone (N=452)
ETS	RAS wt & overall	ETS- vs ETS+	2.03 (1.73-2.39)	1.64 (1.34-2.01)	1.46 (1.23-1.72)	1.82 (1.50-2.20)	1.45 (1.18-1.79)
	RAS wt & left-sided	ETS- vs ETS+	2.04 (1.66-2.51)	1.48 (1.13-1.95)	1.44 (1.18-1.76)	1.86 (1.46-2.37)	1.26 (0.95-1.67)
	RAS wt & right-sided	ETS- vs ETS+	1.99 (1.43-2.77)	2.05 (1.27-3.31)	1.26 (0.86-1.84)	1.56 (1.07-2.29)	1.00 (0.63-1.60)
DpR	RAS wt & overall	ETS- vs ETS+	<Q1 3.33 (2.75-4.03)	2.34 (1.75-3.13)	4.01 (3.16-5.08)	2.61 (2.07-3.30)	2.01 (1.49-2.72)
		$\geq$ Q1, <median	2.95 (2.40-3.63)	2.08 (1.54-2.81)	2.18 (1.71-2.78)	2.51 (1.96-3.21)	1.68 (1.35-2.48)
		$\geq$ median, <Q3	1.84 (1.51-2.24)	1.43 (1.05-1.95)	1.94 (1.51-2.49)	1.66 (1.30-2.13)	1.42 (1.04-1.94)
		$\geq$ Q3					1.87 (1.38-2.54)

*1 Adjusted for age, gender and ECOG-PS.

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Poster Session

Reversion of *RAS* mutations in metastatic colorectal cancer in the CCTG CO.26 clinical trial. First Author: Florence T.H. Wu, University of British Columbia & BC Cancer, Vancouver, BC, Canada

Background: *RAS* mutations in metastatic colorectal cancer (mCRC) drive resistance to anti-EGFR antibodies. It is unclear if *RAS* mutations are ever clonally lost, potentially uncovering a new therapeutic option for patients over time. **Methods:** We examined the temporal evolution of *RAS* mutation status among patients enrolled in CO.26 [NCT02870920] – a phase II clinical trial that assessed durvalumab + tremelimumab in patients with heavily pretreated mCRC – using whole exome sequencing (WES) of archival primary tumor tissue and circulating tumor DNA (ctDNA) sequencing of serial plasma samples that were taken at baseline, week 8 and on progression. **Results:** Six out of 95 (6.3%) patients diagnosed with *KRAS*/*NRAS*-mutated mCRC showed 'neo-*RAS*-wildtype' reversions at the time of baseline or week-8 ctDNA collection for the CO.26 trial. The majority (4/6) had falling tumor mutation burden (TMB) but stable or rising maximum mutation allele frequency (MAF) when reversions occurred. These were unlikely false negatives from non-secreting cancers as there were continued strong presence of other somatic clonal mutations (e.g., *TP53*, *ATM*). The majority (4/6) of reversions were transient, with mutations reappearing with progressive disease. 'Neo-*RAS*-wildtype' reverts had numerically longer median overall survival (OS) from date of cancer diagnosis to death compared to those with persistent *RAS* mutations (7.7 vs. 4.2 yrs, HR = 0.65, 95% CI 0.31 to 1.36, log-rank $P=0.26$). However, 'neo-*RAS*-wildtype' reverts were earlier-stage at diagnosis compared to those with persistent *RAS* mutations (33% vs. 63% had synchronous metastases, $\chi^2 P=0.15$), and had lower disease burden upon enrollment (50% vs. 68.5% had liver metastases, $P=0.17$; 33% vs. 75% had > 4 lesions, $P=0.03^*$). Survival from stage IV diagnosis to death did not differ between those with reverted vs. persistent *RAS* mutations (median 3.8 vs. 3.2 yrs, HR = 0.77, 95% CI 0.35 to 1.72, $P=0.52$). 'Neo-*RAS*-wildtype' reversions were not associated with side of primary tumors ($P=0.41$), archival *BRAF*/*MEK*/*ERK*-mutant status ($P=0.16$, 1.00, 0.09), baseline *HER2* amplifications ($P=1.00$), or baseline TMB ($P=0.21$). **Conclusions:** We identified a 6.3% prevalence of 'neo-*RAS*-wildtype' reversions in the CO.26 trial, however only 2.1% of patients had persistent loss when serial time points were considered. Further research is needed to understand if 'neo-*RAS*-wildtype' reverts may benefit from anti-EGFR therapy. Clinical trial information: NCT02870920. Research Sponsor: The Canadian Clinical Trials Group is funded by the Canadian Cancer Society.

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Poster Session

Predictive impact of *RNF43* mutation (mut) in patients (pts) with pMMR/MSS *BRAF V600E* mutated metastatic colorectal cancer (mCRC) treated with target therapy (TT) or chemotherapy (CT). First Author: Marco Maria Germani, Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa & Unit of Medical Oncology 2, Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy

Background: Encorafenib plus cetuximab is a standard option in the treatment of *BRAF V600E* mut mCRC pts pre-treated with at least one systemic therapy. *RNF43* is a negative regulator of WNT pathway. A recent study showed that *RNF43* mutation is associated with better outcome among pMMR/MSS *BRAF V600E* mut mCRC patients treated with TT but not in an independent cohort of pts not treated with TT (Elez et al. Nat Med 2022). However, no comparison is available between TT vs CT as second-line (2L) treatment for pMMR/MSS *BRAF V600E* mut mCRC according to *RNF43* mutational status. **Methods:** The predictive impact of *RNF43* mut was evaluated in a real-life dataset of 126 pMMR/MSS *BRAF V600E* mut mCRC pts treated with TT (consisting of *BRAF* inhibitor + anti-EGFR antibody $\pm$ MEK inhibitor) vs CT $\pm$ target agent as 2L treatment. A cohort of 36 pts receiving TT after 2L was also analyzed. **Results:** Thirty-one (25%) and 95 (75%) out of 126 pMMR/MSS *BRAF V600E* mut tumours were *RNF43* mut and *RNF43* wt, respectively. In the *RNF43* mut group 14 (45%) received CT and 17 (55%) TT; in the *RNF43* wt group, 56 (59%) and 39 (42%) received CT and TT, respectively. Among *RNF43* mut pts, those treated with TT reported longer PFS (7.1 vs 3.0 months, HR: 0.35 95%CI: 0.16-0.76, $p=0.006$) and higher ORR (42% vs 0%, $p=0.009$) than those receiving CT. On the other hand, no significant difference was observed among *RNF43* wt patients in terms of PFS (4.3 vs 3.7 months, HR: 0.69 95% CI: 0.45-1.05, $p=0.080$) and ORR (28% vs 16%, $p=0.24$). However, no significant interaction between treatment effect and *RNF43* mutational status was reported in terms of PFS ($p_{\text{interaction}}=0.17$) and ORR ($p_{\text{interaction}}=0.96$). After excluding 36 pts in the CT group that received TT after 2L, no interaction effect was observed also in terms of OS ($p_{\text{interaction}}=0.53$). However, among *RNF43* mut pts, those treated with TT reported longer OS (16.5 vs 10.1 months; HR: 0.34 95% CI: 0.11-1.00, $p=0.049$), while no significant difference was observed among *RNF43* wt pts (10.6 vs 6.6 months; HR: 0.66 95% CI: 0.39-1.11; $p=0.12$). In the group receiving TT after 2L, 9 (25%) out of 36 cases were *RNF43* mut and achieved higher ORR (78% vs 26%, $p=0.014$) and longer PFS (10.1 vs 4 months; HR: 0.35 95%CI: 0.14-0.88; $p=0.020$) and OS (11.7 vs 7 months; HR: 0.35 95%CI: 0.15-0.82; $p=0.012$) than *RNF43* wt (N = 27). **Conclusions:** pMMR/MSS *BRAF V600E* mut mCRC patients achieve benefit from TT vs CT independently of *RNF43* mutational status, but a higher magnitude of benefit from TT is observed among those with *RNF43* mut tumors. These findings deserve confirmation in past and current randomized trials (i.e. BEACON and BREAKWATER). Research Sponsor: None.

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Poster Session

Prognostic impact of depth of response (DpR) and early tumour shrinkage (ETS) in patients (pts) with *BRAF V600E* mutated (mut) metastatic colorectal cancer (mCRC) receiving targeted therapy (TT) as second-line treatment. First Author: Guglielmo Vetere, Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa & Unit of Medical Oncology 2, Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy

Background: Encorafenib and cetuximab (EC) is the standard of care for pre-treated patients (pts) with *BRAF V600E* mut mCRC. DpR and ETS previously showed a strong correlation with survival outcomes in mCRC pts receiving 1st-line therapy. We assessed these tumour dynamic response parameters and their association with clinical outcome in pts with *BRAF V600E* mut mCRC treated with TT in second-line. **Methods:** Patients treated in a real-life setting with EC or EC plus binitinib (ECB) in 20 Italian centres were included. Pts with measurable disease and at least one available disease reassessment by CT scan were eligible. Pts experiencing disease progression as best response (i.e. primary resistant) were not evaluable for DpR and ETS. Associations between DpR and ETS and progression free survival (PFS) and overall survival (OS) were tested by univariate and multivariate models. **Results:** 105 pts were included: 89 (85%) and 16 (15%) pts were treated with EC and ECB, respectively. Median PFS and OS were 5.2 and 10.3 mos, respectively. Twenty-nine pts (28%) were primary resistant, while 76 (72%) pts achieved disease control (51 [48%] and 25 [24%] pts had SD or CR/PR, respectively). Among baseline characteristics, the presence of peritoneal metastases was a predictor of primary resistance ($p=0.04$). Among pts evaluable for response parameters ($n=76$), median DpR was 15% and ETS occurred in 28 pts (37%). Mucinous histology was associated with a significantly lower magnitude of DpR ($p=0.005$) and a lower rate of ETS ($p=0.002$). A significant association between DpR and PFS was observed, both as a dichotomous (ie, $\geq$ or < median value) and continuous variable in univariate and multivariate analyses. Also RECIST response correlated with PFS in the two models (table). DpR was associated with OS in the univariate analyses, but this was not confirmed in the multivariate models (table). No correlation between ETS and survival, either as a dichotomous (ie, $\geq$ or < 20%) or a continuous variable, was observed. **Conclusions:** Having a DpR of at least 15% predicts longer PFS and OS in patients with *BRAF V600E* mut mCRC receiving TT as second-line treatment. An independent cohort of pts treated with second-line chemotherapy +/- antiangiogenic is under investigation as control group. Research Sponsor: None.

	DpR Continuous	DpR $\geq$ 15%	DpR < 15%	RECIST CR+PR	RECIST SD
PFS					
HR (95% CI)	0.87* (0.77-0.96)	0.56 (0.34-0.93)		0.54 (0.33-0.88)	
<i>P</i>	.006	.017		.020	
OS					
HR (95% CI)	0.88* (0.78-0.98)	0.55 (0.33-0.92)		0.52 (0.30-0.90)	
<i>P</i>	.021	.024		.020	
HR (95% CI)	0.88* (0.75-0.99)	0.61 (0.34-1.07)		0.58 (0.33-1.04)	
<i>P</i>	.038	.075		.073	
Adj HR (95% CI)	0.93* (0.80-1.08)	0.78 (0.43-1.42)		0.70 (0.36-1.38)	
<i>P</i>	.293	.417		.307	

*for 10% increase.

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Poster Session

Transcriptomic signatures of MSI-high metastatic colorectal cancer to predict efficacy of immune checkpoint inhibitors. First Author: Claire Gallois, Institut du Cancer Paris CARPEM, APHP, Digestive Oncology Department, APHP.Centre - Université Paris Cité, Hôpital Européen G. Pompidou, Paris, France

Background: Microsatellite instability (MSI) is currently the only predictive biomarker of efficacy of immune checkpoint inhibitors (ICI) in metastatic colorectal cancers (mCRC). However, 10-40% of patients with MSI mCRC will experience a primary resistance to ICI. **Methods:** In a cohort of 103 patients with MSI mCRC treated with ICI, 3'RNAseq was performed from primary tumors resected before the beginning of ICI. Previously described single-cell transcriptomic signatures of tumor microenvironment (TME) were analysed. **Results:** The unsupervised clustering of this cohort allowed the identification of three clusters of tumors with distinct transcriptional profiles: cluster A ("stromal^{HIGH}-proliferation^{LOW}"), cluster B ("stromal^{HIGH}-proliferation^{MED}"), and cluster C ("stromal^{LOW}-proliferation^{HIGH}"), with an enrichment of patients progressing at first disease assessment under ICI in the cluster A (30% vs 12% in cluster B and 8.1% in cluster C, $p=0.074$). Progression-free survival (PFS) was also significantly shorter in patients belonging to cluster A, compared to clusters B or C ($p<0.001$) with 2-year PFS rates of 33.5%, 80.5% and 78.3%, respectively. Similar results were observed for overall survival (OS). In multivariate analysis, PFS was still significantly longer in patients belonging to cluster B (HR: 0.26 95%CI 0.11-0.58, $p=0.001$) and cluster C (HR: 0.35 95%CI 0.16-0.78, $p=0.01$), compared to patients belonging to cluster A (Table). No association of identified clusters with PFS during non-ICI-based regimens was identified. **Conclusions:** This unsupervised transcriptomic classification identified three groups of MSI mCRCs with different compositions of TME cells and proliferative capacities of TME/tumor cells. The "stromal^{HIGH}-proliferation^{LOW}" cluster is associated with a lower efficacy of ICI. Research Sponsor: None.

Multivariate analysis for progression-free survival according to the three unsupervised clusters.				
Characteristics	HR ¹	95% CI ¹		p-value
Unsupervised clustering				
Cluster A (stromal ^{HIGH} -proliferation ^{LOW})	—	—		
Cluster B (stromal ^{HIGH} -proliferation ^{MED})	0.26	0.11, 0.58		0.001
Cluster C (stromal ^{LOW} -proliferation ^{HIGH})	0.35	0.16, 0.78		0.010
ICI-based treatment line				
1	—	—		
≥ 2	2.26	1.0, 5.12		0.051
Type of ICI regimen				
monotherapy	—	—		
combination	0.62	0.30, 1.26		0.2
Age	1.02	1.00, 1.05		0.10
Gender				
male	1.31	0.64, 2.68		0.5
female	—	—		
Number of metastatic sites at ICI start				
1 or 2 sites	—	—		
more than 2 sites	1.59	0.78, 3.25		0.2
Neutrophil-to-Lymphocyte Ratio				
< 3	—	—		
≥ 3	0.60	0.29, 1.26		0.2

¹HR = Hazard Ratio, CI = Confidence Interval.

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Poster Session

Intermittent or continuous panitumumab plus FOLFIRI (FOLFIRI/PANI) for first-line treatment of patients (pts) with RAS/BRAF wild-type (wt) metastatic colorectal cancer (mCRC): An update of survival/toxicity and preliminary results of genomic alterations from IMPROVE study. *First Author: Antonio Avallone, Istituto Nazionale Tumori-IRCCS Fondazione G. Pascale, Napoli, Italy*

Background: IMPROVE is a randomized, non-comparative multicenter, phase 2 study which evaluated continuous, until progressive disease (PD), or intermittent FOLFIRI/PANI, in pts with unresectable and previously untreated RAS/BRAF wt mCRC. In the intermittent schedule 8 cycles were followed by a treatment free interval lasting until PD when another 8 cycles were restarted, continuing this strategy until PD occurred on treatment. Primary endpoints was progression-free survival on treatment (PFSOT) at 1 year. In a previous analysis the primary endpoint of the study was met and a reduced skin toxicity was observed in the intermittent arm. Here we report an updated analysis. **Methods:** Updated analysis includes PFSOT and toxicity with 9 months (mo) of additional follow-up. Moreover we report overall survival (OS), skin toxicity burden (STB) score and preliminary data on genomic alterations (GAs) in 46 pts with PD. STB score, incorporating both the frequency and the severity of skin toxicity, was obtained by summing all grades that the pts experienced across all treatment cycles. GAs were performed by NGS on circulating tumor DNA (ctDNA) from paired plasma samples (baseline and progression), focusing specifically on RAS, BRAF and PI3K mutations. **Results:** Pts received FOLFIRI/PANI continuously (arm A, 69 pts) or intermittently (arm B, 67 pts). Median number of FOLFIRI/PANI cycles administered per pt were (arm A/B) 13/16. In arm B, after induction treatment, 24/53 pts (45%) without PD had $\geq$ 2 rounds of 8 FOLFIRI/PANI cycles. ORR (arm A/B) was 63/57%. At a median follow-up of 28 mo (IQR: 21-37), median PFSOT (77% of events) was 11.4 mo (95% CI: 9.1-13.7) in arm A, and 18.1 mo (95% CI: 6.8-29.3) in arm B. Median PFSOT in left sided tumors was 11.7 mo (95% CI: 9.1-14.3) in arm A and 23.9 mo (95% CI: 15.0-32.9) in arm B, compared with 10.7 mo (95% CI: 7.3-14.1) and 7.9 mo (95% CI: 5.7-10.1) in right sided pts, respectively. OS (46% of events) was 31.0 mo (95% CI: 24.7-37.2) in arm A and 32.2 mo (95% CI: 23.6-40.8) in arm B. Main grade $\geq$ 3 toxicities were (arm A/B): skin 30/18%, neutropenia 25/24%; diarrhea 13/15%. Median STB score was 0.77/cycle (IQR: 0.20-1.06) in arm A and 0.36/cycle (IQR: 0.0-0.77) in arm B. GAs in baseline ctDNA were evidenced in 12/46 (26%) pts, persisting to PD in all but one pt. Among the 34 pts without baseline GAs, only 8 (23%) developed $\geq$ 1 acquired GAs (Acq-GAs) to PD. **Conclusions:** Updated analyses confirmed that intermittent FOLFIRI/PANI strategy produces a long PFSOT and a reduced skin severe and skin burden toxicity without any detrimental effect on OS. Preliminary data on Acq-GAs suggest that classical mutations associated with anti-EGFR resistance are infrequent with up-front use of anti-EGFR/chemotherapy. Clinical trial information: NCT04425239. Research Sponsor: partially funded by Amgen.

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Poster Session

Real-world comparison of triplet- versus doublet-chemotherapy with bevacizumab in patients with newly diagnosed metastatic colorectal cancer (mCRC). *First Author: William Joseph Chapin, Abramson Cancer Center at the University of Pennsylvania, Philadelphia, PA*

Background: Meta-analysis of five randomized intensification trials in mCRC demonstrated an overall survival (OS) benefit of triplet chemotherapy (5FU/leucovorin, oxaliplatin, irinotecan) plus bevacizumab (Triplet/Bev) compared to doublet chemotherapy plus bevacizumab (Doublet/Bev) (HR 0.81). Guidelines recommend first-line Triplet/Bev for patients with excellent performance status and normal organ function who can withstand increased toxicity, but such patients are less represented in the real world. In this retrospective cohort study, we examine the real-world effectiveness of Triplet/Bev compared to Doublet/Bev in the U.S. **Methods:** We used the nationwide Flatiron Health electronic health record-derived database, comprising de-identified patient-level structured and unstructured data curated via technology-enabled abstraction from ~ 280 cancer clinics. Included were mCRC patients treated with first-line Triplet/Bev or Doublet/Bev between 10/23/14 and 10/31/22. OS by treatment was assessed using the Kaplan Meier method and adjustment for confounding variables was performed using Cox proportional hazards modeling with stabilized inverse probability of treatment weighting (IPTW). Pre-specified confounding variables included age, gender, race/ethnicity, year of metastatic diagnosis, health insurance, practice setting, KRAS/NRAS/BRAF mutation status, MMR/MSI status, synchronous/metachronous metastases, primary tumor sidedness, CEA, renal dysfunction, hepatic dysfunction, and ECOG performance status. Missing data were imputed using multiple imputation with chained equations. **Results:** Among 10,016 patients, 391 (3.9%) received Triplet/Bev and 9,625 (96.1%) received Doublet/Bev. Patients who received Triplet/Bev were younger (median age 52 vs 63 years) and were more likely to be treated at academic practices (27% vs 8%), to have synchronous metastatic disease (83% vs 65%), and to have KRAS/NRAS/BRAF wild-type disease (30% vs 17%). In the univariate analysis, median OS was 30.0 months (95% CI 24.7 – 34.7) in the Triplet/Bev cohort versus 23.4 months (95% CI 22.8 – 24.1) in the Doublet/Bev cohort (HR 0.73; 95% CI 0.62 – 0.85; $p < 0.001$). In Cox proportional hazards modeling with IPTW, there was no significant difference in hazard of death between Triplet/Bev and Doublet/Bev (HR 0.92; 95% CI 0.75 – 1.12; $p = 0.4$). **Conclusions:** In this large, national, real-world population of patients with mCRC, first-line treatment with Triplet/Bev was not associated with improved survival compared to Doublet/Bev after accounting for differences in baseline patient characteristics. The benefit to Triplet/Bev observed in randomized trials does not translate well to a more heterogeneous, real-world population. Sub-group analyses including by age, tumor sidedness, KRAS/NRAS/BRAF status, and baseline CEA level will be performed. Research Sponsor: None.

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Poster Session

Impact of WNT/B-catenin alterations and metastasis location among patients with metastatic colorectal cancer (mCRC) treated with immune checkpoint inhibitors (ICI) combinations. *First Author: Javier Ros Montaña, Vall d'Hebron Institute of Oncology (VHIO), Vall d'Hebron University Hospital, Barcelona, Spain*

Background: Emerging evidence suggests that WNT mutations and liver/peritoneal metastases in mCRC may have an immunosuppressive role that could affect ICI activity. **Aim:** To evaluate the impact of WNT alterations and liver/peritoneal metastasis among patients with mCRC treated with ICI. **Methods:** Patients from Vall d'Hebron Hospital, with mCRC treated with ICI from 2017-2022 were included. WNT alterations (APC, AXIN1/2, CTNNB1, FBXW7, EPHB2, RNF43 and SOX9) were evaluated using NGS (tissue). Clinical outcomes were calculated using survival Kaplan-Meier curves. Patients' characteristics were collected retrospectively. **Results:** Overall, 104 patients were included (66 MSI patients and 38 MSS patients). Among MSI patients, median age was 63 years (22-95), with 53% female, and 64% of patients received immunotherapy in 1st or 2nd line. Regarding tumor characteristics, 72% were right-sided and 82% harbored WNT alterations. 75% of patients presented with liver/peritoneal metastases. Patients with WNT mutations and peritoneal/liver metastases exhibit lower ORR (46% vs 57% $p < 0.5$ and 45% vs 75%, $p < 0.03$ respectively). Peritoneal/liver metastases were associated with lower PFS (HR 3.6 CI95% 1.27-10.24 $p < 0.02$ respectively). Overall, tumors with WNT pathway alterations tend to have shorter PFS and OS. Liver metastases were associated with lower OS (NR vs 34 months HR 2.49 CI95% 1.01-6.17 $p < 0.05$). Table summarizes outcomes. Among MSS patients, median age was 57 years (41-75), with 25% female and 92% of patients receiving immunotherapy $\geq$ 3rd line. Regarding tumor characteristics, 78% were left-sided and 90% harbored WNT alterations. 79%, of patients presented with liver or peritoneal metastases. WNT mutations were not associated with ORR, patients without liver/peritoneal metastases tend to have higher ORR (12.5% vs 3.3% $p < 0.335$). Patients with WNT alterations had worse PFS (9.23 vs 1.87 months, $p < 0.12$), and liver metastases were associated with lower PFS (6.98 vs 1.79 months HR 2.87 CI95% 1.17-7.09 $p < 0.02$). Regarding OS, tumors harboring WNT alterations have shorter OS (8.4 vs 12 months $p < 0.63$). The presence of liver or peritoneal metastases was associated with lower OS (NR vs 7.85 months HR 3.69 CI95% 1.09-12.55 $p < 0.04$). **Conclusions:** In our cohort, WNT pathway mutations, and liver metastases were associated with worse ORR, PFS, and OS regardless of MSI status. These findings need further validation in a prospective cohort. Research Sponsor: This research has been partially funded by CaixaResearch Advanced Oncology Research Program supported by Fundació La Caixa (LCF/PR/CE07/50610001).

	MSS n:38				MSI n:66			
	Liver (Y/N)	Peritoneal (Y/N)	Liver or Peritoneal (Y/N)	WNT mutation (Y/N)	Liver (Y/N)	Peritoneal (Y/N)	Liver or Peritoneal (Y/N)	WNT mutation (Y/N)
ORR (%)	3.3 vs 12.5	12.5 vs 3.3	3 vs 12.5	3.7 vs 0	47 vs 57	44 vs 65	45 vs 75	46 vs 57
PFS (months)	1.79 vs 6.9	2 vs 1.86	1.79 vs 6.9	1.87 vs 9.23	7.26 vs 16	6.5 vs NR	7.75 vs NR	10.25 vs NR
OS (months)	7.8 vs NR	9.13 vs 8.28	7.8 vs NR	8.44 vs 12	34 vs NR	45 vs NR	45 vs NR	37 vs NR

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Poster Session

Modified FOLFOXIRI plus cetuximab and avelumab as initial therapy in RAS wild-type unresectable metastatic colorectal cancer: Results of the phase II AVETRIC trial by GONO. *First Author: Veronica Conca, Unit of Medical Oncology 2, Azienda Ospedaliera Universitaria Pisana, Pisa, Italy and Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, Pisa, Italy, Pisa, Italy, Italy*

Background: The modified schedule of FOLFOXIRI (mFOLFOXIRI) in combination with an anti-EGFR agent showed a manageable safety profile and remarkable activity in RAS wild-type (wt) metastatic colorectal cancer (mCRC). The association of an active cytotoxic regimen with cetuximab (cet) may increase the exposure of tumour-associated neoantigens and induce immunogenic cell death and antibody-dependent cell-mediated cytotoxicity thus enabling the effect of immune checkpoint inhibitors. The AVETRIC study aimed at exploring the efficacy and safety of first-line mFOLFOXIRI plus cet and avelumab (ave) in RAS wt mCRC patients (pts). **Methods:** AVETRIC is a prospective, open label, multicenter, phase II, single arm trial in which initially unresectable and previously untreated RAS wt mCRC pts received mFOLFOXIRI (irinotecan 150 mg/sqm, oxaliplatin 85 mg/sqm, folinate 200 mg/sqm leucovorin [LV], and 5-fluorouracil [5FU] 2400 mg/sqm) plus cet (500 mg/sqm) and ave (800 mg) every 2 weeks up to 12 cycles followed by maintenance with 5FU/LV plus cet and ave until disease progression. A safety run-in phase including the first 6 enrolled pts was planned. Due to the occurrence of grade 3-4 diarrhoea in 2 (33%) pts, the protocol study was amended to reduce the irinotecan dose to 130 mg/sqm. Primary endpoint was Progression Free Survival (PFS). Fifty-eight pts were needed to detect an increase in median PFS (mPFS) from 10.0 to 19.4 months (mos), setting one-sided α and β errors at 0.05 and 0.10, respectively. The trial is registered at Clinicaltrial.gov, NCT04513951. **Results:** Between Jun 2020 and Dec 2021, 62 pts were enrolled in 16 Italian centres. Main pts' characteristics were: median age 56 yrs, ECOG PS 0 87%, synchronous metastases 94%, liver-only disease 42%, left-sided primary tumour 89%; all pts had BRAF wt and proficient MMR (pMMR) tumours. The primary endpoint was met. At a median follow-up of 16.0 months, 39 (63%) events were recorded and mPFS was 14.1 months (90% CI 12.0-16.7, Brookmeyer-Crowley test $p < 0.001$). Response rate and disease control rate were 82% and 98%, respectively, and R0 resection rate was 21% (27% in liver-only subgroup). Early tumour shrinkage was achieved in 74% pts and median deepness of response was 56%. In pts treated after study amendment ($n = 56$), main grade 3-4 adverse events were neutropenia (27%), diarrhoea (27%), skin rash (14%), asthenia (14%), nausea (11%), stomatitis (7%), febrile neutropenia (2%). Grade 3-4 immune-related adverse events occurred in 6% of pts. Overall survival results are still immature. **Conclusions:** AVETRIC study met its primary endpoint, showing that combining mFOLFOXIRI plus cet and ave achieves promising results in terms of PFS as well as response rate, in pts with pMMR RAS and BRAF wt mCRC. Translational analyses to evaluate the impact of immune-related biomarkers are ongoing. Clinical trial information: NCT04513951. Research Sponsor: GONO Foundation; This study was financially supported by Merck Serono S.p.A., Rome, Italy, an affiliate of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945).

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Poster Session

Exploring the prognostic and predictive impact of genomic loss of heterozygosity (LOH) in patients with metastatic colorectal cancer (mCRC). *First Author: Martina Carullo, Unit of Medical Oncology 2, Azienda Ospedaliera Universitaria Pisana and Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, Italy, Pisa, Italy*

Background: Genomic LOH consists in the loss of chromosomal regions and is associated with the homologous recombination repair (HRR) system deficiency (dHRR). In ovarian cancer, LOH-high predicts benefit from platinum-based chemotherapy and PARP inhibitors. In mCRC, the role of LOH has been poorly investigated. **Methods:** An NGS-based assay (FoundationOne CDx; Foundation Medicine, Inc. Cambridge, MA) was used to determine the percentage of genomic LOH and the presence of pathogenic mutations in HRR-related genes in archival chemo-naïve tumor tissues of mCRC patients included in a real-world registry and in the AtezoTRIBE (NCT03721653) and AVETRIC (NCT04513951) studies. Both these trials assessed the combination of an anti-PDL1 (atezolizumab or avelumab) with the triplet FOLFOXIRI plus bevacizumab or cetuximab. The prespecified cut-off of ≥ 14.08 for LOH-high described for mCRC (Sokol et al., JCO Precis Oncol 2020) was adopted. Tumors with at least one biallelic alteration in any of the 27 genes involved in the HRR pathway (Riaz et al., Nat Commun 2017) included in the FoundationOne CDx panel (BARD1, BRCA1, BRCA2, BRIP1, MRE11A, NBN, PALB2, RAD51, RAD51B, RAD51C, RAD51D, RAD52, RAD54L, RBBP8, XRCC2, ABL1, ATM, ATR, BAP1, CDK12, DNMT3A, ERCC4, FANCA, FANCC, FANCG, FANCL, PARP1) were defined dHRR. **Results:** Overall, 196 samples were analysed. None of 7 MSI-H tumors were classified as LOH-high. Fourteen (7%) and 6 (3%) of 189 MSS tumors were classified as LOH-high and dHRR, respectively. In particular, in LOH-high subgroup, 3 (21%) tumors were defined dHRR, while 3 (50%) tumors were classified LOH-high among dHRR tumors. LOH-high tumors were more frequently BRAF mutated ($p = 0.019$) and dHRR ($p = 0.006$) compared to LOH-low. Among patients receiving triplet chemotherapy +/- biologic agent alone ($N = 55$) or with an anti-PDL1 ($N = 58$), an interaction effect was shown between the effect of the addition of the checkpoint inhibitor and LOH with higher benefit in the LOH-high subgroup ($N = 10$) in terms of both PFS ($p_{\text{interaction}} = 0.002$) and OS ($p_{\text{interaction}} < 0.001$). In the cohort of patients not receiving the anti-PDL1, longer PFS was observed in patients with LOH-low ($N = 125$) respect to LOH-high ($N = 6$) tumors (12.1 vs 5.1 months, HR: 0.11, 95%CI: 0.04-0.26, $p < 0.001$). No differences in PFS or OS were reported between patients treated with first-line oxaliplatin- ($N = 40$) vs irinotecan-based doublets ($N = 25$) or with the triplet FOLFOXIRI ($N = 55$) vs doublets ($N = 65$) according to LOH status. No prognostic or predictive impact of HRR deficiency was shown. **Conclusions:** In MSS mCRC, LOH-high was associated with biallelic alterations in the HRR system, worse prognosis and higher benefit from the addition of anti-PDL1 agents to chemotherapy. Considering the low number of LOH-high tumors in our study, these results deserve confirmation in larger cohorts. Research Sponsor: None.

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Poster Session

Single nucleotide polymorphisms (SNPs) in MHC class I and II genes to predict outcome in patients (pts) with metastatic colorectal cancer (mCRC): Data from FIRE-3, MAVERICC, and TRIBE trials. *First Author: Pooja Mittal, Division of Medical Oncology, USC Norris Comprehensive Cancer Center, Keck School of Medicine, Los Angeles, CA*

Background: The immune system is alerted for virally infected cells in the body by the antigen presentation pathway, which is in turn mediated by the major histocompatibility complex (MHC) class I and II molecules. Cancer cells overcome immune evasion as a major hallmark by downregulation of antigen presentation pathway molecules. Therefore, the present study aimed to explore the effect of genetic variants in MHC class I and II pathways on first-line treatment outcome in mCRC pts. **Methods:** Genomic DNA from blood samples of 775 pts enrolled in three independent, randomized, first-line trials: TRIBE (FOLFIRI-bevacizumab [bev], $N = 215$), FIRE-3 (FOLFIRI-bev, $N = 107$; FOLFIRI-cetuximab [cet], $N = 129$) and MAVERICC (FOLFIRI-bev, $N = 163$; FOLFOX-bev, $N = 161$) was genotyped through OncoArray, a custom array manufactured by Illumina including approximately 530K SNP markers. The impact on outcome of 40 selected SNPs in 22 genes of MHC class I and II pathways (ERAP1, ERAP2, TAP1, TAP2, TAPBP, B2M, HLA-A, HLA-B, HLA-C, HLA-E, HLA-F, HLA-G, CIITA, HLA-DMA, HLA-DMB, HLA-DOA, HLA-DOB, HLA-DPA1, HLA-DPB1, HLA-DQA1, HLA-DQB1 and HLA-DRA) was analyzed. **Results:** We identified several SNPs in multiple genes associated with targeted treatment benefit across different treatment arms in our study population ($P < .05$). Germline variants in ERAP1 rs2287987 were associated with worse PFS in pts receiving FOLFIRI-bev in TRIBE (10.4 vs 8.8 months, HR 1.48, 95%CI 1.04-2.12, $P = .035$) and FIRE-3 trials (11.1 vs 9.9 months, HR 3.46, 95%CI 1.18-10.12, $P = .049$), while rs26653 SNP in the same gene was associated with better PFS in MAVERICC (10.1 vs 14.5 months, HR 0.54, 95%CI 0.35-0.84, $P = .0062$). TAP1 rs1135216, TAP2 rs1800454 and rs1044043, HLA-B rs2770, HLA-G rs1610696, CIITA rs4774, HLA-DRA rs7192 were associated with longer OS and/or PFS in cet-treated pts in FIRE-3; whereas TAP2 rs241447, TAPBP rs3106191, HLA-DNB rs10751, HLA-DOB rs11244, HLA-DPB1 rs3097671 showed worse PFS and/or OS. SNPs in TAP2 (rs1800454), HLA-C (rs1049281), HLA-G (rs1063320), CIITA (rs1139564), HLA-DMB (rs1042337), HLA-DOA (rs375256, rs129303), HLA-DPA1 (rs1042190) and HLA-DRA (rs7192) were specifically associated with clinical outcomes in the FOLFOX-bev arm of MAVERICC but not in control cohorts of pts treated with FOLFIRI-bev. Treatment-SNP interaction analyses with targeted agents (bev vs cet) and chemotherapy backbone (FOLFIRI vs FOLFOX) confirmed a significant treatment interaction for HLA-G, TAP2, CIITA, and HLA-DMB SNPs ($P < .05$). **Conclusions:** Our results highlight an important role for MHC SNPs as prognostic and predictive biomarkers for first-line treatment in mCRC, with differential effects based on biologic agent and chemotherapy backbone. These biomarkers, when further validated, may contribute to personalized treatment strategies for mCRC patients. Research Sponsor: National Cancer Institute, Gloria Borges WunderGlo, Dhont Family, San Pedro Peninsula Cancer Guild, Daniel Butler Research Fund, Victoria and Philip Wilson Research Fund, Fong research project, Ming Hsieh research fund.

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Poster Session

Analysis of primary and acquired resistance to cetuximab from multiomic data in the New EPOC trial. *First Author: Sian Alexandra Pugh, Department of Oncology, Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom*

Background: The use of cetuximab (cetux) with chemotherapy (chemo) in patients with operable liver metastases from colorectal cancer (CRC) conferred a survival disadvantage in New EPOC. Whilst genetic alterations such as emergent sub-clonal mutations in RAS/BRAF, ERBB2 and MET are recognized as mechanisms of resistance to EGFR inhibition (EGFRi), divergent mechanisms such as transcriptomic changes may also be responsible. Of the CRC intrinsic subtypes (CRIS), CRIS-C has elevated EGFR signalling and is thought to have greater sensitivity to EGFRi. **Methods:** Resected primary tumors ($n = 205$; pre neoadjuvant treatment) and/or liver metastases ($n = 144$; post neoadjuvant treatment) from 223 patients, wild type for KRAS (codons 12/13/61) at trial entry, randomized to chemo +/- cetux underwent targeted NGS and/or transcriptome profiling. Primary clinical endpoints were progression free (PFS) and overall survival (OS). **Results:** Repeat NGS identified additional RAS/BRAF mutations in primary tumors from 49 patients (25 KRAS, 15 NRAS, 9 BRAF V600E). Of the 148 patients with confirmed RAS/BRAF wild type primary tumors, 46% were classified as CRIS-C with the remainder being CRIS-A (9.5%), CRIS-B (11%), CRIS-D (8.8%) or CRIS-E (8.1%). CRIS-C patients had a similar PFS with ChemoCetux vs Chemo (HR 0.84 95% CI 0.47-1.5 $p = 0.55$) whereas non-CRIS-C had a shorter PFS (HR 2.12 95%CI 1.24-3.63 $p = 0.006$; p interaction 0.021). OS results were similar (p interaction 0.067). In liver metastases, genetic changes were comparable (Chemo vs ChemoCetux): KRAS (4.1% v 2.1%), NRAS (4.1% v 0%), BRAF V600E (0% v 0%), ERBB2 gain/amplification (20% v 21%) and MET gain/amplification (25% v 18%). However, gain/amplification of MET resulted in shorter OS with ChemoCetux vs Chemo (HR 5.13 95%CI 1.38-19.15 $p = 0.015$) whereas those without MET gain/amplification had a similar OS (HR 1.32 95%CI 0.76-2.28 $p = 0.32$; p interaction 0.029). The same association was found after excluding liver metastases with RAS/BRAF mutations ($n = 101$, p interaction 0.030). Differential expression/mutation analyses did not identify other stratifiers after false discovery correction. **Conclusions:** The shorter survival with ChemoCetux was restricted to patients with a non CRIS-C subtype before treatment supporting the use of this transcriptomic classifier to stratify for EGFRi. After neoadjuvant treatment, gain/amplification of MET was associated with a shorter survival with ChemoCetux. By contrast MAPK pathway mutations were largely unchanged supporting earlier findings that alternative resistance mechanisms predominate when EGFRi is combined with chemotherapy. In summary these results highlight the heterogeneity and differential responses to EGFRi that exist within RAS/RAF wild type CRC and provide insights into the substantial survival detriment observed in the New EPOC trial. Clinical trial information: ISRCTN22944367. Research Sponsor: Cancer Research UK (C317/A7275), Medical Research Council UK.

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Poster Session

Nipavect: Phase II study of niraparib and panitumumab in advanced RAS WT colorectal cancer. *First Author: Olatunji B. Alese, Winship Cancer Institute of Emory University, Atlanta, GA*

Background: Panitumumab (Pmab) is a recombinant monoclonal antibody that binds specifically to the human epidermal growth factor receptor (EGFR) and it is indicated for the treatment of metastatic colorectal carcinoma (mCRC). However, the objective response rates (ORR) for the single agent are historically about 8-11%. EGFR inhibition induces synthetic lethality with poly ADP ribose polymerase inhibitors (PARPi) such as Niraparib, by attenuating DNA repair pathways. Combining PARP and EGFR inhibition has the potential to confer synergistic benefit, while also ameliorating resistance mechanism to EGFRi. We conducted this study to define the safety and efficacy of the combination of Niraparib and Pmab in RAS wildtype (WT) mCRC. **Methods:** Patients (pts) with RAS WT mCRC who have progressed on at least one line of systemic chemotherapy were eligible for the trial. Other selected inclusion criteria were ≥ 18 years of age, ECOG PS 0-1 and measurable disease per RECIST 1.1. Pmab was administered at 6 mg/kg IV on days 1 & 15 of each 28-day cycle, while Niraparib was taken orally at 200mg or 300mg (based on body weight and platelet count) daily throughout the cycle. The primary endpoint was clinical benefit rate (CBR) defined as complete (CR) + partial (PR) response + stable disease (SD) per RECIST v1.1. Multiple secondary endpoints included safety/tolerability, ORR, progression-free survival (PFS), overall survival (OS), and duration of response (DoR). **Results:** A safety run-in cohort of 6 pts was initially enrolled. Following a preplanned safety analysis showing an acceptable toxicity profile, an additional 19 pts were enrolled. Of the total 25 enrolled pts, 24 were evaluable for response. Male - 50%; Whites/African Americans/Asians - 65.2%/21.7%/13%; median age - 58.5yrs. The majority had left sided tumor (92%) and the median line of prior therapy was 2 (range 1-4). CBR was 83.3% (0 CR, 6 PR, 14 SD) and ORR was 25%. mPFS - 5.6mos (95% CI: 3.7, 6.9); mOS - 20.9mos (95% CI: 9.2, NR). Six-month PFS and OS rates were 48.4% and 100% respectively. At a median follow up time of 7.5mos (95% CI: 4.2, 10.4), 3 patients remained on treatment and DoR was yet to be determined. Muco-cutaneous adverse events (AEs) of any grade included rash (58.4%), oral mucositis (20.8%), dry skin (16.7%) and paronychia (4.2%). Most common (grade > 2) treatment related AEs (TRAEs) were anemia (G3; 12.5%), dermatitis, oral mucositis, hypertension and neutropenia (G3; 4.2% each). There were no grade 4-5 TRAEs. **Conclusions:** The combination of Pmab and Niraparib had an acceptable safety profile, and showed considerable antitumor activity in pts with advanced RAS WT mCRC compared to historical rates. Additional biomarker analyses such as survival correlation with immune cell infiltration in paired skin biopsies and HER2/BRAF mutational status are ongoing. Funding and product (Niraparib) for the study were provided by GSK (NCT03983993). Clinical trial information: NCT03983993. Research Sponsor: GSK.

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Poster Session

OniLon: Phase II trial of trifluridine/tipiracil (TAS-102) and nanoliposomal irinotecan (nal-IRI) in advanced colorectal cancer. *First Author: Olatunji B. Alese, Winship Cancer Institute of Emory University, Atlanta, GA*

Background: TAS-102 (FTD/TPI) is a combination of a nucleoside analogue and a thymidine phosphorylase inhibitor, and has showed activity in 5FU-resistant CRC. Nal-IRI achieves higher intra-tumor concentrations than irinotecan (Iri; 142-fold) and its major metabolite, SN-38 (9-fold). This resulted in superior anti-tumor activity compared to free Iri in multiple tumor xenografts. Furthermore, multiple clinical trials have established the activity of nal-IRI in combination with 5FU in pancreaticobiliary cancers. The combination of nal-IRI with the more potent nucleoside analogue TAS-102 may thus result in a more effective systemic therapy. We conducted this study to define the safety and efficacy of the combination of TAS-102 and nal-IRI in advanced CRC. **Methods:** Eligible patients (pts) on this investigator-initiated phase II study had advanced CRC and must have had disease progression on at least one prior therapy. Additional inclusion criteria - measurable disease, ECOG PS 0-1 & adequate organ function. Based on previously published dose escalation phase I data, the pts were treated at the recommended phase II dose of TAS-102 (given orally at 35mg/m² bid on days 1-5) and nal-IRI (60mg/m² IV on day 1) in 14-day cycles. The primary endpoint was objective response rate (ORR) = complete (CR) + partial (PR) response per RECIST v1.1. Multiple secondary endpoints included safety/tolerability, progression-free survival (PFS), overall survival (OS), disease control rate (DCR) and duration of response (DoR). **Results:** Twenty-two pts were enrolled, of whom 20 were evaluable for response. Male - 50%; ECOG PS 1 - 75%; African Americans - 38%; median age - 58yrs (interquartile range [IQR] 49-67). Median line of prior therapy was 1 (IQR 1-2) and 13.6% (3 pts enrolled during the dose escalation phase) had received prior Iri. 47.6% received concurrent Bevacizumab. ORR was 15% (3 PR, 0 CR). 60% had stable disease (SD) as best response; DCR of 75%. mPFS - 9.7 mos (95% CI: 5.6, 14.2); mOS - 10.1 mos (95% CI: 7.3, 15.9). 12-month PFS and OS rates were 34.6% and 39.5% respectively. At a median follow up of 11.9 mos, DoR was yet to be determined and 50% of the pts had maintained response for 12 mos. Median duration of progression free among pts with SD was 7.6 mos (95% CI: 4.6, 13.2), with a 12-month survival rate of 47.7% (95% CI: 15.5%, 74.5%). Median time to response (TTR) was 4.8mos. Most common treatment related toxicities included fatigue and neutropenia (G3; 27.3% each); anemia and leucopenia (G3; 18.2% each). Other G3 AEs included febrile neutropenia, diarrhea, hypokalemia, lymphopenia and nausea (4.5% each). **Conclusions:** We demonstrated that the combination of TAS-102 and nal-IRI had an acceptable safety profile, and showed antitumor activity in patients with advanced CRC. Additional biomarker analyses such as survival correlation with UGT1A1 phenotype and RAS mutational status are ongoing. (NCT03368963). Clinical trial information: NCT03368963. Research Sponsor: Taiho; Ipsen.

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Poster Session

Efficacy and safety of fruquintinib plus investigator's choice of chemotherapy as second-line therapy in metastatic colorectal cancer: A multicenter, single-arm phase 2 trial. *First Author: Wensi Zhao, Renmin Hospital of Wuhan University, Wuhan, China*

Background: Emerging evidence suggested that chemotherapy in combination with anti-angiogenic targeted agents can achieve higher response in multiple solid tumors. Fruquintinib is a highly selective small-molecule VEGFR inhibitor that has been approved for the third-line treatment in metastatic colorectal cancer (mCRC) patients in China. Here, we assessed the efficacy and safety of fruquintinib plus investigator's choice of chemotherapy as second-line therapy in pretreated advanced mCRC patients. **Methods:** In this prospective, open-label, multicenter, single-arm phase 2 trial (ChiCTR2200059280), patients with mCRC progressed after first-line prior systemic treatment were administered fruquintinib (5-3mg, D1-21, Q4w) and investigator's choice of chemotherapy (fluorouracil ± irinotecan ± oxaliplatin, Q3w) for up to 8 cycles. Patients without disease progression (PD) were followed by fruquintinib maintenance until PD or intolerable toxicity. The primary endpoint was progression-free survival (PFS). Secondary endpoints included objective response rate (ORR), disease control rate (DCR), duration of response (DOR), overall survival (OS), and safety. **Results:** As the data cutoff on February 10, 2023, 37 patients have been enrolled and treated, with 31 evaluable for efficacy. Median age was 63 years (range, 44-76) and 22 (59.5%) were male. The left colon cancer involved in 28 patients (75.7%). All patients were microsatellite-stable phenotype and 11 (29.7%) had mutations in KRAS gene. 16 (43.2%) patients received prior anti-VEGF therapy. 20 (54.1%) and 11 (29.7%) patients had liver and lung metastases respectively. At a median follow-up of 8.4 months, 28 patients are still on treatment. The ORR is 48.4%, with 15 partial response. The DCR is 90.3%. At data cutoff, median PFS has not yet reached. 23 patients (74.2%) remained progression free at 6 months. In terms of safety, the regimen was well tolerated, mainly grade 1/2 adverse events (AEs). Grade 3/4 AEs were neutropenia (21.6%), leukopenia (10.8%), thrombocytopenia (5.4%), proteinuria, diarrhea, hand-foot syndrome and hypertension accounted for 2.7% respectively. 5 pts received reduced doses of fruquintinib. No treatment-related deaths occurred. **Conclusions:** Fruquintinib combined with chemotherapy followed by fruquintinib maintenance shows promising efficacy and manageable safety profile for mCRC patients in second-line setting. Updated follow up data will be presented in the future. Clinical trial information: ChiCTR2200059280. Research Sponsor: National Natural Science Foundation of China (grant no.82102954).

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Poster Session

Deep learning-derived spatial organization features on histopathology images to predict prognosis in patients with colorectal liver metastasis, after hepatectomy. *First Author: Xin Wang, Department of Surgery, The Chinese University of Hong Kong, Hong Kong SAR, China*

Background: Histopathological images of colorectal liver metastasis (CRLM) contain rich morphometric information that may predict patient outcomes, but current indicators depend on labor-intensive and subjective visual estimation. Herein, we aimed to develop an automated framework for tissue classification of routine H&E stained whole-slide images and establish a risk-scoring model for better prognosis prediction in patients with CRLM. **Methods:** Using 161,371 hand-delineated image patches, we trained a robust deep convolutional neural network-CRLM-SPA for accurate classification of CRLM into seven tissue types. With the tissue classification results on two independent in-house cohorts (SYSUCC: $n = 433$, BJCH: $n = 404$), we systematically quantified spatial organization features (SOFs), involving whole-slide, tumor-infiltrating and tumor-distal SOFs for different tissue types as well as the interactions between tumor and non-tumor tissues. Subsequently, univariate Cox proportional hazards regression analysis was performed to investigate the association between various SOFs and patient outcomes. Nonredundant SOFs that are clinically relevant were selected to build a risk-scoring model for prognosis using multivariate Cox regression analysis in the SYSUCC cohort, followed by validation in the BJCH cohort. **Results:** CRLM-SPA achieved an overall classification accuracy of $> 93\%$ in an independent set of 17,653 image patches. With the classification result, we calculated various SOFs and built a four-SOF risk-scoring model that significantly predicted overall survival (OS) in the discovery cohort, SYSUCC ($P = 1.40 \times 10^{-5}$; HR = 2.26; 95%CI: 1.55 - 3.29) and the independent validation cohort, BJCH ($P = 4.59 \times 10^{-4}$; HR = 2.00; 95%CI: 1.35 - 2.97). The prognostic performance of our SOF risk-scoring model is independent of the clinical risk score (CRS) system. Further stratification analyses in patients without preoperative chemotherapy (CTX) indicated that adjuvant CTX consistently improved OS in the SOF high-risk subgroups in both cohorts ($P = 0.018$ and 0.049), but not in the SOF low-risk subgroups. Furthermore, a combined scoring system incorporating SOF and CRS considerably improved the prognostic performance in both cohorts over the individual SOF and CRS systems. **Conclusions:** CRLM-SPA showed a high accuracy in tissue classification and robustness in extracting prognostic information from H&E images. The SOF risk-scoring system demonstrated a strong and robust prognostic value that is independent of CRS, and could therefore provide a time- and cost-efficient tool to assist clinical decision making for patients with CRLM. Research Sponsor: Science Technology and Innovation Commission of Shenzhen Municipality; Research Grants Council of the Hong Kong Special Administrative Region.

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Poster Session

The impact of sodium-glucose cotransporter-2 inhibitors on the outcome of patients with colorectal adenocarcinoma. *First Author: Cho Han Chiang, Mount Auburn Hospital, Harvard Medical School, Cambridge, MA*

Background: The mortality of colorectal cancer remains high despite the development of novel anti-neoplastic agents. Preclinical studies have shown that colorectal cancer upregulates the expression of sodium-glucose cotransporter 2 (SGLT2) channels and inhibition of these channels by SGLT2 inhibitors (SGLT2i) reduces tumor proliferation. We aimed to investigate the impact of SGLT2i on the outcome of patients with colorectal cancer. **Methods:** We conducted a retrospective cohort study by including all adult patients with colorectal adenocarcinoma and type 2 diabetes mellitus in two tertiary centers in Taiwan. SGLT2i and non-SGLT2i patients were matched 1:1 based on age, sex, and cancer stage. The primary outcome was overall survival (OS) and progression-free survival (PFS), and the secondary outcomes were previously reported serious adverse events associated with the use of SGLT2i. **Results:** We identified 1347 patients with colorectal cancer and type 2 diabetes mellitus, from which 92 patients in the SGLT2i cohort were matched to the non-SGLT2i cohort. Compared to non-SGLT2i recipients, SGLT2i recipients had a higher rate of OS (5-year OS: 86.2% [95% CI: 72.0-93.5] vs. 62.3% [95% CI: 50.9-71.8], $p = 0.013$) and PFS (5-year PFS: 76.6% [95% CI: 60.7-86.7] vs. 57.0% [95% CI: 46.2-66.4], $p = 0.021$). In Cox proportional hazard analyses, the use of SGLT2i was associated with a 50-70% reduction in the risk of all-cause mortality and disease progression. The rate of cancer-associated mortality was lower in the SGLT2i group (7% vs. 21%, $p = 0.005$). SGLT2i were not associated with an increased risk of sepsis, hypoglycemia, or acute kidney injury. We did not detect any cases of urosepsis or diabetic ketoacidosis in the SGLT2i group. **Conclusions:** The use of SGLT2i was associated with a higher rate of survival in colorectal cancer patients with diabetes mellitus. Research Sponsor: None.

Cox Regression hazard analysis comparing SGLT2i and non-SGLT2i.						
Outcomes	SGLT2i No. of cases	Non-SGLT2i No. of cases	Univariate hazard ratio (95% CI)	P-value	Multivariate hazard ratio ^a (95% CI)	P-value
Primary						
All-cause mortality	7 (8%)	26 (28%)	0.36 (0.15-0.84)	0.018	0.28 (0.10-0.81)	0.018
Disease progression	13 (14%)	32 (35%)	0.47 (0.24-0.90)	0.024	0.40 (0.18-0.86)	0.019
Secondary						
Acute kidney injury	5 (5%)	3 (3%)	3.59 (0.63-20.3)	0.149	2.94 (0.38-22.5)	0.30
Hypoglycemia	3 (3%)	4 (4%)	0.91 (0.20-4.09)	0.90	2.68 (0.32-22.4)	0.36
Sepsis	7 (8%)	12 (13%)	0.89 (0.33-2.40)	0.82	0.64 (0.18-2.30)	0.50
Urosepsis	0 (0%)	6 (7%)	-	-	-	-
Diabetic ketoacidosis	0 (0%)	0 (0%)	-	-	-	-

^aAdjusted for age, sex, cancer stage, Eastern Cooperative Oncology Group (ECOG) Performance Status, chemotherapy regimen, radiotherapy, hypertension, hyperlipidemia, chronic kidney disease, and chronic obstructive pulmonary disease.

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Poster Session

A phase II study of nivolumab and ipilimumab with radiation therapy in patients with metastatic, microsatellite stable colorectal cancer. *First Author: Julie L. Koenig, Harvard Radiation Oncology Program, Boston, MA*

Background: Immune checkpoint inhibitors (ICIs) have limited efficacy in patients with microsatellite stable (MSS) colorectal cancer (CRC). Radiation therapy (RT) may increase the response rate to ICIs through multiple mechanisms. In our phase 2 trial (NCT03104439), 40 patients with metastatic MSS CRC were enrolled to receive ipilimumab and nivolumab with RT (24 Gy/3 fractions) starting on C2D1. Among the 27 patients who received RT (33% dropout rate), the disease control rate (DCR) was 37% and objective response rate (ORR) was 15%. To confirm this signal and address dropout prior to RT, we conducted a phase 2 study of nivolumab and ipilimumab with RT moved to C1D1. **Methods:** In this open-label, single-arm, phase 2 study (NCT04361162), eligible patients had histologically confirmed metastatic MSS CRC, ECOG PS 0-1, and progressed on at least one line of chemotherapy. Treatment consisted of ipilimumab 1 mg/kg every 6 weeks for the first 4 cycles, nivolumab 240 mg every 2 weeks on a 6-week cycle, and RT with 24 Gy/3 fractions to one site starting on C1D1. Treatment continued until disease progression, discontinuation, or withdrawal. The primary endpoint was ORR outside of the RT field by RECIST 1.1 with radiological evaluations every 3 months. The treatment regimen was considered to have promising activity if at least 3 of 30 patients achieved an objective response in unirradiated lesions. Secondary endpoints included DCR, PFS, OS, and safety. A single-stage design was used to enroll 30 patients for intention-to-treat analysis of patients receiving at least one dose of study treatment. The per protocol analysis included patients who completed C1D1. The treatment regimen was considered to have promising activity if at least 3 of 30 patients achieved an objective response in unirradiated lesions, providing 85% power to reject 4% ORR in favor of 15% ORR at a significance level of 15%. **Results:** We enrolled and treated 30 patients (median age 56 years [range 28-85], 60% male, 83% white) from 10/2020 to 05/2022. Patients received a median of 2 (range, 1-7) prior lines of chemotherapy. All patients in the intention-to-treat population also met criteria for inclusion in the per protocol analysis. The ORR was 13% (4/30; 95% CI, 4-31%), DCR was 33% (10/30; 95% CI, 17-53%), median PFS was 2.4 months (95% CI, 1.8-2.9 months), and median OS was 10.6 months (95% CI, 6.8-17.8 months). 16 patients had grade 3+ treatment-related serious adverse events, including lymphopenia (3 patients with grade 4), anemia, diarrhea, colitis, vomiting, alkaline phosphatase increase, hypothyroidism, fatigue, and myositis. **Conclusions:** Treatment with ipilimumab, nivolumab, and RT starting on C1D1 showed promising activity in patients with traditionally immunoresistant metastatic MSS CRC. Further analyses are ongoing to evaluate optimal patient selection and radiation strategies. Clinical trial information: NCT04361162. Research Sponsor: Bristol Myers Squibb.

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Poster Session

Efficacy and safety of IBI351 (GFH925) monotherapy in metastatic colorectal cancer harboring KRAS^{G12C} mutation: Preliminary results from a pooled analysis of two phase I studies. *First Author: Ying Yuan, Department of Medical Oncology, The Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China*

Background: IBI351 (GFH925) is an irreversibly covalent inhibitor of KRAS^{G12C} and has demonstrated promising anti-tumor activity with acceptable safety in advanced solid tumors. Here, we report a pooled analysis of two phase I studies (NCT05005234, NCT05497336) evaluating the efficacy and safety of IBI351 (GFH925) monotherapy for metastatic colorectal cancer (CRC) harboring KRAS^{G12C} mutation. **Methods:** Eligible metastatic CRC patients (pts) with KRAS^{G12C} mutation were included. Pts received IBI351 (GFH925) orally at dose levels of 700mg once daily (QD), or 450/600/750mg twice daily (BID). The primary endpoint was objective response rate (ORR) assessed by investigator per RECIST v1.1. Data cutoff for the analyses was November 30, 2022 unless otherwise specified. **Results:** A total of 45 pts were enrolled (median age: 58.0 years; male: 57.8%; ECOG PS 1: 71.1%; pts with ≥2 prior lines of treatment: 66.7%), including 3, 4, 37, and 1 pts in 700mg QD, 450mg BID, 600mg BID, and 750mg BID cohorts, respectively. The median exposure to therapy was 84 days (range, 7-286), and 36 pts (80.0%) were still on treatment including one patient at 450mg BID with treatment exposure for 286 days. As of December 15, 2022, ORR was 47.5% (19/40, 95% CI: 31.5%-63.9%) and disease control rate (DCR) was 85.0% (95% CI: 70.2%-94.3%) for the efficacy-evaluable pts across all dose levels. The median duration of response (DOR) was not reached. For 32 efficacy-evaluable patients at 600mg BID, ORR and DCR were 43.8% (14/32) and 87.5%, respectively. Treatment-related adverse events (TRAEs) occurred in 40 (88.9%) pts, with the most common being anaemia, white blood cell count decreased, alanine aminotransferase increased, and pruritus. Grade ≥ 3 TRAEs occurred in 9 (20.0%) pts. No drug-related adverse events leading to treatment discontinuation or death occurred. **Conclusions:** IBI351 (GFH925) monotherapy demonstrated promising anti-tumor activity with manageable safety profile in metastatic CRC patients harboring KRAS^{G12C} mutation. These two studies are still ongoing and longer follow-up will provide more solid evidence. Updated data will be presented at the meeting. Clinical trial information: NCT05005234, NCT05497336. Research Sponsor: Innovent Biologics (Suzhou) Co., Ltd.

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Poster Session

Efficacy and safety of irinotecan-eluting HepaSphere transarterial chemoembolization combined with hepatic arterial infusion chemotherapy for unresectable colorectal liver metastases. *First Author: Aiwei Feng, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Interventional Therapy, Peking University Cancer Hospital & Institute, Beijing, China*

Background: Both drug-eluting bead transarterial chemoembolization (DEB-TACE) and hepatic arterial infusion chemotherapy (HAIC) are recommended for unresectable colorectal liver metastases (CRLM) treatment. However, the combined application of DEB-TACE and HAIC is not widely accepted. The aim of this single-center retrospective study was to evaluate the efficacy and safety of Irinotecan-eluting HepaSphere chemoembolization combined with HAIC for unresectable CRLM. **Methods:** Patients with age older than 18 years, histologically confirmed CRLM and treated with Irinotecan-eluting HepaSphere chemoembolization plus HAIC from Oct 2020 to Jan 2022 were enrolled. Patients who had synchronously received other local treatments were excluded. Hepatic progression-free survival (hPFS) and PFS were calculated using Kaplan-Meier method. Adverse events (AE) were evaluated with CTCAE 5.0. **Results:** The eligible population was 101, composed of 66 males and 35 females. Among them, 54% patients had one of KRAS or NRAS or BRAF gene mutation and ECOG of 62% patients was 1. In addition, 59% patients were refractory to second standard line or above systemic therapy and mean interventional treatment cycles were 3.3. As the follow-up cutoff date was Dec 31, 2022, median duration of follow-up was 17.9 months (95% CI, 16.185-19.615). Median hPFS was 8.7 months (95% CI, 6.744-10.658) while median PFS was 6.2 months (95% CI, 5.048-7.352). For the patients who were refractory to second line or above systemic therapy, hPFS and PFS was 6.2 months (95% CI, 4.899-7.501) and 5.2 months (95% CI, 3.682-6.718) respectively. Overall survival has not been reached yet. There were 7 patients achieved clinical complete response. Overall response rate was 41.6% and disease control rate was 82.2%. There was no treatment-related death. 28 patients (27.7%) experienced grade 3 or higher toxicities. The most common treatment related AE were aspartate transaminase/alanine transaminase elevation (41.6%) and bilirubin elevation (40.6%). The hematologic AE included anemia (27.7%), leukopenia (27.7%), neutropenia (14.9%) and thrombocytopenia (28.7%). **Conclusions:** The combination of Irinotecan-eluting HepaSphere chemoembolization and HAIC is effective and safe for unresectable CRLM, even for patients who are refractory to second or above systemic therapy, indicating it is a promising regional treatment with improved outcome. Research Sponsor: None.

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Poster Session

Understanding resistance in V600E BRAF advanced colon cancer treated with BRAF inhibitors plus anti-EGFR antibodies +/- MEK inhibitors: The URBAN study. *First Author: Francesca Bergamo, Medical Oncology 1, Department of Oncology, Veneto Institute of Oncology IOV-IRCCS, Padua, Italy*

Background: The combination of BRAF inhibitors (BRAFi) plus anti-EGFR antibodies is a new standard of care in V600E BRAF mutated (mut) metastatic colorectal cancer (mCRC). Nevertheless, resistance develops during the target therapy (TT). We designed the URBAN study, a translational prospective project, in order to identify possible primary and acquired resistance mechanisms. **Methods:** Patients (pts) with V600E BRAF mut mCRC treated with BRAFi + anti-EGFR +/- MEK inhibitors at Veneto Institute of Oncology were enrolled. Clinical data and liquid biopsy at baseline and progression were collected. The ctDNA derived from plasma was analyzed by the AVENIO expanded kit, a hybridization capture sequencing-based 77 genes pan-cancer assay contained in NCCN Guidelines. Survival outcomes were calculated using Kaplan-Meier curves, log-rank tests and univariate Cox regression models were also performed. The study is exploratory and no formal hypothesis has been postulated. **Results:** Forty consecutive V600E BRAF mut mCRC pts were enrolled. Median age was 63 years (42-77), 47.5% of pts were males. Right CRC were 65% and 20% were MSI-H. Only 5% of pts received TT after second line; doublet regimen was administered in 60% of pts while triplet in 40%. According to the mPFS of doublet arm in the BEACON trial (4.2 months, mo), our population was divided in responder (R), 24 (60%), and non-responder (NR), 16 (40%). In R vs NR group, mPFS was 9 vs 3.2 mo while mOS was 21.6 vs 10.7 mo, respectively. The V600E BRAF mut was detected in 85% of the pre-treatment plasma samples without statistically significant differences in the genomic alterations between R and NR groups, but there was a higher frequency of MET and EGFR amplification in NR group. At progression, the mutation of BRAF was lost in 2 cases in R group. After receiving TT, the most common acquired mutations involved RAS genes: 16 pts (40%) acquired at least one activating mutation in KRAS and/or NRAS. Among these, 9 pts showed multiple mutations of the same RAS gene probably due to both intra- and inter-lesional heterogeneities; none of these pts had MSI-H mCRC. We found a higher number of RAS and MAP2K1 acquired mutations in NR and a trend to acquire EGFR amplification in R group. Inactivating mutations in RNF43 gene was observed in 2 cases in R group. These data did not reach statistical significance, probably due to the low number of cases. Interestingly, 37% of NR pts acquired three or more molecular alterations vs 13% in R group. Furthermore, a higher number of genetic alterations was acquired in pts treated with doublet vs triplet regimen. **Conclusions:** This prospective, observational molecular profiling study provided further evidences to support the use of ctDNA in capturing the dynamic somatic mutational spectrum in V600E BRAF mut mCRC and to identify potential mechanisms of resistance to TT. An expansion of study population is ongoing. Research Sponsor: Partially funded by the Italian Ministry of Health grant "Ricerca Finalizzata Giovani Ricercatori" [grant number GR2019-12368903].

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Poster Session

Optimal molecular-targeted therapies as first-line treatment for *RAS* wild-type, right-sided metastatic colorectal cancer from the Analysis and Research in Cancers of the Digestive System (ARCAD) database. *First Author: Kentaro Yamazaki, Division of Gastrointestinal Oncology, Shizuoka Cancer Center, Shizuoka, Japan*

Background: Although anti-EGFR antibody plus doublet chemotherapy has become the standard of first-line treatment for *RAS* wild-type (wt), left sided metastatic colorectal cancer (mCRC), the optimal molecular-targeted therapy for *RAS* wt, right-sided mCRC is not clear. **Methods:** To evaluate the efficacy between anti-EGFR antibody vs. bevacizumab combination therapy, from 40,889 Individual patient (pt) data from 59 studies in ARCAD mCRC database, 723 pts with *RAS* wt, right-sided mCRC who received a first-line molecular-targeted therapy with backbone chemotherapy (FOLFOX/FOLFIRI when anti-EGFR antibody combination, and FOLFOX/FOLFIRI/CAPOX/FOLFOXIRI when bevacizumab combination) were selected from 10 randomized studies (FIRE-3, CALGB80495, CRYSTAL, PRIME, CAIRO2, OPUS, TRIIBE, TRIIBE2, ATOM, and CCOG1201). Primary objective was overall survival (OS), and secondary objectives were progression-free survival (PFS) and overall response rate (ORR); Hazard ratio (HR) and Odds ratio (OR) were adjusted for ECOG-PS, age, and gender. Propensity score matching (PSM) and inverse probability treatment weighting (IPTW) as sensitivity analysis were also performed. Secondary analyses were limited to *BRAF* wt pts. **Results:** Anti-EGFR antibody and bevacizumab were administered in 329 and 394 pts, respectively, of whom 162 and 151 pts were *BRAF* wt, respectively. Baseline characteristics were as follows (anti-EGFR antibody/bevacizumab): median age, 63.0 years both; female, 47.1/46.4%; and ECOG-PS 0, 53.2/65.2%. The OS and PFS were significantly prolonged in pts receiving bevacizumab combination therapy compared to those receiving anti-EGFR antibody combination therapy (Table). These trends were more pronounced when limited to *BRAF* wt pts (Table). There were no significant differences in ORR for both overall and *BRAF* wt pts. These results were similar in the sensitivity analysis (Table). **Conclusions:** For patients with *RAS* wt or *RAS/BRAF* wt, right-sided mCRC, bevacizumab combination therapy is preferred first-line treatment. Research Sponsor: ARCAD, ARCAD Asia.

		Median OS, months	Median PFS, months	ORR, %
<i>RAS</i> wt	Anti-EGFR vs. bevacizumab	18.4 vs. 21.5	8.0 vs. 9.4	57.5 vs. 56.6
	HR/OR (95%CI)	1.19 (1.01-1.40)	1.21 (1.03-1.42)	1.11 (0.81-1.52)
	PSM; HR/OR (95%CI)	1.27 (1.07-1.50)	1.27 (1.08-1.49)	1.01 (0.86-1.19)
	IPTW; HR/OR (95%CI)	1.28 (1.09-1.51)	1.26 (1.08-1.48)	1.03 (0.88-1.22)
<i>RAS/BRAF</i> wt	Anti-EGFR vs. bevacizumab	18.7 vs. 25.8	8.3 vs. 11.1	63.5 vs. 66.0
	HR/OR (95%CI)	1.52 (1.18-1.96)	1.68 (1.31-2.17)	0.98 (0.59-1.61)
	PSM; HR/OR (95%CI)	1.49 (1.15-1.92)	1.68 (1.30-2.16)	0.98 (0.76-1.27)
	IPTW; HR/OR (95%CI)	1.57 (1.21-2.03)	1.67 (1.30-2.14)	1.11 (0.84-1.47)

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Poster Session

Phase II study of biweekly TAS-102, irinotecan and bevacizumab in pre-treated metastatic colorectal cancer (TABASCO). *First Author: Patrick M Boland, Rutgers Cancer Institute of New Jersey, New Brunswick, NJ*

Background: The efficacy of 2nd line FOLFIRI plus VEGF inhibition (VEGFi) is limited for metastatic colorectal cancer (mCRC). TAS-102 is a novel oral anti-metabolite approved for pts with mCRC following standard treatment with FP, oxaliplatin and irinotecan. TAS-102 has a distinct mechanism of action from 5-FU and overcomes 5-FU resistance in preclinical models, and in the clinic. We hypothesized that the combination of TAS-102 with irinotecan (TAS-IRI) and bevacizumab (BEV) would prove superior to FOLFIRI/VEGFi. **Methods:** Phase II, single-arm study of TAS-IRI and BEV in 2nd-line mCRC. Eligible patients had received prior treatment with a fluoropyrimidine and oxaliplatin in the advanced setting or experienced recurrence within 12 mos of this regimen in the adjuvant setting. Adequate organ function, ECOG PS 0-1, measurable disease (RECIST 1.1), no prior irinotecan or TAS-102 exposure and candidacy for BEV were required. Pts were treated with BEV 5 mg/kg IV, irinotecan 180 mg/m² IV (day 1 and 15), and TAS-102 25 mg/m² orally bid (days 2-6 and 16-20) in 4-week cycles (PMID: 31924737). Treatment continued until disease progression or unacceptable toxicity. The primary endpoint was median progression-free survival (PFS). Assuming a median PFS for historic control (FOLFIRI/VEGFi) of 6 mos vs. 9 mos for TAS-IRI plus BEV (HR: 0.67), treatment of 36 evaluable pts would achieve 80.5% power (at $\alpha = 0.1$) to detect such an effect. **Results:** Forty-nine patients were enrolled; 42 were eligible and 38 had at least one disease assessment (median age 59 yr, 47% male, 74% colon primary, tumor KRAS/ NRAS mutated in 55%/21%). The median PFS was 8.7 mos (range: 6.7-11.8 mos, $p = 0.009$), meeting the primary endpoint. The most common reason for study treatment discontinuation was progressive disease (53%). The objective response rate was 16% (90% CI: 8.0-27.3%); the median OS was 16.5 mo (range: 11.8-25.3). Twenty-eight pts (67%) had a treatment-related adverse event (TRAE) G3 or higher (Table). The most common TRAEs were gastrointestinal and hematologic. Grade 3/4 neutropenia occurred in 34%, with only 1 episode of febrile neutropenia, though G-CSF use was frequently needed to maintain dose density/intensity. **Conclusions:** TAS-IRI plus BEV is an effective 2nd line therapy for patients with mCRC. The median PFS appears higher compared to historical controls (FOLFIRI/VEGFi). Neutropenia is common and can affect dose density/intensity mandating use of G-CSF. A randomized study versus standard of care therapy is warranted. (Clinical trial registration ClinicalTrials.gov NCT04109924). Clinical trial information: NCT04109924. Research Sponsor: NCCN Oncology Research Program.

TRAE	Total (%)	Grade 3/4(%)
Neutropenia	27 (71)	13 (34)
Diarrhea	25 (66)	6 (16)
Nausea	25 (66)	-
Fatigue	22 (58)	-
Alopecia	14 (37)	1 (3)
Anemia	12 (32)	5 (13)
Anorexia	12 (32)	1 (3)
Vomiting	11 (29)	-
Thrombocytopenia	9 (24)	2 (5)
Constipation	7 (18)	-
Epistaxis	7 (18)	-
Infusion related reaction	6 (16)	-
Abdominal pain	5 (13)	3 (8)

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Poster Session

Overall survival of patients with BRAF-mutant metastatic colorectal cancer treated with encorafenib-cetuximab in a real-world nationwide study in the Netherlands. *First Author: Sietske C.M.W. van Nassau, Department of Medical Oncology, University Medical Center Utrecht, Utrecht University, Utrecht, Netherlands*

Background: Approximately 10-15% of patients with metastatic colorectal cancer (mCRC) have BRAF^{V600E} mutated tumors. Encorafenib plus cetuximab (EC) combination treatment was approved following the results of the randomized phase III BEACON trial and is currently recommended for all pretreated patients with BRAF^{V600E}-mutant mCRC. Selection of patients in randomized controlled trials is based on restrictive eligibility criteria and often not representative of the patient population in daily clinical practice. Complementary real-world effectiveness studies can improve knowledge on the generalizability of trial results, and support decision making in clinical practice. **Methods:** This population-based study included all mCRC patients in the Netherlands treated with EC since approval in October 2020 until June 2022. Individual patient data and original pathology reports were collected. Primary endpoint was overall survival (OS), defined as time from EC initiation until death by any cause, analyzed by Kaplan-Meier curves. WebPlotDigitizer was used to reconstruct the Kaplan-Meier survival curve of the BEACON trial. Uni- and multivariable analyses were performed. Subgroup analyses were conducted for patients who would have been eligible for the BEACON trial based on key eligibility criteria: BRAF^{V600E} mutation, 1-2 prior regimens, world health organization performance status (WHO PS) of 0-1, normal neutrophil count, absence of brain metastases, no prior RAS/RAF/MEK treatment, and no concurrent malignancies. **Results:** 155 patients were included with a median follow-up time of 11.1 months. Patient characteristics differed from BEACON in mean age (64 *versus* 60 years), primary tumor sidedness (69% *versus* 50% right-sided) and WHO PS (23% *versus* 51% WHO 0). Median OS of the total real-world cohort was 6.6 months (95% CI: 6.0-8.3) and differed significantly from BEACON (9.3 months; 95% CI: 8.0-11.3; $p = 0.003$). 35% of real-world patients treated with EC would not have been eligible for the BEACON trial, showing an inferior median OS of 6.0 months (95% CI: 4.6-9.2) compared to 7.0 months (95% CI: 6.4-9.8) in trial eligible real-world patients. WHO PS was independently associated with poor survival in multivariable analysis. Patients with WHO PS ≥ 2 had a median OS of 3.9 months (95% CI: 2.4-NA) with a hazard rate of 2.5 (95% CI: 1.1-5.5; $p = 0.003$). **Conclusions:** This largest to date - unselected - population-based cohort of mCRC patients treated with EC showed an efficacy-effectiveness gap for OS. These outcomes should be considered in clinical practice for treatment decision making. Omitting EC for subgroups demonstrating very short OS, such as patients with WHO PS ≥ 2 , needs to be considered. Further research is warranted to adapt treatment guidelines towards a more personalized approach for patients with BRAF^{V600E}-mutated mCRC. Research Sponsor: Zorginstituut.

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Poster Session

Real-world treatment trends and outcomes in elderly patients with metastatic colorectal cancer in the United States. *First Author: Andrew Trunk, Cleveland Clinic (Cleveland, OH), Cleveland, OH*

Background: Prospective data to guide management of elderly patients with metastatic colorectal cancer (mCRC) is limited. Whether elderly patients derive the same degree of benefit from doublet chemotherapy as younger patients is not well understood. In this study we utilized real-world data from patients in the United States (US) to evaluate treatment trends and compare overall survival (OS) in younger versus older patients with mCRC who receive first-line (1L) chemotherapy. **Methods:** The nationwide Flatiron Health electronic health record-derived de-identified database was used to select patients ≥ 50 years old (yo) with mCRC treated with 1L fluoropyrimidine-based chemotherapy with or without the addition of targeted therapy. Overall survival from the initiation of 1L therapy, stratified by receipt of a doublet or single agent cytotoxic chemotherapy regimen was assessed independently within three age cohorts (50-69; 70-74, ≥ 75) using both a cox proportional hazard model and a propensity score weighted analysis to control for potential confounding variables. A subgroup analysis was performed in patients receiving bevacizumab as part of 1L therapy. **Results:** Of 14,440 patients who received 1L chemotherapy, 5,874 (40.7%) were ≥ 70 yo, including 3,656 (25.4%) who were 75 or older. Doublet chemotherapy was received by 7,505 (87.6%) patients age 50-64 yo, 1892 (85.3%) patients age 70-74 yo, and 2297 (62.2%) patients age 75 and above. In all three groups, multivariate analysis of single agent chemotherapy vs doublet chemotherapy showed a benefit to doublet chemotherapy with a hazard ratio of 1.14, (95% CI 1.04-1.24, $p = 0.006$), 1.22 (95% CI 1.05-1.42, $p = 0.011$) and 1.19 (95% CI 1.10-1.29, $p < 0.001$), respectively. Similar results were noted when comparing doublet to single agent chemotherapy in the age 70-74 and ≥ 75 groups using a propensity score weighted analysis. In the subgroup of patients age ≥ 70 who received 1L bevacizumab, 2,604 received doublet chemotherapy and 441 received single agent chemotherapy. Median OS was 19 mos (95% CI: 18-20) vs 13 (95% CI: 11-15) vs with a propensity score weighted HR of 1.35 (95% CI 1.12-1.63, $p = 0.001$). **Conclusions:** A smaller percentage of patients over age 75 receive 1L doublet chemotherapy for mCRC in the US compared to patients age 50-69 or 70-74. Regardless of age, patients who receive doublet fluoropyrimidine-based chemotherapy appear to have improved overall survival compared to single agent chemotherapy. This retrospective US data is in contrast with recently presented data from a prospective phase III trial in Japan (JCOG1018). Elderly patients in the US should not be excluded from receiving doublet chemotherapy for mCRC without further prospective data. Research Sponsor: None.

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Poster Session

MicroOrganoSpheres as a clinically applicable precision oncology platform for the discovery of novel therapies in colorectal cancer. *First Author: Divya Lakshmi Dayanidhi, Duke University, Durham, NC*

Background: Patient-derived models of cancer, such as cell lines, patient-derived organoids, and patient-derived xenografts, are useful models of patient response in the clinic. However, these models are often not clinically applicable within the time periods necessary to inform clinical decision making, as they can take weeks to months to develop. An ideal platform using patient-derived models would be generated from a core biopsy with a subsequent drug screen within 10-14 days to minimize delay in therapy. We recently reported the development of MicroOrganoSpheres (MOS) that can be used in drug screens within 14 days of obtaining a biopsy. In the current study, we use this MOS system as precision oncology platform in colorectal cancer (CRC) to identify new therapies and predict response to therapy. **Methods:** CRC patient tissue samples were collected under a Duke Institutional Review Board approved protocol (Pro00089222). Resections or biopsies were mechanically and enzymatically digested to obtain a single cell suspension. Cells were then plated in Matrigel at a ratio of 20,000 cells:5 μ L Matrigel to establish "mini-bulk" organoid cultures. After establishment for 5-7 days, cultures were harvested with subsequent generation of MOS at a ratio of 50 cells per MOS. After growing for 3-4 days, MOS were used for dose-response curves using oxaliplatin, SN38, and 5-Fluorouracil (5-FU) as well as high-throughput drug screens with the NCI Approved Oncology Drugs Set VI library. **Results:** We developed and optimized a MOS pipeline on over 50 CRC specimens, including 9 primary rectal, 35 primary CRC, 12 CRC liver metastasis, and 1 CRC lung metastasis lines with a success rate of 80% and an average of 10-21 days from biopsy to MOS generation. The high success of generating CRC MOS in a clinically applicable time frame led to the next phase of the project where a total of 10 CRC MOS were tested against standard of care chemotherapy agents used in CRC (oxaliplatin, irinotecan and 5-FU) as well as the NCI Approved Oncology Drugs Set VI within 14-21 days of establishment. We noted a range of sensitivity of approximately 100-fold for standard of care agents. The most sensitive drugs found in the high-throughput screen were Bortezomib, Carfilzomib, and Panobinostat and the most resistant were Gefitinib, Chlorambucil, and Procarbazine hydrochloride. **Conclusions:** These results demonstrate that our MOS pipeline can be used as a precision oncology platform within a clinically applicable time frame to potentially guide therapy. We are now in the process of correlating drug response in MOS to patient outcome data and these findings will be presented at the annual meeting. Research Sponsor: Discretionary funds.

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Poster Session

Effect of trifluridine/tipiracil in combination with bevacizumab on ECOG-PS in refractory metastatic colorectal cancer: An analysis of the phase 3 SUNLIGHT trial. *First Author: Julien Taieb, Paris Cité University, Paris, France*

Background: SUNLIGHT, an international, open-label, randomized, phase 3 study comparing trifluridine/tipiracil (FTD/TPI) in combination with bevacizumab versus FTD/TPI monotherapy in patients with metastatic colorectal cancer (mCRC) met its primary endpoint (overall survival [OS]) and key secondary endpoint (progression free survival [PFS]). Primary and key secondary outcomes in patients with maintained ECOG-PS are reported. **Methods:** SUNLIGHT enrolled patients with ECOG-PS 0/1. ECOG-PS was evaluated at baseline, at each treatment cycle, and at withdrawal visit. Worst ECOG values and time to ECOG worsening of more than 2 were reported. Here we report a post-hoc analysis assessing OS and PFS in patients who remained at ECOG-PS 0 or 1. **Results:** Of the 492 randomized patients, 491 had ECOG-PS 0 or 1 at baseline. The median OS was improved by 3.3 months with FTD/TPI plus bevacizumab (10.8 months with FTD/TPI plus bevacizumab vs 7.5 months with FTD/TPI), hazard ratio of 0.61 (95% CI, 0.49 to 0.77; $P < 0.001$), and median PFS was of 5.6 months vs 2.4 months favoring the FTD/TPI plus bevacizumab group (hazard ratio, 0.44; 95% CI, 0.36 to 0.54; $P < 0.001$). The results showed that FTD/TPI plus bevacizumab significantly improved time to ECOG-PS worsening from 0 or 1 to ≥ 2 when compared with FTD/TPI monotherapy (9.3 months with FTD/TPI plus bevacizumab vs 6.3 months with FTD/TPI (hazard ratio, 0.54; 95% CI, 0.43 to 0.67). Highest ECOG-PS distribution showed comparable proportions over cycles with no clinically meaningful difference ($> 10\%$) in both treatment arms. Considering patients who had discontinued study treatment as of the clinical cut-off date of July 5, 2022, 189/208 (91%) patients in the FTD/TPI plus bevacizumab and 200/235 (85%) patients in the FTD/TPI remained at ECOG-PS 0 or 1 at treatment discontinuation. In patients with maintained ECOG-PS, median OS demonstrated a prolonged survival in the FTD/TPI plus bevacizumab group vs the FTD/TPI group and a decreased death risk (10.58 months [range, 9.03 to 11.24] vs 8.71 months [range, 7.39 to 10.18]; hazard ratio, 0.78; 95% CI, 0.61 to 0.99). PFS consistently showed benefit in patients with maintained ECOG 0 or 1 favoring FTD/TPI plus bevacizumab (5.22 months [range, 4.17 to 5.75] vs 2.55 months [range, 2.1 to 3.58]; hazard ratio, 0.49; 95% CI, 0.4 to 0.61). **Conclusions:** Consistent with the results of the overall study population, FTD/TPI in combination with bevacizumab prolonged overall survival and PFS in patients with maintained ECOG-PS. Maintenance of performance status may allow patients to receive further therapeutic options during the continuum of care. Clinical trial information: NCT04737187. Research Sponsor: Institut de Recherches Internationales Servier; Taiho Oncology.

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Poster Session

Management of Early-onset Metastatic Colorectal Cancer (ERMIONE): A single institution analysis. *First Author: Giustina Valente, Oncologia Medica, Comprehensive Cancer Center, Fondazione Policlinico Universitario Agostino Gemelli-IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy*

Background: Despite rising incidence and mortality reported worldwide for CRC diagnosed in pts aged < 50 yrs, currently early onset metastatic CRC (EOMCRC) are treated as their older counterparts. We aimed to investigate how this specific subgroup is treated in real world. **Methods:** This an observational, retrospective, monocentric study aiming to describe features, management and prognosis of EOMCRC. Pts with EOMCRC treated at our Institution between Apr2002 and Dec2022 were included. Applying a descriptive method, counts and percentages were reported for categorical variables, while median and range for continuous variables. PFS and OS were estimated with the Kaplan-Meier method. A multivariate Cox regression analysis was performed. **Results:** 172 pts were included, of those 60.5% were female and 66% had an ECOG PS of 0. Median age at diagnosis was 43 yrs (range 12-49 yrs). Metastatic disease was mainly synchronous (72.1%), while only 12.2% and 15.7% were stage II and III at diagnosis and developed metachronous metastases. Primary tumor was left-sided in 70.1%. Metastatic site was most frequently liver (67.4%), followed by peritoneum (41.3%), lungs (33.7%), ovary (23.2%) and bones (9.9%). Disease was mostly widespread, while only 30.2% had a single metastatic site. MMR status was available for 87.2% of pts, being proficient in 90% and deficient in 10%. RAS/BRAF status was available for 95.3% of cases, of those 47.5% was RAS/BRAF wt, 48.2% was RAS mt and 4.3% was BRAF mt. 42.4% of cases had a family history positive for cancer. Germline pathogenic or likely pathogenic variants were identified in 6.4% of cases, of those 63.6% involved MMR genes and 18.2% involved HRD genes. Median number of lines of treatment received was 2 (range 1-6). Most frequent first line regimen was a doublet CT (69.8%), followed by a triplet CT (23.8%) and immunotherapy (4.1%). CT regimens were associated to bevacizumab in 45.3% of cases and to antiEGFRs in 29.1% of cases. Throughout the whole continuum of care 8.7% of pts received immunotherapy and 21.5% received treatment within a clinical trial. 70.3% of pts received surgery and/or local ablative treatments (LATs) with radical intent (52.9% surgery, 12.2% both, 4.6% LATs). At a median FU of 38.6 m, mPFS for first line was 13.5 m (95%CI 12.1-15.0 m) and mOS was 41.5 m (95%CI 33.9 - 44.1 m). Median OS was significantly longer for pts who received surgery and/or LATs compared to those who did not (43.4 vs 23.6 m, $p < .0001$). At multivariate analysis, besides surgery and/or LATs ($p = .0007$), BRAF status ($p = .0165$) and ECOG PS ($p = .0209$) independently correlated with OS. **Conclusions:** We confirmed that EOMCRC is more frequently diagnosed as synchronous disease, due to delayed diagnosis. Despite the small population and the retrospective nature, we showed that combining surgery and/or LATs to systemic therapy is associated with increased OS in EOMCRC. These evidence warrant further validation in prospective setting. Research Sponsor: None.

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Poster Session

PolyPEP1018 vaccine in combination with TAS-102 in participants with late-stage microsatellite-stable metastatic colorectal cancer (MSS mCRC): A phase Ib study to evaluate safety, tolerability, immunogenicity and efficacy (OBERTO-201). *First Author: Joleen M. Hubbard, Department of Medical Oncology, Mayo Clinic, Rochester, MN*

Background: PolyPEP1018 is an off-the-shelf, multi-peptide vaccine containing 12 immunogenic epitopes derived from 7 tumor-specific antigens frequently expressed in patients with mCRC. Following early evidence of clinical activity of PolyPEP1018 in first-line MSS mCRC, here we report the results of a phase Ib study of PolyPEP1018 vaccine plus trifluridine/tipiracil (TAS-102) in late-stage mCRC patients. **Methods:** Patients with MSS mCRC who have progressed on ≤ 2 lines of prior chemotherapy regimen for mCRC received PolyPEP1018 subcutaneously on days 1 and 15 and TAS-102 orally twice daily on days 1-5 and 8-15 of a 28-day cycle. Treatment continued for up to 7 cycles, until disease progression or unacceptable toxicity. Immunomonitoring was performed at both blood and tumor levels prior to and on study treatment. The primary endpoint of the study was safety and tolerability. Data on objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), overall survival (OS) and correlation studies will be presented. **Results:** 15 patients started treatment. Median age was 55 years (range 31-71), 73% had liver metastases (mets), 73% had KRAS mutant tumors. The most common side effect related to PolyPEP1018 was Grade (Gr) 1-2 local skin reactions in 93% of patients. Gr 3 events ($n = 15$) at least possibly related to treatment were fatigue, decreased white blood cell, lymphocyte and neutrophil counts, nausea, diarrhea, myalgia, and maculo-papular rash. There were no Gr 4 or 5 events. The ORR was 0%. The DCR was 53.3% in the overall population and 36% and 100% for the patients with liver mets and without liver mets, respectively. The mPFS was 4 months (95%CI 2.2-6.1) in the overall population and 2.3 months (95%CI 2.1-NE) and 7.6 months (95%CI 4.4-NE) for the patients with liver mets and without liver mets, respectively (HR = 5.73 (95%CI 1.21, 27.06); $p = 0.015$). At the data cut-off date (Feb 10, 2023), the mOS was 8.7 months (95%CI 6.9-NE; not mature) in the overall population and it was not reached in patients without liver mets. Patients with increased PFS (≥ 24 weeks) had more robust vaccine-specific humoral and T cell responses induced by higher number of vaccine peptides than patients with PFS < 24 weeks. **Conclusions:** To our knowledge, this is the first study investigating combination of a cancer vaccine with TAS-102 chemotherapy in advanced MSS mCRC. Our results show that PolyPEP1018 plus TAS-102 was well-tolerated with few grade 3 AEs beyond what is expected with TAS-102 monotherapy. Despite no objective tumor responses could be detected, correlative data suggest contribution of PolyPEP1018-induced immunological responses to the improved clinical benefit and the combination warrants further testing. Clinical trial information: NCT05130060. Research Sponsor: US Department of Defense.

3596

Poster Session

VIC regimen (vemurafenib/irinotecan/cetuximab) versus bevacizumab plus chemotherapy as first-line treatment for *BRAF* V600E-mutated advanced colorectal cancer. *First Author: Yijiao Chen, Colorectal Cancer Center; Department of General Surgery; Zhongshan Hospital, Fudan University, Shanghai, China, Shanghai, China*

Background: The need for safe and effective therapies for untreated, *BRAF* V600E-mutated, unresectable locally advanced or metastatic colorectal cancer remains unmet. The purpose of this study was to compare the efficacy and safety of the VIC (Vemurafenib/Irinotecan/Cetuximab) regimen versus bevacizumab plus chemotherapy as first-line setting in Asian patients. **Methods:** In the single-center prospective cohort study, 78 untreated, *BRAF* V600E-mutant, locally advanced or metastatic CRC patients were enrolled. Every two weeks, the VIC regimen and bevacizumab plus doublet or triplet chemotherapy are administered. We evaluated the objective response rate (ORR), the disease control rate (DCR), and the conversion resection rate. In progression-free survival (PFS) and overall survival, the Kaplan-Meier method was utilized (OS). **Results:** In the evaluable population, 32 patients received VIC regimen and 35 patients received bevacizumab plus chemotherapy. The ORR and DCR in the VIC group were significantly higher than in the bevacizumab-therapy group (ORR: 68.8% versus 40.0%, $P = 0.018$; DCR: 100.0% versus 80.0%, $P = 0.023$). The VIC regimen was significantly superior to bevacizumab plus chemotherapy for PFS (median, 11.9 vs 7.9 months; hazard ratio [HR] = 0.48, 95% CI, 0.27-0.87; $P = 0.012$) and OS (median, 24.5 vs 14.4 months; HR = 0.36, 95% CI, 0.16-0.78; $P = 0.007$). In the VIC group, the conversion resection rate for liver metastases was 42.1% (8 of 19 patients), and for local CRC it was 66.7% (6 of 9 patients with initially unresectable local CRC). Rates of treatment-related adverse events of Grade 3 to 4 were 32.4% and 31.1% for the VIC regimen and bevacizumab plus chemotherapy, respectively. **Conclusions:** Among Asian patients with *BRAF* V600E-mutated advanced CRC, the VIC regimen was superior to bevacizumab plus chemotherapy in terms of tumor response and oncological survival, with a tolerable and manageable toxicity profile in the first-line setting. Clinical trial information: NCT05540951. Research Sponsor: None.

3598

Poster Session

Preoperative assessment in lung-limited metastatic patients with colorectal cancer: The Meta-Lung Score. *First Author: Pina Ziranu, Medical Oncology Unit, University Hospital and University of Cagliari, Cagliari, Italy*

Background: Due to the inconsistent data on curative resection of isolated lung metastases (LM) from colorectal cancer (CRC) and the lack of specific recommendations, the therapeutic approaches for metastatic liver disease are mostly applied to LM treatment, despite differences in their biological behavior. Like Fong's criteria in CRC liver metastases, our study proposed a score associated with clinical outcomes in patients (pts) undergoing CRC lung metastasectomy, aiming to better pts' selection for surgery and the most appropriate therapeutic strategy. **Methods:** We retrospectively collected data from 260 pts (aged 18-85) who underwent CRC lung metastasectomy with curative intent from December 2002 to January 2022 at four Italian Centers: the Division of Thoracic Surgery at "A. Businco Cancer Center" in Cagliari, the Division of Thoracic Surgery at "Città della Salute e della Scienza" in Turin, the Department of Thoracic Surgery at "IRCCS Azienda Ospedaliero-Universitaria" in Bologna, and the Medical Oncology Unit of the University Hospital of Cagliari. Statistical analysis was performed with MedCalc (survival distribution: Kaplan-Meier; survival comparison: log-rank test; association between categorical variables: Fisher's exact test). **Results:** We analyzed the impact of different clinicopathological features on overall survival (OS). At the univariate analysis: higher baseline CEA levels ($p = 0.0001$), disease-free survival less than or equal to 12 months (m) ($p = 0.0043$), LM size larger than 2 cm ($p = 0.0187$), multiple resectable nodules ($p = 0.0083$), and positive nodal status of the primary tumor ($p = 0.0011$) were associated with poorer prognosis. In a Cox regression model, these five characteristics retained their independent role for OS ($p < 0.0001$) and were chosen as criteria to be assigned one point each for clinical risk score. The 5-year survival rate in pts with 0 points was 88%, while no pts with a 5-points score survived at 2 years. Based on the 0-2 versus 3-5 score range, we obtained a significant difference in median OS: 101.7 m (95%CI 64.6 - 101.7) vs. 39.5 m (95%CI 27.3 - 87.5) respectively ($p < 0.0001$) stratifying pts into good and poor prognosis. **Conclusions:** The Meta-Lung Score appeared to be an exciting prognostic tool in selecting CRC pts' candidates for radical surgical treatment when LM were diagnosed. Whether early surgery should be considered in pts with a score 0-2, the same choice should be taken with caution in pts with a score 3-5, for whom early chemotherapy would allow better assessment of tumor biology and appropriate selection for surgery. Research Sponsor: None.

Score	Survival (%)					Median OS (m)
	1-yr	2-yr	3-yr	4-yr	5-yr	
0	97%	91%	88%	88%	88%	NR
1	97%	90%	78%	71%	60%	NR
2	97%	80%	65%	54%	46%	45.9 (95%CI 36.1 to 75.5)
3	90%	74%	58%	45%	34%	41.7 (95%CI 29 to 87.5)
4	73%	72%	41%	27%	27%	29.3 (89%CI 8.8 to 62.2)
5	34%	0	0	0	0	12.3 (95%CI 4.6 to 19.5)
Total	95%	83%	70%	60%	55%	75.6 (95%CI 57.6 to 101.7)

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Poster Session

Upfront vs deferred monoclonal antibodies in metastatic colorectal cancer: A target trial emulation using the GEMCAD 14-01 prospective cohort. *First Author: Joan Maurel, Hospital Clínic Barcelona, Barcelona, Spain*

Background: There are no randomized trials comparing the addition monoclonal antibodies (MAB: bevacizumab, cetuximab, panitumumab) to first line chemotherapy (upfront use) versus deferring their addition to the second-line chemotherapy (deferred use) in pts with metastatic colorectal cancer (mCRC). We emulated a target trial comparing upfront vs deferred use of MAB using the GEMCAD 14-01 observational registry. **Methods:** We first specified the (hypothetical) target trial to fully articulate the research question and then emulated it using real-world data. The eligibility criteria of the target trial were a diagnosis of mCRC, being treatment naïve, and a ECOG PS ≤ 2 . The target trial would randomize pts to the following strategies: (1) initiation of MAB within 2 months of starting first line chemotherapy ("upfront MAB") and (2) initiation of MAB within 2 months of starting second line chemotherapy ("deferred MAB"). The primary outcome of the target trial would be overall survival and the causal contrast (or estimand) would be the effect under complete adherence. We emulated this target trial using data from the GEMCAD 1401 registry (ClinicalTrials.gov identifier: NCT02254941), which collected data prospectively from 47 Spanish centers from June 2014 to June 2018. The emulation used the same definitions of eligibility criteria and treatment strategies, and classified individuals according to their baseline data using clones. The effect under complete adherence was estimated by censoring pts when they deviated from the assigned treatment strategy and by using time-varying weights to adjust for baseline and post-baseline confounding. **Results:** A total of 627 pts were eligible in the "upfront MAB" and 397 pts in the "deferred MAB". Median age was in the "upfront vs deferred" 64.6 (interquartile range: 56-71) vs 67.8 (61-75) years, 96% vs 87% had an ECOG 0-1, 80% vs 79% had a Charlson score ≤ 3 , 46% vs 60% had a *RAS* mutation, 6% vs 4% had a *BRAF* mutation, 72% vs 69% had left side primary location, 74% in both strategies had liver metastasis and 42% vs 50% had LDH levels above the normal threshold. Pts in the "upfront MAB" group contributed a total 16,057 months of follow-up and 502 if they died. Pts in the "deferred MAB" contributed a total of 7,774 months of follow-up, and 222 of them died. The 48-month overall survival was 26.7% (95% CI 21.4-38.2%) in the "upfront MAB" group and 21.6% (14.2-41.7%) in the "deferred MAB" group, corresponding to a 48-month survival difference ("upfront MAB" is the reference) of -5.0% (95% CI -17.9 to 17.95) and a hazard ratio of 1.15 (0.88-1.40). **Conclusions:** Our study suggests little or no survival detrimental effect of deferring the use of MAB to the second line of treatment compared with the use of MAB as part of the first line of treatment among pts with mCRC. Clinical trial information: NCT02254941. Research Sponsor: Supported by Instituto Carlos III PI13-01728 and an unrestricted support grant from Grupo Español Multidisciplinar en Cancer Digestivo (GEMCAD).

3599

Poster Session

Targeting EZH2 to overcome the resistance to immunotherapy in micro-satellite stable colorectal cancer: Results from the CAIRE study. *First Author: Lola Jade Palmieri, Medical Oncology Department, Institut Bergonié, Bordeaux, France*

Background: Profound epigenetic and transcriptomic changes induced by EZH2 in tumor cells and immune cells mobilize the elements of the TME, leading to immune-suppressive activity of solid tumors. Targeting EZH2 can enhance anti-tumor immunity by reshaping the tumor microenvironment (TME). The CAIRE study is first study investigating the impact of EZH2 inhibition in combination with immune checkpoint inhibitor in solid tumors. **Methods:** This is a single-arm open-label multicentric phase II trial assessing the efficacy and safety of tazemetostat (800 mg BID) combined with durvalumab (1120 mg every 3 weeks) in patients with advanced microsatellite stable colorectal cancer. The primary endpoint was the disease control rate within 24 weeks after treatment onset defined as the proportion of patients with at least a tumor assessment showing confirmed or unconfirmed complete response, confirmed or unconfirmed partial response or stable disease based on central review according to RECIST 1.1. Secondary endpoints included: 1-year progression free survival (PFS), 1-year overall survival (OS), and safety using NCI-CTCAE v5.0. All patients underwent sequential blood and tissue sampling for translational studies. **Results:** Between July 2021, and June 2022, 47 pts were enrolled at Institut Bergonié (Bordeaux, Centre). Median age was 67.7 (range 39.6 – 84.0). Median number of previous treatment lines was 4: (range 1 – 6). The most common treatment related adverse events were grade 1/2 asthenia, nausea. No death was related to the treatment. Among the 34 pts for whom blinded central review of imaging was available for at least one imaging tumor assessment, best tumor response was confirmed partial response, stable disease and progressive disease in 1 (2.9%), 11 (32.3%) and 22 (64.7%) patients respectively. The disease control rate was 35.3% (95%CI 19.7 – 53.5). **Conclusions:** The CAIRE study met its first endpoint for disease control rate in patients with advanced colorectal cancer. Efficacy data on the whole cohort of patients and full biomarkers analyses will be presented at the meeting. Clinical trial information: NCT04705818. Research Sponsor: Astrazeneca; Epizyme, Inc.

3600

Poster Session

Molecular landscape and survival outcomes on early phase clinical trials in sporadic young onset colorectal cancer. *First Author: Benny Johnson, Department of Gastrointestinal Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Sporadic young onset colorectal cancer (YOCRC, ages 30-49) is a public health crisis with a persistent rise in incidence globally. While a proportion of patients (pts) develop YOCRC due to hereditary predisposition, the majority develop sporadic microsatellite stable (MSS) colorectal cancer with limited options beyond standard of care in advanced settings. We report the early phase clinical trial experience at a large academic cancer center to elucidate clues regarding molecular landscape and impact of clinical trials in refractory MSS YOCRC. **Methods:** Patient and clinical characteristics were summarized using descriptive statistics. Kaplan-Meier method was used to estimate the probabilities of overall survival (OS) and progression free survival (PFS). Log-rank tests were used to assess the differences in OS and PFS between subgroups. Cox proportional hazards regression models were fit to assess the association between OS or PFS and patient characteristics. Statistical analyses were performed using SAS and Splus. **Results:** 240 MSS YOCRC pts were analyzed. Median age 42.8 (20.5-49), > 80% were white and only 10% black. 21% received at least 3 lines of therapy. The top five mutations were *TP53*, *KRAS*, *APC*, *PI3CKA* and *BRAF*^{V600E}. Median OS was 39.2 months (95% CI: 34.8 – 42.5 months). *CTNNB1* mutation was associated with a lower risk of death (HR = 0.28, 95% CI: 0.09 – 0.87, p-value = 0.03) while *BRAF*^{V600E} mutation was associated with an increased risk (HR = 3.28, 95% CI: 2.00 – 5.38, p-value < 0.001). Multivariable Cox model for OS revealed both *CTNNB1* and *BRAF*^{V600E} mutations are significant prognostic factors for OS, unlike *KRAS*. There was no difference in OS or PFS among pts who entered a mutation specific clinical trial vs. those enrolled on an unmatched clinical trial (p = 0.35, p = 0.68, respectively, log-rank test). Median PFS was 1.9 months (95% CI: 1.8 – 2.1 months). *CTNNB1* mutation was associated with a lower risk of progression/death (HR = 0.29, 95% CI: 0.09 – 0.92, p-value = 0.04) while *NRAS* mutation was associated with an increased risk (HR = 2.13, 95% CI: 1.19– 3.80, p-value = 0.01). Among 145 pts who have data on response, 9 had partial response, 41 had stable disease and 95 had progressive disease. *BRAF*^{V600E} mutation is associated with a higher probability of response (OR = 6.89, 95% CI: 1.64 – 28.94, p-value = 0.01) and pts enrolled on matched clinical trials had a higher probability of response (OR = 6.23; 95% CI: 1.24 – 31.09, p-value = 0.03). However, increased response did not translate to improved OS. No survival differences were appreciated based on pts race or BMI. **Conclusions:** *CTNNB1*, *BRAF*^{V600E} & *NRAS* mutations may have prognostic implications in YOCRC. Pts enrolled on mutation specific clinical trials did not achieve improved outcomes compared to unselected trials, highlighting aggressive biology, current lack of therapeutic targets and need for novel drug development in sporadic YOCRC. Research Sponsor: None.

3602

Poster Session

Real-world rates of FDA-approved targeted therapy and immunotherapy prescriptions for patients with metastatic colorectal cancer in the VA's National Precision Oncology Program (NPOP). *First Author: Alice Nono Djotsa, Center for Innovations in Quality Effectiveness and Safety, Houston, TX*

Background: Colorectal cancer is the fourth most common cancer among Veterans and the third leading cause of cancer-related death in the USA. Use of comprehensive genomic profiling (CGP) to guide administration of FDA-approved biomarker directed therapies can improve outcomes among metastatic CRC (mCRC) patients. We sought to compute the rates of actionable biomarkers and prescriptions of associated FDA-approved therapies among Veterans in NPOP. **Methods:** The NPOP database was queried to identify mCRC patients who had undergone CGP via tissue or liquid biopsy between February 2019 and July 2022 and had one of the following 5 actionable biomarker profiles: *NRAS/KRAS/BRAF* wildtype, *BRAF* V600E, MSI-H, TMB-H, or *NTRK* fusion or rearrangement. The VA's Corporate Data Warehouse (CDW) was queried to extract prescription data for seven FDA-approved biomarker-directed therapies (targeted agents and immune checkpoint inhibitors (ICIs)). Rates of CGP-directed therapy prescriptions were assessed based upon biomarker and patient characteristics (sex, race, ethnicity, and rurality). **Results:** A total of 908 mCRC patients underwent CGP, with 81.4% bearing colon adenocarcinoma (COAD) and 18.6% rectal adenocarcinoma (READ). Rates of actionable biomarkers associated with FDA-approved therapies were as follows: *NRAS/KRAS/BRAF* wildtype (34.4%), TMB-H (9.6%), *BRAF*V600E (7.7%), MSI-H (5.6%), TMB-H and MSI-H (5.6%), and *NTRK* Fusion or rearrangement (0.3%). The combined rates of any actionable variant were 47.4% for COAD and 44.4% for READ patients. Relative to patients without actionable biomarkers, patients with *BRAF* V600E mutations were more likely to be older and white; patients with *NRAS/KRAS/BRAF* wildtype were more likely to be younger (all p < 0.001). Among the 424 eligible patients, the frequencies of FDA-approved CGP-directed therapy prescriptions were as follows: MSI-H (70.7%), TMB-H (47.4%), *NRAS/KRAS/BRAF* wildtype (38.5%), and *BRAF*V600E (17.1%). Across all included biomarkers, African Americans (53.4%) were more likely to receive these therapies than whites (36.8%); and patients with prescriptions were more likely to be younger than those without (all p < 0.01). **Conclusions:** Nearly 30% of patients with MSI-H mCRC did not receive efficacious ICIs, and though disease laterality data was not readily available, a substantial number of eligible patients also did not receive EGFR inhibitors. This underuse of EGFR inhibitors has been reported previously [1]. There were racial and age differences in prescription rates. Further studies should evaluate the barriers to prescribing CGP-directed therapies in the care of mCRC patients. Keywords: molecular testing, metastatic colorectal cancer, comprehensive genomic profiling, actionable biomarkers, FDA approved therapies, veterans. [1] Becker et al. 2021 PMID 34250412. Research Sponsor: VA National Precision Oncology Program.

3601

Poster Session

Analysis of fruquintinib adverse events of special interest from phase 3 of the FRESKO-2 study. *First Author: Cathy Eng, Vanderbilt-Ingram Cancer Center, Nashville, TN*

Background: Fruquintinib (F) is a highly selective and potent inhibitor of VEGFRs-1, -2 & -3 designed with improved kinase selectivity to minimize potential off-target toxicities. In the phase 3 FRESKO-2 study (NCT04322539), F demonstrated a statistically significant improvement vs placebo (P) in overall survival (hazard ratio, HR = 0.66) and progression-free survival (HR = 0.32), with a manageable toxicity profile and without deterioration in quality of life in heavily pre-treated patients (pts) with metastatic colorectal cancer (mCRC). Here we report the treatment-emergent adverse events of special interest (AESI). **Methods:** FRESKO-2 was a double-blind, P-controlled multiregional study with 2:1 randomization to F + best supportive care (BSC) or P + BSC. F or P was given 5 mg PO, QD, 3 weeks (w) on, 1 w off, in a 28-day (d) cycle. AEs were coded using MedDRA v25.0 and graded (G) by NCI-CTCAE v5.0. Clinically relevant class toxicities were grouped into respective AESI categories. **Results:** The safety population had 686 pts (F: 456 vs P: 230); 47% were ≥ 65 yrs, 56.9%/43.1% with ECOG 1/0, 71.6% with hepatic metastases, and 50.5% with medical history of hypertension (HTN) at baseline. The median number of prior lines of anti-cancer treatment for metastatic disease F vs P was 4 (2, 16) vs 4 (2, 12); 96.4% with prior anti-VEGF agent; 91.6% with prior TAS-102; and 47.8% with prior regorafenib. Median duration of exposure was longer with F 3.06 months (m) (range, 1.84-5.5) vs P 1.84 m (range, 0.95-2.27). 368 pts (80.7%) on F and 122 pts (53.0%) on P had an AESI. The most frequent AESIs (all G) in ≥ 25% of pts (F vs P) were HTN (38.4% vs 8.7%), dermatological toxicity (34.4% vs 11.7%), and thyroid dysfunction (27.0% vs 1.7%). G ≥ 3 AESIs in ≥ 5% of pts in the F vs P, were HTN (14.0% vs 0.9%), hepatic function abnormal (8.3% vs 9.1%), dermatological toxicity (6.8% vs 0.4%), and infections (6.6% vs 5.7%). AESIs (F vs P) that led to dose reductions (DR) occurred in 13.6% vs 0.9% of pts, drug discontinuation (DD) in 8.3% vs 6.1% of pts. AESIs leading to death were 1.8% vs 1.3% of pts, with infections (1.1% vs 0.4%) being most common. The median time to first occurrence of HTN AESI was in cycle (C) 1, with hypertension (96%) being the most common AE reported. In pts with HTN AESI, 9.7% vs 0.6% had dose reduction (DR) and 1.7% vs 0% had DD. The median time to first occurrence of dermatological toxicity was C1, with palmar plantar erythrodysesthesia (PPE) being most common AE reported (56.1%); 27.3% vs 0% had DR and 3.4% vs 0% had DD. The median time to first occurrence of thyroid dysfunction was C2, with hypothyroidism (76.4%) being most common and none with DR or DD. **Conclusions:** F was well tolerated in heavily pretreated pts and despite underlying medical conditions. AESIs including HTN, PPE and thyroid dysfunction were manageable with low rates of dose reductions and dose discontinuation, which further supports F as a potential safe and new treatment option for refractory mCRC. Clinical trial information: NCT04322539. Research Sponsor: HUTCHMED LTD.

3603

Poster Session

Early tumor shrinkage (ETS) as clinical factor to select maintenance with cetuximab (cet) monotherapy in patients (pts) with RAS/BRAF wild-type (wt) metastatic colorectal cancer (mCRC): A secondary endpoint analysis of the ERMES study. *First Author: Armando Orlandi, Fondazione Policlinico Universitario A. Gemelli-IRCCS-UOC Oncologia Medica, Rome, Italy*

Background: ERMES study aimed to demonstrate non-inferior PFS of maintenance with cetuximab (cet) monotherapy (arm B) compared to FOLFIRI+cet until progression (arm A) in *RAS* and *BRAF* wt mCRC pts. Although study did not meet its primary endpoint it showed better toxicity profile and OS for cet alone and comparable ORR between arms. Here we present results of ETS, a secondary endpoint. **Methods:** ETS was defined as ≥20% reduction of the sum of target lesions at 8 weeks from the start of treatment, and was assessed by blinded independent central review. PFS and OS were compared between ETS+ and ETS- pts according to treatment arm in the modified Per-Protocol (mPP) population. **Results:** 327 of 337 (97%) pts were evaluable for ETS. In arm A, no statistically significant differences were observed between ETS+ and ETS- cohort for PFS (11.9 m, 95%CI 11.28-13.19, vs 12.2 m, 95%CI 10.82-14.93; HR 1.05, 95%CI 0.73-1.50; p 0.77) and OS (30.75 m, 95%CI 25.09-37.73, vs 25.46 m, 95%CI 19.96-34.63; HR: 0.79, 95%CI 0.50-1.24; p 0.29). In arm B, a statistically significant difference was observed between ETS+ and ETS- cohort for PFS (10.62 m, 95%CI 9.86-13.09, vs 8.52 m, 95%CI 7.89-9.37; HR 0.70, 95%CI 0.49-1.00; p 0.036) and for OS (38.88 m, 95%CI 34.53-43.25, vs 27.43 m, 95%CI 20.59-36.64; HR 0.60, 95%CI 0.38-0.93; p 0.019). ETS+ pts reported no statistically significant difference between arm B and arm A in terms of PFS (HR 1.12, 95%CI 0.83-1.49; p 0.43) while experiencing a better OS for arm B compared to arm A (HR 0.72, 95%CI 0.50-1.05; p 0.08). **Conclusions:** In pts achieving ETS, induction treatment with FOLFIRI+cet may be de-escalated to cet alone without detrimental effect on PFS, resulting in less toxicity and better OS. These data support the hypothesis that ETS might be a clinical dynamic predictor of efficacy of a less intensive maintenance strategy, allowing to plan de-escalation to cet alone after 4 months of FOLFIRI+cet induction. Clinical trial information: NCT02484833. Research Sponsor: This research was financially supported by Merck Serono S.p.A., Italy, an affiliate of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945).

3604

Poster Session

Subgroup analyses of safety and efficacy by number and types of prior lines of treatment in FRESCO-2, a global phase III study of fruquintinib in patients with refractory metastatic colorectal cancer. *First Author: Arvind Dasari, Department of Gastrointestinal Medical Oncology, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Effective treatment options are limited for patients (pts) with refractory metastatic colorectal cancer (mCRC). Fruquintinib (F), a highly selective, potent, oral tyrosine kinase inhibitor of VEGFR-1, -2, and -3, was evaluated in the global phase III FRESCO-2 study (NCT04322539) and demonstrated a clinically meaningful and statistically significant improvement in OS and PFS with a favorable safety profile. Here we report subgroup analyses of efficacy and safety by prior lines (PL) and types of anti-cancer treatment (Tx) for metastatic disease (MD). **Methods:** FRESCO-2 was conducted in the US, Europe, Japan & Australia, comparing F + best supportive care (BSC) with Placebo (P) + BSC. Pts were given 5 mg PO, QD, 3 wks on, 1 wk off, in a 28-day cycle. Eligible pts received prior chemotherapy, anti-VEGF, and if RAS wild type, anti-EGFR therapies; if BRAFV600E mutant or MSI-H, and appropriate targeted regimen; and had progressed on, or were intolerant to, trifluridine/tipiracil (TAS-102) and/or regorafenib (R). Subgroup (sbgprs) analyses for efficacy and safety were performed according to number of prior lines of tx (LOT) and by types of therapy. **Results:** A total of 691 pts were randomized; F:461 vs P:230. The median number of prior lines of anti-cancer tx for metastatic disease F vs P was 4 (2, 16) vs 4 (2, 12). F improved OS and PFS compared to P for all sbgprs and prior tx for MD, consistent with those of the ITT population (pop). (Table: OS reported by sbgprs and prior tx for MD). Occurrence of adverse events (AEs) and serious adverse events were generally balanced between F vs P and consistent across all subgroups. The most common $\geq$ G3 AEs in $\geq$ 5% of pts on F within majority of sbgprs were hypertension, asthenia and palmar plantar erythrodysesthesia and were consistent with the overall safety population. Additional analyses based on duration of prior anti-VEGF and last therapy prior to F will be presented at the conference. **Conclusions:** F demonstrated clinically meaningful improvement in OS, PFS with an acceptable safety profile across all sbgprs. These results were consistent with the effect observed in the overall population; irrespective of previous tx with anti-VEGF, anti-EGFR, TAS-102 and R further supporting F as a potential new tx option for pts with refractory mCRC. Clinical trial information: NCT04322539. Research Sponsor: HUTCHMED LTD.

Subgroups (n = F, P)	F (m)	P (m)	HR: 95% CI	Subgroups (n = F, P)	F (m)	P (m)	HR: 95% CI
ITT population (461, 230)	7.4	4.8	0.662; 0.549-0.880	Anti-VEGF (445, 221)	7.4	4.9	0.683; 0.565-0.827
$\leq$ 3 prior LOT (125, 64)	7.6	5.2	0.714; 0.488-1.043	Anti-EGFR (180, 88)	7.4	4.4	0.689; 0.507-0.936
4 prior LOT (122, 59)	7.4	4.7	0.661; 0.454-0.963	TAS-102 (240, 121)	7.7	5.1	0.723; 0.557-0.938
5 prior LOT (93, 47)	8.0	3.4	0.310; 0.199-0.483	R (40, 18)	10.2	8.2	0.772; 0.379-1.573
$\geq$ 6 prior LOT (121, 60)	6.7	5.2	0.818; 0.566-1.183	TAS-102 & R (181, 91)	6.8	4.4	0.600; 0.447-0.805

3606

Poster Session

Cancer of unknown primary with gastrointestinal profiles: A distinct CUP subset. *First Author: Aakash Tushar Shah, Baylor College of Medicine, Houston, TX*

Background: Cancer of unknown primary (CUP) with a “gastrointestinal (GI) profile” appears to be a clinically distinct subset, based on immunophenotyping, specifically staining with cytokeratins 20 (CK20) and 7 (CK7), a type I and II keratin, respectively and caudal type homeobox 2 (CDX2) protein, a transcription factor expressed in nuclei of intestinal epithelial cells. However, only a limited clinicomolecular account of this entity exists. Comprehensive profiling is needed to substantially impact personalized therapeutics and improve prognosis. **Methods:** We identified 401 pts evaluated at MD Anderson Cancer Center. Pts were classified into 3 cohorts based on immunohistochemistry: lower GI profile CUP (LGI-CUP), other-GI profile CUP (OGI-CUP), or non-GI CUP (NGI-CUP). A control group of known lower GI primary cancers was derived from MSK-IMPACT data (cBioPortal, 1075 patients, LGI-KP). Clinical and pathological data including molecular profiling, therapy and survival were logged. Fisher-exact test was used. Kaplan-Meier method was used to estimate overall survival (OS) and compared with log-rank test. **Results:** Among 748 pts, 401 (53.6%) had adequate immunostaining for analysis. Of these, 72 (18.0%), 226 (56.4%) and 103 (25.7%) were classified as LGI-CUP, OGI-CUP, and NGI-CUP, respectively. LGI-CUP were enriched for adenocarcinoma (88% v 86% v 35%, $P < 0.0001$) and good risk Culine score (59% v 51% v 37%, $P = 0.02$), compared to OGI-CUP and NGI-CUP, respectively. While NGI-CUP had greater proportions of poorly differentiated histology (91% v 55% v 66%, $P < 0.0001$) and bone metastases (30% vs 7% v 24%, $P = 0.0001$) compared to LGI-CUP and OGI-CUP, respectively. Comparison of key mutations is shown in table. Median OS of LGI-CUP (14.6 months [95%CI: 12.0 – 17.2]) was similar to OGI-CUP (14.3 months [95% CI: 10.7 – 18.0]) and NGI-CUP (16.2 months [95%CI: 12.4 – 20.0]), $P = 0.75$, but significantly lower than LGI-KP cohort (28.6 months, [95%CI 24.4 – 32.7], $p < 0.001$). LGI-CUP was treated preferentially with fluoropyrimidine-based GI regimen [5-FU/capecitabine +/- oxaliplatin or irinotecan] (77% vs 43% v 5%) compared to OGI-CUP and NGI-CUP, respectively. However, median OS for LGI-CUP treated with 5-FU-based regimens was higher (16.0, 95%CI 13.0 – 19.0) than those treated with non-5-FU-based treatments (10.9, 95%CI 5.6 – 16.2), $P = 0.002$. **Conclusions:** LGI-CUP appears to be a molecularly distinct entity from and NGI-CUP, as well as lower GI CUP from known entities. LGI-CUP patients treated with 5-FU-based regimens appear to have improved survival. Research Sponsor: None.

Key mutations.	LGI-CUP % (reference)	OGI-CUP	P	NGI-CUP	P	LGI-KP	P
TP53	39	39	1	44	0.78	70	0.003
APC	27	7	0.02	0	0.02	70	< 0.0001
KRAS	31	24	0.42	15	0.11	47	.05

3605

Poster Session

Cost-effectiveness analysis of later-line therapies for metastatic colorectal cancer (mCRC) based on a novel methodology of network meta-analysis (NMA) of survival curves. *First Author: Mavis Obeng-Kusi, The University of Arizona, Tucson, AZ*

Background: With advances in the management of mCRC, survival outcomes of patients have improved. While some patients still progress after first and second lines of treatment, there remain options for third or later-line treatment. This study aimed to determine the cost-effectiveness of later-line (>3) treatments for patients with mCRC in the US, based on a NMA of survival curves. Unlike conventional NMA using constant hazard ratios, this method is not constrained by the proportional hazard assumption and uses parametric fitting that incorporates the shape and scale parameters to provide time-varying treatment effects. **Methods:** The NMA compared the efficacy of 6 treatments, atezolizumab+/-cobimetinib (ATE+/-COB), fruquintinib (FRU), regorafenib (REG), TAS-102+/-bevacizumab (TAS+/-BEV), including biosimilar, to placebo (PBO). The study used a 3-state partitioned survival model over a 5-year time horizon incorporating drug acquisition, administration, adverse events, monitoring, and end of life costs, and utilities sourced from literature. Total costs, life-years (LY) and quality-adjusted LYs (QALY) for each treatment were determined. Incremental cost-effectiveness (ICER) and incremental cost-utility ratios (ICUR) were estimated using PBO as a common comparator. **Results:** Over the 5-year period and across the 6 therapies, survival ranged from 0.62 LYs for PBO to 1.15 LYs for TAS+BEV, translating to QALYs ranging from 0.44 for PBO to 0.85 for TAS+BEV. Total costs of treatment ranged from 278,877 for PBO to 417,495 for TAS+BEV (405,002 with biosimilar). TAS+BEV yielded the lowest ICER of an additional 261,421 (237,860 with biosimilar)/LY gained (g) and ICUR of an additional 343,458 (312,504 with biosimilar)/QALYg; while ATE presented the least favorable ICER and ICUR of an additional \$522,602/LYg and \$701,381/QALYg, respectively (Table). **Conclusions:** Among the 6 treatments evaluated, TAS+BEV emerged as the most cost-effective later-line treatment for mCRC while atezolizumab was the least cost-effective. Additionally, replacing BEV with a biosimilar reduces costs and enhances cost-effectiveness, improving access for patients. Research Sponsor: None.

Base case cost-effectiveness and cost-utility analyses.					
Regimen	LY	QALY	Cost (\$)	ICER	ICUR
PBO	0.62	0.44	278,877	Reference	Reference
ATE	0.69	0.50	316,170	522,602	701,381
ATE+COB	0.79	0.57	342,976	369,374	507,025
FRU	0.84	0.62	355,796	352,422	437,455
REG	0.85	0.61	353,604	325,797	439,791
TAS	0.81	0.58	334,000	290,850	387,582
TAS+BEV	1.15	0.85	417,495	261,421	343,458
TAS+BEV_biosimilar	1.15	0.85	405,002	237,860	312,504

3607

Poster Session

Impact of vitamin D on the colon tumor immune microenvironment: Results of a randomized clinical trial of preoperative vitamin D supplementation in patients with stage I-III colon cancer. *First Author: Andressa Dias Costa, Dana-Farber Cancer Institute, Boston, MA*

Background: Although the anti-tumor properties of vitamin D in colorectal cancer (CRC) have been broadly reported, its potential role as a tumor microenvironment (TME) immunomodulator has not been well established. Vitamin D receptor (VDR) and CYP27B1 (1- α -hydroxylase; required to convert vitamin D to its active form) are critical factors in the vitamin D signaling pathway and harbor prognostic significance for CRC. Pre-clinical studies suggest that higher stromal VDR expression enhances chemotherapy efficacy. To characterize the effects of vitamin D on the TME in humans, we conducted a randomized placebo-controlled trial of preoperative high-dose vitamin D supplementation in stage I-III colon cancer patients. **Methods:** Forty-two patients were randomized to receive vitamin D3 50,000 IU/day x 7 days followed by 10,000 IU/day versus placebo prior to resection. Paired pre-treatment biopsy specimens and post-treatment surgical resection specimens from 19 patients who completed the assigned treatment and had sufficient tissue for analysis were collected for spatially-resolved immune cell profiling and evaluation of VDR and CYP27B1 expression using custom multiplex immunofluorescence. Blood samples were collected pre- and post-treatment to assess plasma 25-hydroxyvitamin D [25(OH)D] levels. Linear mixed effects models were used to compare tissue parameters; plasma 25(OH)D level changes were assessed using the Wilcoxon rank-sum test. **Results:** Patients randomized to high-dose vitamin D had increased post-treatment plasma 25(OH)D (median 18.0 to 63.6 (ng/ml)) whereas placebo-randomized patients did not (median 19.1 to 18.6 (ng/ml)) ($p < 0.001$). Analysis of both biopsy and resection tissue revealed highly heterogeneous VDR and CYP27B1 expression. VDR expression was highest in tumor cells, followed by immune and then stromal cells. Although resection tissue from vitamin D-treated patients showed lower VDR expression than specimens from placebo-treated patients in all cells ($p = 0.03$), VDR was preferentially expressed by tumor cells at the tumor invasive front compared to tumor center in the vitamin D arm, while the opposite was observed in the placebo arm. Vitamin D supplementation did not alter CYP27B1 expression. While treatment did not change total immune cell density, resection tissue from vitamin D-treated patients had higher overall CD3⁺CD8⁺ T cell density ($p = 0.04$), particularly CD3⁺CD8⁺ memory T cell density ($p = 0.02$). Additionally, vitamin D supplementation led to greater co-localization between CD3⁺CD8⁺ T cells and tumor cells ($p < 0.001$) compared to placebo. **Conclusions:** In patients with stage I-III CRC, vitamin D supplementation led to changes in vitamin D pathway signaling and evidence of an anti-tumor effect in the TME. Further investigation into the underlying mechanism of action is warranted. Clinical trial information: NCT02172651. Research Sponsor: U.S. National Institutes of Health.

3608

Poster Session

Predictive value of tumor-infiltrating lymphocyte (TIL) dynamics in the tumor microenvironment (TME) during preoperative chemoradiotherapy (CRT) on pathologic complete response (pCR) in microsatellite-stable (MSS) locally advanced rectal cancer (LARC). *First Author: Mitsuho Imai, TR supporting office, National Cancer Center Hospital East, Kashiwa-Shi, Japan*

Background: Preoperative CRT followed by consolidation nivolumab before surgery showed a promising pCR rate in MSS LARC; both high PD-L1 expression and an elevated CD8⁺ T cell/effector regulatory T cell ratio analyzed by pre-CRT samples were independently related to high pCR rate (Bando H, Clin Cancer Res. 2022). Here, we applied AI-powered spatial TIL analysis to the VOLTAGE study to investigate whether dynamic change of TIL in TME may predict pCR in MSS LARC. **Methods:** The VOLTAGE study is a multi-center phase I/II study to evaluate the efficacy of CRT followed by 5 cycles of nivolumab and surgery in patients (pts) with LARC. In this study, tumor samples were obtained at multiple time points; pre-CRT (B1), post-CRT/pre-nivolumab (B2), post-3 cycles of nivolumab (B3), and surgery. In this analysis, a total of 86 H&E whole-slide images (WSI) harvested at B1 and B2 time points from all the pts enrolled in the VOLTAGE study were included in the analysis. Lunit SCOPE IO (Lunit, Republic of Korea), AI-powered H&E-WSI analyzer developed based on 16,443 WSI with pathologists' annotations, was applied to quantify TIL density in TME. **Results:** In a total of 43 pts, pCR rate of MSS and microsatellite instability-high (MSI-H) were 28.9% (11/38) and 60% (3/5), respectively. In MSS subgroup (n = 38), which has a higher unmet need for pCR prediction, tumor samples with pCR (n = 11) had increased TIL density in TME (tTIL) in post-CRT (B2, median [IQR] 726 [249-1607] /mm²) compared to pre-CRT (B1, 598 [366-905] /mm²), whereas those without pCR (n = 27) had decreased tTIL in post-CRT (405 [148-748] /mm²), compared to pre-CRT (B1, 748 [460-1153] /mm²). Intratumoral TIL density changes were more prominent than stromal TIL density changes in MSS tumor samples with pCR (mean fold change x17.7 vs. x1.5). MSS Pts with tTIL change from B1 to B2 (during CRT) more than x1.8 times achieved 75% (6/8) pCR rate, whereas those with tTIL change less than x1.8 had 16.7% (5/30) pCR rate (p = 0.0035). **Conclusions:** Change of TIL density in TME during CRT was significantly correlated with favorable clinical outcome of preoperative CRT and consolidation nivolumab, resulting in high pCR rate in MSS LARC. Research Sponsor: Lunit Inc.

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Poster Session

Combined associations of a healthy lifestyle and body mass index on colorectal cancer recurrence and survival: A cohort study. *First Author: Shabane Barot, Department of Clinical Science and Education, Karolinska Institutet, Södersjukhuset, Stockholm, Sweden*

Background: Colorectal cancer (CRC) risk is associated with modifiable lifestyle factors including smoking, physical inactivity, Western diet, and excess body weight. The impact of lifestyle factors on survival is less known. A cohort study was conducted to investigate the combined effects of a pre-diagnostic healthy lifestyle and body mass index (BMI) on prognosis following CRC diagnosis. **Methods:** Treatment and follow-up data were collected from the patient files of 1098 participants from the Swedish Colorectal cancer low-risk study cohort including stage I-III CRC patients. A healthy lifestyle and BMI (HL) score was computed using self-reported data on smoking status, physical activity, adherence to a Mediterranean diet pattern, and BMI five years before diagnosis, and divided into four categories ranging from least to most healthy. Survival analyses were performed to assess recurrence-free survival and overall survival across categories of exposure, using the Kaplan-Meier method and Cox proportional hazards model, the latter adjusted for age, sex, and educational level. **Results:** Among 1098 participants with stage I-III CRC, 233 (21.2%) had an HL score of 0-1 (least healthy), 354 (32.2%) HL score of 2, 357 (32.5%) HL score of 3 and 154 (14.0) HL score of 4 (most healthy). Participants missing follow-up data (n = 29) or relapsing ≤ 6 months (n = 29) were excluded from the recurrence-free survival analysis. 221 events of cancer recurrence were observed among 1040 participants during a median follow-up time of 4.3 years, and 542 deaths among 1098 participants during a median follow-up time of 6.3 years. Patients with the healthiest lifestyle had an improved recurrence-free survival (HL 4 vs HL 0-1, HRadj 0.51 (95% CI 0.31-0.83) and overall survival (HL 4 vs HL 0-1, HRadj 0.52 (95% CI 0.38-0.70)). Stratifying these results for cancer stage (I-III) and tumor site (colon/rectum) did not alter estimated HRs or 95% CI: s. Avoidance of smoking and being physically active were independently associated with improved recurrence-free survival and overall survival: non-smoking vs smoking HRadj 0.62 (95% CI 0.43-0.90), high vs low levels of physical activity HRadj 0.71 (95% CI 0.54-0.94). **Conclusions:** Our study indicates that pre-diagnostic adherence to a healthy lifestyle may increase the recurrence-free and overall survival of patients with stage I-III CRC. Avoidance of smoking and being physically active were the strongest risk-reducing factors for these outcomes. Research Sponsor: Stockholm County Council (ALF project).

HL-score	Recurrences, n	Deaths, n	Univariate		Multivariate			
			CRC recurrence	All-cause death	CRC recurrence	All-cause death	CRC recurrence	All-cause death
			HR	95% CI	HR	95% CI	HR	95% CI
0-1 p	65	132	1 (ref)		1 (ref)		1 (ref)	
2 p	60	164	0.57	0.40-0.81	0.70	0.55-0.67	0.57	0.40-0.81
3 p	72	177	0.66	0.47-0.92	0.84	0.67-1.06	0.66	0.47-0.93
4 p	24	69	0.51	0.32-0.81	0.65	0.48-0.87	0.51	0.31-0.83

3610

Poster Session

Immunotherapy for localized MSI-H colorectal cancer: Characterizing endoscopic and imaging response. *First Author: Daniel Aaron Fox, Baylor College of Medicine, Houston, TX*

Background: Early data suggests that immunotherapy (IO) for localized colorectal cancer (CRC) is associated with high rates of pathologic complete response (pCR) and durable remission. This study aims to characterize endoscopic, imaging, and pathological outcomes among patients who received IO for localized CRC. **Methods:** This was a single-institution retrospective analysis of patients with MSI-H CRC who received at least one cycle of anti-PD-1 therapy for localized (stage I-III) MSI-H CRC. Patient and tumor characteristics were obtained from the clinical record. Endoscopy reports were assessed using standardized criteria to determine response and imaging was assessed using RECIST v1.1 where applicable. Endoscopic complete response (endoCR) was characterized by flat, white scar and/or telangiectasia without residual ulcer or nodularity. Categorical variables were compared using Fisher's exact test. **Results:** 37 patients who received a median of 8 cycles of pembrolizumab (n = 36) or nivolumab (n = 1) for localized CRC were identified, of which 16 (43%) had a rectal primary. 10 patients (27%) had mucinous features on pathology. The best endoscopic response was complete response (CR) in 13 of 30 (43%) patients, which was achieved after a median of 6 cycles. The rate of endoCR after ≤ 4 cycles of IO was similar to the rate of endoCR after > 4 cycles (29% vs 50%, p = 0.284). The best imaging response was CR in 6 of 32 (19%) of patients. The rate of CR on imaging after ≤ 4 cycles and > 4 cycles of IO was 6% and 36% respectively (p = 0.064). In cases where imaging and endoscopy were available (n = 24), discrepancy in best response was noted in 14 (58%) cases. The most common discrepancy was partial response on imaging when endoCR was noted (n = 6 cases). 16 patients proceeded to surgical resection (after a median of 8 cycles) of which 11 (69%) had pCR despite non-CR on either endoscopy (n = 7) or imaging (n = 9). The endoscopic reports indicating residual disease prior to surgery included findings such as ulceration, scarring, strictures, and an obstructing mass. Of 15 patients who did not proceed to surgery and had follow-up more than 6 months after completion of IO, 13 (87%) had no evidence of progression at a median follow-up of 19.3 months from IO start. **Conclusions:** Discrepancies between endoscopic, imaging, and pathological outcomes were frequent, indicating a need for improved clinical response criteria. Nevertheless, immunotherapy was associated with deep and durable responses in most patients with localized MSI-H CRC. Research Sponsor: None.

3611

Poster Session

The role of image-guided volume-adapted high-dose-rate endorectal brachytherapy boost in total neoadjuvant treatment of distal locally advanced rectal cancer. *First Author: Huangang Jiang, Department of Radiation and Medical Oncology, Zhongnan Hospital, Wuhan University, Wuhan, China*

Background: Endorectal brachytherapy has been used as palliative or preoperative treatment for advanced or locally advanced rectal cancer, with moderate radiation induced toxicity. This study aimed to explore the efficacy of high-dose-rate ¹⁹²Ir brachytherapy combined with external beam radiotherapy (EBRT) in total neoadjuvant treatment (TNT) of distal rectal cancer. **Methods:** From January 2017 to December 2022, eligible rectal adenocarcinoma patients were assessed as clinical stage II -III, with primary tumor located in distal rectum (≤ 5 cm from anal verge). The local staging was determined using endorectal ultrasound and magnetic resonance imaging (MRI). In addition, cases included in this study underwent preoperative semineck endorectal brachytherapy of 8-12Gy/2-3F/1-1.5w, followed by EBRT of 45-50.4Gy/25-28F, fluorouracil-based concurrent and consolidation chemotherapy. The brachytherapy was image-guided volume-adapted, and delivered by multi-channel ¹⁹²Ir source applicators with different diameters. Radiation proctitis was graded from 0 to 4 using Radiation Therapy Oncology Group (RTOG) criteria. **Results:** A total of 40 cases were enrolled in this retrospective study, biopsy-proven and diagnosed as clinical stage II (n = 8), stage III (n = 32). The rates of T4 and positive circumferential resection margin (CRM) were 35% and 87.5% respectively. The median value of the interval from completion of radiotherapy to operation was 86 days (interquartile range: 75-98 days). After neoadjuvant treatment, 2 cases were undergoing the watch-and-wait strategy with sustained clinical complete response (cCR), 38 patients received operation and R0 resection rate was 97.4%. The pathological complete response (pCR) rate was 28.9%, and major pathological regression rate was 67.5%. The theoretical rate of anus preservation was 62.5%, including 6 of 21 cases underwent abdominoperineal resection but achieved pCR, 17 cases underwent low anterior resection or intersphincteric resection, and 2 cases with sustained cCR. After a median follow-up of 37 months (range 12-68 months), the 3-year disease-free survival, local-regional recurrence-free survival and overall survival was 81.1% (95%CI: 64.3%-91.2%), 94.9% (95%CI: 80.6%-98.5%) and 96.9% (95%CI: 82.1%-99.4%), respectively. No patients experienced Grade ≥ 3 radiation proctitis. The median Wexner fecal incontinence score of anus-preserving cases was 1 (range 0-8). Subgroup analysis showed that the complete response rate (pCR or sustained cCR) was lower in cases received 2 fractions brachytherapy than those received 3 fractions (27.8% vs 36.4%). **Conclusions:** The addition of image-guided volume-adapted high-dose-rate ¹⁹²Ir endorectal brachytherapy boost to TNT could improve the pathological tumor response and anus preservation rate in distal locally advanced rectal cancer. Research Sponsor: Oncology Leading Discipline Construction Support Project, Zhongnan Hospital Of Wuhan University (XKJS202005); Discipline Cultivation Funding (Oncology), Zhongnan Hospital of Wuhan University (ZNXKPY2020012).

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Poster Session

The number of lymph nodes examined as a poor prognosis factor in stage II and stage III colon cancer patients undergoing curative surgery. *First Author: JEONGSEOK JEON, Yonsei University College of Medicine, Seoul, South Korea*

Background: The number of lymph nodes (LN) examined is a key factor in determining the stage of colorectal cancer. Over the past 20 years, the examination of fewer than 12 LN has been regarded as a poor prognosis. However, surgical procedures and pathologic examination improvements have increased the number of LN examined. This raised the question of reassessing the best cutoff point for staging colon cancer patients undergoing curative surgery. **Methods:** We reviewed a total of 3,126 eligible patients with stage II-III colon cancer collected from the Yonsei Cancer Center Registry (YCC) database between 2005 and 2015. As a validation cohort, we used clinicodemographic data from 9,604 patients with stage II-III colon cancer identified by the Netherlands Cancer Registry (NCR) between 2006 and 2015. The hazard ratio (HR) obtained from Cox-proportional regression was used to investigate the effect of LN's yield on 6-year overall survival (OS). The optimal LN yield was evaluated by analyzing every cutoff from 3 to 165. We used the Kaplan-Meier method to compare the effect of higher vs. lower optimal LN yield on a 6-year OS. Univariate and multivariate Cox regressions were conducted. **Results:** The proportion of patients with fewer than 12 LN examined dramatically decreased between 2005 and 2015 (17.4% in 2005 vs. 0.6% in 2015, $P < 0.001$). Based on the 12 LN examined as the conventional cutoff number, there was no significant association between 6-year OS and LN yield in all stages II-III patients (HR = 1.21, $P = 0.116$; $n = 3,126$), stage II (HR = 1.39, $P = 0.068$; $n = 1,570$), and stage III (HR = 1.18, $P = 0.297$; $n = 1,557$) colon cancer. Interestingly, a higher cutoff of 20 LN examined was associated with a significant increase in 6-year OS in all patients (HR = 1.51, $P < 0.001$ in patients with LN examined less than 20). Multivariate Cox-proportional hazard regression showed a significant decrease in 6-year OS in stage II (HR = 1.39, $P = 0.026$) and stage III (HR = 1.54, $P < 0.001$) with less than 20 LN yield. Consistent with the result in the YCC database, less than 20 of LN yield was associated with poorer 6-year OS in stage II-III patients (HR = 1.25, $P < 0.001$; $n = 9,604$), stage II (HR = 1.43, $P < 0.001$; $n = 4,689$), and stage III (HR = 1.13, $P = 0.007$; $n = 4,915$) in the NCR, respectively. **Conclusions:** Less than 20 LN examined is associated with a poorer prognosis in patients with surgically treated colon cancer, compared to the current cutoff value of 12. Further validation of re-evaluating criteria on the inadequacy of LN retrieval in high-risk stage II colon cancer is warranted. **Research Sponsor:** A grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (grant number : HI22C0353); The National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (No. 2022R1A2C4001879).

3614

Poster Session

The significance of mucin on rectal MRI in patients with locally advanced rectal cancer being considered for watch-and-wait after neoadjuvant therapy. *First Author: Sean Judge, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Neoadjuvant therapy (NAT) leads to a clinical complete response (cCR) in a significant proportion of patients with locally advanced rectal cancer (LARC) allowing for possible non-operative management. Along with physical exam and proctoscopy, magnetic resonance imaging (MRI) is used to evaluate for residual tumor following NAT. The presence of mucin on MRI leads to uncertainty about residual disease and appropriateness of watch-and-wait strategy (WW) in patients with no evidence of disease on proctoscopy (endoscopic cCR). We set out to determine the impact of radiographic mucin in patients with LARC after NAT. **Methods:** MRI reports between July 2016 to January 2020 at Memorial Sloan Kettering Cancer Center were queried for the presence of mucin in the tumor bed on post-treatment rectal MRI in patients with LARC following NAT. The clinicodemographic, pathologic, and outcomes data from these patients were compiled and analyzed. **Results:** Seventy-one patients were included in the final analysis who fit the pre-specified inclusion criteria (Table). Of the 71 patients with mucin present on post-treatment MRI, 19 patients (27%) entered a watch-and-wait (WW) strategy and 52 patients (73%) were planned for surgery (non-WW). Comparing the WW and non-WW cohorts, there was no difference in age, sex, clinical nodal status, or neoadjuvant regimen. Patients entering a WW protocol had a higher proportion of cT1-T2 tumors (32%) compared to non-WW (4%) ($P < 0.01$). All WW patients had endoscopic cCR, while only one non-WW patient achieved endoscopic cCR. Of 52 non-WW patients, 49 underwent resection and 3 did not have surgery due to disease progression. The pathologic complete response (pCR) rate in the non-WW patients who underwent surgery was 10%. Of 19 WW patients, 4 experienced regrowth (21%), while 15 (79%) have no local regrowth, with a median follow up of 4.2 years (range 2.4-6.3 yrs). Two patients (11%) experienced distant failure. **Conclusions:** The presence of mucin after NAT for LARC should not necessarily preclude a WW strategy in otherwise appropriate candidates who achieve an endoscopic cCR. **Research Sponsor:** U.S. National Institutes of Health.

Characteristic	Patients (No.)		P-value
	WW (n = 19)	Non-WW (n = 52)	
Age, median (range), yrs.	60.6 (30.3 – 75.5)	58.5 (35.2 – 82.8)	0.90
Male	13 (68)	31 (60)	0.58
Clinical tumor (T) classification			
cT1-T2	6 (32)	2 (4)	< 0.01
cT3-T4	13 (68)	50 (96)	
Clinical nodal (N) classification			
cN1-2	18 (95)	43 (83)	0.27
Neoadjuvant Regimen			
Chemotherapy only	0 (0)	1 (2)	0.60
Chemoradiotherapy only	1 (5)	6 (12)	
Total Neoadjuvant Therapy	18 (95)	45 (86)	
Time from NAT completion to surgery, median (range), yrs.	1.1 (0.9-2.5)	0.2 (0.1-2.8)	< 0.01
Pathologic tumor (T) classification			
pCR	0 (0)	5 (10)	< 0.01
pT1-T2	2 (67)	5 (10)	
pT3-T4	1 (33)	39 (80)	

3613

Poster Session

Efficacy and safety of mFOLFOX6 with apatinib as postoperative adjuvant chemotherapy in stage IIIB or IIIC colorectal cancer. *First Author: Xiaodong Gu, Department of General Surgery, Huashan Hospital, Fudan University, Shanghai, China*

Background: Antiangiogenic therapy has shown benefit in metastatic colorectal cancer. However, the role of apatinib in adjuvant treatment of stage IIIB and IIIC colorectal cancer remains unclear. **Methods:** Patients received modified FOLFOX6 once every 2 weeks for a 6-month period (control group) or modified FOLFOX6 for 6 months plus apatinib (500mg) once a day for a 12-month period (experimental group). Progression free survival (PFS), overall survival (OS) and treatment-related adverse events were evaluated in two groups. **Results:** 63 patients have been enrolled in this study. This trial reported a 3-year PFS of 74.2% for modified FOLFOX6 plus apatinib vs. 61.5% for modified FOLFOX6 ($P < 0.05$). 5-year OS was significantly improved in the experimental group compared with the control group (86.3% vs. 72.5%; $P < 0.05$). The most common grade 3 adverse events were hypertension and hand-foot syndrome. No treatment-related grade 4 adverse events or treatment-related deaths were observed. **Conclusions:** Apatinib can prolong PFS and OS when added to adjuvant chemotherapy in resected stage IIIB and IIIC colorectal cancer. The toxicities associated with apatinib were generally acceptable. Clinical trial information: NCT03365765. **Research Sponsor:** Jiangsu Hengrui Medicine Co., Ltd.

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Poster Session

Mismatch Repair system protein deficiency as a factor of resistance to chemo-radiotherapy treatment in patients with locally advanced rectal adenocarcinoma and its influence on disease-free survival. *First Author: Andrea Pretta, Medical Oncology Unit, University Hospital and University of Cagliari, Cagliari, Italy*

Background: Available data on Mismatch Repair system deficit and microsatellite instability are conflicting and are generally derived from a small number of patients due to the rarity of this condition in rectal cancer. Our study aimed to evaluate the frequency and therapeutic implications of Mismatch Repair proteins (MMR) status in patients with locally advanced rectal cancer (LARC). **Methods:** We retrospectively collected data from 318 patients affected by LARC adenocarcinoma (cT3-4 +/- N1-2) treated at the Medical Oncology Unit of the University Hospital of Cagliari, Italy, the Medical Oncology Department, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy and at the Medical Oncology Unit, AOU Ospedali Riuniti, Ancona, Italy. All patients included in the study underwent neoadjuvant concurrent capecitabine and long-course radiotherapy (RT) (total dose of Gy 50.4), afterwards a total mesorectal excision (TME) was performed. MMR expression was evaluated through immunohistochemistry. The primary objective was major TRG (0-1 Ryan's score) while secondary objectives were pathological complete response, disease-free survival (DFS) and overall survival (OS). **Results:** 160 patients (148 pMMR and 12 dMMR) were included in exploratory cohort and 158 (146 pMMR and 12 dMMR) were included in validation cohort. A major TRG has been shown in 64/148 (42,6%) and 63/146 (43,1%) patients with pMMR in exploratory cohort and validation cohort, respectively; while no major TRG have been shown in dMMR patients in exploratory cohort nor in validation cohort. Both exploratory and validation cohorts showed a statistically significant higher median DFS in pMMR patients compared to dMMR ones: NR vs 14 months in exploratory cohort ($p = 0,003$) and NR vs 17 months in validation cohort ($p = 0,02$). **Conclusions:** Our retrospective study indicated an association between dMMR and poor or no response to preoperative chemoradiotherapy. These results are consistent with the role of MMR as a predictor of poor-response to chemoradiotherapy and represent a hypothesis-generating study for the selection of these patients for immunotherapy in the neoadjuvant setting, in which the available data are immature. **Research Sponsor:** None.

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Poster Session

The Ave-Rec trial: Phase II trial of PD-L1/PD-1 blockade with avelumab plus chemoradiotherapy for locally advanced resectable T3b-4/N1-2 rectal cancer—Toxicity and interim efficacy data. *First Author: Michael Michael, Peter MacCallum Cancer Centre, Melbourne, Australia*

Background: Neoadjuvant long course chemoradiotherapy (LCRT) for locally advanced rectal cancer (LARC) results in a complete pathological response rate in 10-30% of patients (pts), but with 20-40% non-responders and 10-15% have local recurrence. Radiotherapy (RT) is immuno-stimulatory by enhancing local/distant tumour cell death, but also immunosuppressive as it stimulates PDL1 production and myeloid-derived suppressor cell activity. Hence PDL1 inhibition may be required to enhance the immuno-stimulatory effects of RT. **Hypothesis:** In pts with resectable LARC, the anti-PDL1 antibody Avelumab given post LCRT may enhance the pathological/imaging response rates whilst reducing local/distant relapse rates. **Methods:** Phase II single arm trial. All pts had standard LCRT (50.4Gy RT plus 5FU [225mg/m²/day/CI] or Capecitabine [825mg/m² BID on days of RT] over 5.5 weeks). Post LCRT (prior to surgery), pts received 4 cycles Avelumab (AV) (10mg/kg, q2 weeks), then surgical resection at 10-12 weeks post LCRT. Fresh tumour biopsy and ctDNA sampling taken pre LCRT, pre Cycle 1 AV and at surgery. Response by FDG PET/CT and pelvic MRI at 8 weeks post LCRT, pre surgery. **Inclusion Criteria:** pts with LARC (MRI stage T3b-4/N1-2/M0), planned for LCRT followed by curative resection, tumoural lower border within 12cm from anal verge, measurable disease (RECIST1.1), ECOG 0-1, adequate organ function and no contraindications to AV therapy. **Endpoints:** (a) *Primary:* Complete pathological response rate post-LCRT (Target ≥ 35%), documented by central pathologist, (b) *Secondary:* MRI and FDG PET/CT imaging responses by RECIST1.1 and PERCIST, respectively. Toxicity. (c) *Exploratory:* Tumoural immune cell subsets/checkpoint expression (by multiplex immunohistochemistry and in-vitro functional assays) and ctDNA analysis. Distant relapse-free survival and the sites of relapse. ANZCTR: NCT03299660. **Results:** 37 pts across 6 sites, with 33 patients (89%) received allocated interventions: LCRT, AV and surgery (where possible). Age median 55 years (31-76). M:F 23:10. Baseline tumoural stage: T3b-d 75%, T4a-b 25%. No pts with dMMR/MSI-H tumour. Overall 33 pts completed LCRT, 31 pts (83%) completed all 4 cycles of AV and 32 pts (86%) had planned surgery (22, ULAR, 2 APR, 2 AR, 6 Other). ORR Pelvic MRI presurgery (N = 33): 2 CR, 14 PR, and 31 DCR. FDG PET/CT (N = 31): 10 CMR, 18 PMR and 3 SMD. Overall 10 pts Grade 3/4 AEs, with 15 G3/4 events. Only 3 pts with treatment-related G3 and no G4 AEs. No specific immune-related G3 AEs observed. Post-operative complications were not unexpected. **Conclusions:** Consolidation Avelumab post LCRT for pts with LARC, was well tolerated with promising activity. Pathological response, biological substudies (immunological and ctDNA) and survival endpoints to be reported. Clinical trial information: NCT03299660. Research Sponsor: Merck Australia.

3618

Poster Session

A prospective evaluation of pelvic radiation vs. no radiation among patients with young-onset rectal cancer: Impact on patient-reported outcomes. *First Author: Kelsey L Corrigan, Department of Radiation Oncology, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: The rise in young-onset rectal cancer (YORC) calls for better understanding of the long-term impact of radiation therapy (RT) on gastrointestinal (GI) toxicity and pelvic organ function. We aimed to prospectively capture the longitudinal trajectories of patient-reported outcomes (PROs) in YORC patients who received RT vs. no RT and to identify factors associated with unfavorable PROs. **Methods:** We prospectively enrolled 120 YORC patients undergoing curative-intent treatment. The validated EORTC QLQ-CR29 was self-administered at time intervals grouped as: 0-11 months, 12-23 months, and 24+ months post-resection. Responses were stratified by receipt of neoadjuvant RT (yes vs. no). The longitudinal change in PROs was described by a linear mixed effects model. Multivariate linear regression was used to determine the impact of treatment factors on long-term PROs. **Results:** The median age at diagnosis was 44. The majority (N = 92, 77%) presented with cT3,4/N+ disease. Preoperative therapy included: no RT (N = 38, 32%; 8 [7%] who received chemotherapy alone, and 30 [25%] who received no neoadjuvant therapy), vs. RT (N = 82, 68%; where 59 [72%] also received concurrent capecitabine). More patients in the RT group had advanced T stage (3 or 4; 94% vs. 56%, $P < 0.001$), distal tumor (median 7 vs. 12.5 cm from the anal verge, $P < 0.01$), and underwent abdominal perineal resection (19 vs. 0%, $P < 0.001$). After a median follow-up of 70 months, all were alive: 103 (86%) were disease-free, 9 (8%) had recurrence with successful salvage, and 8 (7%) had disease progression. In the RT group, sore skin improved at 12-23 and 24+ months (Estimate [B]: -16.5, $P = 0.03$ and $B: -14.4$, $P = 0.03$), dyspareunia improved at 12-23 months ($B: -31.8$, $P < 0.01$), and blood/mucus in stool improved at 24+ months ($B: -8.01$, $P < 0.01$) vs. 0-11 months. At 24+ months, RT receipt was associated with worse stool frequency ($B: 26.4$, $P < 0.01$), urinary frequency ($B: 18.4$, $P = 0.04$), and flatulence ($B: 23.0$, $P = 0.02$). **Conclusions:** YORC often require multimodality therapy including RT. Sore skin, dyspareunia, and blood/mucus in stool improved, but flatulence and frequency can persist beyond 2 years post RT. Proactive counseling and supportive measures are needed to inform treatment choices and mitigate long-term impact. Research Sponsor: University of Texas MD Anderson G.S.Hogan Gastrointestinal Research Fund.

EORTC QLQ-CR29 scores stratified by receipt of neoadjuvant RT at each timepoint post-resection (range from 0-100).

	Mean (SD) 0-11 months		Mean (SD) 12-23 months		Mean (SD) 24+ months	
	No RT	RT	No RT	RT	No RT	RT
Urinary frequency	43 (28)	28 (23)	32 (23)	27 (24)	18 (20)	27 (25)
Blood/mucus in stool	10 (22)	10 (13)	3 (7)	6 (11)	4 (13)	4 (8)
Stool frequency	37 (32)	30 (20)	35 (23)	31 (25)	21 (23)	35 (25)
Flatulence	27 (43)	33 (32)	36 (10)	31 (27)	21 (22)	36 (28)
Sore skin	27 (15)	43 (30)	21 (31)	25 (26)	13 (19)	26 (26)
Dyspareunia	67 (47)	67 (30)	33 (0)	42 (36)	24 (36)	46 (34)

Higher score indicates greater symptom burden.

3617

Poster Session

Organ preservation and total neoadjuvant therapy for rectal cancer: Investigating long course chemoradiation versus short course radiation therapy. *First Author: Paul Bernard Romesser, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: The efficacy of long course chemoradiation (LCRT) vs. short course radiation therapy (SCRT) relative to organ preservation (OP) in rectal cancer (RC) is unknown. We compared OP rates between SCRT and LCRT total neoadjuvant therapy (TNT) strategies. **Methods:** During the COVID-19 pandemic we established an institutional SCRT mandate with no exceptions. For comparison, we identified RC patients treated with LCRT immediately before and after the mandate period. After completion of TNT, patients were restaged by clinical exam, endoscopy, and MRI. A watch and wait (WW) approach was recommended for patients with a clinical complete response (cCR), defined by the MSK regression schema. Total mesorectal excision (TME) was recommended for non-cCR patients. OP was defined as remaining TME-free with no evidence of disease in the pelvis. We performed survival analysis for: local regrowth rate, OP, disease-free survival (DFS), and overall survival (OS). The validated low anterior resection syndrome (LARS) questionnaire (LARS-Q) was used to determine percentage of patients with major LARS. **Results:** We identified 332 consecutive patients with non-metastatic rectal adenocarcinoma treated with TNT (Jan. 2018-Jan. 2021). Patient and tumor characteristics were similar in the LCRT (n = 256) and SCRT (n = 76) cohorts. No significant differences in high-risk features were noted. Most patients had clinical stage III disease (82% in LCRT vs. 83% in SCRT). Induction chemotherapy followed by consolidative radiation was the most common treatment order (78% (LCRT) vs. 70% (SCRT)). The median interval from end of TNT to clinical restaging was 8 weeks (LCRT) and 9 weeks (SCRT). The cCR rate was 46% in both cohorts. Among patients with a cCR, the likelihood of WW management was similar (98% (LCRT) vs. 94% (SCRT)). From start of TNT, the median follow-up was 32 and 28 months respectively for LCRT and SCRT. The 2-year OS (95% vs. 92%), DFS (78% vs 70%), and distant recurrence (20% vs. 21%) rates were similar. Among all patients, the 2-year OP rate was 40% (95% CI 35-47%) for LCRT and 29% (95% CI 20-42%) with SCRT. In those patients managed by WW, the 2-year local regrowth rate was 20% (95% CI 12-27%) with LCRT vs. 36% (95% CI 16-52%) with SCRT. Percentage of patients reporting major LARS symptoms were similar among WW patients post TNT: baseline (23% (LCRT) vs. 18% (SCRT)), 6-months (41% (LCRT) vs. 42% (SCRT)), and 12-months (25% (LCRT) vs. 15% (SCRT)). **Conclusions:** In this nonrandomized comparison, while cCR rates were similar, we observed a numerically higher local regrowth rate with SCRT-TNT than with LCRT-TNT. Rate of major-LARS symptoms were similar with LCRT-TNT than with SCRT-TNT. The ongoing ACO/ARO/AIO-18.1 trial, hypothesizing that LCRT-TNT will increase OP rates relative to SCRT-TNT, will definitively address this question. Research Sponsor: U.S. National Institutes of Health.

3619

Poster Session

Prophylactic hyperthermic intraperitoneal chemotherapy in T4 colorectal cancer: Can it improve the oncologic prognosis? *First Author: Lifeng Sun, The Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China*

Background: Previous studies have shown that T4 stage was one of the risk factors for peritoneal metastasis (PM) of colorectal cancer (CRC). However, there is paradoxical data to prove that prophylactic hyperthermic intraperitoneal chemotherapy (HIPEC) treatment is beneficial for CRC patients. **Methods:** In this cohort study, 220 consecutive CRC patients with T4N0-2M0 were enrolled and recorded from November 2014 to November 2018 with a 3-year follow-up following surgery. A propensity score matching (PSM) approach was applied to balance the clinicopathological characteristics. Finally, 180 patients were matched successfully to further analyze. The 3-year disease-free survival (DFS) was set as the primary outcome, and the PM rate between the two groups after PSM was analyzed. **Results:** Before PSM, of 220 CRC patients enrolled, the 3-year DFS was 83.9% in the HIPEC group, which was better than 67.2% in the control group. The cumulative PM incidence was 2.2% in the HIPEC group and 12.6% in the control group ($p = 0.047$). After PSM, 180 matched patients were formed for further analysis. The DFS and the cumulative PM rate of the patients in the HIPEC group were also better than that in the control group ($p = 0.034$ and 0.047 , respectively). For laparoscopic surgery subgroup analyses, PM rate of the patients with laparoscopic surgery was 13.8% in the No HIPEC group, and 2.6% in the HIPEC group ($p = 0.070$). Through multivariable analysis, it was found that prophylactic HIPEC correlated to better DFS [hazard ratio (HR) 0.43, 95% confidence interval (CI) 0.19-0.95; $p = 0.037$], and N2 stage correlated to worse DFS [HR 1.97, 95% CI 1.09-3.56; $p = 0.025$]. Besides, no post-operative death occurred, the anastomotic leakage rate was 2.2% in the HIPEC group and 0.7% in the control group ($p = 0.439$). **Conclusions:** Prophylactic HIPEC may improve the prognosis in the patients with T4N0-1M0 CRC, but not in the T4N2M0 CRC, and it does not significantly increase the surgery-related complications. Laparoscopic surgery followed by HIPEC for T4 stage CRC is relatively safe, which does not increase the risk of PM. Research Sponsor: the National Natural Science Foundation of China [81472819, 81672342]; Zhejiang Provincial Key R&D Program of China [2019C03018], and Zhejiang Provincial Natural Science Foundation of China [LY20H160038].

3620

Poster Session

Treatments and clinical outcomes in stage II colon cancer (CC) patients (pts) with 12-gene Oncotype DX Colon Recurrence Score assay-guided therapy: Real-world data. *First Author: Baruch Brenner, Rabin Medical Center, Petah Tikva, Israel*

Background: The role of adjuvant chemotherapy (CT) in stage II CC is debated. The validated 12-gene Oncotype DX Colon Recurrence Score test provides a Recurrence Score (RS) result (range, 0-100) which estimates recurrence risk (RR) in stage II/III pts. We studied treatment and clinical outcomes in CC pts in whom treatment decisions incorporated the RS result. **Methods:** This prospectively designed cohort study included all stage II, MMR-P, CC pts who underwent the 12-gene Oncotype DX testing through Clalit between 1/2011 and 12/2016 and had available data with minimum 3-yr follow-up. Kaplan-Meier (KM) estimates and log-rank tests were used to compare RR and CC specific mortality (CCSM) between RS categories. Multivariable analysis (MVA) identified variables associated with RR/CCSM. **Results:** The analysis included 938 pts. Median age, 68 (IQR, 60-76) yrs; 96% had T3 tumors, and 89% had ≥ 12 nodes examined. Median RS was 26 (IQR, 19-33). The 3 RS categories (0-29, 30-40, and 41-100) included 65%, 24%, and 11% of pts, respectively. The overall CT use rate was 24%, with a significant difference between the 3 categories (14%, 36%, and 60%, respectively, $P < .0001$). Pts with very low RS (0-15) comprised 14% of the cohort (CT use rate, 11%). Younger pts, and those with invasion/perforation/obstruction were more likely to receive CT. Clinical outcomes with a median follow up of 6.9 (IQR, 5.5-8.6) yrs are presented (Table). Among untreated pts, KM estimates for RR and CCSM differed significantly between the 3 RS categories ($P < .0001$). Outcome of untreated RS 0-15 pts was excellent. In an MVA model, male sex, presence of invasion/perforation/obstruction and higher RS category (RR 41-100 vs 0-29 and vs 30-40, but not RS 30-40 vs 0-29) were associated with increased RR. For CCSM, the results were similar, but this time age ≥ 70 yrs replaced sex as a significant prognostic variable. Clinical outcomes within each RS group did not differ significantly between treated and untreated pts, but were numerically better with CT in the RS 41-100 group. **Conclusions:** This real-world analysis showed that the RS results provide independent prognostic information in stage II CC. Further studies are needed to investigate the potential role of the RS result as a predictor of CT benefit, but the data suggest that this benefit may be limited to pts with high RS results. Research Sponsor: Exact Sciences.

RS group	N (%)	N untreated	N CT-treated	5-yr recurrence risk (95% CI)		5-yr CCSM (95% CI)	
				Untreated	CT	Untreated	CT
Very low: 0-15 (14%)	136	121	15	6.2% (3.0-12.4%)	13.3% (3.4-40.5%)	3.4% (1.3-8.8%)	13.3% (3.4-40.5%)
Low: 30-40 (24%)	606	524	82	13.0% (10.3-16.2%)	15.7% (9.3-25.1%)	4.7% (3.1-6.9%)	6.1% (2.5-13.7%)
Int.: 41-100 (11%)	225	143	82	15.8% (10.6-22.9%)	18.3% (11.3-28.1%)	5.0% (2.4-10.2%)	3.7% (1.2-10.9%)
High: 41-100 (11%)	107	43	64	30.6% (18.2-46.6%)	24.3% (15.4-36.0%)	19.0% (9.3-34.9%)	17.0% (9.7-28.2%)

3622

Poster Session

Molecular profiling and characterization of the tumor immune microenvironment (TME) in appendiceal carcinoma (AC). *First Author: Muneeb Rehman, Ruesch Center for the Cure of Gastrointestinal Cancers, Lombardi Comprehensive Cancer Center, Georgetown University, Washington, DC*

Background: The rarity of AC presents challenges in understanding disease pathogenesis. We previously showed that AC has higher rates of mutations in *KRAS* and *GNAS* and lower rates of *TP53*, *APC*, and *PIK3CA* than CRC. The appendix also has many lymphoid clusters and regulates IgA production in the large bowel, suggesting that AC may be subject to more lymphocytic regulation than CRC. We sought to characterize the molecular profile and TME across AC histopathological types. **Methods:** AC samples were analyzed by DNA sequencing (592 genes, NextSeq, or whole exome sequencing, NovaSeq), whole transcriptome sequencing (WTS, NovaSeq), and immunohistochemistry (IHC) for molecular profiling, including microsatellite instability (MSI), mismatch repair (MMR), PD-L1 (SP142), and tumor mutational burden (TMB). Microenvironment Cell Population-counter Quantiseq was used to quantify tumor immune contexture using WTS. AC histopathology was derived from pathology reports. Mann-Whitney U and ChiSquare tests were applied as appropriate, with P-values adjusted for multiple comparisons using Benjamin-Hochberg. **Results:** AC (N = 731) were grouped by histology: 5% goblet cell (GC), 6% high-grade adenocarcinoma (HGA), 14% low grade mucinous (LGM), 33% mucinous adenocarcinoma (MA), 1% pseudomyxoma peritonei (PMP), 6% signet ring cell carcinoma (SRC), and 35% adenocarcinoma not otherwise specified (NOS) (see Table). Age at collection and PD-L1+ (0-5.2%) did not differ by histopathology. Seven patients had dMMR (4 NOS and 3 MA). Median TMB was significantly higher in NOS vs. GC (4 mutations/megabase vs 2, $q < 0.001$), NOS vs. LGM (4 vs 3, $q = 0.048$), MA vs. GC (4 vs 2, $q < 0.001$), and MA vs. LGM (4 vs 3, $q = 0.037$). Distinct TME patterns were observed in NOS vs. MA (median cell fraction: dendritic cells 0.07 vs 0, $q < 0.01$; M2 macrophages 0.055 vs 0.042, $q = 0.030$; natural killer cells 0.034 vs 0.031, $q = 0.011$; CD4 T cells 0.006 vs 0, $q = 0.044$) and GC vs. MA (M1 macrophages 0.039 vs 0.057, $q = 0.021$; dendritic cells 0.012 vs 0, $q < 0.01$; B cells 0.061 vs 0.050, $q = 0.013$; M2 macrophages 0.074 vs 0.042, $q < 0.01$; natural killer cells 0.041 vs 0.031, $q = 0.01$; and neutrophils 0.017 vs 0.038 $q = 0.045$). T cell inflamed signature (TIS) and immune-oncology (IO) marker gene expression were higher in HGA and lower in LGM and MA. Somatic mutation rates differed by histopathology (see Table). **Conclusions:** There is significant heterogeneity in TMB, TME, and mutational profiles across AC histologies. MA has a particularly immune-cold TME shown by lower infiltration of lymphocytes, TIS, and IO gene expression. These findings are critical to identify novel biomarkers and develop new therapeutic strategies for AC. Research Sponsor: None.

Gene	AC Subtype					
	GC (N = 36)	HGA (N = 43)	LGM (N = 104)	MA (N = 239)	PMP (N = 10)	NOS (N = 253)
GNAS	2.8%	31%	77.4%	43%	100%	5.6%
KRAS	5.7%	56.1%	94.5%	78.3%	100%	37.4%
TP53	14.7%	26.2%	9.9%	47.2%	0%	56%
APC	2.8%	7.1%	3.2%	5.2%	0%	23.2%

3621

Poster Session

Efficacy and safety of KNO26 in combination with KNO46 in patients with locally advanced unresectable or metastatic HER2-positive other solid tumors. *First Author: Jifang Gong, Beijing Cancer Hospital, Beijing, China*

Background: Besides breast cancer (BC) and gastric cancer, HER2 is also widely expressed in other solid tumors, such as colorectal cancer (CRC), NSCLC, gall-bladder cancer (GBC), renal pelvis cancer (RPC), pancreatic ductal adenocarcinoma (PDAC), etc. The reports of immunotherapy combined with HER2-targeted therapy are limited. KNO26 is a novel bispecific antibody that simultaneously binds to two distinct HER2 epitopes. KNO46 is a novel bispecific antibody that blocks both PD-L1 interaction with PD-1 and CTLA-4 interaction with CD80/CD86. **Methods:** KNO26-203 study (NCT04521179) is an open-label, phase II, multicenter study to evaluate the efficacy and safety of KNO26 (30mg/kg, Q3W, C1D1 and C1D8 loading) combined with KNO46 (5mg/kg, Q3W) in patients (pts) with HER2-positive (defined as HER2 IHC 3+ or HER2 gene amplification) solid tumors. The study consisted of 3 cohorts, including HER2 positive gastric or gastroesophageal cancer (GC/GEJ), BC and other solid tumors. Pts received treatment until disease progression or unacceptable toxicity. Tumor assessments were scheduled every 6 weeks. The primary endpoints were ORR and DOR. The efficacy and safety of KNO26 combined with KNO46 were reported. **Results:** As of 10 November 2022, 26 pts with HER2 positive tumor other than BC and GC/GEJ were enrolled, including 15 CRC, 5 NSCLC, 4 GBC, 1 RPC and 1 PDAC pts. All those pts had previous systemic treatment. The median age was 56 (range 37 ~ 67) years. 15 (57.7%) pts had liver metastasis. 92.3% of pts and all CRC pts had received ≥ 2 lines prior treatment. 5 (19.2%) and 6 (23.1%) pts had received prior anti-HER2 and anti-PD-(L)1 therapy, respectively. All 26 pts were assessed according to RECIST v1.1. The confirmed ORR was 53.8% (95% CI: 33.4, 73.4) with mDOR 6.8 months (95% CI: 2.9, 15.3). The mPFS was 5.6 months (95% CI: 2.9, 16.5) and 12-month OS rate was 80.4% (95% CI: 59.1, 91.4) with median follow-up time 16.6 months. For 15 CRC pts, the ORR was 53.3% (95% CI: 26.6, 78.7) with mDOR 11.7 months (95% CI: 3.2, NE). The mPFS was 12.2 months (95% CI: 2.7, NE). 12-month OS rate was 80.0% (95% CI: 50.0, 93.1) with median follow-up time 16.0 months. Common TRAEs were infusion related reaction (38.5%), AST increased (34.6%), ALT increased (26.9%), conjugated bilirubin increased (26.9%), rash (26.9%), anemia (26.9%) and blood bilirubin increased (26.9%). Most of them were Grade 1 or 2. The most common $\geq$ Gr3 TRAEs were conjugated bilirubin increased (7.7%) and AST increased (7.7%). There was no treatment related death. **Conclusions:** KNO26 combined with KNO46 treatment had demonstrated favorable efficacy and safety profile in HER2 positive other solid tumors (non-GC/GEJ and non-BC). Especially very promising efficacy were observed in ≥ 3 lines HER2 positive CRC. Based on these results, a pivotal study was planned to verify the efficacy and safety of KNO26 and KNO46 combo. Clinical trial information: NCT04521179. Research Sponsor: Alpmab.

3623

Poster Session

Comparison of synchronous neoplasms at colonoscopic diagnosis of early-onset versus average-onset colorectal cancer. *First Author: Oluwadunni Eunice Emiloju, Mayo Clinic, Rochester, MN*

Background: Colorectal cancer (CRC) incidence has steadily increased in adults younger than 50 years (EO-CRC) since the 1990s, with a predominance in the left colon and rectum. Precursor lesions of CRCs are adenomas, including advanced adenomas, and sessile serrated polyps. Given that neoplastic development is age-related, we hypothesized that patients with early-onset CRC (EO-CRC) may have fewer adenomas compared to patients with average-onset CRC (AO-CRC) at diagnosis. **Methods:** We performed a retrospective review of electronic health records at Mayo Clinic or Mayo Health System [2012 to 2021] and randomly selected 150 patients with EO-CRC who met eligibility criteria and matched them with 150 AO-CRC patients based on gender and colonoscopy indication. Known hereditary syndromes or inflammatory bowel disease were excluded. At colonoscopy where CRC was diagnosed, we recorded findings of adenomas, advanced adenomas (> 1 cm, villous histology, or high-grade dysplasia), and sessile serrated polyps (SSP). **Results:** Median age at diagnosis was 43 years for EO-CRC and 67 years for AO-CRC. No significant differences in BMI, family history of CRC, MMR, *BRAF*^{V600E} *KRAS* status or SSPs were found between groups (all $p > 0.05$). Among patients with colon cancer, no difference was found for adenoma number yet patients with EO-colon cancer (EO-CC) had larger polyps [median of 10 mm vs 5 mm, $p = 0.001$] (Table) compared with AO-colon cancer (AO-CC). At least 1 adenoma was found in 56% and 47% of patients with EO-CC and AO-CC, respectively. Moreover, advanced adenomas were significantly more common in the EO-CC group compared with the AO-CC group (42% and 14%, $p < 0.001$) [Table]. Among patients with rectal cancer, non-advanced adenomas were less frequent and although advanced adenoma were similar in frequency, they were more commonly located in the rectum in EO-rectal compared to AO-rectal cancers (Table). **Conclusions:** Patients with EO-colon cancer had a significantly higher likelihood of a synchronous advanced adenoma in the colon compared to those with AO-CRC. Together, these data suggest accelerated carcinogenesis throughout the colorectum in early onset patients, with increased risk for development of synchronous and metachronous CRC. Research Sponsor: None.

Synchronous neoplasia characteristics stratified by age group at cancer diagnosis.							
Characteristics ^a		EO-CC ^b N = 75	AO-CC ^b N = 75	P-value	EO-RC ^b N = 75	AO-RC ^b N = 75	P-value
Adenomas	Detected	42 (56%)	35 (47%)	0.327 ^c	21 (28%)	36 (48%)	0.018 ^c
	Right	27 (64%)	28 (78%)	0.292 ^c	8 (38%)	27 (75%)	0.013 ^d
	Left	31 (74%)	22 (59%)	0.265 ^c	14 (67%)	19 (53%)	0.455 ^c
Advanced Adenomas	Detected	31 (42%)	10 (14%)	< 0.001 ^c	11 (15%)	14 (19%)	0.661 ^c
	High grade dysplasia	15 (20%)	0 (0%)	< 0.001 ^c	2 (3%)	3 (4%)	1 ^d

^a Early onset (EO), average onset (AO), colon cancer (CC), rectal cancer (RC) ^b n (%), median (IQR) ^c Chi-square ^d Fisher's exact ^e Mann Whitney U.

TPS3624

Poster Session

Atezolizumab plus tiragolumab in combination with chemoradiotherapy in localized squamous cell carcinoma of the anal canal: TIRANUS (GEMCAD-2103) trial. *First Author: Jaume Capdevila, Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain*

Background: Radical chemoradiotherapy (CRT) is the standard of care in patients with localized anal squamous cell carcinoma; however, around 30% of patients do not achieve a complete clinical response (CCR) and require salvage surgery. Approximately 84% of anal carcinoma is associated with high risk types of human papilloma virus (HPV), primarily HPV 16 that generates high frequencies of tumor-infiltrating lymphocytes and inflammatory responses that have been linked with upregulation of PD-L1 (up to 74% of patients with squamous cell anal cancer). Additionally, poliovirus receptor (PVR) expression has been described in several squamous cell carcinomas, and has been correlated with PD-L1 expression and poorer prognosis, suggesting dual inhibition of PVR and PD-L1 as a potential mechanism to overcome the resistance to immune checkpoint monotherapy. Moreover, CRT induces the generation of tumor-neoantigens and could act in synergy with immunotherapy in this setting. The trial hypothesizes that the addition of atezolizumab (anti-PD-L1) and tiragolumab (anti-TIGIT) to chemoradiotherapy may lead to enhanced and more durable responses. **Methods:** TIRANUS is a Phase II, single-arm, open-label, non-randomized, multicenter clinical trial of atezolizumab and tiragolumab in concomitance with standard CRT as definitive therapy in treatment-naïve, localized squamous cell carcinoma of the anal canal. Patients receive atezolizumab (1200mg) plus tiragolumab (600 mg) for 2 cycles (Q3W) in concomitance with the 6 weeks of CRT (cisplatin: 60 mg/m² on days 1 and 29; 5-FU: 1000 mg/m² per day on days 1-4 and 29-32; radiotherapy: 1.8 Gy per day / total dose 54 Gy). After the concomitant phase, patients receive atezolizumab (1200mg) and tiragolumab (600 mg) Q3W for 6 additional cycles (consolidation phase). The primary endpoint is CCR rate, defined as the percentage of patients who achieve radiological complete response (CR), disappearance of all lesions according to RECIST 1.1 criteria (locally assessed) and no presence of residual disease assessed by biopsy at the end of consolidation phase (week 26). Secondary endpoints include Locoregional failure rate (LFR), Disease-free survival (DFS), Colostomy-free survival (CFS), Overall survival (OS), quality of life, safety and the determination of immune biomarkers potentially predictors of response in blood and tumor samples. Using a precision analysis by Clopper-Pearson method (asymptotic 95% confidence interval) and an expected CCR rate of 85%, a total of 45 evaluable patients are needed to obtain a precision estimation of $\pm 10.4\%$. Accrual started in February 2023. EudraCT: 2021-005887-24 Clinical Trial identifier: NCT05201612. Clinical trial information: NCT05661188. Research Sponsor: GEMCAD through industry partner Roche.

TPS3626

Poster Session

The Ohio State University Guardant Shield Colorectal Cancer Screening Project. *First Author: Peter Stanich, The Ohio State University Wexner Medical Center, Columbus, OH*

Background: Asymptomatic screening is an effective method for detecting early cancers when prognosis strongly depends on stage at time of diagnosis. Unscreened individuals often have a basic understanding of the importance and availability of colorectal cancer (CRC) screening but have concerns regarding the collection method of the currently available stool-based options or the invasiveness of direct visualization options that deter test completion. We hypothesize that offering a blood-based CRC screening test during a routine healthcare visit can increase screening adherence, especially within hard-to-reach populations and those hesitant about completing CRC screening. **Methods:** The Ohio State University Guardant Shield Colorectal Cancer Screening Project (NCT05716477) is a prospective study in the United States designed to recruit individuals who are currently engaging with mobile health clinics and are not up to date with CRC screening, with the aim of improving health in hard-to-reach populations. The study's primary objective is to evaluate the acceptance of a commercially available blood-based CRC screening test (Shield, Guardant Health, USA) in individuals aged 45-84, who have existing appointments with a mobile health clinic, and are not up to date with guideline recommended CRC screening. The study team screens for eligibility criteria before the appointment and reaches out to the individual to begin the informed consent process. Positive blood-based test results will be triaged to colonoscopy for further evaluation. A post-study survey will be administered to consented individuals aimed to collect data on CRC screening knowledge which will be correlated to patient demographics and uptake. Acceptance will be defined as those approached and with completed specimen collection. Progress: The study initiated on October 25, 2022, with the first patient enrolled on December 20, 2022. Enrollment is expected to continue with a target enrollment of 300 individuals. Clinical trial information: NCT05716477. Research Sponsor: Guardant Health.

TPS3625

Poster Session

Phase II/III study of circulating tumor DNA as a predictive biomarker in adjuvant chemotherapy in patients with stage II colon cancer: NRG-GI005 (COBRA). *First Author: Van K. Morris, Department of Gastrointestinal Medical Oncology, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Detection of circulating tumor DNA (ctDNA) shed into the bloodstream represents a highly specific and sensitive approach for identifying microscopic or residual tumor cells after surgical resection. For patients (pts) with colon cancer (CC), the detection of ctDNA is associated with persistent disease after resection and outperforms traditional clinical and pathological features in prognosticating risk for recurrence. However, for pts with stage II CC, there are currently no validated biomarkers predicting benefit in identifying pts whose residual disease cancer be cleared by adjuvant chemotherapy. We hypothesize that for pts whose stage II colon cancer has been resected and who have no traditional high-risk features, a positive ctDNA status may identify those who will benefit from adjuvant chemotherapy. **Methods:** In this prospective phase II/III clinical trial, pts (N = 1,408) with resected stage II CC without traditional high-risk features and whom the evaluating oncologist deems suitable for active surveillance (i.e., not needing adjuvant chemotherapy) will be randomized 1:1 into 2 arms: standard-of-care/observation (Arm A), or prospective testing for ctDNA (Arm B). Postoperative blood will be analyzed for ctDNA with the Guardant Reveal assay, covering CC-relevant mutations and CC-specific methylation profiling. Pts in Arm B with ctDNA detected will be treated with 6 months of adjuvant (FOLFOX) chemotherapy. For all pts in Arm A, ctDNA status will be analyzed retrospectively at the time of endpoint analysis. The primary endpoints are clearance of ctDNA with adjuvant chemotherapy (phase II) and recurrence-free survival (RFS) for "ctDNA-detected" pts treated with or without adjuvant chemotherapy (phase III). Secondary endpoints will include time-to-event outcomes (OS, RFS, TTR) by ctDNA marker status and treatment, prevalence of detectable ctDNA in stage II CC, and rates of compliance with assigned intervention. Archived normal and matched tumor and blood samples will be collected for exploratory correlative research. Enrollment continues across North America to the 1408-patient phase III endpoint. NCT#: 04068103. Support: U10CA180868, -180822; UG1CA189867; GuardantHealth. Clinical trial information: NCT04068103. Research Sponsor: U.S. National Institutes of Health; GuardantHealth.

TPS3627

Poster Session

BREAKWATER: An open-label, multicenter, randomized, phase 3 study, with a safety lead-in (SLI), of first-line (1L) encorafenib (E) + cetuximab (C) ± chemotherapy (CT) vs standard-of-care (SOC) CT for BRAF V600E-mutant metastatic colorectal cancer (mCRC). *First Author: Scott Kopetz, MD Anderson Cancer Center, Houston, TX*

Background: Globally, 8-12% of patients (pts) with mCRC have BRAFV600E mutations, which confer poor prognosis. Based on BEACON (NCT02928224), EC was approved for the treatment (tx) of previously treated pts with BRAF V600E-mutant mCRC. BREAKWATER (NCT04607421) is evaluating EC ± CT vs SOC CT in pts with BRAF V600E-mutant mCRC. In the BREAKWATER SLI (N = 57), EC + CT showed encouraging antitumor activity. Confirmed ORR by BICR (95% CI) with EC + mFOLFOX6 and EC + FOLFIRI, respectively, was 68.4% (46.0, 84.6) and 75.0% (46.8, 91.1) in 1L, and 37.5% (13.7, 69.4) and 44.4% (24.6, 66.3) in 2L. mPFS by BICR (95% CI) with EC + mFOLFOX6 and EC + FOLFIRI, respectively, was 11.1 months [mo] (8.5, NE) and NE (13.8, NE) in 1L, and 10.8 mo (4.3, NE) and 12.6 mo (6.9, NE) in 2L. These results support the continued evaluation of EC + CT. Based on the SLI, EC + mFOLFOX6 was selected for the phase 3 portion. Here we present the updated study design. **Methods:** BREAKWATER is an ongoing, open-label, multicenter, randomized, phase 3 study evaluating 1L EC ± CT vs SOC CT alone in pts with BRAF V600E-mutant mCRC. Approximately 620 pts will be enrolled in the phase 3 portion and an additional 135 in cohort 3 (Table). Phase 3 and cohort 3 inclusion criteria are age ≥ 16 (or ≥ 18 based on country); no prior systemic tx for metastatic disease; measurable disease (RECIST 1.1); BRAF V600E-mutant mCRC (blood or tumor tissue); ECOG PS 0 or 1; and adequate bone marrow, hepatic, and renal function. Pts who received prior BRAF or EGFR inhibitors, those with symptomatic brain metastases (unless stable for ≥ 4 weeks prior to randomization), or with MSI-H/dMMR tumors (unless ineligible to receive immune checkpoint inhibitors due to a pre-existing medical condition) are excluded. Study treatments and endpoints are shown in the Table. Phase 3 enrollment began in November 2021. Clinical trial information: NCT04607421. Research Sponsor: Pfizer Inc.

Study treatments and endpoints.

	Phase 3	Cohort 3 ^a
Randomization	1:1 ^b	2:1
Stratification	· ECOG PS (0 vs 1) · Regions (US/Canada vs Europe vs Rest of World)	· ECOG PS (0 vs 1)
Treatment (1L)	· Arm A (n ≈ 150): EC ^c · Arm B (n ≈ 235): EC + mFOLFOX6 · Arm C (control; n = 235): investigator's choice of mFOLFOX6 ± bevacizumab, FOLFIRI ± bevacizumab, or CAPOX ± bevacizumab	· Arm D (n = 90): EC + FOLFIRI · Arm E (n = 45): FOLFIRI ± bevacizumab
Endpoints		
Primary	PFS ^d and ORR ^e (Arm B vs C)	ORR ^e (Arm D vs E)
Key secondary	OS (Arm B vs C)	PFS ^d (Arm D vs E)

^aRandomization to Arm A ceased upon site institutional review board/ethics committee and competent authority approval of protocol amendment 5. ^bCohort 3 to begin after phase 3 enrollment is complete. ^cBy BICR. ^dBICR, blinded independent central review. CAPOX, capecitabine/oxaliplatin; FOLFIRI, fluorouracil/leucovorin/irinotecan; FOLFOX, fluorouracil/leucovorin/oxaliplatin; FOLFIRI, fluorouracil/leucovorin/irinotecan.

TPS3628

Poster Session

An open-label clinical trial of RP2 and RP3 oncolytic immunotherapy in combination with atezolizumab and bevacizumab for the treatment of patients with advanced colorectal carcinoma. *First Author: Dale Randall Shepard, Cleveland Clinic, Cleveland, OH*

Background: Colorectal cancer (CRC) is the third most frequently diagnosed cancer and the second leading cause of cancer-related mortality worldwide. PD-1/PD-L1 inhibition, in combination with other modalities, has demonstrated significant benefit in patients (pts) with microsatellite instability-high or mismatch repair deficient CRC. However, these agents have limited, if any, clinical benefit in pts with microsatellite stable (MSS) or mismatch repair proficient (pMMR) CRC. RP2 is an enhanced potency oncolytic herpes simplex virus type 1 which expresses the fusogenic gibbon ape leukemia virus glycoprotein with the R sequence deleted (GALV-GP-R-), granulocyte-macrophage colony-stimulating factor (GM-CSF), and an anti-CTLA-4 antibody-like molecule; RP3 additionally expresses 4-1BB and CD40 activating ligands, but does not express GM-CSF. Both agents have demonstrated preliminary safety and efficacy in pts with solid tumors. This study will evaluate the safety and efficacy of RP2 and RP3 in combination with atezolizumab (Atezo) and bevacizumab (Bev) in pts with advanced MSS and pMMR CRC. **Methods:** Pts with a histologic diagnosis of unresectable and/or metastatic CRC, with documented MSS or pMMR status, and previously treated with up to 3 standard-of-care systemic regimens will be enrolled in the RP2 + Atezo + Bev or RP3 + Atezo + Bev treatment groups (30 pts per group). Further key inclusion criteria include Eastern Cooperative Oncology Group performance status 0–1 and adequate hepatic, renal, and hematologic function. RP2/RP3 will be injected into tumors by direct (including via colonoscopy) or image-guided injection. Pts will receive 8 total doses of up to 10 mL of RP2 or RP3, with a first dose concentration of 1×10^6 plaque-forming units (PFU)/mL, followed by 3 doses of 1×10^7 PFU/mL every 2 weeks, and then 4 doses of 1×10^7 PFU/mL every 3 weeks. Pts may receive a second course of up to 8 injections of RP2/RP3 if study criteria are met. Bev will be administered starting on day 1 (with first dose of RP2/RP3); Atezo will be administered starting week 7 on the same days as RP2/RP3. The primary endpoint is objective response rate; secondary endpoints are safety, overall survival, progression-free survival, duration of response, and complete response rate. Antitumor activity will be evaluated using Response Evaluation Criteria in Solid Tumors version 1.1 as modified for this study. Safety will be assessed by physical examination, clinical laboratory evaluations, vital signs, and monitoring for adverse events (AEs; including serious AEs). Clinical trial information: NCT05733611. Research Sponsor: Replimune Inc.

TPS3630

Poster Session

STELLAR-303: A phase 3 study of XL092 in combination with atezolizumab versus regorafenib in patients with previously treated metastatic colorectal cancer. *First Author: J. Randolph Hecht, David Geffen School of Medicine at UCLA, Jonsson Comprehensive Cancer Center, Santa Monica, CA*

Background: Metastatic colorectal cancer (mCRC) is associated with poor prognosis and limited treatment options for patients who have progressed on first- and second-line chemotherapy. Regorafenib and trifluridine-tipiracil are approved in third- or later-line setting, but survival benefit is limited. Immune checkpoint inhibitor (ICI) therapy with nivolumab ± ipilimumab or single-agent pembrolizumab is approved in microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) mCRC; however, MSI-H mCRC is present in only ~5% patients. Phase 1/2 studies have evaluated the tyrosine kinase inhibitor (TKI) cabozantinib in combination with the ICIs atezolizumab and durvalumab and have demonstrated encouraging clinical activity, with data suggesting greater benefit in RAS wild-type (wt) versus RAS mutant (mut) mCRC (Abrams TA, et al. ASCO GI 2022: Abs 121; Saeed A, et al. ASCO GI 2022: Abs 135). XL092 is a TKI that targets MET, VEGFR2, and the TAM kinases AXL and MER, which are implicated in tumor growth, metastasis, angiogenesis, and immunosuppression of the tumor microenvironment. XL092 displays immunomodulatory properties that may promote an immunopерmissive tumor microenvironment and its half-life of 16–22 hours is supportive of once daily (QD) dosing. The phase 3 STELLAR-303 study (NCT05425940) is evaluating the efficacy and safety of XL092 in combination with atezolizumab versus regorafenib in patients with microsatellite stable or microsatellite instability-low mCRC who have progressed after or are intolerant to standard of care (SOC) therapy. **Methods:** STELLAR-303 is a global, randomized, open-label, phase 3 study. Eligible patients are aged ≥18 years with non-MSI-H/dMMR mCRC (determined by tissue-based analysis) that is measurable per RECIST v1.1 and have an ECOG performance status of 0–1 and adequate organ function. Patients must have progressed during/after or be intolerant to SOC therapies for mCRC; prior regorafenib, trifluridine-tipiracil, or anti-PD-L1/PD-1 ICIs are not allowed. Patients are randomized 1:1 to XL092 100 mg PO QD + atezolizumab 1200 mg IV Q3W or to regorafenib 160 mg PO QD (21 days/28-day cycle); randomization is stratified by geographic region (Asia, other), RAS status (wt, mut), and liver metastases (yes, no). Enrollment of 600 patients is planned (400 RASwt, 200 RASmut). The primary endpoint is duration of overall survival (OS) in the RASwt population, with other efficacy endpoints (progression-free survival, objective response rate, and duration of response per RECIST v1.1 by investigator and change in tumor markers) assessed in the RASwt population and, with OS, in the RASmut populations and in all randomized patients. Additional endpoints will assess safety, quality of life, changes in biomarkers, pharmacokinetics, immunogenicity, and healthcare utilization. Enrollment is ongoing. Clinical trial information: NCT05425940. Research Sponsor: Exelixis, Inc.

TPS3629

Poster Session

Alliance A022101: A pragmatic, randomized phase III trial evaluating total ablative therapy for patients with limited metastatic colorectal cancer: Evaluating Radiation, Ablation, and Surgery (ERASur). *First Author: Kathryn Hitchcock, University of Florida, Gainesville, FL*

Background: For patients with oligometastatic colorectal cancer (CRC), aggressive local therapy of isolated metastases, particularly in the liver, has been associated with long-term progression-free survival and overall survival (OS) primarily based on retrospective evidence. However, in patients with limited metastatic CRC that is deemed inoperable or those with additional disease outside of the liver or lungs, the role of local ablative therapies, including microwave ablation (MWA) and stereotactic body radiation therapy (SBRT), to render patients disease free is less clear. Further, despite the long history of treating oligometastatic CRC with local therapy, which is provider biased and not evidence based, questions remain regarding the benefit of extending the paradigm of metastatic directed therapy to patients with more extensive disease. This trial seeks to use a pragmatic multimodality approach that mirrors the current clinical dilemma. This study is designed to evaluate the safety and efficacy of adding total ablative therapy (TAT) of all sites of disease to standard of care systemic treatment in those with limited metastatic CRC. **Methods:** A022101 is a National Clinical Trials Network randomized phase III study planned to enroll 364 patients with newly diagnosed metastatic CRC (BRAF wild-type, microsatellite stable) with ≤4 sites of metastatic disease on baseline imaging. Liver-only metastatic disease is not permitted, and lesions must be amenable to any combination of surgical resection, MWA, and/or SBRT with SBRT required for at least one lesion. Patients receive first-line systemic therapy for 4–6 months and are then randomized 1:1, stratified by number of metastatic organ sites (1–2 vs. 3–4), timing of metastatic disease diagnosis (de novo vs. secondary), and presence of metastatic disease outside the liver and lungs in at least one site. Patients in Arm 1 will receive TAT which consists of treatment of all metastatic sites with SBRT ± MWA ± surgical resection followed by standard of care systemic therapy. Patients in Arm 2 will continue with standard of care systemic therapy alone. The primary endpoint is OS. Secondary endpoints include event-free survival, treatment-related toxicities, and local recurrence with exploratory biomarker analyses. The study needs 346 evaluable patients combined in the 2 arms to demonstrate an improvement in OS with a hazard ratio of 0.7 to provide 80% power with a one-sided alpha of 5%. The trial utilizes a group sequential design with two interim analyses (25% and 50% of events) for futility. The trial activated in January 2023 and recruitment is ongoing. Support: U10CA180821, U10CA180882; <https://acknowledgments.alliancecfound.org>. U10CA180820 (ECOG-ACRIN); U10CA180868 (NRG); U10CA180888 (SWOG); Clinicaltrials.gov identifier: NCT05673148 Clinical trial information: NCT05673148. Research Sponsor: U.S. National Institutes of Health.

TPS3631

Poster Session

MOUNTAINEER-03: Phase 3 study of tucatinib, trastuzumab, and modified FOLFOX6 as first line treatment in HER2+ metastatic colorectal cancer. *First Author: Tanios S. Bekaii-Saab, Mayo Clinic, Scottsdale, AZ*

Background: The current standard of care (SOC) for the treatment of metastatic colorectal cancer (mCRC) is multi-agent chemotherapy, with or without a VEGF or EGFR inhibitor. Human epidermal growth factor receptor-2 (HER2) is a validated clinical target in breast and gastric cancers. HER2 amplification occurs in 3%–5% of patients with mCRC; the rate of HER2 amplification can increase to approximately 10% in patients with RAS/BRAF wild-type mCRC tumors. Tucatinib (TUC)—a highly selective, HER2-directed tyrosine kinase inhibitor—is approved in multiple regions for HER2-positive (HER2+) metastatic breast cancer, approved in the US for HER2+ metastatic colorectal cancer, and under investigation in gastrointestinal cancers. MOUNTAINEER (NCT03043313) evaluated the safety and efficacy of TUC and trastuzumab (Tras) in patients with treatment-refractory RAS wild-type, HER2+ mCRC. Results from the primary endpoint analysis showed clinically meaningful activity, with a confirmed objective response rate (ORR) per blinded independent central review (BICR) of 38.1% (95% confidence interval [CI] 27.7, 49.3) and median duration of response per BICR of 12.4 months (95% CI 8.5, 20.5). Results also demonstrated TUC + Tras was well tolerated, with a low discontinuation rate (5.8%) and no deaths due to adverse events. MOUNTAINEER-03 will further investigate TUC in combination with modified FOLFOX (mFOLFOX) and Tras in patients with RAS wild-type HER2+ mCRC. **Methods:** MOUNTAINEER-03 (NCT05253651) is a global, open-label, randomized, phase III study for first-line treatment of HER2+ and RAS wild-type mCRC. Approximately 400 patients will be randomized 1:1 to the TUC experimental arm (TUC [300 mg orally twice daily] + Tras + mFOLFOX) or the SOC arm (mFOLFOX alone or in combination with either bevacizumab or cetuximab). HER2 status is determined centrally with tissue-based HER2 immunohistochemistry and in situ hybridization assays. Eligible patients must not have received prior treatment in the metastatic setting but may have received adjuvant treatment if completed > 6 months prior to enrollment. Patients must be ≥18 years old with an Eastern Cooperative Oncology Group Performance Status of ≤1 and RAS wild-type mCRC. Patients with treated stable central nervous system metastases are eligible. Randomization is stratified by primary tumor location (left-sided vs other) and liver metastases (presence/absence). The primary endpoint is progression-free survival per RECIST v1.1 assessed by BICR. Key secondary endpoints are overall survival and confirmed ORR per RECIST v1.1 assessed by BICR. Enrollment is ongoing in North America, Asia, Australia, and Europe. Clinical trial information: NCT05253651. Research Sponsor: Seagen, Inc.

TPS3632

Poster Session

A phase 1/2a, multicenter, open-label study of CNA3103 (LGR5-targeted, autologous CAR-T cells) in patients with metastatic colorectal cancer (mCRC). *First Author: Jayesh Desai, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia*

Background: Leucine-rich repeat-containing G protein-coupled receptor 5 (LGR5) is a cancer stem cell (CSC) marker that is abundant in solid tumors, highly expressed in colorectal cancer and involved in tumor initiation, growth, and metastasis. Its expression is linked to poor survival and poor patient response to therapy in mCRC, and presents an attractive opportunity for selectively targeting a highly specific, functional CSC receptor in this disease. CNA3103 is a first-in-class cell product consisting of autologous T cells transduced to express a CAR to target LGR5. It contains the antigen-binding domain of BNC101, a humanized monoclonal LGR5 antibody previously tested in Phase 1 in mCRC subjects and demonstrated to be safe and well tolerated with no off-target binding activity. **Methods:** This is a first in human, multicenter, open label, Phase 1/2a dose escalation and expansion study to determine the safety of and overall best response to CNA3103 in subjects with mCRC. Up to 44 subjects (24 in Phase 1 and 20 in Phase 2a) will be enrolled. The trial follows a BOIN design with a minimum of 3 consecutively enrolled subjects per cohort, and a 28-day DLT evaluation period. Four cell dose levels (5×10^7 , 1.5×10^8 , 4.5×10^8 , 1.5×10^9) of CNA3103 will be evaluated. A Safety Monitoring Committee (SMC) will oversee the conduct of the study. The pharmacokinetic (PK) profile of CNA3103 in blood will be assessed. Exploratory objectives include evaluation of LGR5+ cells and CNA3103 in tumor biopsies, immune cellular profile, cytokine levels and circulating tumor DNA in blood, and immunogenicity of CNA3103. Main inclusion criteria: mCRC subjects positive for LGR5 expression and failing prior treatment with 5-FU, oxaliplatin and irinotecan-based regimens for metastatic disease; >1 radiologically measurable lesion per RECISTv1.1; >1 biopsiable lesion at baseline; ECOG 0 or 1; serum albumin >3 g/dL; and normal organ and marrow function. Main exclusion criteria: BRAF-mutated disease, clinical ascites/pleural effusions; active autoimmune/ connective tissue disease; history of inflammatory bowel disease or active peptic ulcer disease. The trial is sponsored by Carina Biotech. Phase 1 enrolment is limited to Australian sites. Phase 2a enrolment will take place in Australia and the US. For information, contact Lina Jablonskis lina@carinabiotech.com or +61 437 891 563. Research Sponsor: Carina Biotech.

TPS3634

Poster Session

Colon adjuvant chemotherapy based on evaluation of residual disease (CIRCULATE-US): NRG-GI008. *First Author: Arvind Dasari, Department of Gastrointestinal Medical Oncology, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Currently, there are no biomarkers validated prospectively in randomized studies for resected colon cancer (CC) to determine need for adjuvant chemotherapy (AC). However, circulating tumor DNA (ctDNA) represents a highly specific and sensitive approach (especially with serial monitoring) for identifying minimal/molecular residual disease (MRD) post-surgery in CC patients (pts), and may outperform traditional clinical and pathological features in prognosticating risk for recurrence. CC pts who do not have detectable ctDNA (ctDNA-) are at a much lower risk of recurrence and may be spared the toxicities associated with AC. Furthermore, for CC pts with detectable ctDNA (ctDNA+) who are at a very high risk of recurrence, the optimal AC regimen has not been established. We hypothesize that for pts whose CC has been resected, ctDNA status may be used to risk-stratify for making decisions about AC. **Methods:** In this prospective phase II/III trial, up to 1,912 pts with resected stage III A, B (all pts) and stage II, IIIC (ctDNA+ only) CC will be enrolled. Based on the post-operative ctDNA status using personalized and tumor-informed assay (SignateraTM, bespoke assay), those who are ctDNA- (Cohort A) will be randomized to immediate AC with fluoropyrimidine (FP) + oxaliplatin (Ox) for 3-6 mos per established guidelines vs. serial ctDNA monitoring. Patients who are ctDNA+ post-operatively or with serial monitoring (Cohort B) will be randomized to FP+Ox vs. more intensive AC with addition of irinotecan (I) for 6 mos. The primary endpoints for Cohort A are time to ctDNA+ status (phase II) and disease-free survival (DFS) (phase III) in the immediate vs. delayed AC arms. The primary endpoint for Cohort B is DFS in the FP+Ox vs FP+Ox+I arms for both phase II and phase III portions of the trial. Secondary endpoints include prevalence of detectable ctDNA post-operatively, time-to-event outcomes (overall survival and time to recurrence) by ctDNA status, and the assessment of compliance to adjuvant therapy. Biospecimens including archival tumor tissue, as well as post-operative plus serial matched/normal blood samples, will be collected for exploratory correlative research. Active enrollment across the NCTN started in June 2022. NCT#: NCT05174169. Support: U10-CA-180868, -180822; UG1CA-189867; Natera, Inc. Clinical trial information: NCT05174169. Research Sponsor: U.S. National Institutes of Health; Natera, Inc.

TPS3633

Poster Session

Total neoadjuvant treatment without surgery for locally advanced rectal cancer: Prospective study to assess tumor response, circulating genetic, and epigenetic biomarkers, and stromal transcriptome to interpret clinical outcome (NO-CUT trial). *First Author: Salvatore Siena, Niguarda Cancer Center, Grande Ospedale Metropolitano Niguarda, University of Milano, Milan, Italy*

Background: Total neoadjuvant therapy (TNT) has recently become a standard therapy for locally advanced rectal cancer (LARC). All nonsurgical interventions, including chemotherapy and concurrent chemoradiotherapy (CRT), are administered before either surgical resection of the rectum or non-operative management (NOM), depending on response to TNT. In the case of NOM, the impact of distant relapse on survival remains to be elucidated and circulating tumor DNA (ctDNA) monitoring has been proposed as a tool for early detection of relapse. Furthermore, predictive biomarkers of response to TNT are warranted for the early identification of patient candidates for NOM. In this regard, stromal contribution to sensitivity to pre-operative CRT is investigated by a transcriptomic signature on baseline tumor samples, as previously proposed by Isella C et al., Nature Genet, 2015. **Methods:** NO-CUT is a multicenter one-stage phase II trial aimed at assessing if a TNT approach with CAPOX followed by CRT can safely spare demolitive surgery in patients with LARC achieving a clinical complete response without increasing the risk of distant metastatic relapse. A Brookmeyer and Crowley approach was chosen to test the null hypothesis that the true distant relapse-free survival at 2.5 years rate is $\leq 75\%$ against a one-sided alternative. The NOM cohort of the trial needs to accrue 44 evaluable patients and to be followed for at least 2.5 years. Such design yields a type I error rate of 10% and power of 80% when the true 2.5 years distant RFS proportion is 87%. Since it is assumed that the proportion of patients entering in the NOM cohort of the trial is at least 25%, a total of 180 patients are to be enrolled in NO-CUT study. Patients with medium-low LARC undergo TNT (4 cycles of CAPOX: capecitabine 1000 mg/m² bid days 1-14 q 3 weeks; oxaliplatin 130 mg/m² day 1 q 3 weeks) and 5 weeks of standard pelvic CT-RT, then restaging with imaging (MRI, CT-scan, and ultrasound endoscopy), and tumor biopsy. According to an algorithm defined for assessing tumor response, patients enter either NOM or surgery cohorts. During the follow-up phase of the trial, the NOM cohort is followed with intensive pelvic imaging and periodic blood samplings for 5 years. Tumor samples and ctDNA are studied at baseline, after TNT, and during follow-up. As of January 2023, 161 of planned 180 patients in 4 centers have been enrolled. Supported by grants from Associazione Italiana Ricerca Cancro (AIRC IG 2017-20685) and Fondazione Oncologia Niguarda. Clinical trial information: EudraCT 2017-003671-60. Research Sponsor: AIRC IG; FON (Fondazione Oncologia Niguarda).

TPS3635

Poster Session

The CIRCULATE Spain study: Circulating tumor DNA based decision for adjuvant treatment in localized colon cancer. *First Author: Noelia Tarazona, Department of Medical Oncology, INCLIVA Biomedical Research Institute, University of Valencia, Instituto Carlos III, CIBERONC, Valencia, Spain*

Background: A substantial proportion of colon cancer (CC) patients do not benefit from adjuvant chemotherapy, and almost 40% of them will develop metastases despite initial optimal treatment. We have designed the phase 2 CIRCULATE-SPAIN trial (EudraCT Number: 2021-000507-2) to prove the feasibility of using liquid biopsy detection of minimal residual disease to guide the post-surgical clinical management of localized CC patients. Moreover, it is important to define if conventional versus intensive adjuvant chemotherapy could convert plasma circulating tumor DNA (ctDNA) positive into a ctDNA negative status. **Methods:** CIRCULATE-SPAIN is a trial to prove the feasibility of using liquid biopsy detection of MRD to guide the post-surgical clinical management of early colon cancer patients. It is a multicenter, randomized, open-label phase II "Single-To-double ARm Transition (START)" study in which patients are firstly enrolled into a single arm (Phase IIa) study expandable to a randomized double arm (Phase IIb). The CIRCULATE-SPAIN trial involves two primary endpoints, one for the Phase IIa and a second one for the Phase IIb. The primary objective for Phase IIa is to analyze the potential effect of FOLFOXIRI as an intensive adjuvant treatment for ctDNA clearance as a surrogate biomarker of treatment efficacy. Only if the pre-fixed result of 14 out of 40 patients achieves ctDNA clearance, the trial will be expanded to a phase IIb in which patients will be enrolled to randomly receive intensive adjuvant treatment (FOLFOXIRI) versus conventional adjuvant therapy (CAPOX). The primary objective in this phase is to study differences on the conversion rate between both groups. An academic assay based on tumor informed approach is used for ctDNA determination. Tumor and germline samples analysis are carried out by an in-house-developed bioinformatics pipeline specialized in variant-calling analysis using a custom 29-gene panel. Somatic variants are identified by the germline mutations extraction. Different annotation databases and an internal pathological mutation database are used to rule out potential benign somatic variants. Those candidate somatic mutations with the highest allelic frequency are selected and a specific panel of amplicons is designed to monitor their presence in ctDNA using NGS. Plasma samples analysis is carried out by an in-house pipeline specialized in reducing potential background noise. To assess panel performance in both sample types, the bioinformatics pipelines include a set of methods to calculate and filter according to different quality control metrics. Recruitment for the Phase IIa is ongoing with a total of 67 pre-screened out of which two patients were eligible. Clinical trial information: 2021-000. 507-20. Research Sponsor: Instituto de Salud Carlos III.

TPS3636

Poster Session

The FOxTROT platform: Clinical trials and exploratory research for personalization of neoadjuvant (NA) therapy in locally advanced colon cancer (LACC)—ISRCTN83842641. *First Author: Christopher Williams, University of Leeds, Leeds, United Kingdom*

Background: The FOxTROT1 trial demonstrated a significant reduction in 2-year (yr) recurrence with 6 weeks (wks) of oxaliplatin and fluoropyrimidine (OxPp) NA chemotherapy (NAC) in patients (pts) with LACC, establishing NAC as a new therapeutic option. The ongoing FOxTROT platform will refine and personalize NA therapy in LACC. FOxTROT2 is testing NAC in older pts and those with frailty, who are poorly represented in clinical trials. FOxTROT3 is assessing intensified NAC with modified FOLFOLFOXIRI (mFOLFOLFOXIRI; 5-fluorouracil, oxaliplatin, irinotecan) in fit pts. The FOxTROT platform will also test targeted treatments with established safety and efficacy in defined molecular subgroups. FOxTROT4 is investigating the efficacy and safety of NA encorafenib and cetuximab in BRAF-mutant pMMR LACC. Other arms in setup are shown in Table. **Methods:** FOxTROT platform trials are international, multicenter, open-label, phase I/II/III RCTs. Pts with resectable, cT3-4 N0-2 MO, biopsy-proven colon adenocarcinoma are eligible for recruitment. Pts whose age or frailty precludes mFOLFOLFOXIRI can be considered for FOxTROT2. Pts suitable for mFOLFOLFOXIRI can be considered for FOxTROT3. BRAF-mutant pMMR pts can be considered for FOxTROT4. Pts are randomized 2:1 between intervention and control arms. FOxTROT2 randomizes between 6 wks OxPp NAC (choice of 100% or 80% dose) vs proceeding straight to surgery. Adjuvant chemotherapy (AC) is per physician choice. Primary outcome is 3-yr DFS. 759 pts will be recruited over 5 yrs. FOxTROT3: 6 wks mFOLFOLFOXIRI NAC vs 6 wks OxPp NAC. All pts receive AC but physicians may de-escalate mFOLFOLFOXIRI to OxPp. Hierarchical co-primary endpoints: tumor regression grade (TRG) (blinded central assessment) and 3-yr DFS. 873 pts over 5 yrs. FOxTROT4: 6 wks NA encorafenib and cetuximab vs 6 wks OxPp NAC. AC is per physician choice. Primary outcome: TRG. 45 pts over 3 yrs. Secondary outcomes include: histopathological endpoints, downstaging, minimal residual disease by ctDNA, safety, toxicity, OS, surgical outcomes and patient-reported outcomes; and DFS in FOxTROT4. The FOxTROT platform opened 7th Feb 2022, funded by Yorkshire Cancer Research. At submission, 50 pts had been randomized at 23 centers. Trial design and management is conducted in partnership with patient representatives. A program of translational and radiomics research is running in parallel. International recruitment in France and India will commence in 2023 with additional international partners joining from 2024. Clinical trial information: ISRCTN83842641. Research Sponsor: Yorkshire Cancer Research.

Current FOxTROT arms.

FOxTROT	2	3	4	5	6
Pt group	Older, frailty	Fit for triplet	BRAF mutant	dMMR, frailty	HER2
MMR status	pMMR	pMMR	pMMR	dMMR	pMMR
Neoadjuvant	OxPp	mFOLFOLFOXIRI	Encorafenib/cetuximab	Anti-PD1	HER2-directed
Intervention			OxPp NAC		
Control	Straight to surgery	OxPp NAC		Single arm	Single arm
Recruiting	Yes	Yes	Yes	In setup	In setup

TPS3638

Poster Session

Neoadjuvant short-course radiotherapy followed by chemotherapy plus camrelizumab versus long-course chemoradiotherapy followed by chemotherapy for patients with locally advanced rectal cancer: A randomized, multicenter, open-label phase 3 trial (Union). *First Author: Zhenyu Lin, Cancer Center, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China*

Background: Short-course preoperative radiotherapy (SCPRT) and long-course chemoradiotherapy (LCCRT) are standard neoadjuvant treatments for locally advanced rectal cancer (LARC). Further, the RAPIDO trial found that SCPRT combined with consolidation chemotherapy produced better short- and long-term outcomes than SCPRT alone for patients with high-risk LARC. A phase 2, single-arm trial of neoadjuvant SCPRT followed by camrelizumab (an anti-PD-1 antibody) plus chemotherapy demonstrated promising short-term outcomes in patients with LARC. The Union trial is evaluating the efficacy and safety of neoadjuvant SCPRT followed by camrelizumab plus chemotherapy versus LCCRT followed by chemotherapy in patients with LARC. **Methods:** The Union trial is enrolling patients aged 18-75 with histologically confirmed clinical stage T3-4/N+ adenocarcinoma of the rectum, Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and a tumor inferior margin less than 10 cm above the anal verge. Eligible patients are randomized in a 1:1 ratio to either arm A or arm B. Patients in arm A receive neoadjuvant treatment with SCPRT (a total of 25 Gy in 5 days) followed by camrelizumab (200 mg/m² intravenous drip on day 1, every 3 weeks for 2 cycles) plus CAPOX (oxaliplatin 130 mg/m² intravenous infusion over 2 hours on day 1, capecitabine 1000 mg/m² oral twice daily, days 1-14, every 3 weeks for 2 cycles), surgery, and adjuvant treatment with camrelizumab plus CAPOX (6 cycles) followed by camrelizumab until the medication duration of camrelizumab reaches one year. Patients in arm B receive neoadjuvant treatment with LCCRT (capecitabine 825 mg/m² twice daily, 5 days a week, combined with a total dose of 50.4 Gy in 28 days) followed by CAPOX (2 cycles), surgery, and adjuvant treatment with CAPOX (6 cycles). Randomization is stratified by clinical T stage (≤T3 vs T4) and clinical N stage (N0 vs N+). The primary endpoint is pathologic complete response (pCR). The secondary endpoints are 3-year event-free survival rate, overall survival, RO resection rate, completion rate of neoadjuvant treatment, 3-year disease-free survival rate, tumor regression grading, safety, and quality of life. pCR is evaluated per the AJCC 8th Edition TRG scoring system as assessed by the blinded independent central review. Adverse events are graded by the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0. Quality of life is assessed by the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30. This study began enrollment in July 2021 with a planned enrollment of 230 patients. Clinical trial information: NCT04928807. Research Sponsor: Jiangsu Hengrui Pharmaceuticals Co, Ltd, Shanghai, China.

TPS3637

Poster Session

PACE: A phase III trial of CAPOX versus anti-PD-1 inhibitor as adjuvant therapy for patients with dMMR/MSI-H stage III colon cancer. *First Author: Zhenlin Hou, Department of Colorectal Surgery, Sun Yat-sen University Cancer Center, Guangzhou, China*

Background: Approximately 12% of stage III colon cancer are deficient mismatch repair (dMMR), leading to high levels of microsatellite instability (MSI-H). In the KEYNOTE-177 study, the anti-PD-1 inhibitor Pembrolizumab alone significantly improved progression free survival (PFS) versus chemotherapy as first-line therapy for metastatic colorectal cancer (mCRC) patients with MSI-H/dMMR. We are conducting a phase III randomised trial to determine whether anti-PD-1 inhibitor Sintilimab monotherapy can improve disease free survival (DFS) compared with standard adjuvant chemotherapy in stage III colon cancer patients with dMMR. **Methods:** This is an open-label, multicentre, randomised phase III study. Patients aged ≥ 18 years with completely resected, stage III colon cancer confirmed to have dMMR/MSI-H and ECOG performance status 0-1 are eligible. Approximately 323 patients will be randomly assigned 1:1 to either Sintilimab monotherapy (200 mg IV every 3 weeks for 8 cycles) or CAPOX regimen (capecitabine, oxaliplatin for 4 or 8 cycles according to current standard practice). Adverse events (AEs) will be assessed throughout treatment and for 30 days thereafter (90 days for serious AEs) and graded per NCI CTCAE v4.0. Primary endpoint is 3-year DFS. The study was estimated to provide approximately 80% power to detect a hazard ratio of 0.56 for DFS at a two-sided alpha of 0.05. Secondary endpoints include OS, safety profile, toxicity, and quality of life. Archived tumor tissue and blood samples will be collected for correlative studies. Study enrollment is ongoing. Clinical trial information: NCT05236972. Research Sponsor: None.

TPS3639

Poster Session

Phase II, single-arm, open-label study of dostarlimab monotherapy in previously untreated patients with stage II/III dMMR/MSI-H locally advanced rectal cancer. *First Author: Andrea Cercek, Division of Solid Tumor Oncology, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: For patients (pts) with locally advanced rectal cancer (RC), organ-sparing non-operative management (NOM) following a clinical complete response (cCR) to treatment avoids the potential complications and quality of life impact associated with surgery/chemoradiotherapy. Although neoadjuvant chemotherapy is standard treatment, pts with mismatch repair deficient (dMMR) tumors respond poorly. Efficacy of the programmed death (PD)-1 inhibitor dostarlimab in previously untreated pts with locally advanced dMMR RC was evaluated in a Phase II study. All 12 pts who completed 6 months of treatment had clinical complete response (cCR) and received NOM, with no Grade ≥3 adverse events reported. Further research with a larger multicenter population/longer follow-up is needed to confirm these findings. AZUR-1 will evaluate the efficacy and safety of dostarlimab in pts with previously untreated locally advanced dMMR/microsatellite instability-high (MSI-H) RC. **Methods:** AZUR-1 (NCT05723562) is a global, multicenter, single-arm, open-label, Phase II study. ~100 pts will be enrolled across 10 countries. Key eligibility criteria include age ≥18 years, no prior radiation/systemic therapy or surgery for RC, Eastern Cooperative Oncology Group performance status 0-1 and no tumor-caused symptomatic bowel obstruction. Pts must have a tumor with dMMR status or MSI-H phenotype, determined locally or by the central reference laboratory. Prescreening is available at sites without local dMMR/MSI-H testing; prescreening is not required if dMMR/MSI-H status has been previously determined. Dostarlimab (500 mg) will be administered intravenously every 3 weeks for ≤9 cycles. The primary endpoint is cCR by independent central review (ICR) at 12 months, defined as achieving and maintaining cCR for 12 months (the 12-month period starts from the first disease assessment after last dose of study intervention that demonstrates cCR by ICR). Secondary endpoints include cCR by ICR at 36 months, 3-year event-free survival (EFS3) by investigator assessment, 5-year disease-specific survival, and 5-year overall survival. Pts with cCR by end of treatment will be assessed (CT/MRI, rectal MRI, endoscopy, rectal primary biopsy) every 4-6 months for recurrent disease for 5 years (NOM). Efficacy and safety will be assessed in all pts who received ≥1 dose of dostarlimab. For a range of plausible observed cCR12 rates (60-95%) in the primary analyses, the planned sample size of 100 pts will provide a Clopper-Pearson exact binomial two-sided 95% confidence interval with lower confidence limit within ~10% of the observed cCR12 rate. No interim analyses are planned. References: [1] Cercek, A *et al.* *NEJM* 2022;386: 2363-76. Funding: GSK (219369). Editorial support provided by Fishawack Health, funded by GSK. Clinical trial information: NCT05723562. Research Sponsor: GSK (219369).

TPS3640

Poster Session

Alliance A022104/NRG-GI010: A randomized phase II trial testing the efficacy of triplet versus doublet chemotherapy to achieve clinical complete response in patients with locally advanced rectal cancer—The Janus Rectal Cancer trial. *First Author: Jesse Joshua Smith, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Recent data have demonstrated that in locally advanced rectal cancer (LARC), a total neoadjuvant therapy (TNT) approach improves compliance with chemotherapy and increases rates of tumor response compared to neoadjuvant chemoradiation (CRT) alone. They further indicate that the optimal sequencing of TNT involves consolidation (rather than induction) chemotherapy to optimize complete response rates. Data, largely from retrospective studies, have also shown that patients (pts) with clinical complete response (cCR) after neoadjuvant therapy may be managed safely with the watch and wait approach (WW) instead of pre-emptive total mesorectal resection (TME). However, the optimal consolidation chemotherapy regimen to achieve cCR has not been established, and a randomized clinical trial has not robustly evaluated it as a primary endpoint. Collaborating with a multidisciplinary oncology team and pt groups, we designed this NCI-sponsored study of chemotherapy intensification to address these issues and to drive up cCR rates, to provide opportunity for organ preservation and improve quality of life for pts.

Methods: In this Alliance for Clinical Trials in Oncology randomized phase II trial (1:1), up to 312 pts with microsatellite stable LARC, clinical stage T4N0, any T, N+ or T3N0 requiring abdominoperineal resection or coloanal anastomosis and distal margin within 12 cm of anal verge will be enrolled. Stratification factors include tumor stage (T4 vs T1-3), nodal stage (N+ vs N0) and distance from anal verge (0-4; 4-8; 8-12 cm). Pts will be randomized to receive neoadjuvant long course CRT (LCRT) followed by consolidation doublet (mFOLFOX6 or CAPOX) or triplet chemotherapy (mFOLFIRINOX) for 4 months. LCRT in both arms involves 4500 cGy in 25 fractions over 5 weeks (w) + 900 cGy boost in 5 fractions with a fluoropyrimidine (capecitabine preferred). Pts will undergo assessment 8-12 w post-TNT completion for the primary endpoint of cCR per previously validated criteria and recommended WW and surveillance if cCR is achieved or TME if an incomplete response is noted. Secondary objectives include time-to event outcomes (disease-free and overall survival, organ preservation time and time to distant metastasis) and adverse effects. Statistical power, based on cCR, incorporates a one-sided alpha = 0.048 and power = 90% yielding 312 patients (156 per arm). Biospecimens including archival tumor tissue, matched / normal blood samples and serial rectal MRI will be collected for exploratory correlative research. This study, activated in late 2022, is open across the NCTN and is actively recruiting. Support: U10CA180821, U10CA180882, U24 CA196171; <https://acknowledgments.alliancefound.org>. U10CA180868 (NRG); U10CA180888 (SWOG); Clinicaltrials.gov ID: NCT05610163 Clinical trial information: NCT05610163. Research Sponsor: U.S. National Institutes of Health.

TPS3641

Poster Session

A randomized trial of consolidation-targeted adjuvant therapy with encorafenib and cetuximab versus usual care for patients with stage II/III BRAF V600E colon cancer: Alliance for Clinical Trials in Oncology A022004. *First Author: Rona Yaeger, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Patients with mismatch repair proficient (pMMR) BRAF V600E mutant high-risk stage II (T4) or stage III colon cancer have a substantial risk of recurrence despite standard adjuvant therapy. In patients with metastatic BRAF V600E mutant colorectal cancer, the combination of the RAF inhibitor encorafenib and the EGFR inhibitor cetuximab has been shown to improve overall and progression-free survival compared to standard therapy after at least one prior line of therapy. This study will evaluate if this combination improves disease-free survival (DFS) in patients with resected BRAF V600E mutant pMMR/microsatellite stable (MSS) high-risk stage II (T4) or stage III colon cancer after standard adjuvant therapy. **Methods:** The study has a seamless phase II/III design, enrolling a maximum of 394 patients. BRAF mutation status can be determined locally or submitted for central testing in trial pre-screening. Eligible patients will be randomized 1:1 to usual surveillance versus 6 months of treatment with encorafenib (300mg oral daily) plus cetuximab (500mg/m² intravenous every 14 days). Stratification factors are adjuvant chemotherapy regimen (FOLFOX versus CAPOX), duration of adjuvant therapy (3 months versus > 3 months), tumor stage (T4N0 versus T1-3N1 versus T4N1/TanyN2), and ctDNA marker status (detectable versus undetectable) at randomization. Adjuvant therapy must be completed at most 8 weeks prior to registration. For the phase II component, in the ctDNA detectable cohort, the primary endpoint will be ctDNA clearance rate at 6 months, and, in the ctDNA undetectable cohort, the primary endpoint will be 6-month ctDNA recurrence-free survival, where events consist of death, recurrence, or ctDNA positivity. The primary endpoint of the phase III component is DFS, and secondary endpoints are overall survival, adverse events, and alternative DFS calculated from the date of primary resection, rather than date of study randomization. Patient reported symptoms (PRO-CTCAE) will be collected and analyzed as an exploratory endpoint, and serial blood banking will support future correlative studies. The trial will proceed to the phase III portion if either of the two endpoints in the phase II cohorts is statistically superior in patients receiving encorafenib plus cetuximab. The phase III study sample size will provide 80% power at a one-sided α of 0.05 to detect an approximately 10% improvement in the three-year DFS rate, assuming 68% in the control arm. Two interim analyses will be performed for DFS endpoint. Support: U10CA180821, U10CA180882; <https://acknowledgments.alliancefound.org>. U10CA180820 (ECOG-ACRIN); U10CA180868 (NRG); U10CA180888 (SWOG); Pfizer, Eli Lilly; Clinicaltrials.gov ID: NCT05710406. Clinical trial information: NCT05710406. Research Sponsor: U.S. National Institutes of Health; Pfizer, Eli Lilly.

4000

Oral Abstract Session

ATTRACTION-5: A phase 3 study of nivolumab plus chemotherapy as postoperative adjuvant treatment for pathological stage III (pStage III) gastric or gastroesophageal junction (G/GEJ) cancer. *First Author: Masanori Terashima, Shizuoka Cancer Center, Division of Gastric Surgery, Nagaizumi, Japan*

Background: Nivolumab plus chemotherapy (N+C) in the first-line treatment and nivolumab monotherapy in the third- or later-line have shown survival benefit in patients with unresectable advanced or recurrent G/GEJ cancer. Adjuvant chemotherapy after D2 or more extended gastrectomy is a widely used standard of care for pStage III G/GEJ cancer in Asia. However, standard adjuvant chemotherapy has shown limited efficacy for pStage III G/GEJ cancer. ATTRACTION-5 is the first phase 3 study to evaluate an immune checkpoint inhibitor in combination with adjuvant chemotherapy for pStage III G/GEJ cancer. Here, we report the first confirmatory results of N+C as postoperative adjuvant treatment. **Methods:** The ATTRACTION-5 study is a multicenter, double-blind, randomized study conducted in Japan, Korea, Taiwan, and China. We enrolled patients with pStage III G/GEJ cancer who had undergone D2 or more extended gastrectomy. Investigators selected an appropriate adjuvant chemotherapy (tegafur/gimeracil/oteracil [S-1] therapy or capecitabine plus oxaliplatin [CapeOX] therapy) for each patient, and thereafter patients were randomly assigned (1:1) to the N+C or placebo plus chemotherapy (P+C) arm, using the allocation factors of country and disease stage. The primary endpoint was centrally-assessed relapse-free survival (RFS). The sample size was calculated, based on the results of the ACTS-GC study and the CLASSIC study (The assumed hazard ratio [HR], 0.67; the assumed 3-year RFS, 71% vs 60%). Secondary endpoints were investigator-assessed RFS, overall survival (OS), and 3-year RFS and OS rates. **Results:** A total of 755 patients underwent randomization from February 2017 to August 2019: 377 were assigned to the N+C arm and 378 to the P+C arm. The final analysis of RFS was performed based on the clinical data cutoff of August 2022, with the minimum follow-up of 36 months after the last patient was randomized. The primary efficacy endpoint of centrally-assessed RFS was not met (HR, 0.90; 95.72% CI, 0.69–1.18; $P=0.4363$), with the 3-year RFS rates of 68.4% (95% CI, 63.0–73.2) in the N+C arm and 65.3% (95% CI, 59.9–70.2) in the P+C arm. The completion rate of the planned postoperative adjuvant treatment was 61.5% in the N+C arm and 71.4% in the P+C arm. Incidences of grade $\geq$ 3 TRAEs, serious TRAEs, and TRAEs leading to discontinuation were 54.4%, 25.3%, and 9.2%, respectively, in the N+C arm and 46.8%, 10.7%, and 3.5% in the P+C arm. **Conclusions:** The ATTRACTION-5 study of N+C vs P+C in patients with pStage III G/GEJ cancer after D2 or more extended gastrectomy did not meet the primary endpoint of RFS. The safety profile in the ATTRACTION-5 study was consistent with its known safety profile. Clinical trial information: NCT03006705. Research Sponsor: ONO Pharmaceutical; Bristol Myers Squibb.

4002

Oral Abstract Session

Efficacy, safety and patient reported outcomes (PROs) from the phase III IMbrave050 trial of adjuvant atezolizumab (atezo) + bevacizumab (bev) vs active surveillance in patients with hepatocellular carcinoma (HCC) at high risk of disease recurrence following resection or ablation. *First Author: Masatoshi Kudo, Kindai University Hospital, Osaka, Japan*

Background: In IMbrave050, adjuvant atezo + bev demonstrated a statistically significant and clinically meaningful improvement in recurrence-free survival (RFS) vs active surveillance in patients (pts) at high risk of HCC recurrence following resection or ablation with curative intent. Further, the safety of atezo + bev was generally manageable. Here, we additionally report PRO data from IMbrave050. **Methods:** IMbrave050 (NCT04102098) enrolled HCC pts at high risk of recurrence following resection or ablation. Pts were randomized to Arm A (atezo + bev) or Arm B (active surveillance). Pts in Arm A received atezo 1200 mg + bev 15 mg/kg IV q3w for a period of one year (17 cycles). Pts in Arm B underwent active surveillance for one year and were eligible to crossover to atezo + bev following independent review facility (IRF) confirmation of recurrence. The primary endpoint was IRF-assessed RFS. Pre-specified exploratory analyses included change from baseline in global health status (GHS)/quality of life (QoL), physical functioning, role functioning, emotional functioning, and social functioning. Clinically meaningful deterioration was defined as a $\geq$ 10-point decrease. Pts completed the IL42–EORTC QLQ-C30 (reduced) questionnaire at baseline and then at every odd treatment/surveillance visit through Cycle 17. **Results:** The ITT population included 334 pts in both Arms A and B. With a median follow-up time of 17.4 mo (clinical cutoff date: 21 Oct 2022), IRF-RFS HR was 0.72 (95% CI: 0.56, 0.93; $P=0.0120$). In the safety population, Grade 3 or 4 adverse events occurred in 41% of 332 Arm A pts and 13% of 330 Arm B pts. In ITT pts, IL42 completion rates remained $\geq$ 93% in both arms from baseline through treatment/surveillance Cycle 17. Mean scores at baseline in both arms were high and similar, as measured by the GHS/QoL and physical, role, emotional and social functioning scales. Mean changes from baseline were not considerable through Cycle 17 and were similar between arms as evidenced by overlapping 95% CIs. Pts' GHS/QoL and functioning was maintained through Cycle 17, with no clinically meaningful deterioration observed at any time. **Conclusions:** Statistically significant and clinically meaningful improvement in RFS was seen in pts receiving atezo + bev vs active surveillance. Atezo + bev safety was generally manageable, and consistent with the established safety profiles of each therapeutic agent and with the underlying disease. PRO outcome analyses revealed similar overall health-related QoL (HRQoL) and functioning between atezo + bev and active surveillance, and that treating high-risk pts with HCC with adjuvant atezo + bev following procedures with curative intent did not result in a clinically meaningful deterioration in HRQoL or function. Clinical trial information: NCT04102098. Research Sponsor: Roche.

4001

Oral Abstract Session

Perioperative PD-1 antibody toripalimab plus SOX or XELOX chemotherapy versus SOX or XELOX alone for locally advanced gastric or gastro-oesophageal junction cancer: Results from a prospective, randomized, open-label, phase II trial. *First Author: Shuqiang Yuan, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University Cancer Center, Sun Yat-sen University, Guangzhou, Guangdong, China*

Background: The combination of PD-1 antibody and chemotherapy was shown to be effective in advanced gastric or gastro-oesophageal junction (GEJ) cancer, but has not yet been investigated in the context of locally advanced patients. In this study, we conducted a prospective, randomized, open-label phase II trial to evaluate the effectiveness of adding PD-1 antibody to perioperative chemotherapy in patients with locally advanced resectable gastric or GEJ cancer. **Methods:** In this randomized, open-label, phase II study, patients with resectable gastric or GEJ cancer clinically staged as cT3-4a N+M0 were randomized (1:1) to three preoperative and five postoperative 3-week cycles of SOX/XELOX (C arm) or PD-1 antibody toripalimab plus SOX/XELOX, followed by toripalimab monotherapy for 6 months (C+T arm). The primary endpoint was pathological complete regression/moderate regression rate (TRG 0/1). The secondary endpoints were pathological complete response (pCR), R0 resection rate, recurrence-free survival, event-free survival, objective response rate, disease control rate, overall survival and treatment safety. The study had been completed enrollment, and here, we analyzed the primary endpoint. Mantel-Haenszel test was used to test the difference of pathological regression between the two arms. The trial was registered at ClinicalTrials.gov, identifier: NCT04250948. **Results:** Between Oct 2019 and June 2022, 108 patients (C+T arm, n=54; C arm, n=54) were enrolled and assessed using intention-to-treat analysis. Patients in the toripalimab plus chemotherapy arm achieved higher proportion of TRG 0/1 than those in the chemotherapy arm (44.4% [24/54, 95% CI: 30.9%-58.6%] vs 20.4% [11/54, 95% CI: 10.6%-33.5%]; $P=0.009$). A higher pCR rate was observed in the C+T arm (24.1% [13/54, 95% CI: 13.5%-37.6%] vs 9.3% [5/54, 95% CI: 3.1%-20.3%]; $P=0.039$). Preoperative therapies (3 cycles) were completed in 96.3% of patients and postoperative cycles (>3 cycles) in 81.5%, with no significant differences observed between these two arms. A higher proportion of downstaging was observed in the C+T arm (ypT0-2: 46.3% vs 22.2% [$P=0.002$]; ypstage 0-1: 38.9% vs 16.7% [$P=0.024$]). Surgical morbidity (11.8% in the C+T arm vs 13.5% in the C arm) and mortality (1.9% vs 0%) and treatment-related grade 3-4 adverse events (27.8% vs 25.9%) were comparable between the arms. **Conclusions:** Perioperative PD-1 antibody toripalimab plus chemotherapy demonstrated a significantly improved pathological regression and might be a promising option for patients with locally advanced resectable gastric or GEJ cancer. Clinical trial information: NCT04250948. Research Sponsor: Shanghai Junshi Biosciences Co., Ltd.

4003

Oral Abstract Session

Health-related quality of life (HRQoL) in the phase 3 KEYNOTE-966 study of pembrolizumab (pembro) plus gemcitabine and cisplatin (gem/cis) versus placebo plus gem/cis for advanced biliary tract cancer (BTC). *First Author: Changhoun Yoo, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea*

Background: In the randomized, double-blind, phase 3 KEYNOTE-966 trial (N = 1069; NCT04003636), pembro + gem/cis significantly improved OS versus placebo + gem/cis (HR 0.83; 95% CI 0.72-0.95; $P=0.0034$) and had an expected and manageable safety profile as first-line therapy for unresectable locally advanced or metastatic BTC. We present the protocol-specified exploratory patient-reported outcomes (PROs) from KEYNOTE-966. **Methods:** PROs were assessed using the EORTC QLQ-C30, EORTC QLQ-BIL21, and EQ-5D-5L questionnaires. The analysis population included all treated patients (pts) who completed $\geq$ 1 HRQoL assessment for the specific endpoint. A constrained longitudinal analysis model (covariates: treatment, time, treatment by time interaction, and stratification factors) was used to compare least squares mean (LSM) score changes from baseline (BL) to wk 18 (ie, latest timepoint that completion was $\geq$ 60% and compliance was $\geq$ 80%) in QLQ-C30 global health status (GHS)/QoL, physical functioning (PF), and role functioning (RF), QLQ-BIL21 jaundice and pain, and EQ-5D-5L visual analogue scale (VAS). A stratified Cox proportional hazards model was used to assess the magnitude of the between-arm difference in time to deterioration (TTD) in GHS/QoL, PF, RF, jaundice, and pain (ie, time to first onset of $\geq$ 10-point deterioration from BL in each scale/subscale confirmed by $\geq$ 10-point deterioration from BL at the next visit; established as clinically relevant). **Results:** Questionnaire compliance was $>87\%$ from BL to wk 18 in both arms. LSM changes from BL to wk 18 in QLQ-C30 GHS/QoL, PF, and RF, QLQ-BIL21 jaundice and pain, and EQ-5D-5L VAS were similar between arms. Time to deterioration was also similar between arms: median not reached (NR) vs 21.2 mo for GHS/QoL (HR 0.86, 95% CI 0.70-1.07), NR vs 12.0 mo for PF (HR 0.95, 95% CI 0.78-1.17), 6.5 mo vs 5.8 mo for RF (HR 0.98, 95% CI 0.81-1.18), NR vs NR for jaundice (HR 1.20, 95% CI 0.94-1.54), and NR vs NR for pain (HR 0.79, 95% CI 0.59-1.05). **Conclusions:** HRQoL was maintained when pembro was added to gem/cis. Together with the efficacy and safety data, these results support pembro + gem/cis as a new first-line treatment option for advanced BTC. Clinical trial information: NCT04003636. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

	Pembro + Gem/Cis, LSM (95% CI) Change from BL to wk 18	Placebo + Gem/Cis LSM (95% CI) Change from BL to wk 18	Difference in LS Means (95% CI)
QLQ-C30	n = 518	n = 517	
GHS/QoL	-2.5 (-4.5, -0.5)	-2.5 (-4.5, -0.5)	0.0 (-2.5, 2.6)
PF	-6.4 (-8.3, -4.5)	-7.7 (-9.6, -5.7)	1.2 (-1.4, 3.9)
RF	-7.0 (-9.6, -4.5)	-9.7 (-12.3, -7.1)	2.7 (-0.8, 6.1)
QLQ-BIL21	n = 518	n = 516	
Jaundice	0.1 (-1.1, 1.4)	-0.1 (-1.4, 1.2)	0.3 (-1.4, 1.9)
Pain	-5.9 (-7.8, -4.1)	-4.1 (-6.0, -2.2)	-1.9 (-4.3, 0.5)
EQ-5D-5L	n = 518	n = 517	
VAS	-3.4 (-5.2, -1.7)	-3.6 (-5.3, -1.8)	0.1 (-2.2, 2.5)

Higher GHS/QoL and functioning scores indicate improvement. Lower symptom scores indicate improvement.

4004

Oral Abstract Session

Outcomes by occurrence of immune-mediated adverse events (imAEs) with tremelimumab (T) plus durvalumab (D) in the phase 3 HIMALAYA study in unresectable hepatocellular carcinoma (uHCC). *First Author: George Lau, Humanity and Health Clinical Trial Center, Humanity and Health Medical Group, Hong Kong Special Administrative Region, China*

Background: Immune checkpoint inhibitor (ICI) studies have shown an association between the occurrence of imAEs and outcomes. In the Phase 3 HIMALAYA study (NCT03298451) in uHCC, STRIDE (Single T Regular Interval D) significantly improved overall survival (OS) vs sorafenib (S), and D monotherapy was noninferior to S. STRIDE and D had manageable safety (Abou-Alfa et al. *NEJM Evid* 2022). STRIDE is approved for uHCC in the United States and Japan and recommended for approval by the European Medicines Agency; D is approved in Japan. This exploratory analysis assessed the association between imAEs and outcomes in HIMALAYA. **Methods:** Safety was assessed in participants (pts) who received ≥ 1 dose of STRIDE (T 300 mg [one dose] plus D 1500 mg once every 4 weeks [Q4W]) or D (1500 mg Q4W). imAEs were AEs of special interest associated with drug exposure and consistent with an immune-mediated mechanism of action with no found alternate etiology. Median OS (mOS) and OS rates were estimated using the Kaplan–Meier method. OS hazard ratios (HRs) and 95% CIs were calculated using Cox modeling, with imAEs as a time-varying covariate and stratified by etiology (HBV/HCV/others), ECOG (0/1), and macro-vascular invasion (yes/no) for pts with vs without imAEs of any grade. Pts with > 1 imAE were counted once. **Results:** In total, 388 pts (STRIDE) and 388 pts (D) were included in the analysis. Any grade imAEs, Grade 3 or 4 imAEs, and imAEs leading to discontinuation occurred in 139 (35.8%), 49 (12.6%), and 22 (5.7%) pts, respectively for STRIDE and 64 (16.5%), 25 (6.4%), and 10 (2.6%) pts, respectively for D. imAEs requiring high-dose steroids (≥ 40 mg prednisone or equivalent daily) occurred in 78 (20.1%) pts for STRIDE and 37 (9.5%) pts for D. An improvement in OS was seen with STRIDE in pts with imAEs vs pts without (HR, 0.73; 95% CI, 0.56–0.95). OS rates at 6, 12, and 24 months (mo) were higher for STRIDE in pts with imAEs vs pts without. The association between imAEs and OS was less clear for D and may be limited by small pt number. In a landmark analysis of pts with vs without imAEs within 6 mo of STRIDE (n=307) or D (n=287), OS HRs (95% CIs) were 0.65 (0.47–0.90) and 1.39 (0.95–2.04), respectively. **Conclusions:** In HIMALAYA, imAEs with STRIDE or D were manageable and generally low grade. In this exploratory analysis, the occurrence of imAEs was associated with improved OS for STRIDE, generally consistent with findings for other ICIs. Clinical trial information: NCT03298451. Research Sponsor: AstraZeneca.

	STRIDE imAE	STRIDE No imAE	D imAE	D No imAE
n	139	249	64	324
mOS (95% CI), mo	23.2 (19.1–32.4)	14.1 (11.6–17.9)	17.8 (13.8–25.1)	16.5 (13.1–19.4)
OS HR (95% CI)		0.73 (0.56–0.95)		1.14 (0.82–1.57)
OS rate (95% CI), %				
6 mo	81.3 (75.1–88.0)	77.1 (72.1–82.5)	82.8 (74.1–92.6)	71.8 (67.1–76.9)
12 mo	69.1 (61.8–77.2)	55.2 (49.4–61.8)	60.9 (50.1–74.1)	58.2 (53.1–63.8)
24 mo	48.9 (41.3–58.0)	35.3 (29.8–41.8)	39.1 (28.8–53.0)	39.3 (34.3–45.0)

4006

Oral Abstract Session

Liposomal irinotecan + 5-fluorouracil/leucovorin + oxaliplatin (NALIRIFOX) versus nab-paclitaxel + gemcitabine in treatment-naïve patients with metastatic pancreatic ductal adenocarcinoma (mPDAC): 12- and 18-month survival rates from the phase 3 NAPOLI 3 trial. *First Author: Eileen Mary O'Reilly, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Liposomal irinotecan + 5-fluorouracil/leucovorin (5-FU/LV) is approved in the USA and Europe for mPDAC following progression with gemcitabine-based therapy. A phase 1/2 study (NCT02551991) demonstrated promising anti-tumor activity in patients with mPDAC who received first-line liposomal irinotecan 50 mg/m² + 5-FU 2400 mg/m² + LV 400 mg/m² + oxaliplatin 60 mg/m² (NALIRIFOX). Here, we present results from NAPOLI 3 (NCT04083235), a randomized, open-label, phase 3 study investigating the efficacy and safety of NALIRIFOX compared with nab-paclitaxel 125 mg/m² + gemcitabine 1000 mg/m² (Gem+NabP) as first-line therapy in patients with mPDAC. **Methods:** Eligible patients with histopathologically/cytologically confirmed untreated mPDAC were randomized (1:1; stratified by Eastern Cooperative Oncology Group [ECOG] performance status, geographic region and presence/absence of liver metastases) to receive NALIRIFOX on days 1 and 15 of a 28-day cycle or Gem+NabP on days 1, 8 and 15 of a 28-day cycle. The primary endpoint was overall survival (OS); secondary endpoints were progression-free survival (PFS), overall response rate (ORR) and safety. OS was evaluated when at least 543 events were observed using a stratified log-rank test with an overall one-sided significance level of 0.025. **Results:** Overall, 770 patients (NALIRIFOX, n = 383; Gem+NabP, n = 387) were included. Baseline characteristics were balanced between arms. At a median follow-up of 16.1 months, 544 events had occurred. Median OS was 11.1 months in the NALIRIFOX group versus 9.2 months in the Gem+NabP group; median PFS was 7.4 months versus 5.6 months. Median (95% CI) duration of response was 7.3 (5.8–7.6) and 5.0 (3.8–5.6) months in patients who received NALIRIFOX and Gem+NabP, respectively. Grade 3/4 treatment-emergent adverse events occurring in at least 10% of patients receiving NALIRIFOX versus Gem+NabP included diarrhea (20.3% vs 4.5%), nausea (11.9% vs 2.6%), hypokalemia (15.1% vs 4.0%), anemia (10.5% vs 17.4%) and neutropenia (14.1% vs 24.5%). **Conclusions:** First-line NALIRIFOX demonstrated clinically meaningful and statistically significant improvement in OS and PFS compared with Gem+NabP in patients with mPDAC. The NALIRIFOX safety profile was consistent with the profiles of the regimen components and generally manageable. Clinical trial information: NCT04083235. Research Sponsor: Ipsen.

	NALIRIFOX (n = 383)	Gem+NabP (n = 387)
OS, months, median (95% CI)	11.1 (10.0–12.1)	9.2 (8.3–10.6)
HR (95% CI); p value	0.83 (0.70–0.99); 0.04	
OS rate, %		
12 months	45.6	39.5
18 months	26.2	19.3
PFS, months, median (95% CI)	7.4 (6.0–7.7)	5.6 (5.3–5.8)
HR (95% CI); p value	0.69 (0.58–0.83); < 0.0001	
PFS rate, %		
12 months	27.4	13.9
18 months	11.4	3.6
ORR, % (95% CI)	41.8 (36.8–46.9)	36.2 (31.4–41.2)

LBA4005

Oral Abstract Session

Short-course neoadjuvant FOLFIRINOX versus upfront surgery for resectable pancreatic head cancer: A multicenter randomized phase-II trial (NORPACT-1). *First Author: Knut Jørgen Labori, Department of Hepato-Pancreato-Biliary Surgery, Oslo University Hospital and Institute of Clinical Medicine, University of Oslo, Oslo, Norway*

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2023, issue of the *Journal of Clinical Oncology*.

4007

Oral Abstract Session

Tucatinib and trastuzumab for previously treated HER2-positive metastatic biliary tract cancer (SGNTUC-019): A phase 2 basket study. *First Author: Yoshiaki Nakamura, National Cancer Center Hospital Japan East, Kashiwa, Japan*

Background: Biliary tract cancer (BTC) is an aggressive malignancy with a poor prognosis, and current treatment options for advanced BTC are limited, with second-line therapy, FOLFOX and S-1 offering an objective response rate (ORR) of 5.0% and 7.5%, respectively. Up to 20% of BTCs overexpress human epidermal growth factor receptor 2 (HER2). Tucatinib (TUC) is a highly selective HER2-directed TKI approved for HER2-positive (HER2+) metastatic breast and colorectal cancer. Discussed here are the efficacy and safety results of TUC combined with Trastuzumab (Tras) in pts with previously treated HER2+ metastatic BTC. **Methods:** SGNTUC-019 (NCT04579380) is an open-label phase 2 basket study evaluating efficacy, safety, and tolerability of TUC and Tras in pts with HER2-altered solid tumors. Pts in the BTC cohort had been previously treated with and progressed after ≥ 1 line of systemic therapy for metastatic disease. Eligible pts had locally determined HER2+ (defined as HER2 overexpression determined by immunohistochemistry [IHC] 3+ or HER2 amplification determined by in situ hybridization assay or next-generation sequencing) metastatic BTC. Pts were treated on a 21-day cycle with TUC (300 mg orally twice a day) and Tras (8 mg/kg IV followed by 6 mg/kg every 3 wks). Disease status was determined based on RECIST v1.1 with assessments performed every 6 wks for 24 wks and every 12 wks thereafter. The primary endpoint is confirmed objective response rate (cORR) per investigator assessment. Secondary endpoints include overall survival (OS), disease control rate (DCR), duration of response (DOR), progression-free survival (PFS), and safety. **Results:** Thirty pts were enrolled in the BTC cohort as of data cutoff date of 30 Nov 2022. The median duration of follow-up was 8.3 months. cORR was 46.7% (90% CI, 30.8, 63.0), with 14 responses including 1 complete and 13 partial responses. Median DOR was 6.0 months (90% CI, 5.5, not estimable). DCR was 76.7% (n=23; 90% CI, 60.6, 88.5), and median PFS was 5.5 months (90% CI, 3.9, 8.1). At data cutoff, 13 (43.3%) patients had died, and the 12-months OS rate was 53.8% (90% CI, 35.2, 69.1%). Overall, the most common treatment-emergent adverse events (TEAEs) reported were pyrexia (43.3%) and diarrhea (40.0%). Grade ≥ 3 TEAEs were reported in 18 (60.0%) of 30 pts; however, only 6 (20.0%) and 2 (6.7%) of these pts had Grade ≥ 3 TEAEs related to TUC and Tras, respectively. Two (6.7%) pts discontinued TUC due to TEAEs, cholangitis and liver disorder. No deaths were due to TEAEs. **Conclusions:** The combination of TUC and Tras was well tolerated in pts with previously treated HER2+ metastatic BTC. The observed antitumor activity supports the combination of TUC and Tras as a future chemotherapy-free treatment option for this population with historically poor outcomes. Clinical trial information: NCT04579380. Research Sponsor: Seagen Inc.

4008

Oral Abstract Session

Results from the pivotal phase (Ph) 2b HERIZON-BTC-01 study: Zanidatamab in previously-treated HER2-amplified biliary tract cancer (BTC). *First Author: Shubham Pant, MD Anderson Cancer Center, Houston, TX*

Background: For patients (pts) with locally advanced/metastatic BTC who progress after first-line treatment (tx), standard tx offers limited clinical benefit with modest improvement in survival. HER2-targeted therapies have improved survival in breast and gastric cancer, but there is no approved HER2-targeted therapy for BTC. Zanidatamab (zani), a HER2-targeted bispecific antibody, has shown durable responses in a subset of pts with BTC in a Ph 1 trial. **Methods:** HERIZON-BTC-01, an open-label, global Ph 2b study (NCT04466891), evaluated zani (20 mg/kg IV every 2 wks) in pts with HER2-amplified, locally advanced unresectable or metastatic BTC (gallbladder cancer [GBC], intra-/extra-hepatic cholangiocarcinoma [ICC/ECC]) who had received prior gemcitabine-containing therapy; pts with prior HER2-targeted therapies were excluded. Pt cohort assignment was based on tumor immunohistochemistry (IHC) status: Cohort 1 for IHC 2+/3+ (HER2 positive), or Cohort 2 for IHC 0/1+. Tumors were assessed every 8 wks per RECIST 1.1. The primary endpoint was confirmed objective response rate (cORR) by independent central review (ICR) in Cohort 1. Secondary endpoints included other efficacy and safety outcomes. **Results:** Enrollment is complete with 87 pts (Cohort 1, n=80; Cohort 2, n=7) treated. Median age was 64 yrs (range, 32-79); 54% were female; 66% were Asian; 52% had GBC, 30% ICC, and 18% ECC. Pts had a median of 1 line (range, 1-7) of prior therapy in the locally advanced/metastatic setting. In Cohort 1, cORR was 41% with median duration of response (DOR) of 12.9 months (m; 95% CI: 5.95, not estimable); median study follow-up time was 12.4 m. Among the 33 responders at the data cut (10OCT2022), 49% had ongoing responses and 82% had a DOR of ≥16 wks. Median time to first response was 1.8 m (range, 1.6-5.5). Progression-free survival and overall survival are being evaluated. No responses were observed in Cohort 2. In both cohorts (N=87), tx-related adverse events (TRAEs) occurred in 72% of pts; TRAEs in ≥10% of pts were diarrhea (37%) and infusion-related reaction (33%). Gr 3 TRAEs occurred in 18% of pts, with diarrhea (4.6%) and ejection fraction (EF) decreased (3.4%) in >3% of pts. Two pts (2.3%) discontinued zani due to an AE (EF decreased and non-infectious pneumonitis). Seven pts had serious TRAEs; no AE preferred term occurred in >1 pt. No zani-related Gr 4 AEs or deaths were reported. **Conclusions:** Results of the pivotal HERIZON-BTC-01 study indicate that the HER2 bispecific antibody zani demonstrates rapid, durable responses with a manageable safety profile in pts with tx-refractory HER2-positive BTC. Given these data, zani continues to be developed as a tx option in HER2-positive BTC. Clinical trial information: NCT04466891. Research Sponsor: Zymeworks BC Inc.

	Cohort 1 (n=80)	Cohort 2 (n=7)
cORR, % (95% CI)	41 (30, 53)	0 (0, 41)
Confirmed Best Objective Response, n (%)		
CR	1 (1)	0
PR	32 (40)	0
SD	22 (28)	1 (14)
PD	24 (30)	3 (43)
Disease Control Rate, % (95% CI)	69 (57, 79)	43 (10, 82)

4010

Clinical Science Symposium

Results from the MORPHEUS-liver study: Phase Ib/II randomized evaluation of tiragolumab (tira) in combination with atezolizumab (atezo) and bevacizumab (bev) in patients with unresectable, locally advanced or metastatic hepatocellular carcinoma (uHCC). *First Author: Richard S. Finn, University of California Los Angeles, Los Angeles, CA*

Background: Atezo + bev is the current first-line standard of care for uHCC based on the IMbrave150 study, which demonstrated superior overall survival, progression-free survival (PFS), and objective response rate (ORR) vs sorafenib (Finn, et al. New Engl J Med 2020; Cheng, et al. J Hepatol 2022). TIGIT is a novel inhibitory immune checkpoint present on activated T cells and NK cells. Tira (anti-TIGIT) may synergize with other immunotherapies, such as PD-L1/PD-1 inhibitors. The MORPHEUS platform comprises multiple phase Ib/II trials to identify early efficacy signals and safety of treatment combinations across cancers. Here we report data from a cohort of the MORPHEUS-liver study (NCT04524871) evaluating the combination of tira + atezo + bev vs a control arm (atezo + bev) in patients with uHCC. **Methods:** Patients with previously untreated uHCC were randomized to receive atezo (1200mg IV) + bev (15mg/kg IV) with or without tira (600mg IV) every three weeks. The primary endpoint was investigator-assessed ORR by RECIST V1.1. Secondary endpoints included PFS and safety. **Results:** A total of 58 patients were randomized (tira + atezo + bev, n=40; atezo + bev, n=18). As of 28 November 2022, median follow up was 14.0 months in the tira + atezo + bev arm and 11.8 months in the control arm. Confirmed ORR was higher in the tira + atezo + bev arm (42.5%) vs the control arm (11.1%). Median PFS was longer with tira + atezo + bev (11.1 months; 95% CI: 8.2–NE) vs control (4.2 months; 95% CI: 1.6–7.4), corresponding to a PFS hazard ratio (HR) of 0.42 (95% CI: 0.22–0.82). A similar pattern of increased ORR and PFS was observed for the treatment arms in both PD-L1+ (n=23) and PD-L1– (n=27) subgroups. For tira + atezo + bev vs control arm, grade 3/4 treatment-related AEs were 27.5% vs 33.3% and AEs leading to any treatment discontinuation were 22.5% vs 22.2%, respectively. **Conclusions:** The addition of tira to atezo + bev resulted in higher ORR and longer PFS compared with atezo + bev, and no new safety signals were identified. These data suggest that tira + atezo + bev may be a promising novel first-line treatment option for patients with uHCC, and support further study in this setting. Clinical trial information: NCT04524871. Research Sponsor: F. Hoffmann-La Roche Ltd.

Efficacy outcomes.	Tira + atezo + bev	Atezo + bev
ITT, n	40	18
Confirmed ORR, % (n/N) (95% CI)	42.5 (17/40) (27.0–59.1)	11.1 (2/18) (1.4–34.7)
Median PFS, months (95% CI) HR (95% CI)	11.1 (8.2–NE)	4.2 (1.6–7.4)
PD-L1+, n	16	7
Confirmed ORR, % (n/N)	56.3 (9/16)	14.3 (1/7)
Median PFS, months (95% CI) HR (95% CI)	13.6 (7.1–NE)	2.8 (2.3–NE)
PD-L1–, n	18	9
Confirmed ORR, % (n/N)	27.8 (5/18)	0 (0/9)
Median PFS, months (95% CI) HR (95% CI)	9.1 (4.0–NE)	4.2 (1.5–7.4)
	0.36 (0.14–0.94)	

4009

Clinical Science Symposium

Updated dose escalation results for ReFocus, a first-in-human study of highly selective FGFR2 inhibitor RLY-4008 in cholangiocarcinoma and other solid tumors. *First Author: Mitesh J. Borad, Mayo Clinic Arizona, Scottsdale, AZ*

Background: Oncogenic FGFR2 alterations (fusions/rearrangements (f/r), amplifications, mutations) represent a broad therapeutic opportunity as they drive multiple solid tumors, particularly cholangiocarcinoma (CCA). However, off-isomeric toxicity and on-target resistance limit the benefit of approved pan-FGFR inhibitors (FGFRI). RLY-4008 is the first potent, highly selective, oral FGFR2 inhibitor designed to overcome these limitations by targeting FGFR2 driver alterations and resistance mutations. Here, we present updated dose escalation results from ReFocus (NCT04526106), a seamless Phase I/II, open label study evaluating the safety and preliminary efficacy of RLY-4008 in patients (pts) with advanced, FGFR2-altered solid tumors. **Methods:** Adult pts received RLY-4008 BID, QD, QD discontinuous on a 4-week (wk) cycle following a Bayesian Optimal Interval design. Treatment-related adverse events (TRAEs), PK, ctDNA and anti-tumor activity (RECIST v1.1) were assessed. **Results:** As of 30 Jan 23, 116 pts (82 f/r, 27 mutation, 6 amplification) received RLY-4008 at doses of 20-200 mg/day, including 91 with CCA. 50% had prior FGFRI, and median lines of prior therapies was 3 (1-15). 28/46 ct-DNA-evaluable pts with CCA with prior FGFRI had ≥1 baseline resistance mutation, most commonly at FGFR2 N549X (23/46) or V564X (17/46). RLY-4008 had favorable PK with doses ≥40 mg QD providing FGFR2 occupancy ≥90%. 70 mg QD was the RP2D based on PK, safety, anti-tumor activity and exposure-dependent tumor regressions in FGFRI-naïve CCA f/r pts. Anti-tumor activity was observed in CCA and solid tumors across doses and FGFR2 alterations with radiographic tumor reductions in 74 (64%), SD/PR in 83 (72%), including 4/4 (100%) FGFRI-naïve CCA f/r pts at RP2D achieving confirmed PR. Clinically meaningful disease control and durable responses were observed in pts with FGFR2 f/r CCA. Overall, median treatment duration was 24 wks (range <1-108 wks). 105 pts discontinued (PD (81%), AE (3%), other (7%). Across doses, most common TRAEs were low-grade PPE (57%), stomatitis (56%), dry mouth (38%), alopecia (28%), and dry eye (22%). No grade 4/5 TRAEs were observed. **Conclusions:** These encouraging dose escalation data confirm the broad therapeutic potential of highly selective FGFR2 targeting with RLY-4008 by demonstrating encouraging initial efficacy across FGFR2-altered solid tumors and genomic alterations, with a differentiated safety profile that avoids FGFRI- and FGFR4-related toxicity. Phase 2 of ReFocus continues across solid tumors and with registrational intent in FGFRI-naïve, FGFR2 f/r CCA. Clinical trial information: NCT04526106. Research Sponsor: Relay Therapeutics.

	FGFRI-naïve CCA f/r N = 25	Prior-FGFRI CCA f/r N = 50
ORR n(%) [95% CI]	13 (52% [31.3%-72.2%])	7 (14% [5.8%-26.7%])
mDOR mo (range)	8.2 (1.9-18.6)	5.6 (1.9-7.4)
>24 wk DOR	10/13 (77%)	4/7 (57%)
Response ongoing	6/13 (46%)	2/7 (29%)
DCR n (%)	22 (88%)	40 (80%)

4011

Clinical Science Symposium

Subgroup analysis of double-blind, placebo-controlled Ph. 2 study of nanvuranlat in treatment of pre-treated, advanced, refractory biliary tract cancer (BTC): Patients with high LAT1 expression and response to nanvuranlat. *First Author: Masafumi Ikeda, Department of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital East, Kashiwa, Japan*

Background: L-type amino acid transporter 1 (LAT1, *SLC7A5*) is overexpressed in cancer cells leading to aggressive proliferation and lymphatic metastases. LAT1 sustains energy resources by supplying essential amino acids to the TCA cycle in chemotherapy-resistant cancer cells. LAT1 is a documented marker of poor prognosis. In a placebo-controlled, randomized trial involving patients with pre-treated, advanced, refractory biliary tract cancer (BTC), monotherapy with nanvuranlat (JPH203), a selective LAT1 inhibitor, demonstrated a significant improvement in progression free survival (PFS) compared to placebo. Subgroup analysis was conducted to determine whether the level of expression of LAT1 affects nanvuranlat efficacy. **Methods:** Patients with four different subtypes of advanced BTC were enrolled: intrahepatic and extrahepatic cholangiocarcinoma, and gallbladder and ampulla of Vater cancers. All were refractory to or intolerant of standard chemotherapy and other investigational medicines. Our analysis compared efficacy and safety in the subgroup with high LAT1 expression and all patients group. LAT1 expression was immunohistochemically evaluated in tumor specimens of BTC patients at baseline, as defined by Yanagisawa N, et al. (Cancer Med 2014). **Results:** At data cut-off (Feb 28, 2022), 211 BTC patients consented at 14 centers in Japan, and 104 patients were randomized (2:1) to nanvuranlat (n = 69) or placebo (n = 35) as the full analysis set (FAS) population. Among the samples immunohistochemically evaluable for LAT1, 62.5% had high LAT1 expression. There was no significant difference in background demography between all patient group and the high-LAT1 subgroup. Nanvuranlat met its primary endpoint (FAS by the blinded independent central review (BICR)), demonstrating a statistically significant improvement in PFS by BICR in comparison with the placebo group. The hazard ratios were further improved with nanvuranlat versus placebo, on analysis of the high-LAT1 subgroup of patients in both PFS and OS. Safety was comparable between nanvuranlat and placebo, on analysis of the high-LAT1 subgroup. **Conclusions:** This subgroup analysis indicates that the efficacy of nanvuranlat in PFS and OS is enhanced in BTC patients with high LAT1 expression, when compared with placebo. Safety profiles were similar for nanvuranlat and placebo-treated patients in this subgroup analysis. Clinical trial information: UMIN000034080. Research Sponsor: J-Pharma Co., Ltd.

	Nanvuranlat vs Placebo	Subgroup of Patients with High LAT1 (n=65)	All Patients (n=104)
PFS	Hazard Ratio ¹	0.439	0.557
	95% CI (lower - upper)	0.2254 - 0.8535	0.3435 - 0.9029
	p value ²	0.0131	0.0164
OS	Hazard Ratio ¹	0.670	0.849
	95% CI (lower - upper)	0.3463 - 1.2954	0.5308 - 1.3574
	p value ²	0.2313	0.4934

¹ Stratified Cox proportional-hazard model; ² Stratified log-rank test.

4014

Poster Discussion Session

KEYNOTE-859 study of pembrolizumab plus chemotherapy for advanced HER2-negative gastric or gastroesophageal junction (G/GJEJ) cancer: Outcomes in the protocol-specified PD-L1-selected populations. *First Author: Sun Young Rha, Yonsei Cancer Center, Yonsei University Health System, Seoul, Korea, Republic of (South)*

Background: In the ITT population of the KEYNOTE-859 study of HER2-negative, advanced G/GJEJ cancer (NCT03675737), pembrolizumab (pembro) + chemotherapy (chemo) significantly improved OS (HR 0.78, 95% CI 0.70-0.87; $P < 0.0001$), PFS (HR 0.76, 95% CI 0.67-0.85; $P < 0.0001$), and ORR (51.3% vs 42.0%; $P = 0.00009$) vs placebo + chemo at the protocol-specified interim analysis. The safety profile of pembro + chemo was as expected. We present efficacy outcomes of the protocol-specified PD-L1 combined positive score (CPS) ≥ 1 and CPS ≥ 10 populations. **Methods:** Eligible pts aged ≥ 18 y with HER2-negative, previously untreated locally advanced or metastatic G/GJEJ adenocarcinoma, ECOG PS 0-1, and known PD-L1 CPS were randomized 1:1 to pembro 200 mg or placebo IV Q3W for ≤ 35 cycles, both given with investigator's choice of 5-FU + cisplatin (FP) or capecitabine + oxaliplatin (CAPOX). Randomization was stratified by region (Europe/Israel/North America/Australia vs Asia vs rest of world), PD-L1 CPS (< 1 vs ≥ 1), and chemo (FP vs CAPOX). Per protocol, the primary endpoint of OS and the secondary endpoints of PFS and ORR per RECIST v1.1 by blinded independent central review were tested in the PD-L1 CPS ≥ 1 and ≥ 10 populations. Data are from the interim analysis (median study follow-up, 31.0 mo). **Results:** At baseline, 618 (78.2%) of 790 pts randomized to pembro + chemo and 617 (78.2%) of 789 pts randomized to placebo + chemo had PD-L1 CPS ≥ 1 ; 279 (35.3%) and 272 (34.5%), respectively, had CPS ≥ 10 . Baseline characteristics were generally consistent between treatment arms and populations. In the PD-L1 CPS ≥ 1 population, median OS was 13.0 mo (95% CI 11.6-14.2) for pembro + chemo vs 11.4 mo (95% CI 10.5-12.0) for placebo + chemo (HR 0.74, 95% CI 0.65-0.84; $P < 0.0001$), median PFS was 6.9 mo (95% CI 6.0-7.2) vs 5.6 mo (95% CI 5.4-5.7) (HR 0.72, 95% CI 0.63-0.82; $P < 0.0001$), ORR was 52.1% vs 42.6% ($P = 0.00041$), and median DOR was 8.3 mo (range 1.2+ to 41.5+) vs 5.6 mo (1.3+ to 34.2+). In the PD-L1 CPS ≥ 10 population, median OS was 15.7 mo (95% CI 13.8-19.3) with pembro + chemo vs 11.8 mo (95% CI 10.3-12.7) with placebo + chemo (HR 0.65, 95% CI 0.53-0.79; $P < 0.0001$), median PFS was 8.1 mo (95% CI 6.8-8.5) vs 5.6 mo (95% CI 5.4-6.7) (HR 0.62, 95% CI 0.51-0.76; $P < 0.0001$), ORR was 60.6% vs 43.0% ($P = 0.00002$), and median DOR was 10.9 mo (range 1.2+ to 41.5+) vs 5.8 mo (1.4+ to 31.2+). Among all treated pts in the pembro + chemo ($n = 785$) and placebo + chemo ($n = 787$) arms, immune-mediated AE incidence was 27.1% vs 9.3%. **Conclusions:** The addition of pembro to FP or CAPOX significantly improved OS, PFS, and ORR in the PD-L1 CPS ≥ 1 and ≥ 10 populations. Together with the efficacy and safety results from the ITT population, these data support pembro + chemo as a new first-line treatment option for pts with locally advanced or metastatic HER2-negative G/GJEJ adenocarcinoma, regardless of PD-L1 expression. Clinical trial information: NCT03675737. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

4016

Poster Discussion Session

A randomized study of consolidation chemoradiation (CTRT) vs observation after first-line chemotherapy (CT) in advanced gall bladder cancers (GBC): RACE-GB Study. *First Author: Sushma Agrawal, SGPGI, Lucknow, India*

Background: CT (gemcitabine plus cisplatin) is the standard of care for patients presenting with unresectable advanced GBC but their prognosis remains poor. The value of CT after CT is uncertain. We therefore conducted a randomised trial evaluating consolidation CTRT versus Observation after four cycles of CT in those patients whose disease did not progress during CT (NCT05493956). **Methods:** Responders (partial response and stable disease) to 4 cycles of CT were randomised to CTRT vs observation ($n=135$). CTRT was delivered by 3D-Conformal Radiation Therapy along with concurrent capecitabine @1250 mg/m². The dose of RT was 45 Gy in 25 fractions to GBC and lymphatics followed by a boost of 9 Gy in 5 fractions to the GBC. The primary endpoint was overall survival which was calculated from the date of randomisation. The trial is designed to detect an improvement in 2-year OS from 8% in the control arm to 25% in study arm with 80.0% power at a 0.05 significance level. The required sample size was 130 (65 in each arm) over a duration of 4-5 years. CTRT was delivered by 3DCRT along with concurrent capecitabine @1250 mg/m². The dose of RT was 45Gy in 25 fractions to GBC and lymphatics followed by a boost of 9 Gy in 5 fractions to the GBC. Toxicities documented during CT and CTRT were recorded using the CTCAE version 3.0. and RTOG criteria respectively. Chi square test and Survival analysis was performed for the data analysis. Demographic data and CTRT Dose volume data were correlated with side effects and survival. Statistical analysis was performed with SPSS version-23. **Results:** 67 patients were randomized to observation and 68 to CTRT. Their demographic characteristics were well balanced. 63% were women, 58% had T4 tumours, 42% had N2, 27% needed stenting for obstructive jaundice. The median overall survival in the CTRT arm was 10 months versus 4 months in the observation arm (HR 0.47 [95% CI 0.33-0.68] $p=0.001$). Adverse events (grade 3 or higher) due to CTRT included the following: Nausea 3%, Anemia 9%, GI bleed 6%, hepatotoxicity 13%. Updated survival data and prognostic factors affecting overall survival will be presented in the meeting. **Conclusions:** CTRT after 4 cycles of CT significantly prolonged overall survival but was also associated with adverse events. Clinical trial information: NCT05493956. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology.

4015

Poster Discussion Session

A phase 2 randomized, open-label, multicentre study of sintilimab and anlotinib in combination with gemcitabine plus cisplatin (GemCis) as first-line therapy in patients (pts) with advanced biliary tract cancer (BTC): SAGC. *First Author: Li Jingjing, Department of Hepato-Pancreato-Biliary & Gastric Medical Oncology, Cancer Hospital of the University of Chinese Academy of Sciences (Zhejiang Cancer Hospital), Institute of Cancer and Basic Medicine (IBMC), Chinese Academy of Sciences, Hanzhou, China*

Background: BTC has a higher incidence in China rather than worldwide, with extremely poor prognosis, and the efficacy of standard first-line therapy is rather limited. TOPAZ-1 study suggested the immune check-point inhibitor plus chemotherapy as first line in advanced BTC significantly improved OS and PFS with manageable safety, but the median OS was just 12.8 months. SAGC is the first randomized controlled phase 2 trial to evaluate immune check-point inhibitor plus antiangiogenic targeted drug plus chemotherapy in advanced BTC as first-line treatment. **Methods:** Overall 80 advanced BTC were randomized 1:1 to receive sintilimab (200mg every 3 weeks [Q3W]) and anlotinib (10mg po qd, Days 1-14 Q3W) in combination with GemCis (Gem 1000 mg/m² and Cis 25 mg/m² on Days 1 and 8 Q3W) for up to 8 cycles, followed by sintilimab (200mg every 3 weeks [Q3W]) and anlotinib (10mg po qd, Days 1-14 Q3W) (SAGC group) or GemCis (Gem 1000 mg/m² and Cis 25 mg/m² on Days 1 and 8 Q3W) for up to 8 cycles until disease progression or unacceptable toxicity (GC group). The primary objective was to assess the progression-free survival (PFS). Secondary endpoints included, objective response rate (ORR), overall survival (OS) and safety. Next generation sequencing (NGS) was performed on pre-treatment available tumor tissue in 58 patients to screen dominant patients of the therapy. **Results:** At the time of the final data cutoff (Sep. 22, 2022), median follow-up was 13.4 mo, and 65/80 pts (81.3%) had discontinued tx. The confirmed median PFS was 8.6 months for SAGC group vs. 6.2 months for GC group (HR 0.37, $p < 0.01$) and ORR was 52.8% for SAGC group vs. 29.4% for GC group. Grade 3/4 treatment-related adverse events (TRAEs) occurred in 77.5% of pts receiving sintilimab plus anlotinib plus GemCis and 40% of pts receiving GemCis. The results from NGS suggested that patients with TMB-H and ARID1A-WT may benefit more from combination therapy. **Conclusions:** In pts with advanced BTC, sintilimab plus anlotinib plus GemCis significantly improved PFS and ORR vs GemCis with manageable safety, indicating sintilimab plus anlotinib plus GemCis may be a new first-line standard of care regimen. Clinical trial information: NCT04300959. Research Sponsor: None.

4017

Poster Discussion Session

A multicenter, open-label, randomized phase II study evaluating adjuvant gemcitabine plus cisplatin (GC) and capecitabine with concurrent capecitabine radiotherapy (CAPE-RT) in patients with operated gallbladder adenocarcinoma (GBC): The GECCOR-GB trial. *First Author: Anant Ramaswamy, Tata Memorial Hospital (HBN), Mumbai, India*

Background: Adjuvant gemcitabine plus cisplatin (GC) and concurrent chemo-radiotherapy are commonly used treatment options for resected GBC. **Methods:** GB-GECCOR is a multicentre, open-label randomized non-comparative phase II study in patients of Gallbladder cancer (GBC), with R0 or R1 resection within 3 months of randomization. Patients were randomized 1: 1 to GC arm (Gem 1000 mg/m² and Cisplatin 25mg/m² on day 1 and 8, q 3 weeks) for 6 cycles or CAPE-RT arm (Capecitabine 1000mg/m² BD on days 1-14, q 3 weeks for 2-4 cycles followed by chemoradiation (RT: 45 Gy over 25 fractions concurrent with capecitabine: 825mg/m² twice) followed by 2-4 cycles of capecitabine for a total of 6 cycles). The primary end point was 1-year disease-free survival (DFS). With 80% power to detect the difference between a 59% (minimum sufficient activity of the regimen) and a 77% (sufficient activity for future larger studies with the regimen) 1-year DFS rate assuming an attrition of 10%, a total of 90 patients were required for the study. **Results:** Between May 2019 and February 2022, 90 patients (45 in each arm), were included. Stage II and stage III GBC were seen in 50 (56%) and 40 patients (44%) respectively, with R0 resection observed in 86 patients (96%). Patient characteristics were well balanced between the 2 arms except for R1 resections which were greater in the CAPE-RT arm ($p=0.041$). With a median follow-up duration of 23 months, the 1-year DFS rate was 88.9% (95% CI: 79.5-98.3) in the GC group and 77.8% (95% CI: 65.4 – 90.2) in the CAPE-RT group, respectively. The most common AEs were grade 3/4 neutropenia in 6 patients (13.3%) in the GC group and grade 2/3 HFS in 14 patients (31.1%) in the CAPE-RT group. The distant metastases were seen in 12 patients (26.6%) in each arm and loco-regional metastases in 3 patients (6.6%) in the GC arm. **Conclusions:** In this study of operated GBC, GC and CAPE-RT successfully achieved the minimum pre-specified DFS rates. Within the confines of a non-comparative randomised study, GC had narrowed the gap in survivals of stage III vs. stage II GBCs, which was not noted in the CAPE-RT arm. This study results give credence to the use of both regimens as reasonable standards of care till evaluation in larger phase 3 studies. Clinical trial information: CTRI/2019/05/019323. Research Sponsor: Educational grants to the institute from redxy's lab pvt for this study.

Characteristics	GC arm (%) (n=45)	CAPE-RT arm (%) (n=45)	p-value
Stage			
II	23	27	0.396
III	22	18	
Treatment completion rates	84.4	73.3	
1 - year DFS	88.9 (95% CI: 79.5-98.3)	77.8% (95% CI: 65.4 – 90.2)	
Stage II	95.7	96.3	
Stage III	81.8	50	
2-year DFS	74.8% (95% CI: 60.4-89.2)	73.1% (59.9-86.3)	
Stage II	76.8	92.3	
Stage III	72.2	44.4	
1 - year OS	95.6% (95% CI: 89.4 – 98.7)	88.9 (95% CI: 79.5-98.3)	

4018

Poster Discussion Session

Clinical and genomic characterization of early-onset pancreatic cancer. *First Author: Florian Castet, Gastrointestinal and Endocrine Tumor Unit, Vall d'Hebron Institute of Oncology (VHIO), Hospital Universitari Vall d'Hebron, Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain*

Background: Pancreatic cancer is a leading cause of cancer-related death worldwide. Early-onset tumours (≤ 50 years) have risen alarmingly in recent years. However, the clinical and genomic particularities of early-onset pancreatic cancer (EOPC) remain poorly defined. We aimed to characterize EOPC and study its implications for treatment and prognosis. **Methods:** We performed a retrospective analysis of EOPC patients and a control group of patients ≥ 70 years (defined as average-onset pancreatic cancer, AOPC) followed at a tertiary cancer centre from 2010 to 2022. We collected baseline patient characteristics, tumor molecular profiling, germline genetic alterations, survival and treatment outcomes. We used a targeted gene panel to identify somatic genomic events and classified them according to the ESMO scale for clinical actionability of molecular targets (ESCAT). Key molecular findings were validated in an external cohort. We used a propensity score weighting method and multivariate Cox regression analysis to adjust for covariates. **Results:** We reviewed 824 patients, 336 of whom met all inclusion criteria (EOPC N = 139, AOPC N = 197). EOPC was associated with smoking status (current, 15.9 vs 7.9%, $p = 0.03$), lower prevalence of diabetes (3.7 vs 39.6%, $p < 0.01$), better performance status (ECOG 0, 42.9 vs 19.3%, $p < 0.01$), higher CA19.9 levels (median 574 vs 207.6 U/L, $p = 0.07$) and higher albumin levels (median 4.2 vs 3.9 g/L, $p < 0.01$). EOPC showed a non-significant higher prevalence of germline alterations (22.4 vs 14.5%, $p = 0.18$). After adjustment for baseline covariates, we observed no differences in survival (HR 0.94, 95% CI 0.63-1.4). We found a lower prevalence of *KRAS*^{MUT} tumors in EOPC when compared with AOPC (83.1 vs 91.1%, $p = 0.12$) and validated this finding in an independent cohort of 803 patients (82.9 vs 94.5%, $p < 0.01$). Notably, EOPC were enriched in potentially actionable alterations when compared with AOPC, both in our cohort (19.1 vs 14.4%) and the validation cohort (14.4 vs 7.9%, $p < 0.01$). Moreover, 294 patients in our cohort (EOPC N = 130; AOPC N = 164) were diagnosed with or eventually presented metastasis. EOPC more frequently received first-line 5FU-based chemotherapy (44.1 vs 14.7%, $p < 0.01$) and received a greater number of treatment lines (median 2 vs 1, $p < 0.01$). EOPC had a longer progression-free survival on first-line chemotherapy when compared with AOPC (HR 0.61, 95% CI 0.43-0.87, $p < 0.01$) although there were no differences in response rate. Six EOPC patients received matched targeted therapies and 5 patients with AOPC. After adjusting for the number of treatment lines received, EOPC treated with targeted therapies exhibited longer OS compared with EOPC who did not (HR 0.34 95% CI 0.12-0.93, $p = 0.04$), whereas this trend was not observed in AOPC (HR 0.82 95% CI 0.32-2.11, $p = 0.68$). **Conclusions:** EOPC patients harbor unique clinical and molecular features and may particularly benefit from precision-based oncology approaches. Research Sponsor: None.

4020

Poster Discussion Session

Not all treated *KRAS*-mutant pancreatic adenocarcinomas are equal: *KRAS* G12D and survival outcome. *First Author: Bach Ardalan, Sylvester Comprehensive Cancer Center, Miami, FL*

Background: *KRAS* is an oncogenic driver in pancreatic ductal adenocarcinoma (PDAC) with mutations identified in $> 90\%$ of cases. G12D is the most frequent variant, followed by G12V and G12R. We recently reported on the prognostic impact of distinct *KRAS* mutations. The current study utilized a large clinical and genomic database, to further explore and characterize the prognostic and molecular differences between *KRAS* variants, focusing on *KRAS* G12D and G12R. **Methods:** PDAC samples were tested using whole transcriptome sequencing (WTS; Illumina NovaSeq) and NextGen DNA sequencing (NextSeq, 592 Genes and NovaSeq, WES) at Caris Life Sciences (Phoenix, AZ). Transcriptomic signatures including MPAS (MAPK activation score), T-cell inflamed score and tumor micro environment (TME) characterization were calculated on WTS data. Significance was determined by χ^2 and Fisher-Exact and p-value was adjusted for multiple comparisons (q). Real-world overall survival (rwOS) obtained from insurance claims data was calculated from tissue collection to last contact (comparison done by Kaplan-Meier test). **Results:** 5,555 PDAC patients harboring either *KRAS* G12D (n = 2,671), G12V (n = 1,871) G12R (n = 904) or G12C (n = 109) variants were identified. Patients with *KRAS* G12R mutant tumors had significantly longer OS compared to G12D (396 vs 311 days, HR 0.81, CI 0.74-0.88, $p < 0.0001$). There was no difference among *KRAS* variants in the rate of *TP53*, *CDKN2A* and *SMAD4* mutations. *ARID1A* and *KMT2D* were more frequently mutated in *KRAS* G12D vs. G12R. The MPAS gene signature reflecting MAPK pathway activation trended lower in G12R vs. G12D. Expression of multiple genes in this pathway was statistically lower in the G12R cohort. Immune profiling suggested that: *PDL1* expression is significantly lower in G12R vs G12D (13% vs 19%), TMB-H and dMMR were comparable in G12D vs G12R and several glucose and glutamine metabolism genes were significantly lower in expression when comparing G12R vs G12D - table. OS was improved within the G12R cohort for those patients on metformin (n=273 patients) (416 vs 388 days, HR 0.84, CI 0.72-0.99, $p = 0.037$) while no difference was seen in those with *KRAS* G12D based on metformin use. **Conclusions:** Patients with G12D mutations have significantly lower survival compared to G12R. Significant molecular differences were seen in MAPK pathway gene expression, markers of immune activation, and genes involved in glucose and glutamine metabolism. Intriguingly, metformin use appeared to impact survival in the *KRAS* G12R subgroup. We aim to further explore distinct vulnerabilities based on MAPK pathway activation and dysregulated metabolism. Based on this data, future studies should address the *KRAS* mutation status and explore distinct therapeutic vulnerabilities. Research Sponsor: None.

Association	Gene	FC (G12R/G12D)	q value
Glutamine metabolism	<i>GOT1</i>	0.88	0.025
	<i>GOT2</i>	0.86	<0.001
	<i>SLC2A1</i>	0.82	<0.001
Glucose metabolism	<i>LDHA</i>	0.86	0.001
	<i>RPE</i>	0.89	0.032

4019

Poster Discussion Session

Investigating alterations in cancer driver genes and other potentially targetable mutations in patients with intrahepatic cholangiocarcinoma (iCCA) treated on the randomised phase III multicentre BILCAP clinical trial. *First Author: Valerie Elizabeth Crolley, UCL-University College London (United Kingdom), London, United Kingdom*

Background: The BILCAP clinical trial established adjuvant capecitabine as the standard of care treatment in patients with resected biliary tract cancer. Translational work to investigate the role of cancer driver genes and other potentially targetable mutations in patients enrolled on BILCAP was performed, with this analysis focusing on patients with intrahepatic cholangiocarcinoma (iCCA). **Methods:** Archived fixed formalin (FFPE) tissue samples were collected from consented BILCAP patients. These samples underwent DNA and RNA extraction followed by low-pass whole genome sequencing (lp-WGS), targeted gene sequencing (TGS) and RNA sequencing (RNAseq) for copy number (CN) analysis, mutation analysis and gene fusion analysis. **Results:** 84 of the 447 BILCAP patients had iCCA; 45 successfully underwent lp-WGS and RNAseq, of whom 36 also underwent TGS. The median age was 61 years (95% CI 57.8 – 64.2), 55.6% were female and 23 received capecitabine (51.1%). FGFR2 gene fusions were present in 9 patients (20.0%), as were fusions in NTRK1 (n = 3, 6.7%), FGFR1 (n = 3, 6.7%), FGFR3 (n = 2, 4.4%) and FGFR4 (n = 2, 4.4%). Commonly mutated driver genes included ROS1 (n = 12, 33.3%), MET (n = 10, 27.8%) and ALK (n = 7, 19.4%) with known pathogenic variants seen in IDH1 (n = 4, 11.1%; total number of mutations = 7, 19.4%), BRAF (n = 2, 5.6%; total n = 6, 16.7%), FGFR2 (n = 1, 2.7%; total n = 8, 22.2%), FGFR3 (n = 1, 2.7%, total n = 6, 16.7%), IDH2 (n = 1, 2.7%; total n = 6, 16.7%) and EGFR (n = 1, 2.7%; total n = 4, 11.1%). Commonly amplified (CN ≥ 4 , ploidy < 3) genes included NTRK1 (n = 9, 20.0%), ERBB2 (n = 8, 17.8%), and MET (n = 3, 6.7%). Most of the alterations investigated in this cohort did not significantly affect recurrence risk or overall survival (OS), including FGFR2 fusions (OS HR 1.23, $p = 0.695$; recurrence HR 1.32 $p = 0.555$). However, the presence of a FGFR3 fusion gene significantly reduced OS (OS HR 0.57, $p = 0.0091$; recurrence HR 3.71, $p = 0.0734$), and having ≥ 4 copies of either NTRK1 (OS HR 3.55, $p = 0.0027$; recurrence HR 3.48, $p = 0.0019$) or MET (OS HR 6.06, $p < 0.001$; recurrence HR 6.05 $p < 0.001$) significantly reduced OS and increased the risk of recurrence. **Conclusions:** The BILCAP cohort shows a wide variety of driver and potentially targetable mutations in unselected iCCA patients, comparable to previous early-stage biliary tract cancer datasets. Of note, patients with FGFR3 fusions, MET amplification or NTRK1 amplification had significantly shorter OS, and patients with MET or NTRK1 amplification had significantly reduced OS and significantly increased risk of disease recurrence. MET amplification, NTRK1 amplification and FGFR3 fusions may be important indicators in determining prognosis, and could provide attractive targets for future targeted anti-cancer therapy in iCCA. Clinical trial information: EUCTR2005-003318-13. Research Sponsor: Incyte.

4021

Poster Discussion Session

FOOTPATH: A randomized, open-label phase-2 study of liposomal irinotecan + 5-FU and folinic acid (NAPOLI) versus sequential NAPOLI and mFOLFOX6 versus gemcitabine/nab-paclitaxel in treatment-naïve metastatic pancreatic cancer (mPDAC). *First Author: Benedikt Westphalen, Department of Medicine III and Comprehensive Cancer Center (CCC Munich LMU), University Hospital, LMU Munich, Munich, Germany, Munich, Germany*

Background: The optimal first-line regimen in the treatment of mPDAC remains unknown. Recent data demonstrated superiority of 5-FU/liposomal irinotecan/oxaliplatin (NALIR-IFOX) over gemcitabine/nab-paclitaxel. However, the question remains open if both irinotecan and oxaliplatin are required in first-line treatment and whether these agents can be given sequentially. **Methods:** Eligible patients with histologically confirmed diagnosis of mPDAC were randomized 1:1:1 to receive in Arm A standard treatment (gemcitabine 1000 mg/m² + nab-paclitaxel 125 mg/m²) or investigational therapy applying in Arm B the NAPOLI regimen (liposomal irinotecan 80 mg/m² + folinic acid 400 mg/m² + 5-FU 2400 mg/m²) or in Arm C a sequence of NAPOLI and mFOLFOX6 (oxaliplatin 85mg/m² + folinic acid 400mg/m² + 5-FU 2400 mg/m²). Overall, 274 patients were enrolled at 48 sites in Germany. The primary endpoint was progression-free survival (PFS). Secondary endpoints were overall survival (OS), objective response rate, disease control rate, duration of study treatment and safety. **Results:** In the full analysis set (n=265), neither treatment with NAPOLI (3.1 months, HR 1.224, $p = 0.2123$) nor the sequence of NAPOLI and mFOLFOX6 (6.0 months, HR 0.864 $p = 0.0720$) lead to a statistically significant improvement of PFS over gemcitabine/nab-paclitaxel (4.3 months). Median duration of treatment was 3.5 months in Arm A, 2.0 months in Arm B and 3.7 months in Arm C, respectively. In a first analysis of overall survival, OS in Arm A was 8.7 months (95% CI, 7.1-11.9 months) versus 7.9 months in Arm B (95% CI, 6.6-12.3 months; HR 1.178, $P = 0.348$) and 11.0 months in Arm C (95% CI, 8.4-13.6 months; HR 0.879, $P = 0.154$). Overall, safety was comparable with published data, with higher rates of neutropenia and peripheral neuropathy in Arm A, while diarrhea was more frequent in Arms B and C. **Conclusions:** The study did not show superiority of either NAPOLI or the sequence of NAPOLI/mFOLFOX6 over standard therapy with gemcitabine/nab-paclitaxel. In view of the published evidence, the present data supports the hypothesis that sequential NAPOLI/mFOLFOX6 may be equally effective with regard to OS, but less toxic, compared to mFOLFIRINOX. Clinical trial information: NCT03487016. Research Sponsor: Servier.

	Arm A (Gem/nabPac)		Arm B (NAPOLI)		Arm C (NAPOLI/FOLFOX)	
Median PFS	4.3 months		3.1 months		6.0 months	
Median OS	8.7 months		7.9 months		11.0 months	
AE/SAE	All Grades	Grade 3-4	All Grades	Grade 3-4	All Grades	Grade 3-4
Neutropenia	30.3%	21.3%	9.3%	5.8%	13.3%	6.7%
Diarrhea	38.2%	3.4%	58.1%	11.6%	52.2%	12.2%
Vomiting	21.3%	1.1%	27.9%	4.7%	28.9%	4.4%
Neuropathy peripheral	40.4%	6.7%	14%	n/a	34.4%	3.3%

4022 Poster Discussion Session

Prospective evaluation of the utility of concurrent 18F-FDG PET/CT and 68Ga-DOTA-TOC imaging in gastroenteropancreatic neuroendocrine neoplasms (GEPNENs): The PETNET study. *First Author: Joao Paulo Salar Vasconcelos, BC Cancer, Vancouver Cancer Centre, Vancouver, BC, Canada*

Background: Somatostatin receptor imaging (SRI) is a standard of care for patients with GEPNENs. The additional value of concurrent 18F-FDG PET/CT (FDG PET) remains unclear. We reviewed a prospective functional imaging study to determine the utility of FDG PET in GEPNENs. **Methods:** PETNET is a prospective study in British Columbia, Canada, which provides all 68Ga-DOTA-TOC (DOTA PET) imaging in the province. Every patient receives a DOTA PET scan and an FDG PET within 30 days. PETNET enrolls all patients with an indication for SRI. Scans are ordered per treating physician discretion at any point in the disease course. This abstract focuses on the WD-GEPNEN population. Only the first dual functional imaging scans were analyzed and FDG was interpreted qualitatively (positive/negative). **Results:** From 04/2017-01/2023, 375 patients with NEN were enrolled, 165 (44%) with metastatic GEPNENs. Baseline characteristics are described. Median time between scans was 4 days (IQR 1-11). The proportion of patients with positive FDG PET at baseline increased with WHO grade. For patients with well differentiated G1 to G3 GEPNENs (N=161), overall survival was significantly lower with a positive FDG PET (HR: 4.22; 95%CI 1.61-11.02 p=0.001). FDG remained prognostic when G3 tumors were excluded (N=148) (HR 3.52; 95%CI 1.32-9.42 p=0.007). When analyzing dual tracer PET imaging, patients with DOTA+/FDG- had reduced risk of dying in comparison with DOTA+/FDG+ (HR:0.26; 95%CI 0.09-0.67 p=0.01). After multivariate analysis, FDG positivity remained independently associated with reduced survival (HR 2.87; 95%CI 1.06-7.75 p=0.04) when controlling for grade of tumor and age. **Conclusions:** In this prospective cohort of metastatic GEPNENs, a positive FDG PET was significantly associated with reduced overall survival. These results provide additional evidence to support dual tracer functional imaging use in metastatic well differentiated GEPNENs. Research Sponsor: BC Cancer foundation.

Baseline characteristics.						
	Total	G1	G2	G3 Well Diff	G3 Poorly Diff	Unknown Grade
Number of Patients (%)	165 (100)	73 (44.2)	75 (45.5)	13 (7.9)	2 (1.2)	2 (1.2)
Median Age at Diagnosis, years (IQR)	64 (52-71)	61 (52-69)	65 (55-72)	65 (40-75)	70 (69-71)	51 (45-57)
Median Time from diagnosis to scan, days (IQR)	665 (120-1863)	491 (120-2165)	814 (137-1822)	67 (27-665)	1086 (1065-1107)	1334 (752-1916)
Primary site						
Small Intestine (%)	86 (52.1)	47 (64.4)	37 (49.3)	1 (7.7)	0	1 (50.0)
Pancreas (%)	37 (22.5)	15 (20.6)	15 (20.0)	7 (53.8)	0	0
Other (%)	42 (25.4)	11 (15.0)	23 (30.7)	5 (38.5)	2 (100)	1 (50.0)
DOTA/FDG Result						
DOTA PET + / - (%)	158 (95.8) / 7 (4.2)	70 (95.9) / 3 (4.1)	71 (94.7) / 4 (5.3)	13 (100) / 0 (0)	2 (100) / 0 (0)	2 (100) / 0 (0)
FDG PET + / - (%)	89 (53.9) / 76 (46.1)	29 (39.7) / 44 (60.3)	44 (58.7) / 31 (41.3)	13 (100) / 0 (0)	2 (100) / 0 (0)	1 (50) / 1 (50)

4024 Poster Session

Preliminary translational immune and stromal correlates in a randomized phase II trial of pembrolizumab with or without defactinib for resectable pancreatic ductal adenocarcinoma (PDAC). *First Author: Anser Ali Abbas, Cedars-Sinai Medical Center, Los Angeles, CA*

Background: PDAC is an aggressive cancer and refractory to immunotherapy due to its immunosuppressive tumor microenvironment (TME). Focal adhesion kinase (FAK) is a master regulator of the TME and associated with TME immune suppression. Our current randomized phase II trial evaluates the use of pembrolizumab, a programmed cell death 1 (PD-1) immune checkpoint inhibitor, with or without defactinib, a FAK inhibitor (FAKi), as sequential neoadjuvant and adjuvant therapy in patients with high risk resectable PDAC. We hypothesize that the patients receiving pembrolizumab and defactinib treatment will exhibit a decrease in immunosuppressive fibroblasts and myeloid subtype populations, leading to increased CD8+ T-cell infiltration into the TME compared to patients receiving pembrolizumab alone. **Methods:** We performed quantitative analysis of multiplex immunohistochemistry (mIHC) using 40 biomarkers, evaluating immune and stromal cell types on 14 pre-treatment biopsies and post-treatment resections of PDAC patients enrolled in our platform neoadjuvant clinical trial (NCT03727880). All patients received 2 cycles of gemcitabine+ nab-paclitaxel neoadjuvant chemotherapy and underwent a biopsy after completion of chemotherapy. Patients randomized to Arm A received 2 cycles of pembrolizumab 200 mg IV every 3 weeks and defactinib 400 mg PO BID, and those randomized to Arm B received pembrolizumab alone, followed by surgical resection. Image cytometry was used to quantify immune cell populations and colocalize biomarker expression in distinct cell types. Cell populations were compared using unpaired T-tests. **Results:** Lower FAP+ fibroblast density was significantly associated with higher CD8+ T-cell infiltration in Arm A (p=0.002), but not in Arm B. Patients in Arm A demonstrated a 5.44-fold average increase in CD8+ T-cell percentage between pre-immunotherapy treatment and post-immunotherapy treatment specimens compared to a 2.01-fold increase in patients in Arm B (p=0.02, p=0.09, respectively). Only patients in Arm A showed a significant increase in M1 macrophage cell density (p=0.02) after treatment. Both arms increased in CXCR4+ cell percentage (p=0.011, p=0.06) following neoadjuvant immunotherapy; however, the increase in Arm A was less than in Arm B (0.72 and 0.84-fold, respectively). **Conclusions:** In this analysis, pembrolizumab combined with defactinib was associated with lower fibroblast infiltration, higher anti-tumor M1 macrophage expression and increased CD8+ T-cell infiltration into the TME, versus pembrolizumab alone. The increased expression of CXCR4 across both treatment arms may represent a resistance mechanism and supports CXCR4 as an additional TME target. These preliminary findings warrant continued research into FAK inhibition and immune checkpoint combinatorial strategies. Clinical trial information: NCT03727880. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology; U.S. National Institutes of Health.

4023 Poster Discussion Session

Neoadjuvant hepatic arterial infusion chemotherapy with FOLFOX could improve outcomes of resectable BCLC stage A/B hepatocellular carcinoma patients beyond Milan criteria: A multi-center, phase 3, randomized, controlled clinical trial. *First Author: Wei Wei, Sun Yat-sen University Cancer Center, Guangzhou, China*

Background: The efficacy of operation, as the only radical option for resectable BCLC stage A/B hepatocellular carcinoma (HCC) patients beyond Milan criteria, is still unsatisfactory. This study aimed to investigate to efficacy and safety of preoperative neoadjuvant hepatic arterial infusion chemotherapy (HAIC) with FOLFOX regimen for these patients. **Methods:** In this multi-center, prospective, phase 3, randomized, open-labeled, controlled clinical trial, resectable BCLC stage A/B HCC patients beyond Milan criteria were randomly assigned (1:1) before hepatectomy to receive either neoadjuvant HAIC (treatment group) or operation directly without any neoadjuvant treatment (control group). The primary endpoint was overall survival (OS), the secondary endpoints are progression-free survival (PFS) and safety. **Results:** Between March 2016 and August 2022, a total of 487 patients were screened from seven Chinese hospitals, and 392 patients were randomly assigned to receive neoadjuvant FOLFOX-HAIC before hepatectomy (treatment group, n = 195), or operation directly without any neoadjuvant treatment (control group, n = 197) and were included in the ITT population. Among them, 14 patients from the treatment group and 13 patients from the control group were excluded from the PP population. In the ITT population, the OS rates at 1-, 2-, and 3-year were 97.7%, 86.3%, and 77.1%, respectively, for the treatment group and were 90.0%, 80.9%, and 70.6%, respectively, for the control group. The median PFS of the treatment and control groups was 17.4 months (95% CI, 9.0-25.8) and 9.8 months (8.2-11.4), respectively, in the ITT population. The OS and PFS were significantly better in treatment group than in control group (p = 0.032 and < 0.001, respectively) in ITT population. In the PP population, the OS rates at 1-, 2-, and 3-year were 98.7%, 91.1%, and 79.7%, respectively, for the treatment group and were 89.2%, 79.3%, and 67.7%, respectively, for the control group. The median PFS of the treatment and control groups was 22.7 months (95% CI, 10.9-34.5) and 10.2 months (8.4-12.1), respectively, in the PP population. The OS and PFS were significantly better in treatment group than in control group (p = 0.001 and < 0.001, respectively) in PP population. In treatment group of ITT population, the complete regression (CR) rate, object response rate (ORR), disease control rate (DCR) was 11.3%, 61.5%, and 97.4%, respectively. Safety analysis showed HAIC was quite safe, 191 (97.9%) patients had mild HAIC related adverse events (HRAEs) (grade 0-2). The operation related adverse events (ORAEs) were similar between two groups (p = 0.265). **Conclusions:** Neoadjuvant HAIC with FOLFOX regimen before hepatectomy may bring survival benefits for resectable BCLC stage A/B HCC patients beyond Milan criteria. Clinical trial information: NCT03851913. Research Sponsor: None.

4025 Poster Session

Nivolumab (NIVO) plus chemotherapy (chemo) vs chemo as first-line (1L) treatment for advanced gastric cancer/gastroesophageal junction cancer/esophageal adenocarcinoma (GC/GEJC/EAC): 3-year follow-up from CheckMate 649. *First Author: Yelena Y. Janjigian, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: NIVO + chemo demonstrated superior overall survival (OS) and clinically meaningful progression-free survival (PFS) benefit vs chemo and acceptable safety in previously untreated patients (pts) with advanced GC/GEJC/EAC, leading to approvals in multiple countries including the US. NIVO + chemo continued to demonstrate clinically meaningful improvement in efficacy after 2 years of follow-up. We present efficacy and safety analyses from NIVO + chemo vs chemo from the 3-year follow-up of CheckMate 649. **Methods:** Adults with previously untreated, unresectable advanced, or metastatic GC/GEJC/EAC were enrolled, regardless of programmed death ligand 1 (PD-L1) expression, excluding pts with known HER2-positive status. Pts were randomized to NIVO (360 mg Q3W or 240 mg Q2W) + chemo (XELOX Q3W or FOLFOX Q2W), NIVO + ipilimumab, or chemo. Primary endpoints for NIVO + chemo vs chemo were OS and PFS by blinded independent central review (BICR) in pts with PD-L1 combined positive score (CPS) ≥ 5. **Results:** 1581 pts were concurrently randomized to NIVO + chemo or chemo. With 36-month (mo) minimum follow-up, NIVO + chemo continued to demonstrate OS and PFS benefit vs chemo in pts with PD-L1 CPS ≥ 5 and all randomized pts. The objective response rate (ORR) per BICR in pts with PD-L1 CPS ≥ 5 who had measurable lesions at baseline was 60% (95% CI 55–65) with NIVO + chemo vs 45% (95% CI 40–50) with chemo; in all randomized pts, ORR per BICR was 58% (95% CI 54–62) with NIVO + chemo vs 46% (95% CI 42–50) with chemo. Responses were more durable with NIVO + chemo vs chemo in pts with PD-L1 CPS ≥ 5 (median [m] duration of response [mDOR] 9.6 mo [95% CI 8.2–12.4] vs 7.0 mo [95% CI 5.6–7.9], respectively) and in all randomized pts (mDOR 8.5 mo [95% CI 7.7–9.9] vs 6.9 mo [95% CI 5.8–7.2], respectively). OS benefit with NIVO + chemo was observed across most prespecified subgroups. No new safety signals were identified. A summary of treatment-related adverse events (TRAEs) is shown in the Table. Additional analyses will be presented. **Conclusions:** After 3 years of follow-up, NIVO + chemo continued to demonstrate clinically meaningful long-term survival benefit with acceptable safety, further supporting its use as a standard 1L treatment in previously untreated pts with advanced GC/GEJC/EAC. Clinical trial information: NCT02872116. Research Sponsor: Bristol Myers Squibb.

Efficacy	PD-L1 CPS ≥ 5		All randomized
NIVO + chemo (n = 473)	Chemo (n = 482)	NIVO + chemo (n = 789)	Chemo (n = 792)
mOS (95% CI), mo	14.4 (13.1–16.2)	11.1 (10.0–12.1)	13.7 (12.4–14.5)
HR (95% CI)	0.70 (0.61–0.81)		0.79 (0.71–0.88)
mPFS* (95% CI), mo	8.3 (7.0–9.3)	6.1 (5.6–6.9)	7.7 (7.1–8.6)
HR (95% CI)	0.70 (0.60–0.81)		0.79 (0.71–0.89)
Safety, all treated pts, n (%)	NIVO + chemo (n = 782)		Chemo (n = 767)
Any-grade TRAEs	739 (95)		682 (89)
Grade 3/4	473 (60)		346 (45)
Leading to discontinuation	331 (42)		198 (26)

*per BICR.

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Poster Session

Final survival results of ipilimumab or FOLFOX in combination with nivolumab and trastuzumab in previously untreated HER2 positive esophago gastric adenocarcinoma: The randomized AIO INTEGA trial. *First Author: Joseph Tintelnot, University Cancer Center Hamburg (UCC), University Medical Center Hamburg-Eppendorf, Hamburg, Germany*

Background: In metastatic esophagogastric adenocarcinoma (EGA), the addition of PD-1 inhibitors (i) to chemotherapy has improved the outcome in selected patient populations. The randomized INTEGA trial investigated trastuzumab and PD-1 with FOLFOX or CTLA-4i in 1st line treatment of advanced HER2+ EGA. **Methods:** Patients with previously untreated, metastatic HER2+ (local IHC3+ or 2+/ISH+) EGA, and adequate organ function were randomized to trastuzumab and nivolumab (1mg/kg Q3W x4/240mg Q2W for up to 12 months) in combination with ipilimumab (3mg/kg x4 Q3W; Ipi arm) or mFOLFOX6 (FOLFOX arm) accompanied by a large translational program. The primary endpoint was the 12month overall survival (OS) rate. The trial was registered at ClinicalTrials.gov, NCT03409848. **Results:** Between March 2018 and May 2020, 97 patients were enrolled and 88 randomized across 21 German sites with the following baseline characteristics: female/male 18/70, median age 60.5 (range 41-80), ECOG 0/1 54/34, GEJ/stomach 66/22. Central post hoc biomarker analysis on 82 evaluable patients showed PD-L1 CPS $\geq$ 1/ $\geq$ 5 in 59/46 patients and confirmed HER2 (central IHC3+ or 2+/ISH+) positivity in 77 patients. The observed OS rate at 12 months was 70% (95% confidence interval (CI) 54-81%) in the FOLFOX arm, and 57% (95% CI 41-71%) in the Ipi arm. The progression free survival was 10.7 and 3.2 months, and the overall response rate was 53.5% and 34% in the FOLFOX and the Ipi arm, respectively. Although these data are in favor of the FOLFOX arm, the overall survival curves crossed with increased follow-up (median follow-up of 18.8 months) and thus the final median OS was 22.1 and 23.3 months, numerically favoring the Ipi arm. According to the centrally assessed CPS the OS was: 22.1 and 32.2 months in the CPS $\leq$ 5 group, and 22.7 and 12.6 months in the CPS $\geq$ 5 group for the FOLFOX and the Ipi arm, respectively. Notably, the median tumor burden calculated as the sum of target lesions was numerically lowest in the Ipi arm with higher than median OS. **Conclusions:** In contrast to limited short term efficacy of the Ipi arm as reflected by the lower PFS, the Ipi arm showed favorable OS, that was inversely correlated to the CPS status. Further analysis of baseline clinical and molecular data to better identify the subgroup of patients benefiting the most of trastuzumab/nivolumab/ipilimumab will be presented at the meeting. Clinical trial information: NCT03409848. Research Sponsor: BMS.

Baseline factors	Median OS	All pts	Ipi all	Ipi<median OS	Ipi>median OS	FOLFOX all	FOLFOX<median OS	FOLFOX>median OS
Age	Median	60.5	63	64	61	59.5	59.5	58.5
Gender, f/m	n	18/70	10/34	4/18	6/16	8/36	5/17	3/19
HER2 3+	n (%)	62 (75)	33 (55.5)	14 (67)	19 (86)	29 (73)	12 (60)	17 (77)
Median tumor burden	TL mm	66	55.5	66	54.5	73	70.5	73
CPS<5	n (%)	36 (44)	18 (43)			18 (45)		
	Median OS	26.2	32.2			22.1		
CPS $\geq$ 5	n (%)	46 (56)	24 (57)			22 (55)		
	Median OS	21.9	12.6			22.7		

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Poster Session

AdvanTIG-105: A phase 1b dose-expansion study of ociperlimab (OCI) + tislelizumab (TIS) with chemotherapy (chemo) in patients (pts) with stage IV gastric/gastroesophageal adenocarcinoma (GC/GEJC). *First Author: Se Hyun Kim, Seoul National University Bundang Hospital, Seongnam, South Korea*

Background: T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domains (TIGIT) inhibitor in combination with an anti-programmed cell death protein 1 (PD-1) antibody has shown antitumor activity in solid tumors. AdvanTIG-105 (NCT04047862) is a phase 1/1b open-label study designed to assess the safety and preliminary antitumor activity of OCI, an anti-TIGIT monoclonal antibody (mAb), + TIS, an anti-PD-1 mAb, in pts with unresectable, locally advanced or metastatic solid tumors. In the dose-escalation part, OCI + TIS was well tolerated with preliminary antitumor activity observed, and the recommended phase 2 dose (RP2D) of OCI 900 mg intravenously (IV) every three weeks (Q3W) + TIS 200 mg IV Q3W was established. We report results from the dose-expansion part (GC/GEJC Cohort 9) of the AdvanTIG-105 study. **Methods:** Eligible pts had histologically/cytologically confirmed stage IV GC/GEJC. Pts were excluded if they had squamous cell, undifferentiated or other histological types of GC, had GC/GEJC with positive HER2 expression, or if they had received any prior therapy for metastatic disease. Pts received either the RP2D of OCI + TIS with oxaliplatin + capecitabine Q3W for 6 cycles (C), followed by maintenance therapy with the RP2D of OCI + TIS, + capecitabine Q3W, or the RP2D of OCI + TIS with cisplatin + 5-fluorouracil Q3W for 6 C. Treatment continued until disease progression, intolerable toxicity, or withdrawal of consent. The primary endpoint was investigator-assessed overall response rate (ORR) per RECIST v1.1. Secondary endpoints included progression-free survival (PFS), duration of response (DoR), disease control rate (DCR) per RECIST v1.1, and safety. **Results:** As of September 29, 2022, 60 pts with a median age of 61.5 years (range 35-82) were enrolled; 59 were efficacy evaluable. Median study follow-up was 31.1 weeks (range 1.4-78.4). ORR was 50.8% (95% CI: 37.5, 64.1); DCR was 84.7% (95% CI: 73.0, 92.8) with a median DoR of 4.6 months (95% CI: 3.9, 7.1). Median PFS was 8.2 months (95% CI: 5.8, not evaluable). In a subgroup analysis, ORR in pts with PD-L1 tumor area positivity (TAP) score $\geq$ 5% (n = 27) was 59.3% (95% CI: 38.8, 77.6), and 50.0% (95% CI: 30.7, 69.4) in pts with PD-L1 TAP < 5% (n = 28). All 60 pts reported $\geq$ 1 treatment-emergent adverse event (TEAE), the most common being anemia (43.3%) and platelet count decreased (41.7%). In total, 43 pts (71.7%) had $\geq$ grade 3 TEAEs and 28 (46.7%) had serious adverse events. TEAEs leading to discontinuation of TIS and OCI occurred in 5 (8.3%) pts. TEAEs led to death in 2 (3.3%) pts; one event (neutropenic sepsis) was related to chemo, while the other (pulmonary embolism) was not treatment related. **Conclusions:** OCI 900 mg + TIS 200 mg + chemo was generally well tolerated and showed encouraging antitumor activity in pts with stage IV GC/GEJC. Clinical trial information: NCT04047862. Research Sponsor: BeiGene, Ltd.; This study was sponsored by BeiGene, Ltd. Medical writing support, under the direction of the authors, was provided by Emma Ashman, BSc, of Ashfield MedComms, an Inizio company, and was funded by BeiGene, Ltd.

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Poster Discussion Session

A phase 2 study (DisTinGuish) of DKN-01 in combination with tislelizumab + chemotherapy as first-line (1L) therapy in patients with advanced gastric or GEJ adenocarcinoma (GEA). *First Author: Samuel J Klempner, Mass General Cancer Center, Boston, MA*

Background: DKN-01 is an anti-DKK1 mAb which has demonstrated anti-tumor activity in patients with advanced GEA with low tumor PD-L1 expression, a subset with very limited therapeutic options. DKN-01 has immunomodulatory activity, stimulates a pro-inflammatory tumor microenvironment, and upregulates PD-L1 levels. Here we present 2-year survival data for 1L advanced GEA patients who received combination treatment with DKN-01, the Fc-optimized anti-PD-1 tislelizumab, and CAPOX chemotherapy. The ORR was previously reported (68% in ITT and 79% in PD-L1-low populations). **Methods:** This Phase 2, multi-center, single arm Part A of the DisTinGuish (NCT04363801) study investigated DKN-01 + tislelizumab + CAPOX as 1L therapy in advanced HER2(-) GEA, regardless of DKK1 and PD-L1 expression levels. Tumor DKK1 and PD-L1 were assessed by central laboratories. The primary endpoint was ORR in a modified intent to treat population (>1 dose DKN-01); secondary endpoints included PFS and OS in the ITT population. **Results:** Twenty-five patients were enrolled from September 2020 to April 2021. As of 23 January 2023: Median age was 61 years (22, 80); 17 patients had GEJ adenocarcinoma; 8 had gastric cancer. Twenty-one patients had tumors with evaluable DKK1 expression. Twenty-two patients had tumors with evaluable PD-L1 expression; the majority (73%) were low expressors (vCPS <5%). Median (m) duration on treatment is 11.3 months (mo). Seven patients remain on study, with 4 on-treatment beyond 2 years. The mPFS is 11.3 mo in the overall ITT population and 10.7 mo in patients with low tumor PD-L1 expression. The mOS is 19.5 mo in the overall ITT population and 18.7 mo in the patients with low tumor PD-L1 expression. Treatment related adverse events (TRAEs) were mild with most G1/2. The most common AEs related to the study drug regimen were nausea (72%), diarrhea (64%) and fatigue (60%). Five patients experienced G3 DKN-01-TRAEs including decreased neutrophil count (1), diarrhea (1), vomiting (1), hypophosphatemia (2), and pulmonary embolism (1). **Conclusions:** At 2-years of follow-up, 1L treatment of advanced GEA patients with DKN-01 in combination with tislelizumab and CAPOX resulted in a prolongation of PFS and OS compared with the modern SOC regimen of nivolumab plus chemotherapy, both in the overall population (mPFS 11.3 vs 7.7 mo; mOS 19.5 vs 13.8 mo) and in the PD-L1 low subgroup (mPFS 10.7 vs 7.5 mo; mOS 18.7 vs 12.4 mo), alongside a manageable safety profile. The prolonged PFS and OS observed in the current study are notable, especially in our trial population dominated by patients with tumors of low PD-L1 expression, where the known benefit of anti-PD-1 therapy is limited. The ongoing Part C of this study is evaluating mFOLFOX6/CAPOX plus tislelizumab with or without DKN-01 in the same 1L GEA patient population. Further evaluation of biomarkers is also ongoing. Clinical trial information: NCT04363801. Research Sponsor: Leap Therapeutics.

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Poster Session

A phase 2 study of HLX07 as monotherapy or combination therapy in patients with locally advanced, unresectable, or metastatic esophageal squamous cell carcinoma. *First Author: Jing Huang, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China*

Background: Esophageal cancer is one of the most common cancers worldwide with esophageal squamous cell carcinoma (ESCC) being the predominant histological subtype. Most patients are diagnosed at the advanced stage, and the prognosis remains poor. About 40–84% of ESCC cases showed overexpression of EGFR which was related to shorter overall survival and disease-free survival, indicating that treatment targeting EGFR could be a new strategy. This study aimed to evaluate the efficacy and safety of HLX07, a novel recombinant humanized anti-EGFR monoclonal antibody (mAb), as monotherapy or combination therapy in patients with locally advanced, unresectable/metastatic ESCC. **Methods:** In this open-label, multicenter phase 2 study, patients aged 18–75 years with histologically or cytologically confirmed locally advanced, unresectable/metastatic ESCC or esophageal adenosquamous carcinoma were enrolled. Patients with no prior systemic antitumor therapy were assigned to group A and given HLX07 1000 mg plus serplulimab 200 mg (anti-PD-1 mAb) and chemotherapy (5-FU 2400 mg/m² + cisplatin 50 mg/m²), Q2W IV. Patients who had failed first-line immuno-chemotherapy combination or at least two lines of other systemic antitumor therapy were assigned to group B and given HLX07 monotherapy (1000 mg Q2W IV). The primary endpoints were objective response rate (ORR) and progression-free survival (PFS) assessed by an independent radiological review committee and investigators per RECIST v1.1. Secondary endpoints included other efficacy measures, safety, pharmacokinetics, immunogenicity, and biomarker explorations. **Results:** As of February 4, 2023, 49 patients were enrolled in group A (n=30) and group B (n=19), with a median age of 64.5 and 59.0 years, respectively. 26 (86.7%) patients in group A and all patients in group B were male. The median follow-up duration was 2.9 months, and the preliminary efficacy was presented. Among the 42 efficacy evaluable patients (29 in group A and 13 in group B), investigator-assessed ORRs were 55.2% (95% CI 35.7–73.6%) and 23.1% (95% CI 5.0–53.8%) in the respective groups. Investigator-assessed median PFSs were not reached in group A and 1.5 months (95% CI 1.2–not evaluable) in group B. 15 (50.0%) patients in group A and 5 (26.3%) in group B had grade $\geq$ 3 treatment-emergent adverse events (AEs). AEs of special interest were observed in 16 (53.3%) and 11 (57.9%) patients, respectively, most commonly rash (43.3% vs 47.4%) and hypomagnesemia (33.3% vs 36.8%). No drug-related death was reported. **Conclusions:** The encouraging antitumor activity and manageable safety profile support further development of HLX07 as a new treatment option for patients with advanced ESCC, both in first-line and late-line settings. Clinical trial information: NCT05221658. Research Sponsor: Shanghai Henlius Biotech, Inc.

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Poster Session

Expression molecular subtype as a predictor of outcomes of chemoradiotherapy for esophageal cancer. *First Author: Manabu Muto, Department of Therapeutic Oncology, Graduate School of Medicine, Kyoto University, Kyoto, Japan*

Background: The standard treatment for advanced esophageal cancer is preoperative chemoradiotherapy (CRT) followed by surgery or definitive CRT (NCCN Guideline 2022 ver5). CRT has the advantage of preserving organs and functions and the prognosis for patients achieved complete response by CRT is good. However, it is currently impossible to predict the outcomes of CRT before treatment. We have performed RNA expression analysis of pre-treatment biopsy specimens of esophageal cancer and identified several intrinsic molecular subtypes, as well as E-type (high expression of squamous markers) with good prognosis for CRT and M2-type (high expression of stromal markers) with poor prognosis for CRT (US patent No 10,969,390 B2). Herein, we performed an integrated analysis to confirm the relationship between intrinsic expression molecular subtype classification and prognosis in the pooled population from two prospective cohort studies (UMIN000043637). **Methods:** Two cohort studies were as follows; 1) single institute prospective cohort study conducted at National Cancer Center Hospital East (n=157, UMIN-C000000459), 2) multicenter prospective cohort study conducted at 10 institutions (n=226, UMIN000016141). A total 383 cases met inclusion criteria and the Affymetrix U331Plus 2 panel (47,104 transcripts, 38,572 genes) was used to identify E-type and M2-type. The clinical course and outcome were blinded for subtype classification. Treatment was performed as usual at each institution, and treatment details and outcomes were examined by subtype. **Results:** Among 383 patients, 181 and 164 patients were treated by CRT and surgery, respectively. Ninety-nine percent (n=342) were squamous cell carcinoma. Stage I/II/III/IV were 13/61/86/21 and 17/63/81/3 in CRT group and surgery group, respectively. Among them, 76 (22%), 100 (29%), 169 (49%) patients were classified as E, M2 and others, respectively. Among the patients treated by CRT, CR rate of E-type and M2-type were 62.8% (95% CI, 47.8-75.7) and 33.3% (95% CI, 21.9-47.1) (p=0.006). The 5-year progression free survival (PFS) and overall survival (OS) rates of CRT group was 50.5% (95% CI, 34.7-64.4) and 59.8% (95% CI, 42.6-73.3) for E-type vs. 23.0% (95% CI, 12.0-36.2) and 29.0% (95% CI, 16.8-42.4) for M2-type, with statistically significant difference (p=0.011, p=0.003). Cox regression analysis showed that crude HR for PFS and OS of E vs M2 were 0.50 (95% CI, 0.296-0.859, p=0.012) and 0.41 (95% CI, 0.226-0.750, p=0.004), respectively. In contrast, E and M2-type did not show the survival difference in surgery group. **Conclusions:** For the first time in the world, we confirmed that expression molecular subtype of esophageal cancer has the potential to predict the outcomes of CRT. The results may provide precision medicine in the selection of treatment for esophageal cancer. Research Sponsor: AMED Foundation in Japan.

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Poster Session

Ramucirumab, avelumab and paclitaxel (RAP) as second line treatment in esophagogastric adenocarcinoma: Final results of the phase 2 RAP trial (AIO-STO-0218). *First Author: Peter C. Thuss-Patience, Charité University Medicine Berlin, Department of Haematology, Oncology and Cancer Immunology, Campus Virchow-Klinikum, Berlin, Germany*

Background: The addition of immune checkpoint inhibitors to chemotherapy has improved outcomes in patients (pts) with metastatic esophagogastric adenocarcinoma (EGA), but treatment combinations and optimal pt selection need to be established. Objective: To investigate efficacy and tolerability of the programmed death-ligand 1 (PD-L1) inhibitor avelumab with ramucirumab and paclitaxel in the second line treatment of pts with metastatic EGA (NCT03966118). **Methods:** In this phase 2 multicenter single-arm clinical trial the reported results are based on a median follow-up of 27.4 months. Patients with previously treated metastatic EGA, adequate organ function, and eligibility for immunotherapy were included. Interventions: Pts with metastatic EGA after progression on platinum/ fluoropyrimidine based palliative first line treatment, checkpoint-inhibitor naïve, received ramucirumab 8 mg/kg (d1,15), avelumab 10 mg/kg (d1,15) and paclitaxel 80 mg/m² (d1,8,15) q4w. **Results:** The pre-specified primary end point was overall survival rate at 6 months (mo) (H0≤50%, H1≥65%). A total of 60 patients (pts) were enrolled, 59 were evaluable (intention to treat, ITT). Participants had a median age of 64.0 yrs (range 18-81) and 80% were men. Baseline Eastern Cooperative Oncology Group performance status was 0 in 23 pts (39.0%) and 1 in 36 pts (61.0%); 29 pts (48.2%) had EGA localized in the esophagogastric junction and 30 in the stomach (51.8%). all pts had received prior platin/ 5-FU based chemotherapy, 40pts (67.8%) had prior taxanes. Central post-hoc biomarker analysis (56 pts) showed PD-L1 ligand 1 (PD-L1) combined positive score of 5 or greater in 24 pts (42.9%). The observed overall survival (OS) rate at 6 mo was 71% (95% CI 61-84%) and at 12 mo 43% (95% CI 32-58%). The median OS (ITT) was 10.6 mo (95% CI 8.4-12.8); 9.4 mo (95% CI 7.2-11.7) in pts with PD-L1 CPS < 5 and 14.0 mo (95% CI 6.0-22.1; p = 0.25) in those with PD-L1 CPS ≥ 5. Treatment was generally well tolerated without unexpected toxicities. Translational research identified subgroups with a longer survival possibly due to a higher treatment benefit. Pts with higher than median T cell repertoire (TRB) richness showed an elevated median OS of 20.4 mo compared to pts with lower than median TRB richness (med OS 8.3 mo; HR 0.43, 95% CI 0.23-0.81; p = 0.0079). Pts with lower than median cfDNA burden had a median OS of 19.2 mo compared to pts with higher than median cfDNA (med OS 7.3 mo; HR 0.30, 95% CI 0.16-0.59; p = 0.00022). **Conclusions:** In this multicenter clinical trial, ramucirumab and paclitaxel combined with avelumab showed favorable efficacy and tolerability in the second line treatment of pts with metastatic EGA. PD-L1 CPS ≥ 5, cfDNA below the median or T cell richness above the median seem to predict for even better outcomes with median OS hardly seen before in the second line setting. Clinical trial information: NCT03966118. Research Sponsor: Financially supported by Merck Healthcare KGaA, Darmstadt, Germany, (CrossRef Funder ID: 10.13039/100009945) as part of an alliance between the healthcare business of Merck KGaA and Pfizer.

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Poster Session

A phase Ib/II, multicenter, open-label study of AK104, a PD-1/CTLA-4 bispecific antibody, combined with chemotherapy (chemo) as first-line therapy for advanced gastric (G) or gastroesophageal junction (GEJ) cancer: 2-Year update data. *First Author: Jiafu Ji, Peking University Cancer Hospital & Institute, Beijing, China*

Background: Anti-PD-1 monoclonal antibodies plus chemo as first-line therapy for advanced G/GEJ cancer yields OS and PFS benefits compared to chemo alone while the survival benefits are limited, especially in patients with low PD-L1 expression (CPS<5). Simultaneous blockade of the PD-1 and CTLA-4 pathways has shown synergistic anti-tumor activity and has been proven effective across multiple cancer types. This phase Ib/II dose-escalation study evaluated the safety and efficacy of AK104, a PD-1/CTLA-4 bispecific antibody, combined with XELOX or modified XELOX (mXELOX) in the first-line treatment of G/GEJ cancer cohorts (NCT03852251). **Methods:** Pts with unresectable advanced G/GEJ adenocarcinoma and no prior systemic therapy, regardless of PD-L1 status, were enrolled, excluding known HER2-positive pts. Enrolled patients received AK104 (4 mg/kg, 6 mg/kg or 10 mg/kg Q2W, 10 mg/kg or 15mg/kg Q3W) + chemo (mXELOX Q2W or XELOX Q3W). The primary endpoint was safety and the objective response rate (ORR) based on Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1). **Results:** As of 31 Oct. 2022, 98 pts were enrolled with only 4 pts in 10 mg/kg Q3W, the safety and efficacy of the regimen of 10mg/kg Q3W will be reported in the phase III study and not be reported here. 94 pts were enrolled with median age of 62.7 years (range: 29-75), 70.2% male, 62.8% ECOG PS 1, and 45.7% liver metastasis. The median follow-up was 24.0 months (range: 0.5-33.3). 88 patients (94%) had at least one post-baseline tumor evaluation. The ORR was 68.2% (60/88), with 5 (5.7%) complete responses and 55 (62.5%) partial responses. The disease control rate (DCR) was 92.0% (81/88). The median duration of response (DoR) was 9.69 months (95%CI, 5.82 to 14.00). The median PFS was 9.20 months (95%CI, 6.67 to 10.48). The median OS was 17.41 months (95%CI, 12.35 to 29.77). In pts with PD-L1 CPS ≥ 5 and CPS < 5, the median OS was 20.24 months and 17.28 months, respectively. Treatment-related adverse events (TRAEs) occurred in 97.9% of pts. The most frequent were platelet count decreased (62.8%), white blood cell count decreased (61.7%), neutrophil count decreased (59.6%), anemia (51.1%), aspartate aminotransferase increased (33.0%), nausea (30.9%), and vomiting (30.9%). Grade ≥ 3 TRAEs occurred in 69.4% of pts. No new safety signals were identified. **Conclusions:** AK104, combined with mXELOX/XELOX, showed promising activity and manageable safety in previously untreated patients with advanced G/GEJ adenocarcinoma. AK104 + chemo represents a potential new first-line treatment option for these pts. A phase III study of AK104 combined with chemo as first-line therapy for G/GEJ cancer is underway (NCT05008783). Clinical trial information: NCT03852251. Research Sponsor: Akeso Biopharma, Inc.

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Poster Session

EPCAM CAR T (IMC001) for the treatment of advanced GI cancers. *First Author: Tianhang Luo, Shanghai Changhai Hospital, Shanghai, Shanghai, China*

Background: EpCAM is highly expressed in various cancer types of the GI system and at metastatic sites. It serves as a promising prognostic/predictive marker (CTC) and therapeutic target. IMC001 is an EpCAM-targeted CAR-T cell that showed promising anti-tumor activities in preclinical studies. Here, we report the results of the low and middle dosage groups in advanced gastric cancers (CT03) and GI cancers (CT04). **Methods:** This first-in-human, open-label trial involved two separate single-site trials. Both followed a classic 3+3 design with dose escalation of 0.3, 1 or 3 million CAR-T cells/kg after lymphodepletion chemotherapy. CT03 was an IMC001 monotherapy trial (Stage 1) for gastric cancer, while CT04 had Stage 1 and the combination with RFA or microwave ablation (Stage 2) for GI cancers. Eligible patients were those with EpCAM-positive (more than 10%) cancers who had no further standard treatment options and were ECOG 0 or 1. The objective was to assess the safety, PK/PD profile and preliminary efficacy of IMC001. **Results:** As of January 30, 2023, 12 patients with 6 colorectal and 6 gastric cancers had enrolled, with half receiving 0.3 million and the other half receiving 1 million cells/kg IMC001 infusion. No patient experienced DLT within the 4-week follow-up visits after infusion. All patients experienced ≥ Grade 3 hematologic toxicity. One patient in the low-dose group had a SAE of immune hepatitis (Grade 3), which might have been related to cell therapy, and occurred around 11 days after the CAR-T infusion, prolonging the patient's hospitalization. Manageable CRS (Grade 1 to 3) and no ICANS were observed. Other adverse events related to cell therapy were CTCAE Stage 1-2 nausea, vomiting, asthenia, or pruritus, and these recovered quickly. Analyses of the CAR-T cells in peripheral blood revealed robust engraftment in all patients, with the peak number of CAR+ cells reaching on day 5-7 after infusion. CTC remained under the detection limit for more than 40 weeks after cell infusion. Significant elevations of serum levels of IL-6, IP-10, IFN-γ, IL-15, and MCP-1 were observed in most patients. Preliminary efficacy data showed that 2 out of 6 advanced gastric cancer patients were evaluated as PR and 3 remained SD by RECIST 1.1 at the low and middle dosages (CT03). The first PR patient received a second IMC001 infusion on week 50 and had survived for more than 60 weeks. The second PR patient underwent successful surgical removal of the stomach 28 weeks after IMC001 infusion. The CT04 trial is ongoing. **Conclusions:** This is the first CAR-T therapy ever tested in humans targeting the EpCAM. IMC001 showed a favorable safety profile and reasonable anti-tumor activities at the low and middle dosage levels in patients with advanced EpCAM+ GI cancers, especially in gastric cancer. In addition, our trial has successfully provided a surgical treatment opportunity after CAR-T therapy downstaging of unresectable gastric cancers. Updated data from open cohorts will be presented. Clinical trial information: NCT05028933. Research Sponsor: Suzhou Immunofoco Biotechnology Co., Ltd.

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Poster Session

Global prevalence of CLDN18.2 in patients with locally advanced (LA) unresectable or metastatic gastric or gastroesophageal junction (mG/GEJ) adenocarcinoma: Biomarker analysis of two zolbetuximab phase 3 studies (SPOTLIGHT and GLOW). *First Author: Kohei Shitara, Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan*

Background: There is an unmet need for additional therapies to treat patients (pts) with locally advanced (LA) unresectable or metastatic gastric or gastroesophageal junction (mG/GEJ) adenocarcinoma. Claudin-18.2 (CLDN18.2), a new validated target in these pts, is expressed in normal gastric mucosa cells and often retained in G/GEJ tumor cells. There are limited data on the global prevalence of CLDN18.2 in tumors of pts with LA unresectable or mG/GEJ adenocarcinoma. The SPOTLIGHT (NCT03504397) and GLOW (NCT03653507) phase 3 studies demonstrated clinically meaningful and statistically significant improvement in PFS and OS with the CLDN18.2-targeted antibody zolbetuximab + chemotherapy (mFOLFOX6 or CAPOX, respectively) vs placebo + chemotherapy as 1L therapy in pts with CLDN18.2+/HER2- disease. We report the biomarker analysis of these studies. **Methods:** Pts with LA unresectable or mG/GEJ adenocarcinoma were screened for CLDN18.2 status by IHC before enrollment. Tumors were defined as CLDN18.2+ if they had ≥75% of tumor cells with moderate-to-strong membranous CLDN18 staining per the investigational VENTANA CLDN18 (43-14A) RxDx Assay. HER2 status was evaluated per central or local assessment. Ad hoc PD-L1 IHC was performed via the Dako PD-L1 IHC 28-8 pharmDx assay for a subgroup of enrolled pts. Results exclude pts from mainland China and pts missing data for disease type, Lauren classification, or tumor collection site. **Results:** Across SPOTLIGHT and GLOW, 3576 pts had valid CLDN18 IHC results; 1399 (39.1%) had CLDN18.2+ tumors. CLDN18.2 prevalence was 43.7% (513/1175) in female pts and 36.9% (886/2401) in male pts. CLDN18.2 prevalence was 44.0% (671/1524) in pts in Europe/Middle East, 37.7% (183/485) in pts in N. America, and 36.5% (479/1314) in pts in Asia Pacific. CLDN18.2 prevalence was 41.0% (1056/2576) in pts with gastric adenocarcinoma and 37.3% (302/809) in pts with GEJ adenocarcinoma. CLDN18.2 prevalence trended higher in pts with diffuse (48.9%, 479/980) vs intestinal (38.9%, 265/682) disease. CLDN18.2 prevalence was 41.1% (175/426) in tumors collected from metastatic sites and 38.6% (1195/3094) in tumors collected from primary sites. CLDN18.2 prevalence was similar across other clinical and histopathological characteristics. Of 2908 HER2- pts with valid CLDN18 IHC results, 1264 (43.5%) had CLDN18.2+ tumors. Of 599 enrolled pts tested for PD-L1 expression, 104 (17.4%) had a PD-L1 CPS ≥5. **Conclusions:** The SPOTLIGHT and GLOW phase 3 studies are the largest data sources to date for determining global CLDN18.2 prevalence. CLDN18.2 is a high prevalence biomarker, with high tumor expression in ~35–40% of pts with LA unresectable or mG/GEJ adenocarcinoma, for whom zolbetuximab + chemotherapy represents a potential 1L therapy. Clinical trial information: NCT03504397, NCT03653507. Research Sponsor: Astellas Pharma Global Development, Inc.

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Poster Session

Effect of autologous lymphocytes combined with chemotherapy as the first-line treatment of advanced gastric cancer. *First Author: Xiaoting Ma, Na-National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking/Union Medical College, Beijing, China*

Background: To evaluate the safety and initial efficacy of adoptive cell therapy (ACT) combined with SOX in first-line treatment of locally advanced unresectable or metastatic gastric adenocarcinoma/gastroesophageal adenocarcinoma. **Methods:** In this single-arm, single-center exploratory trial, patients with histologically confirmed locally advanced unresectable or metastatic gastric adenocarcinoma/gastroesophageal adenocarcinoma were randomly assigned (1:1) to receive ACT in combination with S-1 and oxaliplatin (SOX) or SOX alone. The primary endpoint was the incidence of adverse events (AEs). Secondary endpoints were progression-free survival (PFS), overall survival (OS), objective response rate (ORR), and disease control rate (DCR). **Results:** Fifty-nine patients were enrolled in the study between November 20, 2014 and September 6, 2017. 31 patients received ACT combined with SOX (ACT-SOX) and 28 patients received SOX. The most common AEs in both groups were gastrointestinal reaction, leucopenia, neutropenia, anemia, thrombocytopenia, hyperbilirubinemia and elevated aspartate transaminase concentration, with a higher incidence in the SOX group. The median PFS for ACT-SOX and SOX were 6.9 and 4.9 months respectively (HR 0.80, p=0.45), and the median OS were 17.8 and 9.75 months (HR 0.76, p=0.34). Patients who received more than three injections of specific lymphocyte subsets benefited the most from combination therapy. Cox univariate and multivariate analysis showed that tumor metastasis to more than two organs was the main risk factor for PFS and OS. 29 patients in the ACT-SOX group and 25 in the SOX group had measurable lesions. The ORR of ACT-SOX group and SOX group was 55.2% and 32.0%, and DCR of two groups was 93.1% and 88.0%. **Conclusions:** The safety of ACT-SOX in first-line treatment of patients with locally advanced unresectable or metastatic gastric adenocarcinoma/gastroesophageal adenocarcinoma is good. Compared with SOX alone, although the PFS and OS of ACT-SOX did not reach statistical difference, it could further extend the time of PFS and OS, and the absolute improvement time of OS was about 8.05 months. Continuous benefit of ACT-SOX was observed through long-term follow-up. Clinical trial information: NCT02504229. Research Sponsor: None.

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Poster Session

Cell free DNA (cfDNA) assessment of esophagogastric (EG) cancer using MSK-ACCESS. *First Author: Samuel Louis Cytryn, Memorial Sloan Kettering Cancer Center - Fellowship (GME Office), New York, NY*

Background: The incidence of EG cancer is rising, the treatment paradigm is increasingly complex, and the role of predictive biomarkers is critical in selecting optimal therapies. Therefore, longitudinal, non-invasive methods to characterize dynamic tumor molecular profiles, such as cfDNA, are needed. **Methods:** Patients with EG cancer receiving care at Memorial Sloan Kettering (MSK) had cfDNA analysis with an ultrasensitive capture based liquid biopsy for detection of somatic alterations in 129 cancer associated genes (MSK ACCESS). Tumor samples were analyzed with MSK-IMPACT, a capture based next generation sequencing (NGS) platform. **Results:** 100 patients with EG adenocarcinoma underwent cfDNA analysis to evaluate for molecular residual disease with MSK ACCESS. 85 (85%) had tissue NGS with MSK IMPACT. Median TMB was 5.3 mut/Mb (IQR 2.6-7.4) and median number of alterations per sample was 11 (IQR 7-17). 71% had TP53 mutations and 22% had an ERBB2 amplification (amp). 79 (79%) patients had cfDNA obtained prior to treatment (50 [63%] metastatic disease; 29 [37%] localized disease) and 21 (21%) at the time of progression. Alterations were detectable on cfDNA more frequently in patients with later stage disease (p=0.031) and fewer alterations per sample were detected compared to tissue NGS (mean difference 14, 95% CI 10-18, p<0.001). The most common were TP53 (62%), CDKN2A (12%), PIK3CA (10%), ARID1A (10%), and ATM (10%). TP53 was detected with increasing frequency in patients with later stage disease (p=0.004). However, amplifications, which included ERBB2, MYC, EGFR, and FGFR2, were detected exclusively in those with stage IV disease (p=0.005) and cfDNA was less sensitive in detecting amplifications compared to tissue NGS (p<0.001). This is notable as HER2 positivity is determined in part by ERBB2amp. 25 of 30 HER2+ patients had both tissue NGS and cfDNA. 19 (76%) had ERBB2amp on tissue NGS and only 8 (32%) had ERBB2amp on cfDNA (p=0.004). Additionally, copy number was lower on cfDNA compared to tissue NGS (mean difference 13, 95% CI 1.3-24.9, p=0.02) and IHC 3+ tumors were more likely to have ERBB2amp detected than IHC 2+ tumors (p=0.049). However, alterations along the MAPK, PI3K, WNT, and TGF-β pathways, which are associated with trastuzumab resistance and poor survival, were detected with similar frequency on both platforms (40 v 32%, p=0.77). **Conclusions:** Our findings in this large prospective analysis highlight the utility of cfDNA with MSK ACCESS as a complimentary tool for molecular characterization in patients with EG cancer. cfDNA in EG cancer. Research Sponsor: Memorial Sloan Kettering Cancer Center.

Cohort	# Patients	Alterations Detected on cfDNA	# Alterations per sample (SD)	TP53	ERBB2amp
Total tissue NGS	85	N/A	16.6 (19.7)*	71%	22% *
Total cfDNA	100	80%	2.7 (4.1)*	62%	10% *
Untreated (localized)	29	66%*	2.4 (3.0)	44%*	0%*
Untreated (stage IV)	50	82%*	2.8 (5.2)	60%*	10%*
Progressive disease (stage IV)	21	95%*	2.7 (1.7)	91%*	24% *

*Statistically significant difference.

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Poster Session

Health-related quality of life (HRQOL) in patients (pts) with advanced gastric cancer/gastroesophageal junction cancer (GC/GEJC) or esophageal adenocarcinoma (EAC): 36-month results of nivolumab plus chemotherapy (N+C) versus (C) from CheckMate 649. *First Author: Elena Elimova, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada*

Background: CheckMate 649 (NCT02872116) is a randomized, open-label, phase 3 study in first-line treatment of pts with advanced GC/GEJC/EAC. Primary results showed statistically significant improvement in overall survival (OS) for N+C versus C in all randomized pts. Prior analyses conducted for 24-month follow-up (FUP) showed pts receiving N+C maintained HRQOL and experienced delayed deterioration in HRQOL compared with pts receiving C. Here we report additional analyses of HRQOL with 36-month FUP data. **Methods:** Functional Assessment of Cancer Therapy–Gastric Cancer (FACT-Ga) and EQ-5D-3L results were collected at baseline (BL) and every 6 weeks while on treatment. Change from BL in FACT-Ga, EQ-5D Visual Analog Scale (VAS), and Utility Index (UI) scores were analyzed using mixed models. Time to first symptom deterioration (TTSD), time until definitive deterioration (TuDD), and time to improvement (TTI) were estimated with Kaplan-Meier estimators and stratified Cox models; deterioration/improvement events were based on prespecified meaningful thresholds for change scores. **Results:** A total of 1,581 pts were randomized to N+C (n = 789) and C (n = 792); of those, 1,360 pts had BL and post-BL PROs and were included in the PRO population (N+C [n = 694] and C [n = 666]). With additional follow-up, least-squares mean differences from BL remained comparable between groups across visits for HRQOL measurements with exceptions. FACT-Ga total score, GaCS, physical well-being (WB), and emotional WB tended to favor N+C; social WB tended to favor C. For all randomized pts, most time-to-event endpoints favored N+C; like the 24-month analysis, statistically significant delays in deterioration were maintained for TuDD (except FACT-G Social WB) and TTSD (only FACT-GaCS and FACT-Ga total). **Conclusions:** These results confirm the earlier 24-month FUP findings. Compared with C alone, N+C maintained HRQOL with decreased risk of deterioration in pts with previously untreated advanced or metastatic GC/GEJC/EAC. Together with improved OS, data continue to support N+C as a first-line standard treatment for GC/GEJC/EAC. Clinical trial information: NCT02872116. Research Sponsor: Bristol Myers Squibb.

Instrument/Scale	TTSD HR (95% CI)	TuDD HR (95% CI)	TTI HR (95% CI)
Physical WB	0.90 (0.77-1.05)	0.78 (0.64-0.95)	1.06 (0.88-1.27)
Social WB	0.96 (0.81-1.13)	0.88 (0.71-1.09)	0.98 (0.80-1.20)
Emotional WB	1.04 (0.86-1.26)	0.75 (0.59-0.97)	0.98 (0.84-1.15)
Functional WB	0.94 (0.80-1.11)	0.69 (0.56-0.85)	1.08 (0.92-1.27)
FACT-G Total	0.92 (0.77-1.08)	0.72 (0.59-0.89)	0.93 (0.79-1.10)
GaCS Subscale	0.78 (0.64-0.95)	0.73 (0.57-0.94)	1.01 (0.86-1.18)
FACT-Ga Total	0.82 (0.67-0.99)	0.71 (0.55-0.91)	1.07 (0.91-1.26)
EQ-5D UI (UK set)	0.86 (0.73-1.01)	0.75 (0.61-0.91)	1.14 (0.97-1.33)
EQ-5D VAS	0.87 (0.75-1.02)	0.78 (0.64-0.94)	1.12 (0.96-1.31)

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Poster Session

Survival analysis by tumor response of nivolumab treatment in previously treated advanced gastric cancer from the DELIVER trial (JACCRO GC-08). First Author: Yu Sunakawa, Department of Clinical Oncology, St. Marianna University School of Medicine, Kawasaki, Japan

Background: We conducted a prospective observational study, DELIVER trial (UMIN000030850), to evaluate the real-world effectiveness of nivolumab monotherapy in previously treated advanced gastric cancer (GC) and have reported comparable efficacy and safety data (Takahashi, et al. *Gastric Cancer* 2021). There are few evidence regarding the association between tumor response and survival time in later-line treatment with nivolumab alone for advanced GC. We therefore report results from post-hoc exploratory analyses of survival time by tumor response from the DELIVER trial. **Methods:** The DELIVER trial enrolled 501 patients (pts) with advanced gastric or GEJ adenocarcinoma treated with nivolumab alone. Primary endpoint was overall survival (OS), secondary endpoints were response rate (RR), disease control rate, progression-free survival (PFS), tumor regression rate / tumor progression rate at 1st evaluation, tumor growth rate, and safety. The exploratory analyses were performed for survival according to tumor response and depth of response (DpR) in pts with measurable lesions who were receiving nivolumab as 3rd or later-line treatment. The survival data was fixed at the timepoint of 2 years after the last enrollment. **Results:** 234 pts were evaluable (median age 70y [26-90], 79% male, ECOG PS0/1/2 46/43/11%, 32% pts with ascites). Median OS was 6.5 months (95%CI 5.3-8.2) and median PFS was 1.8 months (95%CI 1.6-2.0). The RR was 15.0% (95%CI 10.4-19.5) with 5 complete response (CR) and 30 partial response (PR). The median PFS and OS were not reached for pts with CR, 11.7 and 29.8 months for pts with PR, 3.8 and 11.4 months for pts with stable disease, and 1.5 and 4.2 months for pts with progressive disease, respectively. In addition, the median DpR was -14.1% and was associated with PFS and OS in the Spearman analysis ($r=0.55$ and $r=0.44$, respectively). When the DpR was divided into 5 groups according to tumor shrinkage, there was difference in PFS and OS. **Conclusions:** This exploratory analysis indicated the association between DpR and survival time in pts with advanced GC treated with nivolumab alone in later-line. Increasing DpR was associated with longer median PFS and OS. Clinical trial information: UMIN000030850. Research Sponsor: Ono Pharmaceutical and Bristol-Myers Squibb.

	Median PFS(months)	HR, p-value	median OS (months)	HR, p-value
DpR≤-20% (n=100)	1.5	1	4.3	1
-20%<DpR≤0% (n=60)	1.7	0.57, 0.0011	5.3	0.89, 0.50
0%<DpR<30% (n=35)	3.0	0.24, <0.0001	7.0	0.68, 0.052
30%≤DpR<50% (n=17)	9.8	0.043, <0.0001	30.9	0.17, <0.0001
DpR≥50% (n=22)	15.8	0.049, <0.0001	Not reached	0.14, <0.0001

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Poster Session

Updated results of anlotinib combined with TQB2450 (PD-L1 blockade) as first-line treatment for advanced esophageal squamous cell carcinoma (ESCC): A single-arm, multicenter, open-label phase II clinical trial. First Author: Zhiye Zhang, The First Affiliated Hospital of Henan University of Science and Technology, Luoyang, China

Background: PD-1 blockades combined with chemotherapy in first-line setting exhibited encouraging efficacy for patients with ESCC recently. However, the safety profile of conventional chemotherapy was still disappointing. Therefore, the chemotherapy-free regimen might be a promising strategy. As a novel multitarget TKI mainly targeting VEGFR1-3, anlotinib was a potential first-line combination therapy and second-line monotherapy for patients with ESCC in China. TQB2450 was a novel PD-L1 blockade developed by Chia Tai Tianqing Pharmaceutical Group Co., Ltd. (Nanjing, China). Therefore, this study was designed to explore the efficacy and safety of anlotinib combined with TQB2450 as first-line therapy in advanced ESCC. The preliminary results were reported in 2023 ASCO-GI Symposium (Abs 377) and the update results were reported here. **Methods:** Patients with previously untreated metastatic or locally advanced ESCC, whose age was between 18 and 75 years, with ECOG PS of 0 or 1 and life expectancy of > 3 months were eligible as the inclusion criteria. Eligible patients were administered with anlotinib (12mg, po, d1-14, q3w) plus TQB2450 (1200mg, iv, d1, q3w) until disease progression or unacceptable toxicity. The tumor response was assessed according to RECIST 1.1 and IRECIST using CT scans every 2 cycles for the first 6 cycles, and every 3 cycles thereafter. Adverse events were recorded by severity in accordance with the NCI CTC AE Version 5.0. The predefined sample size was 46. The primary endpoint was ORR. Secondary endpoints included safety, PFS, DCR, DoR and OS. **Results:** From Mar 2022 to Sep 2022, a total of 46 patients were enrolled. At the data cut-off date (Dec, 2022), there were 1 CR (2.2%), 27 PR (58.7%), 14 SD (30.4%) and 4 NE (8.7%). Therefore, the preliminary ORR was 60.9% (95%CI: 45.4%~74.9%), DCR was 91.3% (95%CI: 79.2%~97.6%). The median PFS of the 46 pts was not yet available. Additionally, safety profile exhibited that the regimen was tolerable. The most common treatment-related adverse events in 46 patients with the incidence > 10% were hypertension (28%), hypothyroidism (20%), leukocytosis (20%), hyperthyroidism (17%), anemia (15%), fatigue (15%), neutrophil count decreased (11%), constipation (11%), sinus bradycardia (11%) and hand-foot syndrome (11%). The common grade ≥3 treatment-related adverse events were hypertension (4%), hand-foot syndrome (2%), hyponatremia (2%), platelet count decreased (2%) and lymphocyte count decreased (2%). **Conclusions:** Preliminary results suggested that anlotinib combined with TQB2450 as first-line therapy in advanced ESCC exhibited encouraging efficacy and manageable adverse events. And the conclusions needed to be confirmed in trials continued subsequently. Clinical trial information: NCT05038813. Research Sponsor: Chia Tai Tianqing Pharmaceutical Group Co., Ltd.

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Poster Session

Ultra-sensitive, tumor-informed ctDNA profiling in patients with gastroesophageal cancer and treated with pembrolizumab and longitudinal ctDNA kinetics. First Author: Andrew B. Nixon, Duke University Medical Center, Durham, NC

Background: Metastatic esophagogastric cancer (mEGC) is a lethal disease with poor long-term survival. Recent studies have established anti-PD-1 therapy in combination with chemotherapy as the standard of care for first-line therapy for mEGC. KeyLargo (NCT03342937) was a single arm phase II study of pembrolizumab in combination with oxaliplatin and capecitabine in the first line treatment of patients (pts) with HER2 negative mEGC. While high response rates were noted, not all pts received benefit, emphasizing the need for better biomarkers. Paired tumor biopsies and plasma were collected for optimal biomarker testing. In this retrospective study, we employed a novel, tumor-informed ctDNA approach as a tool for longitudinal disease monitoring and dynamic tumor evolution. **Methods:** Thirty-six pts were enrolled between January 2018 and January 2020. Of 34 evaluable pts, 25 pts achieved a response (ORR = 74%), including 6 pts with a complete response (CR) and 19 pts with a partial response (PR). Our initial analysis includes baseline tumor samples collected from 16 pts with over 59 corresponding on-treatment (OT; up to cycle 35) plasma samples. NeXT Personal, a tumor-informed ctDNA assay, generated personalized liquid biopsy panels derived from somatic variants (SV) from tumor whole genome sequencing. Each personalized assay includes up to 1,800 SVs for sensitive minimal residual disease (MRD) detection and a constant set of 2,100 clinically actionable variants (CAV). **Results:** Of the 36 pts who enrolled on KeyLargo, 32 pts had baseline tumor and longitudinal plasma samples collected and stored for testing. In this initial cohort of 16 pts, MRD events dynamically varied from 5.3 to 302,000 parts per million (PPM). 16/16 (100%) pts were MRD-positive at baseline, with a limit of detection between 1.5 and 4.6 PPM. OT samples were collected every 3 cycles (9 weeks). The ratio of PPM (rPPM) between baseline and the first available OT sample (typically Cycle 4 to 7) correlated with progression free survival (PFS; $p=0.0004$, logrank). rPPM was significantly reduced in pts having a best overall response of PR/CR (98% mean rPPM) versus progressive disease (25% mean rPPM, $p<0.037$, U-test). Two pts demonstrated CR, each with 11/11 (100%) MRD-negative plasma samples over approximately two years. CAVs were identified in longitudinal samples with TP53 repeatedly detected in 5 patients and a PIK3CA mutation emerging in the final 3 (of 9) timepoints from one patient. **Conclusions:** ctDNA was present in all pts at baseline; OT PPM reductions correlated with PFS and best overall response. CAV profiling suggested a de novo PIK3CA variant arising during therapy in one patient. These findings suggest that tumor-informed plasma-based ctDNA profiling in mEGC may detect known CAVs arising during therapy, and with subsequent investigations, may inform therapeutic decisions. Research Sponsor: Personalis, Inc.

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Poster Session

Phase II study of lenvatinib plus pembrolizumab for patients with immunotherapy-naïve advanced gastric cancer following first line therapy. First Author: Deirdre Jill Cohen, Division of Hematology and Medical Oncology, Icahn School of Medicine at Mount Sinai, New York, NY

Background: Immune checkpoint inhibitor (ICI) therapy has demonstrated efficacy in some patients (pts) with advanced gastric cancer (AGC) and is now approved in 1st line combination with chemotherapy. Preclinical studies suggest interplay between angiogenesis and the immune system, with VEGF exerting effects on the anti-tumor immune response including antigen presentation, effector mechanisms and immune cell trafficking. We hypothesized that the combination of VEGF inhibition and ICI may be more beneficial than either agent alone. We designed an open-label prospective phase II trial to evaluate the efficacy of lenvatinib (Len) plus pembrolizumab (Pem) beyond first line therapy in ICI-naïve AGC. **Methods:** Eligible pts included advanced gastric or gastroesophageal junction adenocarcinoma regardless of PD-L1 status, with measurable disease per RECIST 1.1, ECOG ≤1, and progressive disease on ≥1 prior regimen, no prior ICI. Pts received an initial lead-in week of Len 20mg PO daily which was then continued in combination with Pem 200mg IV every 3 weeks from day 8. Therapy was continued until progression or intolerance. Imaging was performed every 6 wks for the first 12 wks and then every 9 wks. Primary end point was objective response rate (ORR). Using the Simon optimal 2 stage design, planned sample size was 29 patients (pts) with 80% power and one-sided alpha of 5%. The study would be considered positive if ≥6 pts achieved an objective response. Secondary endpoints included safety and tolerability, PFS and OS. **Results:** During the course of this study, ICI was approved in the 1st line setting and as a result of changing practice patterns, enrollment was prematurely suspended in 7/2022 with 24 of 29 planned pts. All enrolled pts were included for the safety analysis. All subjects were mismatch repair proficient, 15 pts (62.5%) were CPS positive (≥1), data was missing for 1 pt. 19 pts who completed at least 2 cycles were evaluable for response; 15 were treated in 2nd line and 4 in 3rd line. Five pts (21%) had a partial response, including 1 with CPS=0 and 1 with CPS=1. Median PFS and OS was 12.9 and 21.4 weeks for the entire cohort. The combination was generally tolerable without new safety signals. Dose reductions were required in 3 (13%) pts, overall compliance with Len was 79% of planned doses across the study. Eleven (46%) pts experienced at least one G3 toxicity and one (4%) pt experienced G4 toxicity. Most common G3 toxicities included fatigue (27%), anorexia (18%), lymphopenia (18%), and hyperbilirubinemia (18%). **Conclusions:** Lenvatinib combined with pembrolizumab was well tolerated, responses were seen, but the study did not meet the primary endpoint in ICI naïve AGC. Given the changing landscape of care, ICI is now more broadly used in first line therapy, additional studies are warranted to determine the role of this combination in ICI exposed pts. Clinical trial information: NCT03321630. Research Sponsor: Eisai; Merck; U.S. National Institutes of Health.

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Poster Session

Efficacy of ramucirumab combination chemotherapy as second-line treatment in patients with advanced adenocarcinoma of the stomach or gastro-esophageal junction after exposure to checkpoint inhibitors and chemotherapy as first-line therapy within the prospective phase II IKF-S628/AIO-STO-0417 (MOONLIGHT) trial. *First Author: Michael Masetti, Klinikum rechts der Isar, Technische Universität München, Klinik für Innere Medizin III, München, Germany*

Background: FOLFOX plus nivolumab has become standard of care for first-line therapy of patients (pts) with advanced gastroesophageal cancer (aGEC). The efficacy of 2nd line VEGF-2 inhibition with ramucirumab (Ram) plus chemotherapy after progression to immunochemotherapy remains unclear. **Methods:** Medical records of consecutive pts with aGEC enrolled in the multi-centre randomized phase II AIO-STO-0417 trial who had tumor progression after 1st line FOLFOX plus nivolumab and ipilimumab were retrospectively analysed. Pts were divided into two groups based on the subsequent 2nd line therapy: Ram plus chemotherapy (ramucirumab group) or chemotherapy alone (control group). Outcomes were compared between both groups in the overall population and in subgroup analysis according to best response (CR/PR) under 1st line therapy and tumor PD-L1 expression. **Results:** In total, 83 pts (38 Ram group, 45 control group) were included. The most frequent 2nd line therapy in the Ram group was Ram plus paclitaxel (85%). In the overall population, median progression-free survival (PFS) in the Ram group was longer than in the control group (4.5 vs. 2.9 months). Responders (CR/PR) to 1st line immunochemotherapy who received Ram containing 2nd line therapy (n = 15) showed a clearly prolonged median OS counted from start of 1st line therapy (28.9 vs. 16.5 months), as well as 2nd line OS (9.6 vs. 7.5 months), PFS (5.6 vs. 2.9 months) and DCR (53% vs. 29%) compared to the control group (n = 24). PD-L1 CPS $\geq$ 1 (status known for 77% of pts) was 42% and 44% for the Ram and the control group, respectively. Patients with CPS $\geq$ 1 in the Ram group (n = 16) showed a trend towards better tumor control (ORR 25% vs. 10%, DCR 44% vs. 30%) and improved survival (total OS 11.5 vs. 8.0 months; 2nd line OS 6.5 vs. 3.9 months; PFS 4.5 vs. 1.6 months) compared to the control group (n = 20). **Conclusions:** Ramucirumab is effective as 2nd line treatment after progression on 1st line FOLFOX plus dual checkpoint inhibition, especially in patients with initial response and positive PD-L1 expression. Sequential angiogenesis inhibition with anti-VEGFR-2 targeting therapy following immunochemotherapy might be a promising option to overcome resistance to immunotherapy, which warrants further investigations in a larger cohort. Clinical trial information: NCT03647969. Research Sponsor: Bristol-Myers Squibb; Lilly.

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Poster Session

FLOT plus nivolumab in patients with previously untreated advanced or metastatic adenocarcinoma of the stomach or gastroesophageal junction: Results from the randomized phase 2 IKF-S628/AIO-STO-0417 (Moonlight) trial of the AIO. *First Author: Sylvie Lorenzen, Klinikum rechts der Isar, Technische Universität München, Klinik für Innere Medizin III, München, Germany*

Background: FOLFOX plus nivolumab (nivo) has become standard of care for first-line therapy of patients (pts) with esophagogastric adenocarcinomas. FLOT is a well-established standard of care triplet regime. Some physicians may consider a triplet in patients with aggressive disease. The aim of this Arm C part of the Moonlight trial was to evaluate the safety and efficacy of the combination of FLOT plus nivo. **Methods:** Moonlight is a multi-cohort phase-II trial. The results for Arm C evaluating FLOT + nivo (240 mg) q2w as first-line therapy in all-comers are presented here. Primary endpoint was progression-free survival at 6 months (PFS@6), main secondary endpoints were safety, OS, and overall response rate (ORR). **Results:** Fifty-two patients were enrolled. Baseline characteristics were: median age 61y, GEJ 65%. Sixty-five percent had centrally assessed PD-L1 CPS $\geq$ 1 (available in 96% of pts). Pts. received a median number of 8 cycles of FLOT and nivo and 42% received further line treatment. FLOT plus nivo was well tolerated and feasible with the most frequent adverse events of $\geq$ grade 3 being decreased neutrophils (40.4%), anemia (5.8%) and thromboembolic events (7.7%). After a median follow-up of 9.4 months, 3- and 6-month progression-free survival rates were 85% and 42%, respectively. Median PFS was 6.6 months and median OS 10.8 months. ORR and disease control rate (DCR) were 54% and 87%, respectively. Compared to the pooled study cohorts A and A1 (n = 90 pts) utilizing mFOLFOX plus nivo and ipilimumab (non-randomized comparison), FLOT plus nivo was associated with greater DCR (87% vs. 78%) and 3-months PFS (85% vs. 72%). **Conclusions:** FLOT and nivo is feasible and seems to be associated with improved disease control in the early course of therapy. FLOT plus nivo may represent an option for select patients with aggressive, rapidly progressive disease. Clinical trial information: NCT03647969. Research Sponsor: Bristol-Myers Squibb.

4044

Poster Session

A phase 2 single-arm study of berzosertib in combination with irinotecan in patients with progressive TP53 mutant gastric and gastro-esophageal junction cancer. *First Author: Shannon Stockton, Vanderbilt University Medical Center, Nashville, TN*

Background: TP53 mutations are reported in 30-70% of patients with metastatic/unresectable gastric (G) and gastro-esophageal junction (GEJ) adenocarcinoma and are associated with a poor prognosis. Novel therapeutics are needed. Gastrointestinal cancer cell lines with TP53 mutations demonstrate reliance on the ataxia telangiectasia and Rad3-related protein kinase (ATR) axis for DNA damage repair (DDR) in vitro. The ATR axis is triggered by single-strand DNA breaks and thus combining ATR inhibitors with topoisomerase I (TopI) inhibitors may have a synergistic effect, particularly in patients with TP53 mutant tumors. Irinotecan, a TopI inhibitor, is an established cytotoxic therapy for gastric and GEJ adenocarcinoma. We evaluated irinotecan in combination with the ATR inhibitor berzosertib (formerly M6620) in patients with TP53-mutated gastric and GEJ adenocarcinoma. **Methods:** This was a single-arm phase II study in third-line patients with G/GEJ cancers possessing TP53 mutations (exon 2 and exons 4-11). Patients received irinotecan 180 mg/m² IV and berzosertib 270 mg/m² IV on days 1 and 15 every 28 days. The primary endpoint was overall response rate (ORR) (Ha: 35% and Ho: 15%). A subset of patients underwent biopsies on C1D1 post-irinotecan and C2D2 to evaluate the expression of DDR biomarkers Y-H2AX, KAP1 p-Ser 824, and p-ATR. **Results:** A total of 17 patients were enrolled. Of 16 efficacy-evaluable patients, one experienced a partial response. The ORR was 6.2% thus the primary endpoint was not met. The disease control rate was 56.2%. Median progression-free survival was 4.01 months [95% CI 2.07-Not Reached]. Median overall survival was 6.21 months [95% CI 4.83-8.61]. No new safety signals were observed with the experimental treatment combination and the most common $\geq$ grade 3/4 treatment-related adverse events were neutropenia (4/17, 23.5% patients), anemia (3/17, 17.6%), febrile neutropenia (2/17, 11.8%), and diarrhea (2/17, 11.8%). No grade 5 events occurred. **Conclusions:** Although the primary endpoint of ORR was not met, the combination of irinotecan and berzosertib in patients with TP53-mutated G/GEJ adenocarcinoma was well-tolerated and demonstrated anti-tumor activity comparable to other agents with published later-line data (e.g. ramucirumab-paclitaxel, TAS-102). Analyses of pharmacodynamic biomarkers of DNA damage repair are in process. While further clinical development of berzosertib is not planned, other ATR inhibitors are being explored in combination with irinotecan in gastrointestinal malignancies, including G/GEJ cancer. Clinical trial information: NCT03641313. Research Sponsor: U.S. National Institutes of Health.

Best response in efficacy-evaluable patients.

Best Response (N=16)	
Partial Response	1/16 (6.2%)
Stable Disease	8/16 (50%)
Progressive Disease	7/16 (43.8%)

4046

Poster Session

Osemitamab in combination with capecitabine and oxaliplatin (CAPOX) as a first line treatment of advanced G/GEJ cancer: Updated data of cohort C from a phase I/IIa, multi-center study (TranStar102/TST001-1002). *First Author: Lin Shen, Department of Gastrointestinal Oncology, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Peking University Cancer Hospital & Institute, Beijing, Haidian District, China*

Background: Adding a claudin18.2 antibody to a chemotherapy is a clinically validated approach for patients with high CLDN18.2 expressing tumors. TST001 is a best in class differentiated antibody whose improved CLDN18.2 affinity and enhanced antibody-dependent cellular cytotoxicity, leads to anti-tumor activity in low to medium CLDN18.2 expressors gastric cancer cells. Pre-clinical studies also showed that TST001 has stronger tumor regression effects than the IMAB362-analog at the same dose. **Methods:** The efficacy and safety of osemitamab with CAPOX as 1st line treatment with G/GEJ cancer was explored in a dose escalation and expansion phase 1/2 study in China (Cohort C, NCT04495296). Positive claudin18.2 expression (membranous staining $\geq$ 1+ intensity in $\geq$ 10% of tumor cells) as assessed centrally using the LDT assay was required in the expansion phase only. **Results:** As of Dec 31, 2022, 64 patients were dosed with osemitamab in combination with CAPOX, 15 patients received osemitamab at doses ranging from 1 to 8 mg/kg Q3W in the dose escalation and 49 patients at 6 mg/kg in the dose expansion. The median follow up was 151 days. Patient characteristics were typical of 1st line G/GEJ cancer, with relatively higher percentage of peritoneal disease (48.4%). Nausea (65.4%), vomiting (46.2%) and hypoalbuminemia (65.4%) were the most common adverse events related to TST001 at dose of 6mg/kg in 52 patients (3 patients in dose escalation and 49 patients in dose expansion), most of them were grade 1 or 2 (only one patient experienced grade 3 nausea and vomiting, and one experienced grade 3 hypoalbuminemia). In the expansion cohort, 40 of the 45 patients with measurable lesions had at least one post-treatment tumor assessment. 27 achieved partial response (PR) of which 21 were confirmed. There was no obvious trend in improved efficacy with higher level of CLDN18.2 expression based on overall response rate (ORR). Progression free survival (PFS) and duration of response (DOR) were still immature. **Conclusions:** TST001 in combination with CAPOX as first-line treatment for the patients with G/GEJ cancer is safe and encouraging anti-tumor activities have been observed regardless of the CLDN18.2 expression levels above 1+ intensity in $\geq$ 10% tumor cells per central LDT assay. Updated ORR, mPFS and mDOR will be presented at the time of the congress. Clinical trial information: NCT04495296. Research Sponsor: Suzhou Transcenta Therapeutics Co., Ltd.

4047

Poster Session

Heterogeneous baseline immune cell infiltration landscape as a predictor of pathological complete response in locally advanced esophageal squamous cell carcinoma (ESCC) following neoadjuvant chemotherapy and immunotherapy: Results from a single-arm, phase II clinical trial (SEEK-01). *First Author: Guangyu Yao, Zhongshan Hospital, Fudan University, Shanghai, China*

Background: Neoadjuvant immunotherapy and chemotherapy have shown promise in improving outcomes for patients with locally advanced ESCC, but the response to treatment can vary among patients. Therefore, there is a need to identify predictive biomarkers that can guide treatment decisions and improve patient outcomes. The infiltration of immune cells within the tumor microenvironment has been shown to be an important factor in cancer progression and response to treatment. In this study, we sought to explore the immune microenvironment prospectively related to treatment response of Neoadjuvant immunotherapy by scRNAseq. **Methods:** This was a single-arm phase II clinical trial, planned to enroll 20 locally advanced ESCC patients (cT2-4N0-1M0). After neoadjuvant chemotherapy (paclitaxel-albumin + carboplatin) combined with tislelizumab, patients received minimal invasive esophagectomy (MIE). Prior to neoadjuvant therapy, fresh tumor tissues were obtained via endoscopy and used for scRNAseq analysis, to evaluate the predictive capacity of the immune microenvironment. Pathological outcomes were assessed and divided into pCR, MPR defined as <10% residual tumor excluding pCR, and non-MPR defined as >10%. **Results:** Out of 18 enrolled patients, 15 completed neoadjuvant therapy and MIE surgery since March 2022. Of these 15 patients, 3 achieved pCR, 2 got MPR, and 10 were non-MPR, with a total of 51,208 single cells sequenced. Both groups showed similarly low expression of PD-L1 (5.7% vs. 2.3%). Comparing pCR to non-MPR patients, the former showed a significant increase in T lymphocytes (CD8+ (17.1% vs. 1.1%), Regulatory T (20.2% vs. 4.0%)), plasma cell (22.0% vs. 8.3%), and mature dendritic cell (1.5% vs. 0.5%); a significant decrease in B cells (0.9% vs. 1.9%), neutrophils (1.7% vs. 11.0%), and tumor cell, as well as a similar expression of macrophage (5.6% vs. 6.6%) and monocyte, indicating a clear difference in the immune cell infiltration landscape between two groups. Furthermore, we identified a new subtype of plasma cell which was highly enriched in the non-MPR group, even though the pCR group showed a great increase in plasma cells in total. **Conclusions:** This study demonstrates the heterogeneity of baseline immune cell infiltration landscape in Locally Advanced ESCC, in which pCR and non-MPR patients exhibited entirely different profiles, and provide a potential predictor of response to neoadjuvant immunotherapy. Our findings suggest that baseline immune cell infiltration status, rather than pd-L1 expression, could accurately predict pCR or non-MPR before treatment, which could guide personalizing and minimize the need for trial-and-error approaches. Research Sponsor: None.

4049

Poster Session

Effectiveness and safety of camrelizumab in advanced esophageal cancer: A prospective multicenter observational cohort studies (ESCORT-RWS). *First Author: Zhihao Lu, Peking University Cancer Hospital, Beijing, China*

Background: Camrelizumab, an anti-programmed death 1 (PD-1) monoclonal antibody, has demonstrated survival benefits in patients with advanced or metastatic esophageal squamous cell carcinoma. However, the real-world effectiveness and safety of camrelizumab in patients with advanced esophageal cancer are largely unknown. **Methods:** In this prospective multicenter observational cohort study (NCT04616040), patients with advanced esophageal cancer who were scheduled to receive camrelizumab at the discretion of the physicians in charge were screened for inclusion. Clinical outcomes were treatment emergent adverse events (TEAEs), objective response rate (ORR), disease control rate (DCR), time to treatment discontinuation (TTD), progression free survival (PFS), and overall survival (OS). **Results:** Between Dec. 24, 2020 and Dec. 30, 2022, data were available for 624 patients (median age: 64.5 years; 74 [11.9%] aged ≥ 75 years; 515 [82.5%] men; 20 [3.2%] ECOG PS ≥ 2 ; 602 [96.5%] esophageal squamous cell carcinoma) from 42 institutions in China. All patients received at least one dose of camrelizumab-containing therapy, including 305 (48.9%) in the first-line, 238 (38.1%) in the second-line, and 81 (13.0%) in the third or later line settings. Most patients were treated with camrelizumab plus chemotherapy (487 [78.0%], primarily taxane and platinum-based chemotherapy in 284 [45.5%] patients), followed by camrelizumab plus antiangiogenic therapy (64 [10.3%]), camrelizumab monotherapy (46 [7.4%]), and camrelizumab plus antiangiogenic therapy and chemotherapy (27 [4.3%]). TEAEs occurred in 541 (86.7%) patients, most commonly anemia (41.2%), decreased white blood cell (38.5%), and decreased neutrophil count (28.5%). No new safety signals were noted. At the data cutoff (Dec. 30, 2022), 152 (24.4%) patients were still on treatment. The median follow-up estimated by the reverse Kaplan-Meier method and effectiveness outcomes are summarized in the Table. **Conclusions:** The real-world effectiveness and safety profiles of camrelizumab in advanced esophageal cancer patients are generally consistent with those observed in pivotal clinical trials. Research Sponsor: None.

	ESCORT-RWS		
	1 st line	2 nd line	$\geq 3^{\text{rd}}$ line
Median follow-up (95% CI), months	7.0 (6.2, 8.5)	10.6 (9.3, 12.1)	9.1 (7.0, 12.8)
ORR (95% CI)	54.2 (47.5, 60.8)	31.4 (24.6, 38.9)	28.1 (17.0, 41.5)
DCR (95% CI)	96.0 (92.6, 98.2)	80.0 (73.3, 85.7)	68.4 (54.8, 80.1)
Median TTD (95% CI), months	6.0 (5.1, 7.1)	5.9 (5.1, 6.6)	5.1 (3.4, 6.7)
Median PFS (95% CI), months	10.1 (7.4, 15.5)	7.9 (6.3, 9.1)	7.9 (5.2, 11.1)
Median OS (95% CI), months	17.5 (13.3, NR)	14.0 (10.0, 16.7)	12.9 (7.9, 20.3)

4048

Poster Session

Camrelizumab and chemotherapy as neoadjuvant treatment for locally advanced esophageal squamous cell carcinoma (ESCC): A single-arm, phase II trial. *First Author: Lei Gong, Tianjin Medical University Cancer Hospital & Institute, Tianjin, China*

Background: This study (NCT05476380) aimed to evaluate the safety and efficacy of neoadjuvant camrelizumab plus chemotherapy in patients with locally advanced ESCC, and to explore the potential risk factors of tumor immune microenvironment (TIM) which affect the efficiency of immunotherapy. **Methods:** Patients with resectable locally advanced thoracic ESCC, staged as T1b-4a, N2-3 (≥ 3 stations), and M0 or M1 lymph node metastasis (confined to supraclavicular lymph nodes) were enrolled. Eligible patients received intravenous camrelizumab (200 mg, day 2) plus paclitaxel (175 mg/m², day 1) and cisplatin (75 mg/m², day 1) for three 21-day cycles before surgery. The primary endpoint was major pathological response (MPR), defined as $\leq 10\%$ residual viable tumor cells in resected tissue. In order to screen out the potential biomarkers, the dissected lymph nodes were collected in the pathological complete response (pCR) and non-pCR groups. The infiltrated immune cells and the status of PD-L1 was evaluated by flow cytometry. **Results:** From February 20, 2021 to July 7, 2022, 38 patients were enrolled. 34 (89.5%) patients completed the full three-cycle treatment successfully. 34 patients underwent surgery and all received R0 resection. The MPR and pCR rates were 67.6% (23/34) and 17.6% (6/34), respectively. There were 2 (5.9%) patients having complete response of the primary tumor but residual disease in lymph nodes alone (ypT0N+). 32 (94.1%) patients had any-grade treatment-related adverse events, with the most common being leukocytopenia (73.5%). 18 (52.9%) patients had adverse events of grade 3 or worse. No treatment-related deaths occurred. Based on our findings, positive lymph nodes were one of the important reasons that the patients could not achieved pCR. TIM of the lymph nodes were then tested. Compared with MPR group, the infiltrated lymphocyte cells in the non-MPR group decreased from 93% to 52.4% ($p = 0.02$), the infiltrated CD8⁺ T cells also decreased from 11.8% to 5.9% ($p = 0.02$). However, the CD4⁺ T cells showed no significant difference between the MPR and non-MPR groups (46.2% vs 55%, $p = 0.27$). The expression of PD-L1 in the immune cells is one of the biomarkers for checkpoint inhibitors. In this trial, the expression of PD-L1 in the CD8⁺ T cells showed significant difference between the MPR and non-MPR groups (14.5% vs 6.7%, $p = 0.02$). Myeloid-derived suppressor cells (MDSCs) are a group of vastly heterogeneous immunosuppressive cells derived from immature myeloid progenitors that have been linked to poor patient prognosis and immunosuppression. We found more infiltrations of MDSCs in the non-MPR group compared with the MPR group (9.7% vs 4.7%, $p = 0.04$). **Conclusions:** Neoadjuvant camrelizumab combined with chemotherapy shows promising efficacy and good safety in ESCC patients. Poor response to immunotherapy was related to lymph node metastasis in the TIM. Clinical trial information: NCT05476380. Research Sponsor: Hengrui Medicine.

4050

Poster Session

Modified FOLFOX plus/minus nivolumab and ipilimumab vs FLOT plus nivolumab in patients with previously untreated advanced or metastatic adenocarcinoma of the stomach or gastroesophageal junction: The randomized phase 2 IKF-S628 Moonlight trial of the Arbeitsgemeinschaft Internistische Onkologie (AIO). *First Author: Sylvie Lorenzen, Klinikum rechts der Isar, Technische Universität München, Klinik für Innere Medizin III, München, Germany*

Background: FOLFOX plus nivolumab has become standard of care for first-line therapy of patients (pts) with esophagogastric adenocarcinomas (EGA). The AIO-STO-0417 trial (Moonlight) is a multi-cohort treatment optimization trial that evaluates the combination of FOLFOX alone (Arm B) vs FOLFOX plus nivolumab (nivo) and ipilimumab (ipi) administered in parallel (Arm A/A1) or sequentially (Arm A2) and FLOT plus nivolumab administered in parallel (Arm C) for 1L-treatment of metastatic or advanced inoperable Her-2 negative EGA. The aim is to generate signals whether a. dual checkpoint inhibition or b. a triplet chemotherapy is beneficial in the context of nivolumab therapy for this disease. **Methods:** Pts were randomized 1:1 to Arm A (mFOLFOX q2w plus nivo 240 mg q2w + ipi 1 mg/kg q6w administered in parallel) or B (mFOLFOX alone). In a subsequent phase pts were randomized 1:2 to Arm A1 (identical to Arm A) or A2 (three cycles of mFOLFOX followed by nivo q2w + ipi q6w, with optional repetition). In a final phase, all pts were allocated to single Arm C (FLOT q2w + nivo q2w). The primary endpoint was progression-free survival (PFS) based on the ITT population for Arm A vs Arm B and PFS rate at 6 months (PFS@6) for Arms A2 and C. Main secondary endpoints were PFS and ORR. Here, we present results for Arms A/A1, A2 and B. **Results:** A total of 262 pts were enrolled, Arm A (n=60), Arm B (n=60), Arm A1 (n=30), Arm A2 (n=60) and Arm C (n=52, results presented elsewhere). Baseline characteristics were comparable in all arms. Overall PD-L1 expression (CPS ≥ 1) was low with 41% and balanced between Arms A/A1, A2 and B. Analysis of pooled Arms A/A1 (n=90) showed an increase in toxicity (pts with AEs grade ≥ 3 88% vs 65% in Arm B and 75% in Arm A2, treatment related SAEs grade ≥ 3 A/A1 41% vs B 18% vs A2 17%) but not in activity. Arm A/A1 compared with Arm A2 was more effective in terms of PFS@6 (48% vs 30%), median PFS 5.8 vs 4.0 months and objective response rate (ORR) 46% vs 30%. **Conclusions:** Albeit the small number of pts in each cohort we conclude that in the first-line setting of metastatic EGA. a) Chemo plus dual checkpoint inhibition administered in parallel is associated with an increase in toxicity but not activity. b) Although associated with lower toxicity the use of sequential chemo followed by IO monotherapy is insufficient. The relatively low numbers of patients with PD-L1 CPS ≥ 1 may have impacted these results. Clinical trial information: NCT03647969. Research Sponsor: Bristol-Myers Squibb.

4051

Poster Session

Advancing individualized care in advanced gastroesophageal cancers (GEC): A quality improvement initiative. *First Author: Matthew Strickland, Massachusetts General Hospital, Boston, MA*

Background: Biomarkers have become increasingly important in the treatment of metastatic gastroesophageal cancers (mGEC) with new targeted and immune-based therapies relying on biomarkers to identify patients who may benefit from these therapies. Here, we aimed to identify real-world challenges mGEC care teams face in implementing biomarker testing and evidence-based treatment choices. **Methods:** In July–September 2022, 74 health care professionals (HCPs) who treat mGEC at 3 US community oncology clinics completed surveys assessing practice patterns, challenges, and confidence related to treating mGEC. HCPs (N = 24) participated in interdisciplinary audit and feedback (AF) sessions to examine clinical evidence and develop clinic-specific action plans to address identified gaps. **Results:** Participating practices reported that ~22% of their practice is dedicated to GEC care. Participants represented the interprofessional GEC care team: medical oncologists (27%), radiation oncologists (1%), surgeons (1%), advanced practice professionals (32%), nurse/nurse navigators (32%), and other HCPs (5%). Providers reported testing for HER2, *EGFR*, *FGFR*, *NTRK*, microsatellite instability, tumor mutational burden, and PD-L1 in ~55-65% of advanced GEC patients. Most providers reported HER2 testing at time of diagnosis (91%) with 18% reporting testing at time of clinical or radiologic progression and 24% when new metastases are detected. Top reported barriers to use of predictive biomarker testing were long turnaround times for tests (32%) and keeping up to-date with current testing recommendations (23%). Top reported challenges in selecting therapies for GEC were keeping up with clinical evidence (35%) and delayed, pending, or unavailable biomarkers at the time of treatment selection (20%). Clinic action plans focused on specific gaps including (1) improved HCP education on guideline-concordant biomarker use (2) improving testing turnaround times, and (3) improving referrals to clinical trials based on biomarker results. The educational intervention increased correct identification of guideline concordant treatment for stage IV esophageal cancer (48% pre- and 72% post-AF) and confidence in use of biomarkers for treatment decision-making for patients with GEC (high/very high in 46% pre- and 72% post-AF). **Conclusions:** While molecular testing is becoming increasingly critical for mGEC care, HCPs report challenges with testing workflows and difficulty keeping up with developments in clinical data and guidelines. Clinic-specific interventions to improve biomarker workflows and ongoing educational initiatives to keep HCPs informed of the latest evidence-based best practices in biomarkers and associated therapies can address these gaps to improve outcomes for patients with GEC. Research Sponsor: Supported by an educational grant from Merck Sharp & Dohme Corp.

4053

Poster Session

Circulating tumor DNA and association with CAR-T cell therapy response in gastric and pancreatic cancer patients. *First Author: Sindhu Kubendran, Department of Medicine, University of California San Diego, La Jolla, CA*

Background: Circulating tumor DNA (ctDNA) is a form of cell free DNA that can be used to detect and measure cancer molecular residual disease (MRD) before and after systemic therapy. There are no data pertaining to the assessment of MRD in patients with solid tumors treated with chimeric antigen receptor T-cell (CAR-T) therapy. Here, we evaluated a tumor-informed ctDNA assay in the setting of gastric and pancreatic malignancies treated with claudin18.2 (CTO41)-targeted CAR-T cell therapy (NCT04404595). **Methods:** A single-center review between 7/1/2021 – 1/1/2023 identified 10 patients with pancreatic or gastric carcinoma who received CAR-T CTO41 cell therapy. Eight patients were ctDNA positive prior to treatment and had blood samples serially drawn before and after CAR-T cell therapy. Plasma was analyzed for ctDNA using a tumor-informed Signatera, mPCR-NGS ctDNA assay (Natera, Inc.). The correlative prognostic value of ctDNA to predict response after CAR-T cell therapy was analyzed by RECIST 1.1 criteria. **Results:** Pre- and post-treatment serial ctDNA was available for 8 of 10 (3/5 gastric and 5/5 pancreatic cancer) patients and all 8 were ctDNA positive prior to CAR-T CTO41 cell therapy. The median nadir of ctDNA was on day 14 after CTO41 infusion. Of the 8 patients with detectable ctDNA, 5 (62.5%) became undetectable at some time after CTO41 therapy, while 3 (37.5%) remained ctDNA positive throughout treatment. The disease control rate (DCR) was 80% for anytime negative ctDNA patients (4/5). Of patients with responsive disease after CTO41 CAR-T, 2/3 (67%) achieved undetectable ctDNA and 1/3 (33%) had a ctDNA reduction by 95%. Both patients with stable disease developed undetectable ctDNA. In those patients with progressive disease, 1/3 (33%) had a negative anytime ctDNA. One patient with a complete response had undetectable ctDNA and target lesion response, then later developed progressive disease detectable by ctDNA 3 months prior to radiography. Overall survival was higher (9.1 months vs. 3.7 months) in those who achieved anytime undetectable ctDNA. **Conclusions:** Tumor-informed ctDNA correlates with response to CAR-T cell therapy in gastrointestinal malignancies. Ongoing clinical trials of CTO41 CAR-T cell therapy will continue ctDNA analysis prospectively. Characteristics of initially ctDNA positive patients receiving CAR-T therapy. Clinical trial information: NCT04404595. Research Sponsor: Carsgen Inc.; Natera Inc.

	Never ctDNA (-) (N=3)	Anytime ctDNA (-) (N=5)
Age (years) – mean (SD)	53 (5.3)	55 (17.5)
Female sex – no. (%)	3 (100)	2 (40)
Primary disease – no. (%)		
Gastric	1 (33.3)	2 (40)
Pancreatic	2 (66.7)	3 (60)
Progression Free Survival – no. (%)		
Disease Control Rate = Stable + Partial + Complete Response	1 (33)	4 (80)
Progressive Disease	2 (66)	1 (20)
Overall Survival (months) – mean (SD)	3.7 (2.8)	9.1 (3.8)

4052

Poster Session

Phase II study of telomelysin (OBP-301) in combination with pembrolizumab in gastroesophageal (GEA) adenocarcinoma. *First Author: Manish A. Shah, NYP, Weill Cornell, New York, NY*

Background: OBP-301 is a novel, replication-selective adenoviral construct that incorporates the human telomerase reverse transcriptase gene (hTERT) promoter, which is highly expressed in tumors but not in normal, differentiated adult cells, to regulate expression of the early adenoviral genes, E1A and E1B. OBP-301 has been evaluated as a single agent, and demonstrated immune responses and clinical activity in phase I studies. We examined OBP-301 in combination with pembrolizumab in a multicenter phase II study as a novel mechanism to improve immunotherapy in advanced gastric cancer. **Methods:** Eligible patients had advanced GEA that had progressed on at least 2 lines of prior therapy for incurable, advanced disease. Patients were required to have adequate end-organ function, measurable disease by RECIST 1.1, and a PD-L1 CPS > 1. Patients received OBP-301 at 2x10¹² viral particles via direct tumor injection every two weeks x 4 injections as well as pembrolizumab 200 mg IV every 3 weeks. The primary endpoint was objective response rate (ORR). The null hypothesis that the ORR is < 15% was tested against the Ha ORR > 30%. We used a Simon two-stage design, requiring 3 or more responses in 18 patients in the first stage to proceed to stage two. The study was closed after successfully completing stage one of the Simon's two stage design to formally examine OBP-301 + pembrolizumab in an immunotherapy (IO) refractory GEA population. Tissue was collected for single cell RNA Sequencing to examine the tumor immune microenvironment pre- and post-OBP-301 injections. **Results:** From May 2019 to Oct 2022, we enrolled 16 patients, median age 65 (range 43-81), male n = 13. OBP-301 direct tumor injection was well tolerated, median OBP-301 injections 3 (range 1-5). Toxicity attributed to OBP-301 included grade 2 fatigue/weakness (25%), grade 2 fever (18.7%), and a single incidence each of grade 2 nausea, anemia, grade 3 melena, and grade 4 diabetes mellitus (6.25%). We observed 3 patients (19%) with a partial response (PR), thereby meeting the Simon two-stage threshold. The responses were durable; two patients with PR are currently without evidence of disease (one completed 2 years of pembrolizumab, one underwent resection of primary tumor after 15 months), and the 3rd patient is now in month 12 of treatment. Further, one patient with brain metastases demonstrated regression of metastatic disease following progression on immunotherapy alone. All patients were mismatch repair proficient. **Conclusions:** OBP-301 viral particle injection into the tumor is feasible and safe. OBP-301 with pembrolizumab has encouraging activity in GEA, with durable responses and demonstration of activity in immunotherapy refractory disease. Single Cell RNA Sequencing data of the pre- and post-injection immune effects of OBP-301 will be presented. A formal phase II study of OBP-301 + pembrolizumab in IO refractory GEA patients is underway. Clinical trial information: NCT03921021. Research Sponsor: Oncolytics Biopharma.

4054

Poster Session

Adjuvant nab-paclitaxel plus S-1 versus capecitabine plus oxaliplatin for patients with stage III gastric adenocarcinoma after D2 dissection: A multicenter, open-label, randomized phase 3 study. *First Author: Yu Pengfei, Zhejiang Cancer Hospital (University of Chinese Academy of Sciences Cancer Hospital), Hangzhou, China*

Background: Multiple clinical studies have shown that adjuvant chemotherapy could prolong the survival of patients after radical resection, it is necessary to explore better treatment options for patients with stage III gastric adenocarcinoma (GAC). We designed this study to evaluate the efficacy and safety of adjuvant nab-paclitaxel combined with S-1 (AS) versus capecitabine combined with oxaliplatin (CAPOX) in GAC. **Methods:** Patients with stage III GAC after D2 radical resection and achieved R0 resection were randomized 1:1 to receive adjuvant AS (nab-paclitaxel: 100 mg/m², d1 and 8, q3w; S-1: 40-60 mg, bid, d1-14, q3w) or CAPOX (oxaliplatin: 130 mg/m², d1, q3w; capecitabine: 1000 mg/m², bid, d1-14, q3w) for 8 cycles. Stratification analysis was performed according to histological type (differentiated vs undifferentiated GAC) and AJCC 8th pathological staging (IIIA vs IIIB and IIIC). The primary endpoint was 3-year disease-free survival (DFS) rate, secondary endpoints were overall survival (OS) and safety. **Results:** Between March 20, 2020 and January 17, 2023, 313 patients were randomized to receive AS (n = 156) or CAPOX (n = 157). Baseline characteristics were generally balanced between the two groups. Median follow-up time was 5.16 months. The 1-year DFS rates were 87.14% and 70.16%, in the AS and CAPOX groups, respectively. The median DFS and 3-year DFS rates were not reached. The 1-year OS rate was 88.47% in AS group, and 63.89% in CAPOX group. At date cutoff, 12 patients (peritoneal recurrence, 1 patient; locoregional recurrence, 3 patients; distant recurrence, 8 patients) relapsed in the AS group and 16 patients (peritoneal recurrence, 4 patients; locoregional recurrence, 5 patients; distant recurrence, 8 patients; tumor marker recurrence, 1 patient) relapsed in the CAPOX group; some patients had multiple recurrence sites. 2 patients (1 patient for GAC; 1 patient for other diseases) died in the AS group and 11 patients (9 patients for GAC; 2 patients for other diseases) died in the CAPOX group. The median relative dose intensity of nab-paclitaxel was 90.32%, of S-1 was 80.77%, of oxaliplatin was 77.44% and of capecitabine was 78.55%. The incidence of adverse events (AEs) of any grade and grade 3/4 were 79.49% and 39.74% in the AS group, 72.61% and 22.93% in the CAPOX group. In the AS and CAPOX groups, neutropenia (31.63% vs 20.13%), leukopenia (29.71% vs 17.25%), anemia (27.80% vs 23.00%) and thrombocytopenia (4.15% vs 17.25%) were the most common AEs. **Conclusions:** Compared with CAPOX regimen, AS regimen has better survival rates and acceptable tolerability. AS provided new potential adjuvant regimen for stage III gastric cancer after D2 resection. Clinical trial information: NCT04135781. Research Sponsor: CSPC ouyi Pharmaceutical Group Co., Ltd.

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Poster Session

Perioperative immunochemotherapy (mDCF + avelumab) in locally advanced gastro-esophageal adenocarcinoma: A phase II trial. *First Author: Thierry Alcindor, McGill University Health Center, Montréal, QC, Canada*

Background: Perioperative chemotherapy improves cure rate in locally advanced gastroesophageal adenocarcinoma (GEA). Immune checkpoint inhibitors have activity in GEA. This trial is testing the hypothesis that the addition of avelumab, an anti-PD-L1 antibody, to perioperative mDCF chemotherapy, will increase the pathologic complete response (pCR) rate, a potential surrogate for overall survival, in comparison with a historical pCR rate of 7%. **Methods:** Single-arm phase II study (NCT03288350) of avelumab + chemotherapy (modified docetaxel/cisplatin/5-FU or mDCF) given every 2 weeks x 4 cycles before and after surgery. Planned sample size of 50 operated patients. The hypothesis cannot be refuted if ≥ 6 patients show pCR, the primary endpoint. Inclusion criteria: histologically proven GEA, locally advanced disease (cT3-4 and/or N+), adequate organ function, WHO performance status 0-1. Exclusion criteria: other histology, metastatic stage, use of immunosuppressants, serious autoimmune disease, intake >10 mg prednisone/d. Adverse effects prospectively recorded per NCI CTCAE guidelines. Pathological response and tumor regression grade (TRG) determined by CAP criteria: 0=complete; 1=near complete; 2=moderate; 3 = poor/no response. Data presented as median (range), KM determined survival. **Results:** Study accrual completed August 2022: 51 patients enrolled, 45 M/6 F, age 64 (18-79), ECOG 0 (35) and 1 (16). One patient withdrew consent after 2 treatment cycles and is excluded from efficacy analysis. Tumor anatomic site: Esophagus =19(38%)/gastroesophageal junction 21(42%)/subcardia stomach 10(20%). Staging: cT3 (88%), cT4 (6%), N+ (62%). Histology: all adenocarcinoma; dMMR 9/50 in 18%; CPS <1 , 1-5, 6-10, >10 in 0%/33%/27%/40% of tumors tested. All 4 pre-operative cycles administered to 48/50 (96%); 36/50 received ≥ 2 adjuvant treatment cycles and 23/50 (46%) received all 8 cycles. Grade 3-4 toxicity events from neoadjuvant therapy affected: GI tract (diarrhea 4%); respiratory system (pneumonia 4%); endocrine system (adrenal insufficiency 2%). Other common side effects (grades 1-2, incidence $>15\%$) were: fatigue, diarrhea, skin rash/pruritus. Post-operative mortality at 30 and 90 days was 0/50 (0%) and 1/50 (2%). R0 resection was achieved in 48/50 (96%); a median of 36 (13-78) lymph nodes were resected. Pathological response was TRG 0/1/2/3 in 7/21/16/25 with pCR seen in 7 (14%), meeting the primary endpoint. Major pathologic response (TRG 0 and 1) was seen in 9 (18%), but without correlation with CPS or dMMR biomarker status. At 37.5 (9-71) months follow up, overall survival at 1, 2, and 3 years is 93.6%, 75.7%, and 69.2%. MPR showed a trend to improved survival ($p = 0.06$). **Conclusions:** The neoadjuvant combination of avelumab with chemotherapy (mDCF) shows promising safety and efficacy in gastroesophageal adenocarcinoma, without obvious correlation to known biomarkers. Clinical trial information: NCT03288350. Research Sponsor: EMD Serono as part of an alliance between the healthcare business of Merck KGaA, Darmstadt, Germany and Pfizer.; MUHC Foundation.

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Poster Session

Integration of trastuzumab (T), with or without pertuzumab (P), into perioperative chemotherapy (CT) of HER-2 positive gastric (GC) and esophago-gastric junction cancer (EGJC): First results of the EORTC 1203 INNOVATION study, in collaboration with the Korean Cancer Study Group, and the Dutch Upper GI Cancer group. *First Author: Anna Dorothea Wagner, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland*

Background: 10-20% of GC are HER-2 positive. The role of perioperative anti-HER2-directed treatment is yet undefined. **Methods:** This randomized, open-label phase II-trial investigates the benefit of combining T alone or with P and perioperative CT for GC and EGJC. Between 2015 and 2021, 172 of a planned 215 patients (pts) with centrally confirmed, positive HER-2 status and resectable GC or EGJC (UICC TNM stages Ib-III) were included. Recruitment was prematurely terminated due to slow accrual. Pts were randomized in a 1:2:2 ratio to: Arm A (CT alone) (35 pts); Arm B (CT+T [8mg/kg, followed by 6mg every 3 weeks]) (67 pts); Arm C (CT+T+P [840mg every 3 weeks]) (70 pts). CT was initially cisplatin (80 mg/m² d1) and capecitabine (2 x 1000 mg/m²/d d1) for 3 cycles before and after surgery. After publication of the FLOT-4 study, the protocol was amended. CT changed to four cycles FLOT (AI-Batran Lancet 2019) with FOLFOX or CAPOX as alternative for pts ineligible for FLOT. In the experimental arms, T and P were continued beyond CT at the same dose for a total of 17 cycles. Major pathological response rate (mpRR) determined by central pathology review was the primary endpoint. The study was designed to have 80% power to detect an increase in mpRR from 25% with CT to 45% with CT+T+P or CT+T with a one-sided alpha of 10%. CT+T+P was first tested versus CT and if positive, CT+T would be tested versus CT. **Results:** Out of 172 pts randomized, 161 fulfilled all important eligibility criteria and started their allocated treatment (per protocol population). 62.1% of pts had EGJC and 72.0% an intestinal subtype. Main CT regimens were cisplatin-capecitabine (42.2%) and FLOT (46.6%). In Arm A:B:C, 90.9%, 92.2% and 81.3% completed neoadjuvant treatment. Major reason for treatment discontinuation was toxicity (70%). Surgery was performed in 84.8%, 98.4%, 92.2% pts in Arm A:B:C. R0 resection rates were 83.9%, 90.3% and 85.9%. At present, results of central pathology review of mpRR are available for 126 out of 150 operated pts (84.0%). Pts not operated (n=11) were considered as failures for mpRR. MpRR was 23.3%, 37.0%, 26.4% in Arm A:B:C. The increase of 3.1% (80% CI: [-9.5%, 15.7%]), one-sided $p=0.378$ in Arm C vs. A was not statistically significant. The increase in Arm B vs. A was 13.7% (80% CI: [0.7%, 26.7%]), one-sided $p=0.099$. MpRR was 33.3%, 53.3% and 37.9% in Arm A:B:C after amending the protocol while, in contrast, it was 8.3%, 16.7% and 12.5% before. **Conclusions:** The primary endpoint analysis did not meet the pre-specified criteria of efficacy for the combination of CT+T+P. However, CT+T showed interesting response rates, especially with FLOT as CT backbone. Follow-up data including survival is necessary to define the clinical value of this regimen. Clinical trial information: NCT02205047. Research Sponsor: This study was funded by an unrestricted educational grant from Roche to EORTC.

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Poster Session

Predicting role of circulating tumor DNA and blood-based tumor mutational burden in esophageal squamous cell carcinoma receiving chemoradiotherapy combined with toripalimab: Exploratory analyses from a phase II trial (EC-CRT-001). *First Author: BaoQing Chen, Sun Yat-sen University Cancer Center, Guangzhou, China*

Background: EC-CRT-001 is a phase II trial investigating the efficacy of toripalimab (an anti-PD1 antibody) combined with definitive chemoradiotherapy (CRT) in locally advanced esophageal squamous cell carcinoma (ESCC) and the results demonstrated encouraging antitumor activity and acceptable toxicity. This exploratory analysis was performed to evaluate the role of circulating tumor DNA (ctDNA) and blood-based tumor mutational burden (tMB) for efficacy prediction. **Methods:** Forty-two patients from the phase II trial (NCT04005170) who received toripalimab (240 mg every 3 weeks for up to 1 year, or disease progression, or unacceptable toxicity) combined with definitive CRT (irradiation with 50.4 Gy in 28 fractions concurrent with 5 cycles of weekly paclitaxel in 50 mg/m² and cisplatin in 25 mg/m²) were enrolled. Plasma samples were collected before, during, and after CRT. Targeted next-generation sequencing was performed on a total of 118 plasma samples and 35 matched tumor samples using a panel covering 474 cancer-associated genes. **Results:** Twenty-six (62%) of 42 patients achieved clinical complete response (cCR) at three months after CRT. ctDNA was detected in 29 (72.5%) of 40 patients at baseline. The positive rate of ctDNA decreased to 43.9% (20/41) during CRT and continued to descend to 27.0% (10/37) at the completion of CRT. A higher cCR rate was observed in patients with negative during-CRT ctDNA compared to those with detectable ctDNA (82.6% vs. 38.9%, $P = 0.008$). Patients with post-CRT detectable ctDNA also had poorer cCR rate (30.0% vs. 77.8%, $P = 0.017$). Within a median follow-up of 24.0 months (IQR 13.7-27.9), the median progression-free survival (PFS) was 12.2 months (95%CI: 8.4-16.0) and median overall survival (OS) was not reached for the whole cohort. Patients with during-CRT detectable ctDNA had shorter PFS compared to ctDNA-negative patients (HR = 2.57, 95%CI: 1.18-5.60, $P = 0.014$). Similarly, patients with post-CRT detectable ctDNA also had a significantly increased risk of disease progression (HR = 2.88, 95%CI: 1.21-6.83, $P = 0.012$) and death (HR = 3.67, 95%CI: 1.41-9.55, $P = 0.004$). Moreover, patients with higher tMB (>1) detected during CRT were associated with a favorable OS (HR = 0.33, 95%CI: 0.13-0.88, $P = 0.027$). Improved PFS was also observed in those patients with higher post-CRT tMB (>3) (HR = 0.28, 95%CI: 0.08-0.96, $P = 0.042$). **Conclusions:** Negative ctDNA status and higher tMB during or after CRT were associated with better tumor response and favorable survival in ESCC patients who underwent definitive CRT combined with toripalimab. Dynamic ctDNA has great potential in predicting efficacy and risk of disease progression in ESCC. Clinical trial information: NCT04005170. Research Sponsor: Guangdong Esophageal Cancer Institute (Q202109).

4058

Poster Session

Concordance among the three commercially available PD-L1 assays for esophageal squamous cell carcinoma. *First Author: Lizhen Wang, Roche (China) Holding Ltd., Shanghai, China*

Background: Immune checkpoint inhibitors are now standard-of-care for patients with esophageal squamous cell carcinoma (ESCC). The predictive significance of PD-L1 expression in ESCC has been investigated by different antibodies, scoring algorithms and cutoff values in several phase III trials. However, it remains controversial whether PD-L1 is a predictive biomarker for response to PD-1/PD-L1 blockade. Evaluating the concordance of the commercially available PD-L1 assays is essential to understand the discrepancy in the ESCC clinical trials, and helpful to further investigate the predictive value of PD-L1 expression. **Methods:** 145 archival tumor samples were obtained from 131 patients with ESCC (stage I-IV) at National Taiwan University Hospital. Formalin-fixed, paraffin-embedded archival tumor samples were assessed by three commercially available PD-L1 assays: VENTANA SP263, Dako 22C3 and Dako 28-8 assays. Assays were performed in a College of American Pathologists accredited central laboratory and scored for PD-L1 staining by using multiple metrics including tumor cell score (TC), immune cell score (IC) and combined positive score (CPS) or tumor area percentage (TAP). Analytical concordance was calculated pairwise between assays using the Spearman (ρ) rank correlation coefficient. Classification concordance, including agreement between clinically relevant scoring algorithms, was investigated using positive percent agreement (PPA), negative percent agreement (NPA), and overall percent agreement (OPA) at multiple cutoff values to assess the overlap between populations by using different assays. **Results:** SP263, 22C3 and 28-8 assays showed good analytical correlation for TC staining (Spearman's rank correlation coefficient 0.8-0.9). Correlation was lower for IC (Spearman's rank correlation coefficient 0.59-0.61). There was moderate overlap between populations identified by SP263 and 28-8 or 22C3 based on CPS or TAP algorithm at multiple cutoff values. OPAs for these 3 assays ranged from 68%-88% at various matched algorithms. The SP263 and 22C3 PD-L1 assays appeared relatively more sensitive, assigning a higher proportion of patients as PD-L1 positive or high, compared to 28-8 assay. When using assay-specific clinically relevant algorithm, moderate classification agreement was seen for SP263 versus 22C3 or 28-8. Differences were observed between patient populations with tumor classified as PD-L1 high versus PD-L1 low/negative using CPS ≥ 10 , TAP $\geq 10\%$ and TC $\geq 1\%$. The PPA between 22C3 CPS ≥ 10 and SP263 TAP ≥ 10 or 28-8 CPS ≥ 10 or 28-8 TC $\geq 1\%$ were 75%, 57% and 68% respectively. **Conclusions:** This study is the first dataset to compare various PD-L1 assays in ESCC. Differences in classification of patients with PD-L1 high versus low/negative using clinically relevant algorithms suggest that caution should be taken when comparing data across the trials. Research Sponsor: Roche.

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Poster Session

Multi-dimensional cell-free DNA-based liquid biopsy and early detection of gastric cancer. *First Author: Yu Pengfei, Department of Gastric Surgery, Zhejiang Cancer Hospital, Institute of Basic Medicine and Cancer (IBMC), Chinese Academy of Sciences, Hangzhou, Zhejiang, China*

Background: Gastric cancer is one of the most common cancer types. Most patients were diagnosed at advanced stages and experienced poor prognosis. A non-invasive assay for the detection of early-stage gastric cancer is highly desirable for reducing the gastric cancer-associated mortality. **Methods:** We prospectively collected a study cohort of 249 participants including 110 pathologically confirmed with stage I-II gastric cancer and 139 with non-cancerous conditions. A plasma sample was collected from each patient before conventional screening modalities for gastric cancer. We performed whole-genome sequencing with plasma samples and profiled four types of cell-free DNA (cfDNA) characteristics, fragment size pattern, copy number variation, nucleosome coverage pattern, and single nucleotide substitution. We used these differential profiles to develop an ensemble model to identify gastric cancer patients from non-cancer individuals. We further collected a validation cohort consisting of 73 gastric cancer patients and 94 non-cancer individuals to validate the cfDNA-based assay. Additionally, we compared the performance of our assay and conventional gastroscopy in a hypothetical 100,000 screening population by Monte Carlo simulation. **Results:** The liquid biopsy assay that incorporated four types of cfDNA characteristics was able to identify early-stage gastric cancer patients from non-cancer individuals at an AUROC of 0.962 in the study cohort and 0.972 in the validation cohort. At a specificity of 92.1% (128/139), it achieved a sensitivity of 88.2% (97/110) in the study cohort. With this threshold, in the validation cohort, 91.5% (86/94) of healthy individuals and 91.8% (67/73) of gastric cancer patients were correctly identified. In both study and validation cohorts, the inferred probabilities of cancer showed consistent trends to increase with pathological stages in the cancer group and disease statuses in the non-cancer group. Of note, our approach detected all gastric tumors located in the cardia and fundus (100.0%, 19/19), which could be challenging for gastroscopic examination. Additionally, through in-silico simulations, we showed that our cfDNA-based non-invasive assay may detect 96.3% more gastric cancer cases than conventional gastroscopy owing to higher sensitivity and anticipated better participant compliance in a large hypothetical screening population. **Conclusions:** We introduced a liquid biopsy assay using multiple dimensions of cfDNA characteristics that could accurately identify early-stage gastric cancer from non-cancerous conditions. As a cost-effective non-invasive approach, it may provide population-wide benefits for the early detection of gastric cancer. Research Sponsor: None.

4062

Poster Session

Pembrolizumab, radiotherapy, and chemotherapy in neoadjuvant treatment of malignant esophago-gastric diseases (PROCEED): Assessment of pathologic response and toxicity in a prospective, phase II single-arm trial. *First Author: Pooja Karukonda, Duke Cancer Institute, Durham, NC*

Background: A standard treatment paradigm for locally advanced, resectable, non-metastatic esophageal or gastric adenocarcinomas (EGA) is neoadjuvant chemoradiation (CRT) followed by surgery. Historical pathologic complete response (pCR) rates after CRT with carboplatin/paclitaxel in the CROSS trial are low at 23%. Efficacy of adjuvant immunotherapy has since been shown in this patient population. The main objectives of this trial were to investigate whether neoadjuvant CRT + pembrolizumab improves pCR compared to the historical control of CRT alone, and also determine the associated acute and post-surgical toxicity of this approach. **Methods:** Single-institution, prospective phase II trial (NCT03064490) evaluating the efficacy and safety of neoadjuvant pembrolizumab + CRT followed by adjuvant pembrolizumab in patients with locally advanced operable EGA. CRT (45 Gy/25 fractions with concurrent weekly carboplatin [AUC 2] and paclitaxel [50 mg/m² of BSA]) with 3 cycles of pembrolizumab was administered as neoadjuvant therapy. Patients also received 3 cycles of adjuvant pembrolizumab after surgical resection if they did not experience ≥Grade 3 (G3) toxicity during neoadjuvant treatment. Baseline characteristics were collected. Pathologic response was scored from 0-3 per tumor regression grading. The percentage of patients with pCR (score of 0) are described. Acute toxicities are defined per CTCAE v4 and include relevant events occurring within 90 days after treatment. **Results:** Accrual is complete, with 35 patients with cT2-3N0-2M0 EGA enrolled from 10/10/2017-10/07/2022. 28/32 patients have completed neoadjuvant therapy and surgical resection. 89% of enrolled patients are male, and 94% are white. 97% have an esophageal primary, and 97% underwent R0 resection. 10/28 (35.7%; 95% CI: 17%, 53%) patients achieved a pCR. 22/32 patients have experienced treatment-related ≥G3 non-hematologic toxicity to date (94.2% G3, 5.8% G4). 18 patients experienced ≥G3 toxicity related to neoadjuvant therapy, with 53 events overall, the majority being GI (24.5%) or metabolic/nutritional disorders (24.5%). 10 patients experienced ≥G3 toxicity related to surgery, with 16 events overall, the majority being procedural complications (31.3%) and infectious disorders (31.3%). **Conclusions:** Patients undergoing neoadjuvant CRT + pembrolizumab for EGA experienced higher rates of pCR and acceptable rates of treatment-related toxicity compared to historical controls. This phase II trial demonstrates the safety and efficacy of this treatment paradigm, which warrants assessment in future prospective studies. Clinical trial information: NCT03064490. Research Sponsor: Merck.

4061

Poster Session

Induction chemotherapy plus definitive chemoradiotherapy versus chemoradiotherapy alone in esophageal squamous cell carcinoma: Long-term results and exploratory analyses of a randomized controlled trial. *First Author: Mian Xi, Department of Radiation Oncology, Sun Yat-Sen University Cancer Center, Guangzhou, China*

Background: The previous results of our trial demonstrated that the addition of induction chemotherapy (IC) prior to definitive chemoradiotherapy (CRT) failed to significantly improve response rate or 3-year survival in patients with locally advanced esophageal squamous cell carcinoma (ESCC). Here, we report the long-term results and exploratory analyses to further evaluate the therapeutic value of IC in ESCC. **Methods:** This was a single-institution, open-label, randomized, phase II trial. Patients with previously untreated, unresectable, stage II–IVA ESCC were randomly assigned in a 1:1 ratio to receive induction docetaxel (75 mg/m² on day 1) and cisplatin (75 mg/m² on day 1) every 3 weeks for two cycles, followed by concurrent CRT, or CRT alone. The primary endpoint was overall response rate at 3 months after CRT. Second endpoints were overall survival (OS) and progression-free survival (PFS). The relationship between tumor response to IC and long-term survival was analyzed as an exploratory, post-hoc analysis. Moreover, baseline tumor biopsies were evaluated by RNA-seq to identify patients who are more likely to benefit from IC. **Results:** Between May 2015 and September 2017, 110 eligible patients were randomly assigned to the IC+CRT group (n=55) or the CRT group (n=55). The overall response rate was 74.5% in the IC+CRT group versus 61.8% in the CRT group (P=0.15). At a median follow-up of 74.9 months, the 5-year OS rate was 31.8% in the IC+CRT group and 29.1% in the CRT group (P=0.68; HR, 0.91; 95% CI, 0.58–1.43). Similarly, no significant differences were identified in 5-year PFS between groups (30.5% vs. 25.5%, P=0.51; HR, 0.86; 95% CI, 0.56 to 1.34). Patients who responded to IC had significantly better survival than nonresponders. Six key genes were identified based on RNA-seq and gene expression comparison between responders and nonresponders after IC. Risk-score model was constructed by these key genes and then validated. **Conclusions:** Addition of induction docetaxel plus cisplatin before definitive CRT still failed to provide an obvious survival benefit in ESCC based on long-term follow-up. However, this strategy did result in a significantly improved survival in IC responders. Our results also revealed potential molecular biomarkers to predict who may benefit from IC. Clinical trial information: NCT02403531. Research Sponsor: None.

4063

Poster Session

Development of an artificial intelligence algorithm for adjuvant chemotherapy based on a nationwide registry of patients with gastric cancer by the Japanese Gastric Cancer Association (JGCA). *First Author: Yasuhide Yamada, National Center for Global Health and Medicine, Tokyo, Japan*

Background: Recent marked advances in machine learning have led to expectations of the clinical application of artificial intelligence (AI) to support medical care. **Methods:** A survival analysis model which consisted of 31 covariates was adopted for AI algorithms using machine learning and these were constructed using clinical data sets for training. The performance of AI algorithms was evaluated in order to determine the optimal chemotherapy including surgery alone without any adjuvant chemotherapy with the highest survival rate for each patient. This involved using clinical data for verification to compare survival of an AI-recommended treatment group, for which therapy recommended by AI was actually administered, with an AI-deprecated group, for which therapy recommended by AI was not administered. **Results:** The clinical characteristics of 23653 patients and treatment are described in the Table from 2011 to 2018 in a nationwide registry of gastric cancer patients in Japan by the Japanese Gastric Cancer Association and were made available for this study. S-1 monotherapy was used the most frequently of all adjuvant chemotherapy in this study. We used the 'restricted mean overall survival time' (RMST) of all the patients as metrics. The RMST in the AI-recommended and the AI-deprecated groups were 51.4 and 47.5 months, respectively. Patient data for the verification were matched baseline characteristics by the propensity score. This model predicted effectively overall survival after gastrectomy. The RMST of over 80 years old patients were 43.9 in the AI-recommended and 38.3 months in the AI-deprecated, respectively. This AI algorithm recommended adjuvant S-1 more frequently for patients with higher age, male, American Society of Anesthesiologists – physical status 2, Eastern Cooperative Oncology Group performance status 1, pT3/pT4, pN2/pN3, more than the upper normal limit of preoperative blood urea nitrogen, macroscopic types 2/3, differentiated adenocarcinoma, Roux-en-Y reconstruction, and Clavien-Dindo classification grade II/III. The RMST for pStage IIA/IIIB/IIIC were 55.7/53.9/50.3/45.7/42.2 months in the AI-recommended and 55.1/50.7/43.9/36.9/32.0 months in the deprecated. This AI algorithm showed a higher survival rate in pStage III patients particularly. **Conclusions:** The AI algorithm could readily be integrated into clinical practice to choose adequate adjuvant chemotherapy for each patient based on each patient's baseline data because it trained and verified the nationwide registry has good predictive performance. Research Sponsor: Cross-ministerial Strategic Innovation Promotion Program, Cabinet Office, Japan.

	No. of patients (n=23653)	%
Sex, male	16390	69.3
Age		
<70	10477	44.3
70 – 80	9602	40.6
80+	3574	15.1
pStage		
IA/IB	90/5397	23.2
IIA/IIIB	4760/3672	35.6
IIIA/IIIB/IIIC	4224/2681/1351	34.9
Adjuvant chemotherapy		
None	13614	57.6
S-1	9352	39.5
Others	697	2.9

4064

Poster Session

Efficacy and safety of camrelizumab combined with chemotherapy versus chemotherapy alone as preoperative neoadjuvant therapy for resectable locally advanced esophageal squamous cell carcinoma: Preliminary results from a multicenter, prospective, randomized controlled study. *First Author: Renquan Zhang, The First Affiliated Hospital of Anhui Medical University, Hefei, China*

Background: Camrelizumab combined with chemotherapy has a very ideal therapeutic effect and low toxicity in the treatment of solid tumors. camrelizumab plays an important role in the treatment of locally advanced esophageal squamous cell carcinoma. **Methods:** This study is a prospective, multicenter, randomized controlled study. Inclusion criteria were patients aged 18-75 years with an ECOG score of 0-1 who had not received other treatments previously and had histologically confirmed resectable locally advanced esophageal squamous cell carcinoma (clinical stages cT1-4N1-3M0 and cT3-4N0M0). Patients received camrelizumab combined with chemotherapy (albumin paclitaxel + cisplatin in chemotherapy regimen) or chemotherapy alone (albumin paclitaxel + cisplatin in chemotherapy regimen). The primary endpoints are pathological complete remission (pCR) rate and 5-year overall survival (OS). Secondary endpoints including disease-free survival rate, duration of drug treatment and adverse events and we attempt to explore the correlation between drug efficacy and PD-L1 expression. The target sample size was 400 and patients were divided into two groups according to a 1:1 ratio who were received camrelizumab plus chemotherapy and chemotherapy alone. **Results:** From January 2021 to October 2022, 243 patients with resectable locally advanced esophageal squamous cell carcinoma from four centers were enrolled. Of these, 205 (85.2%) were male and 38 (15.6%) were female. Median age was 65 years. Most patients (182, 74.9%) were in clinical stage III and had an ECOG score of 1 (185, 76.1%). 150 patients had completed all clinical trial cycles and the result showed that among 90 patients who received camrelizumab plus chemotherapy, 25 patients achieved pathological complete remission (pCR), 39 achieved major partial remission (MPR), 11 had stable disease and 1 had progressive disease, with a pCR rate of 27.8% and MPR rate of 43.3%. Among 60 patients who received chemotherapy alone, 6 patients achieved pCR, 13 patients achieved MPR, 19 patients had stable disease and 2 patients had progressive disease, with a pCR rate of 10.0% and MPR rate of 26.7%. The most common adverse events were reactive cutaneous capillary endothelial proliferation (72.1%), nausea (42%), and leukopenia (15.5%), all of which were in grade 1-2 with manageable safety. **Conclusions:** Preliminary results of this study showed that the overall efficacy of camrelizumab plus chemotherapy was better than that of chemotherapy alone and the drug was safe and reliable. In future work, we will continue to analyze the survival outcomes, drug safety and the relationship between drug efficacy and PD-L1 expression and other biomarkers. Clinical trial information: ChiCTR2000040330. Research Sponsor: None.

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Poster Session

Circulating tumor DNA as a marker of recurrence risk in locoregional esophagogastric cancers with pathologic complete response. *First Author: Eric Michael Lander, Division of Hematology/Oncology, Vanderbilt University Medical Center, Nashville, TN*

Background: Following neoadjuvant therapy and definitive surgery, up to one-third of patients (pts) with gastroesophageal adenocarcinoma with a pathologic complete response (pCR; tumor regression grade 0 [TRG0]) will recur, while up to one-half of pts with a near-pCR (TRG1) experience recurrence. Our study aims to evaluate postoperative circulating tumor DNA (ctDNA) as a prognosticator of recurrence in pts with pCR or near-pCR after curative-intent neoadjuvant chemotherapy (NAC) or chemoradiation (CRT) and surgery. **Methods:** We retrospectively identified pts from 11 institutions with stages I-III esophagogastric cancers who completed neoadjuvant therapy and had TRG0 or TRG1 scores at the time of curative-intent surgery. Postoperative plasma samples were collected for ctDNA analysis within a 16-week molecular residual disease (MRD) window after definitive surgery and serially during follow-up from 9/19/19 to 2/21/22. MRD by ctDNA was assessed using a personalized, tumor-informed ctDNA assay (Signatera mPCR-NGS assay). The primary outcome was recurrence-free survival (RFS), measured from the date of surgery to the first documented sign of radiographic recurrence. Survival analysis was performed using the maximum likelihood bias reduction method for Cox regression. **Results:** We obtained 250 blood samples from 45 pts with esophageal (N=18), gastroesophageal junction (N=17), and gastric (N=10) adenocarcinomas who received either NAC or CRT. The median follow-up for this cohort was 22.8 months (range: 0.3-81.7 months). Despite pts achieving pCR (N=12) or near-pCR (N=33), ctDNA-positivity in the 16-week MRD window (N=21) correlated with higher rates of recurrence (66.7%; 2/3) compared to the absence of ctDNA (11.1%; 2/18). Detectable ctDNA was associated with a significantly shorter RFS (HR 23.0, 95% CI 2.0-268.1; p=0.012). 35 pts had ctDNA analyzed at any post-surgical time point, where the recurrence rate was 87.5% (7/8) in ctDNA-positive pts compared to 7.4% (2/27) in ctDNA-negative pts, exhibiting a further reduction in RFS (HR 44.8; 95% CI 5.4-369.7; p<0.0001). Out of 8 ctDNA-positive pts, two (25%) converted from ctDNA-positive to ctDNA-negative with subsequent treatment. **Conclusions:** Within the subgroup of pts with esophagogastric adenocarcinoma and favorable pathologic responses (TRG 0-1) following neoadjuvant treatment, the presence of post-operative ctDNA identified pts with elevated recurrence risk. If validated in larger cohort studies, testing for ctDNA may be a useful biomarker to select pts at risk for recurrence with potential to inform prospective clinical trials for direction of adjuvant therapy. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology; U.S. National Institutes of Health.

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Poster Session

Five-year overall survival with S-1 plus docetaxel as adjuvant treatment in curatively resected pStage III gastric cancer in JACCRO GC-07. *First Author: Wataru Ichikawa, Division of Medical Oncology, Showa University Fujigaoka Hospital, Yokohama, Japan*

Background: JACCRO GC-07 is a randomized controlled trial to explore postoperative S-1/docetaxel compared to S-1 alone after D2 gastrectomy for pStage III gastric cancer (GC) patients. The second interim analysis demonstrated that the significant improvement of RFS was obtained by S-1/docetaxel compared to S-1 alone. The study was terminated by the recommendation of independent data and safety monitoring committee (Yoshida K et al. J Clin Oncol 2019; 37:1296-1304). Preplanned analysis to evaluate RFS at 3 years, the primary endpoint, was also published (Kakeji Y et al. Gastric Cancer 2022; 25:186-196). We report the 5-years follow-up data from the trial. **Methods:** Patients with pStage III GC were randomly assigned to receive either S-1/docetaxel (S-1 80-120mg/body on days 1-14 with a 7-day rest followed by docetaxel 40mg/m² on day 1 and S-1 80-120mg/body on days 1-14 every 21 days for 6 cycles followed by S-1 80-120mg/body on days 1-28 every 42 days for 4 cycles) or S-1 (80-120mg/body on days 1-28 every 42 days for 8 cycles) after D2 gastrectomy. Blocked randomisation was performed and stratified by the stage (IIIA, IIIB, IIIC) and histological type (differentiated or undifferentiated). The primary endpoint was 3y RFS and the secondary endpoints were OS, TTF and safety. This analysis presents the final preplanned assessment of outcomes after 5 years. **Results:** Of 915 randomly assigned patients, 912 patients were included in the intention-to-treat (ITT) analysis. In the final analysis, 426 recurrences and 373 deaths were confirmed among the ITT population during the median follow-up period of 63.72 months (3.52-111.87). The 5y RFS of 59.8% in the S-1/docetaxel group was significantly superior to 50.6% in the S-1 group (HR 0.726, 95% CI: 0.599-0.879, p = 0.0010) and the 5y OS was 67.9% in the S-1/docetaxel group and that of S-1 group was 60.3%, respectively (HR 0.752, 95% CI: 0.613-0.922, p = 0.0059), confirming the significant improving effect on the survival of the patient. **Conclusions:** Adjuvant treatment with S-1 plus docetaxel should be considered for patients with pStage III gastric cancer who underwent D2 gastrectomy without neoadjuvant chemotherapy. Clinical trial information: UMIN000010337. Research Sponsor: Japan Clinical Cancer Research Organization.

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Poster Session

Neoadjuvant docetaxel, oxaliplatin, and s-1 plus surgery and adjuvant s-1 for resectable advanced gastric cancer: Final survival outcomes of the randomized phase 3 PRODIGY trial. *First Author: Yoon-Koo Kang, Asan Medical Center, Seoul, Korea, Republic of (South)*

Background: The phase 3 PRODIGY study compared neoadjuvant docetaxel, oxaliplatin and S-1 (DOS) chemotherapy followed by surgery followed by adjuvant S-1 with surgery followed by adjuvant S-1 for Korean patients with resectable locally advanced gastric cancer (LAGC) (Kang et al. J Clin Oncol. 2021). The planned analysis of the primary endpoint of PRODIGY showed that the addition of neoadjuvant DOS to surgery and adjuvant S-1 improved progression-free survival (PFS). We herein report the long-term follow-up outcomes, including overall survival (OS), from this trial. **Methods:** Patients with histologically confirmed primary gastric or gastroesophageal junction adenocarcinoma with clinical T2-3N+ or T4Nany disease were enrolled from 18 Korean study sites. Patients were randomly assigned to D2 surgery followed by adjuvant S-1 (40-60 mg orally twice a day, days 1-28 q6w for eight cycles; SC group) or neoadjuvant DOS (docetaxel 50 mg/m², oxaliplatin 100 mg/m² intravenously day 1, S-1 40 mg/m² orally twice a day, days 1-14 q3w for three cycles) before D2 surgery, followed by adjuvant S-1 (CSC group). The primary endpoint was PFS. OS was the secondary endpoint. This analysis presents the final assessment of the outcomes after 5 years. **Results:** A total of 266 and 264 patients were randomly assigned to the CSC and SC arms, respectively, among which 238 and 246 patients were treated and included in the full analysis set. As of the data cut-off date (SEP-2022), the median follow-up duration of the surviving patients was 99.5 months (range, 68.6-127.7 months). As compared to SC, CSC significantly increased the OS (adjusted hazard ratio, 0.72; 95% CI, 0.54 to 0.97; stratified log-rank P=0.028) with a 5-year OS rate of 66.8% and 63.0% for the CSC and SC arms, respectively. CSC also significantly improved the PFS (adjusted hazard ratio, 0.71; 95% CI, 0.53 to 0.94; stratified log-rank P=0.019) with a 5-year PFS rate of 60.6% and 56.9% for the CSC and SC arms, respectively. **Conclusions:** The addition of neoadjuvant docetaxel, oxaliplatin and S-1 (DOS) chemotherapy, as part of perioperative chemotherapy, to surgery and adjuvant S-1 prolonged the OS and PFS of Asian patients with LAGC relative to patients treated with surgery and adjuvant S-1 alone. Neoadjuvant DOS chemotherapy should be considered one of the standard treatment options for patients with LAGC in Asia. Clinical trial information: NCT01515748. Research Sponsor: None.

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Poster Session

Neoadjuvant tislelizumab combined with chemoradiotherapy for resectable locally advanced esophageal squamous cell carcinoma (ESCC): Single arm phase II study. *First Author: Peng Jin, Department of Radiation Oncology, Shandong Cancer Hospital and Institute, Jinan, China*

Background: This study aimed to evaluate the safety and efficacy of neoadjuvant tislelizumab combined with chemoradiotherapy in patients with resectable esophageal squamous cell cancer. **Methods:** This is a prospective single-arm clinical trial. A total of 20 patients with newly diagnosed resectable esophageal cancer (cT1-2N+ / cT3-4aN0-3 MO) received 2 cycles of tislelizumab (200mg every 3 weeks for 2 cycles) concurrent with chemoradiotherapy (radiotherapy: 41.4Gy in 23 fractions; chemotherapy: Paclitaxel (Albumin bound) 100mg/m², and Cisplatin 75 mg/m² once every 3 weeks for 2 cycles.) Radical esophagectomy was performed within 4-6 weeks after neoadjuvant therapy. PET/CT was performed at baseline and before surgery. Primary endpoints included pathological response rate (pCR) and major pathological response rate (MPR), the secondary endpoints were disease free survival and safety. Exploratory endpoints include molecular imaging research and immune biomarker to further explore the factors affecting the efficacy of neoadjuvant therapy for esophageal cancer. **Results:** Twenty patients enrolled, all of whom received neoadjuvant tislelizumab combined with chemoradiotherapy. Eighteen patients underwent radical esophagectomy. One patient underwent radical chemoradiotherapy due to lymph node metastases after neoadjuvant therapy. One patient died of pneumonia before surgery. Among 18 patients who underwent surgery, RO was 100% (18/18), 9 patients achieved pCR (50.0%), and 13 patients achieved MPR (72.2%). Most of treatment-related adverse event (TRAE) were grade 1-2, and the most common TRAE was anemia (15, 75.0%). The grade 3 TRAE included 1 leukopenia (5.0%), 1 neutropenia (5.0%), 1 liver damage (5.0%), and 1 elevated cardiac troponin T (5.0%). A significant decrease in SUVmax was observed in both pCR and no-pCR patients after treatment. Baseline SUVmax in no-pCR patients tended to be higher than pCR patients(p=0.0642). Furthermore, a significant increase in circulating CD4⁺ T cells, CD4⁺ effector memory T cells (T_{EM}), and M1 were found after treatment. Among the patients with pCR, the CD4⁺ T_{EM} and cDCs after treatment were higher than those in the no-pCR patients, while Tregs and M2 were lower. **Conclusions:** Neoadjuvant tislelizumab combined with chemoradiotherapy for locally advanced ESCC has promising efficacy and good safety. Clinical trial information: NCT05323890. Research Sponsor: National Natural Science Foundation of China (82172720).

Treatment-related adverse event.					
	Any grade	Grade1-2	Grade3	Grade 4	Grade5
Leukopenia	13	12	1	0	0
Neutropenia	10	9	1	0	0
Anemia	15	15	0	0	0
Thrombocytopenia	6	5	0	1	0
LDH increased	9	9	0	0	0
Liver damage	2	1	1	0	0
Elevated Cardiac Troponin T	4	3	1	0	0
Pneumonia	1	0	0	0	1
Vomiting	2	2	0	0	0
Fatigue	2	2	0	0	0

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Poster Session

Long-term quality of life and nutritional results of stomach-preserving surgery after sentinel node evaluation in patients with early gastric cancer: A multicenter, randomized phase 3 trial (SENORITA). *First Author: Bang Wool Eom, National Cancer Center, Goyang-Si, Gyeonggi-do, South Korea*

Background: In the SENORITA trial, laparoscopic sentinel node navigation surgery (LSNNS) showed no significant difference in overall and disease specific survivals compared with laparoscopic standard gastrectomy (LSG). Here, we present the effect of stomach preservation surgery on QoL and nutritional outcomes, and identify risk factors affecting QoL in stomach preservation surgery. **Methods:** SENORITA was a prospective multicenter randomized trial. Patients diagnosed with early gastric cancer of 3 cm or less were randomly allocated (1:1) to LSNNS or LSG. The primary endpoint was 3-year disease-free survival. This analysis focuses on long-term quality of life and nutritional outcomes of patients who finally underwent stomach-preservation surgery in the LSNNS group. QoL was assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and stomach module (STO22) at 3, 12, 24, and 36 months after surgery. Linear mixed model analyses were used to evaluate differences between treatment groups. This trial is registered with ClinicalTrials.gov, NCT01804998. **Results:** From March 2013 to March 2017, a total of 580 patients were randomly assigned in the SENROTA trial. Among them, 258 patients underwent sentinel node navigation surgery and 198 finally underwent stomach preservation surgery. QoL data was available in 194 patients and compared with those of 257 patients who underwent standard gastrectomy. The stomach-preservation group had better QoL in physical function, dyspnea, and appetite loss of C30 and dysphagia, pain, reflux symptoms, eating restriction, anxiety, taste change, body image, and total score of STO22. Regarding nutritional outcomes, body mass index, hemoglobin, protein, and albumin levels were significantly higher in the stomach-preservation group than in the gastrectomy group. In multivariate analyses, tumor location (greater curvature) was an independent favorable factor affecting global health status, reflux symptoms, eating restriction, and total score of STO22 at 3 months in the stomach-preservation group. Segmental resection was a risk factor for diarrhea and eating restriction at postoperative 3 year. **Conclusions:** The stomach-preservation surgery had better long-term QoL and nutritional outcomes compared with standard gastrectomy. These findings can help decision making about treatment for patients with early gastric cancer, especially or elderly or nutritionally high risk patients. Clinical trial information: NCT01804998. Research Sponsor: This research was supported by the National Cancer Center, Republic of Korea (Grant 1110550, 1410140, 1710160, 2010150).

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Poster Session

GaEsSeer: Early detection of gastric and esophageal cancer by integrating methylation and fragmentomics signatures in cfDNA. *First Author: Yunshi Zhong, Endoscopy Center and Endoscopy Research Institute, Zhongshan Hospital, Fudan University, Shanghai, China*

Background: Esophageal and gastric cancer (EC and GC) are two common cancer types that severely impact patients' health. The 5-year survival rate for EC and GC is as low as 19% and 31%, respectively. However, early detection will significantly increase the survival rate: stage-1 EC has a 5-year survival rate of 51%, while for stage-1 GC it's 69%. Invasive screening methods, such as endoscopy and biopsy, caused low compliance. Computational tomography and carcinoembryonic antigen were limited by low sensitivity. To address this problem, we developed GaEsSeer, a non-invasive targeted-sequencing-based assay that utilizes multiple methylation and fragmentomics features of cell-free DNA (cfDNA) to accurately detect EC and GC signals in blood. **Methods:** cfDNA was tested using the GaEsSeer panel, which was developed using in-house genome-wide sequencing data on EC and GC samples, and public datasets from databases and literature. Methylation features, which was quantified as methylation haplotypes or methylation encoding score, and fragmentomics features including copy number and end motif ratio were taken for modeling. Separate sub-models were trained utilizing each type of feature, which were eventually combined via logistic regression to establish the final predicting model. **Results:** A total of 1770 participants were recruited from multiple centers. This included 787 healthy individuals, 448 cancers (209 EC, 239 GC; stage I:156, -II:120, -III:78, and -IV:58), 174 benign esophageal diseases, and 361 benign gastric diseases. For cancer detection, the methylation-only model had an AUC of 0.909 and 0.897 in training (618 total) and test sets (617 total), respectively; while the AUC of the fragmentomics-based model was 0.885 and 0.911, respectively. The combinatorial model further improved performances, which achieves an AUC of 0.940 and 0.931 in the training and test cohorts, respectively. While the specificity remained at 96.7%, GaEsSeer detected 81.1% EC and 70.3% GC cases in the test cohort. It had a sensitivity of 74.2% and 48.9% for stage-I EC and GC, respectively. GaEsSeer also has high specificities of 87.9% and 89.8% for benign esophageal and gastric diseases, respectively. Additionally, the performance of GaEsSeer was compared with known serum cancer markers such as CEA, CA19-9, and CA72-4; and the results show that it had significantly higher sensitivity than any of these serum markers (54.8% vs 6.4% when against CEA; 53.5% vs 7.1% when against CA19-9; 50% and 16.7% when against CA72-4). **Conclusions:** In this pilot study, we developed the blood-based GaEsSeer assay and a model for EC and GC detection with high accuracy by stacking multiple methylation- and fragmentomics-based submodules together. Further optimization and validation of GaEsSeer using larger prospective cohorts are needed to validate its potentials for clinical application. Research Sponsor: National Key Research and Development Program of China (2019YFC1315800).

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Poster Session

Response to programmed cell death protein 1 antibody in patients with Epstein-Barr virus-associated biliary tract cancer. *First Author: Wen-Zhuo He, Sun Yat-sen University Cancer Center, Guangzhou, China*

Background: Epstein-Barr virus-associated biliary tract cancer (EBVaBTC) has a distinct genomic landscape and increased infiltration of CD3⁺ and CD8⁺ T cells. However, the efficacy of immunotherapy in EBVaBTC remains largely unknown. The aim of this study is to assess the efficacy of programmed cell death protein 1 (PD-1) antibody in EBVaBTC. **Methods:** Consecutive patients with metastatic biliary tract cancer diagnosed at our institution from January 2017 to December 2021 were identified. In situ hybridization was performed to detect EBV. The objective response to PD-1 antibody was assessed. We also analyzed the immune microenvironment of EBVaBTC by multiplex immunofluorescence staining, and performed the proteomic characterization of EBVaBTC. **Results:** A total of 131 patients with BTC who received PD-1 antibody were identified, of which 9 (6.9%) had EBVaBTC. All EBVaBTC cases were intrahepatic cholangiocarcinoma. EBVaBTC was not associated with deficient mismatch repair but with lymphoepithelioma-like carcinoma and hepatitis B virus infection. Four (44.4%) patients achieved a partial response, and the remaining five (55.6%) patients had stable disease. The response lasted for at least 12 months in 8 (88.9%) patients with EBVaBTC, including 4 patients received PD-1 antibody monotherapy. Blood EBV-DNA was detectable in all 9 patients (100%) with EBVaBTC. Multiplex immunofluorescence staining revealed more abundant CD3⁺ and CD8⁺ T cells infiltration in EBVaBTC than that of mismatch repair deficient BTC. A total of 8,379 proteins were identified by proteomics. Comparison of EBVaBTC and paired normal tissue revealed 547 differentially expressed proteins. Enrichment analysis demonstrated that differentially expressed proteins in the EBVaBTC were associated with EBV infection and T cell activation. We also observed the expression of immune checkpoint other than PD-1, including LAG-3 and TIM-3. **Conclusions:** Identification of EBVaBTC may represent a subset of patients with promising response to immunotherapy. Research Sponsor: Natural Science Foundation of Guangdong, China.

Clinical characteristics of involved patients.				
Characteristics	EBVaBTC, n (%)	dMMR BTC, n (%)	BTC not with EBV and dMMR, n (%)	P, chi-square test
Age				0.696
>50	7 (77.8)	4 (66.7)	74 (63.8)	
<50	2 (22.2)	2 (33.3)	42 (36.2)	
Sex				0.442
Male	3 (33.3)	4 (66.7)	57 (49.1)	
Female	6 (66.7)	2 (33.3)	59 (50.9)	
Tumor origin				0.023
Intrahepatic cholangiocarcinoma	9 (100)	1 (16.7)	50 (43.1)	
Extrahepatic cholangiocarcinoma	0 (0)	2 (33.3)	19 (16.4)	
Gallbladder cancer	0 (0)	3 (50.0)	47 (40.5)	
Tumor differentiation				0.059
Well	0 (0)	0 (0)	3 (2.6)	
Moderately	3 (33.3)	0 (0)	52 (44.8)	
Poorly	6 (66.7)	6 (100)	61 (52.6)	
Histology				<0.001
Lymphoepithelioma-like	4 (44.4)	0 (0)	0 (0)	
Conventional adenocarcinoma	5 (55.6)	6 (100)	116 (100)	
HBV infection				0.01
Yes	6 (66.7)	2 (33.3)	25 (21.6)	
No	3 (33.3)	4 (66.7)	91 (78.4)	

Transarterial chemoembolization combined with lenvatinib and camrelizumab for unresectable hepatocellular carcinoma: A prospective, single-arm, multicenter study. *First Author: Zhibo Zhang, The First Affiliated Hospital of Fujian Medical University, Fuzhou, China*

Background: Conversion therapy for unresectable hepatocellular carcinoma (uHCC) has attracted increasing interest in recent years. In 2020 ASCO annual meeting, one abstract reported that the combination therapy of tyrosine kinase inhibitor and anti-PD-1 antibody could be a promising conversion therapy for patients with initially uHCC. This study aims to evaluate the efficacy and safety of transarterial chemoembolization (TACE) combined with lenvatinib and camrelizumab (TACE+LEN+CAM) as a conversion therapy for uHCC. **Methods:** This single-arm, prospective, multicenter study was conducted on patients diagnosed with HCC (with an Eastern Cooperative Oncology Group performance score (ECOG PS) of 0-1 and Child-Pugh class A) who were ineligible for surgery. Enrolled patients received camrelizumab (200 mg every 3 weeks) and lenvatinib (bodyweight $\geq$ 60 kg: 12 mg/day; < 60 kg: 8 mg/day) after TACE treatment. Surgery was performed after treatment response was assessed to meet the criteria of resection. Patients who did not meet the criteria for surgery continued to receive triple treatment until disease progression or intolerable toxicity. Primary endpoints were objective response rate (ORR) and safety. Secondary endpoints included percentage of patients amenable to surgery, the rate of radical (R0) resection, disease control rate (DCR). This study is registered with Chinese Clinical Trial Registry (ChiCTR2100050410). **Results:** Between Oct 25, 2021, and Jul 20, 2022, 55 patients were enrolled and received triple therapy (TACE+LEN+CAM). Of these, 37 (67.3%) patients had portal vein tumor thrombosis. Mean tumor diameter for all patients was 112 ± 83 mm. 52 (94.6%) patients with ≤ 2 target lesions, and 3 (5.4%) patients with > 2 target lesions. As of data cutoff on Dec 20, 2022, the median follow-up was 6.7 months (IQR 5.0-9.89). According to modified RECIST criteria, tumor response in patients included complete response to treatment in 9 patients (18.0%), partial response in 27 (54.0%), stable disease in 6 (12.0%), and progressive disease in 7 (14.0%). The ORR was 72.0%, and the DCR was 84.0%. 26 patients underwent surgery after successful conversion therapy. The MPR and pCR rates in the surgery population were 69.2% and 23.1%, respectively. The conversion rate was 55.3% and the R0 resection rate was 100%. 23 (41.8%) of 55 patients had treatment-related adverse event (TRAEs) that were grade 3-5. No grade 3-5 TRAEs occurred after surgery. **Conclusions:** The triple therapy (TACE+LEN+CAM) significantly improved ORR and the surgical conversion rate of uHCC patients with a manageable safety. Future large-scale randomised trials are warranted. Clinical trial information: ChiCTR2100050410. Research Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

Landmark analysis of OS by response status in previously treated patients (pts) with advanced hepatocellular carcinoma (aHCC): Post hoc analysis of the KEYNOTE-394 study. *First Author: Zhenggang Ren, Zhongshan Hospital, Fudan University, Shanghai, China*

Background: KEYNOTE-224 and KEYNOTE-240 landmark analyses showed that objective response (OR) in pembrolizumab (pembro)-treated pts was prognostic of longer OS after the landmark. Landmark analysis was performed using the KEYNOTE-394 study to determine whether response assessment before landmark is prognostic of longer OS after landmark time in pembro-treated pts. **Methods:** Adults with confirmed HCC, radiographic progression during or after treatment with or intolerance to sorafenib or oxaliplatin-based chemotherapy were eligible for KEYNOTE-394. Landmark analyses of OS for responders, pts with SD, and pts with other status in these analyses at 6, 12, 18, and 24 wk after randomization were performed on the pembro arm. Tumor imaging was performed every 6 wk after randomization. Responders (R) at each landmark were defined as pts with any response assessment of CR or PR before the landmark date; all other pts were defined as nonresponders (NR). SD at each landmark was defined as pts with a response assessment of SD and no better response before the landmark date. Other was defined as pts with responses of PD or a missing/not evaluable status. Response was assessed per RECIST v1.1 by blinded independent central review. HR and 95% CI for survival after the landmark are based on the Cox regression model with the Efron method for handling ties, with response status by the landmark time as a single covariate. **Results:** Median time from randomization to data cutoff date (June 30, 2021) was 33.8 mo (range, 18.7-48.8) for pembro. OS after landmark time was numerically longer for R vs NR, R vs pts with SD, and pts with SD vs pts with Other status. **Conclusions:** KEYNOTE-394 landmark analysis supports the prognostic association between OR with pembro before the landmark and OS after the landmark observed in KEYNOTE-224 and KEYNOTE-240 in previously treated pts with aHCC. Landmark analysis also suggested longer OS after the landmark for pts who achieved a better response to pembro before the landmark. Clinical trial information: NCT03062358. Research Sponsor: Merck Sharp & Dohme LLC., a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

Response to Pembro	Wk	n	OS, median (95% CI), mo	HR (95% CI)
R NR	6	19	41.8 (26.2-not reached)	0.23 (0.10-0.52)
		273	12.5 (10.8-15.8)	
R NR	12	35	40.4 (27.6-not reached)	0.22 (0.12-0.41)
		242	11.1 (9.5-14.0)	
R NR	18	41	39.1 (26.2-not reached)	0.29 (0.17-0.49)
		207	12.6 (9.7-15.3)	
R NR	24	42	37.7 (24.8-not reached)	0.32 (0.19-0.55)
		184	13.2 (10.8-15.6)	
R SD	6	19	41.8 (26.2-not reached)	R vs SD: 0.28 (0.12-0.65)
		139	20.3 (16.4-24.6)	
R SD	12	35	40.4 (27.6-not reached)	R vs SD: 0.27 (0.14-0.50)
		134	5.6 (4.5-9.0)	
R SD	18	41	39.1 (26.2-not reached)	R vs SD: 0.55 (0.41-0.73)
		122	17.3 (12.9-20.6)	
R SD	24	42	37.7 (24.8-not reached)	R vs SD: 0.32 (0.18-0.56) SD vs Other: 0.62 (0.45-0.85)
		120	4.8 (3.3-6.9)	
R SD	6	19	41.8 (26.2-not reached)	R vs SD: 0.28 (0.12-0.65)
		139	20.3 (16.4-24.6)	
R SD	12	35	40.4 (27.6-not reached)	R vs SD: 0.27 (0.14-0.50)
		134	5.6 (4.5-9.0)	
R SD	18	41	39.1 (26.2-not reached)	R vs SD: 0.55 (0.41-0.73)
		122	17.3 (12.9-20.6)	
R SD	24	42	37.7 (24.8-not reached)	R vs SD: 0.32 (0.18-0.56) SD vs Other: 0.62 (0.45-0.85)
		120	4.8 (3.3-6.9)	

Temporal patterns of immune-mediated adverse events (imAEs) with tremelimumab (T) plus durvalumab (D) in the phase 3 HIMALAYA study in unresectable hepatocellular carcinoma (uHCC). *First Author: George Lau, Humanity and Health Clinical Trial Center, Humanity and Health Medical Group, Hong Kong Special Administrative Region, China*

Background: In the Phase 3 HIMALAYA study (NCT03298451) in uHCC, STRIDE (Single T Regular Interval D) significantly improved overall survival versus sorafenib (S) and had manageable safety (Abou-Alfa et al. *NEJM Evid* 2022). STRIDE is approved for uHCC in the United States and Japan and is recommended for approval by the European Medicines Agency. In this exploratory post hoc analysis, we assessed temporal patterns of imAEs for the STRIDE regimen in HIMALAYA. **Methods:** Safety was assessed in participants (pts) who received ≥ 1 dose of STRIDE (T 300 mg [one dose] plus D 1500 mg once every 4 weeks) or S (400 mg twice daily). Treatment causality was investigator-assessed. imAEs were defined as AEs of special interest associated with drug exposure and consistent with an immune-mediated mechanism of action for which no alternate etiology was clear. Safety was summarized descriptively overall and at specific time points after the start of treatment. **Results:** In total, 388 (STRIDE) and 374 (S) pts were included in the safety analysis. Median (range) duration of exposure was 5.5 (0.4-41.9) months for STRIDE (D exposure in STRIDE) and 4.1 (0.1-38.6) months for S. Any grade treatment-related AEs (TRAEs) and Grade 3 or 4 TRAEs were less frequent for STRIDE (75.8% and 25.8%, respectively) versus S (84.8% and 36.9%, respectively). Any grade imAEs and max Grade 3 or 4 imAEs occurred in 35.8% and 12.6% of pts, respectively for STRIDE. Any grade imAEs and max Grade 3 or 4 imAEs with STRIDE occurred at all time points assessed and were most likely to occur within the first three months after treatment. For STRIDE, any grade imAEs of gastrointestinal disorders and skin and subcutaneous tissue disorders were most common within the first month after treatment (3.9% and 3.1%, respectively), whereas any grade imAEs of endocrine disorders were most common between > 1 and ≤ 2 months (6.7%). **Conclusions:** In HIMALAYA, AEs with STRIDE were manageable and generally low grade. Any grade TRAEs and Grade 3 or 4 TRAEs were less frequent for STRIDE versus S. Although imAEs with STRIDE could occur at any time, most were observed within the first three months after treatment. These findings continue to support STRIDE for the treatment of uHCC. Clinical trial information: NCT03298451. Research Sponsor: AstraZeneca.

Pts with event – n (%)	STRIDE (n=388)	STRIDE (n=388)
	Any grade	Max Grade 3 or 4
Time from first dose to imAE, months		
≤ 1	69 (17.8)	34 (8.8)
> 1 to ≤ 2	43 (11.1)	6 (1.5)
> 2 to ≤ 3	23 (5.9)	2 (0.5)
> 3 to ≤ 6	23 (5.9)	2 (0.5)
> 6	23 (5.9)	7 (1.8)

A phase 1b study of E7386, a CREB-binding protein (CBP)/ β -catenin interaction inhibitor, in combination with lenvatinib in patients with advanced hepatocellular carcinoma. *First Author: Masafumi Ikeda, National Cancer Center Hospital East, Kashiwa, Japan*

Background: E7386, a novel oral anticancer agent, inhibits β -catenin binding to its transcriptional co-activator, CBP, thus modulating Wnt/ β -catenin signaling. The objectives of the dose-escalation part in this phase 1b study were to assess safety, tolerability, pharmacokinetics (PK), biomarkers, and preliminary efficacy of E7386 combined with lenvatinib in patients with advanced hepatocellular carcinoma (HCC) or other solid tumors. Here, we present the results from the HCC subpart. **Methods:** In cycle 0, E7386 was administered orally in escalating doses once daily (QD) or twice daily (BID) for 5 or 6 consecutive days. From cycle 1 day 1, E7386 QD or BID, combined with daily oral lenvatinib (8 mg in patients with body weight of < 60 kg or 12 mg in patients with body weight ≥ 60 kg), were administered on a continuous schedule in 28-day cycles in the HCC subpart. Adverse events (AEs) were graded using CTCAE v5.0. Prophylactic antiemetics were not allowed during the dose-limiting toxicities (DLT) evaluation period but were permitted after the occurrence of nausea and vomiting. Tumor response was assessed by investigators using mRECIST (Lencioni and Llovet, 2010). PK and biomarker analyses were conducted using samples collected at defined time points. **Results:** As of the cutoff date (9 December 2022), 25 patients had been treated in the HCC subpart with E7386 dose ranges from 10 to 80 mg QD and from 60 to 120 mg BID. Among 3 patients in the E7386 120 mg BID cohort, grade 3 maculopapular rash (in 1 patient) and grade 5 acute kidney injury (in 1 patient) DLTs were observed. No DLTs were observed in other cohorts. The most common treatment-emergent AEs (TEAEs; any grade) across all cohorts were nausea (n=19; 76.0%), vomiting (n=15; 60.0%), constipation (n=13; 52.0%), palmar-plantar erythrodysesthesia syndrome (n=12; 48.0%), diarrhea (n=11; 44.0%), and proteinuria (n=10; 40.0%). The most common grade ≥ 3 TEAEs ($\geq 5\%$ of patients) were proteinuria (n=5; 20.0%) and aspartate aminotransferase level increased (n=2; 8.0%). Nausea and vomiting were well controlled by a 5HT3 antagonist. Among the 25 treated patients, 9 (36.0%) partial responses (PRs) were observed, including 3 PRs in 10 patients who had received lenvatinib as a prior regimen. C_{max} and AUC for E7386 increased with increasing E7386 dose. **Conclusions:** E7386 100 mg BID, in combination with lenvatinib (8 or 12 mg based on bodyweight) QD, was determined as the recommended phase 2 dose, and was deemed tolerable and manageable with antiemetic administration. The combination showed promising activity in patients with HCC, including those pretreated with lenvatinib. Clinical trial information: NCT04008797. Research Sponsor: Eisai Inc., Nutley, NJ, USA, and Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

4076

Poster Session

Early experience with nivolumab, gemcitabine, and lenvatinib for fibrolamellar hepatocellular carcinoma. *First Author: Paul Kent, FibroFighters Foundation, River Forest, IL*

Background: Fibrolamellar Carcinoma (FLC) is a rare deadly form of liver cancer affecting adolescents and young adults (AYA), presenting at an advanced stage, with up to 80% relapse, and no proven systemic therapies. Effective systemic therapies could convert patients to resectable or prolong progression free survival (PFS) and overall survival. Because of reported successes with nivolumab + lenvatinib (LEN) and of Gemcitabine (GEM) + LEN, and the potential synergy of GEM with NIV through elimination of myeloid suppressor cells in the tumor microenvironment, we offered NIV+LEN+GEM (NLG) to relapsed/refractory FLC patients ineligible for clinical trials. Our objective is to describe our initial experience using NLG in high risk AYA FLC patients. **Methods:** We reviewed the records of all FLC patients discussed at the FibroFighters National Tumor Board who received NLG. **Results:** Twenty-five patients (10F,15M), median age 20 (7-56), all stage IV, received a total of 322 cycles of NLG (median 11 cycles/patient, 19 neoadjuvant, 1 adjuvant, 4 both). The median number of relapses, prior systemic therapies, and surgeries were 2(0-6), 3(0-6), and 2(0-7) respectively. Most patients had failed NIV+LEN (n = 8) or GEM+LEN (n = 7) prior to starting NLG. The 17 patients with at least one evaluation had a mean follow up of 10 months (3-23) and 18 cycles (6-38) of NLG with the best response by RECIST 1.1 of CR(1), PR(6), SD(10), and PD(0), for an objective response rate (PR+CR) of 41% and disease control rate (CR+PR+SD) of 100%, and estimated best volume response median of -20% (-89%,+10%). There have not yet been any progressions. Three of the 7 who were too soon for imaging, have had resolution of ascites. The PFS and Overall Survival at 6, 9, and 12 months are: 1.0/1.0, 0.82/0.82, 0.67/0.67. Two of 17 with carcinomatosis have no evidence of disease on PET and MRI after 10 cycles. Twenty-two of 24 are continuing NLG. Nine of 16 unresectable patients became surgical candidates, of these 4 showed > 50% necrosis histologically at surgery. 13 of 17 showed necrosis on imaging. Eleven of 16 are currently in their longest PFS since diagnosis. Sixteen patients had serial tumor-informed circulating DNA (Signatera) during therapy: Five became negative (0.0 mean tumor molecules/ml plasma), and overall mean drop was -27% (-93%, +111%). No patients have stopped therapy. The most common toxicities were hypertension and fatigue in 25% and 20% respectively, grade 1 or 2. There have been no grade 3 or 4 toxicities to date. **Conclusions:** Our retrospective experience with NLG for FLC offers another potential systemic option for patients who are not surgical candidates or with multiple relapses. NLG was well tolerated and provided excellent disease control to patients with few options. Prospective trials are needed. Research Sponsor: None.

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Poster Session

Efficacy of lenvatinib (LEN) vs sorafenib (SOR) in the first-line (1L) treatment of patients (pts) with unresectable hepatocellular carcinoma (uHCC): A post hoc analysis of patients with nonviral etiology from REFLECT. *First Author: Ari David Baron, Sutter/California Pacific Medical Center, San Francisco, CA*

Background: The randomized phase 3 REFLECT trial demonstrated that LEN was non-inferior to SOR in overall survival (OS; primary endpoint) in 1L uHCC (median: 13.6 months [95% CI, 12.1–14.9] vs 12.3 months [95% CI, 10.4–13.9]) (HR, 0.92; 95% CI, 0.79–1.06). Median progression-free survival (PFS) by independent imaging review (IIR) per mRECIST was 7.3 months (95% CI, 5.6–7.5) for pts in the LEN arm and 3.6 months (95% CI, 3.6–3.7) for pts in the SOR arm (HR, 0.64; 95% CI, 0.55–0.75; $p < 0.0001$). Objective response rate (ORR) by IIR per mRECIST was 40.6% for pts in the LEN arm and 12.4% for pts in the SOR arm (odds ratio, 5.01; 95% CI, 3.59–7.01; $p < 0.0001$) [Kudo 2018, *Lancet*]. Since REFLECT, combination therapies with immunotherapy have become part of the therapeutic arsenal for the treatment of uHCC, and many studies are ongoing. Recent data suggest that viral/nonviral etiology may impact treatment outcomes [Pfister 2021, *Nature*; Rimini 2022, *ESMO Open*]. To add to the current body of evidence, this post hoc analysis evaluated efficacy in pts with nonviral etiology in REFLECT. **Methods:** In REFLECT, pts with uHCC who had not received treatment for advanced disease were randomized to LEN (12 mg/day for bodyweight ≥ 60 kg; 8 mg/day for bodyweight < 60 kg) or SOR (400 mg twice-daily) in 28-day cycles. This post hoc analysis included pts without hepatitis B or C (based on medical history) who were randomized to receive LEN or SOR. PFS, ORR (by IIR per mRECIST), and OS were analyzed. OS and PFS were estimated with the Kaplan-Meier method. **Results:** Of 478 pts randomized to LEN and 476 pts randomized to SOR, 127 and 108 pts, respectively, had nonviral etiology. Among randomized pts with nonviral etiology, median OS was 13.8 mos (95% CI, 10.5–18.7) in the LEN arm and 13.9 months (95% CI, 11.7–17.5) in the SOR arm (HR, 1.03; 95% CI, 0.75–1.43). Median PFS was 7.4 months (95% CI, 5.5–8.7) in pts randomized to LEN with nonviral etiology and 4.0 months (95% CI, 3.6–5.5) in pts randomized to SOR with nonviral etiology (HR, 0.60; 95% CI, 0.42–0.87). ORR was 39.4% (95% CI 30.9–47.9) in pts randomized to LEN with nonviral etiology and 20.4% (95% CI 12.8–28.0) in pts randomized to SOR with nonviral etiology. Fewer (n=34 [26.8%]) pts with nonviral etiology randomized to LEN received anticancer medication during survival follow-up than those randomized to SOR (n=46 [42.6%]). **Conclusions:** In this post hoc analysis, OS, PFS, and ORR in pts randomized to LEN with nonviral etiology were consistent with the overall population of pts randomized to LEN. This post hoc analysis, along with the results of the primary analysis of REFLECT [Kudo 2018, *Lancet*], demonstrates the efficacy of LEN regardless of etiology in uHCC, and supports LEN as a standard of care option for pts with 1L uHCC. Treatment efficacy by etiology should be assessed prospectively in future uHCC trials. Clinical trial information: NCT01761266. Research Sponsor: Eisai Inc., Nutley, NJ, USA, and Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

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Poster Session

An open-label, multicenter, adaptive, phase Ib/II study of QL1706 or QL1604 plus bevacizumab as first-line treatment in patients with advanced hepatocellular carcinoma. *First Author: Feng Bi, Department of Abdominal Oncology, West China Hospital of Sichuan University, Chengdu, China*

Background: Cancer immunotherapy has expanded the treatment options for advanced HCC (aHCC). Atezolizumab plus bevacizumab is approved as the standard of care for patients (pts) with aHCC. QL1706 is a novel dual immune checkpoint blockade containing a mixture of anti-PD-1 IgG4 and anti-CTLA4 IgG1 antibodies (Abs). QL1604 is a humanized mAb against PD-1. The anti-PD-1 Ab of QL1706 has the same protein sequence and was produced by using the same single clone selection method with QL1604. Here we report the safety and efficacy results from a Ph Ib/II study of QL1706 or QL1604 plus bevacizumab (beva) as first-line treatment in pts with aHCC. **Methods:** Eligible pts had histologically or clinically confirmed HCC; had BCLC stage B/C disease and Child-Pugh class A and B liver function; were systemic therapy naive; and were not suitable for radical surgery and/or locoregional therapy, or progressed after surgery and/or locoregional therapy. This study included 3 parts. Part 1 included a safety run-in phase and an expansion phase. Patients were enrolled to receive QL1706 5 mg/kg plus beva 15 mg/kg Q3W. In part 2, pts were randomized to receive QL1604 200 mg or QL1706 5 mg/kg plus beva 15 mg/kg Q3W. In part 3, pts were enrolled to receive QL1706 7.5 mg/kg plus beva 15 mg/kg Q3W. Initiation of part 3 was to be determined based on factorial analysis on the results from parts 1 and 2. Each treatment cycle lasted for 21 days. Treatment continued until disease progression or other discontinuation events. The primary endpoint was safety. Secondary endpoints included efficacy etc. **Results:** As of data cutoff (18 Nov 2022), 76 pts were enrolled in parts 1 and 2 (QL1706: 50; QL1604: 26). The baseline characteristics were balanced between the 2 groups. A total of 43 (86%) pts and 23 (88.5%) pts in QL1706 and QL1604 groups experienced TRAEs. For both groups (QL1706 vs QL1604), the most common TRAEs were platelet count decreased (26% vs 23.1%); followed by AST increased (22% vs 19.2%). A total of 17 (34%) pts and 10 (38.5%) pts in QL1706 and QL1604 groups experienced Gr $\geq$ 3 TRAEs. A total of 25 (50%) pts and 5 (19.2%) pts in QL1706 and QL1604 groups experienced irAEs. The most common irAE in the QL1706 group was rash (16%) (vs 3.8% for QL1604). A total of 8 (16%) pts and 6 (23.1%) pts in QL1706 and QL1604 groups experienced TRSAEs. In the efficacy evaluable population, the ORR was 38.3% (18/47) and 15.4% (4/26) in QL1706 and QL1604 groups. The DCR was 74.5% and 69.2% in QL1706 and QL1604 groups. The mPFS was 6.7 months (95% CI: 3.0–11.4) and 5.4 months (95% CI: 2.4–8.5) in QL1706 and QL1604 groups. The mOS was not reached. **Conclusions:** QL1706 5 mg/kg showed comparable safety profile and numerically higher ORR and longer mPFS vs QL1604 when combined with beva as first-line treatment in pts with aHCC. Ph III head-to-head clinical trial to compare QL1706 or anti-PD-1/PD-L1 Ab plus beva in this population has been planned. Clinical trial information: NCT05603039. Research Sponsor: Qilu Pharmaceutical Co., Ltd.

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Poster Session

Safety and efficacy of transarterial chemoembolization combined with tyrosine kinase inhibitors and camrelizumab in the treatment of patients with advanced unresectable hepatocellular carcinoma. *First Author: Jinpeng Li, Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, Jinan, China*

Background: Combined systemic and local therapy is a promising treatment strategy for patients with advanced hepatocellular carcinoma (HCC). Transarterial chemoembolization (TACE), tyrosine kinase inhibitors (TKI) and PD-1 antibodies are all recommended for patients with unresectable HCC (uHCC). This study was aimed to evaluate the efficacy and safety of TACE combined with TKIs and camrelizumab in the treatment of uHCC. **Methods:** In this multicenter, single-arm phase II trial (ChiCTR2000039508), patients with intermediate-stage uHCC who had a Child-Pugh score ≤ 7 and had not received prior systemic anti-cancer treatment would receive treatment with TACE followed by immunotherapy with camrelizumab 200 mg every 3 weeks plus a TKI agent selected from lenvatinib (12 mg/day for bodyweight ≥ 60 kg or 8 mg/day for bodyweight < 60 kg), sorafenib 400 mg bid or donafenib 200 mg bid until intolerable toxicity or disease progression. During the study treatment, patients assessed as eligible for resection would undergo surgery. The primary endpoint was objective response rate (ORR) per modified RECIST. Secondary endpoints included progression-free survival (PFS), disease control rate (DCR), duration of response (DOR) and overall survival (OS). **Results:** From September 2020 to November 2021, 87 patients (81 men and 6 women; median age, 56 years) were enrolled. Among them, 43 (49.4%) patients had extrahepatic metastases, and 65 (74.7%) patients had HBV infection. As of September 28, 2022, the median duration of follow-up was 13.6 (0.83–24.9) months. A total of 34 patients (39.1%) died, and the median OS was not reached. The median PFS was 10.5 months (95% CI: 7.8–13.1). The ORR rate was 71.3% (62/87), and the DCR rate was 89.7% (78/87) per mRECIST. According to RECIST version 1.1, the ORR rate was 35.6% (31/87), and the DCR rate was 87.4% (76/87). The ORR and PFS showed consistent benefits in subgroups based on ECOG score, HBV infection, baseline alpha-fetoprotein level, combined TKI, and the number of TACE treatments. Ten patients (11.5%) successfully underwent conversion therapy and all achieved R0 resection. Two patients achieved a complete pathological response (pCR) and four achieved a major pathological response (MPR). The most common AEs were hypoproteinemia (92%), elevated lactate dehydrogenase (80.5%), elevated glutamic oxaloacetic transaminase (79.3%), elevated bilirubin (78.2%), abdominal pain (62.1%), nausea (33.3%), and RCEP (26.4%). The incidence of grade 3–4 adverse reactions was 67.8%, and no treatment-related deaths occurred. **Conclusions:** TACE combined with TKI and camrelizumab showed promising clinical benefits. It can effectively control tumor progression and provide opportunities for resection with acceptable safety, which will bring great benefits to uHCC. Clinical trial information: ChiCTR2000039508. Research Sponsor: Jiangsu Hengrui Medicine.

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Poster Session

Safety and efficacy of allogeneic natural killer cells in combination with pembrolizumab in patients with chemotherapy-refractory biliary tract cancer: A multicenter open-label phase 1/2a trial. *First Author: Galam Leem, Yonsei University College of Medicine, Severance Hospital, Seoul, South Korea*

Background: This study investigated the administration of combination therapy, allogeneic natural killer (NK) cells and pembrolizumab, in the treatment of advanced biliary tract cancer to determine the safety and tolerability (phase 1), and the efficacy and safety (phase 2a). **Methods:** Forty patients (phase 1, n=6; phase 2a, n=34) were enrolled between December 2019 and June 2021. The patients were inoperable and no further conventional chemotherapy was anticipated after finishing at least one chemotherapy. The patients received 3x10⁶ NK cells/kg of highly activated allogeneic NK cells (“SMT-NK”) on weeks 1 and 2 and 200 mg of pembrolizumab (Keytruda) on week 1. No treatment was given in week 3. This 3-week schedule (1 cycle) was repeated until confirmed disease progression, intolerable adverse events (AEs), patient withdrawal of consent, or finishing the maximum treatment schedule. The tumor response was evaluated after every three cycles. **Results:** In phase 1, 4 patients (66.7%) experienced 7 AEs, but no severe AEs directly related to the combination of the two drugs was observed. In phase 2a, 126 AEs occurred in 29 patients (85.3%). Severe AEs (≥ grade 3) were reported in 16 patients (47.1%). No dose limiting toxicity was reported. The overall response rate (ORR) was 17.4% in the full-analysis set and 50.0% in the per-protocol set. **Conclusions:** SMT-NKs plus pembrolizumab resulted in no severe AEs directly related to the drug combination. The combination therapy also exerted antitumor activity with improved efficacy compared to recent monotherapy with pembrolizumab in patients with advanced biliary tract cancer. A multi-center, randomized, placebo-controlled, open-label, phase 2b clinical trials to evaluate the antitumor activity of combination therapy of SMT-NKs and pembrolizumab versus pembrolizumab monotherapy in patients with advanced biliary tract cancer is now ongoing with the aim of enrolling 128 patients (ClinicalTrials.gov identifier: NCT05429697). To date, 38 patients have been enrolled and randomly assigned to each group. Within the median follow up period of 5.3 months, the disease control rate (DCR, complete response + partial response) was 27.2% in the combination therapy of SMT-NKs and pembrolizumab group, and 7.1% in the pembrolizumab monotherapy group. The ORR was 54.5% in the combination therapy group and 42.9% in the monotherapy group. So far, no severe drug-related AEs was reported. Clinical trial information: NCT03937895. Research Sponsor: SMT Bio Co.

4082

Poster Session

Tislelizumab (TIS) versus sorafenib (SOR) in first-line (1L) treatment of unresectable hepatocellular carcinoma (HCC): The RATIONALE-301 European/North American (EU/NA) subgroup. *First Author: Arndt Vogel, Hannover Medical School, Hannover, Germany*

Background: HCC is one of the most commonly diagnosed cancers globally. Most cases occur in Asia, although a number of patients (pts) are affected in Europe and North America. In the phase 3, open-label RATIONALE-301 trial (NCT03412773), TIS, a PD-1 inhibitor, showed non-inferior overall survival (OS) versus SOR (hazard ratio 0.85, 95% CI: 0.71, 1.02), and a favorable safety profile, in 1L treatment of pts with unresectable HCC. Here, efficacy and safety of TIS versus SOR in the RATIONALE-301 EU/NA subgroup were compared with the overall population (OP). **Methods:** Systemic therapy-naïve adults with histologically confirmed HCC were randomized (1:1) to receive TIS (200 mg IV Q3W) or SOR (400 mg orally BID) until disease progression, intolerable toxicity, or withdrawal. The primary endpoint was OS; secondary endpoints included objective response rate (ORR), progression-free survival (PFS), and duration of response (DoR) by blinded independent review committee per RECIST v1.1, and safety. **Results:** In the EU/NA subgroup (172/674 pts randomized), at data cutoff (July 11, 2022), median (m) OS follow-up was 37.9 months (mo) (TIS) vs 38.5 mo (SOR). At baseline, fewer pts in the EU/NA subgroup had Barcelona Clinic Liver Cancer (BCLC) Stage C disease (70% vs 78%) and extrahepatic spread (51% vs 62%), and more had a non-viral etiology (60% vs 24%) or underlying HCV infection (28% vs 13%) than in the OP, respectively. Distribution of other baseline characteristics was generally similar between the EU/NA subgroup and the OP. Efficacy data in the EU/NA subgroup were consistent with the OP. Numerically longer mOS and mDoR, higher ORR, and similar mPFS were observed with TIS versus SOR in the EU/NA subgroup. In the EU/NA safety population, incidence of ≥grade 3 treatment-emergent adverse events (TEAEs; 46% vs 66%), ≥grade 3 treatment-related TEAEs (TRAES; 17% vs 50%), and TRAES leading to discontinuation (9% vs 15%) was lower with TIS versus SOR, respectively, similar to the OP. **Conclusions:** In the RATIONALE-301 EU/NA subgroup, mOS of TIS was non-inferior versus SOR, consistent with the findings from the OP. Numerically longer mOS and mDoR, and a higher ORR was seen with TIS versus SOR in the EU/NA subgroup, which had a higher rate of pts with non-viral etiology and a slightly lower number of pts with advanced-stage disease (BCLC Stage C) compared with the OP. Clinical trial information: NCT03412773. Research Sponsor: BeiGene, Ltd.; This study was sponsored by BeiGene, Ltd. Medical writing support, under the direction of the authors, was provided by Adeline Lum Nde, PhD, of Ashfield MedComms, an Inizio company, and was funded by BeiGene, Ltd.

	EU/NA subgroup		OP	
	TIS (n=89)	SOR (n=83)	TIS (n=342)	SOR (n=332)
mOS, mo (95% CI)	18.3 (11.0, 26.6)	13.7 (8.5, 19.0)	15.9 (13.2, 19.7)	14.1 (12.6, 17.4)
ORR, % (95% CI)	19.1 (11.5, 28.8)	2.4 (0.3, 8.4)	14.3 (10.8, 18.5)	5.4 (3.2, 8.4)
mDoR, mo (95% CI)	36.1 (10.1, NE)	9.1 (5.5, NE)	36.1 (16.8, NE)	11.0 (6.2, 14.7)
mPFS, mo (95% CI)	3.7 (2.2, 4.3)	3.9 (2.2, 6.1)	2.1 (2.1, 3.5)	3.6 (2.2, 4.1)

Intent-to-treat analysis set; data cutoff: July 11, 2022.
CI, confidence interval; NE, not evaluable.

4081

Poster Session

Economic evaluation for the US of durvalumab plus gemcitabine and cisplatin (DGC) in advanced biliary tract cancer (BTC). *First Author: Osama Aqel, Center for Health Outcomes and Pharmacoeconomic Research, University of Arizona, Tucson, AZ*

Background: BTCs are a group of relatively rare malignancies comprised of intrahepatic cholangiocarcinoma (CCA), extrahepatic CCA, and gallbladder cancer. The first-line standard of care of gemcitabine and cisplatin (GC) has remained unchanged for the past decade, highlighting the need for novel therapies. The TOPAZ-3 trial demonstrated improved progression-free (PFS) and overall survival (OS) with durvalumab added to GC. This trial-based economic evaluation estimated the cost-effectiveness/utility of DGC versus GC from a US payer perspective. **Methods:** A three state partitioned survival model (Progression-free, Progressed, Death) was developed to compare costs and overall survival outcomes associated with both treatments. PFS and OS curves were digitized, and parametric functions fitted. A 5-year time horizon with a 3% discount rate/year was considered. Costs of treatment (average sales price), administration, and monitoring parameters were sourced from Centers for Medicare & Medicaid Services databases; costs of adverse event management (grade 3/4 with rate ≥ 5%) were sourced from prior BTC economic evaluations. Life years (LY), quality adjusted life years (QALY), incremental cost-effectiveness and utility ratios (ICER/ICUR) were estimated in a base case (BCA) and probabilistic sensitivity analyses (PSA). A cost-effectiveness acceptability curve (CEAC) was plotted to determine the probability of either treatment being cost-effective over the other at different willingness to pay (WTP) thresholds. **Results:** Exponential regression was used to extrapolate DGC and GC survival curves. As shown in the table, the BCA (PSA) shows an incremental cost of DGC over GC of \$131,350 (\$131,212), incremental LY of 0.38 (0.38), and incremental QALY of 0.26 (0.28). The BCA and (PSA) ICERs reveal an additional 345,658 (345,295) per LY gained (g) and an additional 505,192 (468,614) per QALY. The CEAC curve shows that DGC treatment has a 50% probability of being cost-effective at a WTP threshold value of \$25,000 and 100% probability at a threshold of 1,375,000 or above. **Conclusions:** This economic evaluation demonstrates that, in the setting of advanced BTC, DGC is associated with a slight improvement in LY and QALY, yet at a marked incremental cost, requiring a very high WTP threshold. Research Sponsor: None.

BCA (PSA).			
Cost	GC \$15,716 (\$15,812)	DGC \$147,066 (\$147,024)	Difference \$131,350 (\$131,212)
LY	1.07 (1.07)	1.45 (1.45)	0.38 (0.38)
QALY	0.74 (0.77)	1.00 (1.05)	0.26 (0.28)
ICER	\$345,658/LYg (\$345,295/LYg)		
ICUR	\$505,192/QALYg (\$468,614/QALYg)		

Interpretation of ICER and ICUR: incremental cost to gain resp. 1 LY or 1 QALY.

4083

Poster Session

Impact of risk factors on overall survival (OS) in patients (pts) with unresectable hepatocellular carcinoma (HCC) treated with first-line (1L) tislelizumab (TIS). *First Author: Masatoshi Kudo, Kindai University Faculty of Medicine, Osaka, Osaka, Japan*

Background: TIS is a monoclonal antibody with high affinity and specificity for programmed cell death protein 1. In the phase 3 RATIONALE-301 trial (NCT03412773), TIS demonstrated non-inferior OS versus sorafenib (SOR) as 1L monotherapy for unresectable HCC (median [m] OS 15.9 [TIS] vs 14.1 [SOR] months [mo]; hazard ratio [HR] 0.85), with a favorable safety profile. Certain biomarkers are potential prognostic factors and may impact OS in 1L treatment of unresectable HCC; this exploratory analysis examined the effect of albumin-bilirubin (ALBI) grade, platelet count, platelet-lymphocyte ratio (PLR), and neutrophil-lymphocyte ratio (NLR) as predictors of OS in RATIONALE-301. **Methods:** Systemic therapy-naïve adults with histologically confirmed HCC (Barcelona Clinic Liver Cancer Stage C or Stage B that was not amenable to or progressed after loco-regional therapy; Child-Pugh A), with ≥1 measurable lesion per RECIST v1.1, and an ECOG performance status ≤1 were randomized 1:1 to receive TIS (200 mg IV Q3W) or SOR (400 mg orally BID) until disease progression, intolerable toxicity, or withdrawal. The primary endpoint was OS. **Results:** Overall, 674 pts were randomized (TIS n=342; SOR n=332). At data cutoff (July 11, 2022), minimum study follow-up was 33 mo. Demographic and baseline characteristics for biomarkers were generally balanced across arms. Numerically longer (≥2 mo) mOS was observed in biomarker subgroups ALBI grade 1 vs 2 and NLR ≤3 vs >3 with TIS or SOR, and PLR ≤141 vs >141 with TIS. Both platelet count threshold subgroups were accompanied by a smaller difference (<2 mo) in mOS between biomarker cutoffs, which may indicate limited prognostic value for this biomarker. TIS also demonstrated numerically longer OS versus SOR in the same subgroup categories: ALBI grade 1, PLR ≤141, and NLR ≤3. **Conclusions:** This analysis suggests that ALBI grade, PLR, and NLR could have prognostic value for OS, irrespective of treatment. TIS demonstrated numerically improved mOS compared with SOR for PLR ≤141 and NLR ≤3, suggesting higher benefit for pts with a more favorable balance between systemic inflammation and immunity. Clinical trial information: NCT03412773. Research Sponsor: BeiGene, Ltd.; This study was sponsored by BeiGene, Ltd. Medical writing support, under the direction of the authors, was provided by Adeline Lum Nde, PhD, of Ashfield MedComms, an Inizio company, and was funded by BeiGene, Ltd.

	No. events/ No. pts	HR for death (95% CI)	Median OS (mo) (95% CI)	
			TIS	SOR
ALBI grade				
≥2	156/180	0.84 (0.61, 1.16)	9.5 (7.2, 10.8)	9.1 (6.2, 13.1)
1	340/482	0.85 (0.69, 1.06)	19.9 (15.9, 24.2)	16.9 (13.7, 19.8)
Platelet count				
>150K	281/378	0.84 (0.66, 1.06)	14.9 (11.0, 19.8)	13.5 (11.6, 18.4)
≤150K	215/284	0.83 (0.63, 1.08)	16.6 (13.5, 22.7)	14.2 (11.6, 19.0)
PLR				
>141*	204/264	0.90 (0.68, 1.19)	10.5 (7.7, 16.5)	13.1 (8.9, 16.0)
≤141	292/398	0.79 (0.63, 1.00)	19.4 (15.2, 24.0)	14.5 (13.1, 19.2)
NLR				
>3	198/249	0.98 (0.74, 1.30)	9.8 (7.4, 12.9)	13.1 (8.7, 14.3)
≤3	298/413	0.74 (0.59, 0.93)	20.9 (15.9, 25.3)	15.2 (13.2, 19.2)

No., number. Intent-to-treat analysis set.
*Threshold used in RATIONALE-208.

4084

Poster Session

A novel patient-centric longitudinal data registry platform to generate insights into real-world cholangiocarcinoma (CCA) clinical practice. *First Author: Amanda Nottke, Invitae, San Francisco, CA*

Background: Treatment of advanced CCA has changed dramatically over the past five years with the advent of molecularly targeted therapy, now approved in the 2nd line and beyond. However, real world utilization of molecular profiling and targeted therapy is still unknown and these data are critical to empower treatment decision-making. **Methods:** In 2019, the Cholangiocarcinoma Foundation (CCF) and Ciitizen (a wholly owned subsidiary of Invitae Corporation) collaboratively launched a registry platform that directly consents patients and collects comprehensive medical records. De-identified data including clinical characteristics, molecular testing, interventions, and outcomes are extracted and standardized for research use. The data is longitudinal with regularly planned updates; registry participants can be re-engaged to obtain additional data and communicate tailored insights. **Results:** We quantified the rate of molecular testing, the presence of targetable biomarkers, and the utilization and outcomes on matched targeted therapies for 372 individuals with CCA. 328 (88.2%) individuals had molecular testing, with the identified targetable mutations and matched therapies reported. Of 328 individuals who had molecular testing, 111 (33.8%) individuals had one or more targetable mutations (116 mutations total). Only 46% (51) of individuals with targetable mutations received targeted therapy. Of the 54% (60) individuals with targetable mutations that did not receive any matched therapy, the majority (61.7%, 37) were in early disease or first line of treatment and therefore not yet eligible for targeted therapy. These individuals will be informed that based on their molecular profile, a targeted therapy may be an option, and suggest they discuss with their treating physician. **Conclusions:** A novel prospectively-maintained database registry for CCA has been formed in collaboration between a patient advocacy organization (CCF) and industry (Invitae). Prevalence of actionable biomarkers was higher than historically expected and may reflect patient utilization bias of the registry platform. Molecular profiling and access to targeted therapeutics remains suboptimal at this time in CCA. Future directions for the registry include identifying and targeting disparities in care and supporting biopharmaceutical development and regulatory decisions. Research Sponsor: Invitae Corporation.

Biomarker	Evaluable Cohort (n=328)	# (%)	# Not Receiving Matched Therapy	# Receiving Matched Therapy	Matched Therapy Out- comes (mean no. days; #)
IDH1 R132	45 (13.7%)	28	17	ToT: 190 (16) TiP: 158 (9)	
FGFR2 Fusion / Rearrangement	34 (10.4%)	15	19	ToT: 319.4 (19) TiP: 367.5 (10)	
MSI-H / dMMR / TMB-H	25 (7.6%)	12	13	ToT: 368.4 (13) TiP: 210.6 (5)	
HER2 Positive / Amplified	9 (2.7%)	7	2	ToT: 219 (2) TiP: 499.5 (2)	
BRAF V600E	3 (0.9%)	2	1	ToT: 32 (n=1) TiP: 114 (n=1)	

ToT: Time on Treatment; TiP: Time to Progression.

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Poster Session

Sintilimab plus gemcitabine and cisplatin as a first-line treatment for patients with advanced biliary tract cancer: A biomolecular exploratory, phase II clinical trial. *First Author: Zhen-gang Yuan, Department of Oncology, Eastern Hepatobiliary Surgery Hospital, Shanghai, China*

Background: The prognosis of biliary tract cancer (BTC) remains unsatisfactory. Thus, this study aimed to determine the efficacy, safety, and predictive biomarkers of the immune checkpoint inhibitor sintilimab in combination with gemcitabine and cisplatin (GemCis) in advanced BTCs. **Methods:** In this single-arm, phase II study (Trial registration number: ChiCTR2000036652), gemcitabine (1000 mg/m²) plus cisplatin (25 mg/m²) were administered on days 1 and 8, respectively, while 200 mg sintilimab was administered on day 1 of each 21-day cycle for 6–8 weeks, followed by sintilimab alone up to 2 years. The primary endpoint was overall survival (OS). The second endpoints were objective response rate (ORR), progression-free survival (PFS), and disease control rate, assessed using RECIST V.1.1. Multiomics biomarkers associated with clinical response were assessed as exploratory objectives. **Results:** Thirty patients were enrolled between August 2020 and May 2022. The median follow-up duration, OS, and PFS were 12.3 months (95% confidence interval [CI]: 9.1–16.0), 15.9 months (95% CI: 8.6–not reached), and 5.1 months (95% CI: 4.3–8.7), respectively. Here, 36.7% of patients were found to achieve an objective response. The most common grade 3 or 4 treatment-related adverse events were thrombocytopenia (33.3%), with no reported deaths nor unexpected safety events. Biomarker analysis indicated that patients with homologous recombination repair pathway gene alterations (median, PFS: 9.8 vs. 4.5 months, $p = 0.023$; OS: NR vs. 9.0 months, $p = 0.014$; ORR: 77.8% vs. 19%, $p = 0.004$) or loss-of-function mutations in chromatin remodeling genes (median, PFS: 8.7 vs. 4.2 months, $p = 0.021$; ORR: 63.6% vs. 21.1%, $p = 0.046$) presented better tumor response and survival outcomes. Furthermore, transcriptome analysis of the tumor immune microenvironment revealed a markedly longer PFS, and tumor response were associated with higher expression of 3-gene effector T cell signature (median, PFS: 7.8 vs. 4.3 months, $p = 0.02$; ORR: 64.2% vs. 7.1%, $p = 0.004$) and 18-gene inflamed T cell signature (median, PFS: 8.6 vs. 4.3 months, $p = 0.01$; ORR: 64.2% vs. 7.1%, $p = 0.004$). Moreover, our findings highlighted the adverse predictive value of mast cells in immuno-chemotherapy for BTCs for the first time. **Conclusions:** Sintilimab plus GemCis displayed a promising antitumor activity and acceptable safety profile as a first-line treatment in patients with advanced BTC. Multiomics potential predictive biomarkers are identified and warrant further verification. Clinical trial information: ChiCTR2000036652. Research Sponsor: None.

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Poster Session

Liquid-biopsy detection of FGFR2 and other actionable rearrangements in GI malignancies. *First Author: Pashtoon Murtaza Kasi, Weill Cornell Medicine, Englander Institute of Precision Medicine, New York Presbyterian Hospital, New York, NY*

Background: Actionable rearrangements (RE) represent an emerging therapeutic target for GI malignancies. However, there remains uncertainty whether liquid biopsy (LBx) assays testing circulating tumor DNA (ctDNA) can detect RE with the same fidelity as tissue biopsy. Here we report the performance of ctDNA-based comprehensive genomic profiling (CGP) for the detection of RE leveraging an FDA-approved >300-gene platform, with a focus on data from patients with GI malignancies. **Methods:** An institutional research database of clinical CGP results for tissue biopsy (TBx, FoundationOneCDx) and LBx (FoundationOneLiquid CDx) from patients with cancers of the GI tract was reviewed. Sensitivity for FGFR2 RE was studied in patients with cholangiocarcinoma (CCA) or carcinoma of unknown primary (CUP) and both TBx and LBx CGP available. **Results:** Across 7870 GI LBx, 1094 predicted pathogenic RE were detected in 826 cases (10%) including 283 oncogenic kinase RE, 686 inactivating RE, and 125 other gain-of-function RE. FGFR2 RE was the most frequently rearranged gene, enriched in CCA (4.4%, 37/833) and stomach (3.0%, 11/368). EGFR RE (38) occurred across 6 cancer types and included 8 fusions, 15 c-terminal truncations, 4 intragenic deletions/inversions, and 3 kinase domain duplications. BRAF RE (31) were detected among in colorectal (22) and pancreas (9) cases. LBx detected 44 exon 3 skipping (protein stabilizing) RE in CTNNB1 (beta-catenin) across all samples. Other frequent activating RE were detected in MYC (36), FGFR3, RET, ROS1 (21 each), and ALK (13). Potentially targetable inactivating RE were detected in BRCA1 (28), ARID1A (24), STK11 (22), PTEN (17), TSC2 (14), and BRCA2 (8). Focusing on CCA, FGFR2 RE were more prevalent in cases with elevated ($\geq 1\%$) ctDNA tumor fraction (TF, 26/342, 7.6%), matching the prevalence in TBx (7.8%, 505/6,492) with a similar spectrum of fusion partners seen for both TBx and LBx (30% BICC1, 70% rare for both). In 13 CCA/CUP patients positive for FGFR2 RE by TBx, LBx detected 12 (92%) including 8 different fusion partners; the false negative case had TF <1%. In 11 CCA LBx samples with FGFR2 resistance mutations detected, LBx CGP successfully detected a driver FGFR2 RE in 10 and driver C382R mutation in 1. **Conclusions:** Rearrangements are represented across GI malignancies, including many that result in known oncogenic drivers that may be targetable with available therapies. We observe reliable detection of FGFR2 fusions in ctDNA, in contrast to some prior publications. ctDNA represents a pragmatic analyte for detection of rearrangements and other actionable alterations, offering timely result return when tissue is inadequate or unavailable. Research Sponsor: Foundation Medicine Inc.

	CCA	%	Colorectal	%	Stomach, esophagus	%	Other	%
N	833		2891		911		3235	
Any pathogenic RE	132	16	406	14	209	23	239	7
FGFR2 RE	37	4.4	8	0.3	16	1.8	8	0.2
BRAF RE	0	0.0	22	0.8	0	0.0	8	0.2
EGFR RE	2	0.2	13	0.4	7	0.8	3	0.1
RET/ROS1/ALK RE	2	0.2	27	0.9	8	0.9	10	0.3
FGFR3 RE	3	0.4	10	0.3	2	0.2	4	0.1

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Poster Session

Phase II clinical trial of olaparib plus pembrolizumab in the treatment of patients with advanced biliary tract cancer. *First Author: James O'Bryan, MedStar Georgetown University Hospital, Washington, DC*

Background: Over 20% of biliary tract cancers (BTCs) carry mutations in homologous recombination DNA damage repair (HR-DDR) pathways. The PARP inhibitor olaparib (O) blocks tumor DNA repair and may induce response in BTCs with such mutations. Furthermore, HR-DDR mutations may engender neoantigens that improve response to immune checkpoint inhibitors. We propose that treatment with O and the anti-PD-1 monoclonal antibody pembrolizumab (P) will produce a durable anti-tumor response to BTC, especially in patients with HR-DDR mutations. **Methods:** Consent for participation was obtained. Eligibility criteria included age > 18 years with an ECOG score of ≤ 1 and a histologic diagnosis of advanced or metastatic BTC with progression of disease (PD) on prior first-line therapy. Treatment featured oral O (300 mg twice daily) plus intravenous P (200 mg every 3 weeks). Response was measured radiographically using RECIST 1.1 guidelines. The primary endpoint was overall response rate (ORR), with the alternative hypothesis that O + P would improve ORR compared to historical controls (versus the null hypothesis of no improvement). Type I and II error rates were set at 5% and 15%, respectively. Simon's optimal two-stage design was used. Planned sample size was 13 patients in the first stage. Continuation to the second stage would only occur if ≥ 3 patients demonstrated response. The second stage was planned to include 20 additional patients (N = 33 total), which was based on the number needed to demonstrate an improvement in ORR from 17.5% in historical controls to at least 35.0%. **Results:** Of 21 eligible patients, 14 were accrued between June 2020 and March 2022, and 13 were evaluable for efficacy. Patients had a median age of 63 years, were primarily female (71%), Caucasian (50%), and with metastatic disease (93%). Patients received a mean of 6.5 cycles of therapy. Best treatment response included partial response (N = 2), stable disease (N = 5), and PD (N = 6). The ORR was 15.3% (95% CI = 0.02–0.45). Of the partial responders, 1 patient achieved a duration of response of 8 months (mos), and 1 has ongoing response at 24 mos. Median (med) time to progression was 7.7 mos (95% CI = 1.2–9.3), med progression free survival was 5.5 mos (95% CI = 1.2–7.7), and med overall survival was 11.9 mos (95% CI = 5.5–15.4). Most patients (64%) developed at least one treatment-related adverse event (trAE). Grade 3 trAEs were experienced in 5 patients (36%) and included anemia (N = 3), diarrhea (N = 1), and transaminitis (N = 1). **Conclusions:** While O + P has acceptable safety and toxicity, the study did not achieve significant improvement in the primary endpoint. However, the two patients who demonstrated durable treatment response were found to have HR-DDR tumor mutations (including *RAD51*, *ATM*, and *BRCA2*), necessitating further research into the efficacy of O + P for patients with similar tumor genomes. Clinical trial information: NCT04306367. Research Sponsor: Merck & Co.

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Poster Session

Characterizing *KRAS* allele variants within biliary tract cancers. *First Author: Gordon Taylor Moffat, Department of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, ON, Canada*

Background: Biliary tract cancers (BTC) are aggressive malignancies with a poor 5-year survival rate and growing incidence globally. *KRAS* mutations (mut) in BTC are associated with a poor prognosis; however, PD-L1 inhibition with Durvalumab may lead to an improved survival with *KRAS* mut (TOPAZ-1 trial). It is important to understand the genomic landscape and immunophenotype of *KRAS* mut in BTC given the advent of immunotherapeutics and small molecular inhibitors targeting *KRAS* mut. **Methods:** A retrospective pooled analysis was performed from the following patient databases: Princess Margaret Cancer Centre, MD Anderson Cancer Center, Foundation Medicine, along with the publicly accessible cBioPortal for Cancer Genomics that includes the American Association for Cancer Research Project Genie cancer registry of real-world data assembled between 19 leading international cancer centers. Any overlapping cases were excluded. Patients included had a diagnosis of a BTC and completed molecular testing from January 2017 to December 2022. Cohort demographics, *KRAS* allelic variants, concurrent genetic aberrations, and immune biomarkers (PD-L1, TMB, MSI and gLOH) were summarized. Log-rank, Wilcoxon, and Kaplan-Meier tests were conducted for survival analysis. **Results:** 5,813 BTC patients were included, and 1000 patients (17.2%) had a *KRAS* mutation. The prevalence of *KRAS* mut was higher in extra-hepatic cholangiocarcinoma (EH-CCA) (36.1%) and perihilar (PH)-CCA (28.6%) than in intra-hepatic (IH)-CCA (11.82%) and gallbladder cancer (GBC) (7.6%). The most common *KRAS* allelic variant was G12D, and the most common co-mutation was TP53, except in PH-CCA, which was G12V and SMAD4, respectively. In this cohort, race was primarily White (73%). The most prevalent variant in North America was G12D, while G12V and Q61H were more prevalent with genomic African American and genomic East Asian descent, respectively. For patients with *KRAS* mut, GBC had the most PD-L1 high positivity (17%) compared to IH-CCA (7%) and EH-CCA (3%), along with the most MSI-H phenotypes and the highest mean and median TMB compared to other sites, especially in G12V and Q61H variant patients. Genomic loss of heterozygosity was low among all groups. In the survival analysis, patients with the G12V allele subtype had the lowest OS at 17.8 months, followed by Q61H (22.8 months) and G12D (25.1 months) ($p = 0.022$). Survival analysis with *KRAS* co-mut (TP53, SMAD4, CDK2NA, or additional *KRAS* mut) was not significant ($p = 0.7$). In a co-variance analysis of *KRAS* variants and tumour site, there was no difference in IH-CCA and GBC but lower OS in Q61H variants in PH-CCA and G12V variants in EH-CCA ($p = 0.0081$). **Conclusions:** This large series adds to the growing body of comprehensive genomic and immune landscape data of *KRAS* mut in BTC and will be of value in planning specific therapies in this heterogeneous group. Immune profiling studies are ongoing to further describe the immunophenotype of this subset. Research Sponsor: None.

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Poster Session

Trastuzumab (T) plus gemcitabine-cisplatin (GC) for treatment naïve HER2 positive biliary tract adenocarcinomas (BTC): A multicentre open-label, phase II study (TAB). *First Author: Vikas S. Ostwal, Tata Memorial Hospital (HBNI), Mumbai, India*

Background: HER2 over-expression or amplification is seen in 4%-16% of BTCs and is a therapeutic target of interest. Gemcitabine-cisplatin (GC) is one of the standard regimens of choice in advanced BTCs. We aimed to evaluate the clinical activity of GC plus anti-HER2 antibody trastuzumab as initial treatment in HER2-positive BTC. **Methods:** This study was an investigator-initiated, open-label, single-arm, multi institutional, phase II trial in patients (pts) aged 18 years or older with HER2-positive (defined as IHC 3+ or IHC 2+ and FISH positive), treatment naïve BTCs. Patients received GC (Gem 1000 mg/m² IV and Cisplatin 25mg/m² IV on day 1 and 8, q 3 weeks) combined with Trastuzumab at 8mg/kg as initial dose followed by 6mg/kg q 3-weekly till disease progression (PD) or unacceptable toxicities. The primary end-point of the study was an improvement in 6-month progression free survival (PFS) from 40% (historical cohort) to 60% in the study arm. Next generation sequencing to evaluate HER2 and other mutations was conducted on the tissue samples of the patients screened for this study. **Results:** From March 2020 to August 2022, of the 876 patients were screened for HER2 status, 118 (13.4%) were found to have HER2 positive status and 90 of them were enrolled into the study. A majority of patients had GBC (95.6%) and at-least 2 sites of metastatic disease beyond primary (77.8%). With a median follow up of 8.5 months, 72 patients had PD and the median PFS was 7.95 months (95% CI: 6.84 - 9.06; median overall survival (OS) was 9.95 months (95% CI: 9.25 - 10.66). Partial responses (PR) were seen in 8 patients (8.9%) and 61 had stable disease (67.7%) for a disease control rate of 76.6%. Common chemotherapy-related grade 3 or 4 adverse events were anemia [26 (28.9%)], neutropenia [18(20%)] and thrombocytopenia [8(8.9%)] while one patient has Trastuzumab related asymptomatic fall in cardiac ejection fraction ($>=10\%$). The presence of isolated TP53 mutations predicted for inferior PFS compared to patients with other mutations (TERT promoter, HER2, PIK3CA etc) or no detected mutations (6.51 months vs. 12.02 months vs. 10.58 months; $p<0.001$). **Conclusions:** The combination of GC and trastuzumab shows near doubling of survival in treatment naïve HER2 positive BTC in a prospective manner for the first time and sets the stage for a larger phase III trial with the combination. Evaluating mutations like TP53, HER2, TERT promoter and PIK3CA along with HER2 testing could be considered as a preferred modality to select these patients for anti HER2 therapy. Clinical trial information: CTR1/2019/11/021955. Research Sponsor: Educational grants to the institute from redxy's lab pvt ltd for this study.

Mutational spectrum	Individual mutations	Frequency (%)	Median PFS (range)	p value
Multiple mutations	CDKN2A	1 (1.1)	12.02 (9.3 - 14.8)	<0.001
	CTNNB1	2 (2.2)		
	ERBB2	9 (10)		
	FGFR2	1 (1.1)		
	PIK3CA	5 (5.6)		
	TERT promoter	6 (6.7)		
	No mutations	12 (13.3)		
Isolated TP53 mutations	Isolated TP53 mutation	24 (26.7)	10.58 (5.37 - 15.79) 6.51 (5.9 - 7.25)	

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Poster Session

Individual patient-level data validation of surrogate and modified endpoints for immunotherapy in advanced hepatocellular carcinoma: Post-hoc analysis of IMbrave150 and real-world observations. *First Author: Mir Lim, UT Southwestern Medical Center, Dallas, TX*

Background: Immune checkpoint inhibitors (ICIs) have become the preferred treatment for advanced hepatocellular carcinoma (HCC). Surrogate endpoints including overall response rate (ORR) and progression-free survival (PFS) are preferred outcome measures in early-phase trials. However, ICIs can induce atypical patterns of response and progression, calling into question the validity of surrogate endpoints as predictive of overall survival (OS) benefit. We performed a post-hoc analysis of a large, randomized phase 3 clinical trial (IMbrave150) and cross-sectional analysis of a multi-institution real-world environment (RWE) to assess the OS surrogacy of ORR and PFS using Response Evaluation Criteria in Solid Tumors (RECIST), modified RECIST (mRECIST), or immune-modified RECIST (imRECIST) in patients treated with ICIs. **Methods:** The IMbrave150 cohort in our analysis included 279 out of 336 patients treated with atezolizumab and bevacizumab in the intent-to-treat population. The RWE cohort included 328 patients with Child-Pugh A or B disease treated in the first or subsequent-line setting with anti-PD-1/L1 therapies. RECIST, mRECIST, and imRECIST ORR and PFS data for the IMbrave150 cohort was determined by investigators and central review, while RECIST ORR and PFS data for the RWE cohort was determined by treating providers or retrospective review. **Results:** In the IMbrave150 and RWE cohorts, Child-Pugh A patients treated in the first-line setting with CR/PR showed greater OS versus patients with SD/PD (IMbrave150: HR 0.16, 95% CI 0.10-0.26; RWE: HR 0.25, 95% CI 0.15-0.43). CR was associated with the greatest OS benefit, followed by PR, SD, and PD. Patients treated in the second-line setting or with Child-Pugh B disease showed that ORR was able to discriminate OS benefit but hazard ratios were closer to the null. In both cohorts, there was a positive rank correlation between RECIST PFS and OS (IMbrave150: Kendall's $\tau = 0.44$, $p < 0.001$); RWE: Kendall's $\tau = 0.52$, $p < 0.001$). However, only 31-46% of the variance in OS rankings was explained by PFS rankings. mRECIST PFS and imRECIST PFS showed a positive rank correlation with OS, with an explained variance of 30% and 38% for mRECIST and imRECIST, respectively. **Conclusions:** Our results suggest that RECIST ORR is a robust surrogate endpoint in HCC treated with ICIs. In contrast, the explained variance between RECIST PFS and OS in both the IMbrave and RWE cohorts was limited. This may reflect the impact of ICIs on response to subsequent therapies which may extend OS benefit. Although prior studies have proposed that modifications to RECIST may lead to more accurate surrogate markers, mRECIST and imRECIST ORR or PFS in HCC treated with ICIs were not associated with greater predictive performance compared to RECIST. Research Sponsor: None.

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Poster Session

Salvage ipilimumab plus nivolumab in advanced hepatocellular carcinoma after prior anti-PD-(L)1 blockade. *First Author: Stephanie Leigh Alden, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins Hospital, Baltimore, MD*

Background: Combination PD-(L)1/CTLA-4 blockade is approved in patients with advanced hepatocellular carcinoma (HCC) in the first line or after treatment with sorafenib, but it is unclear if combination therapy has efficacy after treatment with anti-PD-(L)1 alone or in combination with a multitargeted inhibitor. We evaluated responses to ipilimumab plus nivolumab in patients with advanced HCC who previously received anti-PD-(L)1 to assess the efficacy and safety of this regimen. **Methods:** We performed a multi-center retrospective review of patients 18 years of age or older with a diagnosis of HCC based on histology or imaging who had received at least one dose of anti-PD-(L)1 therapy prior to receiving ipilimumab plus nivolumab as a subsequent line of therapy. All patients had imaging and/or laboratory monitoring to monitor for disease progression. **Results:** Our cohort contained 32 patients, with a majority being male (88%, $n = 28$) and a median age of 67 years. All patients were Child Pugh A (66%, $n = 21$) or B (34%, $n = 11$) at the start of treatment, with most having an ECOG performance status of 0-1 (84%, $n = 27$). The median number of prior lines of therapy was 2 (range 1-8). Prior anti-PD-(L)1 containing regimens included atezolizumab plus bevacizumab (50%, $n = 16$), other VEGF plus anti-PD-(L)1 combination (31%, $n = 10$), and anti-PD-(L)1 monotherapy (19%, $n = 6$). The objective response rate (ORR) was 22% (1 CR, (3%), 6 PR (19%)), with remaining responses including 8 SD (25%), 16 PD (50%), and 1 NE (3%). Among patients who had an objective response to ipilimumab plus nivolumab, none had an objective response to prior anti-PD-(L)1 treatments. Response rates were similar across major clinical (obese vs. non-obese) and etiological (viral vs. non-viral) subsets of HCC. Response to ipilimumab plus nivolumab was associated with improved PFS and OS: median PFS for PD/SD/NE 2.4 months (95% CI: 2.1-NR) vs. PR/CR not reached (NR) (95% CI: 7.5-NR), $p = 0.004$, and OS for PD/SD/NE 5.9 months (95% CI: 3.1-NR) vs. PR/CR NR (95% CI: NR-NR), $p = 0.02$. Immune related adverse events (irAEs) were reported in 13 patients (41%), and 6 patients experienced grade 3-4 irAEs (19%). One patient in our cohort experienced a fatal irAE (autoimmune hepatitis), and 5 patients discontinued therapy due to irAEs. **Conclusions:** This study demonstrates that ipilimumab plus nivolumab has clinical activity in patients with advanced HCC who previously received anti-PD-(L)1 therapy with an acceptable safety profile, supporting this regimen as second line immune checkpoint inhibitor therapy in advanced HCC. Further studies are required to determine the optimal sequence of therapies in advanced HCC. Research Sponsor: None.

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Poster Session

The metabolic activity assessed by ^{18}F -FDG PET and its correlation with tumor immune status and prognosis in advanced biliary tract cancer patients treated with 1L GemCis plus durvalumab +/-tremelimumab. *First Author: Jeesun Yoon, Medical Oncology, Seoul National University Hospital, Seoul, South Korea*

Background: Gemcitabine/Cisplatin (GemCis) in combination with durvalumab have been established as a global new standard of care in first-line (1L) advanced biliary tract cancer (BTC) in the TOPAZ-1 trial (Oh et al. NEJM Evid, 2022). In our phase 2 study (NCT03046862, Oh et al. Lancet Gastroenterol Hepatol, 2022) exploring GemCis/durvalumab +/- tremelimumab, dynamics of PD-L1 expression after one cycle of treatment has been suggested as a predictor for clinical outcomes. Tumor metabolic activity assessed with ^{18}F -FDG PET is usually associated with prognosis in solid tumors. However, the role of metabolic activity in patients treated with the combination of chemotherapy and immunotherapy has not yet been much studied, in terms of correlation with tumor immune landscape and prognosis. **Methods:** This study recruited 1L, advanced BTC patients in 3 different cohorts. ^{18}F -FDG PET was conducted at baseline (pre-treatment) and at the time of first tumor response evaluation (post-treatment). Metabolic indices of the main tumor lesion were measured, including maximum standardized uptake values (SUVmax), metabolic tumor volume (MTV), and total lesion glycolysis (TLG). Metabolic response evaluation was assessed according to EORTC criteria. Tumor biopsies were done at baseline and after 1 cycle of treatment. **Results:** Among total 124 enrolled patients, 118 patients were included in this PET analysis. The early metabolic response rate was 54.3% (mCR 10.2%, mPR 44.1%, mSD 36.4%, mPD 9.3%). Pre-treatment metabolic parameters (SUVmax, MTV, TLG) were associated with disease status, previous operation history, and CRP level. High pre-treatment SUVmax was associated with poor progression-free survival (PFS) and overall survival (OS). Low post-treatment metabolism and large reduction in metabolism between pre- and post-treatment were associated with responder (vs non-responder), long PFS and long OS. In terms of PD-L1 expression and tumor metabolism, Tumor cell (TC) PD-L1 at pre-treatment was not associated with metabolic parameters; however, high immune cell (IC) PD-L1 expression showed significant association with lower MTV and TLG. In terms of dynamics of PD-L1 and tumor metabolism, post-treatment SUVmax was higher in patients with TC PD-L1 decrease. In patients with decrease of PD-L1 on both TC and IC (worst prognostic group), smaller reduction in metabolism between pre- and post-treatment was observed than the other patients. **Conclusions:** In BTC patients treated with 1L GemCis plus durvalumab +/- tremelimumab, tumor metabolic activity and its dynamics conferred prognostic impact. Furthermore, tumor metabolic activity has a potential to be associated with tumor immune landscape. Clinical trial information: NCT03046862. Research Sponsor: AstraZeneca; National Research Foundation of Korea.

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Poster Session

Efficacy and safety of first-line treatments for patients with advanced hepatocellular carcinoma: A systematic review and network meta-analysis. *First Author: Danni Li, The first hospital of China Medical University, Shen Yang, China*

Background: In recent years, the first-line treatment options for advanced HCC has been increasingly abundant, including transarterial therapies, combination of the immune checkpoint inhibitors (ICIs) and the anti-vascular endothelial growth factor (VEGF) inhibitor, ICIs combined with ICIs, and tyrosine kinase inhibitors. However, it remains to be confusing which treatment pattern would benefit people most, especially for different subgroups. **Methods:** A systematic literature search was conducted on PubMed, Embase, Cochrane Central Register of Controlled Trials, and American Society of Clinical Oncology and European Society of Medical Oncology meeting proceedings for III phase randomized clinical trials (RCTs) investigating first-line treatments for HCC compared with sorafenib. The survival outcomes and toxic effects of RCTs should be reported, including overall survival (OS), progression-free survival (PFS), objective response rate (ORR), and adverse events (AEs) of grade 3 or higher. This systematic review was performed in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Guidelines. The random-effects model was used to calculate the summary hazard ratios (HRs) of OS and PFS. The likelihood of ORR, and AEs of grade 3 or higher was performed by odds ratios (ORs) using a random-effects model. **Results:** A total of 13 phase III RCTs involving 8505 patients were included in this study. Hepatic arterial infusion of oxaliplatin combined with fluorouracil (FOHAIC-1) showed OS, PFS, and ORR benefit over all other first-line therapies, except for the regimen of sorafenib plus HAIC or FOLFOX (OS: HR, 0.88; 95% CI, 0.37-2.09; ORR: OR, 1.53; 95% CI, 0.29-8.13). More importantly, we found that sorafenib combined with FOLFOX was superior to other regimens in patients with HBV infection regarding OS except FOHAIC-1 (HR, 0.57; 95% CI, 0.21-1.52) and tremelimumab-durvalumab (HR, 0.42; 95% CI, 0.16-1.11). While in HCV-infected subgroup, ICIs combined with anti-VEGF inhibitor improved OS benefit compared with tremelimumab-durvalumab (HR, 0.31; 95% CI, 0.11-0.84) and sorafenib (HR, 0.38; 95% CI, 0.16-0.88). HAIC-FO also showed significant OS benefits to other therapies in patients with portal invasion or extrahepatic metastasis. The probability of adverse events of grade 3 or higher was significantly lower with HAIC-FO than with others except for nivolumab (RR, 0.96; 95% CI, 0.51-1.82) and tislelizumab (RR, 0.57; 95% CI, 0.30-1.08). **Conclusions:** This network meta-analysis supports arterial infusion as the first-line treatment for patients with HCC. In portal invasion and extrahepatic metastasis subgroups, HAIC-FO may be a preferred option, with sorafenib combined with FOLFOX as an additional option in those with HBV infection. Besides, novel combination therapy should be focused on in patients with certain subgroups. Research Sponsor: National Natural Science Foundation of China.

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Poster Session

Genomic targetability and survival outcomes of biliary tract cancers (BTC): A retrospective cohort study of the Australian Molecular Screening and Therapeutics (MoST) program. *First Author: Subotheni Thavaneswaran, Garvan Institute of Medical Research and The Kinghorn Cancer Centre, Sydney, NSW, Australia*

Background: Despite advances in therapeutic strategies, advanced BTC continue to have poor outcomes. We examined the genomic composition of these cancers and differences in clinical outcomes based on therapies (tx) received. **Methods:** This study included all BTC patients (pts) undergoing comprehensive genomic profiling (CGP) through an Australia-wide precision oncology program, MoST (ACTRN12616000908437). The primary outcome was overall survival (OS) measured from start of first line (1L) systemic tx. The TOPOGRAPH knowledge base was used to determine genomic actionability of alterations identified, tiered by the strength of supportive clinical evidence. Tier 1/2 are regulatory body (TGA or FDA/EMA) approved therapies in BTC; tier 3A is supported by BTC-specific clinical evidence; 3B by clinical evidence inferred from another cancer type; tier 4, pre-clinical evidence. As targeted therapies are only approved in the subsequent-line setting, a further OS analysis was performed from start of second line tx (2L). **Results:** Between December 2016 and August 2022, 223 pts had CGP results available: 170 cholangiocarcinoma (99 intrahepatic, 46 extrahepatic, 25 unspecified primary site) and 53 gallbladder carcinomas. Of 211 (95%) pts who received any systemic tx, median OS (mOS) was 14.6 (95% CI: 12.2–15.4) months (mo) from the start of 1L tx. Pts having received immunotherapy had a mOS of 20.7 vs 13.9 mo (HR 0.67, 0.44–1.04; p=0.07). For 198 pts with actionable findings across TOPOGRAPH tiers, receipt of matched tx (n=37) was associated with a significantly longer mOS of 21.4 (15.0–31.8) compared with receipt of unmatched tx (n=161), mOS 12.6 mo (11.5C15.2, hazard ratio for death, HR 0.46, p<0.001). Pts with tier 1-3 actionable alterations who received matched tx had a median OS of 30.5 mo (95% CI: 18.8 - not reached, NR) compared with 12.1 mo (9.8–16.1, HR 0.39, p=0.02) if only unmatched tx received. Receipt of tier 3B/4 matched tx (n=13) only showed a trend towards longer survival, 15.6 mo vs unmatched 14.0 mo (HR 0.60, p=0.16). For 149 pts who received >1 line of systemic tx: 35 matched and 103 unmatched alone, mOS (measured from 2L tx) was 11.3 (5.7-28.4) compared with 8.3 mo (6.1-10.6) respectively (HR 0.67, p=0.10). A significantly longer OS was seen for matched vs unmatched, in pts receiving tier 1-3 tx: mOS 19.0 mo vs 8.3 mo (HR 0.43, p=0.04), but not for tier 3B/4, mOS 5.6 vs 6.7 mo HR 1.31, p=0.48. The most common genomic alterations were in *TP53* (86, 39%), *KRAS* (59, 26%), *CDKN2A* (43, 19%), and *ARID1A* (29, 13%), while actionable findings commonly involved *IDH1* (26, 12%), *FGFR2* (20, 9%), *ERBB2* (14, 6%), and *BRAF* (11, 5%). **Conclusions:** Receipt of genomically matched tx, particularly those supported by TOPOGRAPH tiers 1-3 evidence was associated with longer OS for pts with advanced BTC. Our results support the greater use of CGP in the management of these pts. Research Sponsor: Australian Government - Medical Research Future Fund; Omico acknowledges support from Servier and Astra Zeneca.

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Poster Session

Phase I trial of chimeric anti-GPC3 scFv-CD3 ϵ engineered T cells (CT0180) in patients with advanced hepatocellular carcinoma. *First Author: Yi Zheng, Department of Medical Oncology, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China*

Background: Hepatocellular carcinoma (HCC) is associated with poor prognosis and high mortality. Glypican-3 (GPC3) is a heparan sulfate proteoglycan overexpressed in 70-80% of HCC and is considered a potential therapeutic target for HCC. We modified T cells with a fusion protein of anti-GPC3 single-chain fragment variable (scFv) linked to CD3 ϵ , which incorporates into the native T cell receptor/CD3 complex forming chimeric anti-GPC3 scFv-CD3 ϵ engineered T cells (CT0180). Preclinically, CT0180 showed competitive antitumor activity but lower cytokine release compared to 28 ζ or BB ζ chimeric antigen receptor T cells. **Methods:** This is an open-label, dose-escalation/exploration phase I study to investigate CT0180 in patients with GPC3-positive advanced HCC (NCT04756648). The study objectives are to evaluate the safety, preliminary efficacy, and cellular pharmacokinetics of CT0180. Eligible patients underwent sequential apheresis, lymphodepletion, and cell infusion. Anti-angiogenic drug monotherapy was allowed after apheresis as bridging therapy. Lymphodepletion regimen comprised fludarabine 25 mg/m² and cyclophosphamide 300 mg/m² daily for 3 days. Five dose levels (DLs, range 1 $\times$ 10⁶-600 $\times$ 10⁶ cells) with up to 3 cycles were explored using i3 + 3 design, and intra-patient dose-escalation was allowed. Data are reported as of 01-Feb-2023. **Results:** From Feb-2021 to Jul-2022, 7 patients with hepatitis B virus-related HCC were treated with CT0180 (one patient each at 1 $\times$ 10⁶ and 30 $\times$ 10⁶ DLs, 3 at 100 $\times$ 10⁶ DL, and 2 at 300 $\times$ 10⁶ DL). The median age was 46 (28-74) years. Patients had prior 2 lines or more systemic therapy, with at least one antiangiogenic tyrosine kinase inhibitor and/or anti-PD-1/PD-L1 immunotherapy. Most common grade 3-4 adverse events were hematologic toxicities, ie lymphopenia and neutropenia, which were considered to be related to lymphodepletion. No dose-limiting toxicities, immune effector cell-associated neurotoxicity syndrome, or treatment-related deaths occurred. Grade 1 cytokine release syndrome was observed in 6 patients; tocilizumab was given in one patient and no glucocorticoids were used. All 7 patients were evaluable for efficacy, in which 2 achieved partial response (PR) (30 $\times$ 10⁶ and 300 $\times$ 10⁶ DL) and 3 achieved stable disease (SD) (10 $\times$ 10⁶, 100 $\times$ 10⁶ and 300 $\times$ 10⁶ DL). One patient sustained PR for 6.7 months, and one patient sustained SD for 6.1 months with follow-up ongoing. Median follow-up time was 15.9 months, and median overall survival was 11.6 months with 3 patients alive at last follow-up. CT0180 transgene copy number ranged 47-4487 copies/ μ g genomic DNA and peaked on either D3 or D7. Interleukin-6 increased and peaked on D1 after CT0180 infusion in most patients. **Conclusions:** CT0180 demonstrated manageable safety profile and promising antitumor potential. Further exploration of CT0180 in HCC is needed. Clinical trial information: NCT04756648. Research Sponsor: CARsgen Therapeutics Ltd.

4096

Poster Session

A prospective, open-label, randomized, controlled trial of radiofrequency ablation versus stereotactic body radiation therapy for recurrent small hepatocellular carcinoma. *First Author: Yaojun Zhang, Department of Hepatobiliary Oncology, Sun Yat-sen University Cancer Center, Guangzhou, China*

Background: Effective treatments are urgently needed to improve the prognosis of patients with recurrent hepatocellular carcinoma (HCC). Previous studies demonstrated that both radiofrequency ablation (RFA) and stereotactic body radiation therapy (SBRT) were promising therapies for recurrent small HCC. This trial was designed to compare the efficacy and safety of RFA versus SBRT in patients with recurrent small HCC. **Methods:** This is a prospective, open label, randomized controlled trial, in which patients aged between 18 and 75 years with recurrent small HCC (occurred more than 3 months after hepatectomy or RFA, a solitary HCC ≤ 5.0 cm in diameter without vascular invasion or extrahepatic metastasis), KPS score ≥ 90 , Child-Pugh score ≤ 6 , adequate organ function, and estimated life expectancy ≥ 6 months were considered eligible. All patients were assigned 1:1 to RFA or SBRT group, and stratification was performed according to tumor size (≤ 2.0 cm or 2.1-5.0 cm). The primary endpoint was 2-year local progression-free survival. Secondary endpoints were progression-free survival, locoregional control, overall survival, and safety. **Results:** A total of 170 patients were recruited during August 2019 to May 2022 (83 in RFA arm and 87 in SBRT arm). In the ITT population, median age was 56 (range, 33-75) and 15 were female. Baseline characteristics were well balanced between treatment arms. Adverse events occurred in RFA and SBRT were mainly grade 1 or grade 2 in severity, and were gastrointestinal and constitutional symptoms, or abnormal laboratory investigations. The most common adverse events were bilirubin increase (14.6%) and AST increase (13.3%) in RFA group vs ALT increase (20.0%) and AST increase (15.3%) in SBRT group. No Grade 3-4 adverse events or mortality were noted. Late adverse events were hardly observed after 3 months. The follow-up of survival data is ongoing. **Conclusions:** Both RFA and SBRT are tolerable and safe for patients with recurrent small HCC. This randomized controlled trial will report the survival outcomes in 2024, which will make an important contribution in clinical decision-making for recurrent small HCC. Clinical trial information: NCT04047173. Research Sponsor: None.

4098

Poster Session

BOLD-100-001 (TRIO039): A phase 1b/2a study of BOLD-100 in combination with FOLFOX chemotherapy in patients with pre-treated advanced gastric and biliary tract cancer: Efficacy and safety analysis. *First Author: Grainne M. O'Kane, Trinity St. James's Cancer Institute, Dublin, Ireland*

Background: BOLD-100 is a first-in-class ruthenium-based anticancer agent in Phase 1b/2a clinical development for the treatment of advanced gastrointestinal (GI) cancers in combination with FOLFOX. BOLD-100 demonstrated synergy in established preclinical models in combination with various anticancer therapies, particularly in resistant cell lines. **Methods:** This is a prospective, Phase 1b/2a study of BOLD-100 in combination with FOLFOX for the treatment of gastrointestinal cancers including biliary tract (BTC) and gastric (GC) cancers. Patients are administered BOLD-100+FOLFOX on day 1 of each 14-day cycle. Four cohorts are treated at the BOLD-100 RP2D of 625 mg/m² with FOLFOX until progressive disease or unacceptable toxicity. BTC and GC pt cohort data are presented. The primary objective is to evaluate the efficacy of BOLD-100 in three clinical endpoints (PFS, OS, and ORR). Disease Control Rates (DCR) for each cohort are also determined. Bayesian modelling is used to continually reassess these endpoints, the posterior probability of superiority to an historical landmark for each endpoint. **Results:** As of 31Dec22, 22 pts with advanced metastatic BTC and 13 pts with advanced GC median age 61 in each cohort were treated. The BTC pts received a median of 2 prior systemic therapies while the GC patients had a median of 3. All patients presented with stage IV disease. 21/22 BTC patients received prior GEM/Cis and while on study a median of 4 cycles BOLD-100+FOLFOX [range 1-19]. Median PFS was 5.0 [3.1, 8.9] months, median OS 7.3 [4.2, 14] months, ORR 6% [1, 23] and DCR 83% [62, 95] in 18 evaluable patients. Four pts remain on treatment and 3 in follow-up. 10/13 GC pts were previously treated with a platinum; currently there are 9 evaluable patients. To the data cut-off, patients received a median of 6 cycles BOLD-100+FOLFOX [1-16]. Median PFS was 5.5 [2.8, 13] months and median OS 15 [5.4, 63] months. Two pts achieved a partial response and 6 pts had stable disease for an overall DCR of 89% (8/9 [59%, 99%]). Five pts remain on treatment with an additional 6 in follow-up. Study treatment was well tolerated. For the 35 treated patients, 33 reported 1 or more treatment-emergent adverse events (AEs), most commonly neutrophil count decreased (n = 15, 43%), nausea (n = 12, 34%), fatigue (n = 10, 29%), and anemia (n = 10, 29%). Most of the AEs were grade (G) 1-2. 14 patients (40%) reported G3/4 neutrophil count decreased. **Conclusions:** BOLD-100 plus FOLFOX is an active and well-tolerated treatment regimen in the heavily pre-treated Stage IV biliary tract and gastric cancer study populations. There were no new safety signals. The preliminary mPFS, mOS, ORR and DCR data in this interim analysis demonstrate significant improvement over the currently available therapies for these difficult to treat advanced GI cancers. Clinical trial information: NCT04421820. Research Sponsor: Bold Therapeutics Inc.

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Poster Session

Circulating tumor DNA (ctDNA) analyses in patients with HER2-positive biliary tract cancer (BTC) treated with trastuzumab deruxtecan (T-DXd): Exploratory results from the HERB trial. *First Author: Akihiro Ohba, National Cancer Center Hospital, Tokyo, Japan*

Background: In the phase 2 HERB trial (NCC1805; JMA-IA00423), T-DXd exhibited promising activity among patients with HER2-positive BTC (ASCO 2022 ab 4006). HER2 positivity was defined as tumor tissue immunohistochemistry (IHC) 3+ or IHC 2+ with in situ hybridization (ISH) positivity. HER2 gene amplification (HER2-amp) can also be detected in ctDNA, which may be an alternative when tumor tissue is not available. ctDNA may also detect tumor molecular changes during treatment and at disease progression. **Methods:** In this ancillary study, we collected plasma samples for ctDNA analysis (Guardant360) at baseline (BL), day 1 of cycle 2 (C2D1; ie, day 22 of treatment), and end of treatment (EOT). The relationships between clinical outcomes and ctDNA genomic profiles were evaluated. **Results:** Among the 30 patients in the full analysis set of HERB (22 with HER2-positive and 8 with HER2-low BTC), plasma samples for ctDNA were obtained from 30, 29, and 24 at BL, C2D1, and EOT, respectively. HER2-amp was found in ctDNA of 8 BL samples, all of which were from tissue HER2-positive patients. This included 50% (5 of 10) of the IHC 3+ tumors and 25% (3 of 12) of the IHC 2+/ISH+ tumors. Comparing clinical outcomes for patients with HER2-amp in ctDNA (n=8) to those with HER2-positive in tissue (n=22), the confirmed objective response rate (cORR) was 50.0% (95% CI, 15.7–84.3), including all 2 CR cases, vs 36.4% (95% CI, 17.2–59.3); median duration of response was 7.9 (95% CI, 2.8–11.5) vs 7.4 months (95% CI, 2.8–NA), median progression-free survival (PFS) was 6.1 (95% CI, 2.8–20.3) vs 5.1 months (95% CI, 3.0–7.3), and median overall survival was 10.8 (95% CI, 4.7–NA) vs 7.1 months (95% CI, 4.7–14.6). Plasma copy number (median 5.1, range 2.3–9.9) was not associated with response or survival, even after adjusting for maximum variant allele frequency (MAF). Common BL genomic mutations found in ctDNA were in *TP53* (n=19, 63%), *PIK3CA* (n=8, 27%), and *TERT* (n=7, 23%). No mutation was associated with treatment efficacy. Median MAF decreased from 7.3% at BL to 1.6% at C2D1. Decreased MAF was associated with better response (CR, PR, and SD) and longer PFS. Among 24 EOT samples, including 7 from patients with BL HER2-amp in ctDNA, 10 (42%) acquired potential resistance alterations, most related to receptor tyrosine kinase, MAPK, and PI3K pathways. HER2-amp was lost at EOT in 4 of the 7 patients with HER2-amp detected in BL ctDNA. **Conclusions:** Using a ctDNA assay, HER2-amp was detected in 36% of patients with tissue HER2-positive BTC. Those with HER2-amp in ctDNA than HER2-positive in tissue had potentially higher cORR and longer survival with TDXd. Clinical trial information: JMA-IA00423. Research Sponsor: Japan Agency for Medical Research and Development; Daiichi Sankyo.

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Poster Session

A phase II study of olaparib and durvalumab in patients with IDH-mutated cholangiocarcinoma. *First Author: Erica S. Tsang, Princess Margaret Cancer Centre, Toronto, ON, Canada*

Background: IDH1/2 mutations (m) occur in approximately 25% of cholangiocarcinomas (CCAs) (20% intrahepatic, < 5% extrahepatic) and result in the accumulation of R-2-hydroxyglutarate (R2HG). R2HG, suppresses homologous recombination repair and as a result IDH1/2m are hypothesized to predict PARP inhibitor sensitivity. PARP inhibition upregulates PD-L1 and the combination is thought to be synergistic. We conducted a phase II trial of olaparib with durvalumab for patients with IDH-mutated cholangiocarcinoma. **Methods:** Patients with advanced IDHm CCA were enrolled in this phase II open-label study (NCT03991832). Patients received olaparib 300 mg twice daily continuously and durvalumab 1500 mg IV every 4 weeks. Simon's optimal two-stage design was used, with an interim analysis planned for efficacy. 10 patients were accrued in the first stage, with a plan for expansion if ≥ 2 responses were observed. The primary objective was to determine the overall response rate (RECIST 1.1) and disease control rate (DCR). Secondary objectives included progression-free survival, overall survival, and safety of the olaparib and durvalumab combination. **Results:** 10 patients with IDH1m were enrolled in this study between January 2020-August 2021. Median age was 63.5 years (range 49-78), and 50% were female. All patients had a baseline ECOG PS of 0-1. 40% of patients had prior surgical resections and subsequently developed recurrent disease. 20% of patients had ≥ 2 lines of prior chemotherapy, with 90% receiving prior platinum. Median duration of treatment was 1.95 months (range 1.8-13.5). There were no treatment-related grade 3-4 toxicities. Any grade toxicities included fatigue (100%), nausea (60%), anemia (20%), hypothyroidism (20%), elevated liver enzymes (20%). We did not observe any complete or partial responses. The DCR was 30% with 3 patients demonstrating stable disease. One patient remained on treatment for 13.5 months, and was eventually taken off study due to clinical progression. The median PFS was 1.97 months (95% CI 1.73-3.93). Given that no responses were seen in the initial 10 patients, the study did not proceed to Stage 2. **Conclusions:** While the combination of olaparib and durvalumab was well-tolerated, this study was discontinued after Stage I due to lack of efficacy. IDH1/2m may not induce a BRCAness phenotype and further correlative studies are planned to evaluate this. Clinical trial information: NCT03991832. Research Sponsor: AstraZeneca.

4100

Poster Session

Racial and socioeconomic disparities in time to chemotherapy and survival in patients with pancreatic cancer. *First Author: Shivani Shah, Allegheny General Hospital, Pittsburgh, PA*

Background: Pancreatic cancer is traditionally known to be an aggressive malignancy, requiring timely diagnosis and treatment, including chemotherapy and/or surgery. Prior studies have evaluated variances in overall survival (OS) based on race or income; however, research regarding time to treatment based on racial and socioeconomic disparities is underwhelmingly studied. Our project sought to evaluate the impact of race and income on time to chemotherapy and OS in pancreatic cancer patients receiving neoadjuvant or adjuvant chemotherapy. **Methods:** The National Cancer Database (NCDB) from 2004-2020 was reviewed for patients with a diagnosis of pancreatic cancer, including all types and stages. Exclusion criteria included: no documented income level, time to first treatment surgery, or time to chemotherapy. Our patient population was then separated into two cohorts: neoadjuvant and adjuvant. Income level was stratified into the following: < \$30,000, \$30,000-34,999, \$35,000-\$45,999, and > \$46,000. Race was also noted. We utilized a logistic regression to identify factors associated with longer time to chemotherapy (using median time to chemotherapy as a benchmark for early or later initiation of chemotherapy). A Cox proportional hazards model was used to identify factors associated with worse survival. A p-value < 0.05 was deemed significant. **Results:** Our final sample size included 64,640 patients. 6,887 (10.6%) of patients had an income less than \$30,000. 55,340 (85.6%) of patients were Caucasian, 6,379 (9.9%) patients were African American, and 172 (0.002%) were American Indian. 18,679 (28.9%) received neoadjuvant chemotherapy, and 45,961 (71.1%) received adjuvant chemotherapy. Median time to chemotherapy was 27 [0-2048] days and 71 [0-1895] days in the neoadjuvant and adjuvant cohorts, respectively. Within both cohorts, income > \$46,000 was noted to have significantly earlier time to chemotherapy compared to lower income levels. Those privately insured had significantly earlier time to chemotherapy compared to uninsured. The African American population was associated with a later time to first chemotherapy in comparison to Caucasians in both subgroups. A significantly less OS in the African American population was appreciated in the neoadjuvant cohort (HR 0.92, p-value 0.02), but not the adjuvant cohort. **Conclusions:** Our retrospective analysis emphasizes that minorities and/or those with a poor socioeconomic status have significant delay in time to chemotherapy in the neoadjuvant and adjuvant setting. Within the African American neoadjuvant cohort, a significantly worse OS was highlighted. This study emphasizes racial and socioeconomic disparities in our healthcare system. Limitations of our study include its retrospective nature and no information regarding the type of surgery the patients received, which could further account for differences in time to chemotherapy. Research Sponsor: None.

4103

Poster Session

Ex-vivo analysis of programmed cell death on fibrolamellar carcinoma. *First Author: Olutani-Grace Ajay, Rush University Medical School, Chicago, IL*

Background: Fibrolamellar carcinoma (FLC) is a rare liver cancer with surgery as the only established treatment. Relapse is common (>80%) and with 40% unresectable, there is a need for rationale systemic therapy. Empiric combinations, especially with lenvatinib (LEN) and gemcitabine (GEM), show promise, but are lacking a CLIA licensed laboratory rationale. Ex-Vivo Analysis of Programmed Cell Death (EVA-PCD), from Nagourney Cancer Institute, is an attempt to meet this need. **Methods:** Nagourney Institute analyzed FLC tissue (as previously described), with a panel of 34 single/26 combinations of available/promising agents from 18 drug classes. Drug concentration with 50% cell death (LC50), below, within, or above 1-standard deviation of the mean (n ≥ 15), define Highly-Sensitive/Intermediate/Resistant, respectively. Active/Moderate/Inactive are similarly defined but with n < 15. Actionable defines clinically available drug(s), not resistant/inactive and ≥ 6 assays. **Results:** Forty-four samples from 40 patients (17M,23F, age 6-56, 23 states/4 countries) were analyzed: 80% were viable and 69% of high quality for a total of 378 assays (avg 12/ patient). However, all patients had actionable agents, and 78% of the assays showed activity in at least some patients. All the universally resistant/inactive assays (22%) were single agent. 76% of assays were actionable in at least one patient (100% for combinations compared to 62% for single agents). EVA-PCD replicate FLC studies and experience, such as the failure of monotherapy and the importance of LEN. Of 11 patients who had treatment that matched testing, 72% responded as predicted, including 6 with 100% response to LEN and/or QUE as predicted. Overall LEN/QUE, LEN/EVE, TRE, REG, QUE, 5FU/INF performed the best, while single agent ALP, CAB, LAR, VOR, GEM, DAS and IBR all showed 0% activity when tested > 5 times. The largest challenge is the need for an adequate amount of viable tissue to arrive within 24 hours. However our experience demonstrates that it is feasible from other countries and across the US. **Conclusions:** This is the first demonstration of CLIA approved human FLC tumor testing. Data are in line with literature and correlates clinically. Prospective data are needed to fully incorporate EVA-PCD testing into the clinic. Research Sponsor: None.

Drug(s), #	Active	Synergy	Highly Act/ Sens	Inter Mod	Inact/ Res	Drug(s), #	Active	Synergy	Highly Act/ Sens	Inter Mod	Inact/ Resis
LEN + Queerectin (QUE), 12	58	42	8	8	42	GEM + Oxaliplatin, 12	25	0	25	0	75
LEN + Everolimus (EVE), 9	56	56	0	0	44	Phenformin, 14	21	0	21	0	79
Tretinoin (TRE), 17	47	0	47	0	53	5FU + OXA, 6	17	0	17	0	83
Regorafenib, 20	40	0	40	0	60	Celecoxib, 17	12	0	12	0	88
LEN, 15	40	0	15	25	60	Alpelisib (ALP), 12	0	0	0	0	100
QUE, 11	36	0	36	0	64	Cabozantinib (CAB), 6	0	0	0	0	100
5FU + Interferon (INF), 20	35	0	30	5	65	Larotrectinib (LAR), 6	0	0	0	0	100
Irinotecan + Topotecan, 11	27	0	18	9	73	Vorinostat (VOR) OR GEM, 5	0	0	0	0	100
Cobimetinib, 11	27	0	27	0	73	Dasatinib(DAS) OR Ibrutinib (IBR), 4	0	0	0	0	100

4101

Poster Session

Progression-free survival as a surrogate endpoint of overall survival in advanced biliary tract cancer: A meta-analysis of randomized trials and individual-patient level correlation. *First Author: Carles Fabregat Franco, Gastrointestinal and Endocrine Tumor Unit, Vall d'Hebron Institute of Oncology (VHIO), Hospital Universitari Vall d'Hebron, Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain*

Background: Biliary tract cancer (BTC) is a heterogeneous group of diseases commonly diagnosed at advanced stages. Overall survival (OS) is the gold-standard primary endpoint in randomized controlled trials (RCT). However, the increasing use of subsequent lines of therapies and cross-over designs may confound the treatment effect. We therefore explored the use of progression free survival (PFS) as a surrogate endpoint of OS both at the trial-level and at the patient-level. **Methods:** For the trial-level correlation, we conducted a systematic review of RCTs in advanced BTC following the PRISMA guidelines. We searched PubMed, the Cochrane Central Register of Controlled Trials and ClinicalTrials.gov from database inception to June 2022 and identified all randomized phase I/II trials testing systemic therapies for advanced BTC. We used a weighted linear regression to measure the correlation of log-transformed hazard ratios (HR) of OS and PFS based on trial size and calculated the surrogate threshold effect (STE). We used the IQWiG framework to define the strength of evidence. For the individual-level analysis, we included patients with advanced BTC treated with first and second line chemotherapy in the real-world RETUD registry. We estimated the correlation via the iterative multiple imputation method. **Results:** From a total of 1992 studies, we identified 32 RCTs including 70 treatment arms and 5140 patients that fulfilled the inclusion criteria. Twenty-three trials were performed in the first line setting and most were phase II RCTs (N = 23). We found a moderate correlation between OS and PFS (R= 0.79, 95% CI 0.61-0.89). The slope of the regression line was 0.62±0.08, indicating that a 10% risk reduction in PFS will result in a 6.2%±0.8% improvement in OS. The STE was 0.69, suggesting that in a hypothetical trial of 400 patients, a PFS HR of 0.69 will likely result in a significant improvement on OS. Regarding the individual-level correlation, a total of 593 patients with advanced BTC were included. The median age of patients was 68y (IQR 59-74), most were males (54%) and received platinum-based chemotherapy (73.1%). In the first line setting, the median OS was 9.7 months (95% CI 8.7-10.5) and median PFS was 5 months (95% CI 4.5-5.5). We observed a strong correlation between PFS and OS (r= 0.84, 95% CI 0.81-0.86). In the second line setting (N = 259), a similar correlation was observed to the first-line setting (r= 0.76, 95% CI 0.72-0.8). **Conclusions:** At the trial-level, in this analysis treatment effects on PFS were moderately correlated with OS. A HR < 0.69 in PFS suggested that it would likely lead to a significant OS benefit in a hypothetical trial including 400 patients. At the individual-level, PFS and OS were strongly correlated in a real-world cohort. Future validation in patients treated in the context of randomized trials is warranted. Research Sponsor: None.

4104

Poster Session

Alteration of gut microbiota composition in patients with cholangiocarcinoma with non-responsiveness to first-line chemotherapy: A pilot study. *First Author: Thanika Ketpueak, Faculty of Medicine, Chiang Mai University, Muang, Thailand*

Background: Gut microbiota established crucial roles in host metabolism and several diseases, particularly cancers. Distinct bacterial profiles from intestine are found to be a potential factor in carcinogenesis, while some of those are associated with detrimental treatment to the responsiveness in various types of cancer. Association of gut microbiota and treatment outcome has been thoroughly investigated in intrahepatic cholangiocarcinoma (ICCA). The present study aimed to compare gut microbiota profiles between chemotherapy responder and non-responder in ICCA patients. **Methods:** Unresectable or metastatic ICCA patients were recruited in the study. The criteria of all patients were naive to chemotherapy. All patients received first line combination of cisplatin 25 mg/m² and gemcitabine 1000 mg/m² at day1 and day 8 in every 21-day cycle and were given up to 8 cycles. The primary endpoint was to evaluate the association between gut microbiota and the objective response rate. Bacterial genomic DNA samples were extracted from the stool using a commercial genomic DNA isolation kit (Qiagen, Hilden, Germany) and then underwent next-generation sequencing. Data analyses were conducted by using QIIME2 and Analysis of Compositions of Microbiomes with Bias Correction (ANCOM-BC). **Results:** Seventeen ICCA patients were recruited. The objective response rate was 23.5% comparable to historical study. Chemotherapy responder group was defined as partial response patients (N = 4) and chemotherapy non-responder group included stable of disease and progressive disease (N = 13). Baseline characteristics were similar including age, sex, ECOG performance status, numbers of metastatic organ and CA 19-9 in two groups. Median Age were 63 years old (60-70) and 61 (45-73), respectively. Alpha-diversity and beta-diversity were not different between two groups. In chemotherapy non-responder group, some taxa were dominantly observed including Ruminococcaceae, Oribacterium, Oxalobacter, Peptostreptococcus, Aggregatibacter, which had been previously reported increasing in ICCA patients. Interestingly, Ruminococcaceae, which was previously documented to be correlated with vascular invasion, was significantly increased abundance in non-responder group. Moreover, the median progression-free survival (PFS) was improved in chemotherapy responder group compared to non-responder group 11.8 and 6.6 month, respectively. Large sample sizes study to confirm this study result should be developed. **Conclusions:** Distinct bacteria from gut microbiota such as Ruminococcaceae has inversely associated with chemotherapy response in ICCA patients receiving first line cisplatin and gemcitabine combination, suggesting the possibility of the poorer PFS. Research Sponsor: Faculty of Medicine, Chiang Mai University.

Real-world multicentre analysis of patients with hepatocellular carcinoma (HCC) treated with atezolizumab and bevacizumab (A+B): Efficacy, esophago-gastro-duodenoscopy (EGD) uptake and bleeding complications. *First Author: Cha Len LEE, Department of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, ON, Canada*

Background: The IMbrave150 trial established A+B as a standard of care for HCC and an EGD within 6 months (mos) of starting treatment to detect esophagogastric varices and prevent bleeding complications was advised. However, the value of performing EGD in all patients (pts) is unknown. **Methods:** We conducted a retrospective analysis of all HCC pts treated with A+B between July 2020 to August 2022 at 5 cancer centres from the Canadian provinces of Ontario, Alberta and Manitoba (members of the HCC-CHORD Consortium). Pts characteristics and treatment history including efficacy, EGD details and bleeding events were collected. Overall survival (OS), progression-free survival (PFS) and response rate (RR) were calculated. A comparative analysis was conducted to compare the correlation between the EGD uptake and bleeding events. **Results:** A total of 112 pts were identified (median age 66 years, 87% male, 24% East Asian, 67% liver cirrhosis, 33% HCV, 25% HBV, 15% NASH, 23% BCLC B, 71% BCLC C, 91% Child-Pugh A, 29% main portal vein invasion, 45% ALBI grade 1 and 54% ALBI grade 2). Prior to systemic, 61% had locoregional therapies. 90% received A+B as first-line therapy, while 9% received it as second-line and 1% as third-line. Outcomes of pts treated with A+B are shown. Before starting A+B, 78 pts (70%) had completed an EGD within 6 mos. Of these, 32 pts (41%) had evidence of varices on EGD, and 15 (20%) required treatment with either banding or beta-blockers. All bleeding events in this population was 15% (n=17). Bleeding rates in the EGD and non-EGD groups were 18% (n=14) and 9% (n=3), respectively. Bleeding adverse events were 5% (n=6) gastrointestinal vs 10% (n=11) non-gastrointestinal (6 epistaxis, 1 ecchymosis, 1 periodontal and 3 unspecified). The GI bleeding rates in the EGD and non-EGD groups were 6% (n=5) and 3% (n=1). **Conclusions:** Outcomes of HCC pts treated with A+B in Canada are comparable to those observed in the IMbrave150 trial. Our study detected and treated varices at twice the rate of the IMbrave150 trial among the EGD group, reflecting real-world treatment of a high-risk population. Yet, pts who had no EGD before starting A+B, presumably due to a low risk of portal hypertension based on physicians' judgement, did not experience more bleeding/GI bleeding than those who had an EGD. This supports the approach of selective EGD prior to A+B, and more guidelines are needed in this area. Outcomes and response rate of patients(pts) treated with Atezolizumab with Bevacizumab in this study. Research Sponsor: None.

Characteristics	All patients (n=112)
Median OS (95% CI), mos	20.3 (16.5-NR)
Pts with bleeding	20.3 (13.0-NR)
Pts without bleeding	19.7 (16.5-NR) (p=0.78)
Median PFS (95% CI), mos	9.6 (6.1-11.9)
Median follow-up time, mos	10.4 (0.4-47.6)
Complete response	1%
Partial response	35%
Stable disease	41%
Progressive Disease	23%

Application of the albumin-bilirubin (ALBI) grade as predictive marker of atezolizumab plus bevacizumab (A+B) treatment outcomes for patients with advanced hepatocellular carcinoma (HCC): Real-world retrospective analysis at Veterans Health Administration (VHA). *First Author: Munaf Alkadimi, University of Texas Health Science Center at San Antonio, San Antonio, TX*

Background: Most clinical trials use Child-Pugh (CP) for patient selection; this subjective scale was originally developed to assess liver function in cirrhosis, thus cannot be applied to HCC patients with non-cirrhotic background. Alternatively, ALBI grade is an objective and validated prognostic system that has demonstrated improved accuracy to predict survival and liver function decline in HCC patients. Our real-world study aims to assess the ALBI grade as a predictive marker of treatment response in patients with advanced HCC who received (A+B) within the VHA. **Methods:** VHA patients with HCC receiving 1st line therapy with A+B were identified through EMR using ICD-9 or ICD-10 codes between 1 Jan 2007 and 31 Dec 2021. Patients were followed from their A+B initiation date through the earliest of the last VHA visit, loss to follow up, death, or end of study on Jan 31, 2023. Structured electronic health record and chart review data were retrospectively collected to determine patient baseline characteristics, treatment response, overall survival (OS), and progression-free survival. Survival rates were based on patients with at least 6 months or 1 year of time (as indicated) from A+B initiation until the chart was reviewed; patients without a scan or known date of scan were excluded from PFS calculations. The Chi-Squared test was used to compare rates. **Results:** 332 patients were included in the study. The median age was 67 yrs, 99% were males, 63% non-Hispanic White, 26% Black, 86% with ECOG < 1, 84% had CPS class A, 16% had CPS class B and C, 56% had viral hepatitis-caused HCC, 20% had no cirrhosis present, and 60% had prior local therapies. There was a statistically significant difference in progression free survival (PFS) and over survival (OS) amongst different ALBI grades as shown. **Conclusions:** In our retrospective cohort, it was clear that patients with ALBI grade 1 had improved PFS and OS compared to ALBI score grade 3. Patients with ALBI score grade 2 also had a moderate response to treatment with modest OS and PFS compared to patients with ALBI score grade 3. Utilizing stratification ability ALBI grade in future clinical trials may improve prognostic power facilitating ideal patient selection. Research Sponsor: None.

End points for VA HCC patients given AB as 1st line, with break out by ALBI grade at staging.

Characteristic of Interest	ALBI grade	1	2	3	p-value
N		97 (29.2%)	207 (62.3%)	28 (8.4%)	–
OS: 6 mo		84 (86.6%)	150 (72.5%)	9 (32.1%)	<0.001
OS: 1 yr		61 (70.9%)	93 (48.2%)	4 (16.0%)	<0.001
Objective Response Rate (CR + PR)		29 (30.8%)	62 (30.7%)	5 (20.9%)	0.59
Disease Control Rate (CR + PR +SD)		61 (64.8%)	123 (60.9%)	12 (50.0%)	0.40
PFS: 6 mo		62 (66.0%)	118 (59.0%)	7 (29.2%)	0.005
PFS: 1 yr		41 (48.8%)	61 (33.2%)	3 (14.3%)	0.004

Association of a high E2F targets score with survival in hepatocellular carcinoma patients. *First Author: Kohei Chida, Roswell Park Comprehensive Cancer Center, Buffalo, NY*

Background: Hepatocellular carcinoma (HCC) is one of the leading causes of cancer-related mortality. Multiple staging systems have all been proposed to date; however, the optimal tool for stratification of prognosis is still not universally accepted. E2F targets are the essential component of cell proliferation, thus we hypothesized that a score to quantify E2F activity is expected to reflect the aggressiveness and prognosis of HCC. **Methods:** Total of 655 HCC patients from TCGA (The Cancer Genome Atlas) -HCC (n=358), GSE6764 (n=75), GSE76427 (n=115), and GSE89377 (n=107) cohorts were analyzed. The score was generated using MSigDb Hallmark E2F Targets gene set using Gene Set Variation Analysis. **Results:** The E2F targets scores of TCGA-HCC patients showed a bimodal distribution, thus high vs. low score groups were divided by median. As expected, high E2F targets enriched all of the Hallmark cell proliferation-related gene sets; E2F targets, G2M checkpoint, MYC targets v1 and v2, and Mitotic spindle. It also enriched gene sets known to aggravate cancer, such as Glycolysis, mTORC1 signaling, DNA repair, and Unfolded protein response. E2F targets were significantly associated with histological grade, tumor size, and stage, as well as proliferation score and MKI67 expression. Furthermore, a higher E2F targets score was significantly associated with higher intra-tumoral genomic heterogeneity and homologous recombination deficiency, suggesting greater tumor aggressiveness. In agreement, E2F targets score correlated with the pathological progression from normal liver, cirrhosis, dysplasia, to early and advanced HCC consistently in two cohorts (GSE6764 and GSE89377). Further, the abundance of hepatocytes, fibroblasts, adipocytes, and lymphatic endothelial cells were all significantly less in high E2F HCC, which reflects proliferative cancer. On the other hand, there was no relationship between E2F and mutation rates or neoantigens. High E2F was associated with high infiltration of anti-cancerous immune cells; CD8, CD4 memory, and Th1 cells, however, there was no difference in cytolytic activity, and it did not enrich any of immune response-related gene sets. High E2F HCC was associated with worse disease-free (DFS), disease-specific (DSS), and overall survival (OS), and this was the case in both early (I and II) and late (III and IV) stages. A multivariate analysis revealed that the E2F targets score was an independent prognostic factor for OS (HR=1.68, 95%CI= 1.15–2.46, p=0.007) as well as DSS (HR=1.81, 95%CI=1.27–2.59, p=0.001) in patients with HCC. **Conclusions:** We found that the E2F targets score not only indicates cell proliferation, but also is associated with cancer aggressiveness and worse survival. Our findings suggest a possible future use of the E2F targets score as a prognostic biomarker in patients with HCC. Research Sponsor: U.S. National Institutes of Health; Mutsu Rotary Club; U.S. National Institutes of Health; Department of Defense BCRP grants; Roswell Park Comprehensive Cancer Center.

Comprehensive profiling of clock genes expression in hepatocellular carcinoma (HCC). *First Author: Francesca Battaglin, Norris Comprehensive Cancer Center, Keck School of Medicine, University of Southern California, Los Angeles, CA*

Background: The circadian clock mechanism controls the physiological homeostasis of the liver and plays a key role in hepatocarcinogenesis. Recent evidence unveiled core clock proteins as novel therapeutic targets in cancer. Our group showed that clock regulators BMAL1 and CLOCK can promote proliferation of liver cancer cells by modulating the cell cycle checkpoint kinase Wee1. Here we further evaluated the molecular landscape of clock pathway alterations in HCC leveraging multi-platform profiling of patient tumor samples. **Methods:** 780 HCC tested at Caris Life Sciences (Phoenix, AZ) with WTS (Illumina NovaSeq) and NextGen DNA sequencing (NextSeq, 592 Genes and NovaSeq, WES) were analyzed. Clock gene Score (CS) was determined using expression of core clock genes Z scores (positives of *CLOCK*, *ARNTL*, *RORA/B/C* and negatives of repressors *CRY1/2*, *PER1/2/3*, *REVERBA/B*) stratified by quartiles. xCell was used to quantify cell infiltration in the tumor microenvironment (TME). Significance was determined as P-values and adjusted for multiple testing (q) of < .05. Gene expression profiles were analyzed for transcriptional signatures predictive of response to immunotherapy including the T cell inflamed score (TIS) and IFG score. Real world survival was obtained from insurance claims data and Kaplan-Meier estimates were calculated for comparison. **Results:** CS was higher in metastatic sites than primary tumors (median transcripts per million [TPM]: 0.81 vs 0.37, P< .05). No significant differences in patient age and sex were observed between CS Q1 (lowest) and Q4 (highest) cohorts, although a trend towards a higher frequency of males was observed in Q4 (76% vs 68%, Q4 vs Q1, P= .07). CS was positively associated with telomerase subunit TERT mutations (64% vs 52%, Q4 vs Q1, P= .04) and negatively correlated with *FGF3* copy number amplification (2% vs 6%, P= .04) and *WEE1* gene expression (median TPM: 15 vs 28, q< .05). No dMMR/MSI-H tumors were observed in our series and there were no significant associations with tumor mutational burden and PD-L1 protein expression. Expression of immune related genes was lower in tumors with high CS, including *IDO1*, *CD80*, *PD-L1*, *LAG3*, *CD86*, *TIM3*, *PD-1* and *PD-L2* (fold change: 0.57-0.67 q< .05). NK cell infiltration in the TME and the TIS score were also significantly lower in CS-high HCC (q< .05). Individually, lower *CLOCK* and *CRY1* tumor mRNA expression were associated with longer OS (Q1 vs Q4: *CLOCK* HR 0.71, 95%CI [0.51-0.98], P= .04 and *CRY1* HR 0.70 [0.51-0.95], P= .02, respectively). **Conclusions:** This is the most extensive profiling study to investigate the expression of clock genes in HCC. Our data show that clock genes expression impacts patient survival and is associated with alterations in immune-related gene expression and TIS score which suggest a role in the modulation of anti-tumor immunity. These results support the clock pathway role as an oncogenic driver and its potential as a therapeutic target in HCC. Research Sponsor: This work was partly supported by National Cancer Institute (P30CA014089), Gloria Borges WunderGlo Foundation, Dhont Family Foundation, Gene Gregg Pancreas Research Fund, San Pedro Peninsula Cancer Guild; Daniel Butler Research Fund, V foundation for cancer research, Victoria and Philip Wilson Research Fund, Fong research project and Ming Hsieh research fund.

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Poster Session

Evaluating racial disparities for patients with advanced hepatocellular carcinoma (HCC) receiving first line immunotherapy within an equal access system. *First Author: Lauren Diaz Boyle, The University of Texas Health Science Center-San Antonio, San Antonio, TX*

Background: The incidence and mortality of HCC are increasing in the USA. HCC disparities have been reported across the entirety of the cancer timeline, from screening to local and systemic treatment and liver transplant. We aim to analyze the clinical characteristics, outcomes, and racial disparities in patients with advanced HCC receiving first-line Atezolizumab plus Bevacizumab (A+B) in the Veterans Health Administration (VHA) – the only health care system in the USA that provides equal access to all patients. **Methods:** Patients were followed from their A+B initiation date through the earliest of the last VHA visit, loss to follow-up, death, or end of study on Jan 31, 2023. Structured electronic health record and chart review data were retrospectively collected to determine patient baseline characteristics, including self-reported race, number of A+B doses, treatment response, subsequent line of treatment, length of follow-up, and overall survival (OS). The Chi-Squared test was used to compare rates, and Mann-Whitney test was used to compare medians. **Results:** Three hundred twenty-five patients were included. 64% were non-Hispanic White (NHW), and 36% were all other (AO) ethnicities or races combined (26% Black, 8% Hispanic, 2% Asian or Indigenous). The median age for each cohort was similar (66 years for AO vs. 68 for NHW), and ECOG performance was <1 in nearly 90% of each cohort. Viral hepatitis accounted for 70% and 48% of AO and NHW, respectively (p=0.0001). Despite clinical differences in OS and progression free survival (PFS), they were not statistically significant. **Conclusions:** Our VHA real-world data shows that despite having statistically significant etiologies, there was no statistically significant difference in the PFS and OS of patients with advanced HCC receiving first-line A+B in an equal access care system. This study supports our group's findings in other malignant cohorts within VHA where equal healthcare access can mitigate other socio-demographic and biological factors. Research Sponsor: None.

Survival and response rates by race/ethnicity.

	NHW N=208	AO N=117	P- value
Median time from diagnosis to initiation of A+B treatment: months	11.0 (2.3 – 33.5)	19.3 (3.1 – 34.3)	0.36
Number of Atez/Bev doses, median	5 (3 – 11)	6 (3 – 15)	0.22
OS: 6 mo	149 (71.6%)	88 (75.2%)	0.49
OS: 1 yr	89 (47.3%)	64 (58.7%)	0.059
Objective Response Rate (CR + PR)	57 (27.4%)	37 (33.4%)	0.27
Disease Control Rate (CR + PR +SD)	125 (60.1%)	66 (59.5%)	0.91
PFS: 6 mo	116 (57.7%)	66 (60.0%)	0.70
PFS: 1 yr	59 (32.8%)	42 (41.2%)	0.16
Duration of Response (CR,PR,SD), months	8.7 (4.5 – 14.5)	11.7 (5.7 – 16.7)	0.029
Overall Survival Time, months	10.3 (5.0 – 17.9)	14.9 (6.0 – 20.4)	0.091

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Poster Session

Lenvatinib (LEN) combined with tislelizumab (TIS) plus transcatheter arterial chemoembolization (TACE) for unresectable hepatocellular carcinoma (uHCC): A single-arm, phase II clinical trial. *First Author: Xiang Nong, Guangxi Medical University Cancer Hospital, Nanning, China*

Background: uHCC still lacks effective treatments, combination of antiangiogenic targeted drugs and immune checkpoint inhibitors showed promising efficacy. TACE induces tumor necrosis and tumor antigen release, may synergize with immunotherapy. This study was to evaluate the efficacy and safety of TACE in combination with TIS and LEN in patients with uHCC. **Methods:** This study was a single-center, single-arm, open-label phase II exploratory clinical study (NCT05131698). Eligible patients were BCLC C stage and not candidates for surgical resection or liver transplantation, at least one target lesion evaluable, ECOG performance status of ≤ 1, and Child-pugh grade A or B. Enrolled patients received TACE treatment (Ioplatin + raltitrexed + iodine oil) followed by TIS (200 mg, IV, on Day 1 of a 21-day cycle) and LEN (body weight ≥ 60 kg: 12 mg/day; < 60 kg: 8 mg/day) daily. The primary endpoint was overall response rate (ORR) by mRECIST. The secondary endpoints included disease control rate (DCR), overall survival (OS), and progression-free survival (PFS) and safety. **Results:** As of December 28, 2022, 31 enrolled patients with uHCC were treated. Median follow-up time is 11.3 months. Among all patients with BCLC C, 28 patients (90.3%) had microvascular invasion and 17 (54.8%) had portal vein tumor thrombus. As assessed by mRECIST, the ORR and DCR were 71.1% and 87.1%, respectively (2 CR, 6.6%; 20 PR, 64.5%; 5 SD, 16.1%), 4 patients developed tumor progression (12.9%). As assessed by RECIST 1.1, the ORR and DCR were 67.7% and 87.1%, respectively (1 CR, 3.2%; 20 PR, 64.5%; 6 SD, 19.4%), 4 patients developed tumor progression (12.9%). The median PFS was 10.2 months (95% CI: 4.5-NA) , and the median OS was not reached. Any grade treatment-emergent adverse events (TEAEs) occurred in 64.5% (20/31) patients. The most common TEAEs were Increased γ-glutamyl transpeptidase (35%), Increased aspartate aminotransferase (32%), thrombopenia (25%). Only 2 patients experienced grade 3 TEAE (pneumonia). No serious adverse events (SAEs) were reported. **Conclusions:** In this study, TACE combined with TIS and LEN showed preliminary antitumor efficacy and tolerable safety profile in uHCC. Clinical trial information: NCT05131698. Research Sponsor: BeiGene biopharma incorporation.

Variable	All patients (n=31)	
	mRECIST	RECIST 1.1
Confirmed objective response, n (%) [95% CI]	22 (71.1% [52.0- 85.8])	21 (67.7% [48.6- 83.3])
Complete response, n (%)	2 (6.6%)	1 (3.2%)
Partial response, n (%)	20 (64.5%)	20 (64.5%)
Stable disease, n (%)	5 (16.1%)	6 (19.4%)
Disease control, n (%)[95% CI]	26 (87.1% [70.2- 96.4])	26 (87.1% [70.2- 96.4])
Progressive disease, n (%)	4 (12.9%)	4 (12.9%)

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Poster Session

The clinical feasibility of circulating tumor DNA alterations in patients with advanced hepatocellular carcinoma. *First Author: Gwangil Kim, Department of Pathology, CHA Bundang Medical Center, CHA University School of Medicine, Seongnam, South Korea*

Background: Need for individualized treatment based on tumor attributes is being reinforced with the rapid development of targeted therapies and immune checkpoint inhibitors for hepatocellular carcinoma (HCC). Lack of mandatory tissue biopsy for the diagnosis of HCC, continues to be a challenge for development of precision medicine for HCC compared to other solid tumors. Liquid biopsy enables comprehensive genomic profiling of circulating tumor DNA (ctDNA) shed from tumors into the circulation. This could compensate for the lack of tissue-based analysis in HCC providing a non-invasive and safer option for genomic profiling. This study aims to address the concordance between commercially available ctDNA and tissue genomic profiling in patients with advanced HCC and to assess the feasibility of liquid biopsy in the treatment of patients with HCC. **Methods:** Patients subjected to tissue-based next-generation sequencing (NGS) before systemic therapy for advanced HCC at CHA Bundang Medical Center from June 2020 to October 2022 and also had sufficient plasma samples available for ctDNA analysis were included. Oncomine Comprehensive Assay (OCA) ThermoFisher was used for tissue-based NGS and Guardant360 for ctDNA based NGS. For the concordance assessment for the same patient, paired samples of ctDNA and tumor tissue, we investigated the common targeted regions across both the panels. **Results:** Out of hundred thirty patients included in this study, 98% percent of ctDNA samples for these patients were successfully sequenced; ctDNA were detected in 88% of the samples. For the assessment of concordance between intra-patient ctDNA and tumor tissues, we investigated only clinically important (AMP/ASCO/CAP guidelines tier 1 or 2) variants. When we considered the variants detected in tissues as true positive, the concordance between the mutations detected from ctDNA and tissue samples indicated 68.9% sensitivity and 63.1% positive predictive value (PPV). In ctDNA, targetable alterations were detected in 16.9% of samples, such as *ARID1A* mutations (7.7%), *PTEN* mutations (6.9%), *PIK3CA* hotspot mutations (1.5%), *RAS* mutations (1.5%), and one *RET* fusion (0.8%). Regarding the concordance between ctDNA and tumor tissue, the sensitivity for mutation was high for *RAS* mutation (100.0%), *PTEN* mutations (100.0%), and *ARID1A* mutations (75.0%) but low for *PIK3CA* hotspot mutations (0.0%). One *RET* fusion was identified only in ctDNA. **Conclusions:** ctDNA-based genotyping demonstrated clinically acceptable concordance with tissue genomic profiling in patients with advanced HCC. Thus, liquid biopsy using ctDNA help address any challenges associated with the limited use of tissue-based genomic profiling in HCC. Investigation of time between blood and tissue collection and the impact it has on concordance is ongoing. Research Sponsor: This work was supported by the National Research Foundation of Korea [NRF] grant funded by the Korea government [MSIT] [NRF-2020R1C1C1010722 to HUC].

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Poster Session

Molecular subtypes from comprehensive clustering from multi-omics dataset to predict the therapeutic efficacy of immunotherapeutic agent-based treatments in advanced hepatocellular carcinoma. *First Author: Hong Jae Chon, Department of Medical Oncology, CHA Bundang Medical Center, CHA University School of Medicine, Seongnam, South Korea*

Background: In advanced hepatocellular carcinoma (HCC), combined treatment using anti-PD-L1 and anti-VEGF antibodies is a major therapeutic strategy in addition to using anti-PD-1 and anti-CTLA4 target agents. To identify clinically relevant molecular biomarkers for immunotherapeutic agents-based treatment in advanced HCC by comprehensive molecular profiling using genomics alterations and transcriptomic data. **Methods:** Multi-omics data from clinical tumor samples of patients treated with atezolizumab + bevacizumab (94 patients), nivolumab (40 patients), and ipilimumab + nivolumab (32 patients) were obtained from tumor biopsies or surgical resections in a single institution. The targeted panel sequencing was conducted via the Oncomine comprehensive assay (ThermoFisher, USA). QuantSeq mRNA sequencing (Lexogen, USA) was used to generate datasets for the genomic alterations and gene expression profiles. **Results:** A total of 166 target sequences for genomic alterations and 136 transcriptomic sequences were performed in patients with advanced HCC treated with immunotherapeutic agent-based treatment options. High tumor mutation burden was significantly associated with favorable therapeutic efficacy (disease control rate, P=0.036) and progression-free survival (P=0.037) in patients who had atezolizumab with bevacizumab treatment. The genomic alteration of CTNNB1 mutation correlated with the favorable therapeutic efficacy of nivolumab monotherapy (PFS, P=0.022), contrary to TP53 mutation (PFS, P=0.063) which demonstrated unfavorable outcomes. CD274(PD-L1) mRNA expression was significantly associated with a high drug response following nivolumab monotherapy (objective response rate, P=0.047) and oncologic outcomes (PFS, P=0.021). Interestingly, PLA2G4A, known as a downstream molecule of the VEGF signaling pathway, was highly correlated with unfavorable therapeutic efficacy of the combined atezolizumab with bevacizumab treatment (disease control rate, P=0.002) and related oncologic outcomes (PFS, P=0.003). We also identified the clinically relevant molecular subtypes from unbiased clustering using the ontologic pathway collection. We also used gene expression profiles to predict the therapeutic response and oncologic outcomes from immunotherapeutic agent-based treatment options. **Conclusions:** We identified clinically relevant molecular biomarkers from comprehensive clustering of a multi-omics dataset to predict the therapeutic efficacy and oncologic outcomes. Further prospective studies with clinical validation are warranted to confirm clinical implications. Research Sponsor: This work was supported by the National Research Foundation of Korea [NRF] grant funded by the Korea government [MSIT] [NRF-2020R1C1C1010722 to HJC, NRF- 2020R1A2C2004530 to CK].

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Poster Session

Phase 2 multicenter trial of rucaparib and nivolumab as maintenance therapy following first-line platinum-based chemotherapy in patients with advanced biliary tract cancer (BTC): BIIT-02. First Author: Vaibhav Sahai, University of Michigan, Ann Arbor, MI

Background: Gemcitabine, cisplatin and durvalumab followed by maintenance durvalumab is standard of care first-line (1L) therapy for patients (pts) with advanced BTC. In this trial, we investigated the combination of a PARP inhibitor with anti-PD1 antibody in absence of progression after at least 4 months of standard 1L platinum-based chemotherapy. **Methods:** Pts with advanced BTC, ECOG PS 0-1 and absence of progression on 1L platinum-based therapy were enrolled on a phase 2 trial to receive rucaparib 600 mg PO BID in combination with nivolumab 240 mg IV Q2 weeks every 28 days for up to 2 years. The primary endpoint was 4-month progression-free survival (PFS) rate from the date of first study treatment with an alternative hypothesis of 85%. Secondary endpoints included median PFS and overall survival (OS) from first study treatment (PFS1, OS1) as well as from start date of first-line chemotherapy (PFS2, OS2), best overall response, and safety. **Results:** 31 pts were enrolled of which 14 (45%) were women, 25 (80.6%) Caucasian and 24 (77.6%) with ECOG 1. Primary disease site was intrahepatic, extrahepatic hilar and distal, and gallbladder cancer in 21 (67.7%), 4 (12.9%), 1 (3.2%) and 4 (12.9%), respectively. 1L platinum-based treatment included gemcitabine/cisplatin based in 26 (83.9%), FOLFOX in 3 (9.7%) and carboplatin/paclitaxel in 1 (3.2%) pts. Mean (range) cycles of rucaparib and nivolumab were 6.75 (1-24) and 5.9 (1-24). The median follow-up time is 28.7 months using reverse censoring methodology. PFS rate at 4 months was 54.8% (95% CI, 36-70.3), comparable to the 63% null estimate based on ABC-02 trial. Median PFS1 and OS1 are estimated to be 4.6 months (95% CI, 3.7-6.2) and 15.9 months (95% CI, 9.8-24.1). Median PFS2 and OS2 calculated from date of 1L chemotherapy are estimated as 9.9 months (95% CI, 8.3-11.3) and 21.4 months (95% CI, 14.8-26.7). Two (6.4%) pts had partial response (with IDH R132G and KRAS G12D) as best response with stable disease in an additional 22 (71%) pts. Grade 3-5 treatment-related adverse events (TRAEs) occurred in 15 (48.4%) pts, including 1 patient who died on therapy due to possibly-related immune-related myocarditis. The most common grade 2 or greater TRAEs included fatigue (9, 29.0%), anemia (7, 22.6%), neutropenia (6, 19.3%), elevated AST (5, 16.1%) and elevated ALT (4, 12.9%). Reasons for treatment discontinuation included death (2), progression (27), adverse event (1) while 1 patient completed 2 years of study treatment. **Conclusions:** The primary endpoint of PFS rate at 4 months was not met but the preliminary measures of PFS1 and OS1 are much longer than expected, and hypothesis generating for rational combination of PARP inhibitor with maintenance immunotherapy in this rare cancer. Exploratory endpoint of association of genomic analysis with efficacy is ongoing and will be discussed. Clinical trial information: NCT03639935. Research Sponsor: Clovis Oncology, Bristol Myers Squibb Pharmaceuticals; University of Michigan Rogel Cancer Center.

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Poster Session

Geographical and baseline clinical characteristics of participants enrolled in hepatocellular carcinoma (HCC) trials: Analysis of US FDA approvals. First Author: M. Naomi Horiba, FDA, Silver Spring, MD

Background: Globalization of drug development is increasing, with reliance on data from patients accrued to large, randomized studies across continents. In addition to appropriate racial/ethnic representation, trials submitted to support FDA approvals should reflect the etiology and treatment patterns of HCC in the US. We conducted a pooled analysis of patient-level data from the HCC trials supporting approved marketing applications in the US to characterize geographical and baseline variables in clinical trials. **Methods:** Datasets from applications which received FDA approval for HCC between 2010-2022 were identified. The following data was abstracted: country, baseline disease characteristics (median age, HCC etiology, extent of tumor, and Child-Pugh score), and prior treatments received. Geographical region was recoded using categories observed by the United Nations M49 standard, based on country of enrollment reported in the datasets. **Results:** Variables that were defined differently across studies included region of enrollment, some categories of etiology, and prior therapy. Overall, the rate of HBV etiology was higher than that observed among patients with HCC in the US (20%), while the rate of HCV etiology was lower than in the US (50%). **Conclusions:** Variability in patient populations exist across trials submitted to FDA based on the regions that were targeted for enrollment and eligibility criteria. Global trials may be appropriate to support drug approvals for HCC; however, to ensure results are applicable to US patients, sponsors should select sites that represent a similar population with respect to racial/ethnic representation, disease etiology, and treatment patterns. Research Sponsor: None.

	Trial 1 ^{1,2} (n= 602)	Trial 2 (n= 573)	Trial 3 (n=954)	Trial 4 (n=707)	Trial 5 (n=292)	Trial 6 (n=501)	Trial 7 (n=783)
Geographic Region (%)							
Americas ³	13	6	7	24	8	16	18
Asia	1	38	67	25	49	52	48
Europe	80	54	26	48	42	30	34
Oceania ⁴	6	2	0	4	1	2	0
Baseline Characteristics (%)							
Median age (yrs)	67	63	62	63	64	65	65
HBV	18	38	50	38	37	48	31
HCV	28	21	23	21	26	22	27
MVI/EHS	70	81	70	78	81	75	66
Child-Pugh A	97	98	99	96	100	99	99
Prior Nonsystemic Therapy (%)							
Locoregional	40	61	70 ⁵	44 ⁶	64	49	na
Radiation	5	85	11	25	19	10	11
Resection	20	40	na	na	43	42	30
AFP ≥ 400 ng/mL	na	42	36	41	100 ⁷	37	34

¹Trial 1 SHARP (sorafenib); Trial 2 RESORCE (regorafenib); Trial 3 REFLECT (lenvatinib); Trial 4 CELESTIAL (cabozantinib); Trial 5 REACH-2 (ramucirumab); Trial 6 IMbrave150 (atezolizumab/bevacizumab); Trial 7 HIMALAYA (durvalumab/tremelimumab). ²For sorafenib, data sources are FDA review and applicant's study report. ³Americas are North, South, and Central America. ⁴Oceania is Australia, New Zealand, and Pacific Islands. ⁵Prior anticancer procedures. ⁶Transarterial chemoembolization. ⁷AFP≥400 was an eligibility criterion. MVI/EHS = macrovascular invasion or extrahepatic spread; na = not available.

4114

Poster Session

Tracking the evolving ecosystem of recurrent hepatocellular carcinoma after liver transplantation. First Author: Zijie Zhang, Renji Hospital, affiliated to Shanghai Jiao Tong University, School of Medicine, Shanghai, China

Background: Liver transplant (LT) contributes to the cure of hepatocellular carcinoma (HCC) by extending the conventional surgical margin, while removing the concurrent tumor-favoring conditions of the diseased liver. Over the past two decades, HCC has emerged as a preferable indication for LT, accounting for 22-45% of the cases globally. However, despite the stringent selection criteria, recurrence still occurs in a substantial proportion of patients, leaving 10-13 months of median survival after tumor relapse. To address this challenge, a thorough exploration of molecular mechanism behind HCC recurrence after LT is required. Here, for the first time, we performed a comprehensive analysis to depict the evolving and unique ecosystem of HCC in the context of LT and immunosuppressant (IS) administration. **Methods:** We retrospectively reviewed our biobank and collected 91 paired (primary tumors (PT) from the explant after LT and relapsed tumors (RT) from hepatectomy) FFPE tumor samples from 15 patients for whole exome sequencing (WES). Also, from Jan 2021, we prospectively collected surgical tumor specimens and their adjacent non-tumor tissues from 15 primary and 6 post-LT intrahepatic recurrence patients for single-cell RNA sequencing. Moreover, 6 paired samples from 3 patients were used for spatial transcriptomic analysis. **Results:** By analysing WES data, we confirmed that RT samples represent recurrent, instead of *de novo* tumors. Also, the phylogenetic analysis demonstrated strong clonal relationship between PT and RT based on shared SNVs. As to mutation landscape differences of PT and RT, we identified a significantly enriched mutation panel from RT, including *MUC16*, *FAT3*, *APOB*, *COL6A3* and *POTEC*. And the accuracy of this panel for post-LT HCC recurrence surveillance using plasma derived cfDNA sequencing has been preliminarily validated in a prospective cohort of 17 patients. From the single-cell profiling, distinct immune microenvironment between PT and RT is identified. As predicted, proliferating T cells are decreased in RT due to IS. Pseudotime analysis of T cells revealed that T cells from PT mainly distribute at the terminal end of cytotoxic stage whereas T cells from RT mostly represent a naive state, further confirming the T cell blocking effect of IS. In terms of myeloid cells, we surprisingly found that FOLR2+ tumor associated macrophages, which is conventionally considered as a favorable prognosis factor, is increased in RT. Spatial transcriptomics and IHC also confirmed their active interplay with tumor cells at invasive margin. We postulate that such increase might be a result of the healthy nature of liver graft. **Conclusions:** Our comprehensive dissection of the HCC ecosystem provides deeper insights into the tumor relapse after LT. Targeting novel mutations and strengthen the antigen presenting process between increased TAM and disabled T cells can be the future direction in this field. Clinical trial information: NCT04506398. Research Sponsor: None.

4116

Poster Session

Effect of MYC-targeting programmable epigenetic mRNA therapeutics on TME and immunotherapy responses. First Author: Yan Moore, Omega Therapeutics, Cambridge, MA

Background: c-MYC is a master transcription factor (TF) critical for multiple cell physiologies. As a pleiotropic TF, MYC regulates the tumor microenvironment (TME) and impacts cancer cell initiation, growth, and survival. Although MYC expression is normally tightly controlled in normal cells, its activity is frequently dysregulated in cancer (e.g., HCC, NSCLC, Burkitt's lymphoma). A direct MYC targeting anti-cancer agent has remained elusive, largely due the absence of a drug binding pocket and tight autoregulation. The MYC gene and its regulatory elements reside alone within an insulated genomic domain and represents a potential target for gene regulation via an epigenetic approach. **Methods:** We are developing programmable epigenetic mRNA medicines designed to controllably tune gene expression pre-transcriptionally with high specificity and durability. We have rationally designed MYC-targeted Omega Epigenomic (MYC-OEC: clinical candidate OTX-2002; MYC Lung OEC; mouse surrogate muMYC-OEC) to downregulate MYC expression, thereby selectively killing cancer cells while sparing normal cells. We investigated the role of MYC-OECs in the modulation of the TME and demonstrated in human and mouse tumor models that MYC-OECs enhanced the host immune response. **Results:** In HCC and NSCLC cell lines (Hep 3B, SKHEP1, H2009 and H460), treatment with MYC-OECs in vitro significantly inhibited PD-L1 surface expression. Using the muMYC-OEC in vivo, we demonstrated tumor growth inhibition (TGI) in Hepa1-6 liver cancer syngeneic tumor models with 70% of the mice exhibiting complete tumor response with good tolerability. Cancer cells used to rechallenge the cured mice failed to grow, demonstrating that muMYC-OEC monotherapy induced immune memory. In addition to inhibiting tumor growth with either muMYC-OEC or checkpoint blockade immunotherapy (CBI; anti-PD-1 or anti-PD-L1) treatment, combination therapy further enhanced TGI. Tumor-infiltrating lymphocyte profiling demonstrated an increase in activated T cells and a reduction in Tregs following combination treatment, resulting in an increased effector T cell to Treg ratio over monotherapy. Depletion of CD4⁺, CD8⁺ and NK cells in vivo prior to single agent or combination treatment demonstrated a requirement for both CD4⁺ and CD8⁺ T cell activity for TGI. NK cells were dispensable. Taken together, these data demonstrate that the improved CBI/MYC-OEC combination activity is mediated through the recruitment of activated T cells and reduction of immune suppressive Tregs. **Conclusions:** These efficacy and tolerability data support the combination of MYC-OEC and CBI treatment in patients with solid tumors. OTX-2002 is currently being evaluated in a Phase 1/2 clinical trial as a monotherapy and in combination with SoC (i.e., TKI and CBIs) for patients with HCC and other solid tumor types known for an association with MYC. Research Sponsor: Omega Therapeutics.

4117

Poster Session

FDA analysis of treatment efficacy based on etiology of hepatocellular carcinoma. *First Author: May Tun Saung, US Food and Drug Administration, Silver Spring, MD*

Background: Retrospective analyses of trial-level data report that etiology of hepatocellular carcinoma (HCC) (e.g., viral versus [vs.] non-viral) may influence efficacy of systemic therapies used in advanced HCC. FDA conducted an analysis of 9 randomized controlled trials (RCTs; n=5,417) to assess treatment effects based on drug class, treatment line, and HCC etiology. **Methods:** FDA conducted a retrospective, exploratory analysis of 3 RCTs comparing first line (1L) treatment with anti-programmed cell death (ligand)-1-containing regimens (αPD-[L]1) to single-agent anti-vascular endothelial growth factor therapy (αVEGF), and 6 RCTs comparing second line (2L) treatment consisting of αPD-[L]1 or αVEGF to placebo. For each line of treatment (1L or 2L), meta-analyses of overall survival (OS) were performed for the overall treatment effect and by disease etiology, viral (hepatitis B [HBV], or hepatitis C [HCV]) vs. non-viral. Subgroup analyses were performed to investigate the confounding effect of subsequent therapy (yes vs. no) and region (Asian vs. non-Asian) on etiology. Trial-level hazard ratios (HRs) and 95% confidence intervals (CI) were mostly calculated using patient-level data submitted to FDA. Pooled HRs and CIs were calculated using a random-effects model. **Results:** While 1L αPD-[L]1 improved OS compared to 1L αVEGF in the overall population (HR [95% CI]: 0.8 [0.73, 0.88]), treatment effects were comparable for viral (HR [95% CI]: 0.75 [0.6, 0.92]; n=1,435) and non-viral (HR [95% CI]: 0.83 [0.72, 0.95]; n=979) subgroup analyses, and not influenced by subsequent therapy or region. Analyses based on specific viral infection (i.e., HBV or HCV), showed that improvement in OS for αPD-[L]1 vs. αVEGF appeared larger for HBV (HR [95% CI]: 0.7 [0.59, 0.82]; n=833) compared to HCV (HR [95% CI]: 0.83 [0.6, 1.16]; n=602). Treatment effects were also comparable in 2L for different etiologies for both αPD-[L]1 (HR [95% CI] for viral: 0.76 [0.62, 0.93]; n=529 and non-viral: 0.85 [0.65, 1.11]; n=337) and αVEGF (HR [95% CI] for viral: 0.79 [0.69, 0.9]; n=1,288 and non-viral: 0.74 [0.63, 0.88]; n=849), and not influenced by subsequent therapy. Nonetheless, compared to placebo, αPD-[L]1 had a larger treatment effect with HBV (HR [95% CI]: 0.69 [0.5, 0.94]; n=459) compared to non-viral etiologies. **Conclusions:** The results did not demonstrate that etiology of HCC was predictive of OS for both treatment classes based on retrospective, exploratory meta-analyses of 9 RCTs; however, the treatment effects may be more pronounced in patients with HBV who received αPD-[L]1 as 1L or 2L. Uncertainty remains regarding subgroup treatment effects given limited number of trials in the analyses (mostly leading to approvals), overlapping CIs, number of patients in some subgroups, retrospective nature, and exclusion of trials with inadequate data regarding etiology of HCC. Research Sponsor: None.

4119

Poster Session

Adjuvant immune checkpoint inhibitors and association with recurrence-free survival in postoperative hepatocellular carcinoma (PREVENT): A prospective cohort study. *First Author: Le Li, Guangxi Medical University Cancer Hospital, Nanning, China*

Background: Adjuvant therapy may improve survival of patients with hepatocellular carcinoma (HCC) after curative resection, yet no such therapy is universally recommended. This study compared safety and efficacy outcomes between patients at high risk of recurrence who received different types of adjuvant therapy or no such therapy after hepatic resection for HCC. **Methods:** Recurrence-free survival (RFS), overall survival, and adverse events were compared among patients who received adjuvant immune checkpoint inhibitors (ICIs) alone, ICIs with tyrosine kinase inhibitors (TKIs), or no adjuvant therapy at our medical center between 13 March 2019 and 19 March 2022. In some analyses, patients who received adjuvant therapy were matched based on propensity scores to patients who did not, in order to reduce confounding due to baseline differences. This study was registered on ClinicalTrials.gov (NCT05221398). **Results:** Of the 492 patients in our final analysis, 410 (83.3%) received no adjuvant therapy, 50 (10.2%) received ICIs alone, and 32 (6.5%) received adjuvant ICIs and TKIs. During median follow-up of 23.3 months (IQR 15.6 to 31.1 months), HCC recurred in 221 (53.9%) of patients who received no adjuvant therapy, compared to 22 (44.0%) of patients who received ICIs and 18 (56.3%) of patients who received ICIs and TKIs. RFS was significantly longer among patients who received either type of adjuvant therapy (23.9 months, 95%CI 14.0-33.7) than among those who received none (16.8 months, 95%CI 13.2-20.3), and this difference remained significant after propensity score matching (HR 0.61, 95%CI 0.39-0.94, $P = 0.033$). However, overall survival was unaffected by either type of adjuvant therapy, even after propensity score matching. The rate of grade 3 or 4 adverse events was similar between the two types of adjuvant therapy. **Conclusions:** ICIs alone or with TKIs may improve RFS of patients at high risk of recurrence after curative resection. Clinical trial information: NCT05221398. Research Sponsor: None.

4118

Poster Session

Characteristics and outcomes of patients with young-onset versus average-onset cholangiocarcinoma in the United States. *First Author: Udhayvir Singh Grewal, University of Iowa Hospitals and Clinics, Iowa City, IA*

Background: Cholangiocarcinoma (CCA) is a lethal malignancy originating from the epithelium lining the biliary tree, with a rising incidence in the Western world. CCA is commonly diagnosed after the age of 50 years, referred to as average-onset CCA (AOCCA), which has known risk factors and predictors of overall outcomes. However, robust data regarding the characteristics and outcomes of patients with young-onset (diagnosed <50 years of age) CCA (YOCCA) are lacking. **Methods:** Data on patient characteristics, tumor characteristics, incidence, and mortality were retrieved from the SEER database spanning a period from the year 2000 to 2017 (representing 48% of the US population). Intrahepatic CCA (iCCA) was identified with a topography code of C22.0 (liver) and a histology code of 8140, 8160, 8161, 8480, 8481, or 8500 or with a topography code of C22.1 (intrahepatic bile ducts) and a histology code of 8000, 8010, 8020, 8140, 8160, 8161, 8260, 8480, 8481, 8490, or 8500. Extrahepatic CCA (eCCA) was identified with a topography code of C24.1 (extrahepatic biliary ducts) and a histology code of 8000, 8010, 8020, 8140, 8160, 8161, 8260, 8480, 8481, 8490, or 8500, or for any case with a topography code of C22.0, C22.1, or C24.0 and a histology code of 8162 (Klatskin tumor). A comparison was made between the patients with YOCCA and AOCCA. Trends in incidence were analyzed using the Joinpoint regression model. Overall survival distributions were estimated using the Kaplan-Meier method. **Results:** A total of 28,367 patients were included in the analysis, which included 2,082 (7.34%) patients with YOCCA. We noted an increase in the incidence of YOCCA over the study period (annual percentage change=+2.53, $p=0.003$). The majority of the patients in the YOCCA group were males (54.66%), White (50%), and had iCCA (71.9%). When compared to AOCCA, these patients were more likely to be males (54.7% vs 52.4%, $p=0.048$), non-White (39.8% vs 35.5%, $p=0.007$), and have a diagnosis of iCCA (71.9% vs 65.7%, $p<0.0001$). Patients in the YOCCA group were more likely to present with regional spread (31.6% vs 28.4%, $p<0.0001$) and metastatic disease (31.9% vs 25.6%, $p<0.0001$). YOCCA patients were also more likely to receive surgery (33.3% vs 22.7%, $p<0.0001$) and chemotherapy (62.6% vs 37.3%, $p<0.0001$) compared to patients in the AOCCA group. Patients with YOCCA had a significantly better median overall survival (13 months vs. 7 months, $p<0.001$) than patients with AOCCA. **Conclusions:** The current analysis showed a significant increase in the incidence of YOCCA over the 17 years of the study period. Patients with YOCCA were more likely to be non-White, males and present with iCCA. Despite presentation with advanced-stage disease (with regional spread or metastatic disease), patients with YOCCA were more likely to receive cancer-directed therapy and had better overall survival than patients with AOCCA. Research Sponsor: None.

4120

Poster Session

Camrelizumab in combination with apatinib as a perioperative treatment for patients with hepatocellular carcinoma at high risk of recurrence: A prospective, single-arm, phase 2 study. *First Author: Yunlong Cui, Tianjin Medical University Cancer Hospital & Institute, Tianjin, China*

Background: Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide, and a rising cause of cancer-related mortality. To date, the optimal perioperative treatment strategy for HCC patients remains unclear. It is urgent to develop novel and reliable therapeutic interventions to reduce the risk of recurrence and improve survival in patients with locally advanced HCC. **Methods:** This prospective, exploratory, single-arm, phase 2 study enrolled patients with primary resectable HCC who had not received prior systemic therapy. Before surgery, patients received combination treatment with four cycles of camrelizumab (200 mg, Q2W) plus apatinib (250 mg, QD). Each cycle was two weeks. The feasibility of hepatic resection was assessed by radiographic imaging. After 4-8 weeks of surgery, patients continued combination therapy (camrelizumab [200 mg, Q2W] and apatinib [250 mg, QD]) for one year. Primary endpoint was major pathological response (MPR). Secondary endpoints were pathologic complete response rate (pCR), objective response rate (ORR), disease-free survival (DFS), and safety. Exploratory endpoint was microvascular invasion (MVI). This study is registered on ClinicalTrials.gov, number NCT04701060. **Results:** Between Jan 12, 2021, and Aug 17, 2022, 31 patients with a median age of 54 years were enrolled. Among these, 21 patients (67.7%) had hepatitis B virus infection. Before surgical incision, two patients withdrew informed consent. Therefore, ORR based on RECIST 1.1 and mRECIST were 13.8% (4/29) and 48.3% (14/29), respectively. 26 patients underwent hepatic resection, R0 resection rate was 100%, 10 (38.5%) patients achieved MPR, and pCR rate was 7.7%. The reasons for patients not undergoing surgery were disease progression and serious adverse events (AEs). Among patients with MVI, M0 was found in 57.7% (15/26) patients, M1 was found in 34.6% (9/26) patients, and M2 was found in 7.7% (2/26) patients. 1-year DFS rate was 77.4%, and median DFS was not reached. The most common AEs included increased aspartate aminotransferase (74.2%), increased alanine aminotransferase (70.1%), decreased platelet count (61.3%), anemia (58.1%), and decreased lymphocyte count (51.6%). Grade 4 AEs occurred in 7 of 31 patients, and there were no treatment-related deaths. **Conclusions:** Camrelizumab plus apatinib as a perioperative treatment is effective and tolerable in patients with HCC at high risk of recurrence. Preoperative neoadjuvant therapy has reduced the rate of MVI. Because of the short follow-up period, whether perioperative treatment can effectively reduce recurrence rates and improve long-term survival still needs further investigation. Clinical trial information: NCT04701060. Research Sponsor: Jiangsu Hengrui Medicine.

4121

Poster Session

Machine learning-based multimodal prediction of prognosis in patients with resected intrahepatic cholangiocarcinoma. *First Author: Benoit Schmauch, OWKIN, Paris, France*

Background: Intrahepatic cholangiocarcinoma (ICCA) is an aggressive malignancy and the second most common primary liver cancer. About a third of patients may benefit from surgery but recurrence is common and the overall survival is low. Accurate prognosis modeling that can predict response to treatment and outcome remains an unmet clinical need. Deep learning methods provide a new opportunity to better predict prognosis by extracting distinguishing characteristics interrogating multiple data sources, which appears to be superior to unimodal modeling. This study aimed to construct a predictive model of patient outcome and identify predictive biomarkers based on a combination of clinical, genomic, histological and radiological data. **Methods:** We analyzed 83 patients with ICCA that underwent surgery and designed a multi-modal model to predict overall survival (OS) and progression-free survival (PFS). Among these patients, each had one to three hematoxylin/eosin histology slides. As a pre-processing step, each histology slide was decomposed into patches, each patch was fed into a ResNet feature extractor to extract a feature representation of the patch, and the features across patches were aggregated with maximum pooling to yield a 2048-dimensional vector representation for each slide. Among these 83 patients, 76 patients had their tumors profiled for somatic genomic alterations using MSK-IMPACT, a deep targeted-sequencing assay. A binary matrix across altered genes and samples was created as an input to the prediction model. Cox proportional hazard models specific to each modality (clinical data, histological slides, and altered genes) were then designed and their predictions were averaged to produce the final log-risk score. The models were validated using a 5-fold, 5-repeat cross-validation with patient-level splits. **Results:** A model using only clinical and routine histological data achieved a concordance index of 0.74 (95% confidence interval, 0.64-0.82) for OS and 0.73 (0.64-0.78) for PFS. Adding information about genetic alterations improved performance for OS (0.80, 0.70-0.88) and similar performance for PFS (0.72, 0.64-0.79). Both models outperform a staging-based patient stratification. **Conclusions:** This study demonstrates that machine learning models can improve survival prediction using multimodal data after resection of intrahepatic cholangiocarcinoma. Such models have the potential to improve risk stratification and treatment recommendations. Research Sponsor: OWKIN.

Input data	OS	PFS
Cancer stage (AJCC/UICC 8th edition)	0.66 (0.55-0.75)	0.59 (0.49-0.66)
Clinical + Histological	0.74 (0.64-0.82)	0.73 (0.64-0.78)
Clinical + Histological + Altered genes	0.80 (0.70-0.88)	0.72 (0.64-0.79)

4123

Poster Session

Utility of circulating tumor DNA (ctDNA) as a predictive biomarker for disease monitoring in patients (pts) with cholangiocarcinoma (CCA) before and during adjuvant chemotherapy (ACT): Sub-analysis of the randomized phase 2 STAMP trial. *First Author: Changhoon Yoo, Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea*

Background: Detection of circulating tumor DNA (ctDNA) in blood is a powerful predictive biomarker for identifying molecular residual disease (MRD) post-surgery. Not much is known about the utility of identifying MRD using ctDNA in pts with resected CCA, despite its associated poor prognosis. The STAMP trial (NCT03079427), a randomized phase 2 study comparing adjuvant capecitabine (CAP) to gemcitabine plus cisplatin (GemCis) showed no difference in recurrence-free survival (RFS) and overall survival (OS) between the 2 arms. The goal of this analysis was to evaluate the feasibility of monitoring ctDNA to predict the risk of recurrence in pts with resected CCA. **Methods:** A total of 254 plasma samples were collected from a cohort of 89 CCA (hilar, N = 43; distal, N = 46) pts post-surgery at 3 separate time points; pre-ACT (baseline, N = 89), on-ACT C5D1 (after 5 cycles of treatment) (N = 88), and on-ACT C8D1 (after 8 cycles of treatment) (N = 77). Longitudinal ctDNA testing was performed using a personalized, tumor-informed ctDNA assay (Signatera, bespoke mPCR-NGS assay). ctDNA results were analyzed and evaluated for its correlation with RFS and OS. **Results:** At the MRD timepoint (baseline, pre-ACT), 24.7% (22/89) pts were ctDNA-positive, 90.9% (20/22) of whom recurred demonstrating a trend for shorter RFS (HR = 1.7, 95%CI 0.98-2.8, p = 0.069) compared to ctDNA-negative pts. All pts who remained ctDNA-positive on-ACT at C5D1 (N = 17) and C8D1 (N = 15), recurred clinically with a significantly shorter RFS (HR = 8.1, 95%CI 4.3-15, p < 0.0001 and HR = 5.0, 95%CI 2.7-9.4, p < 0.0001, respectively). The primary cancer site (hilar vs distal) or type of ACT (CAP vs GemCis) had no impact on RFS irrespective of ct-DNA result. Pts who remained ctDNA-negative on ACT (N = 56) showed significantly better RFS compared to pts who remained positive (N = 10, HR = 6.6, 95%CI 3.1-14, p < 0.001), or who turned positive (N = 11, HR = 5.2, 95%CI 2.54-10.5, p < 0.001). In multivariate analysis including primary tumor site, sex, pathological grade and ACT regimen, positive ctDNA status at baseline (pre-ACT) remained significant for poor RFS (HR = 1.82, 95%CI 1.04-3.18, p = 0.035). **Conclusions:** Personalized monitoring of ctDNA both pre and on-ACT is feasible and predictive for recurrence in pts with resected CCA. To our best knowledge, this is one of the first reports presenting the clinical implication of ctDNA monitoring on ACT, in pts with CCA. Our findings suggest ctDNA monitoring may help optimize clinical decision-making in pts with resected CCA. Larger prospective studies would be needed to validate the findings of this study. Clinical trial information: NCT03079427. Research Sponsor: Natera; Asan Institution for Life Science.

4122

Poster Session

Efficacy and safety of HepaSphere drug-eluting bead transarterial chemoembolization combined with hepatic arterial infusion chemotherapy in advanced hepatocellular carcinoma. *First Author: Baojiang Liu, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Interventional Therapy, Peking University Cancer Hospital & Institute, Beijing, China, China*

Background: Transarterial chemoembolization (TACE) is widely applied and shows good efficacy in advanced hepatocellular carcinoma (HCC). Recently, hepatic arterial infusion chemotherapy (HAIC) has also gained popularity in the treatment of HCC. Several studies have described the comparison between HAIC and TACE or TACE combined with HAIC. However, the evaluation between TACE plus HAIC and HAIC is rarely reported. Here, we observed the performance of HepaSphere DEB-TACE combined with HAIC (Hepa-HAIC) comparing to HAIC in patients with advanced HCC. **Methods:** 167 patients diagnosed as advanced HCC and treated in Peking University Cancer Hospital from May 2018 to May 2022 were enrolled in this retrospective study, composed of 74 patients received HepaSphere DEB-TACE combined with HAIC-FOLFOX (Hepa-HAIC) and 93 patients received HAIC-FOLFOX. More than 60% patients experienced other treatments before the enrollment. To avoid the selection bias, propensity score matching (PSM) was conducted and applied for the efficacy and safety analysis between these two cohorts. The primary endpoints are progression-free survival (PFS) and overall survival (OS); the secondary endpoint includes objective response rate (ORR), disease control rate (DCR) and safety. **Results:** Propensity-matching yielded 48 pairs and the baselines were almost equal in Hepa-HAIC and HAIC cohorts after matching. Median PFS and median OS were both higher in matched Hepa-HAIC cohort (median PFS:8.9 vs. 5.8 months, P=0.035; median OS:22.4 vs. 9.5 months, P=0.027), which were consistent with pre-matching analysis. The ORR in Hepa-HAIC and HAIC cohorts was 75.0% and 37.5%, respectively; DCR was 93.8% after Hepa-HAIC and 81.3% after HAIC. There was no treatment-related death. Serious adverse events were similar in these two groups, except alanine aminotransferase (ALT) and vomiting. There was more frequency of Grade 3-4 ALT elevation in Hepa-HAIC (33.3% vs. 8.3%, P=0.003) while more incidence of vomiting in HAIC group (29.2% vs. 12.5%, P=0.044). **Conclusions:** All of the observed PFS, OS, ORR and DCR in Hepa-HAIC group are superior to HAIC group, which indicates the combination of HepaSphere DEB-TACE and HAIC may lead to improved outcomes with comparable safety profile in advanced HCC. Research Sponsor: None.

	Hepa-HAIC (N=48)	HAIC (N=48)	P value
ORR	75%	37.5%	P<0.001
DCR	93.8%	81.3%	P<0.001
mPFS	8.9m	5.8m	P=0.035
mOS	22.4m	9.5m	p=0.027

4124

Poster Session

Preliminary results of sequential transarterial chemoembolization and stereotactic body radiotherapy followed by immunotherapy using single tremelimumab regular interval durvalumab in locally advanced, unresectable hepatocellular carcinoma (START-FIT using STRIDE): A single-arm, phase II study. *First Author: Chi Leung Chiang, The University of Hong Kong, Hong Kong, NA, Hong Kong*

Background: Sequential transarterial chemoembolization and stereotactic body radiotherapy followed by immunotherapy (IO) (START-FIT) using anti-PD-L1 has demonstrated promising efficacy in locally advanced HCC (laHCC). We aimed to evaluate START-FIT activity using anti-PD-L1 and anti-CTLA-4 IO backbone. **Methods:** Adult patients with laHCC not suitable for curative resections were recruited. Each with tumor at least 5cm, maximum three tumors, and child-Pugh A5-B7 liver function. Patients had single TACE, 5-SBRT 28 days after, then single Tremelimumab (300mg) and regular 4-week interval Durvalumab (1500mg) at 7 days upon SBRT completion. Primary endpoint was overall response rate (ORR) per modified Response Evaluation Criteria in Solid Tumors (mRECIST); secondary endpoints included progression-free survival (PFS), overall survival (OS), and treatment-related (TR) adverse event (AE) [NCT04988945]. **Results:** During 11 Dec, 20 and 3 Oct, 22, 16 patients were enrolled with median age 66 (range (r): 51-84 years), 14 (87.5%) were male, the lesion(s) diameter median sum was 11.2 cm (r: 5.8-15cm), and 11 (68.8%) had macrovascular invasion (n=6, hepatic vein, n=4, branched portal vein, n=1 both). With median 11.3 months (r: 3.7-24.5 months) follow-up time, the best ORR was 81.3% (95% CI: 54.4-96.0%) (Complete response CR: n=7, 43.8%; partial response PR: n=6, 37.5%; stable disease SD + progressive disease PD: n=3, 18.7%). The 6 and 12-month PFS rates were 86.7% (95% CI: 69.3-100%) and 58.7% (95% CI: 33.6-84.4%), while 6 and 12-month OS rates were 100% (95% CI: 91.7-100%) and 83.3% (95% CI: 62.2-100%) respectively. The 12-month OS with CR vs. PR vs. SD+PD was 100%, 75%, and 50% respectively. Four (25%) and one patient (6.3%) experienced TRAEs and immune-related AE of grade 3 or worse respectively. **Conclusions:** START-FIT using STRIDE is safe and effective in unresectable laHCC resulted in 43.8% CR rate and promising survival. Clinical trial information: NCT04988945. Research Sponsor: Astra.

	N=16	%
Age, median (r), years	66 (51-84)	
Sex		
Male	14	87.5
Female	2	12.5
ECOG performance status		
0	12	75
1	4	25
Aetiology of liver cirrhosis		
Hepatitis B	12	75
Multiple etiologies	2	12.5
Cryptogenic	2	12.5
Child-Pugh score		
A5	12	75
A6	4	25
Albumin Bilirubin Score		
Grade 1	11	68.7
Grade 2	5	31.3
BCLC stage		
A-B	5	31.3
C without extra-hepatic spread	11	68.7
Unresectable Reasons		
Inadequate liver remnant volume and / or poor ICG	4	25
Unable to achieve R0 resection	1	6.3
BCLC stage C without extra-hepatic spread	11	68.7
Tumor vascular invasion		
No	5	31.3
Yes	11	68.7
Branched portal vein invasion	4	25
Hepatic vein invasion	6	37.4
Both	1	6.3
Number of lesion(s)		
1	14	87.5
2-3	2	12.5
Largest lesion size, median (r), cm	10.8 (6.8-15)	
Sum of largest lesion diameters, median (r), cm	11.2 (5.8-15)	
Baseline AFP, ng/ml		
< 400	11	68.8
> 400	5	31.2

4125

Poster Session

Primary analysis of a phase II study of atezolizumab plus bevacizumab for TACE-unsuitable patients with tumor burden beyond up-to-seven criteria in intermediate-stage hepatocellular carcinoma: REPLACEMENT study. *First Author: Kazuomi Ueshima, Kindai University Faculty of Medicine, Osaka-Sayama, Osaka, Japan*

Background: Intermediate-stage hepatocellular carcinoma (HCC) is a heterogeneous disease; therefore, the efficacy of transarterial chemoembolization (TACE) is affected by tumor burden, resulting in a wide range of survival outcomes. Multiple recent guidelines suggest that systemic therapy is preferable for patients with intermediate-stage HCC who are TACE unsuitable because of high tumor burden, such as beyond up-to-seven criteria. The Phase III IMbrave150 study established atezolizumab plus bevacizumab (atezo+bev) as the standard of care in patients with unresectable HCC. Here, we investigated whether atezo+bev is potentially superior to TACE in efficacy and safety in TACE-naïve patients with unresectable intermediate-stage HCC beyond up-to-seven criteria. **Methods:** In this multicenter, phase II study, atezo 1200 mg + bev 15 mg/kg q3w were administered to eligible patients (as defined above plus having Child-Pugh A liver function) enrolled from Dec 2020 to Sep 2021 until discontinuation due to disease progression, adverse events (AEs), or other reasons. Overall survival (OS) follow-up continued for 2.5 years after enrollment. The primary endpoint was progression-free survival (PFS) assessed by mRECIST by investigator; secondary endpoints were objective response rate (ORR), PFS by RECIST v1.1, OS, and safety. In an exploratory analysis, we conducted propensity score matching (PSM) analysis to compare the efficacy between atezo+bev and TACE, the data of which were retrospectively collected in patients treated with TACE in each participating center from Jan 2017 to Dec 2017. **Results:** In total, 74 patients were enrolled (male, 87.8%; mean age, 73.7 years; median [range] maximum tumor diameter by pre-treatment CT, 4.8 [1.0,13.0] cm). Median (min, max) follow-up was 15.0 (1.6, 21.6) months. Median PFS was 9.1 (95%CI: 7.1, 10.2) months (by mRECIST; primary endpoint). ORR was 45.9 (95%CI: 34.3, 57.9) % by mRECIST. Median OS was not reached (NR) (95%CI: NR, NR). 12-month OS rate was 84.6 [95%CI: 74.0, 91.2]%. The most frequent AEs (any grade ≥10% of patients) were hypertension, proteinuria, malaise, anorexia, edema, pruritis, and diarrhea. **Conclusions:** Atezo+bev provides clinical benefits to TACE-unsuitable patients with intermediate-stage HCC beyond up-to-seven criteria. Results of the exploratory PSM analysis will be presented. Clinical trial information: jrcs071200051. Research Sponsor: Chugai Pharmaceutical Co., Ltd.

4127

Poster Session

Robotic and laparoscopic surgery versus open surgery for perihilar cholangiocarcinoma: A meta-analysis. *First Author: Laynara Vitória Da Silva Vieira, Federal University of Piauí, Teresina, Brazil*

Background: Robotic and laparoscopic surgeries provide a new approach for patients with perihilar cholangiocarcinoma (pCCA). However, whether it can achieve similar outcomes to traditional open surgery (OS) remains controversial. Therefore, to compare the outcomes of laparoscopic/robotic surgery with open surgery and investigate the efficiency for Klatskin tumors further, we systematically summarized the currently available data and performed a meta-analysis. **Methods:** A systematic review and meta-analysis were conducted to examine the most recent studies on the topic. The search was updated to January 15, 2023, and was performed on PubMed, LILACS, and Embase. The inclusion criteria were case cohort comparing two arms: robotic or laparoscopic and open surgery for pCCA, based in PICOS principle, while the exclusion criteria were review, letter, and articles with incomplete data. All the included literature was evaluated for quality and risk of bias using the Joanna Briggs Institute's critical appraisal tool and the data were extracted and entered into an Excel spreadsheet by two authors. The data was then analyzed using Review Manager 5.4 applying Odds Ratio and Mean Difference. The study protocol was registered in PROSPERO (CRD42023388478) and was conducted following the PRISMA 2020 checklist. **Results:** A total of 1133 patients were included in the study (411 laparoscopic/robotic, 722 open surgeries), 15 retrospective cohort were used in the meta-analysis. The meta-analysis revealed that laparoscopic surgery resulted in less blood loss (Mean difference -77.87; 95% CI = -89.97, -67.78; $p < 0.00001$, $I^2 = 84\%$), shorter hospital stay (Mean difference -3.25; 95% CI = -4.83, -1.67; $p < 0.0001$, $I^2 = 79\%$) but longer operation time (Mean difference 53.95; 95% CI = 48.09, 59.81; $p < 0.00001$, $I^2 = 86\%$). The mortality rate was not significantly different between the two groups (odds ratio = 0.82; 95% CI = 0.47 a 1.42; $p = 0.48$; $I^2 = 0\%$). Both surgeries showed similar results for age (Mean difference 1.71; 95% CI = -0.62, 4.03; $p = 0.15$, $I^2 = 53\%$), bilirubin (Mean difference -43.45; 95% CI = -77.11, -9.79; $p < 0.01$, $I^2 = 0\%$), BMI (Mean difference 0.25; 95% CI = -0.24, 0.74; $p = 0.31$, $I^2 = 0\%$), and tumor diameter (mean difference -0.06; 95% CI = -0.52, 0.40; $p = 0.80$, $I^2 = 0\%$). **Conclusions:** The limitations of the study evidence are due to the small number of patients included in each article. Concerning blood loss and hospital stay, minimally invasive surgery offers better results. However, open surgery still has a shorter operating time. Both surgeries had similar results in mortality. Minimally invasive surgery is as safe as open surgery for pCCA resection. Research Sponsor: None.

4126

Poster Session

A phase II/III study of camrelizumab plus apatinib as perioperative treatment of resectable hepatocellular carcinoma at intermediate-high risk of recurrence: Primary results of major pathologic response from phase II stage. *First Author: Jian Zhou, Liver Cancer Institute, Zhongshan Hospital, and Key Laboratory of Carcinogenesis and Cancer Invasion (Ministry of Education), Fudan University, Shanghai, China*

Background: Surgical resection remains an important treatment strategy for patients (pts) with liver cancer. However, the 5-year recurrence rate is still 50-70% in surgically resectable pts. Intermediate-high risk factors of recurrence in HCC include single tumor size > 5 cm, multiple tumors, and microvascular invasion. The standardized perioperative regimen for resectable HCC has not been established. This study aimed to assess the efficacy and safety of camrelizumab plus apatinib (C+A) as a perioperative regimen in resectable HCC at intermediate-high risk of recurrence (Clinical trial: NCT04521153). **Methods:** In this multicentre, randomised, phase II/III study, eligible HCC pts (CNLC Ib-IIIa) were randomly assigned in a 1:1 ratio to treatment group and control group. Pts in treatment group received 2 cycles of C (200mg Q2W) plus A (250mg QD) followed by surgery and a post-surgical TACE. At least 6 cycles of sequential treatment of C (200mg Q3W) plus A (250mg QD) were performed after TACE. Pts in control group received surgical resection and a post-surgical TACE. Primary endpoint of phase III stage was 3-year EFS, of phase II stage was MPR (defined as less than 50% residual tumor) rate. In the phase II stage, futility analysis on a phase II outcome was performed after pts in treatment group completed surgical resection and pathological evaluation. If $< 15\%$ of pts achieved an MPR, or $> 20\%$ of pts had progression that precluded surgery, the study would not proceed to phase III stage. **Results:** In phase II stage, 60 pts were randomly assigned to treatment group, and 59 to control group. As of Nov 4, 2022, the last randomised pt underwent curatively surgical resection and pathological evaluation. The median age was 58 years (range, 21-75). 101 (84.9%) were male, and 96 (80.7%) had HBV infection. In treatment group, 58 pts received neo-adjuvant therapy, 52 completed 2 cycles of preoperative therapy and proceeded with planned resection. Surgery was aborted for 6 pts: 3 refused surgery, 2 deaths (1 for tumor rupture of HCC, 1 for immune related hepatitis), and 1 had protocol deviation. The MPR rates in the ITT population were 40% (24/60). Among them, 10% pts (6/60) had $\leq 5\%$ surviving tumor cells in tumor bed. The MPR rate in pts who had surgical resection were 46.2% (24/52). 19.3% pts experienced ≥ 3 grade TRAEs, the most common of which were AST increased (5.3%), hypertension (5.3%), and ALT increased (3.5%). **Conclusions:** The phase II stage of the study did not meet the stopping criteria. Neo-adjuvant camrelizumab plus apatinib therapy exhibits promising pathological response in HCC pts at intermediate-high risk of recurrence, with a tolerable safety profile. The phase III stage of the study is currently ongoing. Clinical trial information: NCT04521153. Research Sponsor: Shanghai shenkang hospital development center; Jiangsu Hengrui Pharmaceuticals Co., Ltd.

4128

Poster Session

Development and validation of a non-invasive cfDNA targeted sequencing assay for early-stage hepatocellular carcinoma detection using cfDNA methylation and fragmentomics. *First Author: Rui Liu, Singlera Genomics Ltd., Shanghai, China*

Background: Hepatocellular carcinoma (HCC) is one of the most common cancers in China, and one of the leading causes of cancer-related deaths in the country. With a 5-year survival rate of only 15-20%, early detection is crucial to improve the treatment and survival of HCC patients. Currently, alpha-fetoprotein (AFP) is commonly used as a serum marker for HCC, but it is not a sufficiently specific and can cause false positive readings due to elevated levels caused by other liver conditions. An alternative method is to use circulating free DNA (cfDNA) released by tumor cells as cancer-screening targets, which has been shown to be a more sensitive and specific biomarkers for HCC detection. This study aims to develop a non-invasive screening assay based on cfDNA features to improve the detection of early-stage HCC. **Methods:** Candidate methylation markers for HCC detection were collected and evaluated using GEO, TCGA and in-house datasets, 1601 of which were incorporated into a targeted sequencing panel named HcSeer. Multiple types of cfDNA features were constructed from the sequencing data, which included methylation-related features such as methylation haplotype blocks (MHBs) and methylated haplotype fraction (MHF), and fragmentomics features such as end motif and CNV. For model building, Cancer and healthy plasma samples were randomly divided into a training and a testing set at a 2:1 ratio. A two-step deep neural network model was built to classify HCC using selected features of both types. **Results:** We previously enrolled a total of 401 plasma samples (200 healthy, 201 HCC) for model construction and the performance of the HcSeer model have been documented. An independent validation cohort of 421 plasma samples (280 healthy, 141 HCC) was currently collected from different centers. In this independent validation, the HcSeer model achieved an AUC of 0.98 with a sensitivity of 96.5% at a specificity of 96.4%. Importantly, HcSeer maintained a high sensitivity for HCC across all stages: 94.3%, 96%, 100% and 100% for stage I – IV cases, respectively. When compared to AFP, HcSeer achieved a significantly higher sensitivity of 94% than AFP's 55% in 137 HCC cases having AFP level tested. When AFP level was combined with the HcSeer model, the sensitivity for HCC further increased to 96%. **Conclusions:** This study demonstrated that the DNA methylation and fragmentomics patterns of cfDNA can accurately distinguish HCC and healthy plasma samples, particularly in the early stages of HCC. The combination of the HcSeer and AFP further improved the accuracy of the prediction. Although this study was limited in sample size, it clearly showed the potential of the HcSeer assay for accurate HCC detection in blood. Research Sponsor: National Key Research and Development Program of China (2019YFC1315800).

4129

Poster Session

Neoadjuvant immunotherapy with ipilimumab plus nivolumab and radiologically and pathologically quantifiable responses through modulation of the tumour microenvironment in resectable hepatocellular carcinoma. *First Author: Antonio D'Alessio, Imperial College, London, United Kingdom*

Background: Liver resection (LR) is a potentially curative option for early-stage hepatocellular carcinoma (HCC), and immune checkpoint inhibitors (ICI) are being investigated in the perioperative setting to improve long-term relapse rates and survival outcomes. **Methods:** PRIME-HCC is a phase Ib study testing nivolumab (3 mg/kg, day 1 and day 22) plus ipilimumab (1mg/kg, day 1 only) (N+I) prior to LR in resectable HCC. Primary endpoint was safety, while secondary endpoints included radiological response (per RECIST v1.1) and pathological response on resection specimens (ReS). Translational endpoints encompassed analysis of tissue samples with multiplex immunohistochemistry (MIHC) and gut microbiota profiling with high-throughput sequencing and their correlation with response. **Results:** As of 7th of February 2023, 25 patients (pts) were enrolled, all Child-Pugh A, mostly male (n=18, 72%), with cirrhosis (n=13, 52%), and viral hepatitis (44%, 4 HBV and 7 HCV). Any-grade adverse events (AEs) occurred in 88% pts (n=22), of which 24% (n=6) grade (G) 3. No G4-5 AEs were recorded. Any-grade treatment-related (tr)AEs were reported by 72% pts (n=18), including 8% G3 trAEs (n=1 ALT/AST elevation and n=1 dyspnea). After a median follow-up of 14.5 months (95% CI 7.0-22.0), 21 pts were assessed for radiological response and underwent surgery. Median time from treatment start to LR was 2.4 months (interquartile range 2.2-2.7). LR was delayed in 1 pt (4.8%) because of G2 tr-hypothyroidism but occurred uneventfully. Objective response rate was 29% (n=5 partial responses, n=1 complete response [CR]); disease control rate was 95% (n=20), with 1 progressor having a mixed HCC/cholangiocarcinoma. Major pathological response (MPR), defined as $\geq 70\%$ tumour regression, was observed in 56% (n=9) of the pathologically evaluable ReS (n=16), with 38% pathological CR (n=6). In the MIHC analyses, pre-treatment biopsies of MPR pts were significantly enriched in peritumoral CD4+ and CD8+ cells, with no intratumoral difference. When comparing baseline biopsies and ReS, MPR pts had a significant decrease of intratumoral FOXP3+/CD4+ regulatory T cells (Tregs), while peritumoral Tregs increased significantly in non-MPR ReS. In baseline stool samples, α and β diversity did not differ across responders (R) and non-responders (NR), nor it changed after ICI. However, pre-treatment stool samples of NR pts were significantly enriched in *Alistipes* and *Collinsella* genera. **Conclusions:** Neoadjuvant N+I is feasible and tolerable for early-stage HCC, with promising radiological and pathological response rates. Study of tissue and gut microbiota highlights tumor and host-related changes. Immune infiltrate and gut microbiota composition lend themselves as predictors of anti-tumour efficacy of N+I combination. Clinical trial information: NCT03682276. Research Sponsor: Funder: Bristol Myers Squibb.; Cancer Research UK (RCCPDB- Nov21/100008); Associazione Italiana per la Ricerca sul Cancro, Institute of Hepatology, Wellcome Trust Strategic Fund (PS3416), the Cancer Treatment and Research Trust (CTRT); Infrastructural support by the Cancer Research UK Imperial Centre and the NIHR Imperial Biomedical Research Centre.

4131

Poster Session

Racial disparities in the outcomes of liver transplantation in the treatment of hepatocellular carcinoma. *First Author: Syeda Ashna Fatima Kamal, Springfield Memorial Hospital/Southern University of Illinois, Springfield, IL*

Background: According to the National Comprehensive Cancer Network (NCCN), liver transplantation (LT) is currently the treatment of choice for patients with early hepatocellular carcinoma (HCC). A retrospective study in 2016 showed a difference in mortality among races in patients undergoing treatment for HCC. Our study is the first to compare the outcomes of mortality, morbidity and hospital utilization of HCC patients undergoing LT among races in the US. **Methods:** This is a retrospective longitudinal study of patients with a primary diagnosis of HCC. We retrieved data from the Nationwide Inpatient Sample (NIS) databases from the years 2016 to 2020 using ICD-10 codes. Multivariate regression analysis was applied to compare the outcomes in races, adjusted for patient and hospital confounders. A T-Test and Chi Square test were performed to compare baseline characteristics. We used STATA Version 17.0 Software for analysis. The p-value was set at $p < 0.05$ for statistical significance. **Results:** Among a total of 112,110 adults with HCC, 2.8% (n=3,150) underwent LT. Blacks had lower rates of LT. Blacks and Hispanics were found to have a lower income ($p=0.000$). No difference in the Charlson Comorbidity index was noted among races ($p=0.5519$), however, Blacks had more smokers ($p=0.0149$). Hispanics had a significant increase in THC compared to Whites (coefficient: 102,058 US Dollars, $p=0.033$, CI95%: -109,404 - 119,787), with no difference in the length of stay among races. Blacks had higher rates of mortality ($p=0.004$), acute kidney injury (AKI) ($p=0.001$), and similar rates of transplant complications. **Conclusions:** Our study showed that while Blacks have lower rates of LT, they have a higher rate of mortality and morbidity following LT. Large scale studies are necessary to help determine factors associated with these findings. Research Sponsor: None.

4130

Poster Session

The efficacy of radical hepatectomy versus stereotactic body radiotherapy for primary hepatocellular carcinoma: A propensity score matching analysis. *First Author: Yulin Hu, shenzhen university, Shenzhen, guangdong, China*

Background: Recent international guidelines have included stereotactic body radiotherapy (SBRT) which outstanding tumor control as a treatment option for hepatocellular carcinoma (HCC) in several settings. However, data evaluating surgery and SBRT are limited, and results published were controversial. The retrospective study aims to compare the efficacy of hepatectomy and SBRT for HCC. **Methods:** The study population started with patients in databases of primary HCC, treated with curative hepatectomy or SBRT, regardless of tumor number, tumor size, cirrhosis and portal vein thrombosis. Patients with prior cancer treatment other than transarterial chemoembolization were excluded. In order to reduce the potential confounding effect of treatment and selection bias, 3-to-1 propensity score models were constructed based on each patient's estimated propensity score. The variables significant for overall survival were considered for the match, including age, sex, Child-Pugh score, ECOG performance status score, maximum diameter, BCLC stage, prothrombin time, total bilirubin, albumin, and white blood cell. Overall survival and progression-free survival were compared. **Results:** A total of 174 patients, 154 in hepatectomy group and 20 in SBRT group, were analyzed. 125 men and 29 women, mean 56.2 years of age, in hepatectomy group. 12 men and 8 women, mean 70.5 years of age, in SBRT group. ECOG was a significant favorable factor for overall survival. Maximum diameter, portal vein embolization, aspartate transferase and albumin was significant favorable factors for disease-free survival of patients with primary hepatocellular carcinomas. Before PSM, patients in the hepatectomy group tended to be younger, had better performance status, less cirrhosis, less tumor number and had better hepatic function than those in the SBRT group ($P < .05$). The 3-year overall survival rate and median progression-free survival time for the surgical resection and SBRT groups were 77.9% vs 35.4 ($P = .003$) and 30 vs 20 month ($P = .486$), respectively. After PSM, 80 patients, 60 in hepatectomy group and 20 in SBRT group, were analyzed. The 3-year overall survival rate and median progression-free survival time for the surgical resection and SBRT groups were 71.9% vs 56.6 ($P = .92$) and 17 vs 26 month ($P = .656$), respectively. The patients of hepatectomy group had less cirrhosis, better liver function and less tumor number than those in 20 with SBRT. **Conclusions:** For primary HCC, regardless of tumor size and tumor number, stereotactic body radiotherapy can provide similar result on overall survival and tumor control compared to hepatectomy. Stereotactic body radiotherapy can also be less invasive and provide less inpatient time. So stereotactic body radiotherapy can be a effective treatment for patients with primary HCC. Research Sponsor: None.

4132

Poster Session

ACTION-1 phase Ib/3 trial of RYZ101 in somatostatin receptor subtype 2-expressing (SSTR2+) gastroenteropancreatic neuroendocrine tumors (GEP-NET) progressing after ¹⁷⁷Lu somatostatin analogue (SSA) therapy: Initial safety analysis. *First Author: Michael Morris, Advanced Molecular Imaging and Therapy, Glen Burnie, MD*

Background: RYZ101 (²²⁵Ac-DOTATATE) is a first-in-class, highly potent alpha-emitting radiopharmaceutical in development for treating SSTR2+ solid tumors. Alpha-particles (as emitted by ²²⁵Ac) have a shorter path length (40–100 μ m) and higher linear energy transfer (80–100 keV/ μ m) than beta-particles, causing more frequent double-strand DNA breaks and potentially higher cancer cell kill rates and less damage to healthy tissues. ACTION-1 (NCT05477576) is a 2-part, global, randomized, controlled, open-label, phase 1b/3 trial of RYZ101 in patients (pts) with advanced well-differentiated SSTR+ GEP-NETs progressing after ¹⁷⁷Lu-SSA therapy. Part 1 (phase 1b) aims to determine safety, pharmacokinetics, and recommended phase 3 dose (RP3D) of RYZ101. **Methods:** Part 1 is an uncontrolled dose de-escalation study with a Bayesian optimal interval design. Escalation (0.197) and de-escalation (0.298) boundaries based on a target dose-limiting toxicity (DLT) rate of 25% were applied. Pts received RYZ101 IV every 8w for up to 4 cycles. Planned dose levels (n=6/level): Level 0 (starting dose), 120 kBq/kg (3.2 μ Ci/kg); if necessary, Level -1, 90 kBq/kg (2.4 μ Ci/kg); Level -2, 60 kBq/kg (1.6 μ Ci/kg). No dose escalation above starting dose was permitted. DLT was assessed for 56d after the first RYZ101 treatment. Treatment-emergent adverse events (TEAEs) were graded by NCI-CTCAE v5.0. Dose de-escalation decisions and safety data review were overseen by a Data Review Committee. Data cut-off: 26 Oct 2022. **Results:** At data cut-off, 9 pts had received RYZ101 at 120 kBq/kg (median dose 8.9 MBq); 7 pts were DLT-evaluable. No DLTs occurred and no dose de-escalation steps were implemented. Baseline characteristics: median age 70y; male (n=6)/female (n=3); ECOG PS 0 (n=4)/1 (n=5); median disease duration 6.9y; primary tumor site GI (n=6)/pancreas (n=3). A safety summary is shown. No treatment-related serious AEs were observed. TEAE requiring dose reductions occurred in 2 pts (Grade 2 platelet count decreased, n=1; Grade 2 thrombocytopenia, n=1). Grade 3 or 4 TEAEs occurred in 3 pts (lymphocyte count decreased, n=2; skin infection, n=1; weight decreased, n=1). One serious adverse event (skin infection) was unrelated to treatment. **Conclusions:** RYZ101 was well tolerated at 120 kBq/kg, which was declared the RP3D. Part 2 (Phase 3) will commence after Part 1 and will compare RYZ101 at the RP3D with standard of care in pts with advanced SSTR2+ GEP-NETs with disease progression following prior ¹⁷⁷Lu-labeled SSAs. Clinical trial information: NCT05477576. Research Sponsor: RayzeBio.

Patients (%)	RYZ101 120 kBq/kg (n=9)
Any TEAE	6 (66.7)
Serious AE	1 (11.1)
Treatment-related TEAE	4 (44.4)
Treatment-related serious AE	0
Grade 3/4 TEAE	3 (33.3)
Fatal TEAE	0
TEAEs leading to treatment discontinuation	0
TEAEs leading to dose modifications	2 (22.2)

4133

Poster Session

Novel use of alternate (Alt) response (Rp) criteria (Cr) for early prediction of outcomes in pancreatic (P) neuroendocrine tumors (NETs): Utilizing banked imaging data from the ECOG-ACRIN E2211 study. *First Author: Namrata Vijayvergia, Fox Chase Cancer Center, Temple University Health System, Philadelphia, PA*

Background: The evaluation of treatment (Tx) Rp in NETs using CT/MRI scans can be difficult. Previous studies, including the E2211, have shown improved progression-free survival (PFS) but no significant difference in Rp as measured by RECIST 1.1 (R1.1) Cr. Thus, making it difficult to determine Tx effectiveness with short-term imaging, further complicated by differences in imaging protocols and inter-reader variability. Incorporating tumor density, using smaller threshold changes in tumor size, and novel quantitative features may be more sensitive and precise than R1.1 (e.g. CHOI in GIST) but they have not been studied for NETs. **Methods:** Banked CT images from the E2211 trial were repurposed to study novel Cr. Three radiologists provided a R1.1 assessment. Density and radiomic features were calculated from a 2D region of interest in the portal venous phase (as per CHOI Cr). Patients were classified as responders (PR), stable disease (SD), or progressive disease (PD) based on R1.1 and CHOI and compared with PFS to determine the best predictor. Radiomic features were analyzed using pyradiomics. Wilcoxon tests were used to compare scan quality by center type, agreement was measured using Cohen's Kappa, and predictive value was quantified using the c-statistic and AUC for time-varying outcomes. **Results:** 67 patients had their scans repurposed for the study. Inter-reader agreement for overall imaging studies was fair, with only 5 of 9 PD cases noted by reviewer 1 being agreed upon by reviewer 2 (proportional agreement for PD = 0.56) and a Kappa of 0.6 (95% CI 0.41 – 0.79). The CHOI Cr showed improved prediction of PFS compared to R1.1 (12-month AUC 0.75 for CHOI vs 0.69 for R1.1, c-statistic 0.66 vs 0.64, p=0.22), and was able to predict improved PFS for PR versus SD at the first interval scan. This was not seen with R1.1 (table). Radiomics and texture analysis as a potential adjunct to CHOI is being studied and results will be presented. **Conclusions:** This study using repurposed banked imaging from an NCTN trial, found that there was significant variability in the interpretation of images, and that the R1.1 Cr had a poor correlation with Rp in pNETs. The CHOI Cr emerged as a better alternative as it may have a better correlation with PFS and the ability to predict outcomes at the point of first disease assessment. Importantly, CHOI Cr can be easily applied in clinical practice to inform treatment decisions. Further research is needed to confirm these findings and define the therapeutic importance. Research Sponsor: U.S. National Institutes of Health.

	PFS	AIC	AUC 12m	c-statistic
CR/PR				
RT1.1	SD 19.2m (95% CI 15.1-NA)	23 m (95% CI 12.9- 30.1)	331.240	0.692
CHOI	23m (95% CI 17.5 – 34.2)	11.7 m (95% CI 8 – 35.4 m)	334.528	0.751
			0.658	

*Higher c-statistic, higher AUC, and lower Akaike Information Criterion (AIC) are indicators of better predictive ability and fit.

4136

Poster Session

Safety and clinical activity of oleclumab (O) ± durvalumab (D) + chemotherapy (CT) in patients (pts) with metastatic pancreatic ductal adenocarcinoma (mPDAC): A phase 1b/2 randomized study. *First Author: Andrew L. Covelev, Fred Hutchinson Cancer Center, Seattle, WA*

Background: In a phase 1 study, the anti-CD73 monoclonal antibody (mAb) O plus the anti-PD-L1 mAb D showed antitumor activity and manageable safety in previously treated pts with advanced PDAC (Overman et al, J Clin Oncol 2018;36[suppl 15]:abs 4123). Here we report a multicenter, open-label study of O ± D + CT in pts with mPDAC. **Methods:** Pts were ≥ 18 years old with ECOG PS 0–1. Part 1 was a dose escalation phase: in Cohort A, previously untreated (1L) pts received O 1500 or 3000 mg IV Q2W for 4 doses then Q4W + D 1500 mg IV Q4W, with Q4W gemcitabine and nab-paclitaxel (GnP). In Cohort B, pts with previous G-based CT (2L) received O 1500 or 3000 mg Q2W for 4 doses then Q4W + D 1500 mg Q4W, with Q4W mFOLFOX. The primary objective for Part 1 was safety and tolerability; secondary objectives included antitumor activity and pharmacokinetics (PK). Part 2 was an expansion phase in which pts were stratified by high/low tumor CD73 expression by IHC. In Cohort A, 1L pts were randomized 1:1:1 to GnP alone (Arm A1), O + GnP (Arm A2) or O + D + GnP (Arm A3). O was given at the recommended phase 2 dose, 3000 mg. Cohort B did not proceed to dose expansion due to emerging therapies in 2L PDAC pts. The primary endpoint for Part 2 was investigator-assessed objective response rate (ORR) by RECIST v1.1; secondary included PFS, OS, safety, PK and antidrug antibody data. **Results:** As of November 11, 2022, 25 pts were treated in Part 1 (Cohort A, n=14; Cohort B, n=11), and 170 pts were treated in Part 2 (Arm A1, n=62; Arm A2, n=38; Arm A3, n=70). In Part 1, dose-limiting toxicities occurred in 1 pt (Cohort B, O 3000 mg: Gr 3 nausea and Gr 3 localized edema). Safety was generally similar in Parts 1 and 2. In Part 2, Gr ≥ 3 treatment-emergent adverse events (TEAEs) occurred in 85.5%, 89.5% and 90.0% of pts in Arms A1, A2 and A3 respectively, most commonly neutropenia (22.6%, 34.2% and 17.1%). In Part 2, TEAEs led to discontinuation in 11.3%, 23.7% and 24.3% of pts respectively. In Part 2, ORR was similar across Arms with a trend toward longer PFS and OS in Arm 3 vs Arm 1. There was a trend toward greater clinical benefit in pts with high CD73 expression when comparing Arm A3 vs Arm A1. **Conclusions:** O + D + GnP had similar safety and a trend toward improved outcomes compared to GnP. Clinical trial information: NCT03611556. Research Sponsor: AstraZeneca.

Part 2 efficacy summary.

	GnP (Arm A1, n=62)	O + GnP (Arm A2, n=38)	O + D + GnP (Arm A3, n=70)
ORR, % (95% CI)	29.0 (18.2, 41.9)	21.1 (9.6, 37.3)	32.9 (22.1, 45.1)
ORR difference, % (95% CI); p value		-8.0 (-27.6, 12.1); 0.36	3.8 (-13.2, 20.7); 0.65
DCR ≥ wk, % (95% CI)	66.1 (53.0, 77.7)	73.7 (56.9, 86.6)	75.7 (64.0, 85.2)
mPFS, mo (95% CI)	6.7 (5.5, 9.0)	5.6 (3.5, 7.5)	7.5 (5.5, 10.9)
PFS hazard ratio (95% CI)		1.160 (0.726, 1.837)	0.719 (0.468, 1.105)
mOS, mo (95% CI)	10.8 (8.2, 13.2)	8.9 (6.9, 11.5)	12.9 (10.1, 15.3)
OS hazard ratio (95% CI)		1.260 (0.790, 1.983)	0.750 (0.498, 1.131)

4135

Poster Session

Prevalence of germline variants in patients with pancreatic neuroendocrine tumors. *First Author: Chirayu Mohindroo, Department of Oncology, Johns Hopkins University School of Medicine, Baltimore, MD*

Background: About 10% of pancreatic neuroendocrine tumors (pNETs) are thought to be related to inherited syndromes, including multiple endocrine neoplasia type 1 (MEN1), multiple endocrine neoplasia type 4 (MEN4), von Hippel-Lindau disease (VHL), neurofibromatosis type 1 (NF1), and tuberous sclerosis complex (TSC). Here, we report the prevalence of pathological/likely pathological germline variants (PV/LPV) in 2 cohorts: 1) High-risk and 2) Unselected. **Methods:** We retrospectively collected clinical data of patients with biopsy proven pNETs seen at MD Anderson Cancer Center (MDACC) and Johns Hopkins Hospital (JHH). Cohort 1 (high risk cohort) included 132 patients seen at MDACC, who underwent germline testing based on high-risk criteria such as early onset, personal or family history of cancer and syndromic features between 2013–2019. Cohort 2 (unselected cohort) included 106 patients seen at JHH, who underwent germline testing following their diagnosis of pNETs between 2020 to 2022. **Results:** In the high-risk cohort (n = 132), 33% (n = 44) had PV/LPV, and 17 % (n = 22) had a variant of unknown significance (VUS). Amongst the 132 patients, 35% underwent multigene panel testing, 53% had targeted germline testing and 12% had a physician documented outside test diagnosis. The demographics consisted of 52%(n = 69) females, 67% (n = 88) white, 54%(n = 71) had metastatic disease, 58%(n = 76) underwent surgical resection. WHO grading (n = 77) is as follows G1 (39%), G2 (59%), G3 (2%). In the unselected cohort (n = 106), 21% (n = 22) had PV/LPV, 28 % (n = 30) had a VUS. Of these, 93% of the patients underwent multigene panel testing. The demographics consisted of 42% (n = 44) females, 67% (n = 88) white, 48% (n = 51) had metastatic disease, 60% (n = 64) underwent surgical resection, WHO grading (n = 93) is as follows G1 (37%), G2 (49%), G3 (14%). **Conclusions:** PV/LPV are prevalent in patients with sporadic pNET irrespective of high-risk features or family history. While in the high-risk patients there is a higher prevalence, we also identified a 21% prevalence of PV/LPV with universal germline testing in the unselected cohort. In both cohorts, we identified a high number of mutations in the DNA repair pathway not previously described, which could affect subsequent therapies and surveillance for patients and their family members. The findings support upfront universal germline testing in all patients with diagnosis of pNETs. Research Sponsor: None.

	MDACC (High Risk Cohort) 33% (n = 44/132)	JHH (Unselected Cohort) 21% (n = 22/106)
PV/LPV		
MEN1	56% (n = 25)	36% (n = 8)
DNA Repair pathway	18% (n = 8) (3 BRCA1 , 3 BRCA2, 1 BRIP1 and 1 BARD1)	40% (n = 9) (PALB2, RAD50, NTHL1, BLM, TP53, BRCA2, RECQL2 , BRCA1, ATM)
VHL	11% (n = 5)	5% (n = 1)
Colorectal cancer related genes	11%(n = 5) (3 MSH2, 2 MUTYH)	9% (n = 2) (MSH3 and MUTYH)
Others	2%(n = 1) (AXIN2)	9% (n = 2) (RET and PRSS1)

4137

Poster Session

Retrospective evaluation of the value of DNA damage repair gene signature in response to platinum-based chemotherapy in advanced pancreatic ductal adenocarcinoma. *First Author: Tian Tian, Preclinical and Translational Research Program, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Barcelona, Spain*

Background: Mutations affecting DNA Damage Repair (DDR) genes have been associated with clinical benefits from platinum-based chemotherapy (PBC) in ovarian and breast cancer. Mutations of DDR genes, including BRCA1/2, PALB2, ATM, ATR, CHK1, or RAD51, are found in around 15% of pancreatic ductal adenocarcinoma (PDAC). Nevertheless, whether advanced PDAC patients harboring DDR gene mutations could benefit more from PBC has not been well established. In this study, we aimed to compare the prevalence of DDR gene mutations between advanced PDAC patients who benefited from PBC and those who did not. **Methods:** We retrospectively analyzed samples from patients with advanced PDAC who received PBC at our institution from 2008 to 2022. Patients with partial response or progression-free survival (PFS) > 6 months were considered responders, and those with progression disease as the best response were considered non-responders. Tumor molecular profiling was performed on tumor samples by Next Generation Sequencing (NGS) of DNA. Fisher's exact test was used to compare DDR genomic alterations in responders vs. non-responders. Overall survival (OS) was defined as the time from the start of PBC to the date of death. PFS was defined as the time between the start of PBC and the first date of documented progression or death, whichever occurs first. Survival outcomes were estimated using Kaplan-Meier curves, and differences were tested using the long-rank test. **Results:** A total of 132 patients with advanced PDAC treated with PBC were included in this study. The median age at diagnosis was 55 years (range 27-79 years), and 71 (53.79%) patients were male. In this cohort, 88 (66.67%) patients were identified as responders. Tumor molecular profiling showed that among responders, 42 patients (47.7%) had genomic alterations in BRCA1/2 or PALB2, and 10 patients (11.3%) had alterations in other DDR genes. In contrast, only 17 patients (38.64%) showed DDR gene alterations among non-responders. Importantly, mutations in DDR genes are significantly associated with the responder group (OR=2.28; 95% CI 1.03-5.17, p=0.04). In line with these findings, patients with DDR gene mutations showed significantly longer PFS (median PFS 9.95 months) compared with patients without DDR gene mutations (median PFS 6.51 months) (HR=0.57; 95%CI 0.39-0.85; p=0.005). Moreover, significantly longer OS was found in patients with DDR gene mutations (median OS 20.5 months) compared with those without DDR gene mutations (median OS 16.8 months) (HR=0.67; 95%CI 0.45-1; p=0.05). **Conclusions:** Genomic alterations in DDR genes are significantly associated with the benefit of PBC treatment in advanced PDAC patients. Our results argue in favor of using DDR genes as a decision-making tool for advanced PDAC patient stratification even before the stand-of-care chemotherapies. Research Sponsor: ISCIII.

4138

Poster Session

Genomic characterization of somatic mutations by race and ethnicity in pancreatic cancer defined through AACR project GENIE. *First Author: J. Alberto Maldonado, Laboratory of Molecular Biology, National Cancer Institute, National Institutes of Health, Bethesda, MD*

Background: *KRAS*, *TP53*, *SMAD4*, and *CDKN2A* are widely recognized as the most common somatic mutations amongst patients with pancreatic ductal adenocarcinoma (PDAC); however, previous genomic studies have disproportionately included non-Hispanic White (NHW) patients with little to no inclusion of racial and ethnic minorities, particularly non-Hispanic Black (NHB) and Hispanic patients. Additionally, little is known about the distribution of *KRAS* point mutations in PDAC in specific racial and ethnic groups. Here, we describe somatic mutation differences in a larger and more racially and ethnically representative PDAC cohort than previously characterized. **Methods:** PDAC mutational data was downloaded from AACR Project GENIE (Genomics Evidence Neoplasia Information Exchange) v13.0, an international data registry of sequenced tumor samples from nearly 150,000 patients, on cBioPortal. PDAC cancer type was identified using OncoTree code. NHW, NHB, Hispanic (of any race), and Asian patients were then selected. Mutational frequency was calculated for all mutations. The primary objective was to compare the mutation frequencies between NHW and other races with respect to the most common mutations. To maximize power, we included any mutation with a frequency $\geq 5.0\%$ where testing for mutation of that gene had been performed in at least 150 patients. Specific point mutations in *KRAS* were also extracted with stratification for racial and ethnic group. Fisher's Exact Test was used to calculate the statistical significance of the differences in mutation frequency between NHW and minority groups. **Results:** Patients in the PDAC cohort included 5,292 individuals (NHW N = 4296, 80.7%; NHB N = 264, 5.0%; Hispanic N = 460, 8.7%; Asian N = 299, 5.7%). As compared to the NHW group, NHB patients had higher rates of *TP53* (78.7% vs 69.0%, $P = 0.0006$) and *PTPR* (5.3% vs 1.8%, $P = 0.0095$) mutations but fewer *GNAS* (0.4% vs 2.8%, $P = 0.0097$) mutations while Asian patients had higher frequency of *ARID1A* mutations (13.0% vs 8.8%, $P = 0.024$). *KRAS* G12D mutation was more prevalent in Hispanic patients (47.0% Hispanic vs 41.1% NHW, $P = 0.0238$), although rate of *KRAS* mutation overall was the same. Prevalence of *KRAS* G12C mutation was equivalent amongst all groups with an overall 1.6% frequency. **Conclusions:** Understanding the genomic landscape of PDAC is critical as we move towards increased use of targeted therapies to treat this disease. In this study, *TP53*, *PTPR*, *GNAS*, and *ARID1A* mutations were shown to occur at different frequencies in specific racial and ethnic groups. G12D mutation of *KRAS* was disproportionately increased in Hispanics. These differences in molecular landscape amongst racial and ethnic groups could contribute to precision medicine strategies used to address this deadly disease. Research Sponsor: NIH Medical Research Scholars Program.

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Poster Session

Phase 2 trial of pembrolizumab and olaparib (POLAR) maintenance for patients (pts) with metastatic pancreatic cancer (mPDAC): Two cohorts B non-core homologous recombination deficiency (HRD) and C exceptional response to platinum-therapy. *First Author: Wungki Park, Memorial Sloan Kettering Cancer Center, Weill Cornell Medical College, New York, NY*

Background: Maintenance olaparib improves PFS in gBRCA1/2m (core HRD) in mPDAC (Golan, NEJM 2019). Whether other HRD indicators, such as gene mutations other than gBRCA1/2m (non-core HRD, Cohort B) and exceptional platinum responders (Cohort C, response ≥ 6 months) may benefit from PARPi in mPDAC remains unanswered. We hypothesized that pembrolizumab and olaparib (POLAR) combination may improve outcome by immunogenic cell death. **Methods:** We conducted an open-label, non-randomized, phase 2 trial of POLAR as maintenance therapy for pts with mPDAC whose disease had not progressed for 4 months (m) in Cohort B or 6 m in C. Herein, we report on Cohorts B & C. Eligibility: ECOG 0-1, mPDAC meeting eligibility of B or C. POLAR (Pembrolizumab 200mg IV Q3W+ Olaparib 300mg BID) until disease progression or limiting toxicity. Objective response rate (ORR), median PFS (mPFS), median overall survival (mOS), disease control rate (DCR), CA 19-9, cfDNA and baseline HRD mutational signature were analyzed. **Results:** Cohorts B and C enrolled N=15 each. N=25 pts evaluable by RECIST 1.1. Median follow-up 9.9 (1.3-22.8) and 11.3 (5.8-23) m, respectively. Efficacy details are shown. G3-5 AEs related to treatment: 5/14 (36%): 1 diarrhea (7%), 1 hyperglycemia (7%), 2 anemia (14%), 1 lipase increased (7%). Cohort B: 9/15 (60%) ATM, 3 CHEK2, 2 MUTHY, 1 BLM, 1 FANCC. Canonical gene mutations for mPDAC were less common for pts in Cohort B, especially in ATM PA group (n=9) vs C. Median genomic instability score (GIS) was computed and higher 28 (0-38) vs 9 (0-24) in Cohort B vs C, $p=0.052$. Median tumor mutation burden (TMB) was not different between B and C (3.3 and 4.1). **Conclusions:** Clinical activity of POLAR maintenance observed in select pts in B and C. Although PFS was modest (mPFS of 4m [2.1-5.4] in B + C), an intriguing survival signal (mOS at 14m [10-NR] from first POLAR dose) was seen in select patients without chemotherapy. Extensive correlative analyses underway to evaluate response and resistance (SPOR: 1P50CA257881-01A1). Cohort A (core HRD) actively accruing. Clinical trial information: NCT04666740. Research Sponsor: Merck Sharp & Dohme LLC; Parker Institute for Cancer Immunotherapy; U.S. National Institutes of Health.

Cohorts (N)	Cohort B (15)	Cohort C (15)	B and C (30)	ATMm (9)
Age at Dx (range), M:F	62 (42-76), 7:8	65 (43-73), 8:7	64 (42-76), 15:15	62 (42-76), 5:4
De novo stage IV (%)	87 (13)	100 (15)	93 (28)	89 (8)
ORR % (# of pts evaluable for RECIST)	0% (11)	13.5% (14)	8% (25)	0% (8)
DCR %	60.0%	46.5%	62% (41-80)	75% (35-97)
Median PFS (95%CI)	4m (4-NR)	3.3m (1.9-5.4)	4m (2.1-5.4)	4m (2-NR)
Median OS (95%CI)	NA (12-NR)	11m (9.1-NR)	14m (10-NR)	NA (12-NR)
KRAS:TP53:SMAD4:CDKN2A (%)	77:54:31:15	87:87:20:53	82:71:25:36	75:75:36:0
Median GIS (range)	28 (0-38)	9 (0-24)	17 (0-38)	24 (1-30)
Median TMB (range)	3.3 (0.8-14.8)	4.1 (1.6-8.2)	3.7 (0.8-14.8)	2.9 (0.8-4.40)

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Poster Session

Efficacy and safety of mitazalimab in combination with mFOLFIRINOX in patients with metastatic pancreatic ductal adenocarcinoma (mPDAC): An interim analysis of the optimize-1 phase 1b/2 study. *First Author: Hans Prenen, Center for Oncological Research (CORE), Integrated Personalized and Precision Oncology Network (IPPON), University of Antwerp, Wilrijk, Belgium*

Background: Mitazalimab is a human CD40 agonistic IgG1 antibody. Targeting CD40 kickstarts the cancer immunity cycle by licensing dendritic cells leading to tumor specific T cell priming and activation. Furthermore, in PDAC CD40 agonists on myeloid cells promote degradation of the desmoplastic tumor stroma, improving influx of T cells and chemotherapeutic agents into the tumor. OPTIMIZE-1 (NCT04888312) is a Phase 1b/2, open label, multicenter study designed to evaluate safety, tolerability, and efficacy of mitazalimab in combination with mFOLFIRINOX (Oxaliplatin 85 mg/m², leucovorin 400 mg/m², irinotecan 150 mg/m², 5-FU 2.4 g/m²) in patients (pts) with previously untreated mPDAC. In the first part of the study (phase 1b), 900 µg/kg mitazalimab was selected as the recommended phase 2 dose (RP2D). **Methods:** In the first 21 day treatment cycle, mitazalimab was administered IV at RP2D on day 1 and 10 and mFOLFIRINOX infusion started on day 8. In subsequent cycles, treatment followed a 14 day cycle where mitazalimab was always administered 2 days after mFOLFIRINOX. The primary endpoint of this ongoing study is overall response rate (ORR) per RECIST v1.1. Secondary and exploratory endpoints include progression free and overall survival, safety, PK and PD biomarker assessments. Futility was prespecified as ORR $\leq 30\%$ in pts treated at RP2D, based on historical data with FOLFIRINOX (Conroy, 2011). **Results:** As of December 8, 2022, 43 pts with untreated mPDAC were treated with mFOLFIRINOX and 450 µg/kg (N = 5) or 900 µg/kg (N = 38) mitazalimab and evaluated for safety. The most common grade (Gr) ≥ 3 TEAEs were neutropenia (16%), fatigue (12%) and hypokalemia (12%). Mitazalimab related Gr > 3 AEs were fatigue in 3 (7.9%) pts, hypokalemia in 2 (5.3%) pts, diarrhea in 1 (2.6%) pt, pneumonia in 1 (2.6%) pt, increased ALT in 1 (2.6%) pt, headache in 1 (2.6%) pt, acute kidney injury in 1 (2.6%) pt. 10 pts (23%) experienced infusion reactions (all Gr 1-2) and 5 (12%) pts discontinued treatment due to TEAEs (pneumonia, gastric obstruction, neuropathy, bacteremia). At cutoff, 23 pts were evaluable for futility. Median follow up was 170 days and median exposure was 163 days. 18 pts (78%) remain on treatment, 6 (26%) beyond the 6 month treatment period. ORR was 52.2% (12 partial responses), an additional 8 pts achieved stable disease, resulting in a 91.3% disease control rate. Combination with mFOLFIRINOX had no impact on mitazalimab PK. The PD biomarker profile was consistent with the mode of action of mitazalimab, including upregulation of MCP-1 and IFN- γ . **Conclusions:** Mitazalimab + mFOLFIRINOX is a feasible regimen with a manageable safety profile. Mitazalimab administered at 900 µg/kg in combination with mFOLFIRINOX shows encouraging antitumor activity in mPDAC, meriting continued development. The study passes futility and continues to full accrual. Clinical trial information: NCT04888312. Research Sponsor: Alligator Bioscience AB.

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Poster Session

Development and evaluation of 5FUCore, OxaliCore, and IrinoCore transcriptomic signatures for predicting response to individual drugs in the FOLFIRINOX regimen: Towards toxicity reduction and personalized chemotherapy in PDAC. *First Author: Nicolas Fraunhofer, Cancer Research Center of Marseille (CRCM), INSERM, CNRS, Institut Paoli-Calmettes, Aix-Marseille University, Marseille, France., Marseille, France*

Background: Recently, we have successfully developed a transcriptomic signature that predicts the response to gemcitabine treatment in patients with localized pancreatic ductal adenocarcinoma (PDAC) (PMID: 36178036) and also in those with metastatic PDAC (PMID: 36496056). This was achieved by using an approach that combined several preclinical PDAC models. The FOLFIRINOX regimen (FFX) consisting of 5-Fluorouracil (5FU), Oxaliplatin, and Irinotecan is the more effective treatment option, but the high toxicity limits its use. In this study, we developed and analyzed three different transcriptomic signatures for the drugs composing FFX separately and evaluated their clinical utility. **Methods:** We combined the transcriptomic profile of 14 patients derived xenograft (PDX) and 31 patients derived cell cultures (PDC) with their corresponding chemotherapy response profiles. We developed predictive signatures for 5FU (5FUCore), Oxaliplatin (OxaliCore), and Irinotecan (IrinoCore), as previously reported for the GemCore signature (PMID: 36178036). They were then validated in three independent cohorts of patients: COMPASS (n = 94), Linehan (n = 28), and a new cohort of 87 advanced PDAC patients. **Results:** Three ICA components that reflect the chemotherapy response profiles for 5FU, oxaliplatin, and irinotecan were evaluated in the COMPASS cohort to determine their ability to identify sensitive patients in the FFX arm. Patients predicted as sensitive to each drug separately had a median overall survival (OS) of 77.6 (95% CI, 67.9-NR, $P = 0.02$), 78.7 (95% CI, 57.6-NR, $P = 0.002$), and 70.4 (95% CI, 57.6-NR, $P = 0.02$) months for 5FU, oxaliplatin, and irinotecan, respectively. Notably, the model that integrated the group of sensitive patients to two or three drugs had the highest median OS in the COMPASS and Linehan cohorts with a HR of 0.25 (95% CI, 0.11-0.57; $P < 0.001$) and 0.11 (95% CI, 0.02-0.70; $P = 0.019$), respectively. Importantly, they also show a better objective response than the other groups ($P = 0.009$). In the advanced PDAC group, the signatures showed a strong ability to discriminate sensitive patients in the FFX arm with a median OS of 20.1 (95% CI, 2.3-NR, $P = 0.006$), 13.64 (95% CI, 9.57-NR, $P = 0.003$), and 15.87 (95% CI, 2.9-NR, $P = 0.002$) months for 5FU, oxaliplatin, and irinotecan, respectively. Finally, we evaluated the best combination of two drugs in the pooled group. Patients sensitive to both 5FU and oxaliplatin showed the best response with 60% of patients achieving partial response. **Conclusions:** The signatures developed provide a tool for predicting responsiveness to the individual therapeutic drugs of the FFX regimen. They may ultimately lead to the development of a personalized strategy for combined chemotherapy regimens, increasing efficacy and reducing toxicity in PDAC. Research Sponsor: Institut Nationale du Cancer, Inca.

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Poster Session

A phase 1b/2 study of surufatinib plus camrelizumab, nab-paclitaxel, and S-1 (NASCA) as first-line therapy for metastatic pancreatic adenocarcinoma (mPDAC). *First Author: Guang-Hai Dai, Senior Department of Oncology, the 5th Medical Center of the PLA General Hospital, Beijing, China*

Background: PD-1 blockade combined with anti-angiogenesis such as surufatinib (targeting VEGFR 1-3, FGFR1 and CSF1-R) might change tumor environment thus improve the efficacy in several solid tumors. A phase 1b/2 clinical study was conducted to explore the efficacy and safety of surufatinib combined with camrelizumab (PD-1 antibody), nab-paclitaxel and S-1 (NASCA) as first-line treatment compared with nab-paclitaxel and gemcitabine (AG) in mPDAC. **Methods:** In phase 1b, patients (pts) with mPDAC received surufatinib (200mg to 300mg, orally daily), camrelizumab (200mg, I.V., D1, Q3W), nab-paclitaxel (125mg/m², I.V., D1, D8, Q3W) and S-1 (40mg bid, D1-14, Q3W). Phase 2 is a prospective, open-label, randomized (1:1) trial comparing NASCA with AG in the first-line setting. The primary objective was recommended phase 2 dose (RP2D) and overall response rate (ORR) per RECIST v1.1. Tumor tissue samples were collected at diagnosis for mIHC to evaluate tumor microenvironment. **Results:** Six pts were enrolled in phase 1b and RP2D was determined as surufatinib 200mg. By Jan 10, 2023, 28 pts were enrolled in phase 2 and 27 pts were evaluable for efficacy (14 in NASCA and 13 in AG). The ORR was 55.0% (11/20) (95% CI: 34.2-74.2) in NASCA and 23.1% (3/13) (95% CI: 8.2-50.3) in AG group. Pts receiving NASCA with liver metastases exhibited significant higher ORR than those without liver metastases (90.0% vs 20.0%, $p=0.0017$). Median progression-free survival was 8.8 months (95% CI: 5.5-12.0) in NASCA and 5.8 months (95% CI: 1.5-10.1) in AG group at the median follow-up of 8.9 months. The most frequent adverse events (AEs) of all grades in pts treated with NASCA were neutropenia (55.0%), hepatotoxicity (45.0%), neuropathy (35.0%) and diarrhea (15.0%). Immune-related AEs were observed in 4 pts (20.0%) with grade 3 hepatotoxicity. Safety was comparable in two groups except for hepatotoxicity and diarrhea. The tissue of 13 pts receiving NASCA were stained for multiple markers of immune cells. CD3⁺T cells infiltrated most in the tumor core, followed by CD68⁺CD163⁺ (M1) macrophages, and FOXP3⁺ T cells. Majority of immune cells and therapeutic biomarkers were expressed at higher levels in the stroma than tumor core. Pts with liver metastases displayed elevated infiltration of tumoral FOXP3⁺ T cells ($p=0.031$), PD-L1⁺CD68⁺ macrophages ($p=0.014$), and decreased density of stromal CD8⁺ T cells ($p=0.064$) than pts without liver metastases. In pts with liver metastases, responders displayed a higher proportion of stromal PD-1⁺ cells than non-responders ($p=0.036$). **Conclusions:** Preliminary results showed that NASCA regimen presented higher clinical activity than the standard AG treatment, especially in pts with liver metastases, with a manageable safety profile. This trial is ongoing and NASCA regimen deserves further exploration in mPDAC. Clinical trial information: NCT05218889. Research Sponsor: HUTCHISON CHINA MEDITECH LTD.

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Poster Session

Correlation of comprehensive molecular mapping of pancreatic ductal adenocarcinoma with XPO1 mRNA expression levels to potential clinical targets. *First Author: Andreas Seeber, Department of Internal Medicine V (Hematology and Oncology), Comprehensive Cancer Center Innsbruck, Medical University of Innsbruck, Innsbruck, Austria*

Background: Encouraging pre-clinical efficacy targeting Exportin-1 (XPO1) - a master regulator of tumor suppressor protein export - has been reported in pancreatic ductal adenocarcinoma (PDAC) and clinical trials are currently ongoing. However, limited data is available regarding expression and function of XPO1 in PDAC. Thus, we investigated XPO1 mRNA expression and its clinical and immune correlates in PDAC. **Methods:** 5,488 PDACs were tested at Caris Life Sciences (Phoenix, AZ) with NGS of DNA (WES) and RNA (WTS). TMB-H was defined as ≥ 10 mutations/MB. The cohort was stratified in quartiles according to XPO1 mRNA expression status, and XPO1-high (XPO1^H) and XPO1-low (XPO1^L) expression were defined as $\geq$ top and $<$ bottom quartile of transcripts per million (TPM). Immune cell fraction was calculated by QuantiSeq method. Gene expression profiles were analyzed for transcriptomic signatures predictive of response to immune checkpoint inhibitors (T cell-inflamed score) and MAPK pathway activation (MPA). The Mann-Whitney U and X2 tests were applied as appropriate, with p-values adjusted for multiple comparisons. Real-world overall survival (OS) data was obtained from insurance claims. TCGA data were used to validate molecular, biological and immunological findings. Single-cell RNA analyses on a publicly available dataset were performed to elaborate cellular localization of XPO1. **Results:** Increased XPO1 mRNA expression was observed in metastatic lesions compared to primary tumors ($p<0.001$). Copy number amplification and mutation prevalence was comparable between XPO1^H and XPO1^L samples ($p>0.05$), along with similar rates of MSI-H/dMMR (1.3 vs 0.9%) and TMB-H (2.0 vs 1.3%; $p>0.05$). XPO1^H PDACs were associated with a significant higher prevalence of T cell-inflamed tumors compared to XPO1^L cases (58 vs 5%; $p<0.05$), consistent with higher immune cell infiltration in the XPO1^H quartile as compared to XPO1^L ($p<0.05$), except for immunosuppressive regulatory T cells and monocytes ($p>0.05$). XPO1^H was associated with a higher MPA score as compared to XPO1^L (2.4 vs -2.1 Arbitrary Units; $p<0.05$). XPO1^H was associated with shorter OS (HR 1.09 [1.1-1.4], $p=0.048$). Validation studies using TCGA datasets corroborate our findings and confirmed increased immune cell infiltration as a function of XPO1. Moreover, single cell data revealed predominant and high expression of XPO1 in the tumor cell compartment. **Conclusions:** This is the first study comprehensively mapping XPO1 mRNA expression and immune-correlates in PDAC. We found that high XPO1 is linked to increased immune cell infiltration with a T cell-inflamed pattern. Our data provided a potential rationale to combine immune checkpoint therapy (+/- XPO1 inhibitors) in XPO1^H PDACs. Research Sponsor: Southtyrolean Fund for the Promotion of scientific Research (SFPR) at the Southtyrolean Health Care System (SABES) and the Paracelsus Medical University Salzburg (PMU).

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Poster Session

A phase II study of nivolumab and ipilimumab with radiation therapy in patients with metastatic, microsatellite stable pancreatic adenocarcinoma. *First Author: Julie L. Koenig, Harvard Radiation Oncology Program, Boston, MA*

Background: Metastatic pancreatic ductal adenocarcinoma (PDAC) is incurable for most patients. While immune checkpoint inhibitors (ICIs) have limited efficacy in microsatellite stable (MSS) tumors, radiation therapy (RT) may promote responsiveness to ICIs. In our phase 2 trial (NCT03104439), 25 patients with metastatic MSS PDAC were enrolled to receive ipilimumab and nivolumab with RT (24 Gy/3 fractions) starting on C2D1. The disease control rate (DCR) was 20% (5/25) and overall response rate (ORR) was 12% (3/25). In 17 patients who received RT (32% dropout rate), DCR was 29% (5/17) and ORR was 18% (3/17). To confirm this signal and address dropout prior to RT, we conducted a phase 2 study of nivolumab and ipilimumab with RT moved to C1D1. **Methods:** In this open-label, single-arm, phase 2 study (NCT04361162), eligible patients had histologically confirmed metastatic MSS PDAC, ECOG PS 0-2, and progressed on at least one line of chemotherapy. Treatment consisted of ipilimumab 1 mg/kg q6weeks for the first 4 cycles, nivolumab 240 mg q2weeks on a 6-week cycle, and RT (24 Gy/3 fractions) to a single site starting on C1D1. Treatment continued until disease progression, discontinuation, or withdrawal. The primary endpoint was RECIST 1.1 ORR by centrally reviewed imaging q3months. Secondary endpoints included DCR, PFS, OS, and safety. 30 patients were enrolled in a single-stage design for intention-to-treat (ITT) analysis of patients receiving at least one dose of study treatment. The per protocol analysis included patients who completed C1D1. The treatment regimen was considered to have promising activity if at least 3 of 30 patients had an objective response, providing 85% power to reject 5% ORR in favor of 15% ORR at a significance level of 20%. **Results:** We enrolled 30 patients (median age 68 years [range 52-80], 60% male, 90% white, 97% ECOG PS 0-1, median 3 [range 2-6] prior lines of chemotherapy) from 05/2020 to 11/2021. ITT ORR was 3% (1/30; 95% CI, 0-17%), DCR was 10% (3/30; 95% CI, 2-27%), median PFS was 2.2 months (95% CI, 1.5-2.6), and median OS was 2.8 months (95% CI, 2.1-5.2). In the per protocol analysis, ORR was 4% (1/28; 95% CI, 0-18%), DCR was 11% (3/28; 95% CI, 2-28%), PFS was 2.3 months (range, 1.6-2.7), and OS was 2.9 months (range, 2.2-5.5). One patient enrolled in hospice after 1 month, had a complete response at 13 months, and is alive at 21 months. 7 patients had grade 3-4 treatment-related serious adverse events, including lymphopenia (grade 4 in 1 patient), neutropenia, fatigue, muscle weakness, ALT/AST increase, hepatobiliary dysfunction, acute kidney injury, hyperglycemia, and hypokalemia. **Conclusions:** The treatment regimen of ipilimumab and nivolumab with RT did not meet the pre-specified criteria for promising activity in metastatic MSS PDAC. Further correlative analyses of the patient with a complete response and evaluation of in-field responses are ongoing. Clinical trial information: NCT04361162. Research Sponsor: Bristol Myers Squibb.

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Poster Session

Clinical genomic implications of transcriptional subtypes in pancreatic cancer. *First Author: Harshabad Singh, Dana-Farber Cancer Institute, Brookline, MA*

Background: Transcriptional profiling of pancreatic cancers (PC) has defined classical and basal subtypes; basal tumors have worse outcomes. Mesenchymal (MES) and neural-like progenitor (NRP) subtypes are increasingly recognized and enriched post-therapy. Initial data suggests worse outcomes to FOLFIRINOX (FFX) compared with gemcitabine nab-Paclitaxel (GnP) in basal tumors. Several clinical trials are ongoing to investigate this. Here, we examined the clinical implications of transcriptional subtypes in a large, real-world dataset. **Methods:** Retrospective IRB exempt, deidentified data was examined from NextGen DNA and RNA sequencing performed on PCs at Caris Life Sciences (Phoenix, AZ). Classical and basal cell states were identified using RNA-seq and the PurlST algorithm in a genomic cohort or GATA6 and KR75 expression levels in a clinical cohort. Tumor microenvironment immune cell composition on RNA seq was performed using QuantiSeq. Survival was obtained from insurance claims data and calculated from first treatment date to last known contact. Kaplan-Meier estimates were calculated for patient cohorts. P values were adjusted using Benjamini-Hochberg correction. **Results:** A total of 7,250 PCs were profiled in the genomic cohort. 3,063 tumors (42.2%) were strongly classical (SC), 2,015 tumors (27.8%) were strongly basal (SB) and the remaining had mixed phenotypes. MES and NRP marker genes were significantly co-expressed with each other, with basal genes, and anti-correlated with classical genes. When compared to SC, SB had significantly higher mutation rates in KRAS (93% vs. 88%), TP53 (83% vs. 72%) and ARID1A (12% vs. 8%), whereas SMAD4 (23% vs. 17%) mutations were more common in SC (all $q < 0.05$). There were no differences in mutation rates in homologous recombination or mismatch repair genes. SB had a significantly higher fraction of M1 macrophages (fold change [FC]: 1.14) and neutrophils (FC 1.16), whereas SC tumors had higher M2 macrophages (FC 1.18), NK (FC 1.2), and dendritic cells. Overall proportions of CD4/8 T cells were low and not different. Interestingly, SB had higher levels of PD-L1 by IHC (4.8% vs. 35%) and higher expression of immune exhaustion genes including CTLA4 (FC 1.19), TIM3 (FC 1.22) and PD-1 (FC 1.43) (all $q < 0.05$). The clinical cohort had 1,623 patients. Basal tumors had an inferior survival (median survival: 8.2 months (mo) vs 13.3 mo (Hazard Ratio (HR) 0.67, $p < 0.00001$)) and showed a significant improvement in outcomes when treated with upfront FFX vs GnP ($n = 80$ vs 90, Median: 15.8 vs 7.4 mos., HR 0.68, $p = 0.021$). This difference between FFX vs GnP was less pronounced in classical tumors ($n = 70$ vs 89, Median: 17.3 vs 15.4 mos, HR 0.70, $p = 0.049$). **Conclusions:** Our work represents the largest known real world molecular comparison of transcriptional subtypes of PC. Differential outcomes for patients with basal tumors treated with FFX versus GnP warrants further investigation in prospective studies. Research Sponsor: None.

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Poster Session

Tumor mutational burden (TMB) in real-world patients with pancreatic ductal adenocarcinoma (PDAC): Differences in genomic alterations (GA) and predictive value for immune checkpoint inhibitor (ICI) effectiveness. *First Author: Amit Mahipal, UH Seidman Cancer Center, Case Western Reserve University, Cleveland, OH*

Background: Currently, ICI therapy is recommended for patients with metastatic PDAC whose tumors exhibit dMMR, MSI-H, or high TMB (≥ 10 mutations/Mb). However, due to the low prevalence of high TMB in PDAC (~1%), few studies have evaluated the role of ICI therapy in this subpopulation. This study aimed to compare GA between PDAC patients with high TMB and low TMB (< 10 mutations/Mb) and to evaluate the effectiveness of ICIs in real-world PDAC patients by TMB status. **Methods:** This study included PDAC patients who underwent genomic testing using Foundation Medicine tissue comprehensive genomic profiling (CGP) assays. GA were compared between tissue specimens with high and low TMB by chi-squared, adjusted for multiple comparisons. Patient clinical data was obtained by the US-wide de-identified Flatiron Health and Foundation Medicine real-world clinicogenomic pancreatic database (CGDB), originated from ~280 US cancer clinics between 01/2011 and 09/2022. Real-world overall survival (OS) and time to treatment discontinuation (TTD) were compared between patients receiving an ICI (high TMB versus low TMB) and between patients with high TMB (ICI versus other therapies) by Cox models. **Results:** We included 21,932 patients with PDAC with tissue CGP data available; 98.7% with low TMB and 1.3% with high TMB. Among actionable alterations, patients with high TMB had higher prevalence of mutations in *BRCA2* ($p < 0.0001$), *BRAF* ($p < 0.0001$), *PALB2* ($p < 0.0001$), and genes of the mismatch repair pathway (*MSH2*, *MSH6*, *MLH1*, and *PMS2*, $p < 0.0001$), but lower prevalence of *KRAS* mutations ($p < 0.0001$). The most common *KRAS* mutation in both groups of patients was G12D. In CGDB, 51 patients received an ICI (10 with high TMB and 41 with low TMB) and 17 patients with high TMB received other therapies. Among patients receiving an ICI, those with high TMB had more favorable median OS compared to those with low TMB (25.7 versus 5.2 months, hazard ratio (HR) 0.27, 95% confidence interval (CI) 0.09 - 0.76, $p = 0.01$) and median TTD (20.7 versus 3.0 months, HR 0.33, 95% CI 0.13 - 0.82, $p = 0.02$). Among patients with high TMB, those receiving an ICI had more favorable OS compared to those receiving other therapies (25.7 versus 6.6 months, HR 0.31, 95% CI 0.10-0.96, $p = 0.043$), nominally favoring ICI use in this small cohort ($n = 10$ versus 17). **Conclusions:** There is no randomized clinical trial evaluating ICI versus other therapies in PDAC. To our knowledge, this is the largest cohort to date comparing ICI effectiveness in PDAC. We observed more favorable OS among PDAC patients with high TMB receiving ICI versus those with low TMB who received an ICI and more favorable to those with high TMB receiving other therapies. This study supports the FDA-approved use of ICIs in patients with PDAC and high TMB and demonstrates the importance of TMB assessment for patients with PDAC. Research Sponsor: Foundation Medicine, Inc.

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Poster Session

Efficacy of immune checkpoint inhibitors in microsatellite unstable/mismatch repair-deficient advanced pancreatic adenocarcinoma: An AGEO European Cohort. *First Author: Lorenzo Pilla, Department of Gastroenterology and Gastrointestinal Oncology, Hôpital Européen Georges-Pompidou, AP-HP, Université de Paris, Paris, France*

Background: Immune checkpoint inhibitors (ICI) have been approved for the use in solid tumors with MSI/dMMR. Nevertheless, the outcome of patients (pts) with MSI/dMMR pancreatic ductal adenocarcinoma (PDAC) seems poorer when compared to other malignancies. This multi-institutional analysis aimed to assess the efficacy and tolerability of ICIs in a large real-world cohort of pts with MSI/dMMR PDAC. **Methods:** Retrospective data were collected for pts with MSI/dMMR PDAC treated with ICIs from February 2016 to May 2022 in 16 different centers across Europe and Israel. Progression-free survival (PFS) and overall survival (OS) were calculated from the start of treatment, and objective response (OR) and disease control rate (DCR) were measured according to RECIST V1.1. **Results:** We identified 31 pts with metastatic MSI/dMMR PDAC. The mean age was 62.1 years (range: 37-82), 45.1% were female and ECOG PS status was predominantly 0 or 1 (83.9%). At the time of ICI treatment 1 pt had locally advanced and 30 had metastatic disease. MSH2/MSH6 deficiency (def) was found in 9 cases, MLH1/PMS2 def in 7, MSH 6 def in 4, MSH 2 def in 3, PMS2 def in 3 and MLH1/MSH6/PMS2 def and, a CpG highland methylator phenotype in 1 pt. MMR status was not available in 4 pts. Germline mutation testing was performed in 20/31 pts (64.5%) and Lynch syndrome was diagnosed in 8 pts (45%). Nineteen pts received pembrolizumab, 8 received nivolumab, 1 received lodapolimab and 3 received ipilimumab/nivolumab (ipi/nivo). The mean number of prior lines of chemotherapy was 1.5 (range 0-4). Among the 31 pts in this analysis, 15 (48.4%) had an OR (3: complete response and 12 partial response) and 6 (19.3%) had stable disease, resulting in a DCR of 67.7%. Ten pts had disease progression (PD) (32.3%). Median PFS was 26.7 months and median OS was not reached with median follow-up (FU) of 18 months. Median duration of response was not reached (95%CI:24.1-NR). Analysis of all responders, with a follow up of 12 months or more ($n=14$), showed that 100% of them maintained their response. In addition 71% of the pts of this cohort are still alive with a median time of follow up since the diagnosis of metastatic disease of 39.9 months. After ICIs discontinuation, 6 pts received chemotherapy. One pt who had PD after 15 months of pembrolizumab switched to ipi/nivo and achieved a CR. Immunotherapy was generally well tolerated; No Grade 3-5 adverse events (AEs) were reported and no therapy discontinuation due an adverse event was observed. **Conclusions:** This retrospective analysis suggests that ICIs are effective and well tolerated in pts with MSI/dMMR advanced PDAC. Hence, our work supports the use of PD-1 inhibition in this group of pts with high unmet medical need. Research Sponsor: None.

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Poster Session

Randomized phase 2 study of nab-paclitaxel and gemcitabine with or without tocilizumab as first-line treatment in patients with advanced pancreatic cancer (PACTO). *First Author: Inna Markovna Chen, Copenhagen University Hospital - Herlev and Gentofte, Herlev, Denmark*

Background: Pancreatic cancer (PC) presents one of the most aggressive malignancies for which currently available treatments are modestly effective. We report the findings of a randomized phase 2 trial (NCT02767557) to test the efficacy of gemcitabine/nab-paclitaxel (gem/nab) with or without tocilizumab (toc), as first-line treatment in patients with locally advanced or metastatic PC. **Methods:** Prior to randomization, a safety cohort of 6 participants received gem 1000 mg/m², nab 125 mg/m² (days 1, 8, and 15 of each 28-day cycle) and toc 8 mg/kg (day 1 of each cycle). Participants were then randomized 1:1 to receive gem/nab or gem/nab/toc. Patients had modified Glasgow Prognostic Score of 1 or 2 and were stratified by performance status (PS) and stage. The primary endpoint was the overall survival (OS) rate at 6 months (OS6). Secondary end points included median progression-free survival (PFS), median OS, overall response rate (ORR), and safety. **Results:** A total of 147 patients were treated; 141 were randomized to receive gem/nab/toc ($n = 70$), or gem/nab ($n = 71$). As of January 9, 2023, the median follow-up was 8.1 months (IQR 4.2-13.9). OS6 was 68.6% (95% CI, 56.3-78.1) in gem/nab/toc group and 62.0% (95% CI, 49.6-72.1) in gem/nab group ($p = 0.41$). No significant differences in the median OS or PFS were observed between the gem/nab/toc group and the gem/nab group (OS, 8.4 versus 8.0 months; HR, 0.75; 95% CI, 0.54-1.05; $p = 0.10$), and (PFS, 5.6 versus 5.5 months; HR, 0.85; 95% CI, 0.61-1.20; $p = 0.36$). The 12, 18 and 24-month OS rates were 37.1% (95% CI, 26.0%-48.3%), 27.1% (17.4%-37.8%), 10% (4.4%-18.3%) for gem/nab/toc and 28.2% (18.3%-38.9%), 7.0% (2.6%-14.5%), 2.8% (0.5%-8.8%) for gem/nab, respectively. The ORR was 37.1% (95% CI, 25.9%-49.5%) in gem/nab/toc group and 35.2% (24.2%-47.5%) in gem/nab group. The incidence of grade 3 or higher treatment-related adverse events was 88.2% in gem/nab/toc and 63.4% in gem/nab group ($p < 0.001$). Of those, neutropenia (55.3% versus 16.9%), and thrombocytopenia (40.8% versus 11.3%) were most common. Two and one treatment-related deaths, respectively, in gem/nab/toc and gem/nab group, occurred during the study. **Conclusions:** In patients with advanced PC, the addition of tocilizumab to gem/nab did not result in improved OS rate at 6 months. Although more patients were alive at 18 months in the gem/nab/toc, long-term survival rates exceeding 24 months were not different between groups. The biomarkers for selection of patients who might benefit from gem/nab combined with tocilizumab are to be identified. Clinical trial information: NCT02767557. Research Sponsor: Celgene; Copenhagen University Hospital - Herlev and Gentofte, Herlev, Denmark.

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Poster Session

Validation of the PDACai signature in predicting relative benefit from front-line FOLFIRINOX (FFX) and gemcitabine/nab-paclitaxel (GA) for patients (pts) with metastatic pancreatic cancer (mPDAC). *First Author: Michael J. Pishvaian, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Washington, DC*

Background: Nearly 50% of pts with mPDAC never receive a 2nd line of therapy for metastatic disease following frontline FFX or GA. Genomic alterations in the DDR pathway (e.g. *BRCA1/2*) are associated with increased progression-free survival (PFS) on platinum-containing regimens (e.g. FFX), but other biomarker-treatment associations that predict benefit from GA and/or FFX in mPDAC remain unexplored. In this retrospective real-world evidence (RWE) study, we use a data-driven machine learning approach to gain new insights from the mutational landscape in mPDAC and validate the PDACai signature in predicting personalized benefit from both FFX and GA. **Methods:** We analyzed real-world outcomes from 711 pts with mPDAC who underwent genomic profiling via the Know Your Tumor program or were referred to Perthera by treating oncologists. Chart-abstracted PFS data on either 1st line FFX or GA were split (60:40) into independent training and validation cohorts for each regimen. All models integrate a shared set of clinical (age < 63 , sex) and lab-agnostic molecular features derived from clinical NGS testing reports (DDR pathway alterations, specific *KRAS* variants, frequently mutated genes). Relative benefit scores predicted by FFX or GA models were evenly binned into three PDACai signature categories representing lower, middle, and upper tertiles for each independent cohort. Statistical differences in median PFS were evaluated using ordinal Cox regression. **Results:** Median PFS followed predicted trends as generated by PDACai for each therapy in training and validation cohorts. The predictive utility of PDACai was confirmed in the independent validation cohorts when comparing PFS on FFX ($p = 0.03744$; HR = 0.75 [95% CI: 0.58-0.98]) and GA ($p = 0.00006861$; HR = 0.65 [95% CI: 0.53-0.8]) across tertiles. **Conclusions:** Response to chemotherapy is heterogeneous and difficult to predict in pts with mPDAC. Using RWE, the PDACai signature successfully predicted relative differences in PFS on both FFX and GA in mPDAC. With prospective validation, personalized insights generated by PDACai from pts with similar biomarker profiles could be used to tailor treatment sequencing in pts with NGS testing results, particularly those without actionable genomic findings. Research Sponsor: Pancreatic Cancer Action Network; Perthera.

Summary of actual PFS in months on 1st line therapies in pts assigned to lower, middle, and upper thirds based on relative PDACai predictions.

Independent Cohort (# Pts)	Lower Tertile mPFS [95% CI]	Middle Tertile mPFS [95% CI]	Upper Tertile mPFS [95% CI]
1st line FFX Training (212)	6.4 [5.6-7.5]	8.0 [6.1-10.6]	15.8 [10.3-NR]
1st line FFX Validation (145)	9.1 [7.0-12.2]	11.1 [7.6-13.7]	13.2 [10.1-28.0]
1st line GA Training (209)	5.5 [4.4-6.5]	7.3 [5.8-8.4]	10.1 [8.1-12.1]
1st line GA Validation (145)	5.6 [4.7-8.6]	8.2 [6.5-15.6]	8.8 [7.7-13.9]

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Poster Session

KRAS G12C-mutated pancreatic cancer: Clinical outcomes based on chemotherapeutic regimen. *First Author: Aaron Ciner, University of Maryland, Baltimore, MD*

Background: Frontline treatment for advanced pancreatic ductal adenocarcinoma (PDAC) has been either 5-fluorouracil, oxaliplatin and irinotecan (FOLFIRINOX) or gemcitabine and nab-paclitaxel (GP) for the past decade. While the NAPOLI-3 trial, utilizing liposomal irinotecan, highlighted the superiority of a triplet regimen over GP, the question remains whether certain subgroups may derive particular benefit from GP. Pre-clinical data in lung cancer suggest that KRAS G12C may facilitate enhanced DNA adduct removal after platinum chemotherapy and confer resistance to this drug class. While multiple KRAS G12C inhibitors have shown early promise in PDAC, multi-agent chemotherapy remains the frontline standard and will likely remain an important therapeutic tool. This study aimed to investigate clinical outcomes after platinum and non-platinum-based chemotherapy in patients with advanced KRAS G12C-mutated PDAC. **Methods:** PDAC samples were tested using whole transcriptome sequencing (WTS; Illumina NovaSeq) and NextGen DNA sequencing (NextSeq, 592 Genes and NovaSeq, WES) at Caris Life Sciences (Phoenix, AZ). Significance was determined by χ^2 and Fisher-Exact and p adjusted for multiple comparisons (q). Real-world overall survival (rWOS) was obtained from insurance claims data and calculated from first of treatment to last contact with comparison done by Kaplan-Meier test. **Results:** A total of 5,555 PDAC patients harboring KRAS pathogenic variants were identified, including 109 with a G12C mutation. For KRAS G12C mutants, median overall survival was 470 days for those who received GP (n=22) compared to 240 days for patients who received FOLFIRINOX (n=9) with a median difference of 230 days (HR 0.32, CI 0.12-0.82, p=0.013). In contrast, median overall survival was higher for patients harboring G12D (392 vs 297 days, p=0.003), G12V (500 vs 356 days, p=0.012) or G12R (469 vs 391 days, p=0.095) mutations who received FOLFIRINOX compared to GP. KRAS G12C mutated PDAC showed the highest rate of PDL1+ staining (27%) compared to other variants (G12R 13% and G12D 19%, q<0.01). TMB-H and MSI-H prevalence were highest in G12C compared to other variants (no statistical significance observed). **Conclusions:** In patients with advanced PDAC and a G12C mutation, median overall survival appears significantly longer in those treated with GP compared to FOLFIRINOX. The opposite trend was seen in patients with other KRAS variants including G12D, G12V, and G12R, consistent with the recently presented NAPOLI-3 trial. PDL1 staining was also highest in the KRAS G12C cohort. While this is the largest reported analysis of outcomes to frontline chemotherapy in KRAS G12C-mutated PDAC, the sample size is small and needs validation in additional datasets. Next steps include evaluating DNA mutational status and RNA expression of genes involved in DNA repair in G12C vs other KRAS variants to better understand the outcome data presented here. Research Sponsor: None.

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Poster Session

Nationwide implementation of best practices in pancreatic cancer care (PACAP-1): Stepped-wedge cluster randomized trial. *First Author: Tara Mackay, Amsterdam UMC, Location University of Amsterdam, Department of Surgery, Amsterdam, Netherlands*

Background: Implementation of new treatment strategies in cancer care is often inadequate and slow. We aimed to implement best practices in pancreatic cancer care using a nationwide stepped wedge design and assess the impact on overall survival. **Methods:** Nationwide multicenter stepped-wedge cluster randomized controlled trial comparing implementation of best practices with usual care (May 22, 2018 – May 29, 2020). Best practices included adequate use of perioperative and palliative chemotherapy, pancreatic enzyme replacement therapy (PERT), and metal biliary stents. The 6-week implementation period in all 17 Dutch pancreatic centers and their regional referral networks included monitoring, return visits, and provider feedback in combination with education and reminders. Primary outcome was one-year overall survival for all disease stages and secondary outcomes included guideline compliance and quality of life. **Results:** Overall, 5580 patients diagnosed with pancreatic cancer were included; 2939 after implementation of best practices versus 2641 before. One-year survival did not differ among the groups (HR 0.98, 95 CI 0.88-1.08). Overall use of perioperative chemotherapy (neoadjuvant and adjuvant) did not significantly differ, but use of palliative chemotherapy significantly increased (23.9% to 30.3%, OR 1.38, 95 CI 1.10-1.74). Also the use of PERT (34.2% to 45.2%, OR 1.64, 95 CI 1.28-2.11); and metal biliary stents (74.1% to 83.3%, OR 1.78, 95 CI 1.13-2.08) significantly increased. The Global Health Score did not differ (AUC 43.8 to 42.7, median difference -1.12, 95 CI -3.13-0.80, n=655). **Conclusions:** This nationwide population-based trial to enhance implementation of best practices in pancreatic cancer care showed successful implementation of most best practices, but no increase in one-year survival and quality of life. Clinical trial information: NCT03513705. Research Sponsor: This research was funded by a grant from the Dutch Cancer Society (grant number UVA2013-5842).

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Poster Session

Molecular and clinical correlates of DSCR1 expression in pancreatic cancer (PDAC). *First Author: Francesca Battaglin, Norris Comprehensive Cancer Center, Keck School of Medicine, University of Southern California, Los Angeles, CA*

Background: Individuals with Down syndrome (DS) have a lower risk for solid tumors and angiogenesis related diseases. DSCR1 is highly upregulated in DS patients and its product, calcipressin-1, was shown to suppress angiogenesis and reduce cancer risk. High DSCR1 expression has been reported to decrease PDAC growth and metastasis in animal models. Here, we analyzed the molecular features and clinical outcomes associated with DSCR1 gene expression in PDAC. **Methods:** 8352 tumor samples tested at Caris Life Sciences (Phoenix, AZ) with WTS (Illumina NovaSeq) and NextGen DNA sequencing (NextSeq, 592 Genes and NovaSeq, WES) were analyzed. Top quartile transcripts per million for DSCR1 expression were considered high (Q4) while bottom quartile low (Q1). Cell infiltration in the tumor microenvironment (TME) was estimated using QuantiSeq. Interferon-gamma (IFG) and T-cell inflamed (TIS) signatures were calculated from RNA data. Statistical significance was determined as P-value adjusted for multiple comparisons (q < .05). Real world survival was obtained from insurance claims data (N = 4223) and Kaplan-Meier estimates were calculated. **Results:** DSCR1 expression was higher in primary tumors than metastases (q < .05). No significant differences were observed between high vs low DSCR1 PDAC in immune-related biomarkers (TMB, dMMR/MSI-H and PD-L1 protein), gene mutations and copy number alterations except for KRAS mutations which were more frequent in DSCR1 Q4 (93 vs 86%, Q4 vs Q1, q < .0001). Gene set enrichment analysis showed that DSCR1 high tumors were enriched in alterations of several pathways including NOTCH signaling, DNA repair, IFG response, myogenesis and adipogenesis (P < .05, false discovery rate < .25). B cells, M1 and M2 macrophages, neutrophils, NK cells, and Tregs were more abundant in the TME of tumors with high DSCR1 while dendritic cells, CD4+ T cells and monocytes were lower (q < .05). DSCR1 Q4 was associated with higher TIS score (50% inflamed vs 3.6%, q < .05) and positively associated with immune-related gene expression including CTLA4, IDO1, CD80, PD-L1, LAG3, CD86, TIM3, IFG, PD-1, and PD-L2 (fold change: 2-4, q < .0001). Overall, DSCR1 expression above median was associated with longer median OS (17 vs 11 months, HR 0.89 [0.83-0.95], P < .0001). When stratified by quartiles, DSCR1 Q4 was associated with longer time on treatment [ToT] with gemcitabine/nab-paclitaxel (HR 0.75 [0.63-0.89], P = .001), and marginal benefit on ToT (HR 0.81 [0.65-1.0]) but longer survival in FOLFIRINOX treated patients (HR 0.73 [0.58-0.92], P = .008). **Conclusions:** This is the first and most extensive profiling study to investigate DSCR1 expression in PDAC. Our data show a strong association between tumor DSCR1 gene expression, several pathway alterations, immune-related gene expression, TME cell infiltration and patient survival. These findings suggest DSCR1 as a candidate prognostic biomarker and as a potential treatment target in PDAC. Research Sponsor: This work was partly supported by National Cancer Institute (P30CA014089), Gene Gregg Pancreas Research Fund, Ming Hsieh research fund, Dhont Family Foundation, San Pedro Peninsula Cancer Guild; Daniel Butler Research Fund, V foundation for cancer research, Victoria and Philip Wilson Research Fund, Fong research project and Gloria Borges WunderGlo Foundation.

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Poster Session

First in class TLR7/8 agonist BDB001 combined with atezolizumab and stereotactic body radiation therapy in patients with advanced pancreatic adenocarcinoma: Results from the AGADIR study. *First Author: Simon Pernot, Department of Medical Oncology, Institute Bergonié Cancer Center, Bordeaux, France*

Background: Pancreatic adenocarcinoma is refractory to immune checkpoint inhibitors such as PD1/PDL1 antagonists. Investigating alternative immunotherapeutic approaches is a crucial need for this devastating disease. The potent immunostimulatory effects of Toll-like receptor (TLRs) have spurred efforts aimed at the development of TLR agonists as new immune-oncology agents. Radiation therapy combined with TLRs agonists has been shown to enhance antitumor immunity in the preclinical setting. **Methods:** AGADIR is a multi-cohort, phase 2, multicenter, open-label study investigating the novel TLR 7/8 agonist BDB001 combined with atezolizumab and stereotactic body radiotherapy (SBRT) in patients with advanced cancers. Cohort A enrolled patients with advanced pancreatic adenocarcinoma. BDB001 was administered IV at the dose of 0.75 mg/m² on days 1, 8, and 15 of cycles 1, 2, and 3. Then from cycle 4 on day 1 every 3 weeks. Atezolizumab was given at the dose of 1200 mg every 3 weeks. SBRT of at least one metastatic lesion was started at least one week after the first administration of atezolizumab and at the latest before the Cycle 2 Day 1. The primary endpoint is disease control rate defined as the proportion of participants with complete response, partial response or stable disease, as per adapted RECIST v1.1, observed within 24 weeks of treatment onset. Secondary endpoints include objective response, progression-free survival, overall survival and safety. All patients underwent sequential blood and tissue sampling for translational studies. **Results:** Between July 2021, and June 2022, 32 pts were enrolled in 3 centers (14 male, 18 female). Median age was 64 years (range 38 – 78). Median number of previous treatment lines was 1 (range 1 – 5). The most common treatment related adverse events were grade 1/2 asthenia, chills and fever. No death was related to the treatment. Among the 21 patients for whom central review was performed at the time of this writing, best tumor response was confirmed partial response, stable disease and progressive disease in 2 (9.5%), 6 (28.5%) and 13 (62.0%) patients respectively. The disease control rate was 38.0% (95%CI 18.1-61.5). **Conclusions:** The AGADIR study met its first endpoint for disease control rate in patients with advanced pancreatic cancer. Efficacy data on the whole cohort of patients and full biomarkers analyses will be presented at the meeting. Clinical trial information: NCT03915678. Research Sponsor: Institut National du Cancer; Roche Parma AG, Seven and Eight Biopharmaceuticals Inc.

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Poster Session

Clinical utility of next generation sequencing (NGS) on circulating tumor DNA (ctDNA) in patients (pts) with pancreatic cancer (PC). *First Author: Fergus Keane, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: ctDNA provides opportunities for identifying targeted therapies, a source to conduct NGS when tissue acquisition is infeasible, detection of minimal residual disease (MRD), and identification of resistance mutations. There are limited large data sets to inform clinical utility and limited correlation of NGS of ctDNA and tumor in PC. Herein, we evaluate the ctDNA detection rate in multiple cohorts of PC and report the ctDNA-tissue genotype concordance in PC at Memorial Sloan Kettering (MSK). **Methods:** Pts with PC at MSK who had ctDNA prospectively collected using the MSK-ACCESS 129 gene ctDNA NGS assay, were identified. ctDNA detection was defined as the identification of a mutation, copy number (no.) alteration or structural variant. Tissue-based NGS using MSK-IMPACT gene assay was performed for pts with adequate tissue, and matched with ctDNA by date. Clinical, pathologic and outcome data were abstracted. Data are summarized with descriptive statistics. Overall survival (OS) estimated by Kaplan-Meier method from date of ctDNA draw to death/last follow up. **Results:** From 08/2019 to 07/2022, N= 414 pts with PC and ≥ 1 ctDNA sample included. Median age 69 years (range 29-92), female N=206 (50%). Stage at ctDNA collection: Stage I-III N= 203 (49%); Stage IV N= 211 (51%). ctDNA detection rate by no. of involved organs; 0 organs (MRD), N=7/30 (23%); 1-2 organs, N=158/270 (58.5%); 3-4 organs, N=82/102 (80.4%); >5 organs, 12/12 (100%). CtDNA detection rate by site of metastasis: Liver only, 75/99 (76%); peritoneum only, 15/25 (60%); lung only, 10/22 (45%). In pts with detected ctDNA median CA 19-9 was 494 U/mL (range 0, 247674) vs 100 U/mL (range 1, 22360) in pts with undetected ctDNA. In pts with detected ctDNA median CEA was 7 ng/mL (range 1, 2020) vs 4 ng/mL (range 1, 99) in pts with undetected ctDNA. In stage IV untreated pts, median OS 13 months(m) (95% CI: 7.3, 16) and 10 m (95% CI: 5.6, -) for ctDNA detected vs undetected, respectively. ctDNA detection rates by stage, and concordance between ctDNA and tissue-based NGS for common driver mutations *KRAS*, *TP53*, *CDKN2A* and *SMAD4* in N=131 matched pairs are summarized in the table. **Conclusions:** ctDNA detection rates are high (89%) in pts with untreated stage IV PC, with high concordance between ctDNA and tissue-based NGS (87% - 95%). In untreated stage I-III PC, detection and concordance rates are lower (<50%). Detection rates are associated with disease burden, site of metastasis, CA 19-9/CEA levels. ctDNA is a promising tool in detection of somatic alterations in PC, particularly in stage IV disease, and is a complementary adjunct to tumor-based NGS. Research Sponsor: None.

Stage	N	ctDNA Detected N (%)	ctDNA Undetected N (%)
Stage IV Untreated	119	106 (89%)	13 (11%)
Stage I – III Untreated	61	26 (43%)	35 (57%)
MRD	30	7 (23%)	23 (77%)
Concordance Per Gene	Untreated All Stages	Stage IV Untreated	Stage I – III Untreated
<i>KRAS</i>	76%	92%	43%
<i>TP53</i>	76%	89%	50%
<i>CDKN2A</i>	92%	95%	96%
<i>SMAD4</i>	85%	87%	89%

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Poster Session

Targeting germline or somatic DNA repair defects (beyond BRCA) in pancreatic cancer with niraparib: A phase II study (NIRA-PANC). *First Author: Anup Kasi, University of Kansas Cancer Center, Westwood, KS*

Background: Targeting a molecular subset of pancreatic cancer (PC) may identify alternatives to percutaneous chemotherapy and chemo-resistance/toxicity. Poly (ADP ribose) polymerase inhibitors (PARPi) have shown efficacy in germline BRCA mutation via synthetic lethality. Preclinical evidence suggests PARPi may target DNA repair defects beyond BRCA. We conducted a Niraparib phase II study in PC patients with germline/somatic DNA repair defects. **Methods:** This is an open-label, phase 2 trial in pts with locally advanced or metastatic PC with germline or somatic mutations, known or tested after consent to pre-screening tumor tissue analysis in DNA repair genes (BRCA1/2, PALB2, ATM, NBN, ATR, BRIP1, IDH1/2, RAD51, RAD51B/C/D, RAD54L, CDK12, BARD1, FAM175A, BAP1, CHEK1/2, GEN1, MRE11A, XRCC2, SHFM1, FANCD2, FANCA, FANCC, FANCG, RPA1, ARID1A), who have progressed on or intolerant of at least one line of therapy, no prior PARPi, with evaluable disease, and ECOG PS 0-1. Eligible pts were treated with Niraparib 300mg or 200mg PO daily for 28 days (1 cycle = 28 days) (200mg dose for baseline weight is < 77 kg or baseline platelet count is < 150,000 μ L) until disease progression, unacceptable toxicity, investigator decision, withdrawal of consent, or death. The primary objective was 6-month PFS rate. The secondary objectives were OS, DCR and safety. Pts were evaluable for safety if they had received > 1 dose of Niraparib and for efficacy if they had also received > 1 follow-up imaging study. **Results:** As of Feb 2023, 36 (13 female, 23 male) pts were enrolled, with a mean age of 62.9 (median 64, IQR 51-73, min 41, max 83, SD 11.25), of whom 27 (8 female, 19 male) were evaluable for efficacy. After a median follow-up of 9.0 months (IQR 6.0-15.1 m), the 6-month PFS rate was 40.7% (11/27 pts; 95% CI 4.7%- 100 %). The median PFS is 4.4 m (CI 2.3 - 6.5 m), and median OS is 9.1 m (7.5 -15.1 m). The disease control rate at 8 weeks was 70.4% (19 of 27 pts; 95% CI 49.8%-86.3%). Of the 27 evaluable pts- BRCA2 mutation was seen in 10 pts, ATM (5), CHEK2 (5), BRCA1 (2), NBN (2), ARID1A (1), FANCA (1), FAM175A (1), RAD51B (1), IDH1 (1), IDH2 (1). Among 36 pts evaluable for safety, treatment-related adverse events occurred in 75% (27/36), and Grade 3 and grade 4 treatment-related adverse events occurred in 31% (11/36). The most common treatment-related AEs were anemia (25%, 9/36), nausea (22%, 8/36), thrombocytopenia (19%, 7/36), vomiting (19%, 7/36), and fatigue (17%, 6/36). Serious treatment-emergent adverse events were reported in 11% (4/36). There were no treatment-related deaths. **Conclusions:** In previously treated pts with locally advanced and metastatic PC harboring DNA repair defects, niraparib monotherapy yielded a 6-month PFS rate of 40%, median PFS of 4.4 months, and median OS of 9.1 months. Clinical trial information: NCT03553004. Research Sponsor: GSK (TESARO); IIT Steering Committee funds at KU Cancer Center.

Outcome	Pts (n =27)	95% CI
6m-PFS	40.7% (11/27)	4.7%- 100%
mPFS	4.4 months	2.3 - 6.5 m
mOS	9.1 months	7.5 -15.1 m
DCR	70.4% (19/27)	49.8%-86.3%

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Poster Session

Impact of novel pan-RAS inhibitors on efficacy and resistance to AMG-510 and MRTX-1133 in pancreatic cancer cell lines. *First Author: Tariq Arshad, Qualigen Therapeutics, San Ramon, CA*

Background: Mutant-activated RAS genes are the most frequently mutated gene family associated with cancer (almost 30% of all cancers contain a mutant RAS gene). KRAS is the predominant isoform mutated in cancer and is the isoform exclusively mutated in pancreatic ductal carcinoma (PDAC). Since almost all PDAC cases harbor a mutant RAS, it is arguably the most RAS-addicted tumor type. There is now considerable evidence implicating mutant KRAS as a driver of PDAC. Recently, several mutant KRAS-targeted therapies (sotorasib and adagrasib) have been developed and show promise in PDAC patients. We have developed a direct inhibitor of RAS with a predicted unique interaction region capable of directly binding to wild-type H- and K-RAS, but which shows preferential binding for KRAS G12D and G12C mutants. This novel inhibitor disrupts the RAS effector domain and blocks the ability of RAS to signal through its effectors. **Methods:** We used *in silico* virtual library screening to identify an initial candidate inhibitor which was effective at inhibiting the 3D growth of PDAC cells without affecting their growth in 2D. Subsequent iterative rounds of medicinal chemistry was then performed to identify a series of derivatives with enhanced activity, as determined by 3D growth inhibition assays and effects on Ras signaling, as determined by Western blot analysis of phosphor-ERK, phosphor-Akt and activation of Ral A. **Results:** Our series of RAS inhibitors effectively block PDAC cell growth in 3D without impacting their 2D proliferation and suppress the interaction of KRAS with its effector cRAF. The inhibitors also effectively inhibit RAS signaling in mutant RAS containing PDAC cells. Since our novel compounds are predicted to bind to RAS at a different site to either AMG-510 (G12C specific inhibitor) and MRTX-1133 (G12D specific inhibitor), we tested the co-operativity of our compounds with these existing agents. Our compounds enhanced the anti-proliferative effects of both MRTX-113 and AMG-510 in mutant KRAS G12D and G12C PDAC cells, respectively. **Conclusions:** We have developed a series of novel RAS inhibitors that directly bind preferentially to mutant KRAS that may serve as new mutant KRAS-targeted therapeutics, and that may also have the potential to enhance the efficacy or suppress the resistance of AMG-510 and MRTX-1133. Research Sponsor: Qualigen Therapeutics; U.S. National Institutes of Health.

4156

Poster Session

Chemotherapy dose density and effect on prognosis for patients with resectable pancreas cancer: A secondary analysis of SWOG S1505. *First Author: Sameer H. Patel, University of Cincinnati Medical Center, Cincinnati, OH*

Background: Chemotherapy is an integral part of multimodality treatment for resectable pancreatic ductal adenocarcinoma (PDAC). Assessing the impact of chemotherapy dose reductions or missed cycles on survival is difficult as few trials prospectively address the prognostic value of this important metric. **Methods:** SWOG S1505 (NCT02562716) was a randomized, phase II study of perioperative (12 weeks neoadjuvant and 12 weeks adjuvant) chemotherapy with mFOLFIRINOX or gemcitabine/nab-paclitaxel for resectable PDAC. Dose density (DD) was defined as the estimated percent of chemotherapy dose received of the total planned per protocol. Thresholds were based on published analyses and balance in sample size across treatment arms. Cox regression analysis of overall survival (OS) according to DD was performed in patients alive at two landmark time points: after surgery (among those who completed surgery) and at 40 weeks (when protocol therapy was to be completed). **Results:** Of the 103 eligible patients enrolled, median age was 64 years, 81% underwent pancreaticoduodenectomy, 15% distal pancreatectomy, and 3% a total pancreatectomy. In the 73 patients who underwent surgery, median neoadjuvant chemotherapy DD was 89%. Patients with ≥ 85% DD had higher median OS from surgery (38.1 v. 17.2 months, p = 0.039) compared to patients with < 85% DD. Of the 82 patients who survived to 40 weeks post randomization, 67 underwent surgery and 58 started adjuvant chemotherapy. The median DD for all perioperative chemotherapy was 67%; DD was significantly higher for neoadjuvant compared to adjuvant therapy (83% vs. 58%, p < 0.001). In this cohort, DD ≥ 70% was associated with better median OS from 40 weeks post randomization (32.2 v. 14.0 months, p = 0.017). DD was not significantly associated with pathologic response, margin status, or lymph node negativity. There were no significant differences in DD between the mFOLFIRINOX and gemcitabine/nab-paclitaxel arms. **Conclusions:** This is the first study to identify a prognostic role for chemotherapy DD in patients undergoing perioperative chemotherapy for resectable PDAC. Patients who received ≥ 85% DD preoperatively and/or ≥ 70% DD perioperatively had significantly higher mOS than those receiving a smaller proportion of protocol therapy. With greater survival benefit in patients who received higher chemotherapy DD, and higher DD being likelier in preoperative vs. postoperative treatment, these data support use of neoadjuvant chemotherapy for resectable PDAC. Moreover, these findings suggest that DD should be considered in prospective studies for localized PDAC to optimize therapy to be received. Research Sponsor: None.

4159

Poster Session

PD-1 blockade plus chemotherapy followed by concurrent SBRT with SIB as preoperative therapy for patients with borderline resectable and locally advanced pancreatic cancer: A biomolecular exploratory, single-arm phase II clinical trial. *First Author: Juan Du, The Comprehensive Cancer Center of Drum Tower Hospital, Medical School of Nanjing University, Nanjing, China*

Background: Pancreatic cancer is fatal malignant tumor with low resection rate and poor prognosis. We aimed to assess the safety and efficacy of a new mode of preoperative therapy for patients with locally advanced (LAPC) or borderline resectable pancreatic cancer (BRPC). **Methods:** This is a single arm, exploratory phase II clinical trial (ChiCTR2000032955). Gemcitabine (1000 mg/m²) and nab-paclitaxel (125 mg/m²; AG) were administered to patients with LAPC or BRPC on days 1 and 8, along with tislelizumab (200 mg) on day 1 intravenously (IV) every three weeks. Concurrently, the patients underwent stereotactic body radiotherapy (SBRT) with simultaneous integrated boost (SIB) during the third cycle of treatment. Surgical intervention was reassessed after four cycles of treatment. Objective response rate (ORR), R0 resection rate, median overall survival (mOS), median progression-free survival (mPFS) and safety were analyzed. Multiomics potential predictive biomarkers were investigated as exploratory objectives. **Results:** Between May 2020 and October 2021, 29 patients were enrolled in the study, 25 of them included in the intention-to-treat analysis. At the end of the last follow-up (November 30, 2022), 15 patients had a best response of partial response, the ORR was 60%. Ten patients underwent resection, and the R0 resection rate was 90% (9/10). The disease control rate (DCR) was 100%. Two of the ten resected patients achieved pathologic complete response and one patient achieved major pathological response. The mPFS, 12-months PFS rate, and 12-months OS rate were 13.7 months (95% CI: 11.7–NR), 64% (95% CI: 47.6–85.8%), and 72% (95% CI: 56.3–91.9%), respectively. Grade 3 or higher adverse events are anemia (8%), thrombocytopenia (8%) and jaundice (8%). Biomarker analysis indicated that patients with continuous carbohydrate antigen 19-9 decline and elevated peripheral blood eosinophil counts during treatment exhibited better survival outcomes. Furthermore, circulating tumor DNA analysis reveals that patients with a >50% decline in maximal somatic variant allelic frequency (maxVAF) between the first clinical evaluation and baseline have a longer survival outcome and higher response rate than those who are not (PFS: 20.03 vs. 10.32 months, $p = 0.024$; OS: not reached vs. 13.47 months, $p = 0.024$; ORR: 90% vs. 35.7%, $p = 0.013$). Moreover, maxVAF decline (> 50%) is significantly associated with the surgical rate after preoperative therapy (70.0% vs. 21.4%; $p = 0.035$). **Conclusions:** Anti-PD-1 inhibitor tislelizumab plus AG chemotherapy followed by concurrent SBRT with SIB displayed promising antitumor activity and acceptable safety profile for patients with LAPC or BRPC. Multiomics potential predictive biomarkers are identified and warrant further verification. Clinical trial information: ChiCTR2000032955. Research Sponsor: National Key Research and Development Program of China (2020YFA0713804); Special Fund of Health Science and Technology Development of Nanjing (YKK20080).

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Poster Session

Tandem duplicator phenotype: A novel targetable subgroup in pancreatic cancer? *First Author: Abdul Rehman Farooq, Princess Margaret Cancer Centre, Toronto, ON, Canada*

Background: Validated biomarkers are urgently needed to provide a more precise approach in pancreatic cancer (PDAC). Homologous recombination deficiency (HRD) is a heterogeneous cohort in PDAC and predicts platinum and PARP inhibitor sensitivity. The BRCA-1 genotype associates with distinct tandem duplications (TDs), however non-BRCA-1 TD phenotypes (TDP) have been observed across tumour types and may be associated with perturbations in CDK12, FBXW17, and CCNE1. Here, we characterize the prevalence and outcomes of TDP in a large series of prospectively sequenced PDAC. **Methods:** Whole-genome sequencing was performed in 191 early stage resected and 275 advanced PDAC cases in the PanCuRx initiative and the COMPASS trial at the Ontario Institute for Cancer Research and Princess Margaret Cancer Centre. Tumors underwent laser capture enrichment prior to sequencing. TD scores were calculated as previously described by Menghi et al, and HRDetect scores assigned. Samples were classified as classical or basal-like by Moffitt. Outcomes of patients with TDP tumors were evaluated. Tumors that are nonHRD and nonTDP are referred to as typical. **Results:** Of 466 cases, 46 were identified as TDP (9.9%; 17 resected, 29 advanced). Subgroups of TDP by etiology included BRCA1 (n=8; 6 germline, 2 somatic), somatic CCNE1 (n=1), and unknown (n=37; no identified alterations in TDP-related genes). Pathogenic germline variants were not found in unique genes other than BRCA1. HRD TDP was associated with a significantly smaller TD size compared to nonHRD TDP (median 12 kb vs. 125 kb, $p < 0.0001$) and median TD load of 114. NonHRD TDP genomes exhibited elevated TD load (median 70 vs. 13, $p < 0.0001$) and HRDetect scores ($p < 0.0001$) compared with typical. NonHRD TDP was not prognostic in resected PDAC disease ($p = 0.6361$) compared with typical. We observed a trend towards improved response to 1st-line platinum therapy in nonHRD TDP vs. typical ($p = 0.066$) for patients with advanced disease. When stratified for only 'classical' RNA subtype cases as per Moffitt classification (HRD TDP: 2 basal-like, 8 classical, 1 unknown; nonHRD TDP: 9 basal-like, 25 classical, 1 unknown), platinum therapy was correlated with better response in nonHRD TDP vs. typical (n = 10, 70% ORR, $p = 0.0108$) highlighting the chemoresistance of the basal-like subgroup. Superior survival was not observed in this small cohort. **Conclusions:** In PDAC, the etiology of nonHRD TDP is unclear but may represent a potential marker for platinum and DNA damage response agents. Further investigation is warranted with a larger sample size. Research Sponsor: None.

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Poster Session

Impact of positive resection margins on recurrence and survival following resection and adjuvant chemotherapy in pancreatic cancer: Results of the PRODIGE 24-CCTG PA-6 trial. *First Author: Aurélien Lambert, Medical Oncology Department, Lorraine Cancer Institute, Nancy, France*

Background: Pancreatic adenocarcinoma (PDAC) has a poor prognosis. Only 10-15% of patients present with resectable tumors upfront, and most patients develop recurrence and die prematurely. The data are incongruous when considering R1 status, direct invasion is not consistently a significant prognostic factor. It is recommended that 7 margins be identified for surgery: the bile duct, pancreatic neck, proximal and distal duodenum, superior mesenteric vein (SMV), superior mesenteric artery (SMA), and posterior pancreas. By analyzing data from the PRODIGE 24-CCTG PA-6 trial that validated the mFOLFIRINOX regimen in adjuvant setting, our main objective was to analyze the prognostic value of margin involvement on disease-free survival (DFS). **Methods:** The protocol recommended that the surgeon inked the resection margins. R1 was defined as direct tumor margin infiltration within 1 mm of one or more resection margins. All patient data were re-evaluated centrally by an external review committee including pathologists, surgeons, and medical oncologists to verify key prognostic factors, including inking and filling of resection margins. **Results:** Among the 400 patients included in the study, the median number of documented margins was 6, IQR (5-7). In 214 patients (53.5%), fewer than 7 margins were reported. The most common margin involvement was on the SMV groove (28.3%), posterior margin (21%), SMA (14.5%), and pancreatic neck transection (5.3%). Margin inking was performed in 64.9% of cases. Misclassification of the R1 status concerned 24.1% of the files after centralized review. When positive, only 3 margins (SMV groove, median and posterior) were significant prognostic factors in univariate analysis (all $p < 0.01$). When combined, one R1 margin among these three had independent prognostic value in multivariate analysis. In multivariate analysis, DFS was significantly different by quality of resection margins in the gemcitabine arm (HR 95% CI 1.97 [1.23;3.16]; $p = .005$) but not in the mFOLFIRINOX arm (HR 95% CI 1.46 [0.91;2.35]; $p = .114$). **Conclusions:** Few studies have examined the prognostic implications of each margin. We consider that every effort should be made to evaluate the 3 best prognostic margins. One finding of this work is the likely effect of mFOLFIRINOX on local invasion in operated patients. It seems that this chemotherapy regimen (unlike gemcitabine) corrects the alteration related to margin involvement, probably explaining all or part of the improved survival. Therefore, the value of additional therapies, such as clouture radiotherapy, should be evaluated in patients with unknown marginal status or in those who did not benefit from mFOLFIRINOX chemotherapy. A patient who received mFOLFIRINOX as adjuvant therapy is more likely to recur with distant metastasis (80%) and with a better survival of 28 months. Clinical trial information: NCT01526135. Research Sponsor: None.

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Poster Session

Artificial intelligence (AI) –powered spatial analysis of tumor-infiltrating lymphocytes (TILs) for prediction of prognosis in resectable pancreatic adenocarcinoma (PDAC). *First Author: Yoojoo Lim, Oncology, Lunit, Seoul, South Korea*

Background: The degree of TIL infiltration in the tumor microenvironment has been suggested as a prognostic factor in multiple cancer types, but the significance in PDAC is not well known. The aim of this study is to assess the prognostic role of AI-based spatial TIL density assessment and immune phenotype (IP) classification in resectable PDAC. **Methods:** We collected hematoxylin and eosin (H&E)-stained whole slide images (WSI) of tumor tissues and clinical data from stage I – III PDAC patients who received curative surgery at Samsung Medical Center, in Seoul, Korea, between Jan 2017 and Dec 2018. For spatial TIL analysis, we used Lunit SCOPE IO, an AI-powered pathology slide analyzer that can identify TIL and segment tumor epithelium and stroma from H&E-stained WSI. It then estimates intratumoral (iTIL) and stromal TIL (sTIL) densities, as well as IP classification of each case. IPs were defined as follows: inflamed IP (IIP) as high iTIL and sTIL; immune-excluded as low iTIL and high sTIL; immune-desert as low TIL overall. Predetermined cutoffs prior to this study were used for the determination of IPs. **Results:** A total of 209 patients were identified, 182 treated with upfront surgery and 27 with preoperative chemo(radio)therapies followed by surgery. The median recurrence-free survival (RFS) and overall survival (OS) of all patients was 16.8 months (95% CI 12.1 - 21.4), and 36.8 months (95% CI 31.2 - 42.4), respectively. In the 182 patients treated with upfront surgery, the median iTIL and sTIL densities were 85.3/mm² (IQR 56.9 – 133.0) and 672.2/mm² (IQR 445.9 – 912.9). 85.7% of the cases were immune-excluded, while 11.5% were IIP. The patients having iTIL higher than the median exhibited longer RFS (HR 0.62, 95% CI 0.42 - 0.92, $p = 0.017$). Also, the patients having IIP exhibited longer OS ($p = 0.045$, HR 2.05, 95% CI 1.00 – 4.22) and a marginally longer RFS ($p = 0.051$, HR 2.03, 95% CI 0.98 – 4.18) compared to those with non-IIP. In the 27 patients who were treated with preoperative therapies, the iTIL densities in the surgical specimens were significantly higher compared to the 182 untreated samples (mean iTIL 168.8/mm² after chemo(radio)therapies vs. 112.6/mm² in upfront surgery, $p = 0.012$), although the increase in the proportion of IIP was not significant. Using the iTIL median of the 182 upfront surgery cases, 17/27 (63.0%) patients had high iTIL in WSIs obtained after preoperative therapies, and these patients were observed to have a significantly better RFS (HR 0.26, 95% CI 0.09 - 0.73, $p = 0.006$). **Conclusions:** While most cases of resectable PDAC were found to have TIL infiltration mainly in stroma, relatively higher iTIL infiltration was associated with better prognosis. An increase in iTIL after chemo(radio)therapies may be associated with better outcomes. Research Sponsor: None.

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Poster Session

Minimally invasive versus open distal pancreatectomy for resectable pancreatic cancer (DIPLOMA): An international randomised trial. *First Author: Mohammed Abu Hilal, Istituto Ospedaliero Fondazione Poliambulanza, Brescia, Italy*

Background: In the absence of randomised trials, the oncological safety of minimally invasive distal pancreatectomy (MIDP) in patients with pancreatic cancer continues to be a matter of debate. **Methods:** An international randomised non-inferiority trial including patients with resectable pancreatic cancer from 35 centres in 12 countries. Patients were randomly assigned to either MIDP (laparoscopic or robotic) or open distal pancreatectomy (ODP). Both patients and pathologists were blinded to the assigned approach. Primary endpoint was radical resection (R0, <1mm free margin) in patients who had ultimately undergone resection. Analyses for the primary endpoint were by modified intention-to-treat, excluding patients who did not undergo a resection. The pre-defined non-inferiority margin was set at -7%. **Results:** Between May 8, 2018 and May 7, 2021, 258 patients were randomly assigned to MIDP (131 patients) or ODP (127 patients). The modified intention-to-treat population included 117 patients in the MIDP group and 114 patients in the ODP group. An R0 resection occurred in 83 (73%) patients in the MIDP group and in 76 (69%) patients in the ODP group (difference 4%, 90% CI -6 to 14%; p=0.039). Median lymph node yield was comparable (22.0 [16.0-30.0] vs 23.0 [14.0-32.0] nodes, p=0.86), as was the rate of intraperitoneal recurrence (41% vs 38%, p=0.45). Other post-operative outcomes were comparable. **Conclusions:** In this trial, the rate of radical resection following MIDP was non-inferior compared to ODP. This confirms the oncological validity of the minimally invasive approach in patients with resectable pancreatic cancer. Clinical trial information: ISRCTN44897265. Research Sponsor: Medtronic and Ethicon.

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Poster Session

A phase I/II study of durvalumab and stereotactic ablative body radiotherapy (SABR) in locally advanced (LA) and borderline resectable (BR) pancreatic cancer. *First Author: Richard Tuli, USF Health Morsani College of Medicine, Tampa, FL*

Background: Pancreatic cancer (PC) is largely refractory to immune checkpoint blockade (ICB) in genomically unselected patients (pts). Synergistic effects of combined ICB and radiotherapy have been suggested in varied solid tumors. Few studies have evaluated this approach in pts with PC. We sought to evaluate the safety and efficacy of PD-L1 inhibitor durvalumab (D) and SABR after induction chemotherapy, in LA and BR PC. Herein, we present phase II data from two cohorts. **Methods:** A multi-institutional, non-randomized phase 1/2 trial of SABR and D was conducted at Cedars-Sinai Medical Center (CS) and Memorial Sloan Kettering (MSK). Key eligibility: ECOG 0-1; unresectable PC, with stable/responding disease following 2-3 cycles gemcitabine and nab-paclitaxel (GnP) or 4-6 months (m) FOLFIRINOX (FFX). CS enrolled pts with BR and LA PC; MSK enrolled pts with LA PC only. All pts received SABR between dose 1 and 2 of D, with slight variation in ablative radiation techniques (CS: 33Gy/5#; MSK: MRI adaptive ablative radiation, 50Gy/5#). D dosed on day 1: 750mg x 4 doses Q14 days, and subsequently Q2 or Q4 weeks x 1 year total, or until resection, progression of disease (POD), or limiting toxicity. Primary endpoint: 6-month progression free survival (6 m PFS). Secondary endpoints: rate of downstaging to resectability, objective response by RECIST v1.1, duration of response, PFS, Overall Survival (OS). PFS and OS estimated from consent date using Kaplan-Meier method. Association between surgery and outcomes was analyzed as a time dependent covariate in univariate Cox regression models for OS and PFS. To assess immunogenomic biomarkers of response, pre- and on-treatment tissue, blood and microbiome samples were gathered. **Results:** Between 08/2017 and 05/2022, N= 36 enrolled. Median age 67.5 years (range 48-79), 39% (14/36) female. Performance Status: N=12 (33%) ECOG 0; N= 24 (67%) ECOG 1. Median duration chemotherapy: 3.5 m (range 1.4, 5.8). Staging: N=31 (86%) LA; N=5 (14%) BR. N = 9 (25%) underwent resection; all R0. Conversion to resection was not associated with PFS (HR 0.45; 95% CI 0.17, 1.17, p=0.1) or OS (HR 0.69; 95% CI 0.26, 1.84, p=0.5). Survival and response data summarized in table. Toxicities of special interest: Grade 3 treatment-related: N= 7; diarrhea N= 2; elevated AST/ALT N= 2; lipase/amylase elevation, N=1; nausea N=1. Grade 4: amylase elevation N=1. **Conclusions:** D and SABR after induction chemotherapy in LA and BR PC is safe, had an encouraging 6-m PFS of 69% and favorable R0 resection rate, warranting further evaluation. Immuno-genomic biospecimen analyses underway. Clinical trial information: NCT03245541. Research Sponsor: AstraZeneca.

Median Follow-Up (95% CI)	23 m (18, -)
6-m PFS (95% CI)	69% (56%, 86%)
Median PFS (95% CI)	8.2 m (6.1, 14)
Median OS (95% CI)	17 m (13, -)
Best Objective Response	
Complete Response	1 (3%)
Partial Response	10 (28%)
Stable Disease	23 (4%)
POD	2 (6%)

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Poster Session

Meta-analyses of factors associated with long-term survival after resection of pancreatic ductal adenocarcinoma. *First Author: Asad Saulat Fatimi, Aga Khan University, Karachi, Pakistan*

Background: Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal malignancies. Long-term survival (>5 years, LTS) is rarely seen even after 'curative-intent' resection. With improved systemic control via effective systemic therapies, LTS is now being reported more frequently. However, our understanding of LTS in PDAC remains limited. The aim of the current study was to perform a systematic review and meta-analysis to quantify the associations between various clinicopathological factors and LTS following resection of PDAC. **Methods:** The PubMed, Embase, Scopus, and Cochrane CENTRAL databases were systematically searched for articles reporting actual patient survival data. Two reviewers independently screened and reviewed articles, extracted relevant data, and assessed the risk of bias in included studies using the Newcastle-Ottawa scale (NOS). Data that compared patients who achieved LTS after resection with those who did not were extracted from the included studies. Meta-analyses using a random effects model were conducted to identify associations between LTS and various patient, tumor, and treatment related factors. **Results:** Overall, 33 studies with 46,981 patients after resection of PDAC were included. Most articles received a 'good' NOS assessment, indicating acceptable risk of bias. The median rate of LTS was 15.27% (IQR: 9.47-20.72). Multiple clinicopathological factors were found to be associated with LTS, including tumor grade (OR: 0.40, 95%CI: 0.31-0.52), tumor stage (OR: 0.36, 95%CI: 0.31-0.41), and margin status (OR: 0.43, 95%CI: 0.36-0.50). Factors that were not associated with LTS included patient age, tumor size, tumor location, or genetic mutations. Notably, adjuvant therapy (OR: 1.68, 95%CI: 1.24-2.28) but not neoadjuvant therapy (OR: 1.08, 95%CI: 0.62-1.87) were associated with LTS. **Conclusions:** This meta-analysis revealed that 15% of patients achieved LTS after resection of PDAC. Multiple clinicopathological factors are associated with LTS whereas presence of 'traditional' negative prognostic factors does not rule out LTS. Further studies are required to identify robust predictors of LTS in resected PDAC. Research Sponsor: None.

Clinicopathological characteristics associated with LTS in resected PDAC.

Parameter		Odds Ratio (95%CI)
Patient Factors	Sex	1.29 (1.01, 1.64)
	Pathologic T-stage	0.40 (0.31, 0.52)
	Pathologic M-stage	0.16 (0.06, 0.38)
	Nodal Disease	0.40 (0.35, 0.45)
	Vascular Invasion	0.50 (0.39, 0.64)
	Perineural Invasion	0.45 (0.29, 0.69)
	Lymphatic Invasion	0.44 (0.32, 0.60)
	Major Vessel Resection	0.62 (0.41, 0.93)
	Adjuvant therapy	1.68 (1.24, 2.28)
Treatment Factors		

4166

Poster Session

Mutation-site localized non-B DNA burden and survival heterogeneity in early-stage pancreatic cancer. *First Author: Qi Xu, Livestrong Cancer Institutes, University of Texas at Austin, Austin, TX*

Background: Pancreatic cancer is a highly aggressive disease with a poor prognosis, and one in which most measure of genomic instability (e.g., tumor mutation burden (TMB), fraction of genome altered (FGA)) have thus far, not proven informative in differentiating survival. Non-B DNA are alternative DNA forms that deviate from the canonical B-DNA structure with potential to increase susceptibility to mutations, leading to the development of cancer. The role of non-B in pancreatic cancer has not been fully explored. Herein, we investigate the relationship between gene mutation sites co-localized with non-B DNA motifs in terms of survival and B-DNA features. **Methods:** Using TCGA data, we derived a genome-wide mutation signature on 104 early-stage pancreatic patients. We introduced a metric, mutation-localized non-B burden (MLNB) by the number of non-b motifs containing mutation sites, normalized to the number of mutations and motif library size. We applied MLNB to patient-specific mutation signatures to derive an MLNB burden for non-B DNA structure motifs: G-quadruplexes (G4), Z-DNA, inverted repeats (IR), mirror repeats (MR), direct repeats (DR), and short tandem repeats (STR). We performed a cluster analysis on MLNB and compared groups based on overall survival (OS) in months (mos) using a log-rank test. Comparisons of B-DNA-derived molecular features among clusters were performed using a Kruskal-Wallis and Fisher Exact test. **Results:** Among the 104 early-stage pancreatic patients with a mutation signature, MLNB clustering resulted in six patient clusters that differentiated by non-B DNA structure, with DR burden the longest OS cluster (n=23, median OS=30mos), significantly (p < 0.05) differing as compared to IR (n=23, median OS=15 mos), STR (n=20, median OS=16mos), MR with lack of IR (n=14, median OS=13mos) and MR with IR (n=16, median OS=8mos). A mix of Z-DNA and G4 burden defined a cluster with shorter OS (n=22, median OS=14mos) as compared to DR, though not significant. Patients with the longest OS, MLNB-DR burden cluster had mutation signatures enriched in MAPK and Notch signaling pathways, as compared to the other clusters enriched with double-stranded break and mismatch repair (IR), hedgehog and WNT signaling (STR), and interleukin-4 signaling (MR) pathways. Among all clusters, CDKN2A deletion was most prevalent except for MLNB-DR burden cluster. No Significant differences were found between the MLNB clusters with age, race gender, KRAS and TP53 mutations, FGA, TMB, tumor purity, Bailey and Moffit subtypes. **Conclusions:** Our results point towards the potential use of MLNB as an emerging marker of site-structure genomic instability. Considering that triplex DNA is emerging as a marker genomic instability, and that we distinguish between two MR groups based on IR burden, our results may provide insights into various instability mechanisms associated with poor survival in pancreatic cancer. Research Sponsor: University of Texas Dell Medical School.

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Poster Session

The five periampullary cancers: Not just different siblings but different families—An international multicenter cohort study. *First Author: Bas Uijterwijk, Fondazione Poliambulanza Istituto Ospedaliero 57, Brescia, Italy*

Background: Cancer arising in the periampullary region can be anatomically classified in pancreatic ductal adenocarcinoma (PDAC), distal cholangiocarcinoma (dCCA), duodenal adenocarcinoma (DAC) and ampullary adenocarcinoma (AAC). Based on histopathology, the AAC is currently subdivided in the intestinal (AmpIT) and pancreatobiliary (AmpPB) subtype. Despite close anatomical resemblance, it is unclear how the ampullary subtypes relate to the remaining periampullary cancers in tumor characteristics and behavior. **Methods:** This is an international multicenter cohort study, including patients after curative intent resection for periampullary cancer retrieved from 45 centers (from Europe, USA, Asia and Canada) between 2010 and 2021. Pre-operative CA19-9, differences in pathology and postoperative pancreatic fistula (POPF, grade B/C), 8-year overall survival (OS) and disease-free interval (DFI) were compared between DAC, AmpIT, AmpPB, dCCA and PDAC. **Results:** Overall, 3809 patients were included of which 348 DAC, 774 AmpIT, 848 AmpPB, 1036 dCCA and 803 PDAC. The best 8-years overall survival was found in patients with AmpIT and DAC (49.8% and 47.9%), followed by AmpPB (34.9%, $p<0.001$), dCCA (26.4%, $p=0.020$) and last, PDAC (12.9%, $P<0.001$). The best 8-years DFI was measured for AmpIT (62.7%) and the worst for both dCCA and PDAC (24.9% and 21.8%). This pattern correlated with the height of the pre-operative CA19-9 but not with the pathology, in which the largest and most progressed tumors were found in DAC. The incidence of POPF was lower in the pancreas-related tumor types (AmpPB 18.5%, PDAC 8.3%) compared to the non-pancreas related types (DAC 27.3%, AmpIT 25.5%, dCCA 27.6%). **Conclusions:** Despite the close anatomic relation of the five periampullary cancers, this study shows that there are prognostic and clinically relevant differences in terms of preoperative blood markers, pathology, complications, long-term survival, and recurrence. More characteristics are shared between DAC and AmpIT and between AmpPB and dCCA than between the two ampullary subtypes. Instead of using collective definitions for “peri-ampullary cancers”, this study emphasizes the need for individual evaluation of each histopathological periampullary subtype with the ampullary subtypes as individual entities in future studies. Research Sponsor: None.

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Poster Session

Detection and localization of gastrointestinal cancers based on multi-dimensional signatures from a single cfDNA targeted sequencing assay. *First Author: Xin-Rong Yang, Department of Liver Surgery and Transplantation, Liver Cancer Institute, Zhongshan Hospital, Fudan University; Key Laboratory of Carcinogenesis and Cancer Invasion (Fudan University), Ministry of Education, Shanghai, China*

Background: Five major gastrointestinal (GI) cancers - colorectal (CRC), gastric (GC), liver (LC), esophageal (EC), and pancreatic cancer (PC) - are responsible for hundreds of thousands of mortalities annually worldwide. Unfortunately, there is a lack of cost-effective, blood-based screening method for their early detection. To address this issue, we aimed to develop GutSeer, a noninvasive, targeted methylation sequencing-based test by leveraging methylation and fragmentomic signatures carried by cell-free DNA (cfDNA). **Methods:** The panel of GutSeer consists of 1656 target regions which were either differentially methylated between healthy and cancer samples, or distinctively methylated in a specific GI cancer. Cancer and healthy participants were recruited and randomly divided into a training and a validation cohort. Their plasma DNA samples were analyzed to generate DNA methylation and fragmentomic features. These multi-dimensional features were integrated to build ensemble stacked machine learning models to differentiate cancer against healthy, and to determine the tissue-of-origin (TOO) of the cancer. **Results:** A total of 1844 cases (787 healthy, 342 LC, 239 GC, 209 EC, 180 CRC, and 87 PC cases) were recruited for this study. A cancer-vs-healthy model achieved an AUC of 0.94 and 0.95 (sensitivity of 77.7% and 77.1% under the specificity around 96%) using either methylation or fragmentomic features only, respectively. Combining both methylation and fragmentomic features further improved performances, achieving an AUC of 0.96 (sensitivity = 86.2% at a specificity of 96.7%). For individual type of cancer, GutSeer has a sensitivity of 93.3% for CRC, 81.1% for EC, 70.3% for GC, 96.5% for LC, and 86.4% for PC. An independent test using 629 benign cases as controls achieved a specificity of 87.1%. A separate TOO model was built using all features and achieved an overall accuracy of 82% for all cancer cases (66.7% for CRC, 87.0% for GC and EC combined, 89.0% for LC, and 63.2% for PC). Same as the cancer detection model, using multi-dimensional features in TOO prediction yielded higher accuracy than when models using only methylation or fragmentomics features (accuracy = 75.6% or 75.4%, respectively). When compared with whole-genome sequencing (WGS) based approaches, GutSeer showed a comparable performance in cancer detection but a higher accuracy in TOO identification, further confirming its effectiveness for detection of GI cancers. **Conclusions:** GutSeer, a non-invasive test integrating multi-dimensional features, was demonstrated to detect and localize the 5 main types of GI cancer with high accuracy. Our results further showed that a reasonably sized panel can perform comparably or even better than WGS-based methods in cancer detection and TOO localization, indicating GutSeer may be a low-cost solution for blood-based early screening for GI cancers. Research Sponsor: National Key Research and Development Program of China (2019YFC1315800).

4168

Poster Session

Incidence, epidemiological characteristics, and cause-specific survival analysis of ampullary carcinoma using the SEER database. *First Author: Rajvi Gor, Jacobi Medical Center/Albert Einstein College of Medicine, Bronx, NY*

Background: Ampullary carcinomas (AC) are rare and comprise only 0.2% of gastrointestinal malignancies, and there is a paucity of studies analyzing them. We studied the incidence, demographics, tumor characteristics, and survival variables of patients with AC using the Survival, Epidemiology, and End Results [SEER] November 2021 database. **Methods:** We identified 3650 patients aged >18 with microscopically confirmed adenocarcinoma of the ampulla using ICD-O-3 site code C241 and histology codes (8140-8147, 8480, 8490, 8500). The epidemiological characteristics and the survival variables included were age, gender, ethnicity, and American Joint Committee on Cancer [AJCC] Staging. The overall 5-year survival (OS), cause-specific 5-year survival (CSS), and CSS plots across different strata were plotted using the Kaplan-Meier Method. The analysis was done using the Cox proportional hazard regression model ($p<0.05$). **Results:** The overall age-adjusted incidence of AC was 0.3 per 100,000 cases. The median age at diagnosis was 69 (Interquartile range - 59, 78). It was more common in males (56.03%) and Non-Hispanic White (58.96 %), with the most common stages at a presentation being stage 2B IIB (22.08%) and stage III (22.11%). The observed overall 5-year survival was 31%, and the cause-specific 5-year survival was 37.5%. The CSS was not significantly associated with gender ($p=0.06$). The estimated hazards of death attributed to AC increase by 13% ($p<0.0001$) for every 10-year increase in age at diagnosis above 67 years. The CSS was also associated with race, with African Americans and Hispanics being associated with higher hazards of death attributed to AC when compared to Non-Hispanic Whites with HR of 1.5 ($p<0.0001$) and 1.12 ($p=0.01$), respectively. **Conclusions:** Ampullary carcinoma is more commonly seen in males and non-Hispanic Whites with a median age of 69 years. Patients are typically diagnosed in stages IIB and III. Lower CSS rates were associated with advancing age, African American, and Hispanic populations. We need further studies to determine whether these disparities between different races are due to socioeconomic, genetic, or biological factors. Additional studies investigating how different treatment options affect AC survival, especially in this population subset, can be explored. Research Sponsor: None.

Characteristic	Total Patients (n=3650)	Hazard Ratio (p-value)
Age, Median (IQR)	69 (59-78)	1.013 (<0.001)
Sex, Male, N (%)	2045 (56.03)	1.11 (0.06)
Race, N (%)		
Non-Hispanic White	2152 (58.96)	1
Hispanic	688 (18.85)	1.12 (0.01)
Non-Hispanic Black	280 (7.67)	1.52 (<0.001)
Non-Hispanic Asian	500 (13.70)	1.07 (0.39)
Non-Hispanic American Indian	21 (0.58)	1.11 (0.80)
Stage		
IA	473 (12.96)	1
IB	462 (12.66)	1.08 (0.39)
IIA	363 (9.95)	1.01 (0.88)
IIB	806 (22.08)	1.17 (0.07)
III	807 (22.09)	1.09 (0.38)
IV	419 (11.48)	1.20 (0.28)
UNK	314 (8.60)	-

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Poster Session

Multi-institutional study evaluating the role of circulating tumor DNA (ctDNA) in management of appendiceal cancers (AC). *First Author: Erika Belmont, University of Chicago Medical Center, Chicago, IL*

Background: AC frequently present with peritoneal metastases (PM) which are difficult to accurately measure with imaging techniques or serum tumor markers. ctDNA is a novel, promising biomarker to assess minimal residual disease (MRD) and therapy response. Its utility in AC with PM is poorly studied due to the rarity of this disease condition. This is a report on the role of ctDNA in AC management. **Methods:** Patients with AC managed at two high volume centers between 01/01/2019 to 12/15/2022 were included in this study. CtDNA measurements were prospectively collected using Signatera tumor informed ctDNA assay during clinical care and these data were abstracted retrospectively. Cox-proportional hazards were utilized for survival analysis. **Results:** 97 patients with AC were included with a median age of 57 (IQR 53-66) years, majority being non-Hispanic white (85%) and female (63%). 68 (70%) patients had ctDNA assay drawn at the time of confirmed clinical disease (radiographic or laparoscopic). The sensitivity of ctDNA was 56% (CI 44% - 67%) for all grades, and 66% (CI 49% - 80%) for grade 3 tumors. 65 (67%) patients underwent cytoreductive surgery (CRS), of which 16 (24.6%) had preoperative ctDNA assays. Sensitivity in this cohort of surgical patients was 25% and positive ctDNA showed poor correlation with PCI score at time of surgery ($n=4$, $r=0.38$, $p=0.14$). Any positive value for post-operative ctDNA was associated with lower disease free survival (DFS) (9 months (CI 5-13) in low grade AC and 10 months (CI 7-14) in high grade AC, compared to not reached for those persistently negative ($p<0.001$) over a median follow-up duration of 17 months. This difference persisted despite adjusting for adjuvant chemotherapy for high-grade disease (aHR = 11.2 (1.4-88.6), $p=0.023$). **Conclusions:** This is the largest study reported to date of tumor informed ctDNA testing in patients with AC. These data show that ctDNA has low sensitivity in both the metastatic unresectable and in pre-operative settings. However, ctDNA positivity after CRS in AC has prognostic value and could be used to guide systemic therapy decisions. Research Sponsor: None.

TPS4171

Poster Session

A phase 2 trial of chemotherapy, pembrolizumab, and propranolol in patients with advanced esophageal/gastroesophageal junction adenocarcinoma (EGAC). *First Author: Sarbajit Mukherjee, Roswell Park Comprehensive Cancer Center, Buffalo, NY*

Background: Chronic stress suppresses the immune system and promotes cancer cell growth. In animal studies, we reported that this is mediated by the beta-adrenergic (BA) pathway. We further showed that concurrently blocking the BA pathway with β -blockers (BB) can improve immune checkpoint inhibitor (ICI) efficacy. Our retrospective data analysis revealed that esophageal cancer (EC) patients taking BB for other non-cancer reasons while receiving chemoradiation had significantly better survival and distant control than those not taking BB. We hypothesized that blocking the effects of adrenergic stress with a commonly used BB, propranolol, will improve response to therapies in EC patients. **Methods:** This is an open-label, non-randomized, phase 2 study of propranolol combined with pembrolizumab and standard chemotherapy in frontline unresectable/metastatic EGAC. Eligible patients must be treatment-naïve, have adequate organ function, have an ECOG performance status of 0–1, and be able to swallow and retain oral medication. Patients with Her-2 positive cancer, active autoimmune disease, active HIV, Hepatitis B or C, or a history of non-infectious pneumonitis/interstitial lung disease that requires treatment, are ineligible. Patients who are on BB for various indications are also ineligible. Eligible patients will receive mFOLFOX6 every two weeks in combination with pembrolizumab 400 mg intravenously every six weeks and propranolol 30 mg orally twice daily. The mFOLFOX6 dosing regimen will consist of *d*-LV 400 mg/m² and oxaliplatin 85 mg/m² followed by bolus 5-FU 400 mg/m² and a 48-hour infusion of 5-FU 2400 mg/m². The study will include an initial safety lead-in cohort of six patients. The primary endpoint is the overall response rate (ORR) determined by RECIST 1.1. Secondary endpoints include safety, progression-free survival (PFS), overall survival (OS), and ORR as determined by iRECIST. Correlative studies will assess baseline levels or changes in the levels of biomarkers, like, peripheral T-cell subsets/myeloid-derived suppressor cells (MDSC)/cytokines/ and perceived stress scale PSS/chronotropic effects of exercise with efficacy (ORR, PFS, OS). Assuming a historic ORR of 50% with standard treatment, 37 evaluable pts are needed to show a 20% increase in ORR with our proposed treatment with 80% power at a one-sided significance level of $\alpha = 0.1$. In stage 1, n1=23 evaluable pts will be enrolled. If there are 13 or more ORRs, an additional n2=14 pts will be enrolled in stage 2. If 24 or more ORRs are observed in the total n=37 evaluable pts, the proposed treatment regimen will be considered promising for further study. The study is currently open to enrollment. Clinical trial information: NCT05651594. Research Sponsor: Department of Defense CA210898P1; Roswell Park Comprehensive Cancer Center internal funding.

TPS4173

Poster Session

Phase 2 trial of zolbetuximab in combination with mFOLFOX6 and nivolumab in patients with advanced or metastatic claudin 18.2-positive, HER2-negative gastric or gastroesophageal junction adenocarcinomas. *First Author: Kohei Shitara, Department of gastroenterology and gastrointestinal oncology, National Cancer Center Hospital East, Kashiwa, Japan*

Background: Zolbetuximab, a chimeric immunoglobulin G1 monoclonal antibody, binds to claudin 18.2 (CLDN18.2) and mediates tumor cell death through antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity. In the pivotal phase 3 SPOTLIGHT study, zolbetuximab with modified FOLFOX6 (mFOLFOX6; leucovorin [folinic acid], fluorouracil [5-FU], and oxaliplatin) significantly prolonged progression-free survival (PFS) and overall survival (OS) in patients with CLDN18.2-positive, HER2-negative gastric and gastroesophageal junction (G/GJ) adenocarcinomas. The phase 2 ILUSTRO trial is investigating the efficacy and safety of zolbetuximab, alone and in multiple combinations, in patients with CLDN18.2-positive, HER2-negative advanced/metastatic G/GJ adenocarcinomas. **Methods:** The ILUSTRO trial is enrolling two new cohorts, 4A (safety cohort) and 4B, with approximately 12 and 50 patients planned, respectively, to assess safety and efficacy of the first-line combination of zolbetuximab, mFOLFOX6, and nivolumab in G/GJ adenocarcinomas. Both cohorts are enrolling patients whose tumors are HER2-negative with high or intermediate CLDN18.2 positivity (moderate to strong immunohistochemistry staining intensity in $\geq 75\%$ of tumor cells [high] or $\geq 50\%$ but $< 75\%$ of tumor cells [intermediate]). In Cohort 4A, patients will receive a loading dose of 800 mg/m² of zolbetuximab with 240 mg of nivolumab and mFOLFOX6 on cycle 1 day 1, followed by 400 mg/m² of zolbetuximab with 240 mg of nivolumab and mFOLFOX6 every 2 weeks (on days 15 and 29 of each 42-day cycle). Up to 12 mFOLFOX6 treatments (4 cycles) will be administered; patients may continue to receive folinic acid and 5-FU alongside zolbetuximab and nivolumab. Tolerability and safety of the combination of zolbetuximab, mFOLFOX6, and nivolumab will be evaluated during a 2-week dose-limiting toxicity assessment period. If the 800 mg/m² loading dose of zolbetuximab was assessed as not tolerable, patients were to be de-escalated to 600 mg/m² as their loading dose but received the same subsequent 400 mg/m² doses of zolbetuximab every 2 weeks. Cohort 4B will receive this combination at the dose level determined in Cohort 4A. Efficacy endpoints include objective response rate, disease control rate, duration of response, PFS, and OS. Safety and tolerability, pharmacokinetics, immunogenicity, and health-related quality of life will also be evaluated. Currently, 20+ sites are recruiting in 6 countries (France, Italy, Japan, Korea, Taiwan, United States); more US sites are planned. Clinical trial information: NCT03505320. Research Sponsor: Astellas Pharma, Inc.

TPS4172

Poster Session

Chemoradiotherapy with concurrent durvalumab for the palliative treatment of oligometastatic esophageal and gastroesophageal carcinoma with dysphagia: A single arm phase 2 clinical trial, PALEO. *First Author: Fiona Day, Department of Medical Oncology, Calvary Mater Newcastle, Waratah, Australia*

Background: Many patients diagnosed with esophageal cancer have dysphagia from their primary tumor and *de novo* metastatic disease. While multiple therapies are available, there is no accepted standard or sequence of therapies to both relieve dysphagia and control distant disease. Our preceding Phase I clinical trial showed that a 2 week hypofractionated chemoradiotherapy (CRT) protocol (30Gy/10# with concurrent weekly carboplatin and paclitaxel) is well tolerated and provides rapid dysphagia relief. Immune checkpoint inhibition has activity in esophageal and gastroesophageal (GEJ) cancer and concurrent radiotherapy may improve T cell priming through tumor antigen release. In PALEO, patients begin durvalumab concurrent with primary tumor CRT, and receive stereotactic body radiotherapy (SBRT) (24Gy/3#) to a single metastasis to maximize the breadth of tumor antigen exposure. Tissue and blood-based studies are planned to identify biomarkers for response, including immunosequencing to test for post-radiotherapy expansion in T cell receptor diversity. **Methods:** Eligible patients have biopsy-proven esophageal or GEJ cancer, either squamous cell or adenocarcinoma histology, with oligometastatic (1-5 metastases on FDG-PET scan outside the primary tumor radiotherapy field) or locoregionally advanced disease unsuitable for surgery, dysphagia (Mellow score > 0), and ECOG PS 0-2. Key exclusion criteria are prior treatment, tumor HER2 positivity, prior thoracic radiotherapy, tracheo-esophageal fistula, esophageal stent in situ and contraindications to immunotherapy. Patients begin durvalumab 1500mg q4w with CRT to the primary tumour (30Gy/10# with weekly carboplatin AUC2 and paclitaxel 50mg/m²), and continuing to disease progression, unacceptable toxicity or 2 years. SBRT to one metastasis (24Gy/3#) is delivered in week 7. Trial primary endpoint is progression free survival rate at 6 months (PFS6) with the aim to rule out a PFS6 rate of 50% in favor of 67.5%, with 80% power and a one-sided 0.05 significance level. Secondary endpoints include dysphagia relief, nutritional status change (patient weight, removal of enteral feeding tubes, PG-SGA score), quality of life, response rate, toxicity, overall survival and exploratory translational endpoints. PALEO is sponsored by the Australasian Gastro-Intestinal Trials Group (AGITG) for conduct at 8 sites in Australia and New Zealand. 6 of planned 54 patients have been enrolled. Clinical trial information: ACTRN12619001371189. Research Sponsor: Australasian Gastro-Intestinal Trials Group (AGITG) Philanthropic Major Donor funding; Hunter Medical Research Institute; This research was conducted with Study Drug support from AstraZeneca PtyLtd; Varian Medical Systems.

TPS4174

Poster Session

A phase 2 basket trial of ulixertinib (BVD-523) in combination with hydroxychloroquine in patients with advanced gastrointestinal malignancies harboring MAPK pathway mutations (BVD-523-HCQ). *First Author: Andrew H. Ko, University of California San Francisco, San Francisco, CA*

Background: RAS-induced signaling through the mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) pathway plays an important role in the pathogenesis of many solid tumors. Ulixertinib (BVD-523) is a first-in-class and best-in-class small molecule inhibitor of ERK 1/2 that is currently being investigated in multiple cancer clinical trials, both as a single agent and as part of combination therapy. Preclinical studies have demonstrated that inhibition of the RAS/MAPK/ERK signaling cascade leads to upregulation of autophagy, a catabolic pathway that includes the lysosomal degradation of proteins to support cellular metabolism during times of cellular stress. Given cancer cells' increased reliance on autophagy to enhance their survival in this context, this study seeks to evaluate the combination of ulixertinib with hydroxychloroquine, an antimalarial drug known to suppress autophagy, in patients with advanced gastrointestinal malignancies harboring mutations in genes involved in MAPK signaling. **Methods:** This is an open-label, multicenter, phase II basket study of ulixertinib in combination with hydroxychloroquine in patients with advanced GI malignancies harboring mutations in one of the following MAPK signaling-associated genes: KRAS, NRAS, HRAS, BRAF (non-V600), MEK1/2, or ERK1/2. The completed Phase 1 dose-escalation trial (NCT04145297) established the recommended Phase 2 dose which will be the doses used in this study; ulixertinib 450mg PO BID combined with hydroxychloroquine 600mg PO BID, both drugs administered daily in 28-day cycles, with tumor assessments after every 2 cycles. The trial has five baskets based on primary disease: cholangiocarcinoma, pancreatic adenocarcinoma, colorectal adenocarcinoma, esophageal adenocarcinoma, and gastric adenocarcinoma. A Simon two-stage design will be employed within each of the 5 disease-specific baskets noted above, with the first stage of enrollment consisting of n=13 patients/ basket. To be considered evaluable, a patient must complete at least one cycle of therapy and receive at least 75% of the prescribed dose during that first cycle. If ≥ 4 patients in a specific basket achieve a response (complete or partial), that basket will then open to Stage 2 with enrollment of an additional 30 patients. Primary study endpoints will include safety/toxicity as well as ORR by RECIST 1.1. The secondary endpoint for efficacy is progression-free survival. Exploratory endpoints include pharmacokinetics of both ulixertinib and hydroxychloroquine, as well as predictive biomarkers from blood and tumor tissue-based samples. At the time of abstract submission, 26 of the planned 65 patients in Stage 1 had been enrolled. Clinical trial information: NCT05221320. Research Sponsor: BioMed Valley Discoveries, Inc.

TPS4175

Poster Session

Alliance A022102: Randomized phase III trial of mFOLFIRINOX +/- nivolumab vs. FOLFOX +/- nivolumab for first-line treatment of metastatic HER2-negative gastroesophageal adenocarcinoma (GEA). *First Author: Haeseong Park, Dana-Farber Cancer Institute, Boston, MA*

Background: Platinum/fluoropyrimidine (FP) with PD-1 inhibitor is now established as the standard first-line therapy for most patients with advanced HER2 negative gastric, esophageal, and gastroesophageal junction (GEJ) adenocarcinoma. The FP doublet chemotherapy backbone, most commonly FOLFOX, is recommended based on marginal survival benefits of taxane-containing triplet therapy at the cost of increased toxicity. Although several agents are approved as standard treatment options in later lines, only about 10% of patients in the US receive a third line of therapy, and very few have the opportunity to benefit from all approved agents in this disease. This challenge will only increase as more agents and targeted therapies are approved. FOLFIRINOX is a triplet regimen commonly used in gastrointestinal malignancies with established safety and often with superior efficacy. Two single arm phase II trials of FOLFIRINOX have reported promising activity in GEA with manageable toxicities. Reported median overall survival (OS) from these trials is around 15 months, which is superior to what is expected from FP doublet first-line chemotherapy (about 11 months). We hypothesize that using upfront triplet therapy with a more effective and less toxic triplet combination will result in improved patient outcomes by optimization of available therapies in GEA. **Methods:** This study is a randomized phase III, open-label, multicenter clinical trial with the primary objective to determine whether modified FOLFIRINOX (FU 2400 mg/m², leucovorin 400 mg/m², oxaliplatin 85 mg/m², irinotecan 150 mg/m² every 2 weeks) as first-line treatment improves OS compared to mFOLFOX in patients with advanced HER2 negative GEA. Eligible patients will have unresectable or metastatic adenocarcinoma of esophagus, GEJ, or stomach with no prior systemic treatment. Patients must have adequate organ function, and measurable or evaluable disease as defined by RECIST 1.1. Prior neoadjuvant or adjuvant therapy is allowed if completed at least 1 year prior to registration. Patients who will receive nivolumab (mandatory for PD-L1 combined positive score > 5) in addition to chemotherapy must not have any contraindications to immune checkpoint inhibitors. Patients with treated, asymptomatic and stable brain metastases are eligible. The total sample size is 382 evaluable patients for this study (191 patients per arm). The study accrual began January 2023. Clinical trial information: NCT05677490. Research Sponsor: U.S. National Institutes of Health.

TPS4177

Poster Session

A randomized, open-label, phase II/III efficacy and safety study of atezolizumab in combination with FLOT versus FLOT alone in patients with gastric cancer and adenocarcinoma of the oesophagogastric junction and high immune responsiveness: The IKF-S633/DANTE trial, a trial of AIO in collaboration with SAKK. *First Author: Salah-Eddin Al-Batran, Institut für Klinische Krebsforschung IKF am Krankenhaus Nordwest, and Krankenhaus Nordwest, University Cancer Center Frankfurt, Frankfurt, Germany*

Background: Perioperative FLOT chemotherapy has become a standard of care for locally advanced, resectable esophagogastric adenocarcinoma (EGA). However, patient outcomes are still unsatisfactory. Immune checkpoint inhibitors combined with chemotherapy have proven activity in advanced Her2 negative EGA with PD-L1 expression (KEYNOTE-590, Checkmate-649). Atezolizumab is a PD-L1 inhibitor with established efficacy and tolerability profiles and will be evaluated in this study in the perioperative treatment of potentially resectable EGA in combination with FLOT. As shown at ASCO 2022 for the phase II part of DANTE, adding atezolizumab to FLOT led to improved tumor downsizing and pCR (24% vs 15%). Of note, regression rates further improved with higher PD-L1 expression (33% vs 12% in tumors with CPS ≥ 10) or in MSI-high tumors (63% vs 27%). Prompted by these results, we decided to transition this trial from the initial phase II to a phase III design. **Methods:** This is a multinational, prospective, randomized, investigator-initiated, open label phase II/III trial. Patients (pts) with locally advanced, potentially resectable EGA (≥ cT2 and/or N-positive) without distant metastases are enrolled. Based on the subgroup analyses of the phase II trial, we decided to limit the future enrollment to pts with high immune responsiveness, i.e. either of the following: MSI-high, PD-L1 CPS ≥ 1, TMB ≥ 10/MB or EBV+. Eligibility status is centrally evaluated. Pts are randomized 1:1 to 4 pre-operative 2-week cycles (8 weeks) of FLOT (Docetaxel 50 mg/m²; Oxaliplatin 85 mg/m²; Leucovorin 200 mg/m²; 5-FU 2600 mg/m²) plus 840 mg atezolizumab q2w followed by surgery and 4 additional cycles of FLOT/atezolizumab, followed by a total of 8 additional cycles of atezolizumab at 1200 mg every 3 weeks as monotherapy (arm A) or FLOT alone (arm B). Primary endpoint is event-free survival (EFS) as assessed by the Kaplan-Meier-Method. An estimated HR of 0.72 would correspond to a median EFS of 41.67 months for the experimental Arm A. This difference is considered clinically relevant. A total of 556 pts (318 events) will be randomized. As 177/295 pts with PD-L1 positive or MSI status were already enrolled into the phase II portion, additional 379 pts will be enrolled into phase III. Main secondary endpoints are rates of locally assessed pathological regression (complete and nearly complete pathological regression), OS, OS and EFS in the subgroup of pts with PD-L1 CPS ≥ 5 and ≥ 10 and pts with MSI, R0 resection, and safety. In addition, a prospective biomarker study including serial circulating tumor DNA analysis before and during treatment will be performed. Recruitment started 2018 and continues for phase III in 2023. Clinical trial information: NCT03421288. Research Sponsor: Roche; Hector Stiftung.

TPS4176

Poster Session

A multi-cohort phase I/IIa clinical trial to evaluate the safety, tolerability, and pharmacokinetics of TST001 administered as a monotherapy, with nivolumab or standard of care in patients with locally advanced or metastatic solid tumors: TransStar101. *First Author: Yelena Y. Janjigian, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Gastric cancer (GC) remains the 4th leading cause of cancer death worldwide, accounting for about 7.7% of all cancer related mortality. Despite recent approval of nivolumab in combination with chemotherapy, the median survival of treatment naïve Gastric Cancer/gastroesophageal junction cancer (G/GEJ) cancer is only approximately 14 months, even in patients with high CPS PD-L1. Targeting claudin 18.2 (CLDN18.2) in combination with chemotherapy is a clinically validated approach for patients with CLDN18.2 expressing advanced G/GEJ cancer. TST001 is a humanized monoclonal antibody with improved affinity to human CLDN18.2 and enhanced antibody-dependent cellular cytotoxicity (ADCC). In pre-clinical studies, TST001 treatment upregulates PD-L1 expression on CLDN18.2-positive tumor cells. The in vivo analysis showed anti-tumor efficacy of TST001 combined with anti-PD-1 antibody and chemotherapy was superior to combination of anti-PD-1 antibody with chemotherapy or combination of TST001 with chemotherapy. Promising anti-tumor activities have been observed in patients with advanced G/GEJ cancer who have been treated with TST001 alone or in combination with chemotherapy, making the combination of TST001, nivolumab and chemotherapy attractive. **Methods:** This is a multi-cohort, open-label, multi-center phase I/II first in human (FIH) study of TST001 administered as single agent, in combination with nivolumab or standard of care in the treatment of patients with locally advanced or metastatic solid tumors. Primary endpoints include characterization of TST001 safety profile and the maximum tolerated dose / recommended phase 2 dose. Secondary endpoints include pharmacokinetics, immunogenicity, pharmacodynamics, and efficacy. The study includes two parts. Part A (completed) is a dose escalation of TST001 as a monotherapy. Part B (ongoing) consists of three independent cohorts: cohort A includes combination TST001 + nivolumab+ leucovorin calcium (folinic acid), fluorouracil, and oxaliplatin (mFOLFOX6) as 1st line treatment for G/GEJ cancer; cohort B includes TST001 in combination with nivolumab in advanced pre-treated G/GEJ cancer; cohort C includes combination therapy of TST001, gemcitabine, and nanoparticle albumin-bound paclitaxel as 1st line treatment for advanced/metastatic pancreatic cancer. Multiple doses and schedules will be assessed during Part B. **Conclusions:** Combination of TST001 with nivolumab and chemotherapy has the potential to improve the outcomes of patients with advanced or metastatic CLDN18.2 expressing G/GEJ cancer. Data from this trial will support the selection of the optimal dose and dose regimen of TST001 in these combinations. Enrollment in the trial is ongoing. Clinical trial information: NCT04396821. Research Sponsor: Transcenta Therapeutics Inc.

TPS4178

Poster Session

An open-label, multicenter study investigating RP3 oncolytic immunotherapy in combination with first- or second-line systemic atezolizumab and bevacizumab therapy in patients with locally advanced unresectable or metastatic hepatocellular carcinoma. *First Author: Tanios S. Bekaii-Saab, Mayo Clinic, Scottsdale, AZ*

Background: Despite advances in treatment for unresectable hepatocellular carcinoma (HCC), long-term survival rates remain poor. The combination of bevacizumab (Bev) and atezolizumab (Atezo) is the preferred frontline therapy for advanced HCC, but a minority of patients (pts) respond, and secondary resistance usually occurs within months. HCC has an immune-suppressed tumor microenvironment, mediated by activated immune checkpoint signaling and angiogenesis pathways, which may contribute to therapeutic resistance. RP3 is a genetically modified herpes simplex virus type 1 (HSV-1) that expresses the fusogenic gibbon ape leukemia virus glycoprotein with the R sequence deleted (GALV-GP-R-), an anti-CTLA-4 antibody-like molecule, CD40 ligand, and 4-1BB ligand. The direct oncolytic effect coupled with immune stimulation by RP3 in the tumor microenvironment is intended to provide systemic antitumor activity and enhance therapeutic response to anti-PD-1/PD-L1 agents, such as Atezo. Preclinical data have demonstrated improved distribution of oncolytic HSV within tumors in combination with Bev, supporting the clinical combination of RP3 with Bev. This study will evaluate the safety and efficacy of RP3 combined with Atezo and Bev as first- (1L) and second-line (2L) systemic therapies for unresectable and advanced HCC. **Methods:** The 1L and 2L cohorts will each enroll up to 30 pts. Pts in the 1L cohort may not have received prior systemic treatment; pts in the 2L cohort must have progressed on or following one prior line of systemic therapy, which must have included a PD-1/PD-L1-directed agent. Key inclusion criteria include advanced, unresectable HCC with ≥ 1 measurable tumor of ≥ 1 cm in longest diameter, Child-Pugh Class A, and Eastern Cooperative Oncology Group performance status of 0–1. Key exclusion criteria include untreated esophageal and/or gastric varices with bleeding or at high risk for bleeding and macroscopic invasion of tumor into any major blood vessel(s) and/or main bile ducts. Pts with a history of medically refractory hepatic encephalopathy and/or hepato-renal syndrome are also excluded. Pts in the 1L cohort will receive 1200 mg Atezo and 15 mg/kg Bev every 3 weeks (Q3W) together with RP3 intratumorally Q3W for a total of up to 8 doses. Pts in the 2L cohort will receive RP3 every 2 weeks for 4 doses with Bev Q3W starting on cycle (C) 1 day (D) 1, then RP3 and Bev Q3W for up to 4 more doses with Atezo Q3W being added on C4D1. The primary endpoint is overall response rate (ORR) by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Secondary endpoints are safety, ORR using HCC modified RECIST, duration of response, complete response rate, and progression-free survival. Clinical trial information: NCT05733598. Research Sponsor: Replimune Inc.

TPS4179

Poster Session

A phase IIa/IIb, open-label trial of BI 907828, an MDM2–p53 antagonist, in patients with locally advanced/metastatic biliary tract carcinoma or pancreatic ductal adenocarcinoma: Brightline-2. *First Author: Lipika Goyal, Department of Medicine, Stanford Cancer Center, Palo Alto, CA*

Background: Biliary tract cancer (BTC) and pancreatic ductal adenocarcinoma (PDAC) carry a median survival of one year in the advanced stages, and effective therapies are urgently needed. Mouse double minute 2 (MDM2) is amplified in ~5–6% of cases of BTC and ~1% of PDAC. MDM2, an E3 ubiquitin ligase, is an endogenous negative regulator of p53. Aberrations affecting MDM2 may drive oncogenesis, and indeed, preclinical as well as emerging clinical data suggest blocking MDM2 in *TP53* wild-type tumors may be a potential therapeutic strategy. BI 907828 is an MDM2–p53 antagonist that binds to MDM2 and blocks its interaction with p53, thereby restoring p53 function, leading to cell-cycle arrest and apoptosis in *TP53* wild-type tumor cells. In ongoing Phase I studies, BI 907828 has demonstrated initial signs of activity in selected advanced/metastatic solid tumors, including BTC and PDAC. **Methods:** Brightline-2 is a Phase IIa/IIb, open-label, single-arm, multicenter study (~60 sites) that aims to assess the efficacy, safety, and tolerability of BI 907828 monotherapy in patients with locally advanced, unresectable, or metastatic *MDM2*-amplified, *TP53* wild-type BTC (adenocarcinoma histology; Cohort 1; n=90) or PDAC (Cohort 2; n=10) [NCT05512377]. Cohorts for other solid tumors may be added via protocol amendment. All patients will receive BI 907828 45mg orally once every 3 weeks. Key inclusion criteria include: ≥18 years of age; locally advanced/metastatic, histologically confirmed unresectable BTC/PDAC; progression or intolerance to standard therapies; local test indicating *MDM2* amplification or *MDM2* copy number ≥8 and *TP53* wild-type (liquid biopsy not permitted); ≥1 measurable target lesion (RECIST v1.1); and ECOG PS 0/1. A key exclusion criterion is prior treatment with an MDM2–p53 antagonist. Treatment will continue until disease progression, unacceptable toxicity, or withdrawal of consent. The primary endpoint is objective response rate (ORR; based on blinded central independent review). Secondary endpoints are duration of response, progression-free survival, overall survival, disease control, occurrence of adverse events, and patient-reported health-related quality of life. In Phase IIa, an interim futility analysis will be performed after the initial 30 patients in Cohort 1 have either been followed for ≥12 weeks or have discontinued. If the cohort passes the non-binding interim futility boundary (ORR = 20%), the study will enter Phase IIb, and 60 additional patients will be enrolled onto Cohort 1, totaling 100 patients planned across Cohorts 1 and 2. The final primary analysis will be performed after all treated patients have been followed for ≥12 weeks or until study discontinuation. As of 13 December 2022, 1 patient has been enrolled. Clinical trial information: NCT05512377. Research Sponsor: Boehringer Ingelheim.

TPS4181

Poster Session

Autologous cytotoxic T-cell receptor T cell therapy (SCG101) against hepatitis B surface antigen phase I/II trial for patients with advanced hepatitis B-related hepatocellular carcinoma. *First Author: Ghassan K. Abou-Alfa, Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, Cornell University, New York, NY*

Background: The overall prognosis of patients with advanced Hepatitis B-related hepatocellular carcinoma (HCC) remains poor, and treatment options are limited. In an IIT study conducted in China (NCT05339321), SCG101 following lymphodepletion (cy-flu) as second-line setting or beyond in patients with Hep B-related HCC has shown acceptable safety profile, reduction in HBsAg levels (>1 log) and tumor control. A phase I/II trial has been initiated to evaluate safety and RP2D of autologous SCG101 T cell therapy in Hepatitis B virus-related HCC (NCT05417932). **Methods:** This multicenter, open-label, 3+3 dose-escalation phase I trial is ongoing across 7 sites in the United States, Singapore and Hong Kong SAR, and a parallel study is done in mainland China across 8 sites. Eligible patients have a histologically confirmed HCC, not amenable to curative intent (surgery or locoregional therapy) and failed ≥2 standard line of therapies, match any of HLA-A*02:01, *02:02, *02:03, *02:04, *02:07, *02:09, *02:16, have positive serum (or tumor) HBsAg, HBV-DNA <2000 IU/ml, BCLC B or C, CP≤7, with measurable disease at screening (mRECIST and RECIST v1.1), ECOG PS<1. Patients with CNS metastasis, prior liver transplant, autoimmune disease or prior cell therapy are excluded. SCG101 T cells are manufactured in Singapore under cGMP and ship to all study sites across the U.S., Singapore and Hong Kong SAR, while SCG101 T cells for the China sites are manufactured in SCG Cell Therapy's China facility. Patients will receive a single dose of SCG101 T cell therapy following lymphodepletion (cy-flu). Endpoints include safety, MTD and RP2D. Secondary endpoints include ORR, DOR, PFS, OS, changes in serum HBsAg. Safety is monitored together with Data Review Committee. The study is actively enrolling, and the phase II portion of the trial is expected to be initiated by H2 2023. Autologous SCG101 T cell therapy may provide a new treatment option for patients with advanced Hepatitis B virus-related HCC. Clinical trial information: NCT05417932. Research Sponsor: SCG Cell Therapy Pte Ltd.

TPS4180

Poster Session

Randomized phase 2 study of maintenance olaparib vs olaparib plus durvalumab for DNA damage repair (DDR) gene mutated unresectable or metastatic biliary tract cancer (BTC) with durable response to first-line platinum-based chemotherapy: OPTIMUM trial. *First Author: YunJung Kim, Clinical Trial Center, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea*

Background: BTC is rare and aggressive disease with heterogeneous genetic profiles. Gemcitabine plus cisplatin (GemCis) with or without durvalumab is the standard first-line therapy but further improvement in survival outcomes is needed. In a prior study (Chae HJ et al, Eur J Cancer 2019), germline or somatic mutations in DDR genes including BRCA are detected more than half of BTC patients and associated with better survival outcomes with platinum-based chemotherapy. As the potential efficacy of Olaparib in DDR-mutated cancers and synergism between PARP inhibitors and immune checkpoint inhibitors, we designed randomized phase 2 trial investigating the efficacy and safety of olaparib monotherapy vs olaparib plus durvalumab in BTC patients as maintenance therapy for BTC patients who showed durable response to first-line platinum-based chemotherapy. **Methods:** This is a randomized, open-label phase 2 study conducted in a single center (Asan Medical Center, Seoul, Korea). Key eligibility criteria include histologically documented locally advanced unresectable or metastatic BTC, no progression at least 16 weeks with first-line platinum-based chemotherapy, DDR mutations on targeted sequencing of tumor tissues and ctDNA, ECOG performance status 0–1, and adequate organ function. Eligible patients will be randomized 1:1 into olaparib monotherapy arm (300 mg twice daily, every 4 weeks) or olaparib plus durvalumab (1,500 mg intravenous, every 4 weeks) arm. Study treatment is continued until disease progression, unacceptable toxicity, withdrawal of consent, or death. Response evaluation is performed every 8 weeks (fixed). Stratification factors are tumor location (intrahepatic vs extrahepatic/gallbladder) and best response to platinum-based chemotherapy (CR/PR vs SD). The six-month progression-free survival rates are the primary endpoint and overall survival, progression-free survival, response rates, and safety profiles are secondary endpoints. A total of 62 patients (31 for each arm) are planned, and 23 (37%) patients (ATM [n=6], BRCA2 [n=7], CHEK2 [n=2], BRCA1 [n=1], RAD51C [n=1], and PBRM1 [n=1]) are enrolled as of Jan 2023. Clinical trial information: NCT05222971. Research Sponsor: AstraZeneca Korea Ltd.

TPS4183

Poster Session

ABC-12: Exploring the microbiome in patients (pts) with advanced biliary tract cancer (BTC) in a first-line study of durvalumab in combination with cisplatin/gemcitabine (cis/gem). *First Author: Mairead Geraldine McNamara, University of Manchester/The Christie NHS Foundation Trust, Manchester, United Kingdom*

Background: Durvalumab/cis/gem improved overall survival (OS) in pts with advanced BTC versus placebo/cis/gem (Oh et al. NEJM Evid 2022). Disruption of the microbiota may impair tumour response to immunotherapy and chemotherapy and a better understanding of its role in the efficacy of these therapeutics in advanced BTC is required. **Methods:** This is a multi-centre, single arm trial exploring the microbiome in pts receiving durvalumab 1500 mg intravenously (IV) Q3w, in combination with cis 25 mg/m², gem 1000 mg/m² (Days 1 and 8, Q3w) up to 8 cycles, followed by durvalumab 1500 mg as monotherapy Q4w, until progression or intolerable toxicity. Pts with an ECOG performance status of ≤1 and histologically-proven BTC, including cholangiocarcinoma and gallbladder carcinoma, who have had no prior systemic chemotherapy for locally advanced or metastatic disease are eligible. Pts must provide a saliva and stool sample prior to commencement of durvalumab/cis/gem and at 18 weeks, or at progression (if earlier than 18 weeks). Taxonomic profiling via 16S Ribosomal ribonucleic acid gene sequencing will examine the differences in the diversity and composition of the pt gut microbiome. Pts must also have availability of a tumour biopsy. This study plans to recruit 70 pts from 10 UK centres (over 12 months). The primary objective is to determine the difference in baseline alpha diversity between “responders” (partial or complete response) and “non-responders” at 18 weeks (RECIST 1.1) in patients treated with durvalumab/cis/gem. Secondary objectives include investigation of the association between microbiome parameters and objective response rate, tumour control (partial + complete response + stable disease), progression-free and OS, and to investigate the interaction between treatment effect and microbiome parameters on clinical outcomes. The tumour biopsy will be used for research into the tumour microbiome and/or factors that may influence response to chemotherapy/immunotherapy, including, but not limited to tumour mutation burden, programmed cell death 1/programmed death-ligand 1 status, and microsatellite instability status. Clinical trial information: ISRCTN11210442. Research Sponsor: Astra Zeneca.

TPS4184

Poster Session

Phase II trial of XmAb20717 (vudalimab) in patients with advanced biliary tract cancers. *First Author: William Joseph Chapin, Abramson Cancer Center at the University of Pennsylvania, Philadelphia, PA*

Background: For patients with advanced biliary tract cancers (BTCs), gemcitabine and cisplatin has been the standard-of-care first-line therapy, with a median overall survival (OS) of 11.7 months. More recently, TOPAZ-1 demonstrated a modest, but significant overall survival benefit (HR 0.80; 95% CI 0.66 – 0.97) to the addition of durvalumab to gemcitabine and cisplatin with a median OS of 12.8 months. However, for patients without targetable molecular variants, second-line and beyond options are limited, with FOLFOX demonstrating an overall response rate (ORR) of 5% and increase in median overall survival by 0.9 months compared to active symptom control. In patients with advanced BTCs, combination immunotherapy approaches with PD-1 or PD-L1 plus CTLA-4 inhibitors have been associated with improved ORRs of 10.8% - 23% compared to ORRs of 3 – 7% observed with single agent PD-1 or PD-L1 inhibitors. XmAb20717 (vudalimab) is a novel, bispecific antibody targeting PD-1 and CTLA-4 which demonstrated an ORR of 14.1% in a phase I dose expansion cohort of patients with advanced malignancies, including patients that had experienced disease progression on prior immune checkpoint inhibitors. **Methods:** We initiated a single-arm, phase II clinical trial with a Simon two-stage mini-max design to evaluate the efficacy of XmAb20717, in terms of ORR, in patients with advanced biliary tract cancers previously treated with gemcitabine-based chemotherapy. In the first stage, 13 patients evaluable for efficacy will be accrued. If no responses are observed in these 13 patients, the study will be stopped for futility. Otherwise, 14 additional patients evaluable for efficacy will be accrued to total 27 evaluable patients. If 4 or more responses are observed in these 27 patients, then the null hypothesis will be rejected. XmAb20717 (10 mg/kg) is administered intravenously on days 1 and 15 of a 28-day cycle. Important inclusion criteria include that patients with FGFR2 fusions, NTRK fusions, or IDH1 mutations must have received molecularly targeted therapy unless contraindicated or refused. Patients are not eligible if they have received prior immune checkpoint inhibitor therapy. Correlative studies will include longitudinal peripheral blood collection for circulating immune cell profiling. As of January, 2023, 8 patients have been enrolled with enrollment ongoing. Clinical trial information: NCT05297903. Research Sponsor: Xencor.

TPS4186

Poster Session

NeoTACE: A multicenter, randomized study evaluating the efficacy and safety of neoadjuvant HAIC for TACE plus donafenib in BCLC B stage hepatocellular carcinoma outside of up-to-seven. *First Author: Xiaodong Wang, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Interventional Therapy, Peking University Cancer Hospital & Institute, Beijing, China*

Background: Transarterial chemoembolization (TACE) is standard treatment for hepatocellular carcinoma (HCC) patients in BCLC B stage, while a number of studies demonstrated compromised effect of TACE for patients with large HCC or tumor burden outside of up-to-7. Recently, two phase 3 studies showed the survival benefit of Hepatic arterial infusion chemotherapy (HAIC) for large HCC and as neoadjuvant treatment for HCC outside of Milan criteria. A Phase 3 study also showed the survival benefit of donafenib for unresectable HCC compared with sorafenib. Here, we propose a prospective randomized study to investigate the benefit of HAIC as a neoadjuvant therapy for TACE plus donafenib in unresectable BCLC B stage HCC outside of up-to-seven. **Methods:** This is a multicenter, open-label, randomized study designed to evaluate the efficacy and safety of neoadjuvant HAIC for TACE plus donafenib compared with TACE plus donafenib in BCLC B stage unresectable HCC outside of up-to-seven. Participants are randomized in 1:1 ratio to either Arm A, receiving 2-4 cycles neoadjuvant HAIC treatment plus donafenib initially, then TACE plus donafenib sequentially, or Arm B, just receiving TACE treatment plus donafenib. HAIC consisted of infusions of oxaliplatin (35 mg/m² for 2 hours), followed by 5-fluorouracil (600 mg/m² for 22 hours) on day1-3 every 4 weeks. The primary endpoint is PFS, and the secondary endpoints are OS, ORR, DCR, and adverse events. We hypothesize that neoadjuvant HAIC for TACE plus donafenib will improve PFS from 6 months to 11 months, with the hazard ratio of 0.55. With one-sided significance level of 0.05 and power of 0.8, the sample size for randomization will be 156. The study, registered with clinical trial ID of NCT05171166, started enrolment in Feb 2022. As of Oct 2022, 65 patients have been enrolled and 11 patients have been randomized. Clinical trial information: NCT05171166. Research Sponsor: Beijing Hospitals Authority Clinical Medicine Development of Special Funding Support (No. ZYLX202117).

TPS4185

Poster Session

Phase II study on safety and efficacy of NMS-01940153E, an MPS1 inhibitor with first-in-class potential, in adult patients with unresectable hepatocellular carcinoma (HCC) previously treated with systemic therapy. *First Author: Lorenza Rimassa, Humanitas University, Department of Biomedical Sciences; IRCCS Humanitas Research Hospital, Medical Oncology and Hematology Unit, Rozzano, Italy*

Background: Monopolar Spindle 1 (MPS1) kinase regulates the spindle assembly checkpoint (SAC) which ensures proper division of chromosomes during mitosis. MPS1 is overexpressed in several tumors, including hepatocellular carcinoma (HCC), where it correlates with tumor features and poor overall and disease-free survival. NMS-01940153E is a novel, highly potent and selective small molecule inhibitor of MPS1 kinase with long residence time and strong preclinical anti-tumor activity in different tumor types. In HCC lines, specifically, NMS-01940153E showed ~2-Log higher anti-proliferative activity compared to sorafenib, lenvatinib, and regorafenib. In a previous open-label first-in-human (FIH) study, CL1-81694-001 (EudraCT 2014-002023-10), signs of activity in HCC were detected. Recently, the treatment paradigm for advanced HCC has changed, with immunotherapy combinations in first line and TKIs shifted in later lines. However, the overall prognosis of patients with advanced HCC remains poor, and there is a strong need of new drugs in this setting. NMS-01940153E novel mechanism of action, inhibiting the SAC and interfering with genomic stability in HCC, may offer a new therapeutic option in HCC. Based on the promising FIH results, a Phase I/II study, MPSA-153-001 (EudraCT 2020-001002-26), was initiated in patients with HCC previously treated with more than one systemic therapy. **Methods:** The Phase II part of the MPSA-293-001 trial is designed as a two-stage study with an interim analysis for futility and safety rules for unacceptable toxicity. The primary objective is to assess the antitumor activity of NMS-01940153E in adult patients with unresectable HCC previously treated with systemic therapy measured as objective response rate (ORR) by investigator-assessed RECIST 1.1. Secondary endpoints are safety, PK, ORR as measured by investigator-assessed mRECIST, DoR, PFS and OS. Exploratory endpoints include biomarkers. NMS-01940153E is administered IV, on days 1, 8 and 15 every 4 weeks at the RP2D of 100 mg/m²/wk, which showed PK in a predicted active range. Key eligibility criteria are 1) diagnosis of HCC; 2) disease progression on standard-of-care treatment including an immune checkpoint inhibitor as first line and at least one TKI; 3) no more than 3 prior systemic treatment lines. Interim evaluation for futility will be undertaken as soon as the first 10 evaluable patients will be enrolled. If at least 1 responder is observed with no safety issues, enrollment will proceed up to 38 evaluable patients. Otherwise, the study will be terminated for futility. An independent DSMB will review the interim results and provide recommendation on the study progress. Recruitment is currently ongoing in Italy and Spain and an FDA "Study May Proceed Notification" was received in January 2023. Clinical trial information: NCT05630937. Research Sponsor: Nerviano Medical Sciences S.r.l.

TPS4187

Poster Session

ADJUBIL: A phase II study of immunotherapy with durvalumab and tremelimumab in combination with capecitabine or without capecitabine in adjuvant situation for biliary tract cancer. *First Author: Thorsten Oliver Goetze, Krankenhaus Nordwest, University Cancer Center Frankfurt, Frankfurt am Main, Germany*

Background: Despite improvements in multidisciplinary management, patients with biliary tract cancer (BTC) have a poor outcome. Only 20% of patients are eligible for surgical resection with curative intent, with 5-year overall survival of less than 10% for all patients. Data regarding pure adjuvant chemotherapy in BTC's are conflicting and the SOC of the western world is currently capecitabine according to the British BILCAP- trial, even though BILCAP was formally negative. Based on the positive data for durvalumab in the TOPAZ- 1 – trial in BTC and for STRIDE- regimen in HCC according to the Himalaya- data, evaluation of IO-combination in the adjuvant setting seems to be promising. Preclinical studies indicate that the antibody combination results in stronger and more durable anti-tumor effects than single therapies by synergistically modulating the immunosuppressive tumor microenvironment which is particularly rich in cholangiocarcinoma. The aim of this study is the assessment of the clinical activity of the anti-PD-L1 (programmed- death 1-ligand) antibody durvalumab and the anti-CTLA-4 (cytotoxic T- lymphocyte-associated antigen 4) antibody tremelimumab in combination with or without capecitabine in patients with resectable BTC in the adjuvant situation. This is a randomized phase II study as a proof-of-concept for a potentially larger research program. **Methods:** The ADJUBIL trial is an open-label, multicenter phase II study, including patients with BTC after curative surgery with no previous systemic treatment. Patients are randomly assigned to receive tremelimumab (300mg, one dose) plus durvalumab (1500mg every 4 weeks; STRIDE, for a maximum of 12 months), with or without capecitabine (for 8 cycles). Forty evaluable patients will be enrolled in the study (1:1) to receive anticancer treatment until disease recurrence or intolerable toxicities. Primary objective is to assess the anti-tumor activity of the treatment in both arms by the recurrence-free survival rate after 12 months (RFS@12). Secondary endpoints are recurrence-free survival, overall survival, toxicity, and quality of life. Exploratory endpoints: Explore predictive biomarkers for recurrence-free survival and overall survival. Study start of the ADJUBIL trial was in June 2021. By January 2023, 12 centers across Germany have been initiated and a total of 8 out of 40 planned patients (1:1) have been enrolled. The study is currently ongoing. Clinical trial information: EUCTR2021-002389-41. Research Sponsor: AstraZeneca.

TPS4188

Poster Session

Durvalumab and tremelimumab for hepatocellular carcinoma in patients listed for a liver transplant. *First Author: Davendra Sohal, University of Cincinnati, Cincinnati, OH*

Background: Hepatocellular carcinoma (HCC) is an aggressive malignancy, developing most often in the setting of liver cirrhosis (Sohal et al Current Oncol Rep 2011; Gordan et al JCO 2020). For advanced disease, immunotherapy has now become standard of care – a combination of atezolizumab and bevacizumab has shown the best overall survival outcome so far (Finn et al NEJM 2020). For earlier stage disease, however, there is no systemic therapy standard. The best treatment for HCC in the setting of cirrhosis is a liver transplant allowing potential cure for both the cancer and cirrhosis. Nonetheless, 25-35% of patients fail to reach liver transplant because of disease progression while waiting for a transplant (Sinha et al, Hepatology 2019) and approximately 15% experience HCC recurrence after transplant (Mehta et al, Transplantation 2020). Taken together, this constitutes a large subset of this patient population who cannot achieve a cure. Given the success of immunotherapy in the advanced setting, it is imperative to study this in the pre-transplant setting, to improve the outcomes cited above. However, there is a theoretical risk of graft rejection with immunostimulatory treatment. **Methods:** This is a single-arm, open-label, Phase II, multicenter study designed to evaluate the safety and efficacy of durvalumab and tremelimumab for the treatment of HCC patients who have cirrhosis or portal hypertension and are eligible for listing for a liver transplant. Eligibility requirements include adult patients with HCC within UCSF criteria, a Child-Pugh score of up to 7, and ECOG PS of 0 or 1. Treatment includes an immunotherapy combination of 1 dose of tremelimumab and 5 doses of durvalumab for up to 4 months. After a minimum 28-day gap following the final durvalumab dose, patients undergo locoregional therapy per institutional standards. After a minimum 72-day gap from the end of immunotherapy, patients undergo liver transplant. Primary outcome is a binary endpoint, and it will be assessed in patients undergoing liver transplant. Historically, 10-20% of patients are expected to experience acute cellular rejection within 30 days of transplant. We propose that an observed proportion of 20% treatment failure will be a clear indicator of safety in this pilot study, whereas an observed proportion of 50% failure will be a clear indicator of failure. Using these guardrails, with at least 20 patients going to transplant, we will have 80.6% power to demonstrate a failure proportion of 20% (4 patients experiencing failure) versus a null of 50% (10 patients experiencing failure), with a one-sided alpha of 0.05. With 25 patients going to transplant, the power will increase to 86% (other parameters being the same). Clinical trial information: NCT05027425. Research Sponsor: AstraZeneca.

TPS4190

Poster Session

A phase II, open-label pilot study evaluating the safety and activity of liposomal irinotecan (Nal-IRI) in combination with 5-FU and oxaliplatin (NALIRIFOX) in preoperative treatment of pancreatic adenocarcinoma: NEO-Nal-IRI study. *First Author: Sherie C. Rogers, University of Florida/UF Health Cancer Center, Gainesville, FL*

Background: Neoadjuvant treatment for potentially curable pancreatic cancer (PDAC) is increasing in acceptability, but a standard regimen has yet to be established. Multiple studies have demonstrated feasibility and effectiveness of the FOLFIRINOX (5-fluorouracil, leucovorin, oxaliplatin and irinotecan) regimen in the perioperative setting. However, FOLFIRINOX often requires dose modifications, delays and growth factor support due to excessive toxicity which can complicate care delivery when given neoadjuvantly. Liposomal irinotecan injection (Nal-IRI) is FDA approved with a well-tolerated safety profile in relapsed, refractory metastatic PDAC. The current study aims to substitute Nal-IRI for traditional irinotecan in the standard FOLFIRINOX regimen (NALIRIFOX) and to demonstrate safe and effective neoadjuvant delivery. **Methods:** This phase 2, open-label, multicenter single-arm study focuses on patients (pts) with operable PDAC without metastatic disease. Other key eligibility criteria include age ≥ 18 years, resectability confirmed by multidisciplinary GI tumor board (resectable vs. borderline), adequate cardiac, renal, hepatic function and ECOG performance status of 0 to 1. Pts receive NEO-N-IRI regimen as per Table every 2 weeks for four months followed by disease reassessment. Pts who remain surgical candidates will undergo surgical resection within 4 to 8 weeks following last dose of therapy. The primary endpoint is to assess safety and feasibility of regimen in perioperative setting. Secondary endpoints include R0 resection rate, clinical, biochemical and radiological response rate and patient-reported quality of life during treatment as measured by the NCI validated FACT-G scale. Enrollment continues to a maximum of 28 evaluable pts to demonstrate a reduction in historical 30-day postoperative complication rate. Microbiota specimens will be collected for exploratory analysis. Clinical trial information: NCT03483038. Research Sponsor: Ipsen; UF Health Cancer Center.

Agent	Dose	Route/Duration
Nal-IRI	50 mg/m ²	IV over 90 minutes
Oxaliplatin	60 mg/m ²	IV over 120 minutes
Leucovorin	400 mg/m ²	IV over 120 minutes
5-fluorouracil infusion	2400 mg/m ²	IV continuous infusion for 46 hours

TPS4189

Poster Session

An open-label window of opportunity trial to evaluate the activity of durvalumab and tremelimumab with platinum-based chemotherapy (gemcitabine and cisplatin) in intrahepatic cholangiocarcinoma. *First Author: Olumide B. Gbolahan, Emory University School of Medicine, Atlanta, GA*

Background: Following surgical resection, the rate of recurrence of intrahepatic cholangiocarcinoma (ICC) is high. Expert groups recommend preoperative systemic therapy, particularly for resectable ICC with features that portend a high risk of recurrence. Based on data from ABC-02 the combination of gemcitabine and cisplatin (GC) is often used. This provides an objective response rate (ORR) of only 20% in ICC. The addition of durvalumab, an anti-PDL1 inhibitor to GC improves overall survival (OS) in the metastatic setting and is associated with an ORR of about 30%. On the other hand, while the addition of nab-Paclitaxel to GC provides an ORR of 34%, it was not associated with an improvement in OS in biliary tract cancer. It is therefore rationale to continue to explore and optimize immune checkpoint inhibitor development in ICC. We designed this study to determine the activity of durvalumab (D) and tremelimumab (T) (anti-CTLA4 ICPI) in combination with GC in resectable ICC with high-risk features. We plan to explore tumor intrinsic and tumor microenvironment related factors that will be associated with response (or lack thereof) to ICPI. **Methods:** This is a multicenter open-label, window of opportunity trial of the combination durvalumab and tremelimumab in combination with GC in resectable ICC with high-risk features. Inclusion criteria includes patients ≥ 18 years with radiologically measurable and biopsy proven ICC that is surgically resectable but with high risk features (based on multidisciplinary tumor board discussion). Prespecified high-risk features include tumor size >5 cm, T1b-T4 lesion, multifocal tumors/tumor with satellite lesions, suspicious or involved lymph nodes (N1) and vascular involvement all thought to be technically resectable. Patients with extrahepatic metastasis will be excluded. D will be administered at 1500mg IV on Day 1 every 3 weeks for up to a maximum of 4 cycles. T, 300mg will be administered on Day 1 of cycle 1 only. G (1000mg/m²) and C (25mg/m²) will be administered by IV infusion on Days 1 and 8 every 3 weeks for a maximum of 4 cycles. The primary outcome measure is to demonstrate an ORR of 52%. Secondary objectives are to assess the feasibility and safety of the combination in ICC. Given the historical objective response rate of 25% and using one-sided exact test for single proportion, we will have 80% power to reject 25% ORR at $\alpha=0.05$ when we observe ORR of 52% (Ho: Po=0.25 vs. Ha: Pa=0.52) from the study sample. The study is open at the O'Neal Comprehensive Cancer Center at the University of Alabama and will be open at other centers in the next few months. Clinical trial information: NCT04989218. Research Sponsor: AstraZeneca.

TPS4191

Poster Session

Alliance A021804: A prospective, multi-institutional phase II trial evaluating temozolomide versus temozolomide and olaparib for advanced pheochromocytoma and paraganglioma. *First Author: Jaydara Del Rivero, National Cancer Institute/National Institutes of Health, Bethesda, MD*

Background: Pheochromocytomas (PHEOs) and paragangliomas (PGLs) are rare neuroendocrine tumors (NETs) that arise from chromaffin cells. Few antitumor therapies have been developed for patients (pts) with advanced PHEO/PGLs (APP). Potent poly (ADP-ribose) polymerase (PARP) is activated after DNA damage and regulates base excision repair, homologous recombination and non-homologous end joining. Inhibition of PARP enzymatic activity blocks PARP-mediated DNA repair, therefore PARP inhibitors can be directly cytotoxic to tumor cells which then permits synergy with agents that increase prevalence of single-strand breaks in tumor models. Temozolomide (TMZ) is an alkylating agent that induces single-strand DNA breaks and therefore is an optimal therapeutic pair with a PARP inhibitor. We are conducting a phase II multi-institutional study to evaluate the antitumor activity of TMZ and olaparib [OLA (a PARP inhibitor)] in patients with APP. **Methods:** Patients with APP with radiographic evidence of disease progression by RECIST v1.1 in the 12 months prior to registration can be enrolled in this phase II randomized study. Patients will be randomized in a 2:1 allocation with more patients to Arm 1. Arm 1 will receive TMZ 75 mg/m² daily and OLA 200 mg twice daily on days 1-7 of a 21-day cycle. Arm 2 will receive TMZ 200 mg/m² daily on days 1-5 of a 28-day cycle. Treatment on Arm 1 will continue for 13 cycles, followed by OLA maintenance until disease progression. Treatment on Arm 2 will continue for 13 cycles or until disease progression. The primary objective is to compare the progression-free survival between the two arms with a planned interim analysis for futility. Secondary endpoints include safety, response rate, and overall survival. Correlative endpoints include biochemical response and biomolecular markers (germline succinyl dehydrogenase mutations and tumor status of the repair enzyme methylguanine-DNA methyltransferase). We anticipate a null PFS median of approximately 5.4 months. We plan to accrue a total of 76 patients (randomized at a rate of 2:1 with more patients enrolled to the TMZ+OLA arm) in 38 months with a minimum follow-up of 2.5 months to achieve 56 PFS events. This design includes one interim analysis for futility using Rho Family spending functions (Rho = 2.5) and will yield 89% power to detect a hazard ratio (HR) of 0.5 (median PFS of 5.4 vs. 10.8 months) assuming exponential survival and using a one-sided log-rank test with type I error rate of 0.11. Clinical trial information: NCT04394858. Research Sponsor: U.S. National Institutes of Health.

TPS4192

Poster Session

LANTana trial protocol: An open label, single arm, phase Ib study to evaluate the effect of pre-treatment with ASTX727 (a demethylating agent) followed by lutetium Lu 177 dotatate in patients with progressive, metastatic neuroendocrine neoplasias (NENs). *First Author: Rohini Sharma, Imperial College London, London, United Kingdom*

Background: Neuroendocrine neoplasias (NENs) are characterised by the presence of somatostatin receptors (SSTR) on cell surface, in particular SSTR2. Somatostatin and its stable analogue (SSA) bind with high affinity to SSTR2. SSA can be radiolabelled, to both stage NENs using positron emission tomography (PET), and to deliver selective radiotherapy; peptide receptor radionuclide therapy (PRRT). PRRT consists of SSA linked to the long acting radionuclide. Radiolabelled SSA binds to SSTR2 and the complex is internalised delivering high dose radiation directly to the cancer. PRRT has been significantly improve survival outcomes and maintain quality of life in metastatic disease. Suitability for PRRT depends on presence of SSTR2 as determined by PET imaging, commonly with [⁶⁸Ga]-dotatate-PET. 20% of patients will have low or no uptake on [⁶⁸Ga]-dotatate-PET precluding PRRT. The upstream promoter region of SSRT2 is methylated, with percentage of methylation correlating with SSTR2 expression. We have shown that the use of the demethylating agent, guadecitabine, increases uptake on PET imaging in such that tumours previously negative on PET imaging, become positive, correlating with a dose dependent increase in tumoural SSTR2 expression. Combination guadecitabine and PRRT was well tolerated in vivo models of NETs. Overall aim was to utilise [⁶⁸Ga]-dotatate-PET as a biomarker of SSTR2 re-expression following treatment with the demethylating agent, ASTX727, such that patients previously unsuitable for PRRT can receive therapy, improving clinical outcome. 1) Utilise [⁶⁸Ga]-dotatate-PET to image epigenetic regulation of SSTR2 in response to ASTX727. 2) Evaluate clinical efficacy and safety of ASTX727 pre-treatment in combination with PRRT. 3) Explore impact on quality of life of combination therapy. **Methods:** 27 patients with no or equivocal uptake on [⁶⁸Ga]-dotatate-PET will be enrolled. [⁶⁸Ga]-dotatate-PET will be performed at baseline and after 8days of ASTX727 (oral, fixed dose 100mg cedazuridine + 35mg decitabine). If there is a significant increase in PET uptake, patients will receive combination ASTX727 and PRRT (Lutathera). Treatment will be repeated every 2months for 4 cycles. Response assessment (RECIST 1.1), tolerability and QoL will be assessed at start of each cycle. Tumour biopsies will be taken at baseline, and after cycle1 of ASTX727 (n=5), for SSTR2 methylation. Methylation will be correlated with PET uptake and outcome. LINE-1 methylation in peripheral blood monocytes will be assessed throughout. Current enrolment: 4. Clinical trial information: NCT05178693. Research Sponsor: AAA.

TPS4194

Poster Session

Phase II trial of BXCL701 and pembrolizumab in patients with metastatic pancreatic ductal adenocarcinoma (EXPEL-PANC). *First Author: Benjamin Adam Weinberg, Ruesch Center for the Cure of Gastrointestinal Cancers, Lombardi Comprehensive Cancer Center, Georgetown University, Washington, DC*

Background: Pancreatic ductal adenocarcinoma (PDAC) has limited therapeutic options and is thought to be a “cold” tumor that does not respond to immunotherapy, due to a tumor microenvironment (TME) consisting of a desmoplastic stroma and poor T cell infiltrate. BXCL701 is an oral synthetic dipeptide that competitively inhibits dipeptidyl peptidases DPP4, DPP8, DPP9 and fibroblast activation protein (FAP). BXCL701 exerts antitumor activity via inhibition of DPP8/9, which is associated with induction of proinflammatory cytokines, as well as inhibition of FAP, which disrupts tumor-stromal interactions. Preclinical xenograft models demonstrate synergy between BXCL701 and an anti-PD-1 monoclonal antibody, reducing tumor growth and promoting an increase in intratumoral CD4+ and CD8+ T cells and NK cells. The combination of BXCL701 and pembrolizumab is already being studied in a phase II trial in patients with prostate cancer (NCT03910660) and a multi-cohort basket study (NCT04171219). **Methods:** This is a phase II trial of BXCL701 administered at 0.2 mg PO BID days 1-7 and 0.3 mg BID days 8-14 during cycle 1 (21 days) followed by 0.3 mg BID days 1-14 every 21 days in all subsequent cycles, given with pembrolizumab 200 mg IV every 21 days (all cycles). The primary objective is to determine the 18-week progression-free survival rate (PFS18weeks) in patients with metastatic PDAC treated in the second-line setting. We estimate that historical 2nd-line PFS18weeks is 30% or less; using a Simon's two-stage (minimax) design, a type I error rate of 0.05 and power of 80% when the true response rate of 50%, we will need 19 patients in stage 1 and 20 in stage 2 (a total of 39). We plan to enroll 43 patients to account for a predicted 10% drop out of unevaluable patients. Eligible patients must have metastatic PDAC and disease progression or intolerance to only 1 line of therapy for metastatic disease, without exposure to prior immunotherapy. Patients must have measurable disease amenable to serial biopsies. Correlative pharmacodynamic studies include imaging mass cytometry to examine 34 markers of the PDAC TME in tissue biopsies, as well as blood-based analyses of KRAS circulating tumor DNA, circulating markers of fibrosis, and IL-6. Enrollment began in Q1 2023. Clinical trial information: NCT05558982. Research Sponsor: BioXcel; Merck.

TPS4193

Poster Session

Open-label, single arm phase II trial investigating the efficacy, safety and quality of life of neoadjuvant chemotherapy with liposomal irinotecan combined with oxaliplatin and 5-fluorouracil/folinic acid followed by curative surgical resection in patients with hepatic oligometastatic adenocarcinoma of the pancreas (HOLIPANC). *First Author: Florian Gebauer, University Cologne, Cologne, Germany*

Background: As of today, the recommendation for patients with adenocarcinoma of the pancreas and hepatic metastases is systemic chemotherapy alone regardless of the number and location of metastases. In the past, case reports have repeatedly reported survival data of patients who received metastatic and primary tumor resection outside the guidelines. However, there are currently no controlled clinical data from prospective studies that have evaluated the effectiveness of systemic chemotherapy in combination with tumor and metastasis resection in the context of hepatic oligometastasis in pancreatic cancer. **Methods:** In this single arm, phase-2 trial, survival data from patients receiving neoadjuvant chemotherapy followed by RO/R1 resection will be compared to historic data from patients with oligometastatic adenocarcinoma of the pancreas. Inclusion criteria are patients with a maximum of 5 liver metastases and histology proven PDAC. The combination of liposomal irinotecan (nal-IRI), oxaliplatin (OX) and 5-fluorouracil (5-FU)/folinic acid (FA) (Nal-IRIFOX) was chosen as neoadjuvant chemotherapy since recent data suggested superior efficacy and less toxicity compared to mFOLFIRINOX. The primary endpoint is overall survival (OS) after RO/R1 resection. Secondary efficacy endpoints are RO/R1 resection rate and progression-free survival (PFS). Secondary safety endpoints are type, frequency and severity of adverse events with severity according to NCI CTCAE version 5.0 and perioperative morbidity and mortality. Eligible patients with hepatic oligometastatic adenocarcinoma of the pancreas will receive neoadjuvant combination chemotherapy in cycles of 14 days for a duration of 16 weeks in total. In patients with progressive disease during or after the first 4 cycles, neoadjuvant chemotherapy will be permanently discontinued. Patients with tumor response or stable disease after the first 4 cycles according to RECIST v1.1 but a non-resectable primary tumor will receive 4 more cycles. Patients with tumor response or stable disease and a resectable primary tumor after the first 4 cycles will undergo explorative laparotomy and synchronous resection of the tumor and hepatic metastases, if feasible. In total 150 patients will be enrolled for this trial with an aim of 55 patients receiving a complete macroscopic synchronous tumor and metastatic resection. The study is currently ongoing on 11 high-volume centers for pancreatic surgery within Germany. This is the first clinical study to prospectively evaluate the value of multimodality therapy concepts in oligometastatic pancreatic cancer. Clinical trial information: NCT04617457. Research Sponsor: Servier.

TPS4195

Poster Session

Phase 1b/2 trial of pepinemab plus avelumab as second line combination immunotherapy for patients with metastatic pancreatic adenocarcinoma. *First Author: Luis I. Ruffolo, University of Rochester Cancer Center & Wilmot Cancer Institute, Rochester, NY*

Background: Monotherapy with immune checkpoint inhibitors (ICIs) is not effective in metastatic pancreatic adenocarcinoma (PDAC), likely due to the unique immunosuppressive tumor microenvironment (TME) of PDAC, thus safe and novel strategies to overcome resistance and facilitate adaptive immune responses are a major unmet need. Preclinical and clinical studies demonstrated that antibody blockade of semaphorin 4D (SEMA4D) promotes tumoral infiltration and activation of DCs and CD8+ T cells and reverses immunosuppression, including attenuation of MDSC recruitment and function, leading to enhanced efficacy of ICIs without increasing toxicity. Pepinemab, a SEMA4D blocking antibody, in combination (combo) with avelumab provided clinical benefit in some patients with ICI-resistant and PD-L1-low NSCLC (NCT03268057). Pepinemab is also being evaluated in combo with pembrolizumab in patients with metastatic squamous cell carcinoma of the head and neck (NCT04815720). The principal goals of this proof-of-concept study are to investigate the safety, efficacy, and TME biomarker changes of treatment with the combo of pepinemab plus avelumab in patients with metastatic PDAC. **Methods:** This single-arm, open-label study (NCT05102721) is evaluating the safety, tolerability, and efficacy of pepinemab in combo with avelumab in patients diagnosed with metastatic PDAC who have either progressed on or are otherwise intolerant to first line chemotherapy. Patients must have received 5FU or gemcitabine-based first line therapy with evidence of intolerance or treatment failure, including progression both during or after completing first-line treatment. Accrual for the Phase 1b portion follows a Bayesian Optimal Interval Design (BOIN), beginning at the highest dose combo; 20 mg/kg pepinemab and 800 mg avelumab Q2W. Phase 2 begins after 16 subjects are enrolled at MTD, permitting a Simon's two stage assessment of futility prior to closing the Phase 1b period. The primary objective for Phase 1b is tolerability, and the primary objective for Phase 2 is therapeutic efficacy compared to historical second-line systemic chemotherapy. The trial anticipates a total evaluable cohort of 40 subjects and is powered to detect a response rate of 23% or greater, with alpha set at 0.1 and 80% power. Exploratory objectives include robust correlative analysis of immune, stromal, and genomic profiling of baseline and on-treatment tumor biopsies to ascertain mechanisms of treatment response and failure. Patient reported outcomes are incorporated throughout the trial to assess disease specific symptoms associated with pancreatic cancer and cancer cachexia. One patient has been enrolled as of Feb 14, 2023. Clinical trial information: NCT05102721. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology; Vaccinex, Inc.; U.S. National Institutes of Health.

TPS4196

Poster Session

A phase 1 study to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics and immunogenicity of LB4330, a peptide fused to CLDN18.2 antibody targeting the tumor antigen associated CD8+ T CELLS in patients with advanced solid tumors. *First Author: Jiajian Liu, Shanghai, China*

Background: PD-1/PD-L1-targeted immunotherapies have become critical roles in the treatment for many tumors. However, there is limited progress in pancreatic ductal adenocarcinoma (PDAC). PDAC is low immunogenicity. PDAC microenvironment is immunosuppressive. More than 70% PDACs have few or no CD8+ T cells around the tumor cell or in the tumor microenvironment (TME). Therefore, immunotherapy like PD-1/PD-L1 antibody alone is rarely effective for PDACs. Some cytokine or analogs may activate CD8+ T cells. An analog specifically activating tumor antigen associated (TAA) CD8+ T cells was designed and fused to anti-CLDN18.2 antibody. This specific bi-functional molecule LB4330 has high affinity to human anti-CLDN18.2 (14pM) and CD8+ T cells. LB4330, as a novel, first-in-class molecule, may activate TAA CD8+ T cells in TME and has potential in alone or in combination with PD-1/PD-L1 mAb, for the treatment of advanced solid tumors, especially for Claudin 18.2 positive PDAC. **Methods:** This is a FIH, phase 1 study to evaluate the safety, tolerability, pharmacokinetics and immunogenicity of LB4330 in patients with advanced solid tumors (MEETCD8-001). The planned sample size is approximately 66 patients in two parts: part 1 dose escalation, will evaluate safety, tolerability, pharmacokinetics (PK), pharmacodynamics, and determine the maximum tolerated dose (MTD) and/or the recommended phase 2 dose (RP2D). Part 2 dose expansion will further characterize the safety profile and preliminary tumor response in advanced gastric and gastroesophageal junction adenocarcinoma and PDAC with Claudin 18.2 expression. In dose escalation stage, patients will be recruited with advanced solid tumors who have failed standard treatment, or for whom standard treatment is not available or applicable at this stage. Exclusion criteria include a greater risk for gastric bleeding, irritable bowel syndrome with symptoms, active virus infections. The primary endpoints are incidence of dose limiting toxicities and adverse events, MTD, and recommended phase 2 dose. Secondary objectives will evaluate PK parameters, preliminary antitumor activity, and immunogenicity of LB4330. Tumor response will be assessed per RECIST and iRECIST every 2 cycles. The Phase I study in advanced solid tumors is ongoing. Enrollment in cohort 1 began in Nov 2022. Clinical trial information: NCT05707676. Research Sponsor: L&L Biopharma Co., LTD., Shanghai, China.

TPS4198

Poster Session

Randomized phase II trial of olaparib + pembrolizumab vs olaparib alone as maintenance therapy in metastatic pancreatic cancer patients with germline BRCA1 or BRCA2 (gBRCA1/2+) pathogenic variants: SWOG S2001. *First Author: Vincent Chung, City of Hope, Duarte, CA*

Background: Olaparib was approved in 2019 as maintenance therapy for gBRCA1/2+ metastatic pancreatic cancer (mPDA) patients (pts). The POLO trial showed an improvement in median progression free survival (mPFS) with olaparib compared to placebo (7.4 vs 3.8 months) for platinum sensitive gBRCA1/2+ mPDA pts. Preclinical studies have demonstrated that PARP inhibitors modulate the immune microenvironment by increasing genomic instability, PD-L1 expression and activating the immune inflammatory stimulator of interferon genes (STING) pathway. Several clinical studies in solid tumors have shown preliminary efficacy with the combination of PARP plus immune checkpoint inhibitors. Based upon these data, SWOG S2001 aims to further improve the PFS of gBRCA1/2+ mPDA pts. **Methods:** S2001 was developed in collaboration with the Alliance and was activated in SWOG in December 2020. Key eligibility criteria include: mPDA pts with gBRCA1/2 pathogenic variants identified with standard of care germline genetic testing and progression-free after receiving at least 16 weeks of platinum-based chemotherapy (FOLFIRINOX, FOLFOX or gemcitabine/cisplatin +/- nab-paclitaxel). One cycle of gemcitabine and nab-paclitaxel is allowed while waiting for germline testing. Zubrod performance status (PS) 0 or 1 pts are eligible. Pts are stratified according to first line chemotherapy, PS 0 vs 1, and disease status after 1st line treatment. The primary objective of this study is to compare PFS in mPDA pts treated with olaparib + pembrolizumab versus olaparib alone as maintenance therapy. Based upon the POLO trial, we expect a mPFS of 7 months in the control arm. Targeting a mPFS of 11.7 months in the experimental arm (hazard ratio 0.6) and assuming 15 months follow-up, 80% power and a 1-sided alpha=0.10, this design requires enrolling 88 pts for a total of 78 eligible and evaluable pts. As of February 2023, 26 participants have been accrued. Prospective serial blood samples will be collected to bank DNA and RNA for future correlative studies. Clinical trial information: NCT04548752. Research Sponsor: U.S. National Institutes of Health.

TPS4197

Poster Session

ASCEND: A randomised, double-blinded, phase II study of gemcitabine and nab-paclitaxel with CEND-1/LSTA1 or placebo in patients with untreated metastatic pancreatic ductal adenocarcinoma. *First Author: Andrew Peter Dean, St. John of God Hospital Subiaco, Subiaco, Australia*

Background: LSTA1 is a novel cyclic peptide with high tumor vascular endothelium specificity that activates an endocytotic/exocytotic transport pathway on stroma and tumor. LSTA1 potentiates greater intratumoral access for co-administered or tethered anti-cancer agents, including small molecules, antibodies, and nanoparticles, leading to increased anti-neoplastic activity. Preclinical studies in solid tumor models have shown co-administrating LSTA1 is effective in augmenting the delivery and activity of multiple anti-cancer agents. LSTA1 has been evaluated in 31 patients in a Phase I study in metastatic pancreatic ductal adenocarcinoma (mPDAC) demonstrating an objective response in 59% of patients, a 79% disease control rate at 16 weeks with a median progression free survival (PFS) of ~9.9 months. No dose limiting toxicities were observed. The ASCEND study will determine whether LSTA1 when added to SOC chemotherapy is active and safe as first-line treatment of mPDAC, and whether an additional dose of LSTA1 administered approximately 4 hours after chemotherapy further improves anti-cancer activity. **Methods:** ASCEND is a randomized, double-blind, placebo-controlled phase II trial evaluating the safety and efficacy of LSTA1 3.2 mg/kg in combination with standard of care chemotherapy (nab-paclitaxel 125mg/m² and gemcitabine 1000mg/m² on days 1, 8, and 15, every 28 days) in patients with histologically proven, previously untreated mPDAC. A total of 155 subjects will be randomized 2:1 in favor of study intervention in two cohorts and stratified by age, ECOG status, presence of liver metastasis, and study site. Patients in cohort A receive single doses of LSTA1 or placebo, and for cohort B, two doses of LSTA1 or placebo spaced 4 hours apart. Tumour assessment occurs every 8-weeks from randomization until disease progression or commencement of a new anti-cancer therapy. The primary endpoint is PFS. Secondary endpoints include objective tumour response safety, overall survival, and patient reported outcomes. At 14 Feb 2023, 70 participants have been enrolled from Australian sites. Sites in Ireland and New Zealand are anticipated to open this year. Clinical trial information: NCT05042128. Research Sponsor: Lisata Therapeutics, Inc.

TPS4199

Poster Session

Phase 3 PANOVA-3 study: Tumor treating fields (TTFields) therapy concomitant with gemcitabine and nab-paclitaxel (GnP) for front-line treatment of locally advanced pancreatic cancer. *First Author: Hani M. Babiker, Mayo Clinic Florida, Jacksonville, FL*

Background: Tumor Treating Fields (TTFields) therapy is a locoregional antimitotic treatment approved for newly diagnosed and recurrent glioblastoma GBM and pleural mesothelioma. TTFields (150 kHz) therapy, with/without chemotherapy, had anti-proliferative and anticlonogenic activity in pancreatic cancer cell lines, and reduced tumor volume and weight more than chemotherapy alone in *in vivo* models. TTFields therapy with gemcitabine and nab-paclitaxel (GnP) was well-tolerated, with promising efficacy in metastatic and locally advanced pancreatic adenocarcinoma (LAPC) in the phase 2 PANOVA study (NCT01971281). LAPC prognosis remains poor despite available therapies, which can negatively impact quality of life (QoL). As such, there remains a need for effective and tolerable treatments. **Methods:** PANOVA-3 (EF-27, NCT03377491) is a prospective, randomized, phase 3 study investigating the efficacy and safety of TTFields therapy with GnP in patients with LAPC, with a planned enrollment of 556 patients. Key inclusion criteria are: a diagnosis of unresectable LAPC (per NCCN guidelines), ECOG PS of 0–2, and no prior treatment. Patients will be stratified by performance status and geographical region and assigned 1:1 to treatment groups to receive TTFields therapy + GnP or GnP alone. GnP will be administered at a standard dose per standard of care. TTFields therapy (150 kHz, 18h/day) will be delivered by the NovoTTF-200T System until local disease progression per RECIST v1.1. Usage will be tracked by the device. Follow-up will be performed every 4 weeks and computed tomography scans of the chest and abdomen will be taken every 8 weeks until disease progression. Patients will be followed every month until death. The primary endpoint is overall survival and key secondary endpoints include QoL, pain-free survival, and puncture-free survival, which will be compared between treatment groups. Other secondary endpoints include progression-free survival (PFS), local PFS, objective response rate, 1-year survival rate, rate of resectability, and safety. Guidance around usage, lifestyle integration and prevention and management of skin adverse events will be provided by Device Support Specialists and field personnel. Usage information will be provided to patients and physicians to facilitate discussions to optimize outcomes by maximizing time on therapy. Together, these novel support approaches aim to optimize patient usage and outcomes. The trial is currently recruiting at 149 sites, globally. The DMC last reviewed the trial in August 2022, and suggested that the trial continue as planned. Clinical trial information: NCT03377491. Research Sponsor: Novocure.

TPS4200

Poster Session

CheMo4METPANC: A phase 2 study with combination chemotherapy (gemcitabine and nab-paclitaxel), chemokine (C-X-C) Motif receptor 4 inhibitor (motixafortide), and immune checkpoint blockade (cemiplimab) in metastatic treatment-naïve pancreas adenocarcinoma. *First Author: Gulam Abbas Manji, Columbia University Medical Center/New York-Presbyterian Hospital, New York, NY*

Background: Metastatic pancreatic ductal adenocarcinoma (mPDAC) is a uniformly fatal disease for which treatments result in limited benefit. Failure of immune checkpoint blockade is attributed to multiple immunosuppressive pathways within the tumor microenvironment. The C-X-C motif chemokine receptor 4 (CXCR4)/C-X-C motif chemokine ligand 12 (CXCL12) axis results in exclusion of anti-tumor immune cells. Preclinical studies demonstrated that simultaneous CXCR4 inhibition (CXCR4i) and anti-programmed cell death 1 (aPD1) resulted in tumor stabilization. We extended these findings by testing multiple combinations of CXCR4i, aPD1, and gemcitabine in the KPC mouse model of PDAC. Mice treated with gemcitabine, CXCR4i, and aPD1 (triple therapy) experienced a survival benefit compared to mice treated with either gemcitabine alone, or with CXCR4i/aPD1. Tumors from mice treated with triple therapy demonstrated increased apoptosis and a favorable tumor immune microenvironment (TIME). Motixafortide with pembrolizumab, fluorouracil, and nanoliposomal irinotecan has shown encouraging results in the second-line setting in mPDAC with a confirmed ORR of 13.2% and progression free survival (PFS) of 3.8 months (m). The goal of this first-in-man trial is to test preliminary safety and efficacy of Motixafortide (CXCR4i), Cemiplimab (aPD1), Gemcitabine, and Nab-paclitaxel (MCGN) in treatment naïve mPDAC. **Methods:** This is an open label, multicenter, investigator-initiated Simon-2-stage phase 2 clinical trial in mPDAC testing MCGN. The study includes a six-patient safety run-in cohort and an additional 4 patients comprising a pilot efficacy signal seeking study (N=10). If ≥ 3 of the 10 patients within the pilot stage were to experience a partial response (PR) by RECIST criteria within 16 weeks, the combination would be considered promising and an expansion cohort of an additional 30 patients was planned. On 09/21/22, we amended the study to forego the planned open-label expansion cohort (N=30) and transition directly to a randomized phase 2 trial testing MCGN compared to Gemcitabine and Nab-paclitaxel (GN) alone (N=102), after completion of the pilot phase of the study. The primary endpoint is PFS. The study has 80% power to detect an improvement in PFS from 6 to 9.2 m (HR 0.65) with a one-sided alpha of 0.20. One interim analysis for futility is planned when 50% of the PFS events are observed. Secondary objectives include ORR, disease control rate, duration of clinical benefit and OS. Required (pilot portion) and optional (randomized portion) paired tumor biopsies will undergo exploratory analysis including interrogation of the TIME. This trial was started in September 2020 and has enrolled 10 patients to the pilot stage as of 02/2023. Clinical trial information: NCT04543071. Research Sponsor: Regeneron Pharmaceuticals; BioLineRx.

TPS4202

Poster Session

Apollo: A randomized phase II double-blind study of olaparib versus placebo following curative intent therapy in patients with resected pancreatic cancer and a pathogenic BRCA1, BRCA2, or PALB2 mutation—ECOG-ACRIN EA2192. *First Author: Kim Anna Reiss, University of Pennsylvania, Philadelphia, PA*

Background: A meaningful subset of PDAC is characterized by a homologous recombination deficiency (HRD). The most well-defined patients within this group are those with pathogenic variants in *BRCA1*, *BRCA2* and *PALB2*. In the metastatic setting, PARP inhibitor maintenance provides a progression-free survival benefit after a period of platinum based chemotherapy^{1,2}, but the role of PARP inhibitors in the curative intent setting is undefined. The OlympiA study established one year of olaparib as the standard of care for patients with *BRCA*-related, early stage breast cancer who completed all other curative-intent treatment³. Therefore, we have designed a randomized, phase II double-blind study of one year of olaparib vs placebo in patients with pancreatic cancer and a germline or somatic variant in *BRCA* or *PALB2* who have completed all curative intent therapy. **Methods:** We have enrolled and treated 29 of 152 planned patients on study NCT 04858334/EA2192. Eligibility criteria include: a pathogenic germline or somatic variant in *BRCA1*, *BRCA2* or *PALB2* as determined by local laboratory (central review required); completion of curative-intent resection and $\geq$ three months of multi-agent chemotherapy; no evidence of recurrent disease. At enrollment, patients must be within 12 weeks of their last anti-cancer intervention. Patients are randomized 2:1 to receive oral olaparib 300 mg twice daily or placebo for 12 28-day cycles. The primary endpoint is relapse-free survival. Overall survival is a secondary endpoint. Tumor tissue, fecal material (for microbiome analysis) and serial ctDNA samples are being collected. 1) Golan T, Locker GY, Kindler HL: Maintenance Olaparib for Metastatic Pancreatic Cancer. *Reply. N Engl J Med* 381:1492-1493, 2019. 2) Reiss KA, Mick R, O'Hara MH, et al: Phase II Study of Maintenance Rucaparib in Patients With Platinum-Sensitive Advanced Pancreatic Cancer and a Pathogenic Germline or Somatic Variant in *BRCA1*, *BRCA2*, or *PALB2*. *J Clin Oncol* 39:2497-2505, 2021. 3) Tutt ANJ, Garber JE, Geyer CE, Jr.: Adjuvant Olaparib in *BRCA*-Mutated Breast Cancer. *Reply. N Engl J Med* 385:1440, 2021. Clinical trial information: NCT04858334. Research Sponsor: U.S. National Institutes of Health; PANCAN.

TPS4201

Poster Session

A phase 1b, open-label, two-part safety, tolerability, and efficacy study of a soluble beta-glucan (odetiglucon) in combination with a CD40 agonistic monoclonal antibody (CDX-1140) in patients with metastatic pancreatic adenocarcinoma whose disease did not progress during first-line (1L) chemotherapy. *First Author: Mark H. O'Hara, Hospital of the University of Pennsylvania, Philadelphia, PA*

Background: Metastatic pancreatic ductal adenocarcinoma (PDAC) is an aggressive and lethal disease with a 5-year overall survival (OS) rate of 3%. Standard of care treatment is continuous cytotoxic chemotherapy which produces modest improvements in OS but is also associated with significant toxicity raising the need for novel treatment paradigms. Although immunotherapy has yet to produce clinical benefit for most patients with PDAC, preclinical modeling demonstrates its potential and show that combinations of myeloid agonists can trigger robust synergistic anti-tumor activity against PDAC tumors that are otherwise resistant to immunotherapy including immune checkpoint blockade (anti-CTLA4, anti-PD1). In this study, odetiglucon (OD), a novel beta glucan pathogen associated molecular pattern (PAMP), will be combined for the first time with CDX-1140, a fully human Ig2K agonistic monoclonal CD40 antibody in the maintenance setting after an induction phase of cytotoxic chemotherapy. OD and a CD40 agonist directly promote the activation and maturation of antigen presenting cells and shift the suppressive TME to enhance T-cell responses through non-redundant myeloid signaling pathways. We hypothesize that the combination of OD and CD40 agonist therapy has the potential to trigger anti-tumor immunity in PDAC and thus, extend and deepen responses to 1L cytotoxic chemotherapy. **Methods:** A two-part Phase 1b study of metastatic PDAC pts who have evidence of response or stable disease following 16-24 wks of chemotherapy is being conducted. Part A uses a 3+3 design; pts will receive OD 4 mg/kg QW + CDX-1140 1.5 mg/kg Q3W. Following a dose-limiting toxicity observation period, the dose will be held at 1.5 mg/kg or decreased to 0.72 mg/kg Q3W. Once preliminary safety is established, the cohort will be expanded to 15 pts. Part B pts will receive OD 4mg/kg + CDX-1140 at the dose identified in Part A Q3W. The study will enroll 30 pts. Main eligibility criteria: Metastatic PDAC having durable stable disease or response to 1L chemotherapy; serum ABA ≥ 20 μ g/mL, and no prior anti-CD40 mAb or immunomodulatory treatment exposure. Primary endpoints are MTD, RP2D, and safety. Secondary endpoints include DOR, PFS, ORR, and OS and exploratory endpoints include evaluating immune pharmacodynamic responses in peripheral blood and tumor. Safety parameters will be listed and summarized using descriptive statistics. ORR will be tabulated by overall frequency; DOR, TTF, PFS and OS will be summarized and presented using Kaplan-Meier and waterfall plots. 5 US sites will participate. Clinical trial information: NCT04834778. Research Sponsor: HiberCell.

TPS4203

Poster Session

ExoLuminate: An observational registry study for detection of pancreatic adenocarcinoma (PDAC) in high-risk or clinically suspicious patients. *First Author: Harmeet Dhani, Biological Dynamics, Inc., San Diego, CA*

Background: The detection of pancreatic ductal adenocarcinoma (PDAC) at early-stages is critical to improving patient survival. However, the lack of a clinically useful biomarker assay poses a challenge for earlier detection. A liquid biopsy test (ExoVita Pancreas) which uses extracellular vesicles (EV) protein biomarkers has been developed for detection of PDAC. In a previous case-control study of n=715 (75 cases of PDAC Stage I and II, 640 controls), the EV-protein biomarker assay yielded a sensitivity of 96.0% and specificity of 91.1%. By optimizing the assay for high sensitivity, we aim to generate evidence for earlier detection of PDAC in high-risk and clinically suspicious patients in the hope of impacting PDAC patient diagnostic journeys. **Methods:** ExoLuminate is a prospective, multi-center, observational registry study to demonstrate that early detection of PDAC using ExoVita is non-inferior to current standard of care methods of surveillance. The study duration will be 36 months (24-month accrual, 12-month follow-up), with a minimum of 1000 subjects to be enrolled between two cohorts as described below. The first cohort enriches for "high-risk" individuals without a cancer suspicion or diagnosis including those with intraductal papillary mucinous neoplasms (IPMNs), personal or family history of pancreatitis, family member(s) who have at least one first-degree relative affected by pancreatic cancer, patients over 50 years of age with new-onset diabetes (NOD), and germline mutations known to be associated with PDAC. The second cohort includes patients with clinical findings suspicious for early-stage PDAC or those with biopsy-proven PDAC. Patients enrolled in the study will have their blood obtained at six-month intervals. The performance of ExoVita liquid biopsy will be compared to standard-of-care imaging and biomarkers such as CA19-9. Through this registry, which began enrollment in December 2022 and is open for accrual (NCT0562552), we aim to demonstrate the clinical utility of a novel liquid biopsy based on detection of EV-derived biomarkers for early diagnosis of PDAC which can provide credence to a new paradigm in early detection to improve patient outcomes. Clinical trial information: NCT0562552. Research Sponsor: Biological Dynamics, Inc.

TPS4204

Poster Session

Alliance A021806: A phase III trial evaluating perioperative versus adjuvant therapy for resectable pancreatic cancer. *First Author: Akhil Chawla, Northwestern University Robert H. Lurie Comprehensive Cancer Center, Chicago, IL*

Background: The role of neoadjuvant chemotherapy in resectable pancreatic cancer has yet to be defined. Recent phase II trial results demonstrate a median overall survival time (mOS) of only 22.4 months after treatment with perioperative modified FOLFIRINOX (mFOLFIRINOX) with 36% not reaching surgery due to disease progression during neoadjuvant therapy. While potential benefits and shortcomings of neoadjuvant chemotherapy have been well documented, to date, no phase III trial has directly compared a perioperative versus an adjuvant chemotherapy strategy in resectable pancreatic cancer. Alliance for Clinical Trials in Oncology A021806 is an actively accruing randomized controlled phase III trial evaluating the efficacy of perioperative chemotherapy with mFOLFIRINOX in patients with resectable pancreatic cancer. **Methods:** To qualify for enrollment, patients must have biopsy-proven localized resectable pancreatic adenocarcinoma as defined by the National Comprehensive Cancer Network. Patients must have good performance status (ECOG 0 or 1) and be candidates to receive mFOLFIRINOX treatment. All patients enrolled undergo central radiologic eligibility review for quality control and are then randomized to either Arm 1 which consists of 8 cycles of neoadjuvant mFOLFIRINOX followed by 4 cycles of adjuvant mFOLFIRINOX or Arm 2 which includes upfront surgery followed by 12 cycles of adjuvant mFOLFIRINOX. The primary endpoint of the trial is overall survival with secondary endpoints evaluating disease-free survival, margin-negative resection rate, surgical complications, and chemotherapeutic adverse events. Additional correlative endpoints include quality of life and radiomic imaging assessments. A total enrollment of 352 patients is planned from the US and Canada; current enrollment for this trial is at 145 patients. An OS interim analysis will be performed when 50% of the events (124) are observed combining the two arms. If the trial continues after interim analysis, the final OS analysis will be performed with a total of 248 events (combined arms). If the Cox model (stratified by tumor location and ECOG PS) comparing OS between arms produces a one-sided p-value < 0.05, then we will conclude that the OS of the perioperative therapy arm is superior to adjuvant therapy. The Alliance A021806 phase III trial aims to define a new standard of care for patients with resectable pancreatic cancer. Clinical trial information: NCT04340141. Research Sponsor: U.S. National Institutes of Health; U10CA180821, U10CA180882; U10CA180820 (ECOG-ACRIN); U10CA180868 (NRG); U10CA180888 (SWOG).

TPS4205

Poster Session

Targeting minimal residual disease (MRD) in resected RAS mutated pancreatic cancer with vaccine TG01/QS-21 +/- PD-1 inhibitor, balstilimab: A randomized phase II study (TESLA). *First Author: Anup Kasi, University of Kansas Cancer Center, Westwood, KS*

Background: MRD detected by presence of circulating tumor DNA (ctDNA) after intended curative treatment is associated with high risk of relapse in pancreatic cancer. Early treatment of patients with presence of ctDNA after completion of surgery +/- adjuvant therapy may offer an opportunity to clear ctDNA and improve outcomes. TG01 is a RAS-neoantigen peptide vaccine adjuvanted by QS-21 (Stimulon) targeting the seven most frequent codon 12-13 RAS mutations. TG01 has previously demonstrated ability to activate mutant RAS specific CD4+ and CD8+ T-cell responses in vaccinated patients and repeated TG01 dosing in resected pancreatic cancer was found to be well tolerated and associated with a median OS of 33.4 months (95% CI 24.0, 45.8)^{1,2}. Checkpoint inhibitors as single agents have not shown anti-tumor activity in pancreatic cancer, suggesting that a priming agent inducing tumor-specific T-cells may be required to support efficacy. Balstilimab is a human monoclonal antibody targeting programmed cell death protein 1 (PD-1) which is intended to reverse the immunosuppressive effects of this signaling pathway in the context of tumor immuno-surveillance by T-cells. **Methods:** Design: A two-arm, open-label, phase II randomized trial of TG01/QS-21 vaccine or TG01/QS-21 vaccine plus balstilimab (n=12 per arm, N=24) with surgically resected Stage 1-3 RAS mutant PDAC who are MRD+ following completion of standard adjuvant chemotherapy. Assay: MRD is detected by a commercially available ctDNA assay (Signatera, Natera). Somatic variants are identified by whole-exome sequencing of the primary tumor and the matched normal (whole blood) sample and a bespoke assay of up to 16 clonal, somatic variants are generated for each patient. This "tumor signature" will be monitored in plasma throughout the study. Treatment schedule: A priming phase of six vaccine administrations once every two weeks followed by a maintenance phase of administrations once every 8 weeks for up to 51 weeks. Balstilimab will be administered every 2 weeks for up to 51 weeks beginning at week 3. Imaging assessment will be done every 12 weeks. Eligibility: Surgically resected pancreatic adenocarcinoma with pathogenic RAS mutation, and no evidence of recurrent disease on baseline imaging. Inclusion criteria also include ECOG PS 0-1, and positive Signatera ctDNA MRD. Objectives: The primary objective is to assess the 6-month molecular disease control rate as defined by ctDNA stable, decreased or cleared. Secondary objectives include safety of TG01/QS-21 with or without balstilimab, 6 and 12-month DFS rate in each cohort, as well as correlation between the depth of molecular response and DFS. Exploratory: changes in clonality of RAS mutations and assess immune response. Enrollment is ongoing. 1) Gjertsen MK et al. *Int J Cancer* 1997, 72(5) 784-90. 2) Palmer DH et al. *Br J Cancer* 2020 122:971-77. Clinical trial information: NCT05638698. Research Sponsor: Targovax.

TPS4206

Poster Session

STAR-221: A randomized, open-label, multicenter, phase 3 trial of domvanalimab, zimberelimumab, and chemotherapy versus nivolumab and chemotherapy in previously untreated, locally advanced, unresectable or metastatic gastric, gastroesophageal junction, and esophageal adenocarcinoma. *First Author: Samuel J Klempner, Mass General Cancer Center, Boston, MA*

Background: The addition of programmed cell death/ligand protein 1 (PD-L1) inhibitors to standard chemotherapy has improved outcomes in patients with HER2-negative unresectable or metastatic esophago-gastric adenocarcinomas. Current first-line (1L) treatment for these patients comprises FOLFOX (oxaliplatin, leucovorin, and fluorouracil) and CAPOX (capecitabine and oxaliplatin) chemotherapy, with or without the addition of a PD-1 inhibitor. Domvanalimab (dom) is an Fc-silent humanized IgG1 monoclonal antibody (mAb) that blocks T cell Immunoglobulin and ITIM domains (TIGIT), reducing immunosuppression of T/natural killer (NK) cells and promoting antitumor activity. Zimberelimumab (zim) and nivolumab are mAbs that bind to PD-1 on T/NK cells, preventing the immunosuppressive effects of PD-L1 and leading to enhanced immune-mediated tumor cell death. Prior studies (including ARC-7) have demonstrated that the combination of dom + zim is safe, tolerable, and has promising activity in patients with lung cancer and esophago-gastric cancers. This study will investigate whether adding anti-TIGIT therapy to the standard combination of anti-PD-1 therapy and chemotherapy in patients with locally advanced unresectable or metastatic gastric, GEJ, and esophageal adenocarcinoma provides additional clinical benefit. **Methods:** STAR-221 (NCT05568095) is a global, phase 3, randomized, open-label study. Eligible patients are adults with locally advanced unresectable or metastatic gastric, GEJ, or esophageal adenocarcinoma treated in the 1L setting with ≥1 measurable lesion(s) per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Patients with known HER2-positive tumors are not eligible. Approximately 970 patients will be randomized 1:1 into 1 of 2 treatment arms. Patients randomized to Arm A will receive either dom 1600 mg + zim 480 mg every 4 weeks (Q4W) in addition to FOLFOX chemotherapy once every 2 weeks (Q2W) or dom 1200 mg + zim 360 mg once every 3 weeks (Q3W) in addition to CAPOX chemotherapy Q3W. Patients randomized to Arm B will receive either nivolumab 240 mg Q2W + FOLFOX Q2W or nivolumab 360 mg Q3W + CAPOX Q3W. Randomization will be stratified by PD-L1 expression (tumor area positivity [TAP] ≥ 5% vs TAP < 5%), ECOG performance status (0 vs 1), and region (USA, Canada, and EU5 countries vs Asia vs rest of world). The dual primary endpoints are overall survival (OS) in the intent-to-treat population and OS in patients with high PD-L1 expression (TAP ≥ 5%). Secondary endpoints include progression-free survival, objective response rate, duration of response, and safety and tolerability. STAR-221 is currently enrolling globally. Clinical trial information: NCT05568095. Research Sponsor: Arcus Biotech.

LBA4500

Oral Abstract Session

Efficacy and safety of atezolizumab plus cabozantinib vs cabozantinib alone after progression with prior immune checkpoint inhibitor (ICI) treatment in metastatic renal cell carcinoma (RCC): Primary PFS analysis from the phase 3, randomized, open-label CONTACT-03 study. *First Author: Toni K. Choueiri, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA*

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2023, issue of the *Journal of Clinical Oncology*.

LBA4501

Oral Abstract Session

Pembrolizumab plus axitinib versus sunitinib as first-line therapy for advanced clear cell renal cell carcinoma: 5-year analysis of KEYNOTE-426. *First Author: Brian I. Rini, Vanderbilt-Ingram Cancer Center, Nashville, TN*

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2023, issue of the *Journal of Clinical Oncology*.

4502

Oral Abstract Session

Final prespecified overall survival (OS) analysis of CLEAR: 4-year follow-up of lenvatinib plus pembrolizumab (L+P) vs sunitinib (S) in patients (pts) with advanced renal cell carcinoma (aRCC). *First Author: Robert J. Motzer, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: In the phase 3 CLEAR trial, L+P showed clinically meaningful and statistically significant benefits in PFS (primary endpoint) and OS, and improved ORR compared with S in 1L aRCC (Motzer NEJM 2021). Here, we report 4-yr follow-up results from the final prespecified OS analysis of CLEAR (data cutoff: 31 Jul 2022). **Methods:** Treatment-naïve pts (n=1069) who had aRCC with a clear-cell component were randomized (1:1:1) to receive: L 20 mg PO QD + P 200 mg IV Q3W; or L 18 mg + everolimus 5 mg PO QD; or S 50 mg PO QD (4 wks on/2 wks off). Stratification factors were geographic region and MSKCC prognostic risk group. This final prespecified OS analysis was triggered by ~304 death events in 2 arms. OS, PFS, ORR, duration of response (DOR), and PFS on next-line therapy (PFS2) were assessed for L+P and S. PFS, ORR and DOR were assessed per independent review using RECIST v1.1. Nominal P-values are shown. **Results:** At a median follow-up (IQR) of 49.8 mos (41.4–53.1) for L+P and 49.4 mos (41.6–52.8) for S, 149 and 159 deaths had occurred, respectively. OS benefit with L+P vs S was maintained (HR, 95% CI; 0.79, 0.63–0.99). OS favored L+P vs S across MSKCC risk groups (HR, 95% CI; favorable [fav]: 0.89, 0.53–1.50; intermediate [int]: 0.81, 0.62–1.06; poor: 0.59, 0.31–1.12). PFS benefit of L+P vs S was maintained (HR, 95% CI; 0.47, 0.38–0.57). PFS favored L+P vs S across MSKCC risk groups (HR, 95% CI; fav: 0.46, 0.32–0.67; int: 0.51, 0.40–0.65; poor: 0.18, 0.08–0.42). ORR was greater with L+P (71.3%; complete response [CR], 18.3%) vs S (36.7%; CR, 4.8%) (relative risk, 95% CI; 1.94, 1.67–2.26). Less pts in the L+P arm (181/355, 51.0%) received subsequent anticancer therapies compared with the S arm (246/357, 68.9%); 56 (15.8%) and 195 (54.6%) received PD-1/PD-L1 checkpoint inhibitors, respectively. Analysis of OS adjusted for subsequent therapies will be presented. PFS2 was longer with L+P vs S (43.3 vs 25.9 mos; HR, 95% CI; 0.63, 0.51–0.77). Grade ≥3 treatment-related adverse events occurred in 74.1% and 60.3% pts in the L+P and S arms, respectively. **Conclusions:** L+P continues to demonstrate clinically meaningful benefit vs S in OS, PFS, ORR, and CR in the 1L treatment of pts with aRCC at 4-yr follow-up, thus supporting the robustness of the primary analysis data from CLEAR. Clinical trial information: NCT02811861. Research Sponsor: This study was sponsored by Eisai Inc., Nutley, NJ, USA, and Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

4503

Oral Abstract Session

Overall survival (OS) by response to first-line (1L) induction treatment with atezolizumab (atezo) + platinum/gemcitabine (plt/gem) vs placebo + plt/gem in patients (pts) with metastatic urothelial carcinoma (mUC): Updated data from the IMvigor130 OS final analysis. *First Author: Enrique Grande, MD Anderson Cancer Center, Madrid, Spain*

Background: For pts without disease progression during 1L plt-based chemotherapy (chemo), maintenance immunotherapy is a new mUC treatment option. IMvigor130 was a global, randomized Phase III study evaluating 1L atezo + plt/gem (Arm A) vs atezo monotherapy (Arm B) and placebo + plt/gem (Arm C) in patients with mUC (Galsky Lancet 2020). The final analysis showed that improved OS in Arm A vs Arm C of the intention-to-treat (ITT) population did not reach statistical significance (Galsky ASCO 2023). Here we report a post hoc analysis examining OS outcomes by response during atezo/placebo + chemo “induction” based on the final OS analysis. **Methods:** For Arms A and C, per protocol, investigators pre-specified the type of chemo pts received (gem + either cisplatin [cis] or carboplatin [carbo]), which was also a randomization stratification factor. Pts without progressive disease (PD) were allowed to continue atezo or placebo after 4 to 6 cycles of plt/gem. This post hoc analysis evaluated post-induction (Wk 18) OS in pts who completed 4 to 6 cycles of chemo followed by ≥1 dose of atezo or placebo and who had a best response of at least stable disease (SD) without PD at any time (up to and including Wk 18 tumor assessment). Post-progression OS was evaluated in pts who had PD at any time (up to and including Wk 18 tumor assessment). OS analyses by type of chemo were also performed. Multivariable Cox proportional hazards models were used, with HRs adjusted for known prognostic factors (and response for non-PD pts) and stratified by enrollment stage. **Results:** The time from last pt randomized to the data cutoff (Aug 31, 2022) was 49 mo (overall ITT population). OS improvements favoring Arm A vs C appeared greater for pts treated with cis than with carbo. In the cis subgroup, OS rates at 36 mo were 47% (Arm A) and 34% (Arm C) for pts who achieved at least SD during induction. Additional efficacy data are shown. **Conclusions:** In this post hoc analysis, the initial response to induction therapy did not seem to impact OS outcomes. Consistent with prior analyses, these data suggest that cis-treated pts may derive a greater benefit from the addition of atezo than carbo-treated pts. Clinical trial information: NCT02807636. Research Sponsor: F. Hoffman La-Roche.

		Post-induction OS: Pts without PD				Post-progression OS: Pts with PD					
		OS events, %	Median OS, mo	36-mo OS, %	OS HR (95% CI)	OS events, %	Median OS, mo	36-mo OS, %	OS HR (95% CI)		
ITT	A	166	70	20.5	35	0.84	91	92	4.3	6	0.75
	C	152	74	19.6	26	(0.63, 1.10)	93	90	3.3	5	(0.54, 1.05)
Cis	A	57	58	28.4	47	0.68	29	90	6.6	8	0.56
	C	59	68	19.9	34	(0.41, 1.11)	33	91	2.5	9	(0.30, 1.04)
Carbo	A	109	76	18.5	28	0.92	62	94	3.8	5	0.77
	C	93	79	19.6	21	(0.66, 1.29)	60	90	3.4	2	(0.51, 1.17)

4504

Oral Abstract Session

Erdafitinib (ERDA) vs ERDA plus cetrelimab (ERDA+CET) for patients (pts) with metastatic urothelial carcinoma (mUC) and fibroblast growth factor receptor alterations (FGFRa): Final results from the phase 2 Norse study. *First Author: Arlene O. Siefker-Radtke, Department of Genitourinary Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: First-line (1L) therapy for cisplatin (cis)-ineligible pts with mUC remains an unmet need and includes alternative chemotherapy or anti-PD-(L)1 monotherapy for PD-L1 positive tumors. FGFRa tumors are enriched for the luminal 1 subtype with lower immune cell infiltrate and potential lower benefit from anti-PD-(L)1 monotherapy. We studied ERDA+CET in 1L, FGFRa, mUC to determine the potential impact in this setting (NCT03473743). **Methods:** Pts aged ≥ 18 y with mUC, susceptible FGFRa and measurable disease (no prior systemic therapy for mUC, cis-ineligible) were randomized 1:1 to once-daily ERDA 8 mg (with pharmacodynamically guided upitration (UpT) to 9 mg) or ERDA 8 mg (no UpT) + IV CET 240 mg every 2 weeks (wks) at cycles 1–4 and 480 mg every 4 wks thereafter. Primary endpoints were investigator-assessed overall response rate (ORR) per RECIST 1.1 and safety; secondary included duration of response (DOR), time to response (TTR), progression free survival (PFS) and overall survival (OS). There were no pre-planned statistical comparisons between treatment arms. **Results:** As of the data cutoff, 87 pts were randomized and treated; 44 to ERDA+CET and 43 to ERDA: median age was 69 vs 72 y; visceral metastases were present in 60.0 vs 63.6%. Median follow-up time was 14.2 months (mo). ORR for ERDA+CET was 54.5% with 6 (13.6%) CRs and 12 mo OS 68%. 11/24 responders were ongoing. ORR for ERDA was 44.2% with 1 CR and 12 mo OS 56%. 9/19 responders were ongoing. 4 pts in each arm were PD-L1 positive. 3/4 (75%) PD-L1 positive pts responded to ERDA+CET vs 0 for ERDA. The most frequent treatment-emergent AEs (any grade) were hyperphosphatemia (68.9 vs 83.7%), stomatitis (59.1 vs 72.1%) and diarrhea (45.5 vs 48.8%) for ERDA+CET and ERDA respectively. Grade ≥ 3 treatment-related AEs occurred in 45.5 (ERDA+CET) and 46.5% (ERDA) of pts. There was one CET-related death in ERDA+CET secondary to pulmonary failure. **Conclusions:** Combination ERDA+CET demonstrated clinically meaningful activity and was well tolerated. These results, in 1L cis-ineligible pts, support previously described activity of ERDA monotherapy in FGFRa mUC. The safety profile was consistent with the known profile for ERDA and CET with no additive toxicity for the combination. Clinical trial information: NCT03473743. Research Sponsor: Janssen Research & Development.

	ERDA+CET (n=44)	ERDA (n=43)
ORR, % (95% CI)	54.5 (38.8, 69.6)	44.2 (29.1, 60.1)
Confirmed CR, n (%)	6 (13.6)	1 (2.3)
DCR, % (95% CI)	79.5 (64.7, 90.2)	88.4 (74.9, 96.1)
Median DOR (95% CI), mo	11.10 (8.77, NE)	9.72 (4.60, NE)
Median PFS (95% CI), mo	10.97 (5.45, 13.63)	5.62 (4.34, 7.36)

4506

Oral Abstract Session

Adjuvant nivolumab plus ipilimumab vs placebo for patients with localized renal cell carcinoma at high risk of relapse after nephrectomy: Subgroup analyses from the phase 3 CheckMate 914 (part A) trial. *First Author: Robert J. Motzer, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: In part A of the CheckMate 914 trial, adjuvant nivolumab plus ipilimumab (NIVO+IPI) did not improve disease-free survival (DFS) vs placebo (PBO) in patients (pts) with localized renal cell carcinoma (RCC) at high risk of post-nephrectomy relapse (Motzer RJ, et al. *Lancet* 2023). Exploratory analyses were conducted to better understand outcomes in key pt subsets and with early NIVO+IPI discontinuation. **Methods:** Key study inclusion criteria were radical/partial nephrectomy with negative margins > 4 and ≤ 12 weeks before randomization; predominant clear cell histology; pathological TNM stage T2a (grade [G] 3/4) NOMO, T2b-T4 (any G) NOMO, or any pT (any G) N1M0; and no evidence of residual disease/metastases. Pts in part A were randomized 1:1 to NIVO 240 mg Q2W ($\times 12$) + IPI 1 mg/kg Q6W ($\times 4$) or equivalent PBO for 24 weeks or until recurrence/unacceptable toxicity. Primary endpoint is DFS per blinded independent central review. Exploratory analyses assessed DFS by key subsets including Fuhrman grade, sarcomatoid features (yes/no), PD-L1 expression, and NIVO+IPI exposure (≤ 6 cycles [1–2 IPI doses] vs > 6 cycles [3–4 IPI doses]). Safety was assessed by exposure. **Results:** 816 pts were randomized to adjuvant NIVO+IPI (N = 405) or PBO (N = 411). At 37.0 months median follow-up (min, 15.4 months), subset analyses suggested a DFS benefit for NIVO+IPI vs PBO in pts with Fuhrman grade 4 or sarcomatoid features. DFS by PD-L1 expression will be reported in the presentation. Pts who received > 6 NIVO+IPI cycles trended toward improved DFS vs pts receiving ≤ 6 NIVO+IPI cycles. Of the 102 pts who received ≤ 6 NIVO+IPI cycles, 3% had sarcomatoid features, and 20% had Fuhrman grade 4; treatment discontinuation in these pts was due to study drug toxicity (75%), unrelated adverse events (AEs; 6%), pt request (5%), recurrence (4%), consent withdrawal/non-compliance (4%), or other (6%), and most pts receiving ≤ 6 NIVO+IPI cycles were discontinued without initial dose delay (NIVO, 84%; IPI, 89%). In the group of patients who received ≤ 6 NIVO+IPI cycles, grade 1–2 all-cause AEs were reported in 35% of pts (grade ≥ 3 , 63%) and 31% of pts discontinued treatment due to grade 1–2 all-cause AEs (grade ≥ 3 , 44%). **Conclusions:** Exploratory analyses suggest that tumor grade and sarcomatoid features influence outcomes with adjuvant NIVO+IPI. Limited NIVO+IPI exposure (≤ 6 cycles) and discontinuation for low-grade AEs may have contributed to the lack of DFS benefit observed in CheckMate 914 part A. Clinical trial information: NCT03138512. Research Sponsor: Bristol Myers Squibb.

	NIVO+IPI	PBO	DFS HR (95% CI)
Fuhrman grade	1-2	n = 136	0.95 (0.58-1.57)
	2	n = 126	0.97 (0.58-1.62)
	3	n = 189	1.08 (0.73-1.60)
	4	n = 80	0.72 (0.44-1.18)
NIVO+IPI exposure	≤ 6 cycles	n = 102	0.74 (0.48-1.13)
	> 6 cycles	n = 302	–

CI, confidence interval; HR, hazard ratio.

4505

Oral Abstract Session

Study EV-103 dose escalation/cohort A: Long-term outcome of enfortumab vedotin + pembrolizumab in first-line (1L) cisplatin-ineligible locally advanced or metastatic urothelial carcinoma (la/mUC) with nearly 4 years of follow-up. *First Author: Shilpa Gupta, Cleveland Clinic, Cleveland, OH*

Background: Despite available therapeutic options, which include carboplatin-based chemotherapy, PD-1/PD-L1 inhibitor monotherapies, and avelumab maintenance, there is an urgent unmet need for effective and durable 1L therapies for cisplatin-ineligible patients (pts) with la/mUC. Both enfortumab vedotin (EV) and pembrolizumab (P) show survival benefits as monotherapies for pts with previously treated la/mUC. The combination of EV+P previously showed a manageable safety profile and promising antitumor activity in Study EV-103 Dose Escalation/Cohort A (DE/A) and Cohort K. Here, we report updated safety, efficacy per RECIST v1.1 by BICR, survival data, and subsequent therapies for DE/A after nearly 4 years of follow-up. **Methods:** In DE/A of this ongoing phase 1b/2 study, 1L cisplatin-ineligible pts with la/mUC received 3-week cycles of EV 1.25 mg/kg (Days 1, 8) in combination with P (Day 1). The primary endpoint was safety/tolerability. Key secondary endpoints included confirmed ORR (cORR), DOR, PFS (all per RECIST v1.1 by BICR and investigator), and OS. Safety and subsequent therapy results are also presented. **Results:** As of 16 Sep 2022, 45 pts with 1L la/mUC (median age 69 yrs [51-90]) received treatment. All pts discontinued treatment and 18 pts remain on study (median follow-up of 47 months). The cORR by BICR after a median of 9 cycles was 73.3% (95% CI: 58.1, 85.4), with a DCR of 84.4% (95% CI: 70.5, 93.5) and CR rate of 15.6%. The median DOR was 22.1 months (95% CI: 8.38, -), with a 12-month DOR of 63.9% (95% CI: 44.19, 78.17). The median PFS was 12.7 months (95% CI: 6.11, -), with a 12-month PFS of 55.0% (95% CI: 38.84, 68.58). The median OS was 26.1 months (95% CI: 15.51, -), with a 12-month OS rate of 83.4% (95% CI: 68.25, 91.72). The most common treatment-related adverse events of special interest for EV were skin reactions (66.7%), peripheral neuropathy (62.2%), and ocular disorders (40.0%). The most common treatment-emergent adverse events of special interest for P were severe skin reactions (24.4%), pneumonitis (8.9%), colitis (6.7%), and hypothyroidism (6.7%). Sixty percent of pts received subsequent cancer-related therapies, including systemic therapy (48.9%), surgery (8.9%), and palliative radiotherapy (8.9%). The most common 2L systemic anti-cancer therapies were P (17.8%), carboplatin-based therapy (11.1%), and EV (6.7%). **Conclusions:** EV+P, continues to demonstrate promising survival trends with rapid and durable responses in 1L cisplatin-ineligible pts with la/mUC. The safety profile of the combination is manageable and stable with a longer follow-up, and no new safety concerns have emerged. These results are concordant with previously reported DE/A data by investigator assessment and support the evaluation of EV+P in ongoing phase 3 studies in UC. Clinical trial information: NCT03288545. Research Sponsor: Supported by Astellas Pharma US; Merck Sharp & Dohme Corp, a subsidiary of Merck & Co, Inc, Kenilworth, NJ; and Seagen Inc.; U.S. National Institutes of Health.

LBA4507

Oral Abstract Session

Multicenter randomized phase III trial of dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin (dd-MVAC) or gemcitabine and cisplatin (GC) as perioperative chemotherapy for muscle-invasive bladder cancer (MIBC): Overall survival (OS) data at 5 years in the GETUG/AFU V05 VESPER trial. *First Author: Christian Pfister, Rouen University Hospital, Rouen, France*

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2023, issue of the *Journal of Clinical Oncology*.

4508

Oral Abstract Session

SWOG S1011: A phase III surgical trial to evaluate the benefit of a standard versus an extended lymphadenectomy performed at time of radical cystectomy for muscle invasive urothelial cancer. *First Author: Seth P. Lerner, Baylor College of Medicine, Houston, TX*

Background: S1011 tested the hypothesis that an extended lymphadenectomy (ELND) is associated with improved disease-free and overall survival (DFS, OS) compared to standard (S) LND in patients with localized muscle invasive bladder cancer (MIBC) undergoing radical cystectomy (RC)(NCT01224665). **Methods:** Eligible patients with cT2-4a N0-2 were stratified by receipt and type of neoadjuvant chemotherapy (NAC), T2 vs T3-4a and PS 0-1 vs 2. Patients were randomized 1:1 after intraoperative exploration determined they did not have disease outside the pelvis. All patients then underwent a standard bilateral pelvic LND including external and internal iliac and obturator LNs. If randomized to the experimental arm additional ELND up to at least the aortic bifurcation including common iliac (CI), pre-sciatic, and pre-sacral nodes was performed. We hypothesized that patients in the ELND arm would have a 10% improvement in 3-year DFS compared to an estimated 55% for patients in the SLND arm (HR = 0.72). Assuming a 1-sided $\alpha=0.025$ and 85% power, 564 eligible randomized patients were required. Final analysis was to occur at 184 DFS events in the SLND arm or after max follow-up (6 yrs) using a stratified logrank(LR) test with $\alpha=0.022$ to account for interim testing. Hazard ratios from Cox model are adjusted for strat factors. Secondary endpoints included OS and safety. **Results:** 36 surgeons at 27 sites in US and Canada were credentialed prior to enrolling patients, 658 were registered from 8/11-2/17, and 618 eligible patients were randomized to ELND (n=292) or SLND (n=300). Median f/up was 6.1 years in both arms. Median age was 69, 21% female, and 9% non-White. Clinical stage was balanced in both arms: T2 (71%) and T3-4a (29%). NAC was given to 57% in both. Pathologic T stage was <T2 in 39% in S and 37% in E and ³ T2 in 61% and 63%, respectively. Median lymph nodes removed was higher in ELND compared to SLND (41 vs 25), but there was no difference in node metastasis with 26% vs 24%, respectively. More ELND patients had N2 or N3 disease. ELND was associated with increased G3-4 AEs compared to SLND: 16% vs 8%. Deaths within 90 days of RC occurred in 26 (4.4%) patients, including 16 in ELND vs 9 in SLND. There was no difference in DFS between E vs S arms (HR 1.10; 95% CI 0.87, 1.42), 1-sided LR p=0.82. OS results were similar (HR 1.15 95% CI 0.89, 1.48), 1-sided LR p=0.87. **Conclusions:** Patients with MIBC undergoing RC and ELND had increased node yield and higher pathologic N stage, but no significant DFS or OS benefit compared to patients undergoing SLND. ELND was also associated with greater morbidity and higher peri-operative mortality. Clinical trial information: NCT01224665. Research Sponsor: U.S. National Institutes of Health.

Adverse Events	SLND (n=297)	ELND (n=292)
	Grade 3 & 4	Grade 3 & 4
Anemia	61 0	9 0 0
Thromboembolic event	11 1	6 1 1
Ileus	0 0 0	6 1 0
Sepsis	0 3 1	0 7 0
Death NOS	0 0 0	0 0 3
Stroke	0 0 0	0 0 1
Multi-organ failure	0 0 0	0 0 1
Mycardial infarction	0 0 0	0 0 1
Maximum grade any AE	20 4 2	34 12 7

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Poster Discussion Session

Tumour factors and the variation in non-muscle invasive bladder cancer recurrence after transurethral resection surgery between sites: Results from the RESECT study. *First Author: Fortis Gaba, Department of Health Policy and Management, Harvard School of Public Health, Boston, MA*

Background: To determine if there is significant variation in early recurrence after transurethral resection (TURBT) surgery between sites taking part in the RESECT study (NCT05154084) after accounting for tumour characteristics. **Methods:** An international, multi-centre, observational study. A mixed effects logistic regression model with tumour size, tumour number, tumour grade, tumour stage as fixed effects and site as a random effect was fitted. Cases with first, presumed non-muscle invasive bladder cancer (NMIBC) undergoing TURBT were included. Cases were excluded if first check follow up had not been completed. Sites were excluded if they did not have at least 10 cases with first check follow up. Local and/or national approvals or ethical exemptions were obtained prior to commencing the study at participating sites. **Results:** After exclusions, 186 sites (UK: 80; Europe: 59; North America: 18; Asia: 17; Africa 7; South America: 3; Oceania: 2), contributing a total 4597 cases (average 25 cases) were included. Median recurrence rate per site was 12% (IQR 0-22) for low grade tumours and 27% (IQR 13-42) for high grade tumours. After controlling for tumour size, number, stage and grade (all significantly and independently associated with early recurrence) there was significant residual variation attributable to site ($p<0.0001$, intra-class correlation, 0.1). Adjustment for sites improved the regression model from an area under the receiver operating characteristic curve of 0.66 to 0.74. Initial analysis of surgical and peri-operative practice showed wide variation, mean 75% (IQR 66-92) cases per site had detrusor muscle resection and 42% (IQR 17-58) had use of single instillation of intravesical chemotherapy. Other differences in operative and perioperative practice were identified through surveys. **Conclusions:** There is significant variation in the early recurrence rate of NMIBC after TURBT surgery between sites that could not be explained by currently understood tumour features. We have identified differences in surgical technique and perioperative practice that may impact this and further investigation is warranted to understand how these factors impact recurrence rates. Clinical trial information: NCT05154084. Research Sponsor: The Rosetrees Trust, The Urology Foundation Action Bladder Cancer UK, Karl Storz, Photocure, The British Journal of Urology International Charity.

Mixed effects logistic regression for early recurrence after first TURBT for NMIBC.			
Tumour feature	OR	p-value	95% CIc
Diameter (cm)			
<1	1.00		
1-3	1.63	<0.001	1.29-2.08
3-7	2.55	<0.001	1.94-3.33
>7	2.42	0.003	1.34-4.38
No.			
1	1.00		
2 to 3	1.49	<0.001	1.24-1.81
>3	1.92	<0.001	1.56-2.36
Stage			
Ta	1.00		
Tis	2.00	0.015	1.15-3.50
T1	1.90	<0.001	1.57-2.30
Grade			
Low	1.00		
High	1.44	<0.001	1.19-1.73
Constant	0.07	<0.001	0.06-0.09
Random intercept – site	0.36	<0.001	0.23-0.57

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Poster Discussion Session

Long-term outcomes of pembrolizumab (pembro) in combination with gemcitabine (gem) and concurrent hypofractionated radiation therapy (RT) as bladder sparing treatment for muscle-invasive urothelial cancer of the bladder (MIUC): A multicenter phase 2 trial. *First Author: Minas P. Economides, New York University, New York, NY*

Background: Trimodality therapy (TMT) is a standard treatment option for MIUC. We previously reported an early analysis of a phase II study of pembro added to standard TMT with maximal transurethral resection of bladder tumor (TURBT), hypofractionated RT and twice weekly gem (ASCO 2021). Herein we present updated follow up safety and efficacy results. **Methods:** In this multicenter phase 2 trial, patients (pts) with clinical T2-T4aNOMO MIUC who were ineligible for or declined radical cystectomy, had ECOG PS 0/1 and eGFR $\geq$ 30 cc/min were enrolled. Pts received pembro 200 mg IV x 1 followed by maximal TURBT and then whole bladder RT (52 Gy/20 fx) with twice weekly gem 27 mg/m² and pembro Q3 wks x 3 treatments. Response was assessed every 12 weeks post-RT with CT/MRI, tumor bed biopsy and cytology. The primary endpoint was 2-yr bladder-intact disease-free survival (BIDFS); first of MIUC, regional or distant metastases, cystectomy or death). Our study had 85% power to detect a 20% absolute improvement in 2-yr BIDFS rate over 60% historical rate (Mak JCO 2014). Key secondary endpoints included safety, 12-week pathologic complete response (CR) rate, metastases-free survival (MFS) and overall survival (OS). **Results:** Between 5/2016 and 6/2022, 54 pts (median age 74 years, 72% male, 83% Caucasian; clinical stage: 74% T2, 22% T3 and 4% T4) were enrolled at 5 institutions. PD-L1 status was available in 43 pts, and 21 pts (49%) had modified proportion score $\geq$ 10. Forty-six (88%) pts completed all therapy. 1/54 (2%), 3/54 (6%), and 4/54 (7%) discontinued RT/ Gem, Gem or Pembro, respectively, most commonly due to toxicity. 6 pts (11%) underwent salvage cystectomies. As of 6/2022, with a median FU of 23 months (1.6- 62.7) there were 12 (22%) tumor recurrences (3 MIUC, 5 locoregional, 4 distant). 4 pts (7%) had non-muscle invasive only recurrences. The efficacy outcomes are shown. 10 pts died during the study period (18%; 3 from disease progression, 1 from treatment toxicity and 6 from unrelated/ unknown causes). There were no new safety signals in our updated analysis: 13 pts (24%) experienced 17 AEs that were Grade 3 or greater (cytopenias [n=7], colitis [n=5], cystitis [n=2], polyneuropathy, fatigue, hypokalemia [n=1, each]). Grade 3 or greater immune-related AEs included 2 pts with colitis, 1 pt with polyneuropathy and 1 pt with Grade 5 colonic perforation. **Conclusions:** TMT combined with pembro was well tolerated and continues to show promising early outcomes data. A large phase 3 trial is underway to further explore this treatment. Clinical trial information: NCT02621151. Research Sponsor: Merck; pembrolizumab.

ITT population (N=54)	2-year % (95% CI)	Median in months (95% CI)
BIDFS	71 (56-82)	47.4 (29.6-NR)
MFS	78 (64-87)	47.4 (47.4-NR)
OS	83 (69-91)	NR
12 week path CR rate	80%	NA

CI, confidence interval; ITT, intention to treat; NA, not applicable; NR, not reached.

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Poster Discussion Session

Fibroblast growth factor receptor 3 (FGFR3) alterations in PROOF 302: A phase III trial of infigratinib (BGJ398) as adjuvant therapy in patients (pts) with invasive urothelial carcinoma (UC). *First Author: Petros Grivas, Division of Oncology, Department of Medicine, University of Washington, Fred Hutchinson Cancer Research Center, Seattle Cancer Care Alliance, Seattle, WA*

Background: Radical surgery with or without (neo)adjuvant cisplatin-based chemotherapy [(N)AC] is standard in fit pts with muscle invasive UC of bladder (UBC) or upper tract (UTUC). However, recurrence rates are high, underscoring the need for novel therapies. Since up to 70% of UTUC and 20% of UBC tumors were reported to harbor *FGFR3* alterations, targeting this pathway is a rational approach. Infigratinib is a selective *FGFR1-3* inhibitor with efficacy in advanced UC with *FGFR3* alterations [Pal et al. 2018]. PROOF 302 investigated the efficacy and safety of adjuvant infigratinib vs placebo in pts with high-risk invasive UC. **Methods:** PROOF 302 was a global, randomized, double-blind, placebo-controlled, phase III trial for pts with high-risk invasive UTUC or UBC ($\leq$ 15%) with *FGFR3* alteration (i.e. mutation, gene fusion / translocation) with residual ($\geq$ ypT2 and/or ypN+) tumor after NAC, or pts ineligible for, or refusing, cisplatin-based AC, $\leq$ 120 days post-surgery. Pts were randomized 1:1 to infigratinib 125 mg or placebo daily on days 1–21 every 28 days for up to 52 weeks or until recurrence, unacceptable toxicity, or death. Primary endpoint: centrally reviewed disease-free survival (DFS). Secondary endpoints: investigator-assessed DFS, metastasis-free survival, overall survival, safety/tolerability. Exploratory endpoints: QOL, pharmacokinetics, genomic analysis of tumor and cfDNA. Assessment of genomic alterations was pursued using descriptive statistics. **Results:** We present the results of the genomic analysis of radical surgery tissues from pts screened for the trial using the FoundationOne platform. Out of 617 pts screened, 188 (30.5%) had alterations in *FGFR 1-4* genes: 102/237 (43%) in UTUC, 85/369 (23%) in MIBC and 1/11 (9%) with unknown tumor origin. Of these 188 pts, median age 74 (32-90 years), 76% were male, 55% had UTUC, 44% had UBC. Genomic alterations are shown. In UTUC, *FGFR3* had 56% single-nucleotide variations (SNV) and insertions/deletions (INDELS), 40% amplifications and 70% structural variants (SV). In UBC, *FGFR3* had 44% SNV and INDELS, 60% amplifications and 30% SV. **Conclusions:** *FGFR3* alterations were seen in only 19% of all pts screened for PROOF-302, a trial that was enriched for UTUC: 71/237 (30%) of UTUC and 48/369 (13%) of UBC. The trial was stopped early by the sponsor, but the genomic analysis provides insights into the prevalence of *FGFR3* alterations; assessment of correlations with the primary/secondary endpoints is ongoing. The nature and frequency of co-occurring alterations in tissue samples is being investigated to help inform combination therapy strategies and putative resistance mechanisms. Clinical trial information: NCT04197986. Research Sponsor: QED therapeutics.

Known tumor origin	FGFR 1-4 (%)	FGFR1(%)	FGFR2(%)	FGFR3(%)	FGFR4(%)
UTUC	102/237 (43)	15%	20%	67%	10%
UBC	85/369 (23)	30%	11%	55%	4%

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Poster Discussion Session

Impact of histology on the efficacy and safety of pembrolizumab (pembro) monotherapy for advanced urothelial carcinoma (UC) in the phase 3 KEYNOTE-045 and KEYNOTE-361 trials. *First Author: Patrizia Giannatempo, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy*

Background: For patients (pts) with advanced UC, pembro monotherapy has shown antitumor activity as first-line (1L) therapy in the phase 3 KEYNOTE-361 (NCT02853305) study of pembro ± platinum-based chemotherapy (chemo) vs platinum-based chemo and as second-line therapy in the phase 3 KEYNOTE-045 (NCT02256436) study of pembro vs investigator's choice chemo. This exploratory analysis evaluated efficacy and safety of pembro monotherapy by UC histology in KEYNOTE-361 and KEYNOTE-045. **Methods:** KEYNOTE-361 enrolled pts with advanced UC and no prior systemic therapy; KEYNOTE-045 enrolled pts with advanced UC whose disease progressed or relapsed after 1L platinum-based chemo. Pure transitional cell (TC) and mixed predominant TC histology, as assessed by investigator, were allowed. Pembro monotherapy was given at a dose of 200 mg IV Q3W for up to 2 y or until disease progression, unacceptable toxicity, or withdrawal of consent in both studies. End points for this exploratory analysis were ORR, DOR, and PFS per RECIST v1.1 by central radiology assessment, and OS and safety in pts with pure TC or mixed predominant TC allocated to receive pembro monotherapy. **Results:** A total of 307 randomly assigned pts (280 [91.2%] pure TC histology; 27 [8.8%] mixed predominant TC histology) from KEYNOTE-361 and 268 pts (186 [69.4%] pure TC histology; 82 [30.6%] mixed predominant TC histology) from KEYNOTE-045 were included. Median follow-up for both studies was ≥32 mo. PFS, ORR, DOR, and OS for pembro were generally similar in pts with mixed predominant TC histology and pts with pure TC histology. In treated pts, grade 3-5 treatment-related AEs occurred at similar rates in KEYNOTE-361 (17.3% [48/277] pure TC; 18.5% [5/27] mixed predominant TC) and KEYNOTE-045 (16.9% [31/183] pure TC; 17.3% [14/81] mixed predominant TC). **Conclusions:** The observed clinical activity and safety profile of pembro monotherapy was generally consistent irrespective of histology in pts with UC in the KEYNOTE-361 and KEYNOTE-045 studies. Small sample size in some subgroups and limited data available to classify histology subgroups were limitations of this exploratory analysis. Clinical trial information: NCT02256436; NCT02853305. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

	KEYNOTE-361 pure TC (n = 280)	KEYNOTE-361 mixed predominant TC (n = 27)	KEYNOTE-045 pure TC (n = 186)	KEYNOTE-045 mixed predominant TC (n = 82)
ORR, % (95% CI)	29.3 (24.0-35.0)	40.7 (22.4-61.2)	21.0 (15.4-27.5)	24.4 (15.6-35.1)
DOR, median (range), mo*	28.2 (2.1+ to 36.1+)	NR (4.0+ to 30.4+)	19.7 (1.6+ to 60.5+)	NR (2.8+ to 60.1+)
	24-mo: 50.0%	24-mo: 60.0%	24-mo: 47.4%	24-mo: 76.5%
OS, median (95% CI), mo	14.8 (11.8-17.9)	16.2 (5.5-NR)	9.7 (7.5-11.8)	11.6 (7.4-16.4)
	24-mo: 36.8%	24-mo: 44.4%	24-mo: 25.2%	24-mo: 31.5%
PFS, median (95% CI), mo	3.9 (2.3-5.5)	2.2 (2.1-18.0)	2.1 (2.0-2.2)	2.1 (2.0-3.5)
	24-mo: 15.9%	24-mo: 24.2%	24-mo: 11.0%	24-mo: 18.9%

NR, not reached. *+ indicates no PD at time of last disease assessment

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Poster Discussion Session

Outcomes by complete response to first-line pembrolizumab or platinum-based chemotherapy in advanced urothelial carcinoma (UC) in KEYNOTE-361. *First Author: Ozgur Ozyilkan, Adana Baskent Üniversitesi, Adana, Turkey*

Background: In the randomized, open-label, phase 3 KEYNOTE-361 (NCT02853305) study, superior efficacy was not demonstrated with first-line pembrolizumab ± chemotherapy versus chemotherapy in patients with advanced UC. Although not formally tested, survival outcomes appeared similar with pembrolizumab monotherapy versus chemotherapy (hazard ratio [HR] 0.92; 95% CI, 0.77-1.11). This post hoc exploratory analysis examined efficacy outcomes in patients with complete response (CR) to pembrolizumab or chemotherapy in KEYNOTE-361. **Methods:** Patients with advanced UC were randomly assigned 1:1:1 to receive first-line pembrolizumab (200 mg IV every 3 weeks for up to 2 years) ± chemotherapy (1000 mg/m² gemcitabine on day 1 and day 8 + cisplatin [70 mg/m²] or carboplatin [area under the concentration curve of 5 mg/ml/min] on day 1 of each 3-week cycle) or chemotherapy alone. Patients were stratified by PD-L1 combined positive score (≥10 vs <10) and investigator's choice of platinum (cisplatin vs carboplatin). End points of this post hoc exploratory analysis were duration of response (DOR) and progression-free survival (PFS) by RECIST v1.1 by blinded independent central review and overall survival (OS) in patients who achieved a CR in the pembrolizumab monotherapy or chemotherapy arms. **Results:** Overall, 34 of 307 patients (11.1%) in the pembrolizumab arm and 43 of 352 patients (12.2%) in the chemotherapy arm had a CR. Median follow-up (time from randomization to the data cutoff date) for patients with CR was 30.7 months (range, 22.6-42.3). Median DOR was not reached (NR; range, 4.4+ to 36.1+ months) in the pembrolizumab arm and 12.8 months (range, 2.1+ to 36.3+) in the chemotherapy arm; 75.5% and 37.1% of patients, respectively, remained in CR for ≥24 months. Median PFS was NR (95% CI, 30.3-NR) with pembrolizumab and 15.1 months (95% CI, 8.8-NR) with chemotherapy (HR, 0.32 [95% CI, 0.15-0.70]). The estimated 24-month PFS rates were 75.5% and 42.2% in the pembrolizumab and chemotherapy arms, respectively. Median OS was NR (95% CI, NR-NR) with pembrolizumab and NR (95% CI, 25.1-NR) with chemotherapy (HR, 0.20 [95% CI, 0.06-0.70]). The estimated 24-month OS rates were 94.1% and 69.5% in the pembrolizumab and chemotherapy arms, respectively. Overall, 9 patients (26.5%) in the pembrolizumab arm and 21 patients (48.8%) in the chemotherapy arm experienced disease progression after an initial CR. Among patients who achieved CR, 2 patients (5.9%) in the pembrolizumab arm and 22 patients (51.2%) in the chemotherapy arm received subsequent therapy. **Conclusions:** This post hoc exploratory analysis suggests CRs with pembrolizumab were more durable than CRs with chemotherapy in patients with advanced UC, with corresponding longer PFS and OS. Further investigation into patient selection is needed to determine which patients could benefit most from first-line pembrolizumab. Clinical trial information: NCT02853305. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

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Poster Discussion Session

Safety analysis by UGT1A1 status of TROPHY-U-01 cohort 1, a phase 2 study of sacituzumab govitecan (SG) in patients (pts) with metastatic urothelial cancer (mUC) who progressed after platinum (PT)-based chemotherapy and a checkpoint inhibitor (CPI). *First Author: Yohann Lloriot, Institut de Cancérologie Gustave Roussy, Université Paris-Saclay, Villejuif, France*

Background: SG, a Trop-2-directed antibody-drug conjugate, was granted FDA accelerated approval for pts with mUC previously treated with PT-based chemotherapy and a CPI. Approval was based on the pivotal TROPHY-U-01 Cohort 1 study of 113 pts, where SG demonstrated an objective response rate (ORR) of 27%, a median overall survival (OS) of 10.9 mo, and a manageable safety profile (median follow up 9.1 mo [range, 0-19.9], Tagawa et al. JCO 2021). A phase 3 confirmatory study TROPIC-04 (NCT04527991) is ongoing. Here, we report updated safety outcomes by UGT1A1 status. **Methods:** Cohort 1 pts were ≥18 y, had progression of UC following PT and a CPI, and ECOG PS 0-1. Pts received SG 10 mg/kg on D1 and D8 of 21-D cycles (growth factor was allowed per investigator discretion). The primary endpoint was ORR per central review by RECIST 1.1. Post hoc safety analyses were exploratory with descriptive statistics reported. **Results:** As of July 26, 2022, the median follow-up was 10.5 mo (range, 0.3-40.9) for treated pts (N=113). As previously reported, pts were heavily pretreated with a median of 3 prior therapies (78% male; median age 66 y; 66% with visceral metastases). Known baseline comorbidities included chronic kidney disease (12%), coronary artery disease (10%), myocardial infarction (8%), and diabetes mellitus II (8%). Grade (Gr) ≥3 treatment-related adverse events (TRAEs) occurrence and treatment-related discontinuation were consistent with prior reports. In total, 94% of treated pts (n=106) had evaluable UGT1A1 status (wild-type [*1]*11, n=45 [42%]; heterozygous [*1]*28, n=47 [44%]; and homozygous [*28]*28, n=14 [13%]). Gr ≥3 TRAEs occurred in 62% of wild-type, 60% of heterozygous, and 79% of homozygous pts. The incidence of treatment-related any Gr diarrhea was 53%, 72%, and 71%, respectively; any Gr neutropenia was 38%, 55%, and 50%, respectively; and any Gr anemia was 38%, 32%, and 29%, respectively. The incidence of treatment-emergent Gr ≥3 diarrhea was 4%, 15%, and 7%, respectively; Gr ≥3 neutropenia was 31%, 36%, and 50%, respectively; and Gr ≥3 anemia was 13%, 19%, and 29%, respectively. TRAEs led to SG discontinuation in 7%, 6%, and 14% of pts with wild-type, heterozygous, and homozygous status, respectively; incidence of SG interruption was 42%, 43%, and 71%, respectively and incidence of SG dose reduction was 38%, 34%, and 43%, respectively. **Conclusions:** With longer follow-up, SG safety profile was consistent with prior reports. The incidence of adverse events varied across UGT1A1 subgroups, with dose interruptions being more frequently observed in homozygous pts. This was an exploratory analysis with relatively low numbers in each subgroup. Additional studies are needed to confirm the impact of UGT1A1 status on safety outcomes with SG in UC. Clinical trial information: NCT03547973. Research Sponsor: Gilead Sciences, Inc.

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Poster Discussion Session

Estimated net benefit of avelumab (AVE) + best supportive care (BSC) vs BSC alone for patients (pts) with advanced urothelial carcinoma (aUC) using a quality-adjusted time without cancer symptoms or toxicity (Q-TWiST) analysis. *First Author: Thomas Powles, Barts Cancer Institute, Experimental Cancer Medicine Centre, Queen Mary University of London, St. Bartholomew's Hospital, London, United Kingdom*

Background: The JAVELIN Bladder 100 (JB-100) trial (NCT02603432) showed that treatment with AVE first-line maintenance (1LM) + BSC significantly prolonged overall survival (OS) and progression-free survival (PFS) vs BSC alone in pts with aUC that had not progressed after 1L platinum-based chemotherapy. Safety and patient-reported outcomes (PROs) were previously reported. This post hoc analysis used JB-100 data to assess between-treatment differences using a Q-TWiST analysis, an integrated measure that incorporates efficacy, safety, and PROs into a single value. **Methods:** Mean OS was partitioned into 3 health states: time with all-cause grade ≥3 toxicity (TOX) prior to progression, time without all-cause grade ≥3 toxicity or symptoms of disease progression (TwIST), and time after progression or relapse (REL). To ensure equal observation time for each arm, analysis time was restricted to a period of 47.7 months from randomization, which was the shorter follow-up time between arms. A range of utility values were explored and weighted by the time in each health state then summed to estimate Q-TWiST to account for differences in quality of life. Mean between-treatment differences for each health state were also calculated. Bootstrap methods were used to estimate CIs for means and difference between means. **Results:** Time in TOX was slightly longer with AVE + BSC vs BSC alone; however, time spent in TwIST was much longer with AVE + BSC. Time in REL with AVE + BSC appears shorter vs BSC alone because pts experienced more time in the progression-free state, which led to less time in REL. Regardless of the range of utility values explored for each health state, the Q-TWiST estimate was always longer with AVE + BSC, with mean differences ranging from 3.7 to 7.1 months (95% CI not including 1). **Conclusions:** Pts receiving AVE + BSC demonstrated a consistently longer Q-TWiST (vs BSC alone), indicating a net benefit. Pts receiving AVE + BSC achieved greater quality-adjusted time by progressing more slowly (shorter REL) and living longer (greater OS). The Q-TWiST advantage reflects the safety profile of AVE in the context of a survival benefit. Restricted health state durations in months (mean, 95% CI). Clinical trial information: NCT02603432. Research Sponsor: This study was sponsored by Pfizer, as part of an alliance between Pfizer and the healthcare business of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945).

	AVE + BSC n=350	BSC alone n=350	AVE + BSC - BSC alone
TOX	1.81 (1.346, 2.196)	1.19 (0.761, 1.602)	0.61 (-0.013, 1.204)
TwIST	11.98 (10.722, 13.202)	5.52 (4.516, 6.530)	6.46 (4.824, 8.114)
REL	12.99 (11.821, 14.087)	16.72 (14.495, 16.993)	-2.74 (-4.593, -1.195)
PFS	13.79 (12.446, 15.102)	6.71 (5.771, 7.631)	7.07 (5.367, 8.802)
OS	26.77 (25.384, 28.165)	22.44 (21.089, 23.758)	4.34 (2.398, 6.236)

Note: Progression data are based on investigator assessment.

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Poster Discussion Session

Long-term safety of avelumab first-line (1L) maintenance for advanced urothelial carcinoma (aUC) in the JAVELIN Bladder 100 trial. *First Author: Joaquim Bellmunt, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA*

Background: In the phase 3 JAVELIN Bladder 100 trial (NCT02603432), patients (pts) with aUC without progression after 1L platinum-based chemotherapy had significantly prolonged overall survival and progression-free survival with avelumab 1L maintenance + best supportive care (BSC) vs BSC alone. The safety profile of avelumab 1L maintenance was consistent with prior avelumab monotherapy studies, with no new safety signals identified and no detrimental impact on quality of life. Results led to the adoption of avelumab 1L maintenance into international guidelines as standard of care. We report post hoc safety analyses after a minimum 2 years of follow-up. **Methods:** Eligible pts had unresectable locally advanced or metastatic UC without progression after 1L platinum-based chemotherapy. Here, pts who received treatment in the avelumab + BSC arm were analyzed. Trial treatment continued until confirmed progression, unacceptable toxicity, or withdrawal of consent. **Results:** At data cutoff (June 4, 2021), median follow-up in the avelumab arm was 38.0 months. In 344 pts who received ≥ 1 dose of avelumab, median treatment duration was 5.8 months (range, 0.5-49.7) and median number of infusions was 11.5 (range, 1.0-106.0). Treatment-related adverse events (TRAEs) of any grade occurred in 269 pts (78.2%). Grade ≥ 3 TRAEs occurred in 67 pts (19.5%); the most common ($>2\%$) were lipase increased (n=12; 3.5%) and amylase increased (n=8; 2.3%). 40 pts (11.6%) had a TRAE that led to avelumab discontinuation. Immune-related AEs (irAEs) occurred at any grade in 111 pts (32.3%) and at grade ≥ 3 in 26 (7.6%). The most common categories of irAEs (any grade in $>5\%$) were thyroid disorders (n=44; 12.8%) and immune-related rash (n=37; 10.8%); the most common categories of grade ≥ 3 irAEs ($>1\%$) were immune-related rash and hepatitis (each n=5; 1.5%). Serious irAEs occurred in 18 pts (5.2%), of which immune-related nephritis/renal dysfunction (n=4; 1.2%) was the most common category. 21 pts (6.1%) had an irAE that led to avelumab discontinuation; the most common categories ($>1\%$) were immune-related hepatitis and nephritis/renal dysfunction (each n=4; 1.2%). Among 118 pts treated with avelumab for ≥ 12 months, irAEs occurred after 12 months in 27 pts (22.9%), including grade ≥ 3 irAEs in 5 (4.2%). The most common category of irAEs occurring after 12 months (any grade in $>5\%$) was immune-related rash (n=12; 10.2%). No category of grade ≥ 3 irAEs occurred after 12 months in >1 pt. **Conclusions:** Post hoc analyses from JAVELIN Bladder 100 confirm the acceptable long-term safety profile of avelumab 1L maintenance. Grade ≥ 3 TRAEs or irAEs occurred in relatively low proportions of pts, and no new safety signals were identified with longer treatment. These results further support the use of avelumab 1L maintenance until progression as standard of care for pts with aUC without progression after 1L platinum-based chemotherapy. Clinical trial information: NCT02603432. Research Sponsor: This study was sponsored by Pfizer, as part of an alliance between Pfizer and the healthcare business of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945).

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Poster Discussion Session

First-line lenvatinib + pembrolizumab treatment across non-clear cell renal cell carcinomas: Results of the phase 2 KEYNOTE-B61 study. *First Author: Chung-Han Lee, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Lenvatinib (lenva) + pembrolizumab (pembro) is a first-line treatment for advanced clear cell renal cell carcinoma (RCC). Initial results of the single-arm, phase 2 KEYNOTE-B61 (NCT04704219) study showed antitumor activity of lenva + pembro in patients (pts) with advanced non-clear cell RCC who had opportunity for ≥ 24 wk of follow-up (n=82). We report results from the complete cohort of pts enrolled in KEYNOTE-B61 (N=158) with extended follow-up. **Methods:** Adults with previously untreated advanced non-clear cell RCC and measurable disease per RECIST v1.1 received lenva 20 mg PO QD + pembro 400 mg IV Q6W for up to 18 cycles (~2 y). The primary end point was ORR per RECIST v1.1 by blinded independent central review (BICR). Secondary end points included DOR, DCR, and PFS per RECIST v1.1 by BICR; OS; and safety. Histology was assessed by investigator (assessment by central review is planned). **Results:** Of 158 treated pts, 93 (59%), 29 (18%), and 21 (13%) had papillary, chromophobe, and unclassified histology, respectively. Additionally, 6 pts (4%) had translocation and 9 (6%) had other histology. 70 pts (44%) had IMDC favorable risk and 88 (56%) had intermediate/poor risk. Median follow-up was 14.9 mo (range 8.7-19.7). ORR was 49% (95% CI, 41-57; 9 CRs [6%]; 69 PRs [44%]). DCR was 82% (95% CI, 75-88). Median DOR was not reached (NR; range, 1.5+ to 15.3+ mo). By Kaplan-Meier estimate, 75% of responders had a response for ≥ 12 mo. ORR and DCR by histology are shown in the table. For the IMDC favorable risk group, ORR was 51% (95% CI, 39-64) and DCR was 87% (95% CI, 77-94). For the IMDC intermediate/poor risk group, ORR was 48% (95% CI, 37-59) and DCR was 78% (95% CI, 68-86). In all pts, median PFS and OS were 17.9 mo (95% CI, 13.5-NR) and NR (95% CI, NR-NR), respectively; 12-mo rates were 63% and 82%. Treatment-related AEs (TRAEs) occurred in 149 pts (94%) and were consistent with results from other studies. The most common ($\geq 30\%$) TRAEs were hypertension (n=90; 57%), diarrhea (n=69; 44%), and hypothyroidism (n=58; 37%). Grade 3-4 TRAEs occurred in 81 pts (51%). Overall, 17 pts (11%) discontinued pembro, 14 (9%) discontinued lenva, and 5 (3%) discontinued both drugs because of TRAEs. No deaths occurred because of TRAEs. **Conclusions:** In pts with advanced non-clear cell RCC enrolled in KEYNOTE-B61, lenva + pembro showed antitumor activity with no new safety signals. These data support the use of lenva + pembro as first-line treatment for pts with non-clear cell RCC, regardless of histology. Clinical trial information: NCT04704219. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA and Eisai Inc., Nutley, NJ, USA.

	Total n=158	Papillary n=93	Chromophobe n=29	Unclassified n=21	Translocation n=6	Other n=9
ORR, % (95% CI)	49 (41-57)	54 (43-64)	28 (13-47)	52 (30-74)	67 (22-96)	56 (21-86)
DCR, % (95% CI)	82 (75-88)	85 (76-92)	69 (49-85)	90 (70-99)	83 (36-100)	78 (40-97)
CR, n (%)	9 (6)	8 (9)	0 (0)	0 (0)	0 (0)	1 (11)
PR, n (%)	69 (44)	42 (45)	8 (28)	11 (52)	4 (67)	4 (44)
SD, n (%)	52 (33)	29 (31)	12 (41)	8 (38)	1 (17)	2 (22)
PD, n (%)	17 (11)	9 (10)	4 (14)	2 (10)	1 (17)	1 (11)

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Poster Discussion Session

The impact of surgery on patients with VHL-associated tumors: An international patient survey. *First Author: Murali Sundaram, Merck & Co., Inc., Rahway, NJ*

Background: Von Hippel-Lindau syndrome (VHL) is a rare hereditary neoplastic disorder caused by mutations in the *VHL* gene. Treatment (tx) options for patients are limited to multiple surgeries dispersed between regular scans, watchful waiting and txs that preserve organ function. **Methods:** An international, cross-sectional survey comprising patients in the United States (US), Canada (CA), the United Kingdom (UK), France (FR), and Germany (DE) was conducted. Patients were recruited via the VHL Alliance; data were collected between Dec 2021 and May 2022. For inclusion, patients must have renal cell carcinoma (RCC), pancreatic neuroendocrine tumors (pNET), and/or central nervous system hemangioblastoma (CNS-Hb). Data collected included demographics, impact of most recent surgery on aspects of condition (1-7 scale 1 being greatly worsened and 7 being greatly improved), tx goals (top 3 goals from a list of 11), and patient preference in treatment. Patients were presented two scenarios "watch and wait" and potentially need surgery, or "take a once-daily pill" to delay a potential surgery. **Results:** 220 patients (68.2% female, median age 40.0, median disease duration 15.8 years) in the US (n=108), CA (n=37), the UK (n=21), FR (n=3), and DE (n=51) completed the study. 146 patients reported RCC (66.4%), n=122 reported pNET (55.5%), and n=190 reported CNS-Hb (86.4%). Among the top 4 symptoms experienced by patients were kidney cysts (n=82, 37.3%), numbness (n=59, 26.8%), dizziness (n=56, 25.5%), and fatigue/low energy (n=54, 24.5%). 205 (93.2%) patients had experienced surgery; n=171 (77.7%) had experienced multiple surgeries (median number of surgeries, 4.0). 166 patients recorded data on their most recent surgery. Of these, patients reported that their most recent surgery worsened (scored 1-3) their fatigue (51.8%), mental health (51.2%), and ability to go about daily life (45.2%). 47.3% of patients selected reduce the number of surgeries as a top tx goal, 46.4% selected being able to go about life as usual, 36.8% delay the need for surgery, and 33.2% improved quality of life. 73% of patients indicated they would prefer to take a pill which would possibly delay the time until surgery, rather than watch and wait to see if the tumor would grow. **Conclusions:** Surgery negatively impacts the lives of patients, leading to a worsening in their fatigue, mental health, and ability to go about daily life. Almost half of patients would like a treatment that reduces the number of surgeries, and over a third would like a treatment that delays the need for surgery. Nearly three quarters of patients would prefer to take a pill that might delay the need for surgery. Tx options that reduce the need for surgery would benefit this patient group. Research Sponsor: Merck & Co.

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Poster Discussion Session

Efficacy of first-line (1L) immunotherapy (IO)-based regimens in patients with sarcomatoid and/or rhabdoid (S/R) metastatic non-clear cell renal cell carcinoma (nccRCC): Results from the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC). *First Author: Chris Labaki, The Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute and Brigham and Women's Hospital, Boston, MA*

Background: Patients with advanced RCC with S/R components exhibit poor clinical outcomes. IO-based combination therapies demonstrated substantial efficacy among patients with metastatic S/R ccRCC, compared to VEGF targeted therapy (VEGF-TT). Recent trials showed promising activity of IO-based regimens in patients with advanced nccRCC. We sought to assess the efficacy of IO regimens among patients with S/R nccRCC. **Methods:** Patients with advanced nccRCC treated with 1L IO regimens (IO/IO or IO/VEGF-TT) or 1L VEGF-TT monotherapy (sunitinib or pazopanib) were included. Cases were categorized as S/R or non-S/R. The primary outcomes were overall survival (OS) and time to treatment failure (TTF) in patients with S/R nccRCC receiving 1L IO or VEGF-TT. Overall response rate (ORR) was a secondary outcome. OS and TTF were compared between groups (IO vs. VEGF-TT) using Cox regression models adjusted for age, IMDC risk groups, and nccRCC subtype. ORR was compared between groups (IO vs. VEGF-TT) using a logistic regression adjusted for the same confounders. **Results:** Overall, 103 patients with S/R nccRCC were included, of whom 33 (32%) received 1L IO regimens. Median follow-up was 31 months. After adjustment for confounding factors, patients with S/R nccRCC treated with IO regimens presented with significantly improved survival outcomes as compared to those receiving VEGF-TT (median OS [mOS]: NR vs. 7.1 and mTTF: 9.4 vs. 2.9 mos for IO regimens and VEGF-TT, respectively). Similarly, a higher ORR was seen in patients with S/R nccRCC receiving IO regimens versus VEGF-TT (34.1 vs. 10.9%, respectively). Among 430 patients with non-S/R nccRCC (IO regimens: n=44), no significant differences in survival outcomes between regimen classes were seen (mOS: 24.4 vs. 14.8 and mTTF: 4.2 vs. 5.0 mos for IO regimens and VEGF-TT, respectively). **Conclusions:** To our knowledge, this represents the largest effort to characterize the outcomes of patients with S/R nccRCC treated with IO regimens. Patients with S/R nccRCC appear to derive a substantial and selective benefit from IO regimens (vs. VEGF-TT). These data support the use of IO-based regimens in patients with S/R nccRCC. Research Sponsor: None.

OS, TTF and ORR in patients with S/R and non-S/R nccRCC treated with 1L IO regimens vs. VEGF-TT.									
	Median OS – IO regimens, mos (95%CI)	Median OS – VEGF-TT, mos (95%CI)	Adjusted HR (95%CI)	Median TTF – IO regimens, mos (95%CI)	Median TTF – VEGF-TT, mos (95%CI)	Adjusted HR (95%CI)	ORR – IO regimens, %	ORR – VEGF- TT, %	P- value*
S/R nccRCC (N=103)	NR (19.3-NR)	7.1 (3.9-13)	0.25 (0.13- 0.49)	9.4 (2.8-NR)	2.9 (2.2-4.3)	0.34 (0.21- 0.59)	34.4	10.9	0.006
Non-S/R nccRCC (N=430)	24.4 (16.6-NR)	14.8 (12.7-18.1)	0.74 (0.46- 1.21)	4.2 (2.8-12.9)	5.0 (4.4-5.7)	1.20 (0.85- 1.71)	22.5	17.5	0.94

*Logistic regression.

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Poster Discussion Session

Phase II study of cabozantinib (Cabo) with nivolumab (Nivo) and ipilimumab (Ipi) in advanced renal cell carcinoma with variant histologies (RCCvh). First Author: Bradley Alexander McGregor, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA

Background: New therapeutic approaches in RCCvh are needed. Herein, we report on treatment intensification with the combination of Cabo/Nivo/Ipi in patients with metastatic RCCvh in a multi-institutional prospective single arm phase II trial. (NCT04413123). **Methods:** Eligible patients (pts) had metastatic RCCvh with ECOG performance status of 0-1 and may have received one line of prior therapy excluding immunotherapy or Cabo. Pts underwent a baseline biopsy and received treatment with Nivo 3 mg/kg and Ipi 1 mg/kg intravenously Q3 weeks (W) for 4 cycles followed by Nivo 480 mg IV Q4W. Cabo was given continuously at dose of 40 mg daily; reductions to 20 mg daily and 20 mg every other day were allowed. The primary endpoint was objective response rate (ORR) by RECIST 1.1. Safety was a secondary endpoint. **Results:** 40 pts have been enrolled. At the time of data cut-off (Dec 9, 2022), 38 pts received at least 1 study drug. 11% (n=4) pts received prior systemic therapy. 45% (n=17) received all 4 doses of Nivo and Ipi; 18% (n=7) received 3 and 37% (n=14) received ≤ 2 doses. 61% (n=23) (15 of whom received 4 cycles Nivo/Ipi) received Nivo maintenance (median number of cycles, 5 (range, 1-21)). 71% (n=27) and 13% (n=5) required Cabo dose reduction to 20 mg and 20 mg every other day, respectively. Median follow-up was 8.4 (range, 2.1-23) months. Objective response was achieved in 8 pts (ORR 21%, two-sided 80% CI, 13%-32%). Median duration of response was not reached with 5 pts maintaining response > 6 months. Median progression-free survival was 8.9 (95% CI, 4.2-12.7) months. 74% (n=28) developed treatment-related grade 3 or higher toxicities; 37% (n=14) developed $\geq$ grade 3 elevation in AST or ALT. 29% (n=11) required high dose steroids (prednisone ≥ 40 mg daily or equivalent). 13% (n=5) discontinued all study drugs due to toxicity. No grade 5 toxicity has been reported. **Conclusions:** The study suggests activity for this combination in patients with RCCvh particularly among those without chromophobe histology. An additional cohort of 20 pts is enrolling with Cabo starting dose of 20 mg daily. Clinical trial information: NCT04413123. Research Sponsor: Exelixis, BMS.

	Total (N=38) N (%)	Histology					Prior Systemic Therapy		Sarcomatoid differentiation	
		Papillary (N=19)	Chromophobe (N=11)	Translocation (N=5)	Unclassified (N=1)	Other (N=2)	No (N=34)	Yes (N=4)	No (N=29)	Yes (N=9)
PR	8 (21%)	6	1		1	0	8	0	5	3
SD	19 (50%)	9	4	4	0	2	17	2	17	2
PD	9 (24%)	4	5	0	0	0	7	2	6	3
NE	2 (5%)	0	1	1	0	0	2	0	1	1

PR=partial response, SD=stable disease, PD=progressive disease, NE=not evaluable.

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Poster Session

Effect of KDR mutations on efficacy of immune checkpoint inhibitors in patients with bladder cancer. First Author: Honghai Dai, Shandong Provincial Hospital, Jinan, Shandong, China

Background: KDR (kinase insert domain receptor) is the most important VEGF (vascular endothelial growth factor) receptor that mediates the signaling transduction initiated by the VEGF ligands. VEGF signaling can activate angiogenesis which plays a crucial role in tumor growth, metastasis, and treatment response. Here we explore the relationship between KDR mutation and its efficacy of immune checkpoint inhibitors (ICIs) in patients with bladder cancer. **Methods:** To explore the association between KDR mutations and the efficacy of ICIs in bladder cancer patients, we collected clinical and mutation data of 215 patients who received ICIs (PD-(L)1 and/or CTLA-4 inhibitors) from MSKCC cohort. Gene expression data and WES mutation data of 413 samples in the TCGA database were obtained from the UCSC Xena for analysis of the differences of potential biological mechanisms between KDR-mutant and KDR-wildtype tumors. TMB was calculated as the total number of somatic non-synonymous mutations per megabase. CIBERSORT was applied to infer 22 immune cell type proportions in TCGA advanced bladder cancers. **Results:** In MSKCC cohort, we observed 5.6% (12/215) samples had KDR mutation. Survival analysis showed that KDR-mutant patients had longer overall survival (OS) than that of wildtype patients (hazard ratio (HR) = 0.27, 95% CI: 0.07-1.09, logrank test P = 0.048); median OS (not reached versus 15 months). Then we compared the TMB between KDR-mutant and KDR-wildtype tumors, the results showed that KDR-mutant group had higher TMB in MSKCC cohort (median [IQR]: 17.58 [11.64-47.81] versus 7.90 [4.92-14.76], P=0.002) and TCGA cohort (median [IQR]: 10.69 [5.87-19.85] versus 4.60 [2.52-8.08], P=0.001). Analysis of 22 immune cell subsets in the TCGA advanced bladder cancers, B cells naive, plasma cells and macrophages M1 were significantly abundant in KDR-mutant tumors (all P < 0.05). **Conclusions:** In ICI-treated bladder cancers, KDR mutation is associated with prolonged OS, higher TMB and activated antitumor immunity, which suggests that KDR mutation may serve as a potential biomarker to guide ICI therapy in bladder cancer. Research Sponsor: None.

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Poster Session

Age-, sex-, and race-related differences in outcomes of patients with muscle-invasive bladder cancer treated with radical cystectomy: The role of biology versus access to standard medical care. First Author: Akshay Sood, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: It remains unclear whether the poor outcomes associated with older age, female sex, and African-American (AA) race in patients with muscle-invasive bladder cancer (MIBC) treated with surgery are due to differential access to standard medical care or intrinsic differences in tumor biology. **Methods:** We designed an integrative study using two complementary datasets to answer our question. We used the SEER-Medicare MIBC dataset (n=2,327) to evaluate the real-world differences in survival outcomes among patients of female v male sex, AA v Caucasian race, and older v younger age before and after adjusting for demographic, tumor, treatment, and access-to-care factors. Next, we used The Cancer Genome Atlas (TCGA) project's MIBC dataset (n=410) to evaluate the biological differences in molecular profiles of bladder tumors in these patient groups. Biological endpoints examined included DNA-level genomic alterations, mRNA expression subtypes, and RPPA-derived proteomic profiles, and clinical endpoints assessed included unadjusted and adjusted cancer-specific mortality (CSM) outcomes. Multivariable GLM, multivariate MMLR, and Fine-Gray competing-risk models were used. **Results:** Population-level analysis demonstrated that patients of female sex (10-y CSM: 51.3% v 43.8%, Gray's p<0.001), AA race (10-y CSM: 56.2% v 46.1%, Gray's p=0.022) and older age (10-y CSM: 47.8% $\geq$ 81 y v 44.1% $\leq$ 70 y, Gray's p=0.032) had worse CSM at presentation. In adjusted analyses, however, only female sex remained associated with worse CSM (HR=1.17, p=0.028). The TCGA analysis revealed that advanced age was associated with increased total mutational burden and neoantigen load, both of which have been associated with improved survival. No other age-related differences were seen in other DNA alterations, mRNA expression subtype distribution, or RPPA proteomic cluster profiles. Similarly, no racial differences were observed in molecular alterations either at the DNA-, RNA-, or protein-level. However, females were noted to have adverse molecular profiles across all levels of molecular expression i.e. DNA-, RNA-, and proteomic-level. Specifically, females were noted to have lower total mutational burden (in stage 3-4 cancers, median 170 v 240, p=0.01), lower neoantigen load (in stage 3-4 cancers, median 382 v 551, p<0.01), higher Msi2 DNA mutational signature (in stage 3-4 cancers, 65.3% v 50.5%, p=0.04), higher basal/sq mRNA subtype (in stage 3-4 cancers, 52% v 34.2%, p=0.02), and lower RPPA cluster1 subtype (in stage 2 cancers, 15.2% v 36%, p<0.01). **Conclusions:** Our findings suggest that the poor outcomes seen among patients of AA race and older age in the real-world are likely driven by multilevel biases in healthcare delivery, while in women they may be a result of a combination of biological and access-to-care factors. Research Sponsor: Wayne B. Duddleston Professorship in Cancer Research to Ashish M. Kamat.

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Poster Session

Prognostic significance of pretreatment immune cell infiltration in muscle-invasive bladder cancer treated with definitive chemoradiation: Analysis of NRG RTOG 0524 and 0712. First Author: Matthew Pierre Deek, Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ

Background: Chemoradiation therapy (CRT) is an organ conserving approach in the treatment of locally advanced bladder cancer. Chemoradiation is thought to potentially result in immunogenic stimulation, and bladder cancer is often a tumor with high immune cell infiltration. Thus, we aimed to profile the tumor immune microenvironment of bladder cancer and identify prognostic immune biomarkers for CRT response by profiling tumor samples from NRG/RTOG 0524 and 0712, two prospective trials of CRT in muscle-invasive bladder cancer (MIBC). **Methods:** Pretreatment tissue samples from both trials were profiled using Cofactor Genomics ImmunoPrism, an RNA sequencing assay that uses gene expression profiles to quantify immune cell populations in the tumor microenvironment (TME). Differential gene expression was estimated for different immune cell type proportions across samples. Kaplan-Meier survival analysis and log rank tests were performed to evaluate differences in overall survival (OS) stratified by genes influenced by immune cell proportions or genes associated with immune response signatures. **Results:** A total of 70 samples (43 from RTOG 0524 and 27 from RTOG 0712) underwent analysis using the ImmunoPrism assay. Immune cell proportions were as follows: CD8 T cells: median 1.2%, CD4 T cells: median 0.8%, Treg cells: median 9.2%, CD19 B cells: median 5.1%, M2 macrophages: median 0.8%, M1 macrophages: median 0%. Unbiased clustering based on gene expression profiles driven by immune cell proportions demonstrated two groups: cluster 1 with a low percentage of immune cells and shorter OS (median 31 months) and cluster 2 with a high percentage of immune cells and longer OS (median 101 months, p = 0.036). Higher expression of genes associated with T cell infiltration (CD8A and ICOS) was associated with improved OS (104 vs 35 months, p = 0.028, HR = 0.48 (0.25 - 0.94), p = 0.031) as was higher expression of IDO1, which is associated with the interferon gamma pathway (104 vs 35 months, p = 0.042, HR = 0.49 (0.24 - 0.99), p = 0.046). **Conclusions:** Bladder tumors have a wide range of immune cell infiltration in the TME. Increased immune cell proportions are prognostic for OS following CRT, as well as a higher expression of genes associated with T cell infiltration interferon gamma signaling. These findings have implications for the integration of immunotherapy in the definitive management of MIBC; and can be explored further in the ongoing NRG/SWOG 1806 trial. Research Sponsor: NRG.

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Poster Session

Determinants of resistance to nivolumab (nivo) monotherapy investigated through genomic and transcriptomic analysis of renal cell carcinoma (RCC) tumors from the HCRN GU16-260 study. *First Author: David A. Braun, School of Medicine, Yale University, New Haven, CT*

Background: Nivo monotherapy demonstrated anti-tumor activity in treatment-naïve RCC in Part A of HCRN GU16-260 across all IMDC groups and in multiple histologies. Patient tumor samples were collected to characterize the tumor-immune microenvironmental determinants of effective anti-tumor immunity with nivo. **Methods:** Whole exome sequencing (WES) was performed on formalin-fixed, paraffin-embedded tissue collected within one year prior to nivo. For single-cell RNA-sequencing (scRNA-seq), eligible patients (pts) with any RCC histology underwent tumor biopsy prior to and/or at resistance to nivo monotherapy. Gene expression signatures discovered through scRNA-seq were used to interrogate previously published bulk transcriptomic data of nivo in the treatment-refractory setting. **Results:** WES analysis (n = 96 tumors) identified recurrent focal amplifications within chromosome 11q13 (amp11q13), which was observed in 6 of 18 (33.3%) of tumors from pts with progressive disease (PD) compared to 0 of 20 (0%) of tumors from pts with complete or partial response (CR/PR; p = 0.005). amp11q13 was associated with worse progression free survival (PFS; p = 0.008) and overall survival (OS; p = 0.010). ScRNA-seq was performed on tumors from 17 pts (8 with baseline only, 7 with progression only, and 2 with paired baseline and progression samples) across 7 trial sites. Trajectory inference analysis of tumor-infiltrating T cells revealed a bifurcating structure, starting with naïve T cells and ending either in terminally exhausted CD8+ T cells or *SLAMF7*+ CD8+ T cells. Surprisingly, the *SLAMF7*+ T cell population expressed high levels of cytotoxic genes (including *GZMA*, *GZMB*, *GNLY*) and markers of tissue residency (*ZNF683*/HOBIT and *ITGAE*/CD103). Of the 14 pts with at least 100 sequenced tumor-infiltrating T cells, the presence of a higher percentage of *SLAMF7*+ CD8+ T cells (relative to total T cells) was associated with primary resistance to nivo (mean percentage in PD [n = 4] pts 32.7%; stable disease [n = 4] pts, 9.1%; CR/PR [n = 6] pts, 2.2%; p = 0.019 for CR/PR vs PD). Of 172 pre-treatment tumors from the nivo arms of the CheckMate-009/010/025 trials that we analyzed by bulk RNA-seq, a signature score derived using genes expressed in the *SLAMF7*+ CD8+ T cell trajectory branch was enriched in pts with PD compared to CR/PR as best response (p = 0.032). **Conclusions:** Bulk genomic and single-cell transcriptomic analyses uncovered somatic alterations (amp11q13) and infiltrating T cell populations (*SLAMF7*+ CD8+) associated with resistance to frontline nivo monotherapy in a phase II study in RCC. Additional independent and functional validation studies are in progress. Research Sponsor: Department of Defense CDMRP KCRP.

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Poster Session

A phase I/II study to evaluate the safety, pharmacodynamics, and efficacy of entinostat in combination with atezolizumab and bevacizumab in patients with renal cell carcinoma. *First Author: Roberto Pili, University at Buffalo, Buffalo, NY*

Background: Immunosuppressive factors such as regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs) limit the efficacy of immunotherapies. We have previously reported that histone deacetylase (HDAC) inhibitors have antitumor effects in combination with PD-1 inhibition by inhibiting the function of Tregs and MDSCs in preclinical models. We hypothesized that HDAC inhibition may enhance or resensitize patients (pts) with renal cell carcinoma (RCC) to immunotherapy. Thus, we conducted a Phase I/II clinical study with the HDAC inhibitor entinostat in combination with the immune checkpoint inhibitor atezolizumab and the VEGF inhibitor bevacizumab in RCC pts, either treatment naïve or previously treated with immune checkpoint inhibitors. **Methods:** The primary objective was to evaluate the safety, tolerability, and efficacy of this combination strategy in a Phase I/II clinical trial. This clinical study was composed of a Dose Finding Phase (Phase I) and a two-stage Phase (Phase II) portion. Due to unforeseen circumstances, enrollment was halted during Stage I of the Phase II portion. In the Phase I dose finding cohorts, according to the 3+3 standard design, pts received oral entinostat at 1 mg (dose level or dl1), 3 mg (dl 2), or 5 mg (dl 3) every 7 days, continuously, with atezolizumab at a dose of 1,200 mg/kg IV every three weeks in combination with bevacizumab at a dose of 15 mg/kg IV every 3 weeks. Phase II patients were split into two distinct cohorts: Cohort A (no prior treatments with PD-1 or PD-L1 inhibitors) and Cohort B (at least one prior treatment with a PD-1 or PD-L1 inhibitor for metastatic disease). Pts treated at dl3 were included in the Phase II efficacy analyses. **Results:** 31 pts (18 and 13 pts during Phase I and II, respectively) were enrolled. Phase I was completed with the following DLTs: hypertension (3) in dl1, encephalopathy and hyponatremia (dl2), pneumonitis and pruritis (dl3). Dl3 was established as the recommended phase II dose. The most common treatment-related toxicities were thrombocytopenia, hypophosphatemia, proteinuria, diarrhea, fatigue, and neutropenia. A total of 21 grade ≥3 events were observed. Nine pts achieved a partial response in Cohort A and one patient in Cohort B with an ORR 60% (CI 32.3-83.7) and 33.3% (28.2-56.4), respectively. According to Simon's optimal two-stage design, the ORR met the Stage I primary objective. The median PFS was 13.7 months (CI 8.7-21.3) in Cohort A and 9.8 months (CI 1.3-NE) in Cohort B. We have collected blood samples to conduct several correlative studies on peripheral blood mononuclear cells. **Conclusions:** The preliminary results from this study suggest that the combination of entinostat and atezolizumab plus bevacizumab is relatively well tolerated and may be active in pts with ccRCC. Clinical trial information: NCT03024437. Research Sponsor: Genentech, Syndax.

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Poster Session

Biomarker-driven prospective clinical trial in renal cell carcinoma: Developing machine learning models to allocate patients to treatment arms using RNA sequencing. *First Author: Anupama Reddy, Vindhya Data Science, Durham, NC*

Background: RNA sequencing has shown promise in defining the biology of individual renal cell carcinoma (RCC) tumors. However, these biomarkers have not yet been translated to the clinic for prospectively assigning optimal treatments to patients. Challenges for RNA-seq biomarker development include translating classifiers across different assays/platforms, normalization of data collected from single patients in the clinic and establishing robust thresholds for assigning prediction groups. We have designed the prospective phase II OPTIC RCC clinical trial (clinicaltrials.gov NCT05361720) to test the utility of an RNA-seq based biomarker in predicting treatment based on biologic drivers relevant to angiogenesis (anti-angiogenesis; TKI) and immune microenvironment (immunotherapy; IO). Here, we will describe the development and optimization of a machine learning model for assigning individual patients to biologically driven clusters in real time to facilitate RNA-seq based biomarker trials. **Methods:** We have utilized RNA-seq data from the IMmotion 151 trial (ref) to develop a machine learning model. Clusters were grouped into three based on their association to tumor biology and treatment: (1) Cluster 1+2 (angiogenic signature → TKI+IO therapy), (2) Cluster 4+5 (immune/proliferative signature → dual IO therapy), (3) Cluster 3+6 (neither signature → exclude). Random forest classifier was used to train a multi-class model to predict the three groups. The model is evaluated using bootstrapped cross-validation. **Results:** Our machine learning classifier was built using 188 genes and has a cross-validation accuracy of 85% and sensitivity of >90% in predicting patients into one of the three biological clusters from our training data. Predictions of the classifier are significantly associated with progression-free survival across different treatments within each of the predicted groups. We also observed significant odds ratios when comparing responders (CR/PR/SD) to non-responders (PD) across the treatment groups. The model was then validated in two independent test sets treated with Angio and IO inhibitors: (1) 61 patient renal cell carcinoma cohort (2) 12 patient clear cell renal cell carcinoma cohort. We observed a significant enrichment of responders to Angio+IO treatment for the predicted Cluster_Angio patients compared to IO treatment (p=0.05), highlighting the importance of matching patients to their optimal treatment. **Conclusions:** We have developed an accurate machine learning model to assign individual patients to RNA-seq clusters in real time. This classifier will facilitate the prospective OPTIC RCC trial. If successful, our biomarker strategy will serve as a proof of concept for selecting optimal treatments for RCC patients. Research Sponsor: Department of Defense.

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Poster Session

Health-related quality of life (HRQoL) of risk-based patient subgroups with advanced renal cell cancer (aRCC) treated with nivolumab plus cabozantinib (NIVO+CABO) vs sunitinib (SUN) in the CheckMate 9ER trial. *First Author: David Cella, Robert H. Lurie Comprehensive Cancer Center, Northwestern University, Chicago, IL*

Background: In CheckMate 9ER, NIVO+CABO improved or maintained HRQoL vs SUN in previously untreated aRCC. We report an exploratory analysis of HRQoL in International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk-based subgroups treated with NIVO+CABO vs SUN in CheckMate 9ER (minimum follow-up, 36.5 mo). **Methods:** Subgroups were stratified by IMDC categories of favorable (F) risk (score = 0) or intermediate/poor (I/P) risk (score = 1–6) at randomization. HRQoL was evaluated using Functional Assessment of Cancer Therapy–Kidney Symptom Index (FKSI-19). Changes from baseline (BL) through wk 151 were analyzed using mixed-model repeated measures (MMRM). Bother due to treatment side effects (FKSI-19 item GP5) was assessed using a generalized estimating equations model (response dichotomized as minimal [“not at all” or “a little bit”] vs notable [“somewhat,” “quite a bit,” or “very much”]). Cox proportional hazards (CPH) modeling was used to evaluate time to confirmed deterioration (TTCD). **Results:** Differences in least square means (LSM) for FKSI-19 scores through wk 151 indicated HRQoL benefit in the NIVO+CABO arm over the SUN arm for I/P-risk patients (n = 505) but not for F-risk patients (n = 146). In the I/P-risk subgroup, longitudinal analysis of FKSI-19 total scores indicated that HRQoL improved through wk 151 in the NIVO+CABO arm but decreased from BL in the SUN arm. HRQoL declined from BL through wk 151 in F-risk patients in the NIVO+CABO and SUN arms. Patients were less likely to be bothered by side effects of NIVO+CABO vs SUN regardless of risk (I/P-risk odds ratio [OR], 0.50; 95% CI, 0.34–0.75; F-risk OR, 0.51; 95% CI, 0.28–0.91). TTCD analysis of FKSI-19 scores of the I/P-risk subgroup indicated that the NIVO+CABO arm had lower deterioration risk than the SUN arm. For the F-risk subgroup, risk based on FKSI-19 total scores was similar for both treatment arms. **Conclusions:** Compared with SUN, NIVO+CABO improved or maintained HRQoL in I/P-risk patients and had less side effect bother in all subgroups. There were no significant differences between treatment arms for F-risk patients. Clinical trial information: NCT03141177. Research Sponsor: Bristol Myers Squibb.

MMRM and CPH analyses of FKSI-19 scores: NIVO+CABO vs SUN ^a				
IMDC risk subgroup	FKSI-19 total or subscale	LSM difference ^b (95% CI)	Hazard ratio for TTCD (95% CI)	
I/P-risk (n = 505)	Total	3.33 (1.96-4.70)	0.58 (0.44-0.76)	
	Disease-related symptoms (DRS)	1.59 (1.01-2.18)	0.55 (0.40-0.76)	
	DRS-physical (DRS-P)	2.12 (1.27-2.96)	0.51 (0.37-0.70)	
	Functional well-being (FWB)	0.54 (0.09-0.98)	0.58 (0.41-0.81)	
F-risk (n = 146)	Total	-0.44 (-2.63 to 1.75)	0.99 (0.64-1.54)	
	DRS	0.15 (-0.67 to 0.97)	1.09 (0.66-1.82)	
	DRS-P	0.04 (-1.21 to 1.30)	0.78 (0.47-1.27)	
	FWB	-0.52 (-1.30 to 0.26)	1.03 (0.61-1.73)	

^aThrough wk 151. ^bPositive value favors NIVO+CABO over SUN; negative value indicates deterioration.

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Poster Session

Effect on outcomes of toxicity-related dose reduction in TKI monotherapy or TKI-IO combination therapy for advanced renal cell carcinoma. *First Author: Giacomo Nuvoletta, Department of Experimental, Diagnostic, and Specialty Medicine, S.Orsola-Malpighi University Hospital, Alma Mater Studiorum University of Bologna, Bologna, Italy*

Background: Tyrosine kinase inhibitors (TKI) in monotherapy or TKI in combination with immunotherapeutic agents (IO) are standard of care first-line treatment for advanced or metastatic renal cell carcinoma (RCC). Dose reduction due to toxicity is extremely frequently and represents an important clinical management issue, with frequent dose reduction, treatment suspension and change of schedule. We examined the outcomes of patient treated with TKI in monotherapy and in combination with immunotherapy (TKI-IO). **Methods:** We performed a retrospective analysis of clinical outcomes in patients with RCC treated with TKI (cohort 1) or TKI-IO (cohort 2) in Italian and Spanish institutions. A descriptive analysis was performed. Univariate logistic regression models were carried out to estimate the association between best response (CR or PR vs SD or PD) and type of TKI (monotherapy or combination therapy). Survival curves were estimated using the Kaplan-Meier method and were compared by the log-rank test. Cox proportional-hazard models were used to obtain hazard ratios (HRs) with 95% Median follow-up was calculated using the reverse Kaplan-Meier method. **Results:** A total of 401 patients were divided in cohort 1 (329 patients) and cohort 2 (72 patients). Median Follow-up was 81.22 months in cohort 1 and 19.02 months in cohort 2. Most frequent toxicities that lead to dose reduction were mucositis (20.13%), Asthenia (16.88%) and Hand-foot syndrome (15.58%). Overall Response Rate was higher in patients that reduced dose, both in cohort 1 (48% vs 29%, $p < 0.01$) and cohort 2 (81% vs 40%, $p < 0.01$). In cohort 1 Progression Free Survival (PFS) was longer in patients with dose reduction (27.14 months vs 16.59 months) (HR 0.77 [0.6; 0.98]; $p = 0.04$). Overall Survival (OS) was also improved (55 months vs 34.17) (HR 0.71 [0.53; 0.93]; $p = 0.01$). In cohort 2, both PFS (39.13 months vs 41.3 months) (HR 0.63 [0.27; 1.48]; $p = 0.29$) and OS (39.13 months vs 55.85 months) (HR 0.65 [0.26; 1.63]; $p = 0.29$) did not statistically differ between patients that reduced dose and patients that did not reduce dose. **Conclusions:** TKI dose reduction due to toxicity seems to be related to improved outcomes, both in ORR and PFS/OS. ORR was statistically improved in both cohort 1 and cohort 2. PFS and OS in cohort 1 favoured patients that experienced dose reduction. PFS and OS in cohort 2 did not show a statistically significant difference, probably due to the short follow-up and small number of patients. However, outcomes seem to show a trend toward favouring patients that reduce dose. Research Sponsor: None.

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Poster Session

Real-world outcomes among patients with advanced/metastatic renal cell carcinoma (mRCC) treated with cabozantinib or other tyrosine kinase inhibitors (TKIs) after checkpoint inhibitor (CPI) therapy. *First Author: Daniel Yick Chin Heng, University of Calgary, Calgary, AB, Canada*

Background: CPI-based therapy is the first-line standard of care for patients with mRCC, but effectiveness data for subsequent targeted therapies are limited. Cabozantinib, a multi-targeted TKI, is indicated for patients with mRCC in the USA and may be prescribed after doublet CPI therapy. **Methods:** Retrospective study of cabozantinib vs other TKI treatment after CPI therapy for mRCC using the US Oncology Network electronic health record database and chart review. Patients initiated TKI therapy between May 1, 2016 and Nov 30, 2021, immediately after CPI therapy. The primary endpoint was real-world response rate over the first 6 months of treatment (wRRR_{6months}) based on physician assessment (complete response (CR): documented CR/indication of remission/disappearance of all lesions/no evidence of disease, or partial response (PR): documented PR/improved disease/responding disease). Covariates were adjusted by inverse probability of treatment weighting. Noninferiority was assessed using a 90% confidence interval (CI) and 10% noninferiority margin; if noninferiority was met, superiority was evaluated using a 95% CI and chi-square test. **Results:** In total, 485 patients were included. Baseline characteristics were similar for the cabozantinib and other TKIs subgroups, including proportions of patients with ≥ 2 metastatic sites (74.7% vs 68.2%) and metastases in bone (45.0% vs 43.5%), brain (8.8% vs 7.1%), liver (18.1% vs 19.5%), lung (35.0% vs 44.2%) and lymph nodes (38.7% vs 31.8%). At 6 months, tumor assessment data were available for 75.5% of patients (cabozantinib, 79.8% of cabozantinib and 66.2% of other TKIs, 66.2%) patients. Adjusted wRRR_{6months} was 62.5% for cabozantinib and 46.0% for other TKIs (rate difference: noninferiority, 16.5% [90% CI, 9.3–23.7], $p < 0.0001$; superiority, 16.5% [95% CI, 7.8–25.1], $p = 0.0002$). **Conclusions:** In patients with mRCC receiving standard of care treatment in the USA, cabozantinib was effective post-CPI therapy, including in patients without prior TKI therapy. Difference in adjusted wRRR_{6months} significantly favored cabozantinib vs other TKIs. These data may inform global jurisdictions that restrict cabozantinib to the post TKI setting. Research Sponsor: Ipsen.

	Cabozantinib (n = 331)	Other TKIs (n = 154)
Age, median (95% CI) yrs	66.6 (65.3–67.6)	68.6 (66.4–70.8)
Men, %	72.8	75.3
ECOG PS ≥ 2 , %	18.1	11.0
IMDC risk: poor / intermediate / favorable / missing, %	13.3 / 31.7 / 4.2 / 50.8	7.8 / 29.2 / 1.9 / 61.0
Prior nephrectomy, %	71.9	70.1
Time from RCC diagnosis to first systemic mRCC therapy, median (95% CI) months	10.0 (5.9–14.8)	5.8 (2.4–13.7)
Treatment line: 2L / 3L / ≥ 4 L, %	32.3 / 46.5 / 21.1	36.4 / 48.1 / 15.6
2L treatment after: ipilimumab + nivolumab / pembrolizumab or nivolumab, %	26.3 / 6.0	24.7 / 11.7
Follow-up from TKI initiation, median (95% CI) months	13.2 (11.4–15.2)	12.4 (10.2–16.7)

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Poster Session

CASSIOPE: A prospective noninterventional study of cabozantinib treatment following prior vascular endothelial growth factor (VEGF)-targeted therapy in patients with advanced renal cell carcinoma (aRCC). *First Author: Michael D. Staehler, University of Munich, Muenchen, Germany*

Background: Cabozantinib is a tyrosine kinase inhibitor approved as monotherapy for aRCC in the USA, and as first-line therapy for patients with intermediate or poor risk aRCC, or after previous VEGF-targeted therapy in Europe. In the METEOR trial, a substantial proportion of patients required cabozantinib dose modifications. We report a real-world study of cabozantinib use for aRCC. **Methods:** CASSIOPE was a non-interventional prospective cohort study (conducted Apr 2018–May 2022; NCT03419572). Enrollment spanned 11 European countries (91 sites) where cabozantinib is marketed for aRCC. Patients had aRCC and had received ≥ 1 prior VEGF-targeted therapy (excluding cabozantinib). Decision to initiate cabozantinib was made prior to enrolment. The primary endpoint was cabozantinib usage (dose interruptions, reductions or discontinuations due to AEs) in the second- (2L) or later- (≥ 3 L) line settings. Secondary endpoints included objective response rate (ORR), progression-free survival (PFS), overall survival (OS) and tolerability. Data were analyzed descriptively for patients with safety follow-up after ≥ 1 cabozantinib dose. **Results:** In total, 679 patients were included (73.0% male; median [range] age 67.0 [29–93] yrs; 85.7% clear-cell aRCC; 80.3% prior nephrectomy). Median (range) observation period was similar for 2L (n = 335; 8.51 [0.2–15.4] mo) and ≥ 3 L cabozantinib (n = 343; 9.26 [0.0–15.0] mo). Usage data are shown. For the overall population, ORR (95% CI) and median (95% CI) PFS according to local assessment were 21.9% (17.5%–26.9%) and 7.8 (6.3–8.7) mo for 2L cabozantinib, and 38.0% (32.7%–43.5%) and 8.7 (7.6–9.6) mo for ≥ 3 L cabozantinib. Median OS (95% CI) was 13.0 (12.6–not calculated [NC]) mo for 2L, and 17.1 (13.8–NC) mo for ≥ 3 L cabozantinib. Most patients (90.4%) reported treatment-related AEs (Grade 1, 71.1%; Grade 2, 70.3% of patients), most commonly any grade diarrhea (52.4%), palmar-plantar erythrodysesthesia syndrome (27.2%), decreased appetite (25.5%), hypertension (21.9%), asthenia (21.6%), fatigue (20.5%) and nausea (20.3%). **Conclusions:** In this real-world study, tolerability of ≥ 2 L cabozantinib was consistent with the METEOR trial safety profile: cabozantinib dose modifications due to AEs were common, but discontinuation rates due to AEs were substantially less frequent. Cabozantinib activity was maintained across lines. Clinical trial information: NCT03419572. Research Sponsor: Ipsen.

	Initiated cabozantinib at 60 mg/day	
	2L n = 237	≥ 3 L n = 196
Dose modification due to adverse events (AE), n (%)	181 (76.4)	153 (78.1)
Dose reduction due to AE, n (%)	134 (56.5)	112 (57.1)
Dose interruption due to AE, n (%)	126 (53.2)	104 (53.1)
Dose discontinuation due to AE, n (%)	54 (22.8)	49 (25.0)
Cabozantinib daily dose, median (range)	47.8 (17.7–60.0)	44.2 (7.8–60.0)
Dose modification due to cabozantinib-related AE, n (%)	164 (69.2)	140 (71.4)

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Poster Session

Use of real-world evidence to benchmark clinical trial results: A case study in von Hippel-Lindau (VHL) disease. *First Author: W. Marston Linehan, National Cancer Institute, Bethesda, MD*

Background: Data from a natural history study can be used to benchmark results from single arm trials with comparable ascertainment of exposures and outcomes. Despite limitations of externally controlled trials, natural history study data can provide important information, especially when clinical trial results provide compelling evidence of change in the established progression of disease. Such results could include partial or complete response for patients receiving drug in a disease where spontaneous regression is not observed. The aim was to conduct a natural history study to benchmark results of a Phase 2 single-arm trial (LITESPARK [LS]-004) for a new HIF-2a inhibitor (belzutifan) using comparable RECIST-based study endpoints. After a median follow-up of 37.8 months, the objective response rate (ORR) for patients with renal cell carcinoma (RCC) in LS-004 was 64.0% (95% CI: 50.6 to 75.8). **Methods:** A study of existing electronic medical records was conducted for VHL patients with disease-associated RCC undergoing active surveillance at the US National Cancer Institute. VHL patients with ≥ 1 cm solid RCC, confirmed by independent review, were followed until death or last encounter. Additional LS-004 exclusion criteria were applied to define the natural history study cohort: ≥ 3.0 cm tumor and procedure performed within 60 days, prior systemic oncologic therapy, and metastasis prior the index date. The index date was the date of the earliest radiology report with measurable disease during the study window (July 2004 - June 2020). An analysis of radiographic outcomes was performed according to RECIST V1.1 for patients with ≥ 3 scans prior to last encounter, death, or renal therapy using an imaging charter similar to LS-004. Adjudication of best overall response (BOR) was performed if there was discordance between assessments by the two independent radiologists. **Results:** The natural history study population included 244 VHL patients (100% genetic confirmation; 55% male; median age: 41 years, median follow-up: 10 years). The median size of largest RCC tumor diameter at baseline was 2.5 cm (IQR: 1.9, 3.1), and 76% of patients had ≥ 1 surgery after the index date. Among patients with ≥ 3 scans (n=178/244), the confirmed real-world ORR within 5 years of follow-up was 1.8% (95% CI: 0.4%, 5.2%), all with partial response. The real-world BOR was progressive disease and stable disease for 22% and 74% of patients, respectively. Within 5 years, 80% of patients had disease progression. **Conclusions:** Using similar trial endpoints, this natural history study demonstrates that spontaneous regression of RCC solid tumors is unlikely for patients with VHL undergoing active surveillance in the absence of therapy, and most patients experience disease progression. These findings help contextualize the antitumor activity and efficacy of belzutifan in the treatment of patients with VHL disease-associated RCC. Research Sponsor: Merck Sharp & Dohme LLC.

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Poster Session

Head-to-head effectiveness and safety of pembrolizumab plus axitinib vs. nivolumab plus ipilimumab in metastatic renal cell carcinoma in the United States. *First Author: Dvir Aran, Faculty of Biology, Technion-Israel Institute of Technology, Haifa, Israel*

Background: Two main first-line combination therapies for metastatic renal cell carcinoma (mRCC) are pembrolizumab plus axitinib (P+A) and nivolumab plus ipilimumab (N+I). No head-to-head clinical trial comparing these treatments has been performed, and the available real-world data (RWD) on their effectiveness is limited. Here, we used RWD to compare the overall survival and posttreatment hospitalization rates of mRCC patients receiving P+A vs. N+I. **Methods:** We included mRCC patients treated with N+I or P+A between 6/2018 and 3/2022, utilizing data from Elevance Health administrative claims and clinical data from AIM Cancer Care Quality Program. Inverse probability of treatment weighting (IPTW) was used to adjust for age, sex, socioeconomic deprivation index (SDI), ECOG performance status (PS), Charlson Comorbidity Index (CCI), and metastatic sites. Real-world overall survival (rwOS) was defined from first treatment until death or last claim and was estimated using weighted Kaplan-Meier method. Favorable risk was defined based on PS (<2) and with a treatment initiated less than 1 year from diagnosis. **Results:** We identified 764 mRCC patients, of them 483 were treated with N+I (63%). The P+A group was slightly older (p=0.08), while other features were similar in both groups. Survival analysis using IPTW showed a borderline significant advantage of P+A vs. N+I (p-value=0.07). Inspection of the Kaplan-Meier curves suggested that P+A provides short-term survival benefit: 12-month rwOS was 86% for P+A vs. 77.8% for N+I (p<0.001), while at 24-months, where power was lower, the curves almost converged (rwOS: 68% in P+A vs. 65% in N+I; p=0.52). In a subset of patients with favorable risk (N=69 P+A, N=68 N+I), the P+A survival improvement extended to at least 24-months (p=0.06). Finally, the N+I group had significantly higher rates of posttreatment hospitalizations (3-months after treatment initiation) compared to the P+A group (31.9% vs. 19.6%; p-value<0.001). **Conclusions:** Our retrospective cohort study suggests that P+A may provide short-term survival benefits over N+I, and this benefit is extended in patients with favorable risk. P+A is also associated with fewer post-treatment hospitalizations. We argue that the higher toxicity of N+I may explain its lower short-term effectiveness and may also explain its lower effectiveness in patients with favorable risk. Research Sponsor: Carlon Digital Platforms.

Baseline characteristics of mRCC individuals who received P+A or N+I treatments.				
	P+A	N+I		P-Value
N	281	483		
Gender, n (%)	64 (22.8)	111 (23.0)	F	1.000
Age, mean (SD)	58.7 (7.4)	57.6 (7.9)		0.078
SDI, mean (SD)	42.6 (25.6)	44.2 (27.6)		0.421
PS, n (%)			0	0.358
	121 (43.1)	231 (47.8)	1	
	146 (52.0)	225 (46.6)	2	
	14 (5.0)	27 (5.6)		
CCI, mean (SD)	0.9 (1.1)	0.9 (1.1)		0.587
No. metastatic sites, n (%)	>=2	306 (63.4)		0.903
	1	177 (36.6)		

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Poster Session

Phase 2 study of batiraxcept (AVB-S6-500, an AXL inhibitor) as monotherapy, in combination with cabozantinib (cabo), and in combination with cabo and nivolumab (nivo) in patients with advanced clear cell renal cell carcinoma (ccRCC). *First Author: Katy Beckermann, Vanderbilt-Ingram Cancer Center, Nashville, TN*

Background: AXL is up-regulated by hypoxia-inducible factor-1 signaling in VHL-deficient tumor cells, playing a critical role in metastasis and resistance to VEGF-targeted therapies. Batiraxcept is a recombinant fusion protein containing an extracellular region of AXL combined with the human immunoglobulin G1 heavy chain (Fc), demonstrating potent and specific AXL inhibition through competitive binding of its ligand GAS6. A prior Phase 1b study showed promising outcomes for batiraxcept + cabo combination in patients who had failed first line (1L) therapy. **Methods:** This trial tested batiraxcept 15 mg/kg every 2 weeks (q2w) in 3 cohorts of ccRCC patients: 1) batiraxcept monotherapy (n=10) in patients with relapsing disease and no curative options; 2) batiraxcept + cabo 60 mg daily (QD) in patients with at least 1 prior therapy (n=25); and 3) batiraxcept + cabo 40 mg QD and nivo 240 q2w or 480 mg q4w in 1L (n=11). Primary endpoint was investigator assessed objective response rate (ORR) by RECIST v1.1, and key secondary endpoints were safety, progression free survival (PFS), and overall survival. **Results:** Enrollment has completed as of 17-January-2023. In the 3 cohorts, IMDC intermediate + poor risk was 80%, 76%, and 27%, and median prior lines of therapy were 4, 2, 0. Prior immunotherapy (IO) was received by 100%, 88%, and 0% patients. One hundred percent of patients receiving monotherapy and 40% of 2L patients receiving batiraxcept + cabo had received prior VEGF-TKIs. We describe efficacy and safety across the 3 cohorts. **Conclusions:** Batiraxcept monotherapy was well tolerated but had limited clinical activity. Batiraxcept-based combinations demonstrated efficacy and tolerability. Given encouraging safety and efficacy signals, batiraxcept + cabo will be further studied in a phase 3 trial of 2L+ccRCC patients whose disease has progressed on prior IO and VEGF-TKI treatment. Exploratory analysis for a baseline serum soluble AXL/GAS6 ratio biomarker was found to have predictability for clinical activity in the phase 1b study evaluating batiraxcept + cabo in patients who had failed 1L therapies; a similar analysis using the biomarker is ongoing for this patient population. Clinical trial information: NCT04300140. Research Sponsor: Aravive, Inc.

	Batiraxcept monotherapy N=10	Batiraxcept + Cabo N=25	Batiraxcept + Cabo + Nivo N=11
ORR (CR + PR confirmed), n (%)	0	9 (36)	6 (55)
(95% CI)	0, 30	18.0, 57.5	16.7, 76.6
Clinical Benefit Rate (ORR+stable disease), n (%), (95% CI)	1 (10)	18 (72)	7 (64)
	0.3, 44.5	50.6, 87.9	30.8, 89.1
mPFS months (95% CI)	1.8 (0.5, 3.7)	7.2 (4.9, NE)	7.6 (2.0, NE)
Censor (n), Events (n)	1, 9	17, 8	6, 5
All batiraxcept related AEs*, n (%)	8 (80)	17 (68)	10 (91)
Grade ≥ 3 batiraxcept related AEs, n (%)	1 (10)	7 (28)	5 (45)

*All cohorts ≥ 20%: Diarrhea, fatigue, and infusion-related reaction.

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Poster Session

Preliminary results from a phase II study comparing sunitinib alone or with stereotactic body radiotherapy (SBRT) for newly diagnosed oligometastatic renal cell carcinoma. *First Author: Yang Liu, Department of Radiation Oncology, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Sun Yat-Sen University Cancer Center, Guangzhou, China*

Background: Although SBRT has become an option for oligometastatic renal cell carcinoma (oligoRCC), current trials supporting SBRT haven't been adequately persuasive given their single-arm, non-first-line design. Our study aimed to explore if SBRT improves oncologic outcomes compared with standard first-line systemic therapy in oligoRCC. **Methods:** This an open-label, double-arm phase II controlled trial enrolling treatment naïve oligoRCC patients (pts), defined as ≤ 5 metastatic lesions (ChiCTR1800017136). No liver or brain metastasis was allowed. Nephrectomy was mandatory before enrollment. Pts were allocated 1:1 to receive either sunitinib alone (control arm) or sunitinib plus SBRT (SBRT arm). Sunitinib was started as 50 mg daily for 4 weeks, followed by 2 weeks off treatment. SBRT was delivered to all metastatic sites within 2 months after sunitinib initiation, with 35-50Gy in 5 fractions. Primary endpoint was objective response rate (ORR); secondary endpoints were disease control rate (DCR), progression-free survival (PFS), overall survival (OS) and safety. Data from pts with ≥ 1 year of follow-up were reported this time. **Results:** Starting in 2018, the trial has currently completed its accrual, with 48 pts enrolled. Forty-two pts had ≥ 1 year of follow-up and were evaluable for the present analysis. PT characteristics for SBRT and control arms: median age 51 vs 59 years (p=0.094); synchronous metastasis 31.8% vs 10.0% (p=0.179); clear cell carcinoma 77.3% vs 80.0% (p=1.000); IMDC low or intermediate risk 86.4% vs 80.0% (p=1.000); solitary metastasis 45.5% vs 25.0% (p=0.167). Thirty-four sites received SBRT, most frequently to bone (61.8%) and soft tissue (17.6%) metastasis. The 1-year local control rate after SBRT was 93.8%. ORR (81.8% vs. 25.0%, p=0.000) and DCR (90.9% vs. 60.0%, p=0.047) were significantly higher in SBRT arm than those in control arm. The 1y-PFS was 72.7% for SBRT arm and 35.0% for control arm (HR 0.33, 95% CI 0.16-0.69, p=0.003). And the 1y-OS was 95.5% for SBRT arm and 80.0% for control arm (HR 1.06, 95% CI 0.31-3.67, p=0.923). Grade 3-4 treatment-related AEs occurred in 66.7% and 62.5% pts in SBRT arm and control arm (p=0.763), respectively. SBRT-related Grade 3-4 toxicity included radiation enteritis (n=1, grade 3) and radiation pneumonitis (n=1, grade 3). **Conclusions:** Our results showed promising efficacy and acceptable toxicity of SBRT plus sunitinib when compared with sunitinib alone for oligoRCC. Complete results are awaited in 2023 after follow-up completion of the entire cohort. Clinical trial information: ChiCTR1800017136. Research Sponsor: None.

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Poster Session

Immune landscape of patients with metastatic non-clear cell renal cell carcinoma (nccRCC) treated with atezolizumab plus bevacizumab. *First Author: Renee Maria Saliby, Dana-Farber Cancer Institute, Boston, MA*

Background: The treatment of metastatic nccRCC remains an area of unmet clinical need. A multicenter phase II trial of atezolizumab/bevacizumab in patients with advanced nccRCC or any RCC type with ≥ 20% sarcomatoid differentiation (NCT02724878) demonstrated clinical activity of these agents, with objective response rates of 50% in patients with sarcomatoid clear-cell RCC (sccRCC) and 26% in patients with nccRCC. We aim to understand the intratumoral and circulating factors that impact immunotherapy response in this population. **Methods:** We collected blood samples prior to therapy and on-treatment (following 2 cycles of therapy) and quantified levels of plasma soluble factors (cytokines and growth factors) using a fluorescent bead array platform. We used high dimensional flow cytometry on peripheral blood mononuclear cells to analyze the composition and phenotype of peripheral immune cells. Immunohistochemistry and immunofluorescence were performed on available formalin-fixed, paraffin-embedded tumor tissue samples (archival or on-study biopsy) collected prior to the start of therapy. We assessed relationships between biomarkers and outcomes using pairwise Wilcoxon rank-sum test and log-rank tests, and univariate Cox regression models. **Results:** We collected blood samples from 60 patients with paired tumor samples from 38 patients. Baseline circulating inflammatory cytokines MIP-1b, IL-1, MCP-1, IL-6, and IL-13 were highly correlated with one another, forming an "inflammatory module" that was increased in IMDC-poor risk patients and associated with worse progression-free survival (PFS) (p = 0.028). At baseline, elevated circulating VEGF-A was associated with a lack of response (p=0.03) and worse PFS (p=0.021). Whereas a larger increase in on-treatment levels of circulating VEGF-A was associated with clinical benefit as defined by Braun et al. (Nat Med. 2020) (p=0.01) and improved overall survival (p=0.006). Among peripheral immune cell populations, an on-treatment decrease in circulating PD-L1+ T cells was associated with improved outcomes: reductions in CD4+ PD-L1+ (HR:0.62[0.49-0.91], p=0.016) and CD8+ PD-L1+ T cells (HR:0.59[0.39-0.87], p=0.009) correlated with improved PFS. Within the tumor, a higher percentage of terminally exhausted (PD-1+, TIM-3+ and/or LAG-3+) CD8+ T cells at baseline was associated with worse PFS (p=0.028). **Conclusions:** Among patients with advanced nccRCC or sccRCC, a baseline high systemic inflammatory state and high circulating VEGF-A are associated with worse outcomes after treatment with atezolizumab and bevacizumab. High levels of intratumor terminally exhausted CD8+ T cells were associated with worse PFS. These results highlight the importance of an integrative approach to explore biomarkers of response in advanced variant histology RCC which may inform future therapeutic approaches. Research Sponsor: Genentech-Roche.

4536

Poster Session

Unique molecular underpinnings by genetic ancestry in localized clear cell renal cell carcinoma. *First Author: Roy Elias, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD*

Background: Clinical studies evaluating the impact of race on outcomes in renal cell carcinoma (RCC) are inconsistent and conceivably influenced by both biological and socioeconomic factors. Self-reported African Americans (AA) are also largely under-represented in clinical trials and molecular studies of clear cell (cc) RCC compared to their White (W) counterparts. Herein, we sought to comprehensively characterize molecular differences by genetic ancestry in localized ccRCC. **Methods:** We performed whole exome (WES) and transcriptome (RNAseq) sequencing on a case-matched cohort of AA and W patients (pts) who underwent nephrectomy for localized ccRCC at our institution. Germline single nucleotide polymorphisms were combined with reference panels from the 1000 Genomes Project, and ancestry was estimated using ADMIXTURE. Molecular subtypes were defined according to the IMmotion151 (IMm151) subtypes, and a random forest model was trained to predict subgroups. **Results:** From an initial selected cohort of 84 pts, WES and RNAseq data of adequate quality were available for 61 pts including 28 of African (AFR) and 33 of European (EUR) descent. We augmented our institutional cohort with a 3:1 EUR:AFR matched subset of the TCGA KIRC by stage, nuclear grade (NG), and gender. The final analytic cohort contained 75 pts of AFR and 177 pts of EUR descent. There were no significant differences in stage, NG, or gender between AFR and EUR groups. We observed that *VHL* [OR 0.22, CI [0.11-0.43], $p < 0.001$] and *PBRM1* [OR 0.4, CI [0.19-0.79], $p = 0.005$] mutations are enriched in pts with EUR ancestry and identified a unique association of *KMT2C* somatic mutations [OR 3.7, CI [1.1-13.5], $p = 0.027$] with AFR ancestry. Consistent with a lower frequency of *VHL* mutations, gene-set variation analysis revealed lower enrichment for angiogenesis (-0.23 vs 0.045; $p < 0.001$) in AFR vs EUR ancestry, respectively. AFR ancestry was associated with an increased proportion of the "Proliferative" IMm151 subtype (14.9% [n = 11/74] vs 3.4% [n = 6/177], $p = 0.002$). There was no association between overall survival (OS) and ancestry; however, IMm151 subtypes stratified OS with longest survival in the "Angiogenic/Stromal" group (median OS NR) and shortest OS in the T-Effector/Proliferative subtype (5.5yrs CI [2.3 - NR], $p = 0.01$). **Conclusions:** Our findings indicate that genetic ancestry is associated with distinct molecular subtypes of ccRCC. Biological drivers of ccRCC pathogenesis and therapeutic response may vary by ancestry, underscoring the need for racially diverse representation in future studies. Research Sponsor: Dan Haganman Endowment Fund.

4538

Poster Session

Characterizing progression to subsequent lines of therapy in metastatic renal cell carcinoma (mRCC) after nivolumab plus ipilimumab (Nivo+Ipi): Results from the International mRCC Database Consortium (IMDC). *First Author: Audreyllie Lemelin, Tom Baker Cancer Centre, University of Calgary, Calgary, AB, Canada*

Background: Treatment patterns and number of lines of therapy for patients with mRCC are not well characterized in the era of immunoncology-based combinations. We aimed to quantify the attrition rates by line of therapy and to examine predictors of receiving second-line (2L) treatment. **Methods:** Using the IMDC, patients with mRCC who received first-line (1L) Nivo+Ipi were included. Clinical and pathologic characteristics and outcomes were extracted. Chi-square tests were used to compare categorical variables between patients who received 2L and those who did not. A logistic regression model was used to assess predictors of 2L therapy initiation in eligible patients. **Results:** 995 patients treated with 1L Nivo+Ipi were identified, of whom 704 stopped 1L and were thus eligible for 2L therapy. Reasons for stopping 1L included progressive disease (PD) in 39.5%, toxicity in 25.0%, death in 4.3%, complete response in 1.6% and other in 29.7%. Among 2L eligible patients, 410 (58.2%) received 2L whereas 294 (41.8%) did not. Patients who stopped 1L for PD were more likely to initiate 2L than those who stopped for other reasons (81.7% vs 43.0%, $p < 0.001$). Patients who received 2L were more likely to have clear-cell histology (75.1 vs 62.9%, $p = 0.02$), bone metastases (39.8 vs 29.6%, $p = 0.01$), and only one site of metastases (18.3 vs 10.5%, $p = 0.01$) and less likely to be poor risk by IMDC criteria (27.1 vs 34.4%, $p = 0.03$). After adjusting for IMDC criteria, no predictors of receiving 2L therapy remained significant. The overall response rate to 1L therapy was lower in patients who received 2L than in those who did not: 18.5% (76/366) and 33.7% (99/245), respectively ($p < 0.001$). Among 258 patients who stopped 2L, 145 (56.2%, overall 20.6%) started third-line (3L) therapy. Of the 98 patients who stopped 3L, 52 (53.1%, overall 7.4%) started fourth-line therapy. **Conclusions:** In our study, we found that over half of eligible patients received the subsequent line of therapy. We were unable to identify predictors of 2L therapy initiation. Attrition rates between lines of therapy have important implications for patient counseling, cost analyses, and clinical trial design. Research Sponsor: None.

Baseline characteristics of patients eligible for, and of patients who received or did not receive 2L treatment.				
	Eligible for 2L (N=704)	2L=NO (N=294)	2L=YES (N=410)	P value (univariable)
IMDC				
Favorable	58 8.2%	23 7.8%	35 8.5%	0.03
Intermediate	350 49.7%	127 43.2%	223 54.4%	
Poor	212 30.1%	101 34.4%	111 27.1%	
Clear cell histology	493 70.0%	185 62.9%	308 75.1%	0.02
De novo metastatic disease	388 55.1%	163 55.4%	225 54.9%	0.75
Nephrectomy	417 59.2%	164 55.8%	253 61.7%	0.11
Only one site of metastases	106 15.1%	31 10.5%	75 18.3%	0.01
Sites of metastases				
Brain	58 8.2%	31 10.5%	27 6.6%	0.06
Liver	129 18.3%	53 18.0%	76 18.5%	0.85
Bones	250 35.5%	87 29.6%	163 39.8%	0.01

4537

Poster Session

Nivolumab plus cabozantinib in patients with non-clear cell renal cell carcinoma: Updated results from a phase 2 trial. *First Author: Chung-Han Lee, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Identification of effective systemic therapy for non-clear cell renal cell carcinoma (RCC) remains a unmet need. We reported a two arm, phase 2 trial of cabozantinib plus nivolumab (CaboNivo) that showed promising efficacy in the treatment arm comprised primarily of papillary and unclassified histology. (Lee, JCO, 40: 2022). Herein, we report updated results with extended follow up. **Methods:** Patients had advanced non-clear cell RCC, 0 or 1 prior systemic therapies excluding prior immune checkpoint inhibitors, and measurable disease by RECIST. Cabo 40 mg/day plus Nivo 240 mg every 2 weeks or 480 mg every 4 weeks was given for both arms. Arm 1 was comprised of papillary, unclassified, or translocation associated RCC; and Arm 2 had chromophobe RCC (closed early for lack of efficacy). The primary endpoint was objective response rate (ORR) by RECIST; secondary endpoints included progression-free survival (PFS), overall survival (OS), duration of response (DOR) and safety. Arm 1 was a single stage design that met its primary endpoint and was expanded to produce more precise estimates of ORR. Correlative analyses by next generation sequencing were performed and will be presented. **Results:** A total of 40 patients were treated in Arm 1 (data cutoff: Dec 13, 2022). Median follow up time was 34 months (range 20, 51). Twenty-six patients (65%) were previously untreated, and 14 (35%) had 1 prior treatment line: 10 (25%) received prior VEGF-targeted therapy and 8 (20%) received prior mTOR-targeted therapy. ORR is 48% (95% CI 31.5–63.9). Median PFS is 13 months (95% CI: 7, 16). Progression-free survival is 51% (95% CI: 34, 65) at 12 months and 23% (95% CI: 11, 37) at 24 months. Median OS is 28 months (95% CI: 23, 43). Overall survival is 70% (95% CI: 53, 82) at 18 months and 44% (95% CI: 28, 60) at 36 months. PFS and OS were similar for previously treated and untreated patients. For responders, median DOR was 17 months (95% CI: 10, 36). Adverse effects of any grade were experienced by 35 patients (88%); grade 3/4 adverse events were experienced by 22 patients (55%). Grade 3/4 AST and ALT elevations were 18% and 23% respectively. Other common grade 3/4 adverse events were hypertension (5, 13%) and pain (4, 10%). Study therapy was discontinued in 9 patients (28%) for toxicity. **Conclusions:** Updated results with extended follow-up highlight efficacy and safety for CaboNivo in metastatic non-clear cell RCC pts with papillary, unclassified, or translocation associated histologies. Clinical trial information: NCT03635892. Research Sponsor: BMS, Exelixis.

	1 st line (any histology)	2 nd line (any histology)	Unclassified w/o papillary features (6)	Translocation-associated (2)
ORR	54% (33, 73)	36% (13, 65)	47% (30, 64)	50% (1, 99)
CR	1 (4%)	-	1 (3%)	-
PR	13 (50%)	5 (36%)	14 (44%)	1 (50%)
SD	12 (46%)	8 (57%)	17 (53%)	2 (33%)
PD	-	1 (7%)	-	1 (50%)

*Includes 16 unclassified with papillary features, 11 high grade papillary and 5 FH-deficient RCC.

4539

Poster Session

Disease-free survival in operated patients with nmRCC using machine learning. *First Author: Gaëlle Margue, Department of Urology, Bordeaux University Hospital, Bordeaux, France*

Background: In patients operated for a non-metastatic renal cell carcinoma (nmRCC), risk evaluation of disease recurrence enables the therapeutic strategy to be adapted after surgery. Usual risk group stratification does not fully exploit the power of machine learning (ML) applied to multimodal data. We developed a ML model capable of calculating the risk of recurrence after surgery for nmRCC patients. **Methods:** A multicentric cohort of patients undergoing surgery between May 2000 and January 2020 for a nmRCC (pT any, N any, MO) was analyzed from data collected prospectively in the French research network on kidney cancer UroCCR (ClinicalTrials.gov: NCT03293563). Using clinical, biological, histological and radiological features, we developed a signature of patient-specific DFS. Participating medical centers were randomly assigned to training or validation cohorts with a 2:1 ratio of patients. The ML signature managed missing data using multiple imputation based on gradient-boosted trees and chained equations. Several ML models were trained in a repeated 5x10-fold cross-validation procedure to optimize the integrated Area Under the ROC Curve (iAUC) between 0.5- and 5-years following surgery. The performance of the selected ML signature was then evaluated on the validation cohort and compared with usual risk scores. **Results:** 3354 patients were randomly assigned to a training cohort (n=2239 from 10 centers) and a validation cohort (n=1115 from 13 centers). Our risk score achieved an iAUC of 0.81 (0.76, 0.85) on the validation cohort and significantly outperformed the GRANT ($p < 0.001$), SSIGN ($p = 0.03$), and UISS ($p < 0.001$) risk scores. The Leibovich-2018 score was only defined in 51% of the patients, due to incomplete data. Permutation-based feature importance and Shapley values were used to estimate the contribution of each feature. The stratification of patients into four risk groups achieved an iAUC of 0.78 (0.74, 0.83) on the validation cohort. 190 (17%) patients were stratified in the low-risk group, with an actual 5-year DFS higher than 98% and no death observed within this horizon window. 188 (17%) patients were stratified in the high-risk group, with an actual 5-year DFS of 48%. **Conclusions:** The machine learning model estimating individual disease recurrence risk outperformed the predictive performances of usual risk scores while handling incomplete data in predictors. This could help in identifying patients for whom surveillance could be reduced and those who could be candidates for adjuvant therapies. Research Sponsor: INCA, France.

Risk score performances estimated on the validation cohort.					
Risk score	N (%)	iAUC(0.5, 5 yrs) (CI 95%), risk score	iAUC(0.5, 5 yrs) (CI 95%), ML	p-value	
ML	1115 (100)	-	0.81 (0.76, 0.85)	-	
GRANT	995 (89)	0.65 (0.60, 0.70)	0.81 (0.76, 0.85)	< 0.001	
SSIGN	934 (84)	0.78 (0.72, 0.83)	0.81 (0.76, 0.85)	0.03	
UISS	872 (78)	0.70 (0.65, 0.75)	0.81 (0.76, 0.85)	< 0.001	
Leibovich 2018	572 (51)	0.75 (0.66, 0.83)	0.77 (0.68, 0.84)	0.20	

4540

Poster Session

Health-related quality of life (HR-QOL) measures in renal cell carcinoma (RCC): Patient-reported relevance of items of the FKSI-19, EORTC QLQ-C30, and EQ-5D. *First Author: Cristiane Decat Bergerot, Oncoclinicas, Brasília, Brazil*

Background: Given the need to balance both quantity and quality of life among patients with advanced cancer, developing a robust, relevant, and consensus-driven patient-focused measurement strategy is a necessity. Our study expands upon previous findings (Bergerot *et al.*, The Oncologist 2023) in evaluating the perceived relevance of questions on the FKSI-19, EORTC QLQ-C30, and EQ-5D among patients with RCC. **Methods:** Eligible patients were diagnosed with RCC and asked to evaluate the relevance of each question of the FKSI-19, EORTC QLQ-C30, and EQ-5D (items rated as relevant vs non-relevant). Patients also responded to 2 open-ended questions regarding topics not covered by these measures and their perception of wearable technologies. Questions identified as meaningful required $\geq 66\%$ "relevant" ratings. Descriptive statistics were collated, and open-ended questions were analyzed by 2 independent reviewers (CB, PB). **Results:** 116 patients were recruited from Brazil and the US. Most (69%) were male with a median age of 64 (32-88) years. 83% were diagnosed with advanced disease, and 75% received immunotherapy and/or targeted therapy as primary treatment. Few items across surveys were identified as meaningful including 8/19 FKSI-19 questions (lack of energy, fatigue, appetite, sleeping, worry, able to work, enjoyment and quality of life), 3/30 EORTC QLQ-C30 questions (tired, overall health and quality of life), and 0/5 EQ-5D questions. Patients suggested items pertaining to treatment side effects, emotional symptoms, physical function, social/family support, and financial distress should be included. Notably, 58% of patients were open to using wearable devices to assess HRQOL. **Conclusions:** Our multi-institutional international study confirms findings from our single-institution pilot data suggesting that HRQOL measures for RCC require substantial refinement. These data will inform development of a novel-RCC specific HRQOL tool in a joint effort between experts and patients. Research Sponsor: Kidney Cancer Association's 2021 Psychosocial Focus Award (PI: C D Bergerot).

4542

Poster Session

T cell receptor-engineered T cells targeting a human endogenous retrovirus in kidney cancer. *First Author: Stefan Barisic, Laboratory of Transplantation Immunotherapy, Cellular and Molecular Therapeutics Branch, NHLBI, NIH, Bethesda, MD*

Background: Previously, our group described a novel human endogenous retrovirus type E (CT-RCC HERV-E) that is selectively expressed in most clear cell renal cell carcinomas (ccRCC). Here, we report the characterization and preclinical testing of a T cell receptor (HERV-E TCR) that targets an HLA-A11-restricted 10-mer peptide antigen (CT-RCC-1) that is derived from CT-RCC HERV-E. **Methods:** From a patient with ccRCC who had prolonged immune-mediated tumor regression following an allogeneic hematopoietic stem cell transplant, we identified a CD8⁺ T cell clone with HLA-A11-restricted specificity for the CT-RCC-1 peptide. The TCR of this clone was encoded into a retroviral vector containing a truncated CD34 cassette as a selection marker. Gene-engineered T cells expressing the HERV-E TCR (HERV-E T cells) were characterized for tumor recognition, lysis, and cross-reactivity. In vivo anti-tumor activity was assessed in a xeno-murine model using a human subcutaneous ccRCC tumor graft. A good manufacturing practice (GMP)-compliant method to produce HERV-E T cells was implemented for a subsequent clinical trial in humans with metastatic ccRCC. **Results:** When transduced into human T cells, the HERV-E TCR showed CD8-dependent specific recognition and lysis of HERV-E-expressing ccRCC cells that were HLA-A11+. The extent of tumor cytotoxicity correlated with CT-RCC HERV-E mRNA expression levels and HLA-A11 surface density ($r=0.82$). Cross-reactivity assessment established that there were no naturally occurring peptides with substantial sequence identity to CT-RCC-1 that could serve as alternative targets for HERV-E T cells. Further, immunopeptidomics and in silico analyses provided strong evidence that presentation of the CT-RCC-1 epitope depends exclusively on the transcription of the CT-RCC HERV-E genomic region. In a murine model, human HERV-E T cells mediated regression of established human ccRCC tumor grafts, significantly prolonging animal survival compared to controls that either received non-transduced T cells or no T cells (median survival 50 days vs. 20 and 20 days, respectively; $p<0.001$). Finally, the GMP-compliant production of HERV-E T cells yielded pure populations (i.e., $>90\%$ TCR-transduced) of HERV-E T cells that were highly cytotoxic to ccRCC tumor cells. The expansion numbers of GMP-produced cells were sufficient for testing the safety of the adoptively infused T cells in a phase I clinical trial. **Conclusions:** Here, we provide the first data showing T cells armed with a HERV-E TCR acquire specific anti-tumor activity in vitro and in vivo against ccRCC cells. These preclinical data provide the foundation for an ongoing first-in-human phase I clinical trial evaluating the safety of HERV-E T cell infusions in patients with advanced ccRCC. Research Sponsor: U.S. National Institutes of Health; O'Neill Renal Cell Cancer Research Fellowship Fund.

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Poster Session

Core biopsy (bx) accuracy and safety of biopsy and preoperative immunotherapy in predicting histological subtype and nuclear grade in ECOG-ACRIN EA8143 perioperative nivolumab (nivo) versus observation in patients (pts) with renal cell carcinoma (RCC) undergoing nephrectomy. *First Author: Naomi B. Haas, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA*

Background: PROSPER is a phase 3 National Clinical Trials Network study that accrued pts with clinical stage $\geq T2$ or $T_{any}N+$ RCC of any histology planned for radical/partial nephrectomy. Pts were randomized to perioperative nivo followed by primary tumor resection and 9 cycles of nivo postoperatively or standard surgery followed by observation. To address concerns that core kidney bx might 1) not provide accurate diagnosis and 2) delay surgery due to adverse events (AEs) or scheduling, the study was amended from requiring all patients to undergo core bx prior to treatment for confirmation of RCC, to only require bx in patients randomized to the nivo arm. Herein, we report the accuracy and safety of primary tumor core bxs in predicting final histology and nuclear grade by both site and central pathology review as well as time from enrollment to surgery. We also report AEs of preoperative nivo. **Methods:** Concordance of both core bx and primary tumor by site and central pathology review of histology and grade (1-2 vs 3-4) are reported, along with the Cohen's Kappa value, which measures the agreement and concordance (kappa=0 is no concordance and 1 is highest). AEs relating to core bxs and preoperative nivo, as well as time from enrollment to surgery for each arm, comparing pre- and post-amendment (dropping bx requirement in surgery alone arm) are also reported. **Results:** 387/404 pts in the nivo arm and 171/415 pts in the surgery alone arm had core bxs. 632 patients had both central pathology and site review available. 41 of all randomized patients (819) were considered as non-RCC and 26/41 were identified via bx. The median times from enrollment to surgery for nivo and control arms pre-amendment were 32d vs 19 d, and post-amendment were 21 d vs 14 d, respectively. The median (25th-75th percentile) number of days from last preoperative nivo to surgery was 14 d (9-20). AEs related to core bx, generally from bleeding, were reported in 13/558 (2.3%) pts. 2/13 bxs resulted in life-threatening complications. 21/353 (6%) of pts receiving nivo pre-surgery had $\geq$ grade 3-5 AE attributed to nivo. 181/353 (51%) pts had any grade AE attributed to nivo. Concordance between bxs and primary tumor pathologies for determining histological subtype was Kappa = 0.62. Agreement between central pathology and originating site review of primary tumor for determining nuclear grade was Kappa = 0.56, and concordance of histology was Kappa = 0.78. **Conclusions:** The PROSPER trial use of core bxs in advance of neoadjuvant therapy was generally safe, largely consistent with primary tumor histology and grade, and did not delay resection of the primary tumor. AEs of preoperative nivo were consistent with nivo AEs in metastatic disease. This approach is valid for future neoadjuvant trials. Clinical trial information: NCT03055013. Research Sponsor: U.S. National Institutes of Health; BMS.

4543

Poster Session

Immunoglobulin as a predictive biomarker for the efficacy of immune checkpoint inhibitor combined with VEGF-TKI in metastatic renal cell carcinoma. *First Author: Honglei Cui, Department of Urology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China, Beijing, China*

Background: The combination of immune checkpoint inhibitor (ICI) and vascular endothelial growth factor tyrosine kinase inhibitor (VEGF-TKI) is recommended as the first-line treatment in patients with metastatic clear cell renal cell carcinoma (ccRCC). However, no effective serum biomarker has been used to predict the therapy response and potential benefits. Abnormal content and changes of immunoglobulin (IG) in serum or cancer tissue may indicate cancer progression and impact the prognosis. We examined the content of serum IG and analyzed the alteration after treatment to assess the efficacy of ICI and VEGF-TKI. **Methods:** Eighty-four patients with metastatic ccRCC were enrolled in this study. The total serum IG level was determined as the sum of IgA, IgG, and IgM. The data of baseline level and alteration of IG after 3-mo treatment was complete in 72 ccRCC patients. These patients were then divided into two groups based on alteration in their IG levels: the IG-increased group and the IG-decreased group. This study aimed to investigate the correlation between the baseline level of immunoglobulin (IG), changes in its content after 3-mo of treatment, and clinical outcomes. **Results:** Eighty-four patients were retrospectively enrolled with a median follow-up of 17.3 months (2.5-45.1). The objective response rate (ORR) was 41.67%, and the median overall survival (OS) was 31 months in our cohort. The baseline level of IG was not associated with ORR or OS. However, dynamic alteration in IG level after 3-mo treatment had a significant impact on ORR and OS in ccRCC patients. The ORR was 2.7% in the IG-increased group and 80.0% in the IG-decreased group. The OS was 21.0 months (95% CI 14.0-NA) in the IG-increased group and 48.0 months (28.0-NA) in the IG decreased-group (Hazard ratio [HR] 4.59, $p=0.003$). **Conclusions:** The change of serum IG level after 3-mo treatment served as an effective predictor of drug response and the prognosis for metastatic ccRCC patients. Value of serum IG needs to be validated in multi-centers and the mechanism of it should be further investigated. Research Sponsor: None.

4544

Poster Session

Global circulating free DNA methylation and fragmentome deconvolution in patients with metastatic renal cell carcinoma treated with immunotherapy (GOLDEN). First Author: Pavlina Spiliopoulou, Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, ON, Canada

Background: Metastatic renal cell carcinoma (mRCC) lacks molecular biomarkers. Cell-free methylated DNA immunoprecipitation sequencing (cfMeDIP-seq) is a new, non-invasive approach to the detection of RCC-derived DNA in the circulation. In the GOLDEN study (NCT03702309), we explored the role of cfMeDIP-seq and fragmentomic dynamics as a biomarker, during immune checkpoint inhibition (ICI)-based treatment in mRCC patients (pts). **Methods:** Blood samples from mRCC pts were collected before and during treatment. Response to treatment was defined by the treating oncologist as: response, any degree of radiological tumor regression; stable disease (SD), no radiological change; or progressive disease (PD), radiological/clinical progression. More than 10ng of plasma cfDNA was subject to cfMeDIP-seq. A prognostic pan-cancer methylation signature previously generated using TCGA tissue methylation arrays was applied to cfMeDIP-seq output and cancer-signal methylation (CSM) score was calculated. An RCC-specific methylation signature, previously generated by identifying differentially methylated regions between RCC pts and controls, was applied (Nuzzo *et al*, *Nat Med* 2020). Genome-wide fragmentation profiles were generated using DELFI. Using medians as cut off, log-rank test was performed to assess overall survival (OS) and progression-free survival (PFS). **Results:** Thirty-five patients were enrolled and n=33 received systemic treatment. 31/35 pts (89%) had clear cell and 4/35 (11%) non-clear cell histology. Median age was 61 (30-81) years and the M:F ratio was 6:1. Patients' IMDC prognostic risk score was favorable n=6/35 (17%), intermediate n=23/35 (65%) and poor n=6/35 (17%). 20/33 (61%) patients received ipilimumab/nivolumab, 10/33 (30%) nivolumab and n=3/33 (9%) pembrolizumab/axitinib. There were n=14/33 (42%) responders, n=4/33 (12%) pts with SD and 15/33 (45%) pts with PD. Patients with high pan-cancer CSM score at baseline trended towards worse OS (HR 3.86, p = 0.079). Fragmentomics signature, consisting of increased proportion of short cfDNA fragments, showed a trend for worse PFS (HR = 3.04, p = 0.075) in on-treatment samples. Using the RCC-specific methylation signature, we found that those with an increase in signature score from baseline to on-treatment had better PFS (HR=2.4x10⁻¹⁰, p=0.002, n=10) and a trend towards better OS (HR=0.17, p=0.074, n=10). We hypothesize that RCC tissue-specific cell death early during ICI treatment could underpin this increase in the methylation score. **Conclusions:** This small study is the first report on the role of cfMeDIP-seq-derived methylation and fragmentomic signatures in patients with mRCC undergoing ICI-based treatment. We found several trends and one significant association between these signatures and pt outcomes, which support further validation in larger cohorts. Clinical trial information: NCT03702309. Research Sponsor: KCRNC-KCC-CUASF Research Grant.

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Poster Session

Adjuvant everolimus in patients (Pts) with localized non-clear cell renal cell carcinoma (RCC): Subgroup analysis from the Everest trial (SWOG S0931). First Author: Shuchi Gulati, University of California Davis Comprehensive Cancer Center, Sacramento, CA

Background: In S0931, adjuvant treatment with the mTOR inhibitor everolimus respectively yielded disease-free survival (DFS) and overall survival (OS) hazard ratios (HR) of 0.85 (95% CI 0.71-1.00) and 0.90 (95% CI 0.71-1.13) in pts with resected, localized RCC. Previously, everolimus had been shown to be active in chromophobe RCC (chRCC; Tannir *et al* Eur Urol 2016) and papillary RCC (papRCC; Escudier *et al* Eur J Cancer 2016). We sought to evaluate the efficacy of everolimus within these non-clear cell subsets of EVEREST. **Methods:** 1545 adult pts with treatment-naïve, non-metastatic, fully-resected RCC at intermediate high-(pT1 G3-4 N0 to pT3a G1-2 NO) or very high-risk (pT3a G3-4 to pT4 G-any or N+) for recurrence were randomized 1:1 to 54 weeks of everolimus 10 mg PO daily or placebo within 12 weeks of radical or partial nephrectomy. Exploratory analyses of RFS and OS chromophobe and papillary subgroups were performed. **Results:** A total of 99 eligible pts had chRCC; 109 had papRCC (16 type I; 37 type II; 56 NOS). Median follow-up is 6.3 years. Pt characteristics were balanced between the 2 arms in each histological group. Thirty-four (34%) pts in the chRCC subgroup and 50 (46%) pts in the papRCC subgroup had very high-risk disease. Fewer pts completed all 54 weeks of everolimus in each subgroup compared to placebo (49% vs. 74% in the chRCC subgroup and 46% vs. 71% in the papillary subgroup). DFS and OS for each subgroup are shown. **Conclusions:** Non-clear cell histology accounted for a considerable proportion (~13%) of S0931 pts. The estimated everolimus HRs for DFS and OS in the chRCC subset are consistent with the overall trial result, but those same modest HRs were not seen in papRCC, in contrast to prior reports of mTOR inhibitor activity in this subtype. Although inferences are limited by sample size and wide CIs, this is the largest experience in chRCC or papRCC among any adjuvant trials presented to date. Clinical trial information: NCT01120249. Research Sponsor: U.S. National Institutes of Health; Novartis.

	Chromophobe		Papillary	
	Placebo (N=46)	Everolimus (N=53)	Placebo (N=52)	Everolimus (N=57)
DFS events	10	10	15	20
DFS HR (95% CI), p-value	0.89 (0.37, 2.13), p=0.79		1.19 (0.61, 2.33), p=0.61	
Deaths	7	7	10	16
OS HRo (95% CI), p-value	0.93 (0.33, 2.65), p=0.89		1.47 (0.67, 3.24), p=0.34	

HR for everolimus vs. placebo, 2-sided p-value from unadjusted Cox model. CI = confidence interval.

4545

Poster Session

Genomic determinants of progression-free survival after second line of therapy (PFS-2) for patients on immunotherapy-based combination therapies for advanced clear cell renal cell carcinoma. First Author: Kelly N. Fitzgerald, Memorial Sloan Kettering Cancer Center, New York, NY

Background: The role of somatic genomic mutations in predicting outcomes in clear cell renal cell carcinoma (ccRCC) is poorly defined. Both ipilimumab/nivolumab (IO/IO) and several combinations of VEGFR-targeted tyrosine kinase inhibitor (TKI/IO) are preferred first-line treatment options for metastatic ccRCC. The impact of somatic mutations on PFS-2 for IO combination therapies was evaluated in this retrospective analysis. **Methods:** One-hundred forty-one patients with ccRCC had sequencing with MSK-IMPACT and initiated 1st line combination IO at Memorial Sloan Kettering (MSK) Cancer Center between 1/1/2014 and 12/30/2020. Treatment groups are defined as IO/IO (n=76) and TKI/IO (n=65). PFS-2 is defined as time from start of 1st line to progression on next therapy, or death, and is estimated using Kaplan-Meier method. PFS-2 association with each mutation was assessed via log-rank test and a model-based approach. Restricted mean survival time (RMST) up to 48 months was calculated for PFS-2 and modeled using a generalized linear model adjusted for IMDC risk. To test for heterogeneity of effect among treatment groups, an interaction test between somatic mutation and treatment group is performed in the model. **Results:** *VHL*, *PBRM1*, *SETD2*, mTOR pathway, *BAP1*, and *TP53* were the most common somatic mutations. Only *BAP1* was significantly associated with PFS-2: median PFS-2 was 44 months for patients without *BAP1* mutation and 17 months for patients with *BAP1* mutation (log-rank p=0.006). After adjusting for IMDC risk group, 48 month RMST for PFS-2 was 13 months lower in patients with *BAP1* mutation. An interaction test performed in the RMST model showed no significant variation in the treatment effect of IO/IO or TKI/IO based on the presence or absence of *BAP1* mutation (p=0.97), although sample size limits power to detect differences. Results for other somatic mutations are shown. **Conclusions:** PFS-2 was significantly inferior for ccRCC patients with somatic *BAP1* mutation treated with IO-based therapy. Interaction test did not suggest a significant advantage for IO/IO or TKI/IO for mutation-present or -absent groups. Clinical stratification remains key for selecting TKI/IO or IO/IO for patients. Research Sponsor: Memorial Sloan Kettering Cancer Center Support Grant/Core Grant P30 CA008748.

Gene	N (%) altered	Median PFS-2, months (95% CI)		Log-rank P	RMST difference*, months (95% CI)	Interaction P
		mutation present	mutation absent			
<i>VHL</i>	110 (78%)	33 (25, 46)	NE (12, NE)	0.42	-8 (-23, 6)	0.83
<i>PBRM1</i>	67 (48%)	29 (21, 51)	33 (23, 50)	0.69	-3 (-14, 8)	0.76
<i>SETD2</i>	53 (38%)	31 (17, 62)	34 (23, 50)	0.68	-4 (-15, 8)	0.29
mTOR pathway	38 (24%)	27 (15, 67)	34 (26, 49)	0.76	1 (-12, 14)	0.61
<i>BAP1</i>	34 (24%)	17 (11, 27)	44 (29, 53)	0.006	-13 (-26, 0.3)	0.97
<i>TP53</i>	21 (15%)	47 (15, NE)	32 (25, 49)	0.42	10 (-5, 26)	0.26

*NE, not estimated. *Calculated after 48 months of follow-up and adjusted for IMDC risk in a generalized linear model (PROC RMSTREG, SAS v9.4).

4547

Poster Session

Response to immune checkpoint inhibitor (ICI) rechallenge in patients with metastatic renal cell carcinoma who progressed on prior ICI: A systematic review and meta-analysis. First Author: Garima Gupta, University of Kentucky, Lexington, KY

Background: Several immune checkpoint inhibitor (ICI)-based combination regimens are standard-of-care for first-line treatment of metastatic renal cell carcinoma (mRCC). These include dual ICI and ICI-tyrosine kinase inhibitor (TKI) combinations. While single-agent ICI is recommended as subsequent-line therapy for ICI-naïve patients, there is limited knowledge regarding efficacy of rechallenging with a different ICI or using different ICI combinations in patients who have progressed on prior ICI therapy. This is a clinically critical question as most mRCC patients would have already received ICI therapy at progression. The aim of this study is to address the above by performing a systematic review and meta-analysis. **Methods:** PubMed, Cochrane Library and Web of Science were systematically searched to identify studies of later-line ICI rechallenge after progression on any previous ICI in mRCC patients from database inception to December 31st, 2022. Patients who had progressed on prior ICI and rechallenged with ICI as single agent/dual/TKI combination as any subsequent line of therapy in both retrospective and prospective studies were included. Exclusion criteria were phase I or any phase studies combining ICI with unapproved drugs, case reports and case series. We calculated the pooled objective response rate (ORR) and disease control rate (DCR) using mixed effects model treating individual studies as a random effect. We further stratified studies into prospective and retrospective and performed subgroup analyses. **Results:** A total of 11 studies, 6 prospective and 5 retrospective with a total of 603 patients were initially identified. Out of the 6 prospective studies, 3 had an adaptive design of using salvage ipilimumab/nivolumab in patients who had either progressed or had stable disease as the best overall response on nivolumab monotherapy. These studies were excluded as they did not meet our inclusion criteria. A total of 8 studies with 400 patients were included in the final analysis. The ORR was 28% (95% CI, 0.27-0.36) and the DCR was 70% (95% CI, 0.47-0.85) with no significant differences between prospective and retrospective studies. Our ORR is higher than an earlier meta-analysis reporting an ORR of 14% with salvage ipilimumab/nivolumab after previous treatment with ICI. **Conclusions:** This meta-analysis demonstrates a modest ORR and an impressive DCR. Therefore, it provides strong clinical rationale to consider rechallenging with ICI-based therapy for later-line treatment of mRCC patients who have progressed on prior ICI. Research Sponsor: None.

		Prospective	Retrospective	Both
ORR	Studies	4	4	8
	Patients	239	161	400
DCR	ORR (95% CI)	0.28 [0.13, 0.50]	0.29 [0.14, 0.50]	0.28 [0.27, 0.36]
	Studies*	3	2	5
	Patients	195	79	274
	DCR (95% CI)	0.71 [0.40, 0.90]	0.67 [0.35, 0.89]	0.70 [0.47, 0.85]

*Studies were excluded because DCR was not reported.

4548

Poster Session

Serum soluble MAdCAM-1: A new biomarker for cancer immunotherapy.
First Author: Carolina Alves Costa Silva, Gustave Roussy Cancer Campus, Villejuif, Ile-de-France, France

Background: Antibiotics (ATB) deviate the gut taxonomic microbiota composition and have a deleterious impact on survival in ICI-treated pts. ATB downregulate the ileal mucosal addressin cell adhesion molecule-1 (MAdCAM-1), leading to the recirculation of immunosuppressive enterotrophic T cells into the tumor and ICI resistance. Here, we aimed to assess the prognostic impact of MAdCAM-1 in ICI-treated mRCC pts. **Methods:** The GETUG-AFU 26 NIVOREN phase II trial (NCT 0301335) is a multicentric study that assessed the activity and safety of Nivolumab in pts with clear cell mRCC after anti-angiogenic therapy. We measured serum soluble MAdCAM-1 (sMAdCAM-1) levels (correlating ileal MAdCAM-1 transcripts) using Human Luminex Discovery Assay in the available plasma. Progression-free survival (PFS), overall survival (OS) and clinical benefit rate (CBR) were assessed using sMAdCAM-1 median as a cut off value (high if >median and low if <median). Multivariate Cox analysis adjusted for established risk factors: ATB, gender, age, international Metastatic RCC Database Consortium (IMDC) score, number of previous lines, hypoalbuminemia, and brain, bone and liver metastasis. Two independent cohorts of metastatic lung and bladder cancer patients validated the data. **Results:** Overall, 212 pts were included. Median age was 64 years (22-87), and pts were mostly male (82%). ATB users had lower levels of sMAdCAM-1. Low sMAdCAM-1 pts had diminished OS compared to high sMAdCAM-1 pts [HR 2.97 (95%CI 1.99-4.44), $p<.0001$]: 13.3 (95%CI 9.8-14.9; 72/106) versus 25.3 (95%CI 24.1-NR; 36/106) months. Also, low sMAdCAM-1 pts had diminished PFS [HR 1.92 (1.43-2.57), $p<.0001$]: 2.6 (95%CI 2.4-2.8; 99/106) versus 5.2 (95%CI 4.6-5.7; 86/106) months. Interestingly, sMAdCAM-1 was independently associated with OS [HR 2.40 (1.52-3.80), $p=0.0002$] and PFS [HR 1.55 (1.13-2.13), $p=0.0071$] in multivariate analysis. Low sMAdCAM-1 pts had lower CBR (37% versus 63%, $p=0.0004$). Serum sMAdCAM-1 also predicted OS in 381 ICI-treated patients with lung and bladder cancer. **Conclusions:** Low sMAdCAM-1 is associated with ATB intake, ATB-independent gut dysbiosis and worse outcomes, in ICI-treated pts with metastatic lung, bladder and RCC cancer. ELISA determination of sMAdCAM-1 might guide the selection of patients amenable to microbiota-centered interventions, such as *Akkermansia sp.*, and fecal microbiota transplantation. Clinical trial information: NCT0301335. Research Sponsor: Institut National du Cancer, Direction Générale de l'Offre de Soins; Bristol-Myers-Squibb.

4550

Poster Session

Association of host immune signatures with response to immunotherapy-based regimens in patients with metastatic renal cell carcinoma (mRCC).
First Author: Eddy Saad, Dana-Farber Cancer Institute, Boston, MA

Background: Treatment options for mRCC have evolved to include VEGF targeted therapies (VEGF-TT), immune checkpoint inhibitors (ICIs), or combinations of both. The interaction between the tumor and its immune microenvironment has been shown to influence clinical outcomes in patients treated with immunotherapy-based regimens. The aim of this study was to characterize the T-cell and B-cell immune repertoires in patients with mRCC treated with VEGF-TT, ICI or a combination of both, and evaluate their associations with clinical outcomes. **Methods:** We identified patients with mRCC at Dana-Farber Cancer Institute treated with VEGF-TT, ICI or both, and for whom tumor and/or blood samples were available. Bulk RNA-sequencing (RNA-seq) and T-cell receptor sequencing (TCR-seq) were performed on peripheral blood mononuclear cells (PBMCs), collected before and during therapy. Bulk RNA-seq was additionally performed on available pre-treatment primary tumor samples. Immunoglobulin heavy chain (IgH) isotypes were inferred from bulk RNA-seq data using TRUST4. Parameters of the T-cell and B-cell repertoires were evaluated in responders vs. non-responders to systemic therapies, and between pre- and on-treatment samples within patient subgroups. **Results:** In total, blood (PBMC) samples from 386 patients were available across all treatment cohorts. Following quality-control, TCR-seq and RNA-seq data were available for 367 and 134 patient samples, respectively. Responders to ICI-based regimens (ICI or VEGF-TT+ICI) presented a trend towards an increased baseline (pre-treatment) TCR clonality as compared to non-responders ($p=0.06$), corresponding to a less polyclonal T cell repertoire in responders at baseline. No significant changes in clonality were seen between pre- and on-treatment samples among responders to ICI regimens ($p=0.14$), as opposed to non-responders where a significant increase was identified ($p=0.001$). The analysis of IgH isotypes in baseline blood samples showed higher fraction of IgG1 in responders (vs. non-responders) to ICI regimens ($p=0.01$). This was further confirmed in the analysis of IgH isotypes inferred from tumor samples ($p=0.04$). No significant differences in IgH isotype fractions were identified between responders and non-responders to VEGF-TT. **Conclusions:** We were successfully able to characterize T-cell receptor and IgH repertoires in a large cohort of patients with mRCC and evaluate their associations with ICI response. Our results show that baseline TCR clonality and IgG1 antibody fraction are associated with the response to ICI regimens, suggesting a potential role for immune biomarker development. Research Sponsor: US Department of Defense.

4549

Poster Session

Biomarkers of response to first-line nivolumab therapy in patients with advanced renal cell carcinoma (RCC) enrolled in the HCRN GU16-260 trial.
First Author: Nourhan El Ahmar, Brigham and Women's Hospital, Boston, MA

Background: The HCRN GU16-260 study showed that nivolumab (nivo) monotherapy is active in treatment-naïve patients (pts) with RCC. Although efficacy correlated with tumor cell (TC) PD-L1 expression, more clinically relevant biomarkers are needed. We previously showed that levels of CD8+ tumor-infiltrating lymphocytes (TIL) expressing PD-1 but not TIM-3 and LAG-3 (CD8+ PD1+ TIM3- LAG3-) were associated with response to nivo in previously treated clear cell RCC (ccRCC) pts (Pignon, 2019; Ficial, 2021). Here, we sought to validate these findings in the first-line setting. **Methods:** Primary tumor tissues from pts with ccRCC ($n=67$) and non-ccRCC ($n=13$) were analyzed by multiparametric immunofluorescence (IF), and the density of CD8+PD1+TIM3-LAG3- TIL was quantified by image analysis. The correlation of the log-transformed biomarkers with objective response rate (ORR) and progression-free survival (PFS) was assessed in the ccRCC cohort and the combined (ccRCC + non-ccRCC) cohort ($n=80$) using Cox or logistic regression analysis, or Chi-square/Fisher's exact test (as appropriate) for statistical inference – alpha level was set at 5% (1-sided). **Results:** In both the ccRCC and the combined cohort, density of CD8+PD1+TIM3-LAG3- TIL (IF biomarker) measured as continuous variable was associated with ORR (ccRCC: OR = 1.54, $p=0.017$; combined: OR = 1.35, $p=0.040$) and PFS (ccRCC: HR = 0.79, $p=0.015$; combined: HR = 0.85, $p=0.016$). At a cutoff optimized for maximum sensitivity for ORR, ccRCC patients with a high (61/67) vs low (6/67) IF biomarker had higher ORR (44.3% vs. 0% $p=0.039$) and longer median PFS (10.9 months vs. 4.2 months, $p=0.016$). Of note, when combined with the IF biomarker, TC PD-L1 expression ($\geq 1\%$) further separated the clinical outcomes of ccRCC pts. **Conclusions:** High levels of CD8+ PD1+ TIM3-LAG3- TILs were associated with response to first-line nivo in pts with advanced RCC and the combination with TC PD-L1 status further separated the outcomes of pts with ccRCC, validating our previous findings. Further investigations into the role of myeloid inflammation as determinant of clinical outcome to nivo therapy are ongoing. Clinical trial information: NCT03117309. Research Sponsor: Department of defense.

	Biomarker levels	N of pts	ORR		median PFS	
			N (%)	*p-value	months	*p-value
Combination of TC PD-L1 and IF biomarker (n=67)	IF High/PD-L1+	12	9 (75%)	0.006	24.7	0.031
	IF High/ PD-L1-	49	18 (36.7%)		10.6	
	IF Low/PD-L1 + or -	6	0 (0%)		4.2	

*2-sided p-value.

4551

Poster Session

CD8 cell PET imaging with 89-Zr-crefmirlimab berdoxam (crefmirlimab) in patients with metastatic renal cell carcinoma (mRCC) receiving checkpoint inhibitors (CPIs): Association with response and tissue CD8 expression.
First Author: Sumanta Kumar Pal, City of Hope, Duarte, CA

Background: Novel imaging modalities using frequently expressed RCC antigens, such as CAIX, have shown promise in early-stage disease (Shuch B *et al* ASCO GU 2023). In advanced RCC, no tissue-based biomarkers have been well established to predict outcome with contemporary regimens, e.g., checkpoint inhibitors (CPIs) or targeted therapy (TT). We hypothesize that functional imaging of CD8 T-cells (CD8s) with crefmirlimab (a ~80 kDa ⁸⁹Zr-labelled minibody with high affinity for CD8) may predict response given the essential role of CD8 T-cells (CD8s) in mediating CPI response. **Methods:** Eligible pts had pathologically verified RCC, metastatic disease and an intent to initiate standard of care CPI therapy. Patients received crefmirlimab PET/CT within 1 wk of CPI infusion and 4-6 weeks after initiating therapy. Baseline biopsy was mandated, along with repeat biopsy 0-2 weeks following the second PET/CT scan. PET signal was characterized as SUV_{max}, SUV_{peak} and SUV_{mean} of the biopsied lesions, up to 5 index lesions and representative CD8 avid lymph nodes. Mean SUV_{max} in responders and non-responders were compared using students t-test (1-sided). CD8 expression in tissue was characterized as the number of positive cells per mm²; PET avidity and CD8 expression were compared using the Spearman correlation coefficient. **Results:** 17 pts (9 M: 8 F) were enrolled; most pts had clear cell histology (12; 71%) followed by unclassified (3; 17%) and papillary (2; 12%). The most commonly rendered CPI-based regimens were nivolumab alone (6 pts; 35%) and cabozantinib/ nivolumab (3 pts; 17%). Follow-up data was available in 15 of the patients. By RECIST v1.1, 3 of 15 patients were classified as responders (best overall response [BOR] of complete response or partial response) and 12 patients were classified as non-responders (BOR of stable disease or progressive disease). Average SUV_{max}, SUV_{peak} and SUV_{mean} per patient among all quantified index lesions and representative lymph nodes were 10.02, 6.95 and 6.11 for baseline and 8.82, 6.23 and 5.39 during treatment, respectively. Average SUV_{max} at baseline was 14.68 in responders to CPI and 8.28 in non-responders ($P=0.006$). On treatment SUV_{max} was 10.93 in responders to CPI and 8.22 in non-responders ($P=0.19$). A strong correlation between CD8 expression in baseline tissue and normalized SUV_{mean} was observed ($r=0.77$; 95%CI 0.53-0.91). **Conclusions:** To our knowledge, this is the first series in RCC to demonstrate that functional imaging of immune cells (here, CD8s) may segregate response to CPIs, with responders having a higher baseline SUV and a larger decrement in SUV with therapy. Our results are bolstered by a significant correlation between tissue and imaging CD8 expression. Larger studies are underway to validate this noninvasive strategy. Clinical trial information: NCT03802123. Research Sponsor: ImaginAb.

4552

Poster Session

Role of cytoreductive nephrectomy (CN) in metastatic clear cell renal cell carcinoma (mccRCC) in the era of immunotherapy (IO): An analysis of the National Cancer Database (NCDB). *First Author: Maroun Bou Zerdan, SUNY Upstate Medical University, Syracuse, NY*

Background: The role of CN remains questionable after the well intentioned two large prospective trials, SURTIME AND CARMENA, failed to show the benefit of CN for mcrRCC, with Sunitinib as standard of care. **Methods:** We identified stage IV mcrRCC only patients (pts) who received IO with or without surgery in the NCDB 2004-2018. Overall survival (OS) was calculated among three groups of IO alone (group (gr)1), IO followed by CN (gr2), CN followed by IO (gr3). Cox models compared OS by treatment group after adjusting for sociodemographic, health, and facility variables. **Results:** From 615,519 renal cancer cases, 2,903 met our criteria. 6.96% of ccRCC had sarcomatoid histology. Pts in the gr 2 and gr 3 had 63%, 95% CI [0.265-0.510] and 46%, 95% CI [0.487- 0.594], $P = 0.001$, risk reduction in mortality compared to IO alone. Black race compared to white race, education attainment quartile < 6.3% compared to > 17.6%, uninsured pts compared to privately insured, and pts treated at community cancer center compared to academic center had an increased mortality risk by 16%, 95% CI [0.980-1.387] ($P = 0.083$), 26%, 95% CI [1.054-1.511] ($P = 0.011$), 30%, 95% CI [1.003-1.683] ($P = 0.047$), 44%, 95% CI [1.161-1.779] ($P = 0.001$) respectively. Median income quartiles ranging > 63k, had 25% reduction in mortality over income quartiles < 40k, 95% CI [0.630-0.902] ($P = 0.002$). Regardless of the sequence of CN, partial nephrectomy was minimally used. Pts with brain and liver metastasis had a 48% ($P = 0.063$) and a 79% ($P = 0.001$) chance of increased risk of mortality. **Conclusions:** Pts receiving CN regardless of sequence with IO did better than IO alone in this national registry-based adjusted analysis for mcrRCC. International Metastatic Renal Cell Carcinoma Database Consortium risk stratification of pts was not done however Charlson-Deyo Comorbidity Index, visceral/brain metastasis were accounted for in OS analysis. Limitations inherited in the retrospective nature of this study are lack of randomization and pts' and physicians' choice. We believe the role of CN does warrant prospective validation in the era of IO for stage IV ccRCC. OS at 2 and 5 yrs for all three groups, with respective 95% CI. Research Sponsor: None.

	IO (%) 95% CI	IO+CN (%) 95% CI	CN+IO (%) 95% CI
2 YRS FOLLOW-UP	29.88 [27.56-32.23]	70 [60.62-78.67]	55 [52.38-57.54]
5 YRS FOLLOW-UP	10.74 [8.63-13.11]	37.60 [25.33-49.82]	30.47 [27.78-33.20]

4554

Poster Session

⁸⁹Zr-DFO-girentuximab for PET/CT imaging of clear cell renal cell carcinoma: Results from phase 3 ZIRCON study. *First Author: Brian M. Shuch, Institute of Urologic Oncology, David Geffen School of Medicine at UCLA, Los Angeles, CA*

Background: Conventional tools (eg, CT, MRI, biopsy) have limitations for characterizing renal mass histology; approx. 25% of patients with an indeterminate renal masses (IDRM) <4cm undergo surgery for benign disease. Accurate noninvasive techniques to risk stratify the IDRM remains an unmet need. Girentuximab is a monoclonal antibody that targets carbonic anhydrase IX (CAIX), an enzyme highly expressed in clear cell renal carcinoma (ccRCC). Radiolabeled ⁸⁹Zr-DFO-girentuximab is highly specific for CAIX and can aid differentiation between ccRCCs and other renal lesions. ZIRCON evaluated the performance of ⁸⁹Zr-DFO-girentuximab PET/CT for detection of ccRCC. **Methods:** In this open label, multicenter trial, patients with an IDRM (≤ 7 cm; cT1) who were scheduled for partial nephrectomy within 90 days from planned ⁸⁹Zr-DFO-girentuximab administration were eligible. Enrolled patients received a single dose IV (37 MBq $\pm 10\%$; 10mg girentuximab) on Day 0 and underwent PET/CT imaging on Day 5 (± 2 d). Blinded central histology review determined ccRCC status. The co-primary objectives were to evaluate both the sensitivity and specificity of ⁸⁹Zr-DFO-girentuximab PET/CT imaging in detecting ccRCC in patients with IDRM, using histology as the standard of truth. Key secondary objectives included sensitivity and specificity of TLX250-CDx PET/CT imaging in the subgroup of patients with IDRM ≤ 4 cm (cT1a). Other secondary objectives included positive and negative predictive values, and evaluation of safety and tolerability. The Wilson 95% confidence intervals (CI) lower bound for sensitivity and specificity had to be >70% and 68% respectively for ≥ 2 independent readers to declare the study successful. **Results:** 300 patients received ⁸⁹Zr-DFO-girentuximab (mean age, 62 ± 12 y; 71% Male). Of 288 patients with central histopathology of surgical samples, 193 (67%) had ccRCC, and 179 (62%) had cT1a. Of 284 evaluable patients, the average across all 3 readers for sensitivity and specificity was 86% [80%, 90%] and 87% [79%, 92%] resp. for coprimary, and 85% [77%, 91%] and 90% [79%, 95%] resp. for key secondary endpoints. For all evaluable patients, positive and negative predictive values were $\geq 91.7\%$ and $\geq 73.7\%$, resp. PET+ ccRCC had higher mean CAIX expression compared with PET- ccRCC patients ($p < 0.05$). Sensitivity and specificity were consistent with masses ≤ 2 cm ($n=46$) of which, 26 were ccRCC+, 13 ccRCC-, and 3 unevaluable at central histopathology. Of 263 adverse events (AEs) in 124 patients, 2 AEs of mild intensity were treatment related. **Conclusions:** ZIRCON study confirms ⁸⁹Zr-DFO-girentuximab PET/CT is a well-tolerated and accurate modality for noninvasive identification of ccRCC in IDRM. This tool could be included in the diagnosis/management of patients with IDRM, limiting unnecessary treatment of benign lesions. Clinical trial information: NCT03849118. Research Sponsor: Telix Pharmaceuticals.

4553

Poster Session

Belzutifan plus lenvatinib for patients (pts) with advanced clear cell renal cell carcinoma (ccRCC) after progression on a PD-1/L1 and VEGF inhibitor: Preliminary results of arm B5 of the phase 1/2 KEYMAKER-U03B study. *First Author: Laurence Albiges, Gustave Roussy, Villejuif, France*

Background: The oral HIF-2 α inhibitor belzutifan demonstrated antitumor activity with manageable safety as monotherapy in pts with heavily pretreated ccRCC and in combination with a VEGF-TKI in pts who previously received a PD-1/L1 inhibitor. KEYMAKER-U03B (NCT04626518) is phase 1/2, multicenter, multi-arm, open-label, adaptive umbrella study. We present preliminary results from arm B5 for belzutifan + lenvatinib. **Methods:** In all arms, adults with histologically confirmed ccRCC, KPS $\geq 70\%$, and disease progression on or after PD-1/L1 inhibitor and VEGF-TKI treatment (in sequence or in combination) were enrolled. In arm B5, pts received belzutifan 120 mg PO QD + lenvatinib 20 mg PO QD. The study comprised a safety lead-in phase to establish the recommended phase 2 dose (RP2D), followed by an efficacy phase. Primary end point for the safety lead-in phase was safety and tolerability to establish RP2D; co-primary end points of the efficacy phase were safety and ORR per RECIST v1.1 by blinded independent central review (BICR). Secondary end points include clinical benefit rate (CBR; CR + PR + SD ≥ 6 mo), DOR and PFS per RECIST v1.1 by BICR. Response will be presented in pts who had an opportunity to receive ≥ 2 postbaseline scans due to ongoing enrollment. PFS was evaluated in all enrolled pts and safety in all treated pts. End points will be evaluated in each arm separately; no comparisons will be made across arms. **Results:** As of September 29, 2022, 32 pts were enrolled and 30 received treatment. Median age was 60.5 y, 78% were male and 78% had intermediate/poor IMDC risk. 23 pts were on treatment at data cutoff date. Median follow up was 6.9 mo (range: 0.1-18.2). Safety of belzutifan 120 mg + lenvatinib 20 mg was manageable. Of 10 evaluable pts in the safety lead-in phase, only 1 experienced a dose-limiting toxicity (grade 1 dyspnea). Among pts who had opportunity for ≥ 2 postbaseline scans ($n=24$), ORR was 50% (95% CI, 29-71; all PRs); CBR was 54% (95% CI, 33-74). Median DOR was not reached (NR; range: 1.4-+14.0+ mo); 74% of responders remained in response for ≥ 12 mo by KM estimation. For all enrolled pts, median PFS was 11.2 mo (95% CI, 4-NR); 6-mo rate was 55%. In the safety analysis, 28 pts (93%) experienced a treatment-related AE (TRAE), most commonly ($\geq 40\%$) anemia (43%), fatigue (43%), and hypertension (43%). Grade 3-4 TRAEs occurred in 15 pts (50%); most commonly hypertension (27%) and anemia (17%). 1 pt experienced grade 2 hypoxia. No pt died due to a TRAE. **Conclusions:** Preliminary data from the belzutifan + lenvatinib combination exhibited promising antitumor activity in pts with ccRCC that progressed on PD-1/L1 inhibitors and VEGF-TKIs. Safety findings were consistent with individual profiles of each agent. The combination is being further evaluated in the phase 3 LITESPARK-011 study. Clinical trial information: NCT04626518. Research Sponsor: Merck Sharp & Dohme LLC., a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

4555

Poster Session

Impact of smoking status (SS) on the clinical outcomes of patients with metastatic renal cell carcinoma (mRCC) treated with first line (1L) immunotherapy (IO)-combination regimens: Results from the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC). *First Author: Georges Gebrael, Huntsman Cancer Institute at the University of Utah, Salt Lake City, UT*

Background: Active smoking is associated with decreased overall survival (OS) in patients (pts) with mRCC treated with VEGF targeted therapy (VEGF-TT) (Kroeger N. et al. 2019, IMDC investigators). Conversely, smoking history has been linked to improved OS in pts with advanced non-small cell lung carcinoma (NSCLC) receiving 1L pembrolizumab monotherapy (Popat S. et al., 2022). Herein, we assess the association between SS and outcomes in pts with mRCC treated with 1L standard of care (SOC) IO-based regimens. **Methods:** Real-world data from the IMDC were collected retrospectively. We included mRCC pts who received either dual IO therapy or IO + VEGF-TT in the 1L setting and known SS at disease diagnosis. Pts were categorized as current, former and non-smokers. The primary outcomes were OS, time to treatment failure (TTF) and objective response rate (ORR) on 1L IO-based regimens. OS and TTF were evaluated using Cox regression, adjusting for age at 1L treatment, IMDC risk groups, BMI, histological type and time from diagnosis to 1L treatment initiation. ORR was compared between the SS groups using a logistic regression, adjusting for the same confounders. **Results:** 989 pts were eligible and included. 438 (44.3%), 415 (42%), and 136 (13.7%) pts were non-smokers, former, and current smokers at diagnosis, respectively. Median time from diagnosis to initiation of 1L IO-based treatment was 0.47 years (IQR 0.13-2.15). At baseline, there were no significant differences in age at 1L, IMDC risk groups, KPS status, BMI, and presence of sarcomatoid features across the 3 groups ($p > 0.05$). Median follow up was 21.2 months from 1L IO-based treatment initiation. On multivariable analysis, no significant differences in OS, TTF or ORR were seen between the SS groups ($p > 0.05$). **Conclusions:** To our knowledge, this represents the first and largest effort to evaluate the impact of smoking on clinical outcomes in pts with mRCC treated with IO-based regimens. There was no association between SS at diagnosis and the clinical outcomes of patients with mRCC receiving current 1L SOC IO-based regimens. As opposed to other cancer types (i.e., NSCLC), current or past smoking history did not appear to be predictive of benefit from IO-based therapy. Research Sponsor: None.

	Non-smokers (n = 438)	Former Smokers (n = 415)	Current Smokers (n = 136)
mOS, mo (95% CI)	48.2 (44.1-NR) Ref.	NR (53.5-NR) 0.80 (0.56-1.13) $P = 0.2$	37.4 (31.4-NR) 1.19 (0.76-1.88) $P = 0.44$
Adjusted HR (aHR) for OS (95% CI)			
mTTF, mo (95% CI)	7.8 (5.5-9.4) Ref.	7.3 (6.2-9.3) 0.82 (0.67-1.02) $P = 0.08$	6.4 (3.1-12.7) 0.77 (0.56-1.06) $P = 0.11$
aHR for TTF (95% CI)			
ORR, % (95% CI)	40.9 (35.9-46.1) Ref.	48.5 (43.2-53.8) 0.44	41.7 (32.6-51.3) 0.26
P-value*			

mOS=median OS; mTTF=median TTF; CI=Confidence interval. * Multivariable logistic regression.

4556

Poster Session

Assessment of short-chain fatty acid (SCFA) and circulating cytokine trends in a clinical trial of nivolumab/ipilimumab and CBM588 in metastatic renal cell carcinoma (mRCC). *First Author: Nazli Dizman, Yale University School of Medicine, New Haven, CT*

Background: Recent evidence suggests that blood and stool SCFA levels (including acetic acid and butyric acid) are associated with clinical outcomes with immune checkpoint blockade in melanoma (Nomura *et al.* JAMA Network Open 2020). Herein, we report trends in plasma SCFA and cytokine levels in a randomized phase I clinical trial of CBM588, a live bacterial product containing a butyric acid-producing bacterium, *C. butyricum*, in patients with mRCC treated with immune checkpoint blockade. **Methods:** Treatment naive patients with clear cell and/or sarcomatoid mRCC and intermediate- or high-risk IMDC disease were randomized to nivolumab/ipilimumab or nivolumab/ipilimumab and CBM588 in a 1:2 fashion. Blood samples were collected at baseline and on treatment (week 12 +/- 5 weeks). Quantitative assessment of plasma SCFAs and cytokines was performed by liquid chromatography-mass spectrometry and a Human Cytokine 30-plex protein assay, respectively. Changes in SCFAs and cytokine levels were assessed using paired sample T-tests. **Results:** A total of 29 patients were randomized to the nivolumab/ipilimumab (n=19) and nivolumab/ipilimumab with CBM588 (n=10) arms. Objective response rates (ORR) with nivolumab/ipilimumab with and without CBM588 were 58% and 20%, respectively. No statistically significant change in SCFA levels was observed between baseline and on-treatment samples in either arm. Notably, however, a numerical increase in levels of acetic acid (414.3 vs 814.0 nmol/g) and isobutyric acid (7.9 vs 9.0 nmol/g) was seen in the nivolumab/ipilimumab and CBM588 arm. In contrast, both factors decreased in the nivolumab/ipilimumab arm (563.1 vs 401.1 nmol/g and 10.0 vs 8.8 nmol/g, respectively). In patients with an uptrend in isobutyric acid levels with nivolumab/ipilimumab and CBM588, ORR was 64% compared to 50% in those without an uptrend in such levels). Similarly, patients with increases in butyric acid with nivolumab/ipilimumab and CBM588 had an ORR of 66%, compared to 43% among those without an increase in butyric acid levels. Correlations between acetic acid and chemokines, including CCL2 and CCL4, were observed with correlation coefficients of 0.83 and 0.82, respectively (p<0.001 for both). **Conclusions:** A substantial increase in isobutyrate levels in CBM588 responders is indicative of altered amino acid metabolism (specifically, valine and leucine) by modified gut flora in these patients. These observations, combined with alterations in serum cytokines, provide biologic rationale for the clinical activity seen with CBM588 in combination with nivolumab/ipilimumab in this trial. Clinical trial information: NCT03829111. Research Sponsor: Kidney Cancer Association Trailblazer award; Gateway Foundation.

4558

Poster Session

Characterization of the immunophenotype and tumor specificity of CD8+ T-cells in chromophobe renal cell carcinoma (ChRCC) and renal oncocytic neoplasms. *First Author: Chris Labaki, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA*

Background: ChRCC is an uncommon kidney cancer variant that has a poor prognosis in the metastatic setting, with limited response to current standard-of-care immune checkpoint inhibitors (ICIs) used for other RCC histologies. We evaluated the tumor-immune microenvironment of ChRCC and other related oncocytic neoplasms to better understand the immunophenotype of these tumors. **Methods:** We performed paired single-cell RNA sequencing (scRNA-seq), single-cell T-cell receptor sequencing (scTCR-seq), and CD45 immunohistochemistry (IHC) of ChRCC, renal oncocytoma (RO) and low-grade oncocytic tumor (LOT) tumor and matched normal samples. Bulk RNA-sequencing (RNA-seq) data of clear cell RCC (ccRCC), papillary RCC (pRCC) and ChRCC were additionally analyzed using The Cancer Genome Atlas (TCGA) kidney cancer cohorts. T cell antigenic specificities from scTCR-seq were inferred using a comprehensive database of annotated T-cell receptor sequences (VDJdb). Single-cell transcriptomic signatures were used to infer the tumor specificity (Oliveira G, Nature, 2021 and Lowery FJ, Science, 2022) and viral specificity (Oliveira G, Nature, 2021) of CD8+ T-cells from ChRCC, as compared to those from ccRCC (Braun DA, Cancer Cell, 2021). **Results:** ChRCC and other oncocytic tumors had a lower infiltration of CD45+ immune cells as compared to ccRCC (p<0.01). Single-cell analysis was performed on 46,817 cells from 5 tumors (ChRCC: n=3, RO: n=1 and LOT: n=1) and 4 normal samples. Across all tumors, CD8+ T cell clusters displayed a lower expression of immune checkpoints (i.e. *PDCD1* [PD-1], *CTLA4*, *LAG3*, *HAVCR2* [TIM-3], and *TIGIT*) as compared to ccRCC. This was further validated in a bulk RNA-seq analysis using TCGA data, with a significantly lower expression of all immune checkpoints in ChRCC compared to both ccRCC (p<0.01) and papillary RCC (pRCC; p<0.01). Analysis of the T cell receptor repertoire (scTCR-seq) of ChRCC, RO and LOT samples did not show any pattern of clonal expansion, and a higher proportion of T cells in ChRCC were inferred to have a viral specificity, as compared to ccRCC (0.79 vs. 0.1%, respectively). CD8+ T cells from ChRCC (vs. ccRCC) displayed a significantly lower expression of two signatures of tumor specificity (p<0.01), and a higher expression of the viral-specific signature (p<0.01). **Conclusions:** In ChRCC, there is low infiltration by CD45+ immune cells. Although infiltrating CD8+ T cells have a predominantly non-exhausted immune phenotype, they likely lack anti-tumor specificity (i.e. are “bystander” T cells). These findings may help to understand the molecular basis for the lack of response to immunotherapy recently identified among patients with advanced ChRCC, and support future therapeutic strategies to increase infiltration of tumor-specific T cells into the tumor microenvironment. Research Sponsor: Department of Defense (DOD).

4557

Poster Session

Association of neutrophil to eosinophil ratio (NER) with clinical outcomes in patients with metastatic renal cell carcinoma (mRCC) treated with first-line (1L) immune checkpoint inhibitors (ICI)-based regimens. *First Author: Marc Eid, Dana-Farber Cancer Institute, Boston, MA*

Background: ICI-based regimens (ICI + ICI or ICI + VEGF targeted therapy [VEGF-TT]) represent current standard of care systemic therapies for the management of patients with mRCC. Robust biomarkers capable of predicting the therapeutic efficacy and safety of such regimens are still lacking. Eosinophils have been shown to play an important role in the response to immunotherapy. While recent investigations in RCC evaluated NER as a biomarker of poor response to immunotherapy, they did not fully account for the impact of different lines of therapy and the therapeutic classes of ICI-based regimens. We aimed to comprehensively evaluate the association of NER with clinical outcomes in patients with mRCC treated with 1L ICI regimens. **Methods:** We retrospectively reviewed data from patients with mRCC treated with first line ICI-based regimens (dual ICI or ICI + VEGF-TT) at Dana-Farber Cancer Institute. Clinicodemographic information was collected, including tumor histology, ECOG performance status, IMDC risk score. We examined NER at baseline and at 6, 12, and 24 weeks while patients were still receiving treatment. The primary endpoint was overall survival (OS). Time to treatment failure (TTF) was a secondary endpoint. The association of NER with OS and TTF was evaluated using Cox regression models, adjusted for age, gender, BMI, histology, IMDC risk score and autoimmune disease. **Results:** Overall, 156 patients were included in the current analysis, with a median age of 61 years (IQR: 54-67). 60 patients received dual ICI therapy, while 96 were treated with ICI + VEGF-TT combinations. In the ICI+ICI group, a higher NER at baseline, 6 and 12 weeks was associated with worse OS. In the ICI + VEGF group, a higher NER only at 6 weeks appeared to be associated with worse OS. No association between NER and TTF was found. **Conclusions:** To our knowledge, this is the first study to investigate, across therapeutic classes, the association of NER with clinical outcomes in patients with mRCC treated with 1L ICI-based regimens. Higher NER was linked to poor survival outcomes, especially in patients receiving dual ICI therapy. Future translational studies are needed to clarify these findings. Research Sponsor: None.

Association of NER with OS in the ICI+ICI and ICI+VEGF-TT groups.				
	0 Weeks	6 Weeks	12 Weeks	24 Weeks
Median NER – ICI+ICI (IQR)	21 (11.2-32.9)	12 (7.5-19)	9 (7 -22)	10 (6.9-15)
HR for OS (95% CI)	4.8 (1.2-19.1)	1.2 (1.1-1.3)	1.04 (1.02-1.08)	1.04 (0.9-1.2)
Median NER – ICI+VEGF-TT (IQR)	16.4 (13.2-23.7)	13 (9.5-17.6)	12.5 (8.8-20.9)	13.7 (7.7-20.9)
HR for OS (95%CI)	1.0 (0.98-1.02)	1.03 (1.01-1.06)	0.96 (0.91-1.01)	0.95 (0.9-1.02)

Abbreviations: CI, confidence interval; IQR, interquartile range; HR, hazard ratio.

4559

Poster Session

Germline mutations in hereditary renal cell carcinoma (RCC) genes among 32,240 patients with all cancer types. *First Author: Maria Isabel Carlo, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Germline pathogenic variants (PVs) in *VHL*, *FH*, *BAP1* and others cause hereditary syndromes with increased risk of renal cell carcinoma (RCC). Defining the clinical spectrum of these syndromes has been limited by ascertainment bias and their relative rarity. Using a large population of cancer patients who underwent germline and somatic tumor testing, we analyzed the landscape of germline PVs in RCC genes in individuals with all cancer types. **Methods:** We identified patients with germline PVs in RCC genes (*VHL*, *FH*, *SDHB*, *MET*, *FLCN*, *BAP1*) in the MSK-IMPACT cohort, an institutional protocol of patients who had somatic and germline sequencing. The *MITF* E318K variant was analyzed separately given its uncertain role in RCC risk. Objectives were to determine whether patients met clinical criteria for their respective hereditary syndromes, analyze biallelic inactivation in all tumor types, and explore under-recognized cancer associations. Fisher test was used to compare frequency of variants to population. **Results:** Of 32,240 patients who consented to germline results, 55% were female; most common cancer types were breast (n=3600), pancreas (n=3554), prostate (n=3427), with 1166 (3.6%) with RCC. 110 (0.34%) had a germline variant in a RCC syndrome gene (*BAP1*=26, *SDHB*=24, *FH*=24, *FLCN*=19, *VHL*=16, *MET*=1). Of 110 germline positive, 56% met clinical criteria for their hereditary syndrome, and 40% had RCC. For *VHL*, *FH*, *SDHB* and *MET*, a high proportion of patients met criteria for their hereditary syndromes, but this was much less for *FLCN* (Birt-Hogg-Dubé) and *BAP1*. Biallelic inactivation in the tumor, supporting causality, was very high except in *FLCN*. Possible novel cancer associations were liver cancer in *BAP1* (n=5;19%) and colon cancer in *FLCN* (n=4;17%). Additionally, 114 patients had the *MITF* E318K variant; which was not enriched in RCC cases (only 1 RCC) compared to other cancers or population control (odds ratio 0.45; p-value = 0.16, 95% confidence interval: 0.1 - 1.2). **Conclusions:** Germline analysis in a large pan-cancer cohort identifies a high prevalence of patients with hereditary RCC syndromes, variability in clinical phenotype and suggestion of novel cancer associations. The low number of *MITF* E318K variant carriers in RCC cases calls into question its role in RCC risk and warrants further study. Research Sponsor: Robert Wood Johnson Foundation; U.S. National Institutes of Health.

Germline Gene	Met clinical criteria for hereditary syndrome	Number of cancers/individual (median)	History of RCC	Tumor biallelic inactivation
BAP1	10/26 (38%)	1.5	8 (31%)	8/9
SDHB	18/24 (75%)	1	6 (25%)	16/20
FH	17/24 (71%)	1	20 (83%)	13/15
FLCN	5/19 (26%)	1	4 (21%)	5/14
VHL	11/16 (69%)	≥3	5 (31%)	NA
MET	1/1 (100%)	1	1 (100%)	NA

4560

Poster Session

Patient priorities and expectations of systemic therapy in metastatic renal cell carcinoma. *First Author: Dena Battle, KCCure, Alexandria, VA*

Background: As treatment options for metastatic Renal Cell Carcinoma (RCC) have increased in number, selecting therapy has become more complicated. When prioritizing agents today, guidelines recommend selection based primarily on risk classification, as well as consideration of efficacy data, patient characteristics, quality of life, cost, and patient preference. Understanding how patients prioritize treatment selection and define treatment success is crucial to improving patient/provider communication and to improving future drug development. **Methods:** The survey was developed by the Kidney Cancer Research Alliance (KCCure) and was broadcast between 07/2022 and 09/2022 to patients via website, mailing lists and social media platforms. Those who agreed to participate were surveyed for demographics (age, gender, race, income, country) and clinical characteristics (date of the diagnosis, disease stage, treatment history). Descriptive statistics summarized the survey data. **Results:** 399 out of 1,062 patients surveyed had metastatic disease. 80% of patients were receiving or had received systemic therapy, 20% of patients had not yet received systemic therapy. 52% were female and 48% were male, with a median age of 57 years (range 28-86). Patients identified as white (89%) and living in the United States (86%). 69% of patients reported that they did not know their IMDC or risk status, 10% were favorable risk, 11% were intermediate risk and 10% were poor risk. When asked to select the most important outcome for treatment selection on a rank-choice scale from 1 to 8, the chance to eliminate all evidence of disease (complete response) scored highest (6.6), followed by durability of response (5.1), improved quality of life (5.0), rapid reduction of tumors (4.9), ability to go off therapy (4.2), low risk of toxicity (4.0) and reduction of tumor symptoms (4.0). Patients ranked low cost as the least important factor in selecting treatment (2.3). 70% of patients defined "long-term" response to therapy as five years or longer, and over a quarter of patients (26%) defined long-term response as 10 years or longer. When asked to define treatment success, patients rank radiological reduction in tumor size (83%) as the most important factor, followed by stable disease (67%), improved quality of life (48%) and the ability to return back to work (22%). The lowest ranked choice was "I just trust my doctor" (17%). **Conclusions:** Most patients are not familiar with their risk classification and may not realize the significance of this factor in treatment selection. Patients rank complete response as the most important outcome/desire when considering treatment options. Cost is the least important factor for patients in selecting treatment. Patient perceptions of long-term response to therapy may differ from provider perceptions. More research is needed to improve patient/provider communication in the therapy selection process. Research Sponsor: None.

4562

Poster Session

Pathologic concordance rate and outcomes by histologic subtype in advanced papillary renal cell (pRCC) carcinoma: An analysis from the SWOG S1500 (PAPMET) trial. *First Author: Abhishek Tripathi, City of Hope Comprehensive Cancer Center, Duarte, CA*

Background: The PAPMET trial demonstrated significantly improved progression-free survival (PFS) with cabozantinib vs. sunitinib in advanced pRCC (median: 9.0 vs. 5.6 mos; hazard ratio (HR): 0.60; 95% CI 0.37–0.97). Until recently, pRCC was subclassified as type 1 vs. 2 based on histologic features. During conception of the PAPMET study, we hypothesized that patients with type 1 pRCC will derive more benefit from cabozantinib compared to those with type 2 disease, given enrichment of MET alterations in the former. In this secondary analysis, we report the outcomes stratified by histologic subtype per central review. **Methods:** Patients with advanced pRCC who had received up to 1 line of therapy were randomized to receive either sunitinib, or cabozantinib, crizotinib or savolitinib stratified by pRCC subtype (type 1, type 2 or not otherwise specified [NOS]). Pathologic data from local pathology review was catalogued. Central pathology review was conducted by 3 expert genitourinary pathologists who independently reviewed tumor specimens. Discordant opinions among these pathologists were individually arbitrated and a unified diagnosis was assigned. Central pathology review results were considered the true positive and the sensitivity, and the positive predictive value (PPV) of local review was estimated for histologic subtypes. Clinical outcomes (objective response rate (ORR) and PFS) were compared between histologic subtypes (by central review) in the cabozantinib and sunitinib arms. **Results:** Amongst the 147 patients with available local and central pathology review, 17.7% (n=26), 53% (n=78) and 29.3% (n=43) were characterized as having type 1, 2 or NOS/mixed pRCC by local review compared to 29.3% (n=43), 45.6% (n=67) and 25.2% (n=37) respectively by central review. Individual cases were frequently reclassified and local pathology review demonstrated low sensitivity (type 1: 49%, type 2: 67% and NOS: 43%) and PPV (type 1: 80%, type 2: 57% and NOS/mixed: 37%) across subtypes. During central review, complete agreement amongst the 3 pathologists was seen in only 33.3% (n=49) of cases and was highest in type 2 tumors (40%; n=27). Compared to sunitinib, cabozantinib demonstrated numerically higher ORR and PFS in both type 1 and type 2 pRCC subgroups. **Conclusions:** Designation of pRCC subtype by central review did not identify a subset of patients with greater clinical benefit from cabozantinib. Further, classification of subtype was challenged by discordance in both local and central review. Supporting the removal of type 1 and 2 designations from the 2022 WHO guidelines, these findings highlight the limited clinical value and significant challenges associated with subtyping of pRCC. Clinical trial information: NCT02761057. Research Sponsor: AstraZeneca plc, Exelixis, Inc., and Pfizer, Inc.; U.S. National Institutes of Health.

	Type 1		Type 2	
	ORR (%)	PFS (mos, 95% CI)	ORR (%)	PFS (mos, 95%CI)
Sunitinib	0	8 (7.3,21.8)	9.5	3.1 (2.6, 6.1)
Cabozantinib	13.3	9.8 (5.14, 15.4)	26.6	6.1 (3.2, 9.8)

4561

Poster Session

Association between intra-tumoral microbiome and clinical benefit (CB) from immunotherapy (IO) in patients with metastatic renal cell carcinoma (mRCC). *First Author: Luis A Meza, City of Hope Comprehensive Cancer Center, Duarte, CA*

Background: Specific bacteria and microbial diversity in the gut may drive response to IO in patients (pts) with mRCC (Routy et al Science 2018; Salgia et al Eur Urol 2020). Despite the evidence of bacterial proliferation in RCC tumors (Heidler et al Urol Int 2020), the impact of the intra-tumoral microbiome in RCC has been poorly delineated. Here, we explored its association to CB in mRCC pts receiving IO-based regimens. **Methods:** We identified pts with mRCC and available RNA sequencing (RNA-seq) data from tumor tissue collected prior to start of IO. Intra-tumoral microbiome analysis was performed on formalin-fixed paraffin-embedded samples. Following quality and adapter trimming, RNA-seq reads were mapped to a human genome to filter host reads using the STAR alignment tool. Taxonomic classification was performed using Kraken2 and Bracken. Following removal of common contaminants, the relative abundances among all non-human species were calculated. Microbial diversity was assessed using the Shannon index and statistical analysis performed using a t-test. Relative microbial abundance was compared between tumors from pts with or without CB from 1st line IO treatment using the Kruskal-Wallis test. P-values less than 0.05 were considered significant. **Results:** A total of 96 pts (71:25, M:F) with mRCC were included in this analysis. Of these, 85 (89%) had clear cell histology and 68 (71%) were IMDC intermediate/poor risk. The median age at the time of tissue sampling was 62.7 yrs old and most of the samples analyzed (57%) were collected from the primary site. IO, alone or in combination, was received as 1st line treatment in 57 pts (59%), with the most common regimen being nivolumab/ipilimumab (47%). CB from 1st line IO was observed in 39 (68%) pts. Tumors from pts achieving CB from 1st line IO had elevated microbial diversity compared to tumors from pts without CB (p=0.01). Tumor samples from these pts also had a significantly higher relative abundance of several bacterial genera compared to tumors from pts without CB. These included *Pasteurella*, *Escherichia*, and *Cloacibacterium* (p<0.05). No significant differences in bacterial diversity were observed between CB and no-CB pts receiving IO as 2nd line or beyond. **Conclusions:** This is the largest study exploring the association between the intra-tumoral microbiome of mRCC and CB from IO. In line with gut microbiome studies, an increased intra-tumoral Shannon diversity index was also associated with CB to IO in our 1st line cohort, further suggesting that bacterial diversity could be a driver of response. Additionally, several genera associated with CB are particularly relevant. For instance, members of the *Pasteurella* genus have been implicated in the activation of c-myc, a proto-oncogene that has been shown to induce PD-L1 expression. Research Sponsor: None.

4563

Poster Session

Kidney cancer mortality in the United States between 1999 and 2020: An observational analysis of outcomes by gender, race, and ethnicity. *First Author: Nour Abdallah, Cleveland Clinic, Cleveland, OH*

Background: Kidney cancer (KC) is one of the leading causes of cancer mortality, with recent data showing an increase in incidence and mortality worldwide. Gender, racial, and ethnic disparities can impact KC outcomes. Studies investigating the outcomes of diverse patient populations spanning the cytokine, targeted therapy and immunotherapy eras have been limited. This study aims to investigate trends in age-adjusted mortality rates (ASMR) by gender, race, and ethnicity in the US at national and state levels. **Methods:** We utilized the Center for Disease Control Wonder database to extract national and state-wide KC mortality data (ICD-10 C64) from 1999-2020. ASMR and 95% confidence intervals (CI) were extracted based on gender, race and ethnicity reported per 100,000 population. To evaluate the difference between metro and non-metro regions, we divided the national trends based on 2013 Urban NCHS Urban-Rural scheme. Jointpoint regression analysis was performed to evaluate trends. **Results:** In total, 284,224 KC deaths were reported over twenty years, with an overall decrease in ASMR in recent years. Males had significantly higher ASMR throughout the study period, with a lower decrease than females. Amongst racial groups, American Indians (AI) had the highest mortality in 1999 (5.7). However, due to the smaller decrease of ASMR in Whites compared to Non-Whites, Whites showed the highest ASMR (3.9) in 2020. According to ethnicity, Non-Hispanic Whites (NHW) had significantly higher ASMR than Hispanics in 1999 (4.0 vs. 3.5) and 2020 (3.5 vs. 3.0) with a similar rate of decline (-11.4% vs. -12.5%). State-wise, ASMR decreased in all states except Utah (+45.8%), Arkansas (+18.4%), Hawaii (+15.4%), Montana (+5.3), Kansas (+2.7) and Nevada (+2.6). Interestingly, non-metro regions showed higher ASMR throughout the study period. Also, while there was a steep decline in ASMR (15%) in metro regions, only a minimal decline (-4.7%) was observed in non-metro regions. **Conclusions:** Over the last two decades, there has been a decrease in the ASMRs across all genders, races and ethnicities and in most states in the USA. The decrease in ASMR is likely multifactorial, related to earlier detection and improved treatments. However, differences in outcomes by gender, race, and ethnicity persist, highlighting the need for strategies to better understand the etiology of differences and mitigate disparities across social determinants of health across gender, racial, and ethnic groups. Research Sponsor: None.

ASMR; 95% CI	1990	2020	Percentage change
Overall	4.0 (3.9-4.1)	3.4; 3.4-3.5	-15.0
Urbanization: Metro	3.9 (3.8-4.0)	3.3; 3.2-3.3	-15.4
Non-metro	4.3 (4.1-4.5)	4.1; 4.0-4.3	-4.7
Gender:	2.7 (2.6-2.7)	2.1; 2.0-2.1	-22.2
Female			
Male	5.8 (5.7-5.9)	5.0; 4.9-5.1	-13.8
Race:	5.7 (4.4-7.2)	3.5; 2.9-4.1	-38.6
AI			
Asian	1.8 (1.4-2.1)	1.6; 1.5-1.8	-11.1
AA	4.1 (3.8-4.4)	3.3; 3.1-3.4	-19.5
White	4.0 (4.0-4.1)	3.9; 3.9-3.9	-2.5

4564

Poster Session

Microbial metabolism of tryptophan is associated with resistance to immune checkpoint (ICB) therapy in renal cell cancer (RCC). *First Author: Shahla Bari, Duke University School of Medicine, Durham, NC*

Background: Metastatic RCC has a poor prognosis. Despite improvement in treatment outcomes with ICB and targeted therapy, many patients fail to respond to first line therapy and deep and durable responses remain elusive. The tryptophan metabolite kynurenine, an agonist of the immunosuppressive aryl hydrocarbon receptor (AhR), is associated with resistance to ICB. However, IDO (Indole 2,3 dioxigenase) blockers which inhibit tryptophan metabolism to kynurenine failed to show benefit in clinical trials, suggesting the presence of alternate AhR activation. We hypothesize that microbial metabolism of tryptophan to indole metabolites may be associated with AhR activation and ICB resistance. **Methods:** We prospectively collected stool and plasma of 79 treatment naïve metastatic RCC patients, treated with ICB +/- Tyrosine kinase inhibitors (TKI). Samples were collected at treatment initiation and at time of first response assessment (12+/-3 weeks). We evaluated stool metagenomics and untargeted stool and plasma metabolomics among responders (R) and non-responders (NR). We focused on kynurenine/tryptophan and indoles/tryptophan ratio to evaluate differential host and microbial metabolism of tryptophan. A responder was classified as progression free survival (PFS) greater than six months. We also performed global metabolomics on tumors of germ-free (GF) & specific pathogen free (SPF) mice to identify microbial & host metabolites. **Results:** Among 79 patients, 28 were treated with combination ICB, while 51 patients were treated with ICB + TKI. Median follow up for entire cohort was 9.5 months. 65% of patients had PFS > six months, while 27% of all patients had continued response at one year. Using unpaired t test comparing baseline relative abundance of metabolites between R vs NR - plasma Kynurenine/tryptophan ratio was significantly higher in NR vs R, at baseline (0.04 vs 0.02, p=0.017) and further increased in NR at 3 months (0.05 vs 0.02, p=0.02). Microbial metabolites of Tryptophan -Indole pyruvic acid (IPA), Indole carboxylic acid (IpA) and Indole acetaldehyde (IAA) were differentially associated with ICB resistance and was significantly higher in NR (IcA: 8.0 vs 4.96, p=0.03; IPA: 76.8 vs 64.9, p=0.02; IAA: 76.8 vs 64.6, p=0.026). We also noted differential enrichment of microbial KEGG enzymes associated with IPA, IAA and IcA production in the stool of NR patients compared to R. Microbial origin of IpA, IAA and IcA was confirmed by its absence in tumor of GF mice. **Conclusions:** This is first study in metastatic RCC which shows the association of indoles (microbial metabolites of tryptophan) with resistance to ICB. These indoles are known to be potent AhR agonists and are associated with immunosuppression suggesting that microbial metabolism of tryptophan may represent a novel pathway for ICB resistance in RCC patients. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology.

4566

Poster Session

Disitamab vedotin, a novel humanized anti-HER2 antibody-drug conjugate (ADC), combined with toripalimab in patients with locally advanced or metastatic urothelial carcinoma: An open-label phase 1b/2 study. *First Author: Xinan Sheng, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Genitourinary Oncology, Peking University Cancer Hospital and Institute, Beijing, China*

Background: Disitamab vedotin has shown promising data across a spectrum of HER2 expression in patients with locally advanced or metastatic urothelial carcinoma (la/mUC) who progressed on chemotherapy. This study was conducted to evaluate the safety and efficacy of disitamab vedotin plus anti-PD-1 antibody in advanced urothelial carcinoma. **Methods:** This is an open-label, multicenter, phase 1b/2 trial to evaluate the safety and activity of RC48-ADC combined with toripalimab, a humanized immunoglobulin G₄ monoclonal antibody against PD-1 in mUC. Patients received RC48-ADC at 1.5 or 2 mg/kg, in combination with 3mg/kg toripalimab every two weeks in a dose-escalation and expansion cohort until confirmed disease progression assessed by the investigators, unacceptable toxicity, or voluntary withdrawal. The primary endpoint was safety; secondary endpoints included efficacy and tumor tissue biomarkers. **Results:** Forty-one la/mUC patients were enrolled (22 males; median age 66 y [42-76]; 61% treatment-naïve). 54% of patients had visceral metastases (mets), including 24% with liver mets. The primary site was in upper tract UC in 54%. HER2 expression IHC 2+ or 3+ was in 59% patients, and PD-L1 positive in 32%. No dose-limiting toxicity was observed and the recommended dose was RC48-ADC 2mg/kg plus toripalimab 3mg/kg every two weeks. By the cutoff date of 18 November 2022, the confirmed ORR was 73.2% (95%CI: 57.1, 85.8), including 9.8% CR. The ORR was 76.0% for treatment-naïve patients. In HER2 IHC 3+/2+, IHC 1+, and IHC 0 subgroups, the ORR was 83.3%, 64.3%, and 33.3%, respectively. The ORR was 61.5% and 78.6% in PD-L1 positive and negative subgroups. DCR was 90.2% (95% CI, 76.9–97.3), with a median progression-free survival (PFS) of 9.2 months (95%CI: 5.7-10.3) and 2-year overall survival (OS) rate of 63.2%. All patients experienced treatment-related adverse events (TRAEs). The most common TRAEs were AST/ALT increase (68.3%), peripheral sensory neuropathy (61.0%), asthenia (61.0%), γ -glutamyl transferase increase (56.1%), hypertriglyceridemia (53.7%), and appetite decrease (51.2%). Grade 3 or greater TRAEs occurred in 43.9% of patients. Twenty-three patients (56.1%) had immune-related AEs (14.6% $\geq$ G3), including immune-related skin reactions, hyperglycemia, pneumonitis, hepatitis, and myositis. **Conclusions:** RC48-ADC in combination with toripalimab demonstrated promising efficacy in patients with la/mUC and a manageable safety profile. A phase 3 study is currently ongoing to compare the safety and efficacy of this regimen with standard of care. Clinical trial information: NCT04264936. Research Sponsor: RemeGen.

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Poster Session

Gender disparities in metastatic RCC therapies and outcomes. *First Author: Olivia French Gordon, George Washington University Hospital, Washington, DC*

Background: The incidence of metastatic renal cell carcinoma (mRCC) is rising globally in both males and females. Previous studies have shown that females with mRCC experience better overall survival (OS) when compared to males. In the era of immunotherapy (IM) as part of standard of care, gender-based outcome disparities are unclear. In this study, we identify gender-specific trends in treatment regimen and OS. **Methods:** The National Cancer Database (NCDB) was queried from 2004 to 2019 for a retrospective cohort analysis of mRCC patients. 51,596 males and 25,528 females were reviewed. The primary endpoints were OS and predictors of receipt of IM. Kaplan-Meier (KM) analysis was used to assess gender-based OS and compare OS in patients who received or did not receive CN or IM. Binomial logistic regression was performed to examine gender as a predictor of treatment received. Cox proportional hazards model assessed the impact of age, gender, sites of metastases, Charlson-Deyo comorbidity classification, insurance type, treatment facility, year of diagnosis, CN, and IM on OS. **Results:** In KM analyses, females had lower median OS compared to males (7.200 months vs 8.940 months, p<0.001). Higher median OS was found in patients who received IM (21.3 vs 7.6 months; p<0.001) and CN (22.1 vs 5.13 months; p<0.001). Logistic regression demonstrated that females were less likely to receive IM after controlling for the variables listed above (OR 0.839 (95% CI: 0.787 - 0.894), p<0.001). Cox regression demonstrated that when adjusting for clinicopathologic variables and treatment regimen, female gender independently conferred a statistically significant negative impact on OS (HR = 1.039 (95% CI: 1.015-1.063), p=0.001). **Conclusions:** While CN remains an efficacious treatment option, advances in IM have led to targeted therapies that improve OS in mRCC patients. We demonstrate that a gender-based discrepancy in mRCC survival persists. In contrast to previous literature, our analysis found worse OS as well as an underutilization of IM in female mRCC patients. Moreover, females with mRCC have increased mortality even when accounting for IM. Therefore, further investigation is needed to elucidate the causes of survival discrepancy in the modern era of mRCC treatment. Research Sponsor: None.

	Male	Female	p-value
Median Age	65	68	<.001
Immunotherapy	6,537 (12.9%)	2,557 (10.2%)	<.001
Radical Nephrectomy	15,496 (31.2%)	6,955 (28.2%)	<.001
Clear Cell RCC Histology	39,888 (77.3%)	19,543 (76.6%)	.019
Clinical T stage	0 (106, 0.3%)	0 (31, 0.2%)	<.001
	1 (10,868, 28.4%)	1 (5,239, 28.0%)	
	2 (10,953, 29.7%)	2 (5,172, 27.6%)	
	3 (11,404, 29.8%)	3 (5,746, 30.7%)	
	4 (4,897, 12.8%)	4 (2,533, 13.5%)	
CDCC	0 (35,463, 68.7%)	0 (17,401, 68.2%)	<.001
	1 (10,029, 19.4%)	1 (5,276, 20.7%)	
	2 (3,596, 7.0%)	2 (1,743, 6.8%)	
	3+ (2,508, 7.1%)	3+ (1,108, 4.3%)	

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Poster Session

Real-world response rates and clinical outcomes of patients treated with first-line (1L) platinum-based chemotherapy (PBC) in advanced urothelial cancer (aUC). *First Author: Helen H Moon, Kaiser Permanente, Riverside, CA*

Background: Standard of care has been established as 1L PBC followed by avelumab 1L maintenance (1LM) in eligible pts based on the JAVELIN Bladder 100 trial (NCT02603432) which showed that avelumab 1LM significantly prolonged overall and progression-free survival (OS, PFS) in pts with aUC with no disease progression after 1L PBC. Contemporary and robust real-world (rw) data are limited in pts treated with 1L PBC; however, because response status to PBC determines avelumab 1LM eligibility, it is critical to understand rw rates. This study aimed to assess current rw rates and rw outcomes in pts treated with 1L PBC. It also sought to understand avelumab 1LM eligibility and its early utilization since FDA approval on June 30, 2020. **Methods:** A non-interventional, retrospective cohort study of pts with aUC in the US was conducted using data from Flatiron Health's electronic health record database. Pts were included if they were diagnosed with aUC between Jan 1, 2017, and Sep 30, 2021, received 1L PBC, did not have a progression event and had an observed rwR (complete response [rwCR]/partial response [rwPR]) or stable disease (rwSD) during 1L. Pt characteristics and rw outcomes were described based on response type (rwCR/PR, rwSD); rwPFS and rwOS were measured from time of 1L PBC initiation using the Kaplan-Meier method. **Results:** 1,245 pts with aUC received 1L PBC and had rwR data available during study period. Of these, 80% (n=998) may have been eligible to receive avelumab 1LM (rwCR/PR: 60%, rwSD: 20%). Key characteristics and outcomes by rwR are summarized. During the study period that occurred after FDA approval of avelumab 1LM, 435 pts discontinued 1L PBC, 78% (n=339) of these pts had observed rwCR/PR/SD during 1L PBC, and 29% (n=97) of maintenance eligible pts received avelumab 1LM. Follow-up time for avelumab 1LM treated pts was short (median 7.5 months from initiation of 1LM) and outcomes were immature at the end of the study period. **Conclusions:** In this rw study, a large proportion of pts with aUC treated with 1L PBC had rwR or rwSD (~80%) and may have been eligible for avelumab 1LM, which is the standard of care supported by international guidelines. RwR rate appears slightly higher compared to historic data, and may reflect better general patient care, as shown in recent large phase 3 trials (NCT02853305, NCT02516241, NCT02807636). Early uptake of avelumab 1LM was observed, and future studies with longer follow-up may demonstrate increased utilization and allow assessment of potential impact on outcomes. Research Sponsor: Pfizer; Merck KGaA.

Key characteristics and outcomes.	rwCR/PR (n=752)	rwSD (n=246)
Age, median, years	70	71
Male, %	72.2	78
White, %	65.6	68.7
ECOG PS (0/1, 2+, unknown), %	68.9, 8.4, 22.7	67.9, 10.2, 22
Cisplatin- / carboplatin-based, %	58.6 / 41.4	54.9 / 44.7
rwPFS (95%), months	9.1 (8.5-9.9)	6.5 (6.0-8.1)
rwOS (95%), months	23.2 (20.8-26.6)	18.7 (14.9-24.4)

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Poster Session

Enfortumab vedotin (EV) with or without pembrolizumab (P) in patients (pts) who are cisplatin-ineligible with previously untreated locally advanced or metastatic urothelial cancer (la/mUC): Additional 3-month follow-up on cohort K data. *First Author: Terence W. Friedlander, University of California, San Francisco Medical Center, San Francisco, CA*

Background: There is a high unmet need for effective and durable first-line (1L) treatment options in cisplatin-ineligible la/mUC. EV and P have shown survival benefit as monotherapies in 2L+ la/mUC, and preclinical studies demonstrate that EV induces hallmarks of immunogenic cell death, which may be further augmented by PD-1 inhibitors (e.g., P). Promising results from EV-103 dose escalation/Cohort A (DE/A) provided rationale for this randomized Cohort K for which we are disclosing additional follow-up to previous reports (Rosenberg, ESMO 2022) on efficacy and safety. **Methods:** Untreated cisplatin-ineligible pts with la/mUC were randomized 1:1 to EV (1.25 mg/kg, day 1, day 8) as monotherapy (EV mono) or in combination with P (200 mg, day 1) using 3-week cycles. The primary endpoint was confirmed objective response rate (cORR) per RECIST v1.1 by blinded independent central review (BICR). Secondary endpoints included duration of response (DOR), disease control rate (DCR), progression-free survival (PFS), overall survival (OS), and safety. No formal statistical comparisons were planned between treatment arms. **Results:** 149 pts were treated; EV+P, n=76; EV, n=73. Median follow-up (95% CI) for EV+P, 17.6 (16.03, 20.37) months; EV+P cORR (95% CI), 64.5% (52.7, 75.1); median DOR not reached; DCR, 86.6% (77.1, 93.5); median PFS, and OS not reached. PFS rate at 6 and 12 months (95% CI), 73.8% (62.01, 82.42) and 54.5% (41.74, 65.61); OS rate at 6 and 12 months (95% CI), 88.2% (78.48, 93.65) and 81.5% (70.78, 88.61). Median follow-up (95% CI) for EV mono, 18.2 (15.90, 20.07) months; cORR (95% CI), 45.2% (33.5, 57.3); median DOR, 13.2 months (6.14, -); DCR, 79.5% (68.4, 88.0); median PFS and OS, 8.2 (6.05, 15.28) and 21.7 (15.47, -) months; PFS rate at 6 and 12 months, 64.2% (51.09, 74.69) and 40.3% (26.62, 53.60); OS rate at 6 and 12 months, 83.6% (72.87, 90.31) and 69.7% (57.68, 78.87). EV treatment-related adverse events of special interest (AESIs) include skin reactions (EV+P, 67.1%; EV mono, 45.2%), peripheral neuropathy (EV+P, 63.2%; EV mono, 54.8%), and hyperglycemia (EV+P, 14.5%; EV mono, 11.0%). In EV+P, the most frequent (any grade) P treatment-emergent adverse events of special interest were severe skin reactions (27.6%), hypothyroidism (13.2%), and pneumonitis (9.2%). **Conclusions:** With an additional 3 months of follow-up, EV+P continues to show a high cORR with rapid and durable responses as 1L treatment in cisplatin-ineligible pts with la/mUC, including a manageable safety profile with no new safety concerns after extended treatment exposure. DOR, PFS and OS will evolve with further follow-up and continue to trend similarly to those of DE/A; EV monotherapy was consistent with prior results. Clinical trial information: NCT03288545. Research Sponsor: Seagen Inc.

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Poster Session

Final results from SAUL, a single-arm international real-world study of atezolizumab (atezo) in 1004 patients (pts) with pretreated locally advanced/metastatic urinary tract carcinoma (UTC). *First Author: Cora N. Sternberg, Englander Institute for Precision Medicine, Weill Cornell Medicine, New York, NY*

Background: In the SAUL study (NCT02928406), clinical outcomes in a broad population were similar to findings from phase 3 trials of anti-PD-(L)1 in highly selected pts. We report the final analysis 4 y after enrolling the last pt. **Methods:** Eligible pts had locally advanced/metastatic urothelial or non-urothelial UTC that had progressed during or after 1–3 prior lines of therapy for advanced UTC (or within 12 months of [neo]adjuvant therapy). Unlike most phase 3 immunotherapy trials, pts with autoimmune disease (AID), ECOG PS 2, creatinine clearance (CrCl) ≥ 15 –30 mL/min, and/or stable CNS metastases were eligible. Pts took atezo 1200 mg q3w until disease progression or unacceptable toxicity. The primary endpoint was safety. Secondary endpoints included overall survival (OS) and duration of response (DoR). **Results:** Among 997 treated pts, 10% had ECOG PS 2, 5% had CrCl < 30 mL/min, 4% had a history of AID, and 7% had 2–3 prior lines of therapy. At data cutoff (Dec 20, 2022; median follow-up 55 mo), 78% of pts had died. Median treatment duration was 2.8 mo (range 0–62 mo; mean 9.5 mo), 96 pts (10%) took atezo for > 3 y, and 68 (7%) for > 4 y. Grade ≥ 3 adverse events (AEs) occurred in 51%; AEs led to atezo discontinuation in 8%. We show outcomes overall and in key subgroups. OS was > 4 y in 136 pts (14%); 132 responders had OS > 2 y. **Conclusions:** After 55 mo median follow-up, median OS was 8.6 mo and 3-y OS was 21% in a real-world population including important understudied subgroups. Long-term safety data continue to support the tolerability of atezo in pts with complex comorbidities. AESIs were not increased in pts typically considered to be at increased risk of immune-related AEs. OS was similar to trials in highly selected pts. Ongoing analyses are characterizing pts with exceptional long-term outcomes. Clinical trial information: NCT02928406. Research Sponsor: F. Hoffmann-La Roche Ltd.

Endpoint	All pts (n=1004)	AID (n=36)	Concomitant ste-roids (n=55)	CrCl < 30 mL/min (n=46)	ECOG PS 2 (n=100)	CNS meta-stases (n=14)	PD-1 IC2/3 (n=268)	0 prior lines (n=362)
Median OS, mo (95% CI)	8.6 (7.8–9.7)	8.5 (7.3–11.7)	6.1 (3.1–10.1)	5.7 (3.4–11.0)	2.1 (1.5–2.4)	3.7 (1.5–7.0)	11.2 (8.8–16.1)	8.6 (7.3–10.4)
OS rate, % (95% CI)								
1 y	41 (37–44)	21 (18–49)	33 (21–45)	25 (14–39)	11 (6–19)	19 (4–44)	48 (42–54)	41 (35–46)
2 y	27 (24–30)	21 (9–36)	25 (14–37)	23 (12–36)	8 (3–14)	0 (NE–NE)	34 (28–40)	27 (22–32)
3 y	21 (19–24)	18 (7–32)	19 (10–31)	13 (5–25)	6 (2–13)	0 (NE–NE)	30 (24–36)	21 (17–26)
Overall response rate, % (95% CI)	16 (14–18)	19 (8–36)	18 (9–31)	17 (8–31)	5 (2–11)	0 (0–23)	24 (19–29)	16 (12–20)
Median DoR, mo (95% CI)	27.8 (18.9–43.3)	11.1 (4.4–45.5)	10.7 (4.2–42.0)	20.7 (4.2–NE)	6.4 (4.1–14.2)	–	35.2 (15.2–NE)	35.4 (13.9–NE)
Treatment-related grade ≥ 3 AEs, %	16 ^a	31	15	9	14	14	20 ^b	16 ^c
	15 ^a	19	16	7	10	0	20 ^b	16 ^c

^an=997, ^bn=264, ^cn=360.

AEs = AE of special interest; PD-1 IC2/3 = $\geq 5\%$ PD-1-expressing tumor-infiltrating immune cells; NE = not estimable.

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Poster Session

Mismatch repair deficiency and microsatellite instability-high in urothelial carcinoma: A systematic review and meta-analysis. *First Author: Elias Chandran, National Cancer Institute, Bethesda, MD*

Background: Mismatch repair deficiency (dMMR) and microsatellite instability-high (MSI-H) occur in a small subset of urothelial carcinoma (UC) and confer a sensitivity to immunotherapy in multiple solid tumors. Due to the rarity of this patient subset in UC, there is a lack of prospective data on their prevalence or of clinical outcomes with immunotherapy and other treatment modalities. **Methods:** We performed a systematic review with the objectives of estimating the prevalence of dMMR and MSI-H in urothelial bladder cancer (BC) and upper tract urothelial carcinoma (UTUC) apart from estimating survival and clinical outcomes of treatment. We searched for published prospective and retrospective studies, review articles, case reports, case series, conference proceedings, letters, commentaries, and editorials on dMMR and MSI-H in BC and UTUC published up to 10/26/2022 in PubMed, Cochrane CENTRAL, Embase and Web of Science: Core Collection databases. The study protocol is registered on the PROSPERO database (CRD42022365690). Prevalence data were analyzed using meta-analysis with random-effects models and are reported here. **Results:** A total of 1,750 studies were screened, of which 125 were included. Thirty-six studies (including 5,113 patients) reported frequencies of dMMR, and 42 studies (including 21,291 patients) reported on MSI-H. Of the total included patients, sex was reported in 11,225, with 72.6% being male and 27.4% female. Age ranged from 17–97 years. Reported primary site was BC in 64.4%, UTUC in 16.3% and not stated in 19.3%. Disease stage reported in 5,341 patients was M0 in 75.0% and M1 in 25.0%. Of the M0 patients, tumor stage data were available in 3,149 patients: T1 in 33.6% and T2–T4 in 66.4%. The pooled weighted prevalence of dMMR in UC patients was 6% (95% CI 5–8%). The breakdown for BC and UTUC were 2% (95% CI 1–3%) and 9% (95% CI 7–12%), respectively. The three most frequent MMR protein loss patterns in UC, BC and UTUC are shown in the table. Out of 42 studies reporting MSI status, 21 used polymerase chain reaction (PCR) and 21 used next-generation sequencing (NGS). Pooled weighted prevalence of MSI-H in UC was 3% (95% CI 2–3%). In BC, the prevalence was 1% (95% CI 1–1%) and in UTUC, it was 11% (95% CI 8–13%). **Conclusions:** dMMR and MSI-H were observed more frequently in UTUC than BC. Further analysis on survival and clinical outcomes of dMMR/MSI-H UC with different treatment modalities is ongoing. Additionally, clinical trials in dMMR and/or MSI-H UC are in development to study immunotherapeutic strategies to improve outcomes in both early and advanced stages for this small but important subset of patients. Research Sponsor: None.

Tumor	UC	BC	UTUC
MMR protein loss pattern (frequency)	MSH2/MSH6 63/3,903 (1.6%) MSH6 57/3,903 (1.5%) MLH1/PMS2 13/3,903 (0.3%)	PMS2 9/1,671 (0.5%) MLH1/PMS2 8/1,671 (0.5%) MSH6 7/1,671 (0.4%)	MSH2/MSH6 56/1,465 (3.8%) MSH6 49/1,465 (3.3%) MLH1/PMS2 4/1,465 (0.3%)

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Poster Session

A phase I study of bintrafusp alfa and NHS-IL12 (M9241) alone and in combination with stereotactic body radiation therapy (SBRT) in patients with metastatic genitourinary (GU) malignancies. *First Author: Nicholas I. Simon, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD*

Background: Bintrafusp alfa is a novel bifunctional fusion protein targeting PD-L1 and TGF- β which has demonstrated clinical efficacy in some tumor types and a manageable safety profile. M9241 is an immunocytokine that allows targeting of the pro-inflammatory IL-12 cytokine to exposed DNA in necrotic portions of tumors. SBRT can help promote anti-tumor responses and may potentially synergize with immunotherapy by inducing DNA damage. **Methods:** This is an open label, non-randomized, three arm phase I trial of bintrafusp alfa and M9241 combination therapy administered alone (Arm 1), or with either sequential (Arm 2), or concurrent (Arm 3) SBRT. Eligible patients must have metastatic non-prostate GU cancers with measurable disease. Bintrafusp alfa was used at a flat dose of 1200mg (q2w) for arms 1–3 and a fixed dose of SBRT (24Gy in 3 fractions) was used for arms 2–3. M9241 was administered at 16.8mcg/kg (q4w) for Arm 1 and decreased if side effects occur. Arm 1 used bintrafusp alfa and M9241 alone, with the maximum tolerated dose (MTD) of M9241 being dose level 1 (DL1) for Arm 2. Arm 2 used SBRT followed by bintrafusp alfa and M9241, with the MTD of M9241 being DL1 for Arm 3. Arm 3 used concurrent SBRT with bintrafusp alfa and M9241. The primary objective was to determine the safety and highest tolerable doses of each arm. Secondary objectives include objective response rate (ORR), progression free survival (PFS), and overall survival (OS). **Results:** Study enrollment began in 12/2019, with interim safety analyses performed quarterly. A total of 16 patients have enrolled, 12 in Arm 1, three in Arm 2, and one in Arm 3 at data cutoff 1/2/23. The first six patients enrolled in Arm 1 had no DLTs allowing Arm 2 to open. Arm 2 had no DLTs after 3 patients enrolled allowing Arm 3 to open. At data cut off four of 16 patients remained on treatment. The median age was 63 and 19% were female. The most frequent TRAEs were fatigue (grade 2, 38%), lipase increase (grade 2+3, 31%), and anemia (grade 2+3, 31%). Grade 3 hematuria occurred in 2 patients (13%); a grade 4 creatinine increase occurred in one (8%). There were no grade 5 TRAEs. Two (13%) patients had treatment discontinued and 5 (31%) had dose reductions due to AEs. Of the 16 patients enrolled on study, 11 were evaluable at data cutoff. Currently three patients (38%) on Arm 1 and one patient (50%) in Arm 2 had objective responses, corresponding to an ORR of 36.4% (4/11). All responses have been partial responses. On Arm 1 the responding patients included one with small cell carcinoma of the renal pelvis, one with Leydig cell tumor, and one with urothelial carcinoma. On Arm 2 the responding patient had a Sertoli cell tumor. **Conclusions:** The use of bintrafusp alfa and M9241 either alone or in combination with sequential or concurrent SBRT has shown clinical activity in pts with GU tumors and has not been associated with any DLTs. Clinical trial information: NCT04235777. Research Sponsor: U.S. National Institutes of Health.

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Poster Session

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Poster Session

Biomarkers of response to sacituzumab govitecan (SG) and efficacy after treatment with enfortumab vedotin (EV) in advanced urothelial carcinoma (aUC): Analysis of the UNITE study. *First Author: Tanya Jindal, University of California San Francisco, Helen Diller Family Comprehensive Cancer Center, San Francisco, CA*

Background: SG is an antibody-drug conjugate (ADC) with accelerated FDA approval for aUC refractory to platinum-based chemotherapy and immune checkpoint inhibitor (ICI). SG activity following treatment with EV, the most commonly used ADC in the post-platinum/ICI setting, and biomarkers of response to SG are not well described. We hypothesized that SG would be active after EV in aUC. **Methods:** Patients (pts) treated with SG monotherapy who had next-generation sequencing (NGS), were identified in the retrospective UNITE study. Observed response rate (ORR) was determined for evaluable pts with scans after ≥1 SG cycle. All pts were assessed for baseline clinical characteristics, as well as molecular biomarkers including tumor mutational burden, somatic gene alterations (alt) in ≥ 10% of pts and presence of ≥1 DNA damage response (DDR) mutations. ORRs were compared with Chi-squared test. Kaplan Meier method and cox proportional hazard (cph) models were used to assess progression-free survival (PFS) and overall survival (OS) from SG start. Pt characteristics and molecular biomarkers were evaluated in univariate analyses (UVA), followed by evaluation of biomarkers in separate multivariate cph analyses (MVA), while accounting for clinical features. **Results:** Among 90 pts treated with SG at 9 US sites, 78 had NGS data. Median age at SG start was 68, 65 (72%) men, 73 (81%) Caucasian, 56 (62%) with pure urothelial histology, 60 (67%) primary bladder tumor and 67 (74%) ECOG PS 0/1. Most (n=84, 93%) received SG after EV, and 33 (37%) had ≥4 prior therapies for aUC. ORR with SG was 23% (15/66); 24% in pts with prior CR/PR/SD on EV and 14% after primary PD on EV. Median follow-up from SG start was 8.7 mos, PFS and OS were 3.5 mos and 7.1 mos. In pts with NGS, ORRs to SG were higher in *MTAP* altered pts (50% vs 19%; p = 0.05). In UVA, low neutrophil to lymphocyte ratio (NLR), high Hgb, no prior smoking history, < 3 prior therapies, as well as *BRCA2* and DDR alts were associated with longer OS (p<0.05 for all). In MVA, pts with alt in either *TP53* or *MDM2* had longer OS. **Conclusions:** SG has notable activity after EV in heavily pretreated pts with aUC, with ORR consistent with SG phase 2 trial data in post-platinum/ICI only pts. We identified several clinical and genomic biomarkers, including *TP53/MDM2* alt, that are potentially associated with improved outcomes with SG treatment. Research Sponsor: None.

Characteristics	mOS: HR (95% CI)	p	mPFS: HR (95% CI)	p
Age	0.97 (0.93 – 1.01)	0.10	0.99 (0.96-1.03)	0.86
Histology (variant vs pure UC)	1.15 (0.57 - 2.32)	0.69	0.94 (0.49-1.82)	0.86
ECOG PS (≥ 2 vs <2)	1.56 (1.01 - 6.50)	0.05	3.19 (1.36 – 7.57)	<0.01
Smoking History (Yes vs No)	2.67 (1.32 - 5.50)	<0.01	2.14 (1.17-3.92)	0.01
NLR	1.14 (1.06 - 1.21)	<0.01	1.13 (1.07-1.20)	<0.01
Hgb	0.70 (0.54 – 0.89)	<0.01	0.88 (0.72-1.06)	0.01
<i>TP53</i> / <i>MDM2</i> (alt vs wild-type)	0.36 (0.15 – 0.84)	0.02	0.81 (0.40-1.64)	0.55

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Poster Session

Outcomes with immune checkpoint inhibitors (ICI) in patients (pts) with *MTAP* alterations (alt) in advanced urothelial carcinoma (aUC). *First Author: Rafee Talukder, University of Washington, Seattle, WA*

Background: *MTAP* loss of function alt in aUC has been associated with poor prognosis. *MTAP* is an enzyme involved in the adenine salvage pathway and deficiency of the protein leads to susceptibility to antifolate agents, e.g., pemetrexed. *MTAP* loss has also been correlated with immunosuppressive tumor microenvironment, inducing a “cold tumor” that may be less responsive to ICI. Response and outcomes to ICI in pts with *MTAP* altered aUC need further assessment. We hypothesized that pts with *MTAP* altered aUC would have lower response and shorter survival on ICI. **Methods:** We used our database from 26 centers (US/Europe) of pts with aUC treated with ICI. We included pts with available NGS data who received ICI for aUC. We excluded pts with pure non-UC, treated with adjuvant ICI, ICI combinations, or on clinical trials. Outcomes (observed response rate [ORR], progression free survival [PFS] and overall survival [OS]) were compared in pts who received either 1st line [1L] or 2nd line and beyond [2+L] ICI with and without *MTAP* alt. We compared ORR using logistic regression; PFS and OS were compared using Kaplan-Meier and Cox proportional hazards. We separately describe outcomes in pts with *MTAP* alt who received avelumab switch maintenance. **Results:** 211 pts from 8 centers met inclusion criteria with available *MTAP* alt status; 174 received ICI as distinct aUC treatment line (16% had *MTAP* alt; n=28) either in 1L or 2+L setting; 37 pts received avelumab switch maintenance (19% had *MTAP* alt; n=7). Pts with known *MTAP* status were 72% men, 91% White, 72% pure UC, 25% upper tract UC, 64% ECOG PS 0-1, 56% visceral mets, 18% bone mets, 15% liver mets. Median follow up from starting ICI was 44 months [mo] (IQR 29-51). ORR to ICI (1L + 2+L) in pts with *MTAP* alt was 25% (95%CI 10-47) vs 47% (95%CI 39-55%) in pts without *MTAP* alt [OR 3.11 (95%CI 1.15-7.82)]. PFS for pts with *MTAP* alt was not significantly different vs pts without *MTAP* alt (median 3 vs 6 mo, respectively: HR 1.46 [95%CI 0.91-2.35]). OS was similar between groups (median 14 vs 15 mo, respectively: HR 0.93 [95%CI 0.53-1.63]). Table describes outcomes by ICI treatment line (1L, 2+L, maintenance) in pts with and without *MTAP* alt. **Conclusions:** In pts with aUC receiving ICI, the presence of *MTAP* alt was significantly associated with lower ORR and a trend towards shorter PFS compared to absence of *MTAP* alt. Limitations include retrospective nature, small sample size, selection/confounding biases, lack of randomization and central scan review. Findings need external validation and might inform discussion on the optimal therapy sequence in aUC. Research Sponsor: None.

<i>MTAP</i> alt	N	ORR % (95%CI)	N	mPFS, mo (95%CI)	N	mOS, mo (95%CI)
1L						
Yes	14	21 (7-49)	14	2 (1-5)	14	9 (2-23)
No	94	59 (47-68)	94	6 (4-9)	94	15 (10-28)
2+L						
Yes	10	22 (6-58)	9	3 (2-6)	9	14 (2-NR)
No	56	27 (17-41)	56	4 (3-6)	56	9 (6-13)
Avelumab maintenance						
Yes	7	Best response to avelumab 0 CR, 1 PR, 1 SD 5 PD	7	2 (1-5)	7	15 (9-20)
No	30	2 CR, 3 PR, 11 SD, 14 PD	30	3 (2-7)	30	11 (8-19)

Independent biomarkers predictive of outcomes with enfortumab vedotin (EV) in patients (pts) with advanced urothelial carcinoma (aUC): Analysis of the UNITE study. *First Author: Tanya Jindal, University of California San Francisco, Helen Diller Family Comprehensive Cancer Center, San Francisco, CA*

Background: EV is used for treatment-refractory aUC with activity also noted in a frontline trial. Independent biomarkers associated with EV treatment outcomes are lacking. **Methods:** UNITE is a multi-site retrospective study of pts treated with EV and other agents. In this analysis we included pts treated with EV monotherapy and available next generation sequencing (NGS) data. Assessed biomarkers included genomic alterations (alts) in ≥5% of pts, tumor mutation burden (TMB) and PD-L1 expression. Pts were evaluable for observed response rate (ORR) if they had scans after ≥1 EV cycle. Biomarkers were evaluated individually in univariate analyses (UVA) and in separate multivariate analyses (MVA) which accounted for clinical variables. Progression-free survival (PFS) and overall survival (OS) from EV start were assessed using Kaplan Meier method and cox proportional hazard (cph) modeling. ORR was assessed using logistic regression. **Results:** Among 303 pts with NGS treated with EV monotherapy at 16 US sites, 207 had TMB and 146 had PD-L1 data. Median age was 70; 218 (72%) men, 262 (87%) White, 196 (66%) with pure urothelial histology, 212 (71%) with lower tract primary tumor, 204 (67%) had ≥2 prior therapies. ORR was 53% (140/264); mPFS was 6.0 mos, mOS was 13.1 mos. In UVA, longer OS was associated with higher Hgb, albumin and GFR (>30cc/min), lower neutrophil to lymphocyte ratio, older age, and absence of liver mets. MVA included these variables along with histology as covariates. In multivariate cph models, better outcomes were associated with alts in *ERBB2*, *KDM6A* and *PIK3CA*, while inferior outcomes with low TMB (<10 Mut/Mb) and high PD-L1 (CPS ≥ 10). **Conclusions:** MVA of this large, multi-site, retrospective cohort of aUC pts, identified several putative biomarkers independently associated with EV treatment outcomes. Longer OS was associated with *ERBB2* and *KDM6A* alts, low PD-L1 and high TMB. Limitations include lack of central scan review, pt selection and confounding biases. These findings require external validation, while their underlying mechanisms merit translational study. Research Sponsor: None.

Biomarker	OS: HR (95%CI), p	PFS: HR (95%CI), p	ORR: OR (95%CI), p
<i>ERBB2</i> (n=33)	0.50 (0.3-0.9), 0.03	1.12 (0.7-1.8), 0.62	0.83 (0.4-1.9), 0.65
<i>KDM6A</i> (n=36)	0.57 (0.3-1.0), 0.04	0.92 (0.6-1.4), 0.69	1.06 (0.5-2.4), 0.89
<i>CDKN2B</i> (n=46)	1.40 (0.9-2.2), 0.13	1.45 (1.0-2.1), 0.06	0.57 (0.3-1.2), 0.15
<i>PIK3CA</i> (n=46)	0.85 (0.5-1.3), 0.48	0.94 (0.6-1.4), 0.75	2.25 (1.1-5.1), 0.04
<i>RB1</i> (n=40)	1.52 (1.0-2.4), 0.07	1.15 (0.8-1.7), 0.51	0.58 (0.2-1.4), 0.22
<i>FGFR3</i> (n=70)	1.20 (0.8-1.7), 0.35	1.29 (0.9-1.8), 0.12	0.89 (0.5-1.7), 0.71
<i>CDKN2A/MTAP</i> (n=70)	1.22 (0.8-1.8), 0.30	1.25 (0.9-1.7), 0.19	0.76 (0.4-1.5), 0.41
PD-L1 High (n=80)	1.66 (1.0-2.7), 0.04	1.40 (0.9-2.1), 0.10	0.41 (0.2-0.9), 0.04
TMB Low (n=149)	1.92 (1.1-3.3), 0.02	1.26 (0.8-1.9), 0.28	1.19 (0.6-2.5), 0.65

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Poster Session

EphrinB2 (B2) expression predicts poor response to PD1/L1 antibodies (Ab) in metastatic urothelial carcinoma (mUC). *First Author: Sarmad Sadeghi, University of Southern California, Los Angeles, CA*

Background: B2 is a ligand for EphB4 which enhances tumor invasion, proliferation, survival and promotes angiogenesis. A prior analysis of TCGA data from 409 muscle invasive bladder cancer (MIBC) patients (pts) demonstrated that high (34%) B2 gene expression had poor survival vs. low (66%) expression (Hazard Ratio 0.7 p = 0.02). Our phase II trial of sEphB4-HSA (JCO PMID 35984996) which targets B2, in combination with pembrolizumab in previously treated mUC (N=70) demonstrated an objective response rate (ORR) of 37%. Among pts with high expression of B2, ORR was 52% with 24% complete response (CR). This retrospective study examined the ORR to PD1/L1 Ab in pts with mUC and its correlation with B2 mRNA expression. **Methods:** Pts with mUC who had received anti PD1/L1 Ab were eligible if they had radiographic response data and tumor tissue for B2 testing. Pts' demographics and disease characteristics were abstracted. Radiographic images were reviewed using RECIST 1.1. Tumor specimens were analyzed for intensity of B2 expression using in-situ hybridization (ISH). Scores of 2-4 were considered High (Hi) and 0-1 were considered Low (Lo) expression. Standard descriptive statistics were used to summarize study results. Fisher's exact test was used to test the association of ORR with B2 expression using SAS 9.4. **Results:** 120 (N) pts from University of Southern California (USC, n=49), Dana Farber (DFCI, n=55), and University of Colorado (UC, n=16) met were included. 88 pts were male (73%). Median age was 72. PD1/L1 Ab were administered in the post-platinum progressive disease (n=95, 79%) and first-line setting (n=25, 21%) and included pembrolizumab (n=88, 73%), atezolizumab (n=26, 22%) and nivolumab, avelumab, and durvalumab, 3%, 1%, and 1%, respectively. Objective response rate (ORR) defined as radiographic CR plus partial response (PR) were calculated and summarized. Among all pts (N=120), ORR was 20% (95% CI 13-28). 62% had B2 Hi expression with a response rate of 12%, and 38% had B2 Lo expression with a response rate of 33%, p=0.009. These proportions were similar for each institution. **Conclusions:** In addition to conferring poor prognosis in MIBC, B2 expression is associated with poor ORR to PD1/L1 Ab monotherapy in mUC. Given that the combination of B2 inhibition & pembrolizumab was more active in B2 expressing mUC, these data provide further rationale for investigating B2 as a mechanism of resistance to PD1/L1 ab, biomarker of response and a therapeutic target. Research Sponsor: None.

	Subgroups			
	All	USC	DFCI	UC
B2 Any (%)	120 (100)	49 (100)	55 (100)	16 (100)
Median Age (range)	72 (48-91)	72 (48-87)	73 (48-91)	69 (51-85)
Male (%)	88 (73)	37 (76)	36 (65)	15 (94)
ECOG 0, 1, >1 %	40, 35, 25	51, 22, 27	40, 40, 20	13, 56, 31
Visceral Metastases (%)	71 (60)	26 (55)	36 (65)	9 (56)
B2 Any ORR (%)	24 (20)	10 (20)	11 (20)	3 (19)
B2 Lo (%)	49 (41)	21 (43)	19 (35)	6 (38)
B2 Lo ORR (%)	15 (31)	6 (29)	7 (37)	2 (33)
B2 Hi (%)	74 (62)	28 (57)	36 (66)	10 (63)
B2 Hi ORR (%)	9 (12)	4 (14)	4 (11)	1 (10)

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Poster Session

Clinical utility of plasma ctDNA sequencing in metastatic urothelial carcinoma. *First Author: Clara Helal, Institut Gustave Roussy, Villejuif, France*

Background: Genomic stratification may help to improve the management of patients with metastatic urothelial cancer (mUC) given the recent identification of targetable molecular alterations in this disease. However, collecting tissue samples in mUC remains challenging. We assessed the clinical utility of plasma circulating tumor DNA (ctDNA) sequencing in mUC. **Methods:** mUC patients were prospectively enrolled in the STING trial (NCT04932525) whereby ctDNA was profiled using the FoundationOne Liquid CDx Assay (324 genes, tumor mutational burden [TMB], microsatellite instability status). Each individual genomic report was reviewed and discussed weekly by a multidisciplinary tumor board (MTB). Actionable targets were classified by ESCAT tier leading to molecular-based treatment suggestions whenever it was possible. **Results:** Between January 2021 and June 2022, 140 mUC patients underwent molecular profiling. Median time to assay results was 20 days. ctDNA abundance was correlated with number of prior lines and number of metastatic sites. ctDNA analysis reproduces the somatic genomic landscape reported by previous tissue-based cohorts. Concordance for serial tumor tissue was moderate ($r=0.545$ CI95: [0.121-0.801], $p=0.016$). At least one actionable target was detected in 63 patients (45 %) with a total of 35 actionable alterations including TMB high (≥ 12 mutations/Mb) (N= 39, 21.1%), FGFR3 (N= 20, 10.8%) and HRD alterations (N= 14, 7.6%). The MTB recommended a matched therapy for 63 patients (45.0%). In total, 8 patients (5.7 %) were treated with an overall response rate of 50% (95%: 15.70-84.30) and a median PFS of 5.2 months (CI95%: 4.1 - NR). FGFR3 alterations were associated with lower progression-free survival in patients treated with immunotherapy. **Conclusions:** Overall, our analysis demonstrates that genomic profiling with a large panel of ctDNA in mUC is a reliable and feasible approach to timely initiate genotype-matched therapies. Clinical trial information: NCT04932525. Research Sponsor: Gustave Roussy, Cancer Campus, Grand Paris.

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Poster Session

Evaluating the use of circulating tumor DNA (ctDNA) in patients with urothelial cancer in the context of FGFR-targeted therapy. *First Author: Elena Schönlaue, Department of Medical Oncology, BC Cancer-Vancouver Centre, Vancouver, BC, Canada*

Background: Fibroblast growth factor receptor (FGFR) inhibitors (e.g., erdafitinib) are increasingly important in the management of FGFR-mutated urothelial carcinoma. FDA-approved archival tissue testing for specific FGFR alterations was implemented as a companion diagnostic for erdafitinib. However, longitudinal sequencing studies indicate variable tumor FGFR status over time, and erdafitinib resistance mechanisms in metastatic urothelial carcinoma (mUC) are underreported. This ongoing study aims to evaluate the accuracy of cell-free DNA (cfDNA) compared to archival tissue testing in mUC for FGFR alterations detection, and to evaluate genomic mechanisms of erdafitinib resistance in cfDNA at progression. **Methods:** Patients with progressing mUC who were undergoing archival tissue testing for FGFR1-3 mutations and/or fusions and who had blood samples drawn during the management of their metastatic disease were eligible. Plasma cfDNA and matched leukocyte DNA were subjected to deep targeted sequencing with a custom panel including UC-specific gene loci and all clinically approved hotspots in FGFR1+2 and all exons and introns of FGFR3. **Results:** As of January 2023, 109 patients from 6 sites were enrolled. Median age at diagnosis was 71, 33% had upper urinary tract primaries, and 76% were male. Tissue and cfDNA results for comparison were available for 69 patients to date. Actionable somatic FGFR alterations were found in the tissue of 15 patients (31%); the most common alteration was the FGFR3 p.S249C mutation (67%). 50 of the analyzed cfDNA samples had detectable somatic circulating tumor DNA (ctDNA) variant allele fraction of 0.5% (72%). Of those, 49 had an evaluable tissue test result. Analysis of this subset revealed high concordance (92%) between the two test methods. With the assumption that archival tissue testing is considered the 'gold standard', sensitivity is 93% and specificity is 91%. The four discordant results comprised one cfDNA test with undetectable *FGFR3-TACC3* fusion, which was detected in tissue and three positive ctDNA test results in patients with *FGFR* wild-type tissue tests. In one case at erdafitinib progression, ctDNA revealed multiple subclonal populations with distinct FGFR3 gatekeeper mutations suggesting polyclonal resistance. **Conclusions:** This ongoing study suggests cfDNA is a valuable minimally invasive adjunct to tissue-based assays for the detection of FGFR alterations to identify patients for FGFR inhibitor therapy and to monitor for mechanisms of resistance. Research Sponsor: Bladder Cancer Canada.

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Poster Session

Activity of cabozantinib (CABO) plus durvalumab (DURVA) in patients (pts) with advanced urothelial carcinoma (UC) or non-UC variant histologies (VH) after platinum chemotherapy: Interim results from the phase 2 ARCADIA trial. *First Author: Patrizia Giannatempo, IRCCS Foundation National Cancer Institute, Milan, Italy*

Background: Combining multitargeted receptor tyrosine kinase inhibitor (TKI) with checkpoint inhibitors has shown synergistic effect in pts with UC due to the immunomodulatory propriety of VEGFR inhibitors. We investigated if the combination of CABO and DURVA in pts with advanced UC and non-UC histology (VHs) in a phase II study (NCT03824691). Herein the preliminary results of the interim analysis. **Methods:** Patients affected by UC and VHs recurred or progressed after failure of at least one line of platinum-based chemotherapy for metastatic disease have been treated with CABO 40 mg daily, orally, and are administered DURVA 1500 mg IV, q28 days, until disease progression (PD, by RECIST 1.1) or onset of unacceptable toxicity. Key inclusion criteria were ECOG-PS 0-1 and adequate organ function. Response was evaluated by RECIST criteria v.1.1 every 8 wks. The primary endpoint of the study was OS. Secondary endpoints included safety (CTCAE v.4.03), objective response-rate (ORR), duration of response (DoR), progression-free survival (PFS). The assumption was to detect an improvement in the median OS from ≤ 6 months (H0) to ≥ 9 months (H1). **Results:** Between September 2019 and February 10, 2023, the ARCADIA study enrolled 63 pts: this interim analysis was performed after obtaining at least one post-baseline tumor assessment data from 58 pts. The median follow-up was 23.5 mos (interquartile [IQ] range: 7.7-27.7 mos); 27% were female, the median age was 64 yrs (range: 42-81), 20 pts (34%) had a pure/predominant non-UC VH: 9 (45%) a squamous differentiation/sarcomatoid tumor, 5 (25%) an adenocarcinoma, 4 (20%) a small-cell neuroendocrine tumor, 1 (5%) a clear-cell tumor, and 1 a nested VH (5%). Eleven pts (19%) had received ≥ 2 prior systemic anticancer therapies. In 58 response-evaluable pts, 12 (20%) complete responses (CR) and 11 partial responses (PR) were obtained, the ORR being 39.7% (95%CI: 27.1-53.4) and disease control rate was 69% (95%CI: 55.5-80.5). In the cohort of pts with VH, the ORR was 45% (95%CI: 23.1-68.5). Median PFS was 7.6 mos (95%CI: 4.6-13.6 mos) and median OS was 11.6 (95% CI 6.8-20.3 months). Median exposure of treatment was 4.8 mos; 35 pts (55.5%) of 63 pts had all-grade treatment-related adverse events (AE) and 4 pts (6.3%) reported grade 3 (treatment related) AE with no grade 3-5 events. Dose-reductions of CABO were needed in 25 pts (39%). No treatment-related deaths were reported. **Conclusions:** CABO in combination with DURVA showed promising preliminary activity with a manageable safety profile in pts with advanced UC and in non-UC VH after previous chemotherapy exposure, deserving further evaluation of the combination that is ongoing with ARCADIA and other clinical trials. More mature results with longer follow-up will be presented. Clinical trial information: NCT03824691. Research Sponsor: Ipsen, Astra Zeneca.

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Poster Session

Efficacy of sacituzumab govitecan (SG) in locally advanced (LA) or metastatic urothelial cancer (mUC) by trophoblast cell surface antigen 2 (Trop-2) expression. *First Author: Yohann Lorient, Institut de Cancérologie Gustave Roussy, Villejuif, France*

Background: Patients (pts) with mUC have an estimated 5-year overall survival (OS) rate of 14%. Trop-2 is a transmembrane glycoprotein with elevated expression in many cancers, including UC. SG is a Trop-2-directed antibody-drug conjugate with accelerated FDA approval for pts with LA unresectable or mUC who previously received platinum (PT) and a checkpoint inhibitor (CPI). SG has demonstrated activity in 3 phase 2 TROPHY-U-01 mUC cohorts: Cohort 1 (C1), 28% objective response rate (ORR); Cohort 2 (C2), 32% ORR; and Cohort 3 (C3), 41% ORR. Here, we assess efficacy outcomes in C1-3 by Trop-2 archival tumor expression. **Methods:** Pts (≥ 18 years) with previously treated (PT [C3], CPI [C2], or both [C1]) LA or mUC received SG (10 mg/kg IV) on D1 and D8 of 21-D cycles; C3 pts also received pembrolizumab (200 mg) on D1 of 21-D cycles. The primary endpoint was ORR by independent review. Archival tumor samples collected at enrollment were assessed for Trop-2 protein expression using SP295 anti-Trop-2 antibody by IHC with assessment by histological scores (H-scores; scale, 0-300) and % of membrane-positive tumor cells (Roche Tissue Services). Trop-2 association with clinical endpoints was evaluated using unstratified Cox proportional hazards models for survival data and logistic regression for ORR. **Results:** At data cutoff, 192 pts were enrolled in C1-3; 144 pts (75%) had samples evaluable for Trop-2 prevalence and 139 pts (72%) were evaluable for efficacy analysis by Trop-2 expression (5 pts not assigned to any cohort were excluded). Baseline characteristics for pts with evaluable samples were consistent with the overall population. Median (IQR) Trop-2 H-score and % of membrane-positive tumor cells for evaluable pt samples were 215 (180-247) and 92% (75-98), respectively; these readouts were highly correlated ($p=0.82$, $P<0.001$). ORRs for C1 samples with below (n=42) and above (n=45) median Trop-2 H-scores were 24% and 29% ($P=0.59$), respectively; median progression-free survival (PFS) was 3.4 and 6.7 months (HR=0.765, $P=0.262$), respectively; and median OS was 9.9 and 10.9 months (HR=0.978, $P=0.927$), respectively. Median PFS for C1 samples with below and above median Trop-2 membrane positivity were 3.9 and 6.2 months (HR=0.835, $P=0.443$), respectively. Analyses of efficacy endpoints for C2 and C3 pt samples by Trop-2 expression were consistent with C1 results. **Conclusions:** In this analysis of archival tumor samples from pts with pretreated LA or mUC, Trop-2 protein was highly expressed across cohorts, supporting prior Trop-2 expression analyses in UC. Similar outcomes were observed between C1 pts with samples that were below and above median Trop-2 H-score with most pronounced numerical differences observed for PFS. These results suggest that SG activity may be independent of Trop-2 expression in UC, but additional studies are needed to confirm these results. Clinical trial information: NCT03547973. Research Sponsor: Gilead Sciences Inc.

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Poster Session

The effect of antibiotic (Abx) use on immune checkpoint inhibitor (ICI) efficacy in patients (pts) with metastatic urothelial carcinoma (mUC) in a real-world setting. First Author: Ubenthira Patgunarajah, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH

Background: Use of Abx may negatively affect outcomes with ICI, possibly due to negative impact on gut microbiota. We previously showed that in our real world cohort of 138 mUC pts, Abx use within 30 or 60 days (d) of ICI initiation did not impact overall survival (OS). We now report updated follow-up (fu) and results from our expanded cohort of 310 mUC pts who received ICI. **Methods:** We performed a retrospective analysis of adult pts with mUC treated at the Cleveland Clinic between 2015 and 2022 who received 2 or more cycles of ICI with pembrolizumab (P), atezolizumab (A) or avelumab (Av). Effect of Abx use within 30 and 60 (d) of ICI initiation was correlated with progression free survival (PFS) and OS. OS and PFS were estimated using Kaplan-Meier method and compared using log rank test. **Results:** Median age of pts was 71 years (41-90) and 75% pts were males. 224 pts (72.3%) received P, 82 (26.4%) A and 4 (1.3%) Av. Fluoroquinolones (31.1%), penicillins (29.6%) and cephalosporins (19.7%) were most commonly used Abx. With a median fu of 47 weeks (3.86- 325.3), median OS in pts who received Abx within 60 (d) prior to ICI was 11.79 months (mos) vs 14.55 mos in those who did not receive Abx (p=0.007) and median PFS was 3.68 mos vs 5.29 mos respectively (p=0.038). Median OS in pts who received Abx within 30 days prior ICI was 10.41 mos vs 14.46 mos in those who did not receive Abx (p=0.037). There was a non-significant trend for worse PFS in pts who received Abx within 30 (d) prior to ICI (3.06 mos vs 5.03 mos, p=0.238). There was no effect on OS or PFS with Abx use 30 or 60 (d) after ICI initiation. **Conclusions:** In our real-world cohort of mUC pts receiving ICI, Abx use 60 and 30 (d) prior to ICI initiation was associated with significant worse OS and worse PFS for the former group but Abx use after ICI initiation did not have an effect on OS or PFS. These findings have the potential to influence clinical practice, including a higher threshold for giving Abx to mUC pts starting ICI. Further prospective studies are warranted. Research Sponsor: None.

	N	OS (mos)	95% CI (mos)	p-value	PFS (mos)	95% CI (mos)	p-value
No Abx 60 days before ICI	179	14.55	13.01, 23.2		5.29	3.84, 7.13	0.038
Abx use 60 days before ICI	131	11.79	9.46, 14.49	0.007	3.68	2.89, 5.52	
No Abx 60 days after ICI	215	14.29	12.06, 18.66		5.39	4.27, 6.14	0.083
Abx use 60 days after ICI	95	11.99	6.9, 17.38	0.419	3.06	2.27, 5.32	
No Abx 30 (d) before ICI	243	14.46	13.01, 18.96	0.037	5.03	3.84, 6.01	0.238
Abx use 30 (d) before ICI	67	10.41	6.8, 15.21		3.06	2.46, 5.82	
No Abx 30 (d) after ICI	267	14.23	12.12, 17.05	0.15	5.03	3.71, 5.95	0.234
Abx use 30 (d) after ICI	43	8.25	5.82, 18.27		3.15	2.27, 6.21	

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Poster Session

Assessing tumor-infiltrating immune cells and outcomes with cisplatin-versus carboplatin-based treatment in advanced urothelial cancer (UC): Survival analysis of three platinum-treated UC cohorts. First Author: Konrad Stawiski, Medical University of Lodz, Lodz, Poland

Background: The association between tumor-infiltrating immune cells and the response to platinum-based chemotherapy (cisplatin vs carboplatin) in advanced urothelial cancer is not well characterized. We dissected the immune microenvironment of 3 large UC cohorts to define populations of immune cells associated with survival following carboplatin- or cisplatin-based chemotherapy. **Methods:** Two advanced UC cohorts – Hospital del Mar (HM; n = 55) and GREEK (n = 62) – treated with platinum-based chemotherapy were profiled using bulk RNA sequencing (RNA-seq) with tumor-infiltrating immune cells inferred using CIBERSORTx. Our findings were validated in a publicly available platinum-treated UC cohort (n = 93; Taber et al. Nat Comm 2020). Additionally, we assessed the impact of tumor-infiltrating immune cells in IMWigor210, an anti-PD-L1 treated cohort. Analysis was adjusted by tumor stage, and treatment regimen (cisplatin, carboplatin, atezolizumab) to determine associations between tumor-immune cell populations and overall survival (OS). **Results:** In platinum-treated patients, increased lymphoid cell infiltration was associated with improved OS. Specifically, the presence of naive and memory B-cells and CD4+ T cells was associated with prolonged OS (Table). Interestingly, infiltration of memory B-cells was associated with a better prognosis in patients treated with cisplatin (HR = 0.14) and detrimental in patients treated with carboplatin (HR = 249.53; difference p = 0.006). Additionally, macrophages (HR = 3.44; p = 0.027) and resting dendritic cell (HR = 41.47; p = 0.009) infiltration was associated with worse OS in patients treated with platinum therapy alone, but enrichment of pro-inflammatory M1 macrophages was associated with prolonged OS in patients treated with immunotherapy (p < 0.001). **Conclusions:** Immune cell infiltration is associated with differential outcomes to cisplatin- and carboplatin-based chemotherapy in advanced UC. Our findings suggest better OS in advanced UC treated with cisplatin in tumors enriched with memory B-cells compared to carboplatin treatment. Research Sponsor: None.

Cohort description with initial TNM- and treatment-adjusted hazard ratios (with 95%CI) of selected cell fractions.

Cohort	HM	GREEK	TABER	Pooled
T4 vs. T2 or T3	14 (22.6%)	19 (34.5%)	20 (21.5%)	-
N+ vs. N0	28 (45.2%)	26 (47.3%)	40 (43.0%)	-
M1 vs. M0	21 (33.9%)	26 (47.3%)	18 (19.4%)	-
Lymphoid lineage	0.24 [0.06-0.92]	0.13 [0.03-0.56]	0.48 [0.16-1.42]	0.29 [0.14-0.59]
B-cells (naive & memory)	0.14 [0.01-1.92]	0.04 [0.00-0.82]	0.28 [0.05-1.58]	0.16 [0.04-0.60]
B-cells memory	0.16 [0.01-2.37]	0.01 [0.00-0.62]	0.31 [0.06-1.64]	0.18 [0.05-0.68]
T-cells	0.24 [0.05-1.21]	0.20 [0.03-1.28]	0.52 [0.12-2.16]	0.32 [0.12-0.80]
T-cells CD4+	0.13 [0.02-0.83]	0.35 [0.04-2.79]	0.50 [0.12-2.08]	0.31 [0.12-0.84]

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Poster Session

Presence of CD8+ cytotoxic T-cells in proximity to tumor cells, TIM3, CTLA-4 and prognostic implications for muscle-invasive urothelial cancer. First Author: Nicolaus F. Debatin, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Background: Although it is well known that the quantity of specific immune cell types can provide prognostic information in bladder cancer, only little is known about the prognostic relevance of the localization of immune cells within the tumor microenvironment. **Methods:** To study the spatial interplay of different immune cell subpopulations and its prognostic role in bladder cancer, 2463 urothelial bladder carcinomas were immunostained with 21 antibodies (i.e., TIM-3, PD-L1, PD-1, CTLA4, CD3, CD8, CD4, FOXP3, CD20, CD68, CD163, CD11c, panCK, Ki67, CD31, Vimentin, HLA-DRa, Myosin-11, Desmoglein 3, PAX-8, and CDH16) using BLEACH&STAIN multiplex fluorescence immunohistochemistry in a tissue microarray format and analyzed using a framework of neuronal networks for image analysis. Thus, Spatial immune parameters were compared with histopathological parameters and overall survival data. **Results:** The identification of more than 300 different immune cell subpopulations and the characterization of their spatial relationship resulted in numerous spatial interaction patterns. 32 immune parameters showed prognostic significance in univariate analyses of which 16 were independent from pT, pN, and histologic grade in muscle-invasive bladder cancer. The strongest association to clinical outcome was identified for intraepithelial CD8+ cytotoxic T-cells (AUC: 0.70) while stromal CD8+ cells were less relevant (AUC: 0.64, p=0.016). A favorable prognosis of inflamed cancers with high levels of “exhaustion markers” suggests that TIM3, PD-L1, PD-1, and CTLA-4 on inflammatory cells do not hinder anti-tumoral immune response in tumors rich of tumor infiltrating tumor cells. **Conclusions:** The density of intraepithelial CD8+ T-cells was the strongest prognostic feature in muscle-invasive bladder cancer. Given that tumor cell killing by CD8+ cytotoxic T-lymphocytes through direct cell-to-cell-contacts represents the “terminal end route” of anti-tumor immunity, the quantity of “tumor-cell adjacent CD8+ T-cells” may constitute a surrogate for the efficiency of cancer recognition by the immune system that can be measured straightaway using conventional brightfield IHC in routine pathology as the CD8 labelling index. Research Sponsor: None.

4584

Poster Session

Genome-wide aneuploidy detected in circulating cell-free DNA of patients with metastatic urothelial cancer as a predictive biomarker of response to pembrolizumab. First Author: Youssra Salhi, Erasmus MC Cancer Institute, Rotterdam, Netherlands

Background: Pembrolizumab is the standard of care second-line treatment of metastatic urothelial cancer patients. However, success rates are low and there is risk for significant toxicity. Therefore, reliable biomarkers to select patients who will or will not benefit from pembrolizumab are urgently needed. An earlier study showed that a high aneuploidy score (i.e. Z-score ≥ 5) at baseline in cell free DNA (cfDNA), based on the modified fast aneuploidy screening test-sequencing system (mFast-SeqS), associated with poor response to pembrolizumab. However, a low aneuploidy score (Z-score < 5) at baseline was not discriminative. The aim of this study was to evaluate early during treatment (after the first cycle pembrolizumab), whether the cfDNA based mFast-SeqS aneuploidy scores can discriminate patients with expected benefit from therapy from those who will not benefit. **Methods:** The mFast-SeqS to assess aneuploidy was performed on blood samples collected from 74 patients with metastatic urothelial cancer (mUC) at baseline and after cycle 1 of pembrolizumab. Responders were defined as patients with stable disease (SD) or partial/complete response (PR, CR) according to RECIST v1.1. and continued treatment beyond 6 months from initiation of pembrolizumab. Non-responders did not fulfil these criteria. **Results:** Paired samples were available in 60 out of 74 patients. At baseline 25% (n=15) of patients had a high aneuploidy score and 75% (n=45) had a low aneuploidy score. Two patients (13%) with a high baseline score were responders and 13 (87%) were non-responders. In all responders, there was a marked decrease in aneuploidy score after one cycle of pembrolizumab (p=0.005), irrespective of their baseline score. About half of patients (47%) with a low baseline score were non-responders and in those patients there was a significant increase of the aneuploidy score post cycle 1, when compared to the responders (p=0.039). **Conclusions:** The aneuploidy score based on mFast-SeqS may stratify mUC patients for expected lack of benefit early during treatment (after 1 cycle) with second line pembrolizumab, providing an opportunity to switch treatment and to spare patients from potential unnecessary toxicity. Clinical trial information: NCT03263039. Research Sponsor: Merck Sharp & Dohme LLC.

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Poster Session

Final analysis results from a multicenter clinical study of tislelizumab combined with gemcitabine and cisplatin as neoadjuvant therapy in patients with cT2-T4aN0M0 MIBC. *First Author: Tianxin Lin, Department of Urology, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China*

Background: To evaluate the efficacy and safety of tislelizumab combined with gemcitabine and cisplatin as neoadjuvant therapy for patients (pts) with clinical T2-T4aN0M0 (cT2-T4aN0M0) muscle-invasive bladder urothelial cancer (MIBC). At predefined interim analysis, the study has met the first stage aim. Here reported the results of the predefined final analysis. **Methods:** This phase II study enrolled pts tolerated with the cisplatin therapy. Eligible pts received tislelizumab 200 mg in day 1 (D1), cisplatin 70 mg/m² D2, and gemcitabine 1000 mg/m² D1 and D8 every 21 days for four cycles. Radical cystectomy (RC) was performed within 6 weeks after last dose treatment. The primary end point was pathologic complete response (pCR, pT0N0M0). Secondary end points were pathologic downstaging ($\leq$ pT1N0M0) (pDS), EFS, OS and safety. Simon two-stage design was used. If >5 pts achieved pCR in the first stage (n=22), study would proceed to the second stage and enroll 33 additional pts. If >18 of 55 pts achieved pCR, we would deem the study to have met the primary endpoint. **Results:** At the data cut off time of 14th Dec 2022, 63 pts (38 cT2, 19 cT3, and 6 cT4a) have completed neoadjuvant therapy, with median age of 64 (48-75) years. The median relative dose intensity of tislelizumab, cisplatin and gemcitabine were 92.3%, 85.7% and 85.6%, respectively. At this time, 55 pts underwent RC and completed 30 days post-surgery follow-up. The median time from last dose to RC was 4.4 (range: 0.6-13.3) weeks. Eight pts refused RC. Among 55 efficacy evaluable pts, 27 (49.1% [90% CI, 37.4-60.9]) pts achieved pCR, while 41 (74.5% [95% CI, 61.0-85.3]) pDS. Pts with cT2 achieved 55.6% (20/36) pCR and 86.1% (31/36) pDS. Among 14 non-responders, 3 of them (1 cT2, 2 cT3) achieved pT0, but with pathologic N1. Clavien-Dindo grade $\geq$ 3 postoperative complications occurred in 7.9% pts. Most common neoadjuvant therapy related AEs of any grade were hematologic toxicities (88.9%), nausea (77.8%), and vomiting (50.8%). Grade $\geq$ 3 neoadjuvant therapy related AEs occurred in 60.3% pts, which were hematologic toxicities (58.7%) in most. The frequently occurring immune-related AEs (irAEs) (>5%) included dizziness (14.3%), fatigue (12.7%), ASL/ALT increased (7.9%), rash (7.9%), pruritus (7.9%), and GGT increased (6.3%). Grade $\geq$ 3 irAEs occurred in 2 pts (pneumonia, n=1; cardiomyopathy, n=1). **Conclusions:** The study met its primary endpoint. Neoadjuvant tislelizumab combined with gemcitabine and cisplatin showed promising anti-tumor activity with high pCR and well tolerance in MIBC pts. Clinical trial information: ChiCTR2000037670. Research Sponsor: BeiGene (Beijing) Co., Ltd.

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Poster Session

CDH1-mutated clinically advanced urothelial bladder cancer (UBC): A genomic landscape and real-world clinical outcome study (RWCOS). *First Author: Kyle M Rose, H. Lee Moffitt Cancer Center, Tampa, FL*

Background: CDH1 mutated bladder cancers are characterized by plasmacytoid histology and are associated with an aggressive clinical course. **Methods:** Cohort 1: 6,676 clinically advanced UBC patients underwent hybrid capture based comprehensive genomic profiling (CGP) to evaluate all classes of genomic alterations (GA) as well as microsatellite instability (MSI), tumor mutational burden (TMB), and genomic loss of heterozygosity (gLOH, high $\geq$ 16%). Tumor cell PD-L1 expression was determined by immunohistochemistry (Dako 22C3). GAs were compared between CDH1 mutated and wild-type (WT) patients using Chi-square. Cohort 2: 586 UBC patients underwent a RWCOS using the de-identified Flatiron Health-Foundation Medicine urothelial clinicogenomic database. The de-identified data originated from approximately 280 US cancer clinics (~800 sites of care) between January 2011 and April 2022. Differences in real-world progression-free survival (rwPFS) and overall survival (rWOS) were evaluated by Cox proportional hazard models. **Results:** Cohort 1: 217 UBC patients featured a CDH1 short variant mutation with 65.2% featuring plasmacytoid histology (PLC). The PLC cohort was slightly younger, with a higher proportion of male patients, and MSI-High status. Cell-Cycle regulatory GAs were significantly higher in the non-PLC cohort, specifically CDKN2A (25.5% vs 9.7%, p=0.01) and CDKN2B (23.6% vs 5.8%, p<0.01). CDH1-mutated UBCs featured a higher MSI high frequency (2.7% vs 0.8%; p=.002), mean TMB (14.8 vs 9.9mut/Mb p<.0001), RB1 GA (52.5% vs 20.3%; p<.0001), PTEN GA (9.2% vs 4.3%; p=.006) and PIK3CA GA (29.5% vs 21.8%; p=.02), but lower gLOH (6.8% vs 15.9%; p=.009), CDKN2A loss (12.4% vs 38.3%; p<.0001), MTAP loss (10.1% vs 25.1%; p<.0001), and FGFR3 GA (9.7% vs 18.1%; p=.002). TP53 GAs and PD-L1 expression levels were similar between groups. From cohort 2: 22 (3.7%) patients featured CDH1 mutations. When compared with the CDH1 WT patients, the age, gender, ethnicity and ECOG status were similar. CDH1 mutation was associated with less favorable outcomes for 270 UBC patients treated with immune checkpoint inhibitors (ICPI) including rwPFS (2.8 vs 3.5 months; p=.096) and rWOS (3.3 vs 9.5 months; p=.03). Similar comparisons for 316 UBC patients treated with chemotherapy showed no significant adverse impact of CDH1 mutation status on either rwPFS (7.9 vs 6.2 months; p=.11) and rWOS (13.4 vs 13.4 months; p=0.83). **Conclusions:** In addition to its classic association with PLC histology, CDH1-mutated UBC features an unique genomic landscape including higher MSI and TMB, activating GAs in the MTOR pathway, but lower frequency of FGFR3 GAs. RWCOS further supports that CDH1 mutation predicts resistance to ICPI-based treatment, but does not systemic chemotherapy. These findings support CGP to guide therapeutic approaches based on the personalized genomic signature of UBC. Research Sponsor: None.

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Poster Session

Survival outcomes in patients with muscle-invasive bladder cancer receiving neoadjuvant chemotherapy stratified by number of cycles. *First Author: Anumita Chakraborty, Temple University Health System, Philadelphia, PA*

Background: Neoadjuvant cisplatin-based chemotherapy (NAC) prior to radical cystectomy is the standard of care for patients with muscle invasive bladder cancer (MIBC). Three or more cycles of NAC are commonly administered based on outcomes in prior prospective trials, however many patients are intolerant of 3 cycles of NAC due to toxicity. The prognosis of patients receiving fewer than 3 cycles of NAC has yet to be elucidated. **Methods:** This is a retrospective single-center study to quantify pathologic response, recurrence-free survival (RFS), and overall survival (OS) from time of first NAC in patients treated with < 3 cycles of NAC compared to patients treated with $\geq$ 3 cycles of NAC. Inclusion criteria include: diagnosis of MIBC between 2004-2017, $\geq$ 5 years of follow up, deceased or had recurrence prior to 5 years follow up but with adequate follow-up data. Patients were excluded from the study if they were found to have metastatic disease prior to initiation of NAC, lost to follow up prior to 5 years with no evidence of recurrence or death, or had progression of disease during NAC. The primary objective of this study was to determine RFS and OS in patients stratified by cycles of NAC. Patient characteristics were compared using chi-square tests, Fisher's exact tests, and Wilcoxon rank sum tests. Kaplan Meier curves and log-rank tests were used to compare RFS between subgroups, and Cox proportional hazards models were used to compare RFS adjusting for ECOG performance status, baseline GFR, stage, type of NAC regimen, and patient age at first dose of NAC. 5-year OS was calculated as a percentage of patients surviving at 5 years. **Results:** A total sample of 195 patients were treated with NAC for MIBC, of which 30 (15.3%) patients received < 3 cycles and 165 (84.6%) patients received $\geq$ 3 cycles of NAC. 53 patients received gemcitabine and cisplatin (GC) and 142 patients received methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC). Complete pathologic response (ypT0N0) was observed in 7.4% of patients receiving < 3 cycles and in 26.8% of patient receiving $\geq$ 3 cycles of NAC (p = 0.024). Significant pathologic response (< ypT2) was obtained in 22.2% of patients receiving < 3 cycles of NAC and in 41.8% of patients receiving $\geq$ 3 cycles (p > 0.05). Median RFS in patients with < 3 cycles of NAC was 8.8 months (95% CI 6.51, 13.4) and 54.5 months with $\geq$ 3 cycles of NAC (95% CI 29.8, 111.9). Based on a log-rank test there is a statistically significant difference in unadjusted RFS between the two groups (p < 0.001). The 5-year OS in patients receiving < 3 cycles of NAC was 13.3%, and the 5-year OS in those receiving $\geq$ 3 cycles was 53.3%. **Conclusions:** Early cessation of chemotherapy due to intolerance had significant implications on pathologic response, RFS and OS. Clinicians should prioritize administering at least 3 cycles of cisplatin-based chemotherapy when feasible to optimize outcomes. Research Sponsor: None.

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Poster Session

Survival outcomes of sarcomatoid versus classic urothelial carcinoma of bladder. *First Author: Rohan Garje, Miami Cancer Institute, Baptist Health South Florida, Miami, FL*

Background: Sarcomatoid urothelial carcinoma (SUC), a rare bladder cancer variant, has both epithelial and mesenchymal differentiation along with frequent TERTC228T promoter mutations and has poorer prognosis. In this study, we compared survival outcomes of SUC with classic urothelial carcinoma (CUC) in patients with T2-T4, N0-N1 bladder cancer after definitive therapy. **Methods:** All cases meeting our inclusion criteria for SUC and CUC during 2004-2019 were identified from National Cancer Database. Sociodemographic and clinicopathological characteristics were analyzed via descriptive and comparative statistics. Propensity-score matching was performed to adjust for baseline differences between SUC and CUC. Overall survival (OS) was compared using Cox proportional-hazards modelling and visualized through Kaplan-Meier curves. **Results:** 30072 cases of CUC and 480 of SUC were identified. Propensity-score matching resulted in N = 478 patients in both groups. Matched cohorts had no baseline differences in age, sex, race, comorbidities, insurance status, income, distance to hospital, hospital location, rural versus urban residence, histological grade, and proportion getting regional lymph node surgery. Overall, there were 675 males and 281 females, 435 underwent surgery (Sx), and 521 surgery plus chemotherapy (Sx+Cx). For SUC, median survival with Sx vs Sx+Cx was 29.5 months (95%CI 20.0-50.6) vs 43.1 months (95%CI 25.3-64.4) respectively. For CUC, median survival was 56.1 (95%CI 53.7-58.6) vs 78.0 (95%CI 75.1-81.1) months with Sx vs Sx+Cx respectively. **Conclusions:** SUC has poorer prognosis than CUC. Perioperative chemotherapy along with surgery was associated with improved survival outcomes compared to surgery alone in patients with SUC. Further studies investigating novel immunotherapy agents are warranted to improve oncologic outcomes. Research Sponsor: None.

Cox Proportional Hazard Ratios (HR) for different variables. Ref. Reference.		
Variables	HR (95% CI)	P value
Histology		
Classic Urothelial carcinoma	Reference	
Sarcomatoid	1.39 (1.14-1.69)	0.001
Age category		
< 65 years	Ref	
$\geq$ 65 years	1.33 (1.02-1.74)	0.036
Sex		
Male	Ref	
Female	1.11 (0.89-1.38)	0.361
Race		
Black	Ref	
Hispanic	0.93 (0.48-1.79)	0.825
Other	0.80 (0.36-1.77)	0.586
White	0.79 (0.51-1.22)	0.287
Insurance		
None	Ref	
Private	1.40 (0.64-3.07)	0.402
Public	1.60 (0.72-3.53)	0.248
Income		
< \$48,000	Ref	
$\geq$ \$48,000	0.93 (0.74-1.15)	0.489
Area		
Metro	Reference	
Urban/Rural	1.14 (0.86-1.50)	0.359
Distance to hospital		
< 50 miles	Ref	
$\geq$ 50 miles	0.75 (0.56-1.00)	0.049
Facility type		
Non-Academic	Ref	
Academic	1.07 (0.87-1.32)	0.517
Location		
Central US	Ref	
Mountain & Pacific	1.08 (0.79-1.46)	0.631
New England & Atlantic	1.07 (0.86-1.31)	0.549
Charlson-Deyo Comorbidity		
0	Ref	
1	1.11 (0.88-1.40)	0.395
2	1.42 (1.00-2.00)	0.047
3 or more	1.59 (0.98-2.91)	0.060
Treatment type		
Surgery only	Ref	
Chemo & Surgery	0.86 (0.71-1.04)	0.130
Regional Lymph Node Surgery	0.96 (0.71-1.31)	0.814

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Poster Session

Accuracy of genome-wide mutational analysis for tumor-informed ctDNA-guided MRD monitoring in bladder cancer. *First Author: Iver Nordentoft, Aarhus University Hospital, Aarhus, Denmark*

Background: Neoadjuvant chemotherapy (NAC) followed by radical cystectomy (RC) is the standard management of localized muscle-invasive bladder cancer (MIBC). However, about 45% of patients develop metastases within 2 years after RC. Biomarkers for treatment efficacy evaluation and early detection of minimal residual disease (MRD) are needed for earlier treatment initiation and monitoring of treatment response. Tumor-informed detection of mutations in cell-free DNA (cfDNA) has shown promising results to monitor MRD. However, the low tumor fraction after surgery and limited input material obtained from a typical plasma sample limits the probability of detecting low metastatic burden scenarios. Here we implemented and applied a whole-genome sequencing (WGS) approach to monitor circulating tumor DNA (ctDNA) for sensitive ctDNA detection. **Methods:** 110 MIBC patients undergoing NAC and RC were enrolled. cfDNA was extracted from ~1mL plasma (n=978) and procured from longitudinal plasma sampling during NAC and pre-RC and post-RC. WGS of tumor/germline pairs (30x/20x) and plasma cfDNA (>20x) was performed, facilitating detection of genome-wide genomic alterations and quantification of ctDNA using the C2inform method. **Results:** For each patient we developed a tumor-informed WGS model by integrating genome-wide mutation and copy number variation data coupled with advanced signal processing and AI-based error suppression. Patient-specific somatic variant patterns were used for detection and measuring ctDNA levels in low-input blood samples by WGS. Post-RC ctDNA analysis identified patients with recurrence with 78% sensitivity and 95% specificity and with a median lead time over radiographic imaging of 118 days (full follow-up included). When restricting follow-up time to 12 months following the latest ctDNA test, a sensitivity of 86% and specificity of 94% was achieved. ctDNA status was associated with recurrence-free (p<0.0001) and overall survival (p<0.0001). Furthermore, ctDNA clearance during NAC was also associated with recurrence-free survival (p=0.0051). The APOBEC associated signatures SBS2 and SBS13 were identified as the primary contributors to the mutational landscape of the primary tumors and *TP53*, *KMT2D*, *PIK3CA*, *RB1* and *KDM6A* were the main affected driver genes. Half of the tumors displayed whole genome doubling. Moreover, our analysis of plasma samples after treatment showed the presence of chemotherapy-induced mutational signatures not present in the primary tumor, along with increases in copy numbers on chromosomes 19q and 20, and a focal amplification of the *FGFR3* gene on chromosome 4. **Conclusions:** Our results highlight the clinical potential of personalized genome-wide mutation integration as an ultra-sensitive, non-invasive method for MRD detection and treatment response monitoring. Research Sponsor: The Novo Nordisk Foundation, The Danish Cancer Society, Aarhus University and Aarhus University Hospital; C2i Genomics Inc.

4591

Poster Session

Biology and performance of pre- and post-pembrolizumab (pembro) vesical imaging-reporting and data system (VI-RADS) to predict the pathological response in muscle-invasive urothelial bladder cancer (MIBC): Full data analysis from a clinical trials pipeline. *First Author: Andrea Necchi, Vita-Salute San Raffaele University, Milan, Italy*

Background: The VI-RADS is a standardized reporting system that uses multi-parametric magnetic resonance imaging (mpMRI) parameters to predict the probability of MIBC. It has been also used in studies using standard neoadjuvant chemotherapy. No studies have analyzed the performance of VI-RADS to predict the pT0 or pT≤1 response post-immunotherapy (IO) in MIBC. **Methods:** In PURE-01 study patients (pts) were staged with mpMRI before and after treatment (3 cycles of pembro) prior to radical cystectomy (RC). All mpMRI scans were centrally reviewed. Logistic regression models analyzed pre- and post-pembro VI-RADS against pT≤1 (primary endpoint) and pT0 (secondary endpoint). VI-RADS scores were dichotomized between 0-3 (0=no evidence of disease) and 4-5. Covariates included cT-stage, age, gender, PD-L1 combined positive score (CPS) and tumor mutational burden (TMB). Model performance was also tested in the ongoing NureCombo (nivolumab+nab-paclitaxel; NCT04876313) and SURE-01 (sacituzumab govitecan; NCT05226117) studies. Transcriptome-wide expression profiling was matched with VI-RADS scores. **Results:** In PURE-01, 115 pts had centrally-reviewed MRI scans (N=230 mpMRI), treated between 02/17 and 08/18. In total, 32 (27.8%) had pure/predominant non-urothelial carcinoma (UC) histology, 54 (47%) had a cT3-4N0 MIBC. Pre-pembro: 21 pts (18.3%) had no measurable disease (VI-RADS=0), 37 (32.2%) a VI-RADS 1-3 score, and 57 (49.5%) had a VI-RADS 4-5 score. 20 pts (17.4%) had a downstage from VI-RADS 4-5 to VIRADS 0-3 post-pembro. Pre-pembro VIRADS 4-5 were associated with higher angiogenesis and epithelial-mesenchymal transition (EMT) activity vs VI-RADS 0-3 (p=0.011 and 0.033). Both pre-pembro and post-pembro VI-RADS 0-3 scores were the only significant covariates against pT≤1 endpoint on multivariable analyses (MVA): the strongest effect was seen with post-pembro VI-RADS 0-3 against pT≤1 response (OR: 23.4, 95%CI: 7-95.3, p<0.0001). The AUC of this model was 0.90. Model-based decisions were supported in the range of threshold probabilities of 10-80%. Post-pembro VI-RADS 4-5 were characterized by higher stromal signature scores vs VI-RADS 0-3. When post-therapy VI-RADS were tested in evaluable pts from the combined NureCombo+SURE-01 cohort (N=17pts, 34 mpMRI): 90% of post-VI-RADS 0-3 revealed a pT≤1 stage at radical cystectomy. **Conclusions:** VI-RADS scores mirrored distinct biological features in MIBC, recapitulating tissue biomarkers of IO response. VI-RADS scores post-IO revealed a strong association with pathological downstaging and represented a robust feature based on which selecting pts for bladder-sparing strategies. Results seemed to be also applicable to other novel neoadjuvant therapies beyond IO monotherapy. Clinical trial information: NCT02736266. Research Sponsor: Associazione Italiana per la Ricerca sul Cancro (AIRC).

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Poster Session

Phase I/II randomized clinical trial of in-clinic acupuncture prior to BCG in patients with high-risk non-muscle invasive bladder cancer. *First Author: Sarah P. Psutka, University of Washington, Fred Hutchinson Cancer Center, Seattle, WA*

Background: Acupuncture can reduce pain and urinary urgency and frequency. Treatment-related dose-limiting dysuria and irritative bladder symptoms are common in patients receiving intravesical Bacillus Calmette-Guerin (BCG) for the treatment of non muscle-invasive bladder cancer (NMIBC). We evaluated the feasibility, safety, and tolerability of weekly in-clinic pre-procedure acupuncture among patients receiving induction BCG. **Methods:** Patients with high-risk NMIBC undergoing induction BCG were randomized 2:1 to a standardized acupuncture protocol (Acu) or an attention waitlist control. Acu patients received acupuncture prior to each of 6 weekly BCG instillations. Feasibility was assessed via recruitment, retention, and intervention adherence. Acupuncture safety and tolerability were assessed via physician-reported CTCAE v5.0 and adverse events (AEs). Secondary endpoints included BCG treatment adherence, patient-reported BCG-related toxicity, and bladder cancer-specific and generic quality of life (QOL), assessed with the EORTC-QLQ-NMIBC-24 and -C30 surveys. Subjective assessments of acupuncture acceptability were assessed through patient exit surveys. **Results:** Between 1/21 and 7/22, 43 patients were randomized to Acu (n=28) vs. Control (n=15). Median age was 70.3 years and 76% were male. Week 7 follow-up surveys were completed by 93% of patients; 6 patients withdrew early due to disease progression, refractory gross hematuria, or for patient preference. Acupuncture was successfully delivered prior to each BCG treatment in Acu patients with no acupuncture-related AEs or interruptions to induction BCG. BCG-attributed AEs were reported by 91% Acu and 100% Control patients, including pain (28% vs. 43%, respectively, p=0.34) and urinary symptoms (62% vs. 79%, respectively, p=0.31). Comparing Acu with Controls, change in QOL over the study period demonstrated greater improvements in median urinary symptoms (9.5, IQR 0.0-19.0 vs. 0.0, IQR -14.3-7.1, p=0.02) and a trend towards improvement in median pain scores (16.7, IQR 0.0-16.7 vs. 8.3, IQR 0.0-33.3 p=0.68) among patients in the Acu arm. 96% of Acu patients reported that acupuncture was “very/extremely helpful” and 91% would recommend acupuncture to other patients. **Conclusions:** Acupuncture prior to induction BCG treatments is feasible and safe. In this Phase I/II trial, we observed reductions in pain and a trend towards improved urinary function scores over successive treatments among patients undergoing in-clinic pre-BCG instillation acupuncture. Patients receiving acupuncture reported high degrees of satisfaction with treatments. Future larger randomized controlled trials are needed to further characterize the efficacy of acupuncture with respect to pain, urinary symptoms and impact on QOL, and continuation of maintenance therapy during BCG treatment. Clinical trial information: NCT04496219. Research Sponsor: Early Phase Clinical Research Support Application, Cancer Center Support Grant Award ID# P30 CA015704-44.

4592

Poster Session

Survival outcomes of micropapillary versus classic variant, loco-regional bladder cancer: A 2004-2019 National Cancer Database analysis. *First Author: Rohan Garje, Miami Cancer Institute, Baptist Health South Florida, Miami, FL*

Background: Micropapillary (MP) is a rare histologic variant of urothelial cancer (UC) with luminal-type characteristics and p53-like gene expression, leading to chemotherapy resistance and poor prognosis. However, contemporary outcomes of MP variant T2-T4, NO-N1 loco-regional bladder UC after definitive therapy are underreported, which this work sought to determine. **Methods:** A retrospective review was performed of all eligible cases of MP and classic UC (CUC) available during 2004-2019 from National Cancer Database. Socio-demographic, pathological, and clinical attributes were analyzed via descriptive and comparative statistics. Propensity-score matching was performed to adjust for baseline differences between MP and CUC. Overall survival, being the primary outcome, was compared using multivariable Cox proportional-hazards modeling and visualized through Kaplan-Meier curves. **Results:** 30072 cases of CUC and 397 of MP were identified. After propensity-score matching, 395 patients remained in both groups, with matched cohorts having no baseline differences in age, sex, race, Charlson-Deyo comorbidity index (CCI), insurance status, income, distance to hospital, hospital location, rural versus urban residence, tumor pathological grade, proportion receiving radiotherapy, and proportion getting regional lymph node surgery. In both matched cohorts there were 313 males (79%) and 82 females (21%). Both cohorts had 334 (85%) T2 cases, 41 (10%) T3 cases, and 20 (5%) T4 cases. Both cohorts had 375 (95%) N0 cases and 20 (5%) N1 cases. MP variant was associated with inferior survival compared to CUC (HR 1.26, 95%CI 1.03-1.54, P=0.024). Older age (≥65 years) and higher CCI were also associated with inferior survival. Irrespective of histology, patients undergoing surgery (S) plus chemotherapy (C) had better survival compared to S alone (HR 0.77, 95%CI 0.62-0.94, P=0.012). Regional lymph node surgery resulted in improved survival (HR 0.59, 95% CI 0.42-0.83, P=0.002). Sex, race, insurance, income, and hospital type did not impact survival. Median and two-year OS are summarized. **Conclusions:** Survival outcomes of MP are poorer than CUC of bladder. Surgery combined with perioperative chemotherapy was associated with better survival compared to surgery alone in patients with MP and CUC. Studies evaluating novel immunotherapies and antibody drug conjugates in perioperative setting are needed to improve outcomes. Research Sponsor: None.

Cohort	Median OS (months)	Two year OS (%)
MP with S + C	47.4 (34.8, 61.9)	70.2 (64.7, 75.7)
MP with S only	24.9 (20.2, 31.2)	52.2 (43.5, 61.0)
CUC with S + C	78.0 (75.1, 81.1)	72.0 (71.4, 72.7)
CUC with S only	56.2 (53.7, 58.6)	65.9 (65.1, 66.7)

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Poster Session

Open versus robotic-assisted radical cystectomies: A risk analysis. *First Author: Rishabh Simhal, Department of Urology, Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia, PA*

Background: Radical cystectomy (RC) is standard of care for muscle-invasive bladder cancer, but it comes with significant perioperative risk with half of patients experiencing major postoperative complications. Robot-assisted radical cystectomies (RARC) have aimed to decrease patient morbidity and have become increasingly adopted in North America. Currently, both open radical cystectomies (ORC) and RARC are frequently performed. To contribute to the existing literature using newly available data from the American College of Surgeons National Surgical Quality Improvement Project (NSQIP), representing one of the most recent, largest multi-institutional studies, while uniquely accounting for a variety of factors including type of urinary diversion, cancer staging, and neoadjuvant chemotherapy. **Methods:** RC procedures performed between 2019-2020 were identified in NSQIP and the corresponding Cystectomy Targeted database. Cases in the ORC group were planned open procedures, and cases in the RARC group were robotic with intra- or extracorporeal diversions, including unplanned conversion to open cases for intention-to-treat. Chi-square and t-tests were performed to compare baseline demographics and operative parameters. Multivariate analysis was performed for outcomes including major complications, minor complications, and 30-day mortality, while adjusting for operative approach, medical comorbidities, functional status, age, race, sex, BMI, ASA-classification, preoperative labs, type of urinary diversion, pathological staging, prior pelvic surgery or radiation, need for preoperative transfusion, preoperative sepsis, emergent or elective surgery, and recent chemotherapy. **Results:** 4,022 RC cases were identified. Of these, 3,146 (78.2%) received planned ORC while 876 (21.8%) received RARC. Baseline demographics of the patients who received ORC versus RARC were largely similar, with no significant difference in age or medical comorbidities. RARC was associated with longer operative times and shorter hospital length of stay compared to ORC. On multivariate analysis, ORC was associated with a higher rate of 30-day mortality [OR 3.1; 95% CI 1.3-7.2; p=0.009], reintubation, cardiac arrest, superficial wound infection, bleeding requiring transfusion [OR 4.7; 95%CI 3.6 - 6.1; p<0.001], prolonged postoperative nasogastric tube use, rectal injury, and urethral fistula or urine leak compared to RARC. **Conclusions:** In the NSQIP database, ORC is associated with higher rates of 30-day mortality and operative complications, most notably bleeding, compared to RARC. This study is unique in the size of the cohorts compared, the timeliness of the data (2019-2020), and the ability to control for factors, such as type of urinary diversion, pathological bladder cancer staging, and use of neoadjuvant chemotherapy. Research Sponsor: None.

4595

Poster Session

Study EV-103: Neoadjuvant treatment with enfortumab vedotin monotherapy in cisplatin-ineligible patients (pts) with muscle invasive bladder cancer (MIBC): Updated results for Cohort H. *First Author: Thomas W. Flaig, University of Colorado Cancer Center Anschutz Medical Campus, Aurora, CO*

Background: Cisplatin-ineligible pts with MIBC have no established neoadjuvant treatment options known to prolong survival before undergoing radical cystectomy and pelvic lymph node dissection (RC+PLND). Enfortumab vedotin (EV) is an antibody-drug conjugate directed to Nectin-4, which is highly expressed in urothelial cancer. In a phase 3 study, EV showed improved overall survival vs standard chemotherapy and a tolerable safety profile in pts with advanced urothelial cancer previously treated with a platinum agent and a PD-1/L1 inhibitor (Powles NEJM 2021). In Cohort H of the EV-103 phase 1b/2 study, preliminary results, including pathological complete response (pCR) and pathological downstaging (pDS) rates, showed antitumor activity in cisplatin-ineligible pts with MIBC who received neoadjuvant EV treatment (Petrylak ASCO GU 2022). Here we report updated results, including event-free survival (EFS) and subsequent cancer-related therapy. **Methods:** Cohort H of the EV-103 phase 1b/2 study (NCT03288545) enrolled cisplatin-ineligible pts with MIBC (T2-T4aNOMO) and ECOG PS ≤2 who were eligible for RC+PLND. Pts received neoadjuvant EV (1.25 mg/kg) on Days 1 and 8 every 21 days for 3 cycles before undergoing RC+PLND. The primary endpoint was pCR rate (ypT0 and NO) by central pathology review. Key secondary endpoints included pDS rate (ypT0, ypTis, ypTa, ypT1, and NO), EFS based on investigator assessment, and safety. **Results:** 22 pts (median age 74.5 yr, range 56-81) were enrolled and treated; 17 pts (77.3%) remain on study. Pts had stage cT2 (68.2%), cT3 (27.3%), or cT4 (4.5%) disease. 68.2% of pts had transitional cell carcinoma only; 31.8% had a mixed histology. 86.4% of pts completed all 3 cycles of EV treatment; the median duration of EV treatment was 2.1 months (range 0.7-2.3). The pCR rate was 36.4% (95% CI, 17.2, 59.3) and the pDS rate was 50.0% (95% CI, 28.2, 71.8). Median EFS has not been reached. The EFS rate at 12 months was 76.4% (95% CI, 52.2, 89.4). All pts underwent surgery with no delays due to EV-related TAEs. The most common EV-related TAEs were fatigue (45.5%), dysgeusia (36.4%), and alopecia (31.8%); 18.2% of pts had grade ≥3 EV-related TAEs. 68.2% of pts had surgery-related TAEs and 31.8% pts had grade ≥3 surgery-related TAEs. The most common surgery-related TAEs were procedural pain (18.2%), anaemia (13.6%), and constipation (13.6%). 3 pts died due to AEs unrelated to EV treatment; in 2 pts the AEs occurred >30 days after RC+PLND. 36.4% of pts received subsequent cancer-related therapy. **Conclusions:** Neoadjuvant EV monotherapy treatment showed promising results for antitumor activity and EFS with a manageable safety profile in cisplatin-ineligible pts with MIBC. These results support ongoing phase 2 and 3 programs in MIBC evaluating EV alone or combined with pembrolizumab (EV-103 Cohort L, KN-905, KN-B15). Clinical trial information: NCT03288545. Research Sponsor: Seagen Inc. and Astellas Pharma Inc.

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Poster Session

The impact of neoadjuvant chemotherapy on 30-day radical cystectomy outcomes. *First Author: Kerith Ruoyao Wang, Department of Urology, Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia, PA*

Background: Neoadjuvant chemotherapy (NAC), often a cisplatin-based regimen, is recommended before radical cystectomy (RC), as studies have shown a modest survival benefit. However, NAC may confer toxicity and augment preoperative frailty, affecting perioperative outcomes. We investigated the relationship between NAC and 30-day RC outcomes using the National Surgical Quality Improvement Program (NSQIP). **Methods:** RCs performed between 2019-2020 were identified in NSQIP and the corresponding cystectomy-targeted database. Baseline demographics, comorbidities, and operative parameters were compared via Pearson's chi-square and t-tests between patients who received NAC before RC and RC alone (RCA) groups. Patient frailty was compared using the NSQIP frailty index (mFI-5), a validated 5-item score including points for diabetes, functional status, chronic obstructive pulmonary disease, heart failure, and hypertension. Multivariable logistic regression was used to compare outcomes, adjusting for age, race, robotic or open approach, urinary diversion type, comorbidities, ASA classification, and functional status. Minor complications included superficial SSI, pneumonia, UTI, bleeding requiring transfusion, AKI, or C. diff infection. Major 30-day complications included sepsis, DVT, stroke, reintubation, renal failure, MI, PE, septic shock, wound dehiscence, deep wound infection, cardiac arrest, readmission, reoperation, or mortality. All statistical tests were two tailed, p<0.05 considered significant. **Results:** 4,482 RCs were identified. Of these, 1889 (42%) patients received NAC. Compared to RCA, NAC patients were younger (66.9 years vs 70.4 years, p<0.001), had higher rates of white race, being functionally independent, preoperative weight loss, and cigarette use. NAC also had lower ASA class, fewer comorbidities, and lower frailty (mFI-5 0.8 vs 0.9, p<0.001). Compared to RCA, NAC patients had more robotic cystectomies (23% vs 19%, p=0.0003), received more continent diversions, had a shorter length of stay (7.1 vs 7.8 days, p<0.001), and more commonly had pT0 tumors compared to RCA (18.4% vs 5.9%, p<0.001). On MVA, NAC patients had higher rates of minor complications, most notably increased bleeding requiring transfusion [OR 1.8; 95%CI 1.6-2.1; p<0.001]. There was no difference in major complications between NAC and RCA, except NAC was associated with higher rates of sepsis [OR 1.4; 95%CI 1.1-1.8; p=0.003]. There was no difference in 30-day need for reoperation, readmission, or mortality. **Conclusions:** In the largest study to date on this topic, we found that NAC for RC is often given to younger, healthier patients, and is not associated with higher rates of major complications or mortality. NAC is associated with higher rates of bleeding and sepsis, which may be related to the immunosuppressive effects of chemotherapeutics. Providers should discuss with patients the benefits and risks of NAC before RC. Research Sponsor: None.

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Poster Session

A first-in-human trial of intravesical enfortumab vedotin (EV), an antibody-drug conjugate (ADC), in patients with non-muscle invasive bladder cancer (NMIBC): Interim results of a phase 1 study (EV-104). *First Author: Ashish M. Kamat, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: A majority of patients (pts) with bladder cancer present with non-muscle invasive disease; for pts with high-risk tumors, standard of care (SOC) is resection of tumor followed by intravesical Bacillus Calmette-Guerin (BCG). Once pts experience recurrence and develop BCG-unresponsive disease, SOC is radical cystectomy (RC), which many pts are unfit for or refuse. EV is an ADC directed to Nectin-4, which is highly expressed in bladder tumors. Intravenous EV has demonstrated survival benefit in pts with previously treated la/mUC. In preclinical models with intravesical administration, EV was well tolerated and showed antitumor activity. Here we present the first clinical data for intravesical administration of EV in pts with NMIBC. **Methods:** EV-104 (NCT05014139) is an ongoing phase 1, open-label, multicenter, dose-escalation and expansion study of intravesical EV evaluating the safety, tolerability, PK, and antitumor activity of intravesical EV in pts with high-risk BCG-unresponsive NMIBC with carcinoma in situ (CIS) with or without papillary disease who are ineligible for or refuse RC. Dose escalation phase aims to identify the MTD or recommended dose of intravesical EV at the following dose levels: 125mg, 250mg, 500mg, and 750mg. Pts receive intravesical EV weekly for 6 weeks in the induction phase, followed by 9 monthly maintenance doses. Preliminary safety, PK, and efficacy data for 125mg and 250mg doses are presented in this abstract. **Results:** As of data cutoff (1 Dec 2022), 6 pts received intravesical EV across 2 dose levels: 4 pts at 125mg completed 6 induction cycles and proceeded to maintenance; 2 pts at 250mg had received at least 3 doses of intravesical EV. Of 6 pts across doses, there were no Grade ≥3 TRAEs, treatment-related SAEs, TRAEs leading to dose reduction or discontinuation. 4 of 6 pts (3 at 125mg and 1 at 250mg) experienced ≥1 treatment-related adverse event (TRAE) of Grade 1 or 2. Most common TRAEs were fatigue (3 of 6) and micturition urgency (2 of 6). As of data cutoff, no DLTs were observed for 125mg; the DLT evaluation period for 250mg was not complete. All blood PK analyses (ADC and unconjugated MMAE) for pts at 125mg were undetectable; no PK data was available for 250mg. Of 4 pts receiving 125mg of intravesical EV, 3 achieved CR and continue in response. The fourth pt discontinued tx due to persistent disease but remains on study. Pts at 250mg had not been evaluated for response at data cutoff. Detailed safety and additional efficacy data will be presented. **Conclusions:** Preliminary data from EV-104 show intravesical EV is well tolerated with no evidence of systemic exposure at 125mg. Preliminary antitumor activity was observed at 125mg with 3 of 4 pts achieving a CR. Dose escalation is ongoing to identify the MTD or recommended dose for dose expansion. Clinical trial information: NCT05014139. Research Sponsor: Seagen Inc. and Astellas Pharma Inc.

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Poster Session

CABOSUN II: Results from a phase 2, open-label, multi-center randomized study of cabozantinib (CABO) vs. sunitinib (SUN) for non-clear cell renal cell carcinoma (NCCRC). *First Author: Andrew Johns, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: NCCRC are a diverse group of rare diseases with limited data to guide treatment. CABO is highly effective in clear cell RCC, but it is unknown whether it is superior to SUN, the historic standard of care for metastatic NCCRC. **Methods:** CABOSUN II (NCT03541902) was a randomized phase II study at 3 centers for patients (pts) with metastatic NCCRC. Sixty pts were planned to detect CABO as better than SUN with a 1-sided test. Pts were randomized 1:1 to CABO 60mg daily or SUN 50mg daily (4 weeks on, 2 weeks off). SUN dose modification to 2 weeks on, 1 week off was allowed for toxicity. Stratification was by papillary RCC (PRCC) vs. non-PRCC (NPRCC), good/intermediate vs. poor risk disease by IMDC criteria, and prior TKI use. The primary outcome was progression-free survival (PFS) by RECIST v1.1 compared between the 2 arms using the log-rank test. Secondary outcomes were objective response rate (ORR), overall survival (OS), and adverse event (AE) rates (2-sided tests). **Results:** 32 pts were randomized to CABO (N=15) or SUN (N=17) between 9/2018 and 6/2021. The trial stopped early due to a change in standard therapy for PRCC not based on these pts' outcomes. Age range was 22-88 years with medians 57 and 61 for CABO and SUN. Pts were primarily white (84%) and male (72%), with good/intermediate risk (88%), and these were balanced between arms. More pts on the CABO arm had bone metastases (62% vs. 24%). NPRCC were chromophobe (N=6; 5 randomized to SUN), unclassified (N=5), and MIT family translocation (N=3; all randomized to CABO). With median follow-up of 33.3 months and 20 PFS events, median PFS for CABO vs. SUN was 8.2 vs. 13.8 months (1-sided p=0.96). There were no statistically significant differences in ORR or OS between the arms. AEs were in line with previous studies. **Conclusions:** CABO was not superior to SUN for metastatic NCCRC in this study. Both arms had high rates of stable disease or better. Despite stratification by PRCC or NPRCC, there were major differences in NPRCC subtypes between the arms that may have impacted the results. More pts with chromophobe histology, an often indolent subtype, received SUN while all pts with MIT family translocation, a relatively aggressive subtype, received CABO. Permitted SUN dose modifications may have also influenced outcomes. While the PAPMET study showed CABO to be superior to SUN for PRCC, optimal treatments for rare, NPRCC remain a pressing need. Clinical trial information: NCT03541902. Research Sponsor: Exelixis.

		CABO (N=15)	SUN (N=17)	TOTAL (N=32)	P-value
PFS	Events	11	9	20	0.96
	Median (mos) [95% CI]	8.2 [4.3-NR]	13.8 [11-NR]	11.0 [7.6-14.9]	
OS	Events	9	7	16	0.67
	Median [95% CI]	28.0 [17-NR]	34.9 [28.6-NR]	28.7 [28.0-NR]	
ORR	N (%), [95% CI]				0.59
	Partial Response	2 (13.3), [1.7-40.5]	1 (5.9), [0.2-28.7]	3 (9.4)	
	Stable Disease	8 (57.1)	9 (52.9)	17 (54.8)	
	Progressive Disease	4 (28.6)	6 (35.3)	10 (32.3)	
	Not Evaluable/Missing	1 (6.7)	1 (5.9)	2 (6.3)	

NR=Not reached.

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Poster Session

Gender and postoperative surgical margin status in MIBC: An analysis of the National Cancer Database. *First Author: Olivia French Gordon, George Washington University Hospital, Washington, DC*

Background: Women with muscle-invasive bladder cancer (MIBC) continue to experience persistent disparities in health outcomes despite accounting for less than 1/3 of newly diagnosed bladder cancer cases. Multiple studies have acknowledged the aggressive profile of female bladder cancer. This study aims to identify tangible areas to intervene and improve the delivery of oncologic care. **Methods:** The National Cancer Database (NCDB) was queried from 2004-2017 to conduct a retrospective cohort analysis of men and women with MIBC (cT2a-T4). N=41,037 patients with MIBC were reviewed, (30,313 male; 10,724 female). The primary endpoints were OS and surgical margin status. Logistic regression was performed to determine whether female sex conferred differential impact on surgical margin status when controlling for baseline clinical stage, age, receipt of neoadjuvant chemotherapy (NAC), Charlson-Deyo Comorbidity Classification (CDDC), and facility type. Cox proportional hazards assessed the impact of age, gender, margin status, CDDC and NAC on OS. **Results:** Logistic regression showed that sex, age, baseline clinical stage, CDDC, facility type and NAC were significant predictors of surgical margin status (p<.001). Female sex was found to have a 14.4% higher probability of having positive residual margins (HR 1.144 (95% CI: 1.07-1.23), p<.001). When adjusting for age, margin status, CDDC and NAC, Female gender (OS HR 1.063 (95% CI: 1.03-1.09), p<.001), positive microscopic margins (OS HR 2.0 (95% CI: 1.90-2.10), p<.001) and positive macroscopic margins (OS HR 2.62 (95% CI: 2.40-2.90), p<.001) independently portended poorer OS and necessitated increased adjuvant XRT (p<.001). Unexpected demographic findings included a significantly greater number of females than expected with a median household income <\$38,000 (p= 0.047) and a greater number of females in the upper quartile of patients without a HS diploma (p<.001). The median days from diagnosis to definitive surgical treatment was significantly lower compared to males (58 vs 67 days; p<.001). **Conclusions:** Women with MIBC faced obstacles to getting treatment (less education and lower median income). Despite these hurdles they may be more proactive with their health as seen by a shorter time from diagnosis to the surgical table. However, this proactivity has yet to pay off as women undergoing surgical treatment for MIBC were significantly less likely to have clear margins post-operatively. The urologic community must mirror female patient's proactivity and further investigate the gender disparity in surgical treatment of MIBC. Research Sponsor: None.

	Males	Females
Median Age	73	75
Clinical Stage: T2	24,100 (79.5%)	8,163 (76.1%)
T3	3,721 (12.3%)	1,702 (15.9%)
T4	2,492 (8.2%)	859 (8.0%)
AJCC pN+	8210 (25%)	3135 (26.5%)
Positive Margins	2020 (6.7%)	820 (7.6%)
NAC	6010 (19.4%)	1925 (17.5%)

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Poster Session

Associations of diet with survival of patients (pts) with metastatic cancer of the urothelium (mUC) and renal cell carcinoma (mRCC) on immune checkpoint blockade (ICB). *First Author: Brendan John Guercio, James P. Willmot Cancer Center/URMC - JPWCC, Rochester, NY*

Background: The gut microbiome is an emerging modifiable predictor of ICB efficacy. Diet impacts the gut microbiome and fiber intake is associated with longer progression-free survival (PFS) in advanced melanoma treated with ICB. Whether diet impacts ICB benefit in mUC or mRCC remains unknown. **Methods:** Using a prospective cohort design, baseline dietary data were collected from pts with mUC or mRCC initiating ICB at Memorial Sloan Kettering Cancer Center using the extensively validated Harvard Willett Food Frequency Questionnaire. Tumor mutational burden (TMB) was estimated by next generation sequencing (MSK-IMPACT). The primary endpoint was radiologist assessed PFS, with secondary endpoint of overall survival (OS). Fiber intake was stratified as high or low using the median intake in our cohort. Associations between fiber intake and clinical outcomes were assessed using Kaplan-Meier curves plus univariable (UV) and multivariable (MV) Cox proportional hazards regression. Models were adjusted for prior ICB exposure. Models for mUC controlled for TMB and Bellmunt risk factors. Models for mRCC controlled for histology (clear vs non-clear cell) and IMDC risk score. **Results:** From 2/2021-6/2022, 88 pts eligible for analysis were enrolled with median follow-up of 10.1 months (mo) (mUC n = 40; mRCC n = 48). Median fiber intake was 17.5 g/day (interquartile range 12.5-24.5). Among pts with mUC, high fiber intake (≥ 17.5 g/day) was associated with longer PFS (UV hazard ratio [HR] 0.56, 95% CI 0.26-1.19, p = .13; MV HR 0.39, 95% CI 0.16-0.93, p = .03). Similar trends were observed for mRCC. In subgroup analyses, PFS was numerically longer with high fiber intake among mUC pts on maintenance avelumab (median PFS 6.1 vs 3.0 mo, n = 14) and in pts with mRCC treated with first-line (1L) ipilimumab + nivolumab (median PFS 18.0 vs 5.7 mo, n = 14) and 1L ICB + tyrosine kinase inhibitor (median PFS not reached vs 5.1 mo, n = 21). Among pts with mUC on non-maintenance ICB, pts with high fiber intake had numerically higher PFS at 6 mo (38% vs 14%, n = 26). **Conclusions:** This pilot study indicates that high fiber intake is associated with longer PFS among pts with mUC on ICB. Trends towards longer PFS and OS with high fiber intake were observed among pts with mRCC. Analyses of the gut microbiome are underway to investigate mechanisms of action. Research Sponsor: Bladder Cancer Advocacy Network; U.S. National Institutes of Health.

Hazard ratios for survival outcomes by high vs low fiber intake.				
Outcomes	mUC (n = 40)		mRCC (n = 48)	
	HR (95% CI)	p	HR (95% CI)	p
UV PFS	0.56 (0.26-1.19)	0.13	0.58 (0.27-1.25)	0.16
MV PFS	0.39 (0.16-0.93)	0.03	0.70 (0.31-1.60)	0.39
UV OS	0.94 (0.33-2.68)	0.90	0.11 (0.01-0.84)	0.04
MV OS	1.14 (0.37-3.513)	0.82	0.18 (0.02-1.54)	0.12

4600

Poster Session

Association of ¹⁸F-FDG PET characteristics and survival outcomes using whole body tumor analysis in patients (pts) with metastatic genitourinary (GU) malignancies. *First Author: Nicholas I. Simon, National Cancer Institute, Bethesda, MD*

Background: ¹⁸F-FDG PET scans are widely used for staging and monitoring pts with metastatic GU malignancies. In addition to identifying lesions, ¹⁸F-FDG PET scans provide semi-quantitative parameters (SUV_{max}, SUV_{mean}, total lesion glycolysis (TLG)) that can be used to characterize disease burden and treatment response. These parameters can demonstrate how treatment response varies across different patients as well as across different lesions within the same patient. This study was done to determine which parameter provides the best prognostic information for pts with metastatic GU malignancies. **Methods:** 101 patients with metastatic GU malignancies from two separate, prospective trials with at least two ¹⁸F-FDG PET scans were analyzed. All regions of interest were contoured for both the baseline and follow-up ¹⁸F-FDG PET scans. Regions of interest (ROI) were quantified and matched between timepoints using TRAQinform IQ technology (AIQ Solutions) to identify which were new, increasing, stable, decreasing, or disappeared. Imaging features were extracted from each patient, including basic features (SUV_{max}, SUV_{mean}, TLG, and changes in these features) and heterogeneity (intrapatient heterogeneity of disease and response) features. Cox regression was used to determine univariate predictive power of each measure. The TRAQinform Profile was calculated to predict either progression-free (PFS) or overall survival (OS) using 5-fold cross-validation of a random survival forest. The performance of individual features and the TRAQinform Profile was evaluated using the c-index. **Results:** 54pts were treated with single agent cabozantinib (cabo) on a phase II trial and 47 pts were treated with cabozantinib and nivolumab, with or without ipilimumab (cabonivo +/- ipi), on a phase I trial. Most pts had urothelial carcinoma (N = 65). Other histologies included prostate (4), penile (1), renal cell carcinoma (RCC) (6), renal medullary carcinoma (4), testicular (4), adenocarcinoma of the bladder (8), squamous cell carcinoma of the bladder (2), sarcomatoid bladder (1), sarcomatoid RCC (1), and small cell carcinoma (4 bladder, 1 prostate). 2389 ROIs were analyzed, with a range of 1 to 151 per patient. The TLG at the follow-up image was the strongest predictor of both PFS (c-index = 0.62) and OS (0.69), followed by number of increasing ROI (0.61, 0.64), and percentage of all ROIs classified as new or increasing (0.57, 0.63). SUV_{max} (0.49, 0.47) and SUV_{mean} (0.47, 0.56) at follow-up were found to be weaker predictors of PFS and OS. TRAQinform Profile was able to predict the responder's vs suboptimal responders to study treatment (c-index = 0.73, 0.75). **Conclusions:** The TRAQinform Profile analysis of ¹⁸F-FDG PET scans provided both prognostic and predictive information for patients with metastatic GU malignancies treated with either cabo or cabonivo +/- ipi. Research Sponsor: AIQSolutions; U.S. National Institutes of Health.

TPS4601

Poster Session

KEYNOTE-905/EV-303: A phase 3 study to evaluate the efficacy and safety of perioperative pembrolizumab or pembrolizumab plus enfortumab vedotin (EV) for muscle-invasive bladder cancer (MIBC). *First Author: Andrea Necchi, Vita-Salute San Raffaele University; IRCCS San Raffaele Hospital and Scientific Institute, Milan, Italy*

Background: Standard of care for MIBC is neoadjuvant cisplatin-based chemotherapy followed by radical cystectomy + pelvic lymph node dissection (RC + PLND), but many patients with MIBC are ineligible for cisplatin-based chemotherapy. In the phase 1b/2 KEYNOTE-869/EV-103 study, combination therapy with the PD-1 inhibitor pembrolizumab and the Nectin-4-directed antibody-drug conjugate EV showed promising antitumor activity in cisplatin-ineligible patients with locally advanced or metastatic urothelial carcinoma. KEYNOTE-905/EV-303 (NCT03924895) is a multicenter, randomized, open-label, phase 3 study to evaluate efficacy and safety of perioperative pembrolizumab alone or combined with EV versus RC + PLND alone in patients with MIBC who are ineligible for or decline cisplatin-based treatment. **Methods:** Patients with treatment-naïve MIBC (T2-T4aN0M0 or T1-T4aN1M0) and predominantly ($\geq 50\%$) urothelial histology who are cisplatin ineligible or decline cisplatin-based treatment and have an ECOG PS score of 0-2 are eligible. Cisplatin ineligibility will be defined as meeting ≥ 1 of the following criteria: impaired renal function with calculated creatinine clearance 30-59 mL/min; ECOG PS 2; grade ≥ 2 audiometric hearing loss per CTCAE v4.0; or NYHA class III heart failure. Patients will receive neoadjuvant pembrolizumab 200 mg intravenously (IV) every 3 weeks (Q3W) for ≤ 3 cycles followed by RC + PLND and adjuvant pembrolizumab 200 mg IV Q3W for ≤ 14 cycles (arm A); RC + PLND followed by observation (adjuvant nivolumab permitted based on clinical indication and regulatory approval [arm B]); or neoadjuvant EV 1.25 mg/kg + pembrolizumab 200 mg IV Q3W for ≤ 3 cycles followed by RC + PLND and adjuvant EV + pembrolizumab for ≤ 6 cycles and adjuvant pembrolizumab 200 mg IV Q3W for ≤ 8 cycles (arm C). In the neoadjuvant and adjuvant phases of arm C, pembrolizumab will be administered on day 1 and EV will be administered on days 1 and 8 of each cycle. Enrollment is complete for arm A; patients will continue to be randomly assigned 1:1 to arm B or arm C. Stratification factors are tumor stage (T2N0 vs T3/T4aN0 vs T1-T4aN1), geographic region (United States vs Europe vs rest of world), and cisplatin eligibility (cisplatin ineligible or cisplatin eligible but declines treatment). The primary end point is event-free survival between arm B and arm C. Secondary end points are event-free survival (arm A vs arm B) pathologic complete response, overall survival, disease-free survival, pathologic downstaging rates, and safety. Enrollment is planned for 308 patients, and recruitment is ongoing in Africa, Asia, Australia, Europe, North America, and South America. © 2023 American Society of Clinical Oncology, Inc. Reused with permission. This abstract was accepted and previously presented at the 2023 ASCO-GU Annual Meeting. All rights reserved. Clinical trial information: NCT03924895. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

TPS4603

Poster Session

LITESPARK-024: Randomized phase 1/2 study of belzutifan with or without palbociclib for treatment of advanced renal cell carcinoma (RCC). *First Author: David F. McDermott, Beth Israel Deaconess Medical Center, Boston, MA*

Background: Immunotherapy is a standard-of-care first-line treatment for advanced clear cell RCC (ccRCC). However, many patients (pts) will develop resistance to first-line therapy, and effective second- and later-line treatment options are therefore needed. The von Hippel-Lindau (*VHL*) gene is inactivated in approximately 90% of ccRCC cases and results in the constitutive activation of hypoxia-inducible factor 2 α (HIF-2 α), a key oncogenic driver in RCC. Belzutifan, a first-in-class HIF-2 α inhibitor, has demonstrated antitumor activity with manageable safety in previously treated pts with advanced ccRCC. The cyclin-dependent kinase (CDK) pathway is also associated with poor clinical outcomes in ccRCC. In RCC cell lines, the CDK 4/6 inhibitor palbociclib inhibited cell growth. CDK 4/6 inhibition has shown synergistic antiproliferative effects with HIF-2 α inhibition in HIF-2 α -dependent *VHL* $-/-$ RCC cell lines. Palbociclib could therefore potentially enhance the efficacy of belzutifan as combination therapy for previously treated pts with advanced RCC. **Methods:** LITESPARK-024 is a 2-part, open-label, multicenter, phase 1/2 randomized study (NCT05468697). Part 1 is intended to establish the recommended phase 2 dose (RP2D) of belzutifan + palbociclib using a modified toxicity probability interval design. After the RP2D is established, part 2 will directly compare the safety and efficacy of belzutifan monotherapy with belzutifan + palbociclib in pts with advanced ccRCC. In both parts, pts with measurable disease per RECIST v1.1, a KPS score of $\geq 70\%$, and histologically confirmed unresectable stage IV RCC with a clear cell component with disease progressing on or after receiving at least 2 systemic treatments (both an anti-PD-1/L1 monoclonal antibody and a VEGF receptor-targeted tyrosine kinase inhibitor, in sequence or in combination) will be enrolled. Up to 30 pts will be enrolled into 3 dose groups in part 1 and will receive belzutifan 120 mg once daily + palbociclib (75, 100, or 125 mg) daily for 21 consecutive days followed by 7 days off. In part 2, approximately 150 pts will be randomly assigned 2:1 to receive belzutifan 120 mg once daily + palbociclib RP2D (21 consecutive days/7 days off) or belzutifan 120 mg once daily. Pts will be stratified by IMDC risk (0 vs 1-2 vs 3-6) and sarcomatoid histology (yes vs no) at randomization in part 2. The primary end point for part 1 is to assess dose-limiting toxicities and adverse events and to determine the RP2D of belzutifan + palbociclib. The primary end point for part 2 is ORR per RECIST v1.1 by investigator assessment. Secondary end points for part 2 are CBR, DOR, and PFS per RECIST v1.1 by investigator assessment, OS, and safety and tolerability. Enrollment began in July 2022. Clinical trial information: NCT05468697. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

TPS4602

Poster Session

ARC-20: A phase 1 dose-escalation and dose-expansion study to investigate the safety, tolerability, and pharmacology of HIF-2 α inhibitor AB521 monotherapy in patients with clear cell renal cell carcinoma and other solid tumors. *First Author: Toni K. Choueiri, Dana Farber Cancer Institute and Harvard Medical School, Boston, MA*

Background: Renal cell carcinoma (RCC) is one of the 10 most common neoplasms in the United States. Patients with clear cell RCC (ccRCC) commonly have inactivation of the von Hippel-Lindau tumor suppressor protein, resulting in accumulation of hypoxia-inducible factor alpha (HIF α) subunits (especially HIF-2 α) and leading to tumor growth. AB521, an orally bioavailable small molecule inhibitor of HIF-2 α , potentially inhibits transcription of HIF-2 α -dependent genes in cell lines and preclinical species. Single doses of AB521 (3 mg, 10 mg, 30 mg, and 100 mg) and multiple ascending doses of AB521 (15 mg, 30 mg, and 50 mg) have been previously studied in healthy volunteers. ARC-20 is a first-in-patient study to investigate the safety, tolerability, and pharmacology of AB521 monotherapy in patients with solid tumors and evaluate the clinical activity of AB521 in previously treated patients with ccRCC. **Methods:** ARC-20 (NCT05536141) is a phase 1, multicenter, open-label study. Eligible patients are adults with solid tumors with ≥ 1 measurable lesion(s) per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 and an Eastern Cooperative Oncology Group performance status of 0 or 1. ARC-20 has 2 stages, dose escalation and dose expansion. The dose escalation stage uses a standard 3+3 design and includes patients with pathologically confirmed solid tumors and no other available treatment options. Patients will be sequentially assigned to 1 of 4 cohorts evaluating doses of AB521 ranging from 20 to 200 mg/day. Intermediate dose cohorts may be evaluated based on emergent safety or pharmacologic data. The dose expansion stage will evaluate approximately 30 patients with histologically confirmed ccRCC who have received previous treatment for metastasis with an anti-programmed cell death protein 1 (anti-PD-1) therapy and a vascular endothelial growth factor (VEGF)-targeting tyrosine kinase inhibitor (TKI). Patients previously treated with a HIF-2 α -targeting therapy are not eligible for dose expansion. Results from the dose-escalation stage will inform the dose and schedule used during dose expansion. Primary endpoints are the incidence of dose-limiting toxicity and adverse events. Secondary endpoints include objective response rate, AB521 plasma concentration, and AB521 pharmacokinetics. Exploratory endpoints include changes in expression of erythropoietin and other HIF-2 α driven biomarkers in blood and tumor tissues, along with progression-free survival for ccRCC patients during dose expansion. Clinical trial information: NCT05536141. Research Sponsor: Arcus Biosciences.

TPS4604

Poster Session

NRG-GU012: Randomized phase II stereotactic ablative radiation therapy (SABR) for patients with metastatic unresected renal cell carcinoma (RCC) receiving immunotherapy (SAMURAI). *First Author: William A. Hall, Medical College of Wisconsin, Milwaukee, WI*

Background: The treatment for patients with metastatic RCC is evolving. The current standard of care for patients presenting with de novo metastatic disease is combination immunotherapy (IO)-based treatment. At the time of this shift in the systemic treatment strategy, the role of immediate cytoreductive nephrectomy has also been in flux. For patients with de novo disease, there has been a shift towards initiation of upfront systemic rather than immediate cytoreductive nephrectomy. SABR is a highly focused radiation technique that delivers a high dose of radiation over a limited number of fractions. The SAMURAI trial seeks to evaluate SABR as an alternative approach to treat the primary tumor in patients with metastatic RCC receiving IO, who are not recommended for surgery, or who decline surgery. **Methods:** This is a randomized phase II trial for patients with metastatic RCC with an intact primary tumor. Eligible patients include those with any histology RCC who are candidates to receive standard IO combination treatment and are those not recommended for upfront surgery or decline surgery. Patients will be randomized to SABR + IO combination versus IO combination alone. The primary objective of the study is to determine whether the addition of SABR to the primary tumor in combination with IO improves outcomes compared to IO alone in patients with metastatic, unresected, RCC. The primary endpoint is nephrectomy and radiographic progression-free survival (nrPFS) with progression determined as per iRECIST criteria. Patients are eligible if they are not recommended for upfront surgery, have a primary tumor treatable with SABR, and are candidates for IO. Choice of IO combination regimen will be at the discretion of the treating physician and will include either IO-IO or regimens of IO in combination with a VEGF inhibitor (IO-VEGF). 240 patients will be randomized in a 2:1 ratio favoring SABR plus IO combination (n=160) as compared to standard of care IO combination alone (n=80). The sample size will provide 90% power at a one-sided alpha level of 0.05 to detect a hazard ratio for nrPFS of 0.62, i.e., an approximate 40% reduction in the rate of events. Secondary endpoints include objective response rate by iRECIST and RECIST, radiographic progression free survival by RECIST and iRECIST, time to second line therapy, rate of cytoreductive nephrectomy, treatment free survival, and overall survival. Exploratory analyses will assess potential prognostic and predictive biomarkers. The trial is currently open and accruing through the NRG oncology cooperative group (NCT05327686) and study information can be found through the Cancer Trials Support Unit website www.ctsu.org. Clinical trial information: NCT05327686. Research Sponsor: U.S. National Institutes of Health.

TPS4605

Poster Session

Phase 1b/2 study of combination ^{177}Lu girentuximab plus cabozantinib and nivolumab in treatment naive patients with advanced clear cell RCC. *First Author: Elshad Hasanov, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Complete response (CR) is still a rare event in patients with advanced clear cell renal cell carcinoma (ccRCC). The combination of nivolumab plus cabozantinib was recently approved for the first-line treatment of ccRCC based on the CheckMate 9ER phase III study demonstrating improved progression-free survival (PFS) and objective response rate (ORR) in comparison to sunitinib. However, the CR rate was only 9%. Since the anti-tumor effects of immune checkpoint inhibitors are dependent on the presence of activated tumor-infiltrating T cells, drugs that could synergize with T cells' anti-tumor activity can allow us to improve CR rates. Activation of the cGAS-STING pathway, the master regulator of anti-tumor immunity which is induced by radiation-induced DNA damage, is one promising mechanism that has been investigated. Many studies have shown that radiation treatment augments immune checkpoint inhibition. However, it is not always possible to radiate all metastatic lesions. Therefore, targeted peptide receptor radionuclide therapies (PRRT), have been developed by conjugating radioisotopes to receptor binding analogs targeting specific cancer cell surface proteins, thereby delivering targeted radiation to cancer cells in the body with minimal damage to surrounding healthy cells. ^{177}Lu girentuximab is the first antibody-radioisotope designed for ccRCC, targeting carbonic anhydrase IX-expressing cells, which includes > 90% of ccRCC. It has been tested in metastatic ccRCC as a single agent and shown to be safe and effective in stabilizing disease in 57% of pts. In this study, we hypothesize that ^{177}Lu girentuximab-induced DNA damage will potentiate the STING pathway, and this activation will synergize with nivolumab and cabozantinib to promote trafficking and infiltration of activated T cells to tumors and achieve higher CR rates. **Methods:** Up to 100 patients with treatment naive, biopsy-proven ccRCC with adequate organ/marrow function with ≥ 1 evaluable lesion by RECIST 1.1 will be enrolled. A 5-patient safety lead-in will evaluate myelosuppression. Ongoing safety, and fertility monitoring will employ a Bayesian approach. The sample size was chosen for reasonable operating characteristics to distinguish a CR rate of 18% as better than 9% using a beta(0.09, 0.91) prior. Secondary endpoints are objective response, PFS by RECIST 1.1, and overall survival. ^{177}Lu -girentuximab 1480 MBq/m² (61% of single agent MTD) will be administered every 12 weeks for up to 3 treatment cycles. After the first cycle, nivolumab and cabozantinib will be added starting with the second cycle at standard dose. To explore the effects of the combination therapy on inducing activated T cell infiltration, patients will undergo pre/post-treatment PET scan with [^{18}F]F-AraG radiotracer as well as biopsies for single cell, spatial transcriptomics and proteomics studies. Research Sponsor: Telix Pharmaceuticals; DOD grant W81XWH-22-1-0456.

TPS4607

Poster Session

A phase II study of olaparib (AZD2281) in patients (Pts) with metastatic/advanced urothelial carcinoma and other genitourinary (GU) tumors with DNA-repair defects. *First Author: Elias Chandran, National Cancer Institute, Bethesda, MD*

Background: Olaparib is a poly-ADP-ribose polymerase (PARP) inhibitor that induces synthetic lethality in tumor cells with dysfunctional DNA damage repair (DDR) from loss of function of *BRCA* or other DDR genes. It improves survival in advanced ovarian, pancreatic, prostate and breast carcinoma with DDR gene alterations and is FDA approved for these indications. PARP inhibitors still have an undefined role in non-prostate GU tumors. We hypothesize that PARP inhibitors will have activity in DDR deficient tumors, regardless of histology. We are conducting a phase 2 trial of olaparib in non-prostate GU cancers with DDR gene defects. **Methods:** Eligible pts must have metastatic/advanced urothelial carcinoma or other non-prostate GU cancers and have measurable disease by RECIST 1.1. Pts in Cohorts 1 and 2 must harbor tumor or liquid pathologic DDR alterations identified by FoundationOne CDx (F1CDx) panel and reviewed by a molecular genetics review panel: Cohort 1 includes *BRCA1*, *BRCA2*, *ATM*, *BAP1*, *MSH2*, *PALB2*, and *BRIPI1* alterations, and pts with high tumor mutational burden (TMB) (>15 mutations/megabase); Cohort 2 (exploratory cohort) includes *ABL1*, *ATR*, *ATRX*, *BARD1*, *BRD4*, *CCND1*, *CHEK1*, *CHEK2*, *DOT1L*, *FANCC*, *FANCE*, *FANCG*, *FANCL*, *IKBKE*, *MEN1*, *MLH1*, *MSH2*, *MSH6*, *MUTYH*, *NPM1*, *PMS2*, *POLD1*, *POLE*, *RAD51*, *SMARCB1*, *STEK11*, and *TP53* alterations. Cohort 3 (natural history) will include pts without pathologic alterations in any Cohort 1 or 2 genes. Pts with eligible gene alterations (Cohorts 1 and 2) will be given olaparib 300mg twice daily until progressive disease, unacceptable adverse events, withdrawal of consent or death. They will have circulating tumor cells (CTCs) collected at baseline and every 4 weeks, and CT restaging every 8 weeks. Pts in Cohort 3 will receive standard of care treatment and have baseline CTC collection and be followed for survival. The primary objective is to evaluate the objective response rates (ORR) in Cohorts 1 and 2. Secondary objectives include progression-free survival (PFS), overall survival (OS) and safety. In these cohorts, the trial will have a Simon optimal two-stage design. In Cohort 1, 25 evaluable pts will be required to provide 90% power with $\alpha = 0.1$ to differentiate between a promising ORR of 30% versus an unacceptably low ORR of 10%. In Cohort 2, 35 evaluable pts will be required to provide 90% power with $\alpha = 0.05$ to differentiate between a promising ORR of 30% versus an unacceptably low ORR of 10%. Exploratory objectives include estimating the distribution of DDR alterations in non-prostate GU malignancies, assessing the effectiveness of NGS in detecting DDR alterations in circulating tumor DNA (ctDNA), assessing levels of baseline CTCs and changes in CTC level with olaparib, and correlating with clinical outcomes. This is an ECTCN network clinical trial and is open to enrollment. Clinical trial information: NCT03375307. Research Sponsor: U.S. National Institutes of Health.

TPS4606

Poster Session

SOGUG-vexillum: Phase II non-randomized clinical trial of nivolumab/ipilimumab maintenance following first-line chemotherapy in unresectable locally advanced or metastatic urothelial cancer. *First Author: Guillermo de Velasco, Medical Oncology Department, Hospital Universitario 12 de Octubre, Madrid, Spain*

Background: The current standard of care in non-progressors to first-line platinum-based chemotherapy for unresectable locally advanced or metastatic urothelial carcinoma (UC) is maintenance treatment with avelumab plus best supportive care (BSC). The Checkmate 032 trial showed that the highest ORR (42.4%) was achieved by the combination of Nivolumab 1 mg/kg and Ipilimumab 3 mg/kg in refractory mUC (1), with a manageable safety profile and better outcomes compared to other treatment arms. The trial aims to consolidate the clinical benefit achieved from first-line chemotherapy with the combination of nivolumab 1mg/kg plus ipilimumab 3mg/kg followed by nivolumab. **Methods:** This single arm, open-label, multicenter study evaluates the effectiveness of Ipilimumab and nivolumab followed by nivolumab maintenance therapy in delaying disease progression in patients with unresectable urothelial cancer that did not progress after first-line chemotherapy. Main eligibility criteria include: Male or female subjects ≥ 18 yrs old with written informed consent, ECOG performance status 0 or 1, unresectable locally advanced or metastatic transitional cell carcinoma of the urothelium (UCC), patient inclusion within 3-12 weeks after the last chemo dose, no progressive disease per RECIST v1.1, available tumor tissue at baseline, adequate normal organ and marrow function (Haemoglobin ≥ 9.0 g/dL, ANC > 1500 per mm³, platelets $\geq 100,000$ per mm³, bilirubin $\leq 1.5 \times$ ULN, transaminases $\leq 2.5 \times$ ULN, creatinine clearance > 30 mL/min). The primary endpoint is Progression Free Survival (PFS). Secondary objectives include: objective response rate (ORR), duration of response (DoR), overall survival (OS), chemotherapy overall survival (cOS), and chemotherapy progression-free survival (cPFS). Additionally, the study also has safety secondary objectives. Dynamic biomarker analysis will be performed. As of January 2023, 5 out of the planned 66 patients have been enrolled in the study. 1) Sharma P et al. J Clin Oncol. 2019. Clinical trial information: EudraCT 2021-005364-22. Research Sponsor: BMS.

TPS4608

Poster Session

A phase III randomized trial of eribulin (E) with or without gemcitabine vs standard of care (SOC) for metastatic urothelial carcinoma (UC) refractory to or ineligible for PD/PDL1 antibody (Ab): SWOG S1937. *First Author: Sarmad Sadeghi, University of Southern California, Los Angeles, CA*

Background: UC is 2nd most common genitourinary cancer. Current SOC offers platinum-based (PB) first line chemotherapy (chemo) with ddMVAC or gemcitabine-cisplatin (GC) regimens. For cisplatin ineligible patients (pts), SOC includes gemcitabine-carboplatin (GCa), and in select pts pembrolizumab. Eribulin is approved for pts with FGFR alterations and Enfortumab vedotin (EV) is approved for previously treated pts. A phase I/II CTEP study of eribulin (E) for metastatic UC (mUC) established the activity of E in UC with objective response rate (ORR) of 37.5% and a median progression free survival (PFS) of 4.1 months (mo) and median overall survival (OS) of 9.5 mo (N=150). A phase II CTEP study of gemcitabine-eribulin (GE) in cisplatin ineligible mUC showed an ORR of 50%, median OS of 11.9 mo and median PFS of 5.3 mo (N=24). The most common Grade 3-4 toxicities included: neutropenia 63%, anemia and fatigue 29%. Pts with liver metastases benefited from therapy with 5 responders in 7 pts for GE vs 12 out of 49 E. **Methods:** This is a phase III, randomized 3 arm study comparing E vs. GE vs. SOC (docetaxel, paclitaxel, or gemcitabine). E is given at 1.4mg/m² on day (D) 1 and 8 of a 21 D cycle. In the GE arm, gemcitabine is added to E at 1000 mg/m² dose to D1 and D8. SOC follows standard dosing of the agents. There is no limit to the number/sequence of prior regimens. A simplified summary of eligibility criteria is presented here. All pts must have: received frontline systemic treatment such as PB chemo or a non-platinum regimen; received PD1/PDL1 Ab or be deemed ineligible for PD1/PDL1 Ab; received EV. Assuming a median OS for the SOC arm of 7 mo the study seeks to find at least a 50% increase in median OS to 10.5 mo (Hazard Ratio (HR) = 0.667). One-sided 0.0125 type I error to account for testing of two primary hypotheses (Each arm vs. SOC). 87% power to detect a 3.5 mo improvement in OS. We require 140 eligible (155 total) pts in each arm for a total of 465. The study was activated in Feb 2021 and accrual is ongoing. Clinical trial information: NCT04579224. Research Sponsor: U.S. National Institutes of Health.

TPS4609

Poster Session

MAIN-CAV: Phase III randomized trial of maintenance cabozantinib and avelumab versus avelumab after first-line platinum-based chemotherapy in patients (pts) with metastatic urothelial cancer (mUC; Alliance A032001). *First Author: Shilpa Gupta, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH*

Background: First-line platinum-based chemotherapy followed by maintenance avelumab (Av) is the current preferred standard of care in patients (pts) with mUC who do not progress after platinum-based chemotherapy. There is an unmet need to further improve outcomes by combining Av with an effective, non-cross resistant therapy with non-overlapping toxicity. CABO is an oral inhibitor of MET, VEGFR and TAM family receptors involved in tumor growth, angiogenesis and immune cell regulation and has shown efficacy in UC in combination with PD-1/PD-L1 inhibitors. We hypothesize that CABO-Av combination will be synergistic in pts with mUC with an acceptable safety profile and will improve upon the benefit seen with Av maintenance in mUC. **Methods:** MAIN-CAV is a phase III randomized, multicenter, international trial for locally advanced/mUC pts (including N3 only disease) who do not progress after 4-6 cycles of any platinum-based chemotherapy (gem-cis, gem-carbo, MVAC or ddMVAC). 654 adult pts will be randomized 1:1 within 3-10 weeks (wk) after last dose of chemotherapy to receive Av 800 mg IV every 2 wk or combination of Av and CABO 40 mg orally daily for up to 2 yrs. Key eligibility criteria include ECOG PS 0-1, no prior use of immunotherapy (exception of BCG), no central nervous system metastases, no major surgery within 4 wk, no uncontrolled hypertension or cardiovascular disorders. Pts will be stratified based on 1) best response to 1L therapy: complete response vs partial response vs stable disease and 2) presence or absence of visceral metastases. The primary endpoint is overall survival (OS) with assumptions of one-sided alpha of 0.025, power of 80%, median OS of 21 months (mo) on Av arm and hazard ratio (HR) of 0.75, thus hypothesizing a median OS of 28 mo on CABO-Av combination arm. Key secondary endpoints include progression-free survival, safety, tolerability, and activity of CABO-Av compared to Av alone based on RECIST 1.1 and iRECIST criteria and PD-L1 status of pts' tumors. Quality of life (QOL) will be assessed using EQ-5D-5L, PROMIS-Fatigue 4a, EORTC QLQ-C30, EORTC QLQ-BLM30 between pts on CABO-avelumab vs avelumab alone. Biomarkers of response and resistance to Av will be assessed using baseline archival tissues, baseline and serial blood, ctDNA, stool and urine. Imaging studies will test correlation of established and new radiomic signatures with OS, adverse events and QOL and incorporate both radiologic and biologic features to predict outcomes. This trial would be the first to systematically address whether adding a multitargeted TKI, CABO to Av leads to improved clinical outcomes compared to Av alone. Clinical trial information: NCT05092958. Research Sponsor: U.S. National Institutes of Health; Exelixis, EMD Serono.

TPS4611

Poster Session

TROPHY-U-01 Cohort 4 (C4): Sacituzumab govitecan (SG) in combination with cisplatin (cis) as first-line (1L) therapy, followed by maintenance avelumab plus (+) SG or zimberelimab (zim) + SG in patients (pts) with treatment (Tx)-naïve metastatic urothelial cancer (mUC). *First Author: Chethan Ramamurthy, Mays Cancer Center, Philadelphia, PA*

Background: SG is a Trop-2-directed antibody-drug conjugate. In the TROPHY-U-01 study, SG monotherapy showed a 27% objective response rate (ORR) and 10.9 months median overall survival (OS) with an overall manageable safety profile in pts with mUC who received platinum (PT)-containing chemotherapy and a checkpoint inhibitor (CPI), resulting in accelerated FDA approval in this population. PT-based chemotherapy followed by avelumab maintenance is standard 1L therapy in pts with Tx-naïve mUC. Zim (anti-PD-1) is a CPI under clinical investigation for antitumor activity. C4 of TROPHY-U-01 will evaluate safety, tolerability, and clinical activity of SG+cis followed by maintenance avelumab+SG or zim+SG in cis-eligible pts with Tx-naïve mUC. **Methods:** TROPHY-U-01 (NCT03547973) is a multicohort, open-label, global, phase 2 study. C4 will evaluate 1L SG in combination with cis in pts with cis-eligible mUC or unresectable locally advanced disease. Eligibility requirements include ECOG PS 0-1; no prior anticancer monoclonal antibody within 4 weeks of study drug initiation; no history of active interstitial lung disease or noninfectious pneumonitis; adequate hematologic and hepatic function. Pts will be treated with cis at 70 mg/m² on D1 of 21-D cycles (if creatinine clearance [CrCl] ≥60 mL/min) or at an optional split dose of 35 mg/m² on D1 and D8 of 21-D cycles (if CrCl 50-59 mL/min), followed by SG (5, 7.5, or 10 mg/kg, based on 10-pt safety lead-in of a 3+3 design) on D1 and D8 of 21-D cycles. Granulocyte colony-stimulating factor support is not allowed in the safety lead-in but was permitted during escalation and expansion. SG+cis will continue for up to 6 cycles, followed by maintenance (4 to 8 wk after last induction dose of SG+cis and when RP2D is determined) in the absence of progression. Dose escalation maintenance consists of avelumab 800 mg q2w, then SG 10 mg/kg on D1 and D8 of 21-D cycles. Dose expansion maintenance consists of zim 360 mg (D1 of a 21-D cycle) and SG 10 mg/kg (D1 and D8 of 21-D cycles) and will begin once safety lead-in of 6-8 pts receiving zim+SG of a 21-D cycle in Cohort 5 is deemed safe and completed. Pts will continue Tx until progression, unacceptable toxicity, or loss of clinical benefit. Primary endpoint is ORR per RECIST v1.1 by central review. Secondary endpoints include progression-free survival, duration of response, and clinical benefit rate per central review and investigator assessment. OS and safety will also be evaluated. All statistical analyses will be performed using a two-sided hypothesis test approach at the overall 5% level of significance. Time to event endpoints will be assessed via the Kaplan-Meier method. Enrollment is ongoing; up to 57 pts expected across ~120 sites in North America and Europe. Clinical trial information: NCT03547973. Research Sponsor: Gilead Sciences, Inc.

TPS4610

Poster Session

A phase II trial with copanlisib plus avelumab as maintenance therapy for metastatic bladder cancer after platinum-based chemotherapy. *First Author: Hizra Farrukh, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA*

Background: Bladder cancer is the tenth most common malignancy and the fourteenth most common cause of cancer death worldwide. Currently, platinum-based chemotherapy followed by avelumab maintenance immunotherapy is the first-line standard of care for advanced bladder cancer (aBC). Even though maintenance avelumab therapy has improved overall survival, its efficacy is still disappointing with a response rate of less than 10% and progression-free survival benefit of 1.7 months. The phosphoinositide 3-kinase (PI3K) pathway harbors more activating alterations than any other growth signaling pathway in aBC. Furthermore, PI3K δ and γ are expressed by immune cells and regulate their function. Activation alterations along the PI3K pathway are putative molecular drivers and can possibly be targeted for the treatment of aBC. In preclinical studies, we found that a pan-PI3K class I inhibitor, copanlisib, potentiates anti-programmed cell death 1 (PD1) antibody in syngeneic bladder cancer mouse models with or without activation alterations along the PI3K pathway (Zhu S, J Immunother Cancer. 2021). We hypothesize that copanlisib potentiates avelumab as maintenance therapy for aBC. **Methods:** This is a multi-center, single-arm, open-label Phase II trial with a lead-in safety phase to determine the efficacy and toxicity of combination copanlisib and avelumab maintenance therapy in aBC. The major inclusion criteria are patients with aBC without disease progression after platinum-based chemotherapy and no contraindication for avelumab and copanlisib. With a type I error of 5% and power of 80% with a log-rank test, we will need 26 patients for this study. With an attrition rate of 10%, we will enroll 29 patients from four US Department of Veterans Affairs Medical Centers. Copanlisib will be administered through intravenous infusion (IV) at 60 mg on Day 1, 8 and 15, and avelumab will be administered 800 mg IV on Day 1 and 15 of each 4-week treatment cycle for up to 26 cycles. Imaging will be repeated every two cycles during first year of therapy and thereafter every 3 cycles or clinically indicated. The primary endpoint is progression-free survival (PFS). The secondary endpoints include CT or MRI determined radiographic overall response rate, toxicity, overall survival, and molecular correlative studies. Kaplan-Meier estimates will be presented together with median PFS with 2-sided 95% confidence intervals (CI). In particular, the PFS rates at 3, 6, 9, 12 and 15 months will be estimated with corresponding 2-sided 95% CIs. Adverse events will be assessed according to CTCAE v5. Tumor response is determined according to Response Evaluation Criteria in Solid Tumors version (RECIST) 1.1 criteria. This study is currently open for enrollment. Clinical trial information: NCT05687721. Research Sponsor: VA Office of Research and Development; Bayer.

TPS4612

Poster Session

ALTER-UC-007: A prospective phase 2 study of anlotinib with gemcitabine and cisplatin or anlotinib with penpulimab as perioperative treatment for patients with muscle-invasive urothelial carcinoma (MIUC). *First Author: Hailiang Zhang, Department of Urology, Fudan University Shanghai Cancer Center, Shanghai, China*

Background: Radical surgery involving cystectomy and nephroureterectomy is the standard of care for patients with localized muscle-invasive urothelial carcinoma (MIUC). In recent years, neoadjuvant- and adjuvant-containing multimodality therapies have gradually been adopted in attempt to eradicate micrometastatic disease and improve the outcomes achieved with radical surgery alone. This study aims to evaluate the efficacy and safety of anlotinib (a multi-target tyrosine kinase inhibitor of angiogenesis) with gemcitabine and cisplatin or anlotinib with penpulimab (a humanized anti-PD-1 IgG1 monoclonal antibody) as neoadjuvant and adjuvant therapy in patients with MIUC. **Methods:** In this open-label, prospective, phase 2 study, eligible patients include those with histologically confirmed clinical stage T1-T4N1-3M0, T3-4N0M0 MIUC (tumors of the bladder, renal pelvis, ureter and urethra) fit and planned for radical cystectomy, nephroureterectomy or ureterectomy. Main exclusion criteria are distant metastatic disease; prior chemotherapy, anti-angiogenic therapy, radiation therapy or immunotherapies; active autoimmune disease; uncontrolled hypertension or patients at high bleeding risk. Patients will be enrolled and receive treatment based on PD-L1 status in tumor tissue. The PD-L1 status of eligible patients will be centralized and assessed using an anti-PD-L1 antibody and an immunohistochemical (IHC) assay. PD-L1 positivity was defined as combined positive score (CPS) ≥1 (previously reported as and equivalent to CPS ≥1%). The study treatment is stratified into two cohorts based on PD-L1 expression levels. In cohort 1, the PD-L1 negative patients with MIUC will receive neoadjuvant anlotinib (12 mg orally QD D1-14 every 3 weeks) + gemcitabine (1000 mg/m², intravenously [IV] on days 1 and 8) + cisplatin (35 mg/m² IV on days 1 and 8) for a maximum of 4 cycles followed by radical surgery and 2 cycles of adjuvant treatment post-surgery. In cohort 2, PD-L1 positive patients will receive anlotinib (12 mg orally QD D1-14 every 3 weeks) + penpulimab (200 mg IV every 3 weeks) for a maximum of 4 cycles followed by radical surgery and 2 cycles of adjuvant treatment post-surgery. After the completion or discontinuation of the study treatment, safety follow-up and survival follow-up will be performed. Tumor imaging was performed by computed tomography (preferred) or magnetic resonance imaging at baseline, and every 6 weeks during treatment, then every 6 months through year 2. Objective response rate (ORR) is the primary endpoint. Secondary endpoints included pathological complete response rate (pCR), disease-free survival (DFS), overall survival (OS) and safety. Recruitment have begun in October 2022. Currently, the study is active with 1 participant has been enrolled. Clinical trial information: ChiCTR2200063085. Research Sponsor: Chia Tai Tianqing Pharmaceutical Group Co., Ltd.

TPS4613

Poster Session

A phase 3 multicenter study to evaluate the safety and efficacy of padeliporfin vascular targeted photodynamic therapy (VTP) in treatment of low-grade (LG) upper tract urothelial cancer (UTUC). *First Author: Jonathan Coleman, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Padeliporfin VTP is a combination product: drug, padeliporfin is administered IV and a device, a laser light delivery system, includes a source of light (the laser) that emits near-infrared (NIR) light at 753 nm, and optic fiber that delivers the light to the target lesion(s) in the upper tract urothelium. In Phase 1 NCT03617003 study 19 patients(pts) received up to 2 endoscopic VTP treatments with 6 mos follow-up(FU). Pts with residual or recurrent UTUC (high grade(HG)or LG) who failed prior endoscopic treatment/unable/unwilling to undergo surgery were included. Primary endpoint, Maximum tolerated dose (MTD) of laser light fluence, was identified using dose escalation model with a modified continual reassessment method with increasing light fluence (100-200 mW/cm). Secondary endpoint was efficacy, defined by absence of visible tumor and negative urine cytology 30 days post-treatment. 14(74%) pts received the MTD of 200mW/cm, 2 (11%) of whom experienced DLTs (flank pain grade 2 and 3). Response rate at 30 days was 94% (50% CR, 44% partial). 8 pts received 2nd VTP, with a final observed 68% complete response (CR) rate. Most frequent adverse events: transient flank pain (79%) and hematuria (84%). No treatment-associated ureteral strictures were reported. All patients had preserved kidney at the 6-mos FU(Wesley Yip,2022). **Methods:** Padeliporfin VTP is being evaluated in a phase 3 study in patients with UTUC LG,100 patients are planned to be enrolled. Enrollment started in Mar 2021 and is ongoing in USA, EU&Israel,3 pts are enrolled. Pts are being treated with padeliporfin VTP in two phases: Induction and Maintenance treatment Phases (ITP and MTP). ITP consists of 1-3 VTPs every 28 days. If CR is not achieved after 1st VTP, up to 2 additional VTPs are allowed. If CR is achieved in the ITP, pts are allowed into the MTP (12 mos). In the MTP VTPs can be provided every 3 mos for pts with recurrent tumor that is deemed treatable, defined as LG with the largest tumor (index) 5-15 mm, in up to 2 locations in the kidney or one ureter location ≤20 mm. Long Term FU Phase: Pts completing the MTP, will be followed for safety for 48 mos with no VTPs. Primary objective is to demonstrate efficacy and durability of effect of padeliporfin VTP treatment. Secondary objective-evaluation of padeliporfin VTP-related safety and tolerability. **Key inclusion criteria:** Up to 2 biopsy-proven LG UTUC tumors with the largest tumor (index) 5-15 mm, located in the calyces, renal pelvis or in the ureter, with no HG cells. Ureter involvement in one location ≤ 20 mm. **Key exclusion criteria:** Current HG or muscle invasive urothelial bladder cancer. CIS current or previous in the upper urinary tract. History of ≥ T2 urothelial cancer in the past 2 years. DSMB last reviewed the trial in Sep 2022 and suggested the trial continue as planned. Clinical trial information: NCT04620239. Research Sponsor: Steba biotech.

TPS4615

Poster Session

A phase I dose-escalation clinical trial with PLZ4-coated paclitaxel-loaded micelles (PPM) in patients with recurrent or refractory non-myo-invasive bladder cancer. *First Author: Hizra Farrukh, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA*

Background: Bladder carcinoma is one of the top ten cancers in the US with approximately 75% of patients initially presenting with non-myo-invasive bladder cancer (NMIBC). The current standard of care for NMIBC is transurethral resection (TUR) followed by intravesical instillation, usually with Bacille Calmette-Guérin (BCG). Despite combination treatment, 20-80% of patients' disease recurs and 25% progress to invasive stages. The study drug, PLZ4-coated paclitaxel-loaded micelle (PPM), is a solvent-free injectable nanoscale micelle formulation of paclitaxel (PTX). Preclinical data on bladder cancer-specific targeting ligand named PLZ4 has shown potential to specifically deliver chemotherapeutic micelle into bladder cancer cells, both in vitro and in vivo (Zhang, Urol Oncol 2012). In a toxicokinetic study, female Sprague Dawley rats were given intravesicular injections of PPM once weekly for 6 consecutive weeks. No drug related mortality was reported, and no systematic exposure of PPM was observed in toxicokinetic analysis. The purpose of this phase I trial with PPM is to determine the toxicity and recommended Phase II dose. **Methods:** This is a single arm, open label, Phase I dose-escalation first-in-human trial with an expansion cohort for the treatment of recurrent or refractory NMIBC with PPM. Eligibility includes BCG unresponsive carcinoma in situ or Ta/T1 urothelial carcinoma. Treatment with pembrolizumab is not an inclusion or exclusion criteria as intravesical taxane has comparable efficacy as intravenous pembrolizumab. Up to 29 patients will be recruited at VA Boston Healthcare system. PPM will be given once weekly for six weeks, 50 ml of solution regardless of patient's size or weight will be administered as intravesical instillation. A 3 + 3 design is adopted for this Phase I trial. There are three dose levels at the dose escalation stage: Dose level I: PTX 25 mg or 0.5 mg/ml; Dose Level II: PTX 50 mg or 1.0 mg/ml; Dose Level III: PTX 75 mg or 1.5 mg/ml. At the expansion cohort, up to 12 patients will be treated with PPM at PTX dose of 50 mg or 1.0 mg/ml to determine the efficacy. The primary objective is to evaluate the safety and tolerability of PPM administered through intravesical instillation and determine the recommended Phase II dose of PPM. The secondary objectives are to evaluate the tumor response at 6 weeks after last treatment, determine systemic absorption within 6 hours after intravesical instillation of PPM and assess progression free survival. The efficacy will be determined by urine cytology and cystoscopy after finishing treatment. Molecular correlative studies will be performed. The toxicity will be assessed by Common Terminology Criteria for Adverse Events v5.0. Patients will be followed at 3 month intervals for 2 years or until disease recurrence or progression. This study is currently open for enrollment. NCT05519241. Clinical trial information: NCT05519241. Research Sponsor: VA Office of Research and Development.

TPS4614

Poster Session

An in-progress phase 2 window of opportunity (WOO) trial of targeted therapy with erdafitinib for patients with recurrent FGFR3-altered non-muscle-invasive bladder cancer (NMIBC). *First Author: Neeta DSouza, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Alterations to FGFR3 are the most common somatic mutations in non-muscle invasive bladder cancer (NMIBC), present in 40-60% of high-grade Ta and > 80% of recurrent low grade Ta tumors. FGFR3 mutations are also known to be associated with a "cold" tumor microenvironment (TME) that may mediate BCG resistance. Erdafitinib, a targeted inhibitor of FGFR 1-4, is the first FDA approved targeted therapy for locally advanced/metastatic bladder cancer. As FGFR3 mutations are present 3-5x more commonly in NMIBC than metastatic disease, erdafitinib is a logical therapeutic candidate for FGFR3-altered NMIBC. Through this ongoing phase II trial, we seek to determine the safety and efficacy of erdafitinib for the treatment of intermediate and high risk FGFR3-altered NMIBC after prior intravesical therapy. **Methods:** To address the need for expanded targeted therapeutics for NMIBC, we launched an investigator-initiated phase II window of opportunity (WOO) trial of erdafitinib (NCT04917809, PI Pietzak). We are currently enrolling patients with intermediate or high risk NMIBC with history of ≥1 or more induction courses of BCG and/or intravesical chemotherapy who present with a clinically staged Ta papillary recurrence on office cystoscopy. Patients are also required to have an oncogenic FGFR3 mutation or fusion, as confirmed by OncoKB on MSK-IMPACT, to be included in the trial. Trial patients are treated with 6 mg oral erdafitinib daily for 28 days during the "window of opportunity" time period between office cystoscopy and transurethral resection of the recurrent bladder tumor (TURBT). The primary outcome is the rate of objective response, defined as complete (no visible tumor) or partial (> 50% reduction of measured diameter by Response Evaluation Criteria for Tumors of the Bladder [RECIT-Bladder]) as compared to cystoscopy at TURBT. We are employing an optimal Simon two-stage binomial design, assuming an objective response of > 15% would and < 2% would not be worthy of further study. We plan to enroll 16 patients in the first stage and 9 in the second (87% power). Secondary outcomes include safety (CTAE 5.0), patient reported outcomes, and recurrence-free survival. Correlative studies will be conducted with urine, blood, and tumor tissue samples. Urine and blood are collected before (day 1), during (day 14) and after treatment (day 28) and will undergo immune and molecular studies to understand shifts in the microenvironment in the setting of response and resistance. This trial is being conducted in parallel with a co-clinical trial of patient derived organoid/xenograft models (MSK 19-015, PI Pietzak) to further refine the understanding of FGFR3 mutational resistance to standard treatment and the effects of targeted immunotherapy on tumor clinicogenomics. Clinical trial information: NCT04917809. Research Sponsor: U.S. National Institutes of Health; Bladder Cancer Advocacy Network, Wofchuck Family Young Investigator Award; Janssen Pharmaceuticals, Merck & Co. Inc., QED Therapeutics, Chugai Pharmaceuticals, UroGen Pharma, and Steba Biotech; UpToDate.

TPS4616

Poster Session

Phase 2 trial of intravesical cabazitaxel, gemcitabine, and cisplatin (CGC) for the treatment of non-muscle invasive BCG unresponsive urothelial carcinoma of the bladder. *First Author: Guarionex Joel DeCastro, Columbia University Irving Medical Center, New York, NY*

Background: For patients with non-muscle invasive bladder cancer (NMIBC) unresponsive to Bacille Calmette-Guerin (BCG), multi-agent intravesical trials have been limited. The goal of this Phase 2 study is to investigate the efficacy of intravesical chemotherapy consisting of sequential cabazitaxel, gemcitabine, and cisplatin (CGC) in the salvage setting. Phase 1 results reporting on 18 subjects demonstrated adverse events limited to local Grade 1 and 2 toxicities. Partial funding support for the trial was provided by a pharmaceutical company. **Methods:** This is a Phase 2 trial (NCT02202772) presently enrolling patients with BCG unresponsive NMIBC as defined by the FDA who refuse or are ineligible for radical cystectomy. All patients undergo pre-treatment transurethral resection of bladder tumor (TURBT) and a 6-week regimen of intravesical cisplatin (100mg), gemcitabine (2gm), and cabazitaxel (5mg). Each drug is instilled weekly except for cisplatin, which is given every other week. Complete response is defined as having no evidence of cancer on post-induction biopsy and negative urine cytology at 3 months. Complete responders proceed with monthly and bimonthly maintenance therapy without cisplatin in the first and second years, respectively, for a total of 24 months. **Results:** To date thirty-one patients have been enrolled (with target accrual of 33), of whom seven are female. One patient withdrew consent before first evaluation cystoscopy. Mean age thus far is 72 years. All patients have previously received at least two prior induction cycles of BCG, and meet FDA criteria for BCG unresponsive disease. All patients have biopsy proven high grade disease at enrollment; 8 (27%) have high grade T1 disease; and 20 (67%) patients have CIS. **Conclusions:** Salvage options for BCG unresponsive NMIBC are limited. The CGC protocol has been demonstrated to be safe in a previous Phase 1 study, and accrual for this Phase 2 is near completion. Clinical trial information: NCT02202772. Research Sponsor: funding from Columbia University Medical Center/Cancer Center; Sanofi.

TPS4617

Poster Session

Adding mitomycin (MM) to bacillus Calmette-Guérin (BCG) as adjuvant intravesical therapy for high-risk, non-muscle-invasive urothelial bladder cancer (NMIBC): BCGMM; ANZUP 1301. *First Author: Dickon Hayne, UWA Medical School, University of Western Australia, Perth, Australia*

Background: Adjuvant intravesical BCG decreases disease recurrence and progression in high-risk, NMIBC, however recurrence occurs in 30% of those affected, despite optimal therapy. Meta-analyses evaluating addition of intravesical MM to BCG showed lower rates of recurrence and cancer-specific mortality in people with NMIBC who received combination regimens. Phase 3 randomized trials to definitively test this combination are lacking. The BCGMM trial (NCT02948543) will determine the effects of adding MM to the standard BCG after resection of high-risk NMIBC. This is the largest study evaluating this approach in high-risk NMIBC, is of particular relevance given the current BCG shortage, and has the potential to change global practice. **Methods:** This open-label phase 3 trial is randomizing 500 participants stratified by stage, site of disease, and presence of carcinoma in-situ, in a 1:1 ratio to Arm A (BCG induction weekly x6 then monthly x10) or Arm B (BCG weeks 1, 2, 4, 5, 7, 8; months 4, 5, 7, 8 + MM weeks 3, 6, 9; months 3, 6, 9, see figure below). This provides 85% power to detect an absolute improvement of 10% in 2-year disease free survival (DFS) at 2p = 0.05. Stage 1 (n = 130) was to determine rates of treatment completion, activity reflected by cystoscopic findings at 3 months, adverse events, resource use, and health related quality of life, established feasibility. Stage 2, including an additional 370 participants, will provide information on DFS, time to recurrence and progression, overall survival, and identification of potential predictive biomarkers, is estimated to complete accrual by Q2 2023. Progress As of Jan 2023, 484 of 500 planned participants have been recruited from 16 Australian and 1 UK site. In stage 1, successful treatment completion, defined as 75% or more of planned treatment doses, was achieved by 76% in the experimental group (BCGMM) versus 60% in the control group (BCG alone). Clinical trial information: NCT02948543. Research Sponsor: Cancer Australia (Stage 1); ANZUP and ANZUP's 'Below the Belt' Research Fund & National Health and Medical Research Council (NHMRC) (Stage 2).

TPS4618

Poster Session

Phase 1b/2 dose expansion, open-label study to evaluate safety and anti-tumor activity of intravesical instillation of TARA-002 in adults with high-grade non-muscle invasive bladder cancer. *First Author: Wei Sun, Protara Therapeutics, New York, NY*

Background: Bladder cancer is the most common malignancy involving the urinary system, with over 700,000 individuals living with bladder cancer in the US in 2019. In the US, approximately 80,000 new cases and 18,000 deaths occur each year due to bladder cancer. Approximately 70% of new urothelial bladder cancer cases are classified as non-muscle invasive bladder cancer (NMIBC). With the current Bacillus Calmette-Guérin (BCG) shortage and limited effective alternate therapies, there continues to be a significant unmet need for treatment options for patients with NMIBC. TARA-002 is being developed for intravesical instillation for the treatment of high-grade (HG) NMIBC. TARA-002 is a lyophilized biological preparation for instillation containing cells of *Streptococcus pyogenes* (Group A, type 3) Su strain treated with benzylpenicillin. The chemical characteristics of TARA-002 are intended to be comparable to OK-432. Therefore, nonclinical and clinical evidence with OK-432 and TARA-002 support the ADVANCED-1 study (dose escalation Phase 1a [NCT05085977] and dose expansion Phase 1b/2 [NCT05085990]). The dose for the planned Phase 1b/2 study (ADVANCED-1-Ph1b/2) will be based on the recommended Phase 2 dose (RP2D) established in the Phase 1a study. **Methods:** ADVANCED-1-Ph1b/2 is a Phase 1b/2, dose expansion, open-label study of intravesical instillation of TARA-002 in adults with HG carcinoma in situ (CIS) NMIBC. The purpose of this study is to evaluate the safety and anti-tumor activity of TARA-002 administered intravesically for the treatment of subjects with CIS NMIBC ($\pm$ Ta/T1) with active disease. The study includes approximately 102 eligible male and female subjects $\geq$ 18 years of age enrolled in 2 cohorts based on their prior BCG experience. Cohort A includes subjects unable to obtain BCG or subjects who have not received BCG in the last 24 months prior to CIS diagnosis, and Cohort B includes subjects with CIS who are BCG unresponsive after completion of adequate BCG therapy (at least 5 of 6 doses of an initial induction course plus either at least 2 of 3 doses of maintenance therapy or at least 2 of 6 doses of a second induction course). Those with current or a history of penicillin allergy or current evidence of any condition, therapy, or laboratory abnormality that might confound the results are excluded. The overall study duration is 6 months/24 weeks per subject for Ph1b/2-Cohort A (includes induction, reinduction [if applicable]), and 24 months/96 weeks per subject for Ph1b/2-Cohort B (includes induction, reinduction [if applicable], maintenance until 18 months). The ADVANCED-1 study started in March 2022. Phase 1a is open for enrollment. Phase 1b/2 is expected to begin enrollment in May 2023. Clinical trial information: NCT05085977; NCT05085990. Research Sponsor: Protara Therapeutics, Inc.

LBA4619

Oral Abstract Session

Phase 3 THOR study: Results of erdafitinib (erda) versus chemotherapy (chemo) in patients (pts) with advanced or metastatic urothelial cancer (mUC) with select fibroblast growth factor receptor alterations (FGFRalt). *First Author: Yohann Loriot, Department of Cancer Medicine, Gustave Roussy Institute, INSERM 981, University Paris-Saclay, Villejuif, France*

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2023, issue of the *Journal of Clinical Oncology*.

LBA5000

Oral Abstract Session

Prostate irradiation in men with de novo, low-volume, metastatic, castration-sensitive prostate cancer (mCSPC): Results of PEACE-1, a phase 3 randomized trial with a 2x2 design. First Author: Alberto Bossi, Department of Radiation Oncology, Institute Gustave Roussy, Villejuif, France

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2023, issue of the *Journal of Clinical Oncology*.

5002

Oral Abstract Session

Prognostic impact of PSA nadir (n) ≥0.1 ng/mL within 6 months (m) after completion of radiotherapy (RT) for localized prostate cancer (PCa): An individual patient-data (IPD) analysis of randomized trials from the ICECAP collaborative. First Author: Praful Ravi, Dana-Farber Cancer Institute, Boston, MA

Background: RT + androgen deprivation therapy (ADT) is a standard of care in treatment of intermediate- and high-risk localized PCa. Identification of early surrogate measures for long-term outcome measures such as PCa-specific survival (PCSS), metastasis-free survival (MFS) and overall survival (OS) could expedite development of new systemic therapies added to RT/ADT while potentially identifying patients (pts) for therapy (de)escalation. **Methods:** IPD from the RT+ADT trials in the ICECAP repository with evaluable PSA follow-up were eligible for inclusion. Pts were grouped based on their trial-allocated treatment: RT alone, RT+stADT (short-term ADT: 3-6m), RT+ltADT (long-term ADT: 18-36m). PSAn was defined as the lowest PSA recorded within 6m after RT completion. A 12m landmark analysis for PCSS, MFS and OS was performed to account for guarantee-time bias. Multivariable Cox proportional hazards regression was used to estimate associations of PSAn < or ≥0.1ng/mL with MFS and OS, and a multivariable Fine and Gray distribution used for PCSS to account for competing risk of non-PCa deaths. Models were adjusted for age, ECOG performance status, clinical T stage, Gleason score and PSA at randomization. **Results:** 10,415 pts from 16 RCTs were included: 2629 (25%) allocated to RT, 6033 (58%) to RT+stADT, and 1753 (17%) to RT+ltADT. Median follow-up was 10.1years (yrs). 2339 (98%), 4756 (84%) and 1258 (77%) of patients allocated to RT, RT+stADT and RT+ltADT respectively achieved a PSAn ≥0.1ng/mL within 6m after RT completion. After adjustment, PSAn ≥0.1ng/mL was associated with poorer PCSS, MFS and OS in pts allocated to RT+stADT (PCSS hazard ratio [HR] = 1.97 [95% CI 1.52-2.92], MFS HR = 1.27 [1.12-1.44], OS HR = 1.26 [1.11-1.44]) and RT+ltADT (PCSS HR = 1.97 [1.11-3.49], MFS HR = 1.58 [1.27-1.96], OS HR = 1.59 [1.27-1.99]). A weaker association was noted in pts allocated to RT (PCSS HR = 1.82 [0.51-6.49], MFS HR = 2.23 [1.20-4.14], OS HR = 1.72 [0.97-3.05]). Table shows 5-yr MFS, 10-yr PCSS and 10-yr OS based on PSAn within 6m after RT completion. **Conclusions:** PSAn ≥0.1ng/mL within 6 mths after RT completion was strongly prognostic for PCSS, MFS and OS in pts receiving RT+ADT for localized PCa in this IPD analysis of > 10,000 patients. This could be used as an early signal-seeking endpoint in trials evaluating novel systemic therapies with RT + ADT and to help identify pts for therapy (de)escalation trials. Research Sponsor: None.

	RT only (n = 2376)	RT + stADT (n = 5658)	RT + ltADT (n = 1626)
5-year MFS, %			
PSAn < 0.1ng/mL	91 (74-97)	83 (80-85)	87 (83-91)
PSAn ≥0.1ng/mL	79 (77-81)	76 (74-77)	74 (71-76)
10-year PCSS, %			
PSAn < 0.1ng/mL	92 (72-98)	91 (86-94)	88 (79-94)
PSAn ≥0.1ng/mL	84 (81-86)	83 (82-85)	83 (80-86)
10-year OS, %			
PSAn < 0.1ng/mL	52 (31-69)	62 (57-67)	63 (54-71)
PSAn ≥0.1ng/mL	58 (55-61)	56 (54-57)	50 (47-54)

5001

Oral Abstract Session

Development and validation of an AI-derived digital pathology-based biomarker to predict benefit of long-term androgen deprivation therapy with radiotherapy in men with localized high-risk prostate cancer across multiple phase III NRG/RTOG trials. First Author: Andrew J. Armstrong, Duke Cancer Institute Center for Prostate & Urologic Cancers, Durham, NC

Background: Androgen deprivation therapy (ADT) improves survival and reduces risk of metastasis in men with high-risk localized prostate cancer (PC) receiving radiotherapy (RT). Predictive biomarkers are needed to guide ADT duration to maximize benefits and minimize risks. We sought to train and validate the first predictive biomarker for long-term (LT) vs short-term (ST) ADT using multiple phase III NRG Oncology randomized trials. **Methods:** Pre-treatment prostate biopsy slides were digitized from six phase III NRG/RTOG randomized trials of men receiving RT +/- ADT. The artificial intelligence (AI)-derived clinical and histopathological predictive biomarker was trained on RTOG 9408, 9413, 9902, 9910, and 0521 to predict differential benefit of LTADT on distant metastasis (DM). After the AI biomarker was locked, it was validated on RTOG 9202, which randomized men to RT + STADT (4 mo) vs LTADT (28 mo). The predictive utility of the AI biomarker was evaluated for the primary and secondary endpoints of DM and PC-specific mortality (PCSM), respectively, for ADT duration with Fine-Gray interaction models. Event rates were estimated by the cumulative incidence method. Deaths from other causes were treated as competing risks. **Results:** The AI-derived biomarker was trained on 2,641 men (median follow-up of 9.8 years, IQR [8.2, 11.5]) and validated on 1,192 men from RTOG 9202 (median follow-up of 17.2 years, IQR [9.1, 19.6]), where 80% had at least one high/very high (H/VH) risk feature (ct3-4, Gleason 8-10, PSA > 20, or primary Gleason pattern 5). Consistent with published results, LTADT significantly improved DM (subdistribution HR [sHR] 0.64, 95% CI 0.50-0.82, p < 0.001) in the validation cohort. The AI biomarker was prognostic for DM (sHR 2.35, 95% CI 1.72-3.19, p < 0.001). A significant biomarker-treatment interaction was observed (p = 0.04), in which AI-biomarker (+) men (n = 785, 66%) had reduced DM with LTADT (sHR 0.55, 95% CI 0.41-0.73, p < 0.001), but no benefit was observed (sHR 1.06, 95% CI 0.61-1.84, p = 0.84) for AI-biomarker (-) men (n = 407, 34%). The 10-year DM rate difference between RT + LTADT vs RT + STADT was 13% in AI-biomarker (+) men vs 2% in AI-biomarker (-) men. Similar trends were observed for PCSM outcomes. Risk classification (NCCN intermediate [n = 221, 43% (+)] vs other H/VH risk [n = 954, 71% (+)]) was prognostic but not predictive of LTADT benefit. **Conclusions:** We have successfully validated the first predictive biomarker of LTADT benefit with RT in localized high-risk PC using an AI-derived digital pathology-based platform in the phase III NRG/RTOG 9202 trial. The predictive AI biomarker identified 34% of men that could derive similar benefit with STADT, avoiding the side effects of prolonged ADT, and 43% of intermediate risk men who would benefit from LTADT. Research Sponsor: Artera; U.S. National Institutes of Health; This project was supported by grants UG1CA189867 (NCORP), U10CA180822 (NRG Oncology SDMC), U24CA196067 (NRG Specimen Bank), U10CA180868 (NRG Oncology Operations) from the National Cancer Institute (NCI).

5003

Oral Abstract Session

Presence of somatic/germline homologous recombination repair (HRR) mutations and outcomes in metastatic castration-resistant prostate cancer (mCRPC) patients (pts) receiving first-line (1L) treatment stratified by BRCA status. First Author: David Olmos, Hospital Universitario 12 de Octubre. Instituto de Investigación Sanitaria Hospital 12 de Octubre, Madrid, Spain

Background: Understanding of the association between HRR mutations and outcomes in mCRPC pts is limited. This analysis investigated the prevalence and outcomes of pts with/without HRR mutations (somatic and/or germline), stratified as BRCA, non-BRCA, or HRR non-BRCA, who initiated 1L mCRPC treatment with novel hormonal therapy (NHT) or taxane. **Methods:** Eligible pts from PROREPAIR-B (NCT03075735), PROSENZA (NCT02922218), PROSTAC (NCT02362620), and PROSAB (NCT02787837) studies underwent paired somatic/germline DNA analyses using a custom NGS panel that included *ATM*, *BRCA1*, *BRCA2*, *BRIP1*, *CDK12*, *CHEK2*, *FANCA*, *HDAC2*, *PALB2*, *RAD51B*, and *RAD54L*. Those with pathogenic (likely) mutations in ≥ 1 allele of ≥ 1 gene were considered deficient (HRR). rPFS, PFS2, and OS were reported for BRCA, non-BRCA, and HRR non-BRCA subgroups; associations between mutations and outcomes were assessed using inverse probability weighted Cox models, which balanced the baseline (BL) characteristics between subgroups. Hazard ratios (HRs) with 95% confidence intervals (CIs) and p values are presented. **Results:** Of 729 pts, 223 (30.6%) were HRR, including 96 (13.2%) BRCA. 60.4% of pts were treated with NHT and 39.6% with taxane in 1L; 80.7% received at least second-line treatment. Median age at BL was 72.2 years, 63.5% had Gleason > 7, 53.1% had ECOG ≥ 1, and 13.3% presented with visceral metastases. BL characteristics after adjustment were similar (standard mean difference: <0.1 in HRR and maximum 0.11 for all pts). BRCA pts had significantly worse rPFS, PFS2, and OS than non-BRCA pts; BRCA pts also had significantly worse PFS2 and OS than HRR non-BRCA pts. There were no significant differences between the outcomes of somatic and germline BRCA pts. **Conclusions:** BRCA pts, regardless of somatic/germline origin, had significantly worse rPFS, PFS2, and OS than the total non-BRCA population and significantly worse PFS2 and OS than non-BRCA pts in the HRR subgroup. It is crucial to screen early for HRR mutations, particularly in *BRCA1/2*, to begin timely, targeted mCRPC treatment and improve prognosis. Research Sponsor: Janssen Pharmaceuticals.

Median rPFS, PFS2, and OS (months) comparison of BRCA, non-BRCA, and HRR non-BRCA subgroups.

	BRCA (n=96) vs. non-BRCA (n=633)		BRCA (n=96) vs. HRR non-BRCA (n=127)	
rPFS	Median (95% CI) [‡]	BRCA: 7.0 (6.1-8.4)	BRCA: 7.0 (6.1-8.4)	
HR (95% CI)		Non-BRCA: 10.6 (9.7-11.5)	HRR non-BRCA: 8.9 (7.0-9.9)	
		1.7 (1.3-2.2) [‡]	1.3 (1.0-1.9)	
PFS2	Median (95% CI) [‡]	BRCA: 12.7 (11.4-14.7)	BRCA: 12.7 (11.4-14.7)	
HR (95% CI)		Non-BRCA: 17.9 (16.8-18.7)	HRR non-BRCA: 14.6 (12.4-16.7)	
		1.9 (1.6-2.4) [‡]	1.5 (1.1-1.9) [‡]	
OS	Median (95% CI) [‡]	BRCA: 18.1 (16.5-19.9)	BRCA: 18.1 (16.5-19.9)	
HR (95% CI)		Non-BRCA: 27.7 (25.7-29.5)	HRR non-BRCA: 21.6 (18.0-24.1)	
		2.0 (1.6-2.5) [‡]	1.4 (1.1-1.9) [‡]	

*p<0.05; ‡p<0.0001; †observed.

5004

Oral Abstract Session

TALAPRO-2: Phase 3 study of talazoparib (TALA) + enzalutamide (ENZA) versus placebo (PBO) + ENZA as first-line (1L) treatment for patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) harboring homologous recombination repair (HRR) gene alterations. *First Author: Karim Fizazi, Institut Gustave Roussy, University of Paris-Saclay, Villejuif, France*

Background: TALAPRO-2 is the first phase 3 study to combine the poly(ADP-ribose) polymerase inhibitor TALA with the androgen receptor inhibitor ENZA in pts with 1L mCRPC unselected (Cohort 1—previously reported) or selected (Cohort 2) for HRR gene alterations. Here, we report results of the prespecified, independently powered analysis of pts with mCRPC with HRR gene alterations from Cohorts 1 and 2. **Methods:** From February 2019 to January 2022, 399 pts (169 from Cohort 1) were randomized 1:1 to receive TALA 0.5 mg or PBO (all received ENZA 160 mg) once daily. Randomization was stratified by prior abiraterone or docetaxel for castration-sensitive PC (yes vs no). Key eligibility criteria: mildly or asymptomatic mCRPC with disease progression at study entry, HRR-deficient status prospectively confirmed by tumor tissue and/or ctDNA testing (genes tested: *ATM, ATR, BRCA1, BRCA2, CDK12, CHEK2, FANCA, MLH1, MRE11A, NBN, PALB2, RAD51C*), ECOG PS ≤ 1 , ongoing androgen deprivation therapy, no prior life-prolonging therapy for CRPC. Primary endpoint: radiographic progression-free survival (rPFS) by BICR per RECIST 1.1 and PCWG3. **Results:** 200 pts received TALA + ENZA and 199 PBO + ENZA. TALA + ENZA significantly improved rPFS by BICR (HR 0.45; 95% CI, 0.33–0.61; 2-sided $P < 0.001$; median PFS not reached vs 13.8 months). The HR for rPFS by BICR was 0.20 (95% CI, 0.11–0.36; $P < 0.001$) for the *BRCA1/2* subgroup ($n=155$) and 0.68 (95% CI, 0.46–1.02; $P = 0.06$) in those without a *BRCA1/2* alteration ($n=240$). The first interim analysis of OS was immature: 21.5% (TALA + ENZA) and 26.6% (PBO + ENZA) pts had died; HR 0.69 (95% CI, 0.46–1.03; $P = 0.07$). TALA + ENZA delayed time to PSA progression, cytotoxic chemotherapy, and antineoplastic therapy, and improved ORR, PSA response, and investigator-assessed PFS2. Grade (G) 3–4 treatment-emergent adverse events (TEAEs) were reported for 66.2% (TALA + ENZA) vs 37.2% (PBO + ENZA). There were more $G \geq 3$ hematologic TEAEs (anemia, neutropenia, thrombocytopenia, and leukopenia) with TALA + ENZA vs PBO + ENZA. TEAEs led to discontinuation of TALA in 10.1% vs PBO in 7.0%; discontinuation rates of ENZA were 7.6% (TALA + ENZA) vs 7.0% (PBO + ENZA). Time to definitive clinically meaningful deterioration in global health status/quality of life (GHS/QoL) was significantly longer with TALA + ENZA vs PBO + ENZA (HR 0.69; 95% CI, 0.49–0.97; $P = 0.03$; median 27.1 vs 19.3 months). **Conclusions:** TALA + ENZA demonstrated a statistically significant and clinically meaningful improvement in rPFS over standard of care ENZA as 1L treatment for pts with mCRPC and HRR gene alterations, while delaying time to definitive clinically meaningful deterioration in GHS/QoL. Toxicity was generally manageable and consistent with known safety profiles of TALA and ENZA. Clinical trial information: NCT03395197. Research Sponsor: Pfizer Inc.; Astellas Pharma Inc. provided enzalutamide.

5006

Oral Abstract Session

Long term follow-up analysis of plasma miR371 expression to detect early relapse in patients with clinical stage I testicular germ cell tumors on surveillance. *First Author: Lucia Nappi, Vancouver Prostate Centre, Department of Urologic Sciences, University of British Columbia, Vancouver, BC, Canada*

Background: Clinical Stage I (CSI) is the most common presentation of germ cell testicular tumors (GCT) and patients are usually managed with active surveillance, in absence of reliable biomarkers of relapse. Circulating plasma miR371a-3p (miR371) has demonstrated high sensitivity and specificity in advanced non teratoma GCT. However, its operating characteristics and power to detect early relapse are still undefined. **Methods:** CSI GCT patients enrolled in the British Columbia provincial biobank with available plasma samples after radical orchiectomy were included in this study. Plasma miR371 was qualitatively assessed by RT-PCR. Sensitivity, specificity, negative and positive predictive values (NPV, PPV) and AUC in predicting tumor recurrence were evaluated in the post-orchietomy blood samples and/or during the follow-up prior to or at the time of the clinically evident relapse. Relapse free survival (RFS) was correlated to post-orchietomy miR371 status. **Results:** One-hundred-one patients were analyzed, 35 (34.6%) experienced a disease relapse with a median follow-up of 41 months. miR371 was positive in 22/35 of the relapsed patients. The specificity and PPV were 100% (95% CI: 94.5 - 100 for both), sensitivity 62.8% (95% CI: 44.9 - 78.5), NPV 83.5% (95%CI: 76.7 - 88.6) and AUC 0.81 (95% CI: 0.71 - 0.91). No false positive results were observed. The RFS of the patients with positive post-orchietomy miR37 was significantly shorter (median: 3.5 months vs. not reached; $p < 0.0001$) compared to the patients with a negative post-orchietomy miR371 (HR: 16.9; 95% CI: 2.1 - 135.7; $p < 0.0001$). miR371 sensitivity correlated with tumor burden, time between tumor relapse and miRNA testing and histology (nonseminoma > seminoma). **Conclusions:** miR371 has high specificity and PPV in detecting GCT at an early stage and could be used to predict GCT relapse during surveillance and to guide treatment selection after orchiectomy. Further studies have been planned for validation of miR371 clinical utility. Research Sponsor: Michael Smith Health Research BC, US Department of Defense.

5005

Oral Abstract Session

LuPARP: Phase 1 trial of ^{177}Lu -PSMA-617 and olaparib in patients with metastatic castration resistant prostate cancer (mCRPC). *First Author: Shahneen Sandhu, Department of Medical Oncology, Peter MacCallum Cancer Centre; and Sir Peter MacCallum Department of Oncology, University of Melbourne, Melbourne, VIC, Australia*

Background: ^{177}Lu -PSMA-617, a PSMA-directed, radionuclide therapy improves progression free survival (PFS) and overall survival (OS) in patients (pts) with mCRPC. Although many pts benefit from treatment, approximately a third have primary resistance, median PFS is 5.1 months and all pts inevitably relapse. Poly (ADP-ribose) polymerase (PARP) is implicated in repairing radiation-induced DNA single-strand breaks (SSBs). The potent PARP inhibitor (PARPi) olaparib results in the conversion of DNA SSBs to lethal double-strand breaks. Multiple preclinical studies have shown enhanced anti-tumor activity from combined PARPi and radiotherapy. LuPARP aims to evaluate the safety and efficacy of the combination of ^{177}Lu -PSMA-617 and olaparib. **Methods:** 48 pts with mCRPC and high PSMA expression (SUVmax ≥ 15 at a site of disease, and SUVmax ≥ 10 at other measurable sites) without discordant FDG positive/PSMA negative disease will be enrolled in two stages: dose-escalation (standard 3+3 design) and dose-expansion at the recommended phase 2 dose (RP2D). ^{177}Lu -PSMA-617 is administered at 7.4 GBq IV on day 1, every 6 weeks for up to 6 cycles in conjunction with 9 prespecified dose schedules of olaparib. The dose-limiting toxicity (DLT) period is 6 weeks. The primary objectives are establishing the DLTs and RP2D. Secondary objectives are toxicity, radiological PFS (rPFS), PSA response rate (PSA50-RR), PSA-PFS, objective response rate (ORR) and OS. Responses are assessed by 3-weekly PSA and conventional and PSMA PET/CT imaging every 12 weeks. **Results:** 29 pts (median age 70 years: range: 52–84; prior docetaxel: 97%; prior androgen receptor pathway inhibitor: 100%) received ^{177}Lu -PSMA-617 on day 1 with escalating doses of olaparib (cohorts 1–6: 50mg - 300 mg BD days 2–15) or alternate olaparib schedules (cohort 7: 200 BD days - 4 to 14; cohort 8: 300 BD days - 4 to 14; cohort 9: 300 mg BD days -4 to 18) for up to 6 cycles. No DLTs were reported. Common treatment related adverse events (TRAE) ($\geq 10\%$) were Grade (G) 1–2 and included xerostomia (83%), nausea (62%), fatigue (34%), constipation (31%), anorexia (17%), vomiting (14%) and diarrhea (10%). Hematologic TRAE included anemia (G1: 14%; G2: 7%; G3: 7%), thrombocytopenia (G1: 14%; G2: 7%; G3: 3%) and neutropenia (G1: 3%; G3: 7%) that were transient and without clinical sequelae. Across cohorts 1–9, the PSA50-RR was 62% (18/29) and PSA90-RR was 48% (14/29). Five of the 7 pts (71%) with RECIST measurable disease had a partial response. **Conclusions:** The combination of ^{177}Lu -PSMA-617 and olaparib is well tolerated and has promising activity. Three further patients are being enrolled to cohort 9 to confirm the RP2D ahead of dose-expansion. Clinical trial information: NCT03874884. Research Sponsor: Prostate Cancer Foundation; AstraZeneca and Advanced Accelerators Application (AAA), a Novartis Company.

Cohorts	Olaparib Schedule	PSA50 response
1	50mg/BD D 2-15	1/3
2	100mg/BD D 2-15	2/3
3	150mg/BD D 2-15	2/3
4	200mg/BD D 2-15	1/3
5	250mg/BD D 2-15	3/4
6	300mg/BD D 2-15	3/3
7	200mg/BD D - 4:14	3/4
8	300mg/BD D - 4:14	2/3
9	300mg/BD D - 4:18	1/3

5007

Oral Abstract Session

The genomic and transcriptomic landscapes of chemotherapy naïve vs post-chemotherapy germ cell tumors. *First Author: Aditya Bagrodia, University of California San Diego Health, La Jolla, CA*

Background: Cisplatin resistance occurs in up to 30% of patients with advanced germ cell tumors (GCTs). Despite effective salvage treatment regimen, there is a 50% risk of cancer-specific death. Previously, we identified molecular features, including *TP53* mutations and *MDM2* amplification, associated with cisplatin resistance (Bagrodia, 2016). Herein, we evaluate the genomic and transcriptomic landscapes of chemotherapy naïve vs post-chemotherapy GCT's to uncover genetic factors that might drive cisplatin resistance. **Methods:** GCTs ($N = 138$) were tested at Caris Life Sciences (Phoenix, AZ) with next-generation sequencing of DNA (592-gene or whole exome) and RNA (whole transcriptome). Prevalence was calculated for pathogenic SNVs/indels and copy number amplifications (CNA ≥ 6 copies). Primary ($N = 65$) and metastatic ($N = 73$) sites were defined based on the biopsy site. A specialized genitourinary pathologist blindly reviewed selected H&E-stained slides and designated tumors as chemotherapy naïve ($N = 66$) or post-chemotherapy ($N = 17$) based on treatment related changes. Differentially regulated pathways were assessed by gene set enrichment analysis (GSEA). Transcriptomic signatures predictive of response to immunotherapy (T cell-inflamed) and platinum sensitivity (PSS, high score suggests increased platinum sensitivity) were applied. Mann-Whitney U and χ^2 tests were applied, with P-values adjusted for multiple comparisons. **Results:** Primary and metastatic GCT had slight differences between putative drivers of platinum therapy resistance: *KIT* (15% vs 1), *TP53* (10% vs 17), *KRAS* (13% vs 9) mutations and *MDM2* CNA (4% vs 3), all $p > 0.05$. When comparing post-chemo vs chemo naïve GCTs, no significant differences in the genomic landscape were observed ($p > 0.05$). Chemo naïve tumors were shown to be enriched for gene sets associated with *KRAS* signaling and epithelial-to-mesenchymal transition. Additionally, they trended towards a higher proportion of T cell-inflamed tumors as compared to post-chemo samples (32% vs 18, $p = 0.36$). The average PSS for chemo naïve was slightly higher than post-chemo (CN: 0.07 Arbitrary Units (AU), $N = 62$ vs PC: -1.82, $N = 16$, $p = .52$). Chemo naïve tumors with *TP53*, *KRAS*, or *KIT* mutation or *MDM2* CNA had a lower PSS (-4.16 AU, $N = 18$) than tumors with none of those alterations (2.17, $N = 38$), $p = 0.05$. Finally, chemo naïve tumors with *MDM2* CNA ($N = 2$, -16.26 AU) had the lowest PSS followed by tumors with mutations in *TP53* ($N = 6$, -2.04), *KIT* ($N = 2$, -1.77) and *KRAS* ($N = 9$, -1.05) (mutations were mutually exclusive except for a concurrent *KRAS* and *TP53* mutation). **Conclusions:** This study provides evidence that chemo naïve GCTs with mutations in *TP53*, *KRAS*, *KIT* or *MDM2* CNA have higher expression of genes associated with resistance to platinum-based chemotherapy. These findings contribute to a better understanding of the molecular characteristics of GCTs and may inform prognosis and treatment. Research Sponsor: None.

5008

Oral Abstract Session

Primary retroperitoneal lymph node dissection (RPLND) in seminoma stage IIA-IIC ≤ 3 cm: Combined results of the SWENOTECA (Swedish Norwegian Testicular Cancer Group) and Cologne. *First Author: Torgrim Tandstad, St. Olav's University Hospital, Trondheim, Norway*

Background: Chemotherapy or radiotherapy have been standard treatment for stage II seminomas with excellent survival but are associated with significant long-term treatment-related toxicities. Several prospective trials have shown primary retroperitoneal lymph node dissection (RPLND) to be an effective and safe alternative. The current SWENOTECA treatment program recommends primary RPLND in seminoma stage IIA to IIB ≤ 3 cm with 1-2 metastatic nodes as the standard treatment modality. We present preliminary results combined with data from Cologne. **Methods:** Within SWENOTECA, RPLND is centralized to 5 hospitals and Cologne is a tertiary centre for patients recruited from different parts of Germany. Both patients with recurrence after initial stage I disease and patients with primary stage IIA and IIB at diagnosis were included. We collected information on operation time, bleeding, peri- and postoperative complications. We also analyzed histologic outcome and whether adjuvant chemotherapy was given. We followed the patients for any recurrence of disease. **Results:** We have included 94 patients operated from May 2018 to November 2022. The number of operations per site varied from 4 to 28. The mean age of patients at time of RPLND was 41.8 years (range 21-79). Overall, 54 patients had recurrence after initial stage I disease and 40 patients had primary stage IIA/IIB disease at diagnosis (one missing data). At time of RPLND 62 patients had IIA-disease and 31 stage IIB-disease (one missing data). The histology from RPLND showed seminoma in 83 patients, benign/necrosis in eight patients, vital non-seminomatous GCT in one patient, teratoma only in one patient and lymphoma in one patient. Mean number of resected nodes was 19, and mean number of positive nodes were 1.5. Twenty-six patients (28%) were operated with robotic laparoscopic technique. Ten patients (10.6%) had a Clavien-Dindo postoperative complication > 2 . Twenty-three of the patients were given adjuvant oncological treatment after RPLND, most of them one course of BEP. The patients have been followed for in median 18 months (range 2-59). Nine patients (9.6 %) have had recurrences, all but one in the first year after RPLND. **Conclusions:** Our early results of primary RPLND of seminomas IIA-IIB ≤ 3 cm are promising. Longer follow-up is required to ensure this as a safe treatment option. Research Sponsor: Public health care in Norway and Sweden.

5010

Poster Discussion Session

Prostate-specific membrane antigen ligand positron emission tomography (PSMA-PET) disease extent and overall survival (OS) in patients (pts) with high-risk nonmetastatic castration-resistant prostate cancer (nmCRPC): An international multicenter retrospective study. *First Author: Boris A. Hadaschik, University of Duisburg-Essen and German Cancer Consortium (DKTK)–University Hospital Essen, Essen, Germany*

Background: PSMA-PET was positive for distant metastases (39% distant nodes, 24% bone, 6% visceral organ) in $>50\%$ of nmCRPC pts who were nonmetastatic by conventional imaging (Fendler et al. *CCRP* 2019). However, the prognostic impact of PSMA-PET disease extent and its association with oncologic outcomes is unknown. We assessed the prognostic utility of PSMA-PET disease extent in nmCRPC pts defined by conventional imaging for OS and new metastases-free survival (nMFS). **Methods:** 200 pts (6 centers) with nmCRPC by conventional imaging and prostate-specific antigen doubling time (PSADT) ≤ 10 mo and/or ISUP grade group ≥ 4 underwent PSMA-PET. Clinical course and treatment management after PSMA-PET imaging were recorded for 4-9 y. Pt characteristics and PSMA-PET disease extent were analyzed retrospectively. OS and PSMA-PET nMFS (time from primary PSMA-PET to appearance of new distant metastases by PSMA-PET or death) were analyzed for pt subgroups based on disease extent by univariate Cox regression. **Results:** Median OS was 74 mo, similar to the SPARTAN study of nmCRPC pts (74 mo; Smith et al. *Eur Urol* 2021). Polymetastatic disease (≥ 5 distant lesions by PSMA-PET) was associated with shorter OS (median 61 mo vs not reached [NR]) and shorter PSMA-PET nMFS (HR 1.8, 95% CI 1.1-2.9; median 38 vs 60 mo; $p=0.021$). Any metastatic disease by PSMA-PET and whole-body PSMA tumor volume were not prognostic for OS and PSMA-PET nMFS (all $p>0.05$). Initial pN1 status was associated with shorter OS (median 55 mo vs NR), but not with PSMA-PET nMFS ($p>0.05$). Baseline age, baseline Gleason grade ≥ 8 , prior radiotherapy (RT), and PSA and PSADT at time of primary PSMA-PET were not associated with outcomes (all $p>0.05$). Management after PSMA-PET imaging was mostly local/targeted therapy in pts with no visible/locoregional disease (40/30%) and androgen receptor signaling inhibition therapy in pts with nodal/bone distant metastases (35/43%). **Conclusions:** Polymetastases (>5) by PSMA-PET and initial pN1 status were significantly associated with worse OS. PSMA-PET disease extent provides a potential novel additional risk stratification for pts with nmCRPC without distant metastasis based on conventional imaging. Further validation is needed to prove its independent prognostic value. Clinical trial information: NCT01946204. Research Sponsor: SPARTAN was funded by Janssen Research & Development.

Subgroup (N=200)	N (%)	OS	
		HR (95% CI)	P
Age <65 y	49 (25)	0.97 (0.52-1.81)	0.92
Gleason grade ≥ 8	151 (76)	1.41 (1.77-2.58)	0.27
pN1	45 (23)	2.01 (1.17-3.45)	0.012*
Prior definitive RT	64 (32)	1.58 (0.93-2.70)	0.092
Prior salvage RT	40 (20)	0.64 (0.31-1.31)	0.22
PSA ≥ 5 mg/dL	97 (49)	1.29 (0.76-2.19)	0.34
PSADT ≤ 6	85 ^a (64)	0.87 (0.45-1.66)	0.66
Extrapelvic disease, any	109 (55)	1.41 (0.83-2.40)	0.21
Extrapelvic disease, ≥ 5 lesions	37 (19)	1.93 (1.08-3.46)	0.027*

^an=132, ^{*}p<0.05.

5009

Poster Discussion Session

PSMA PET guided salvage radiotherapy among patients with prostate cancer in the post-prostatectomy setting: A single center post-hoc analysis. *First Author: Clayton P Smith, UCLA Department of Radiation Oncology, Los Angeles, CA*

Background: Prostate-specific membrane antigen (PSMA) positron emission tomography (PET) shows improved sensitivity and specificity for detection of locoregional and distant metastatic prostate cancer (Pca) compared to conventional imaging, especially at lower PSA levels as is often the case in the biochemically recurrent (BCR), post radical prostatectomy (RP) setting. Providers are now utilizing PSMA PET findings to guide their salvage radiotherapy (sRT) treatment fields and doses, although it is not well understood how PSMA PET guided sRT impacts patient outcomes. **Methods:** This was a *post-hoc* analysis of 5 prospective studies of PSMA PET conducted at UCLA from 2016 to 2021 that included patients with recurrent Pca following RP. Patients were included in this retrospective study if they initiated sRT within 3 months of PSMA PET, had at least 12 months of follow up after sRT completion, had available sRT treatment details, and did not have distant metastases (DM) by conventional imaging on upfront staging. Patients treated with palliative RT were excluded. BCR following sRT was defined as an increase in PSA of 0.2 ng/ml above the post sRT nadir. Metastasis directed therapy (MDT) was defined as sRT to all PSMA+ N1 and M1 lesions. Baseline patient demographics, PSMA PET findings, sRT & ADT treatment details, and patient outcome data were collected. **Results:** 176 patients were included in this study. Median time between RP and PSMA PET was 38 months (range 1-329). Median PSA at the time of the PSMA PET was 0.625 ng/mL (range 0.063-35). PSMA PET was positive in 128 patients (73%): 21 (12%) mIT+NOMO, 55 (31%) mITxN1M0 and 52 (30%) mITxNxM1 with 19 (11%) mITxNxM1a, 31 (18%) mITxNxM1b, and 2 (1%) mITxNxM1c. Median number of lesions seen on positive PSMA scans was 1 (range 1-8). 39 (22%) patients were subsequently treated with sRT to the prostate bed (PB) only, 59 (34%) to PB + pelvic lymph nodes (PLNs), 33 (19%) to PLNs only, 7 (4%) to PB + PLNs + DM, 7 (4%) to PLNs + DM, and 31 (18%) to DM only. 59 (34%) patients were treated with concurrent ADT at a median duration of 6 months (range 1-39). At a median follow-up of 32 months (range 12-70) after sRT, 80 patients (45%) did not develop BCR or imaging relapse (IR) following sRT, 24 patients (14%) developed BCR but not IR, 1 patient ($<1\%$) developed IR only, and 70 patients (40%) developed both BCR and IR. The median time to BCR and IR following sRT was 15 months (range 1-48) and 19 months (range 6-61), respectively. 1 year post sRT biochemical recurrence free survival was 77%. Of the 83 patients treated with MDT, 32 (39%) did not develop subsequent disease relapse. **Conclusions:** This *post-hoc* analysis assessed the outcomes of 176 patients treated with PSMA PET guided salvage RT, proving it to be an effective method for treating both pelvic and extrapelvic recurrent Pca. Further investigation is needed to assess the full extent of patient outcomes in this population. Research Sponsor: UCLA.

5011

Poster Discussion Session

Do bone scans over-stage disease compared to PSMA PET? An international multicenter retrospective study with blinded independent readers. *First Author: Wolfgang P. Fendler, Department of Nuclear Medicine, West German Cancer Center, University Hospital Essen, University of Duisburg-Essen, Essen, Germany*

Background: PSMA positron emission tomography (PET) has a higher accuracy than computed tomography (CT) and bone scans to stage patients with prostate cancer. However, we do not understand how to apply clinical trial data based on conventional imaging to patients staged using PSMA PET. Therefore, we aim to evaluate the ability of bone scans to detect osseous metastases using PSMA PET as a reference standard. **Methods:** In this multicenter retrospective diagnostic study, 167 patients with prostate cancer, who were imaged with bone scan and PSMA PET performed within 100 days were included for analysis. Each study was interpreted by three blinded readers, and the results of the PSMA PET were used as the reference standard. Endpoints were positive predictive value (PPV), negative predictive value (NPV) and specificity for bone scans. Additionally, inter-reader reproducibility, positivity rate, uptake on PSMA PET, and number of lesions were evaluated. **Results:** 167 patients were included in the study, with 77 at initial staging, 60 in the BCR/CSPP setting and 30 in the CRPC setting. BS findings for metastatic disease validated by PSMA PET were tabulated. In all patients, the PPV, NPV and specificity for bone scans were 0.73 [0.61,0.82], 0.82 [0.74,0.88] and 0.82 [0.74,0.88]. In patients at initial staging, the PPV, NPV and specificity for bone scans were 0.43 [0.26,0.63], 0.94 [0.85,0.98], and 0.80 [0.68,0.88]. At initial staging 13/23 (57%) of positive bone scans were false positive. Inter-reader agreement for bone disease was moderate for bone scans (Fleiss k, 0.51) and substantial for the PSMA PET reference standard (Fleiss k, 0.80). **Conclusions:** In this multicenter retrospective study, the PPV of bone scans was low in patients at initial staging with majority of positive bone scans being false positives. This suggests that a large proportion of patients considered low volume metastatic by bone scan actually have localized disease. Research Sponsor: UCLA, UCSF, UKEssen.

n=167 patients	Initial staging	BCR/CSPP	CRPC	Overall
BS+/PSMA+ (TP)	10 (13)	17 (28)	21 (70)	48 (29)
BS-/PSMA- (TN)	51 (66)	28 (47)	5 (17)	84 (50)
BS+/PSMA- (FP)	13 (17)	5 (8)	0 (0)	18 (11)
BS-/PSMA+ (FN)	3 (4)	10 (17)	4 (13)	17 (10)

5012

Poster Discussion Session

Health-related quality of life (HRQoL) and pain outcomes for patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) who received abiraterone (abi) and olaparib (ola) versus (vs) abi and placebo (pbo) in the phase III PROpel trial. *First Author: Antoine Thiery-Vuillemin, CHRU Besançon Hôpital J.Minjoz, Besançon, France*

Background: PROpel (NCT03732820) met its primary endpoint and showed significantly prolonged investigator-assessed rPFS with abi + ola vs abi + pbo at primary analysis (data cut-off [DCO]: 7/30/21; median 24.8 vs 16.6 months (m); hazard ratio [HR] 0.66, 95% confidence interval [CI] 0.54–0.81; $P < 0.001$). HRQoL (based on The Functional Assessment of Cancer Therapy-Prostate [FACT-P] total score) was not different when ola was combined with standard-of-care abi. We present data at the final prespecified overall survival (OS) DCO (10/12/22). **Methods:** PROpel is a randomised, double-blind trial in 1L mCRPC. Time to pain progression (TPPP) was based on the Brief Pain Inventory-Short Form (BPI-SF) Item 3 'worst pain in 24 hours' and opiate analgesic use (analgesic quantification algorithm) score. Time to first symptomatic skeletal related event (SSRE) was time to use of therapy to prevent/relieve skeletal symptoms, new bone fractures, spinal compression or surgery on bone metastases. HRQoL was assessed by change from baseline (BL) in FACT-P total and subscale scores, BPI-SF pain severity, pain interference and worst pain score between arms using a mixed model for repeated measures. **Results:** At median follow-up of 33.6 m with abi + ola and 32.1 m with abi + pbo, 17.0% pts (68/399) in the abi + ola arm and 15.1% pts (60/397) in the abi + pbo arm had pain progression (PP) events. The % of pts who had not experienced PP with abi + ola vs abi + pbo was 76.9% vs 77.2% at 24 m and 70.7% vs 71.0% at 36 m. No meaningful difference in TPPP was observed (16% maturity, HR 1.06, 95% CI 0.75–1.50, $P = 0.75$ [nominal], median not reached [NR] either arm). The % of pts who had not had a SSRE with abi + ola vs abi + pbo was 86.1% vs 82.2% at 24 m and 80.8% vs 78.5% at 36 m. No meaningful difference in time to SSRE was observed (12% maturity, HR 0.82, 95% CI 0.55–1.22, $P = 0.32$ [nominal], median NR vs NR). Least-squares mean changes from BL between arms in BPI-SF pain severity (difference, -0.06; 95% CI -0.23–0.12), pain interference (difference, -0.12; 95% CI -0.31–0.06), worst pain score (difference, -0.12; 95% CI -0.35–0.11) and FACT-P total score (difference, -0.54; 95% CI -3.00–1.92) suggest no clinically meaningful difference in HRQoL with abi + ola vs abi + pbo. Least-squares mean change from BL values for FACT-P subscale scores were consistent with FACT-P total score result. **Conclusions:** PROpel demonstrated a significant delay in rPFS for pts receiving abi + ola vs abi + pbo. Most pts in the trial did not experience a PP event. Abi + ola showed no difference in HRQoL (assessed by FACT-P total and subscale scores, BPI-SF domain and worst pain scores) vs abi + pbo, suggesting pts can derive clinical benefit from abi + ola while maintaining a similar HRQoL compared with a current standard-of-care treatment. Clinical trial information: NCT03732820. Research Sponsor: This study was supported by AstraZeneca and Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, who are codeveloping olaparib.

5014

Poster Discussion Session

Patient reported quality of life (QOL) and survival outcomes: Analysis of ECOG-ACRIN E3805 chemohormonal androgen ablation randomized trial (CHAARTED) in prostate cancer (PCa). *First Author: Daniel Sentana Lledo, Beth Israel Deaconess Medical Center, Boston, MA*

Background: Chemohormonal therapy with androgen deprivation therapy and docetaxel (ADT+D) improves overall survival (OS) and quality of life (QOL) at 12 months compared to ADT alone in metastatic hormone sensitive prostate cancer (mHSPC). However, the prognostic relationship between QOL, disease characteristics, and OS has not been described in this population. **Methods:** In this post-hoc exploratory analysis of the CHAARTED trial, the QOL instrument Functional Assessment of Cancer Therapy-Prostate (FACT-P) was completed by patients treated with ADT and ADT+D. Log-rank test and Cox proportional hazards models were used to test the association between QOL and OS by clinical and disease characteristics. **Results:** 790 men were included in the study (ADT+D, $n = 397$; ADT, $n = 393$). Baseline higher QOL by FACT-P ($n = 790$) was associated with better OS in univariate regression (HR 0.70 [0.55, 0.90], $p = 0.005$), however the association was not significant in multivariate analysis (HR 0.80 [0.62–1.04], $p = 0.09$). There was a trend towards improved survival for patients with the lowest baseline QOL (lowest quartile) treated with ADT+D compared to ADT (HR 0.75 [0.53, 1.05], $p = 0.09$). In contrast, patients with the highest baseline QOL (highest quartile, 63% high volume disease) had similar survival regardless of treatment arm (HR 0.92 [0.63–1.36], $p = 0.69$). Higher 3-month QOL by FACT-P ($n = 654$) was associated with survival in the multivariate analysis independently of treatment arm (HR 0.76 [0.58, 1.0], $p = 0.05$). Patients with the highest 3-month QOL had comparable survival regardless of treatment arm (HR 1.11 [0.73, 1.67], $p = 0.63$), while patients with the lowest 3-month QOL experienced a survival benefit with ADT+D compared to ADT (HR 0.69 [0.48, 0.99], $p = 0.047$). **Conclusions:** In this analysis, 3-month QOL by FACT-P was significantly associated with survival for patients with mHSPC. Patients with the poorest QOL ("most symptomatic") appeared to experience survival benefit from ADT+D regardless of disease volume. Conversely, patients reporting the highest QOL ("least symptomatic") did not seem to benefit from ADT+D despite a predominance of patients with high volume disease in that cohort. These findings suggest that consideration of QOL may enhance decision making and patient selection when considering chemohormonal treatment for mHSPC. Research Sponsor: U.S. National Institutes of Health; Sanofi.

Associations between 3-month FACT-P total score (quartile) and overall survival.

	N	UVA (n=654)		N	MVA* (n=646)	
		HR (95% CI)	p-value		HR (95% CI)	p-value
3-month FACT-P total score						
[39.6, 105]	165	-	-	165	-	-
[105, 121]	160	0.89(0.69, 1.15)	0.39	160	0.9(0.69, 1.17)	0.42
[121, 133]	163	0.81(0.63, 1.05)	0.11	163	0.86(0.66, 1.12)	0.26
[133, 155]	158	0.71(0.55, 0.93)	0.011	158	0.76(0.58, 1.1)	0.05
Missing	8			0		

* Adjusting for treatment arm, performance status, disease volume, Gleason score, and prior local therapy.

5013

Poster Discussion Session

Patient-reported outcomes (PROs) among men receiving talazoparib (TALA) + enzalutamide (ENZA) vs placebo (PBO) + ENZA as first-line (1L) treatment for metastatic castration-resistant prostate cancer (mCRPC): Results from a phase 3 study (TALAPRO-2). *First Author: Neeraj Agarwal, Huntsman Cancer Institute (NCI-CCC), University of Utah, Salt Lake City, UT*

Background: TALAPRO-2 (NCT03395197) showed statistically significant improvement in radiographic progression free survival with TALA + ENZA ($n=402$) vs PBO + ENZA ($n=403$) (HR=0.63 95% CI 0.51–0.78; $P < 0.001$) in men receiving 1L treatment for mCRPC. Here we report PRO endpoints from TALAPRO-2. **Methods:** PROs were assessed at day 1 (baseline) and at scheduled visits until radiographic progression (every 4 weeks until week 53, and then every 8 weeks) using the EORTC QLQ-C30 and its prostate cancer module, QLQ-PR25. Prespecified PRO analyses included overall mean change from baseline (per longitudinal repeated measures mixed-effects model) and time to definitive clinically meaningful (≥ 10 -point change) deterioration (TTD). Between-arm comparisons of TTD were made using a stratified log-rank test and a Cox proportional hazards model. **Results:** Of the 805 men randomized and treated, 793 had a baseline score followed by at least 1 post-baseline score; TALA + ENZA ($n=395$), PBO + ENZA ($n=398$). Although the treatment effect on global health status (GHS)/quality of life (QoL) significantly favored PBO + ENZA, the predefined threshold of clinical meaningfulness was not met; moreover, no significant differences between the arms were observed in any functioning scales. A significantly longer TTD in GHS/QoL was observed for TALA + ENZA; HR=0.780 (95% CI: 0.62, 0.99), $P=0.038$; median: 30.8 months vs 25.0 months. A numerical greater delay in TTD in urinary symptoms was longer for TALA + ENZA; HR=0.759 (95% CI: 0.543, 1.061), $P=0.105$; median not reached vs 35.9 months. Additional PRO results will be presented. **Conclusions:** Compared with PBO + ENZA, in the TALA + ENZA arm there was 1) a modest deterioration disfavoring GHS/QoL (deterioration was not clinically meaningful based on the predefined threshold), and 2) a maintenance in all functioning scales. TTD in GHS/QoL was significantly longer with TALA + ENZA vs PBO + ENZA, reflecting improved disease control. These results complement the benefit-risk assessment of TALAPRO-2. Clinical trial information: NCT03395197. Research Sponsor: Pfizer Inc.

Overall change from baseline in PROs.

Scale	TALA + ENZA Estimated Mean (95% CI)	PBO + ENZA Estimated Mean (95% CI)	Estimated Mean Difference (95% CI)	P Value
GHS/QoL	-5.8 (-7.2, -4.3)	-3.2 (-4.7, -1.7)	-2.5 (-4.6, -0.5)	0.0139*
Physical	-6.1 (-7.4, -4.7)	-4.5 (-5.9, -3.1)	-1.6 (-3.6, 0.4)	0.1142
Role	-6.1 (-7.8, -4.5)	-4.5 (-6.2, -2.8)	-1.6 (-4.0, 0.7)	0.1787
Emotional	-1.6 (-2.8, -0.3)	-0.6 (-1.9, 0.7)	-0.9 (-2.7, 0.9)	0.3105
Cognitive	-6.3 (-7.7, -5.0)	-5.7 (-7.1, -4.3)	-0.6 (-2.6, 1.3)	0.5120
Social	-5.1 (-6.5, -3.8)	-4.3 (-5.6, -2.9)	-0.9 (-2.8, 1.0)	0.3628

Positive scores indicate better functioning, and GHS/QoL. *Did not meet the predefined threshold of clinical meaningfulness.

5015

Poster Discussion Session

A prospective trial of apalutamide and abiraterone acetate plus prednisone in Black and White men with metastatic castrate-resistant prostate cancer. *First Author: Daniel J. George, Duke Cancer Institute Center for Prostate and Urologic Cancers, Durham, NC*

Background: Abi Race was the first prospective parallel cohort study of abiraterone acetate plus prednisone (AAP) in Black and White men with metastatic castrate-resistant prostate cancer (mCRPC) and demonstrated greater prostate-specific antigen (PSA) response, time to PSA progression (TTP) and toxicity rates among Black patients (pts). We designed the PANTHER trial to estimate clinical outcomes among Black and White pts with mCRPC treated with apalutamide, abiraterone, plus prednisone. **Methods:** This parallel cohort multicenter study treated androgen receptor pathway inhibitor naïve mCRPC pts with oral apalutamide (240 mg/d), abiraterone (1000 mg/d) and prednisone (10 mg/d) (AAP) continuously until disease progression, unacceptable toxicity or 2 years. The primary endpoint was radiographic progression free survival (rPFS); secondary endpoints were to estimate TTP, overall survival (OS) and best PSA response, among Black and White pts, separately. Exploratory endpoints included safety and correlative biomarkers of outcome by race and ancestry. **Results:** Between July 2017 and January 2021, we enrolled 43 Black and 50 White pts from 8 sites. Baseline prognostic characteristics were largely similar with some differences. We report an interim analysis as the pts are still followed for OS. At the time of the abstract submission, there were 18 and 36 rPFS events and 15 and 30 deaths in Black and White pts, respectively. We present the time to event endpoint rates at 12 and 24 mos and PSA declines for Black and White pts. **Conclusions:** We hypothesize that treatment with the combination of AAP may result in clinical efficacy in Black men with mCRPC. Black pts were underrepresented in the phase III ACIS trial which compared AAP to AAAP and demonstrated longer rPFS but not OS. Further studies of AAP combination therapy among Black men with advanced prostate cancer are needed to determine potential clinical benefits in this understudied population. Clinical trial information: NCT03098836. Research Sponsor: Janssen; DOD CDMRP.

Endpoint	Black men (95% CI)	White men (95% CI)
12 mo rPFS rate	79% (68, 92)	51% (39, 67)
24 mo rPFS rate	63% (50, 80)	38% (26, 55)
12 mo TTP rate	81% (69, 94)	59% (43, 80)
24 mo TTP rate	59% (46, 77)	39% (25, 60)
12 mo OS rate	95% (89, 100)	84% (73, 97)
24 mo OS rate	83% (74, 95)	65% (52, 80)
>50% PSA decline	40 (93%)	34 (68%)
No PSA decline	1 (2.3%)	7 (14%)
PSA decline to < 0.1 ng/mL	21 (49%)	14 (28%)

5016

Poster Discussion Session

Primary analysis of STARTAR: A phase 2 salvage trial of androgen receptor (AR) inhibition with androgen deprivation therapy (ADT) and apalutamide with radiation therapy (RT) followed by docetaxel in men with PSA recurrent prostate cancer (PC) after radical prostatectomy (RP). *First Author: Tian Zhang, University of Texas Southwestern Medical Center, Dallas, TX*

Background: ADT with salvage RT improves survival for men with PSA recurrence after RP. For high risk PSA recurrence, current standard ADT duration is up to 2 years with RT; shortening but intensifying systemic therapy may improve outcomes. The STREAM trial showed 6 mo enzalutamide with ADT/RT had 3-year progression free survival (PFS) of 53% in a high risk population, including lymph node (LN) positive. Given docetaxel (doce) improves survival in mHSPC, we evaluated the combination of salvage RT, ADT/apalutamide (apa) and doce in this setting. **Methods:** STARTAR is a multicenter investigator initiated phase 2 trial for salvage treatment of PSA recurrent PC post-RP, conducted in the DOD Prostate Cancer Clinical Trials Consortium. Key inclusion criteria included Gleason 7 with T3/positive margin/N1 or Gleason 8-10 PC, PSA relapse <4 years post-RP (inclusion PSA 0.2-4 ng/mL), and <4 positive LNs, standard imaging negative. Patients (pts) received ADT with apa for 9 months, RT (66-74 Gy to the prostate bed +/- pelvic LNs over 6-8 wks) starting wk 8, and then completed 6 cycles of concurrent doce 75mg/m2 q3 wks. The primary endpoint was 36 month PFS, defined as composite of freedom from PSA>0.2 + post-RT nadir with subsequent rise, clinical progression, other therapy start, or death, among pts with testosterone (T) recovery (>100ng/dL). Kaplan-Meier estimates for PFS were used to determine landmark 24 mo and 36 mo rates and compared to PFS rates from prior trials using a binomial test. **Results:** From 3/2018 to 2/2020, 39 pts were enrolled. As of 12/2022 data cutoff, median follow up was 36 months. Baseline characteristics: Gleason 7 in 54%; Gleason 8-10 in 46%; 23% LN positive; median PSA 0.58 ng/mL (range 0.21-3.40), and median time from RP 7.6 mo (range 2-98). 37 pts (95%) and 23 pts (62%) completed at least 1 and all 6 cycles doce, respectively. All pts achieved undetectable PSA nadirs. At 24mo and 36mo, PFS rates were 84% and 72%, respectively, with 95% pts recovering T at 36 mo. Compared to 40% historical PFS and 53% STREAM PFS rates, the 72% 36-mo PFS rate was statistically significantly improved (p<0.001 and p=0.013, respectively). Common any-grade adverse events (AEs) included 98% hot flashes, 88% fatigue, 77% alopecia, 57% dysgeusia, and 53% rash (28% grade 1; 15% grade 2, 10% grade 3), with 5% febrile neutropenia. **Conclusions:** In this first phase 2 trial of ADT, apa, salvage RT, and 6 cycles of doce for high risk PSA recurrence, the primary endpoint 3-year PFS rate improved to 72%, indicating durable remissions beyond historic controls. Intensifying systemic treatments in the non-metastatic hormone sensitive but high risk salvage setting may be feasible and efficacious, with fewer pts experiencing cancer progression over time. Clinical trial information: NCT03311555. Research Sponsor: Janssen.

5019

Poster Discussion Session

Final results from phase I study of PSCA-targeted chimeric antigen receptor (CAR) T cells in patients with metastatic castration resistant prostate cancer (mCRPC). *First Author: Tanya B. Dorff, Department of Medical Oncology & Experimental Therapeutics, City of Hope Comprehensive Cancer Center, Duarte, CA*

Background: Chimeric antigen receptor (CAR)-engineered T cell therapies are being pursued for the treatment of mCRPC. Prostate Stem Cell Antigen (PSCA) is highly expressed on the surface membrane in mCRPC and with limited expression on normal tissues. We are completing a phase I study of PSCA-targeted 4-1BB-co-stimulated CAR T cell therapy in mCRPC. **Methods:** CAR T cells were manufactured at City of Hope's cGMP facility. Patients (pts) were required to have disease progression after at least 1 androgen receptor targeted therapy but there was no limit on other prior treatments. The primary objective was to define the dose limiting toxicities (DLT) as well as to describe preliminary bioactivity and activity. CAR T persistence and cytokine levels were evaluated by flow cytometry and Luminex. Circulating tumor cells (CTC) were measured by an unselected assay (Kuhn). **Results:** 14 pts were treated, median age 69, median baseline PSA 88. 12(86%) had previously been treated with chemotherapy; 9 received two taxanes and 3 docetaxel only. 79% of screened pts had PSCA expression >2+ in >80% of cancer cells. Two of 6 pts encountered DLT (grade 3 cystitis) at 100M + lymphodepletion (LD) chemotherapy. The protocol was amended to reduce the LD dose to 300 mg/m2 cyclophosphamide D1-3. No DLTs occurred in 5 pts treated in the modified LD 100M cohort. Cytokine release syndrome (CRS), best response by RECIST, CAR T cell expansion and persistence are presented by dose level in the table. CAR T expansion was greater with LD than without. PSA declines were seen, as well as radiographic improvement, though RECIST response was limited to stable disease (SD) by concurrent bone metastases. Cytokine peaks were higher in patients with anti-tumor effect noted. CTC decreases in both marrow and peripheral blood were seen, associated with PSA declines. **Conclusions:** PSCA-CAR T cells have anti-cancer activity in mCRPC with DLT of cystitis. LD was required for greater expansion and activity; lower dose LD improved toxicity without clear negative impact on expansion. Clinical trial information: NCT03873805. Research Sponsor: Prostate Cancer Foundation; DOD.

Dose level	N	DLTs	CRS	RECIST Response	PSA decrease at day 28	Expansion	% Continued Persistence thru Day 28 where persistence is a Copy No ≥ 7.5 copies/ug of DNA (no./total no.) 95% CI
						Max Log ₁₀ (Copies/ug of DNA) Mean, 95% Confidence Interval (CI)	
100M (Starting Dose)	3	0	3 PD	Gr 2	33% (1/3) 95%CI [1%, 91%]	2.1 95%CI [1.6, 2.6]	66% (2/3) 95%CI [9%, 99%]
100M +LD	6	2	4 SD	Gr 2	33% (2/6) 95%CI [4%, 78%]	3.2* 95%CI [2.5, 4.0]	66% (4/6) 95%CI [22%, 96%]
100M+ modified LD	5	0	3 SD	Gr 1	20% (1/5) 95%CI [1%, 72%]	2.8 95%CI [2.3, 3.4]	60% (3/5) 95%CI [15%, 95%]

5018

Poster Discussion Session

Phase I dose-escalation results of prostate-specific membrane antigen-targeted radionuclide therapy (PSMA-TRT) with alpha-radiolabeled antibody ²²⁵Ac-J591 and beta-radioligand ¹⁷⁷Lu-PSMA I&T. *First Author: Scott T. Tagawa, Weill Cornell Medicine, Division of Hematology & Medical Oncology, NewYork-Presbyterian Hospital, New York, NY*

Background: PSMA may be targeted by antibodies (mAb) or small molecules (SML), with different kinetics and biodistribution. mAb with longer circulation time and marrow exposure, but decreased access to luminal PSMA expression (e.g. salivary glands, intestine, kidney). SML diffuse to all sites of PSMA expression and then excreted. Alpha radionuclides emit more energy over shorter range vs beta. Pre-clinical data combining mAb and SML supports synergy, with enhanced uptake and retention of SML. Here, we present phase I dose-escalation results of a phase I/II trial investigating combo ²²⁵Ac-J591 with ¹⁷⁷Lu-PSMA-I&T (aka PNT2002). **Methods:** Eligibility criteria include progressive mCRPC, ≥1 prior AR pathway inhibitor (ARPI), prior chemo (or unfit/refuse), ≥1 lesion with SUVmax >liver. Doses: ¹⁷⁷Lu-PSMA-I&T (6.8 GBq); ²²⁵Ac-J591 (30, 35, or 40 KBq/kg), up to 2 doses of combo TRT 8 weeks (wks) apart with ¹⁷⁷Lu SPECT following each dose. Primary objectives: dose-limiting toxicity (DLT) and recommended phase II dose; phase II will test the proportion of patients (pts) obtaining >50% PSA decline (PSA50). DLT defined as G4 myelosuppression lasting >1 wk, Gr>2 non-hematologic adverse event (AE), any Gr attributed AE delaying therapy >3 wks. Additional endpoints include progression-free and overall survival, radiographic response rate, safety, circulating tumor cell (CTC) changes, pt reported outcomes, PSMA imaging, blood/tissue correlatives. **Results:** 18 pts treated (6 at each dose level); 3 did not receive the 2nd dose due to progressive disease or withdrawal. Median age 70 (range 54-86), PSA 54.4 (2.43-9614). 13 (72%) with bone, 9 (50%) lymph node, 2 (11%) liver, 2 (11%) lung mets. 10 (56%) pts CALGB risk category high, 7 (39%) intermediate, 1 low. Previous therapies: 11 (61%) with >1 ARPI, 12 (67%) chemo, 5 (28%) sip-T, 3 (17%) radium-223. 2 of 6 pts with DLT at 40 KBq/Kg (Gr 2 or 3 thrombocytopenia delaying cycle 2 by >3 wk); no DLT observed in other cohorts. As submission, 7 pts (39%) remain on study, including 1 without progression at 16 months and another with undetectable PSA at 10 months. With follow up ongoing, 17 (94%) with PSA decline, 9 (50%) with PSA50. Of those with paired CTC counts, 4 of 5 (80%) converted from unfavorable to favorable CTC count, 4 of 8 (50%) from detectable to undetectable, 1 of 2 (50%) remained undetectable. AEs include 3 (17%) neutropenia (all Gr <2), 12 (67%) thrombocytopenia (3 Gr 3), 10 (56%) anemia (3 Gr 3), 10 (56%) pain flare (1 Gr3 in pt with cord compression), 12 (67%) xerostomia (one Gr2), 11 (61%) nausea (all Gr 1), 9 (50%) fatigue (all Gr 1). **Conclusions:** The combination of dual-PSMA targeting with mAb + SML and alpha + beta is feasible with follow up ongoing. Efficacy will formally be tested in the upcoming phase II portion of the study with ²²⁵Ac-J591 at 35 KBq/Kg and ¹⁷⁷Lu-PSMA I&T at 6.8 GBq. Clinical trial information: NCT04886986. Research Sponsor: Weill Cornell Medicine; U.S. National Institutes of Health; POINT Biopharma.

5021

Poster Session

Clonal hematopoiesis in the phase 3 Alliance A031201 trial of metastatic castration resistant prostate cancer (mCRPC) treated with androgen receptor (AR)-targeted therapies. *First Author: Jeffrey Lee Jensen, University of North Carolina Hospital, Chapel Hill, NC*

Background: Somatic mutations in hematopoietic progenitor cells accumulate with age leading to clonal expansion in a process called clonal hematopoiesis (CH). CH increases the risk of developing myeloid neoplasms and shortens overall survival (OS), primarily linked to increased cardiovascular (CV) mortality. The impact of CH in metastatic solid cancers has been conflicting, with shorter OS in a broad cancer cohort but prolonged OS in metastatic colorectal cancer, which may be influenced by prior cytotoxic therapy that can promote emergence of CH. As AR pathway inhibitors (ARPIs) are associated with CV adverse events (AE), exploring the impact of CH in patients (pts) with mCRPC is of interest. **Methods:** A 9 gene targeted DNA sequencing panel designed to capture common CH mutations (*DNMT3A*, *TET2*, *ASXL1*, *PPM1D*, *TP53*, *CHEK2*, *SRSF2*, *SF3B1*, *JAK2*) was applied to pre-treatment peripheral blood samples of 957 pts enrolled in the Alliance A031201 phase 3 trial of enzalutamide versus enzalutamide plus abiraterone/prednisone in the first line mCRPC setting. No difference in OS was found between treatment arms. The primary endpoint was the impact of CH on OS; secondary and exploratory endpoints included progression-free survival (PFS) and associations with baseline comorbidities and AEs (hematologic and CV). Cox proportional-hazards and logit models were adjusted for treatment arm, age, and radiation therapy (RT). **Results:** CH was common with 57% of pts having low CH (VAF>0.5% in 1+ mutation, L-CH), 24% having standard CH (VAF>2%, CH), and 7% having high CH (VAF>10%, H-CH). 4% of pts had 2+ CH mutations and 1% had 3+ mutations. Patients with CH were older (73.1 vs 70.2) and had higher rates of prior RT (58.4% vs 55.7%) and prior chemotherapy (3.9% vs 2.2%). No differences in OS were detected in pts with L-CH, CH, or H-CH. Similarly, no differences in PFS or baseline CV comorbidities were seen in any CH group. Pts with H-CH and *TET2*-mutated CH had statistically higher odds of any CV event (adjusted p=0.0004 and p=0.010, respectively) There was also a difference in the occurrence of major adverse CV events (MACE) by H-CH status (5.8% vs. 1.9%, adjusted p=0.042), while there was no difference seen for CH (3.4% vs 1.8%, adjusted p=0.147). Regarding hematologic AEs, one pt with a *TP53* mutation (VAF 0.94%) developed myelodysplastic syndrome. **Conclusions:** CH did not affect OS or PFS in pts with mCRPC treated with ARPIs in the A031201 trial. However, CH with VAF>10% and *TET2*-mutated CH were associated with an increased rate of all CV AEs, suggesting an additive effect of ARPI therapy and CH on adverse CV outcomes. Confirmatory studies are warranted to assess whether CH should be considered in the risk-benefit discussion for pts receiving ARPIs. Research Sponsor: Prostate Cancer Foundation.

5022

Poster Session

Association of adaptive immunity/inflammatory genes with survival in prostate cancer. *First Author: Austin Hopper, University of California San Diego, La Jolla, CA*

Background: Advances in immunotherapy have had little impact in prostate cancer (PCA). We have previously examined the immune microenvironment in both localized and metastatic PCA and found that primary PCA shows local inflammation/adaptive immunity whereas metastatic disease shows a shift towards immune suppression (Deichate, 2022). Herein, we examine immune remodeling in PCA by evaluating changes in gene expression between localized and metastatic disease with heterogeneous treatment patterns in both primary and metastatic samples. **Methods:** Tumors from PCA (N = 5,419) were tested at Caris Life Sciences (Phoenix, AZ) with NextGen Sequencing of DNA (592-gene or whole exome) and RNA (whole transcriptome). Samples collected from the prostate gland (N = 3,284) or metastatic sites (N = 2,135) were analyzed. The Mann-Whitney U test was applied as appropriate, with P-values adjusted for multiple comparisons ($q < .05$). Real-world overall survival (OS) data was obtained from insurance claims and Kaplan-Meier estimates were calculated for molecularly defined subpopulations. Survival for tumors with high (-H) and low (-L) expression of genes of interest, defined as top and bottom quartile of expression (transcripts per million, TPM) across all tumors, was investigated. Differentially regulated pathways were assessed by gene set enrichment analysis (GSEA). **Results:** Compared to metastatic PCA, primary samples had increased median expression of pro-inflammatory genes *IL-6* (1.2-fold), *SELE* (1.9-fold), *NRK* (6.3-fold), *CEBPD* (1.2-fold), *NFKB2* (1.4-fold) and *FOXP3* (1.4-fold) (each $q < .05$). GSEA identified enrichment of *E2F* target genes in primary samples, while metastatic samples were enriched in inflammatory response, *KRAS* signaling and *IL2/STAT5* signaling pathways. The expression of inflammatory genes affected OS differently based on site. *IL-6*, *NRK* and *SELE-H* levels in primary samples were associated with increased OS. Within metastatic samples, *CEBPD-H* was associated with decreased OS and *NFKB2-H* was associated with an increased OS. *FOSB-H* was associated with increased OS in both primary and metastatic samples. **Conclusions:** We identify significant differences in the expression of inflammatory regulators and cytokines between localized and metastatic PCA tumors, which correlate with OS. These changes in the immune microenvironment can be leveraged for rational immunotherapy development and better targeted approaches. Research Sponsor: UCSD Department of Radiation Medicine and Applied Sciences.

	Primary			Met		
	HR	CI	p	HR	CI	p
IL6	0.55	0.45-0.68	< 0.001	0.88	0.72-1.09	0.237
NRK	0.46	0.35-0.61	< 0.001	0.90	0.69-1.18	0.452
SELE	0.51	0.42-0.63	< 0.001	0.87	0.70-1.07	0.19
CEBPD	0.93	0.78-1.11	0.422	1.22	1.02-1.45	0.025
NFKB2	0.90	0.74-1.11	0.3	0.68	0.54-0.84	<0.001
FOSB	0.56	0.47-0.66	< 0.001	0.78	0.65-0.95	0.013

5024

Poster Session

Clinical implications of molecular alterations in intraductal carcinoma of the prostate. *First Author: Benjamin Miron, Fox Chase Cancer Center, Philadelphia, PA*

Background: Intraductal carcinoma of the prostate (IDC-P) is a recent addition to the 2016 WHO classification system and little is known about the nature of its true incidence and biology. Clinically, it has been observed to be associated with higher grade group tumors and a more aggressive disease course with a high risk of local recurrence and distant metastasis. However, the molecular underpinnings which define IDC-P are not well elucidated. Initial case series with molecular profiling have suggested an enrichment of alterations in DNA damage/repair (DDR), PI3K, WNT and MAPK pathways. We now present comprehensive molecular profiling data from the largest cohort of IDC-P reported to date in order to better characterize this relatively new histologic entity. **Methods:** Eligible patients included those with radical prostatectomy tumor tissue labeled as IDC-P on testing requisition with available tissue-based DNA and RNA sequencing utilizing a commercially available CLIA-certified assay (Caris Life Sciences). Prostatic tumor specimens were analyzed using NextGen DNA sequencing (NextSeq, 592 genes and NovaSeq, WES). Digitized H&E slides underwent central pathological review by a board certified pathologist (SW) specializing in genitourinary malignancies to confirm presence of intraductal histology according to the 2022 WHO classification. **Results:** 31 of 44 submitted cases were confirmed to be IDC-P on central review. Median age of patients was 64 yrs (range 44-79). The majority of cases (26/31 - 84%) were Grade Group 5 and all were Grade Group 3 or higher. Overall the most frequently detected alterations were in *TP53* (39%), *TMPPRSS2* fusion (39%), *FOXA1* (16%), *CDK12* (10%), *PIK3CA* (10%), *SPOP* (10%), *ATM* (7%), *AKT1* (7%) and *RB1* (5%). The most commonly altered pathways were in cell cycle regulators (50%), DDR (*BRCA1/2*, *ATM*, *CDK12*) (23%), and PI3K/AKT/MTOR (23%) and WNT (10%). The *FOXA1* mutation rate in this cohort was higher compared to the localized prostate cancer cohort from the TCGA (16% - 5/31 vs 6% - 82/1325). In the IDC-P cohort, there were no tumors which demonstrated mismatch-repair deficiency (dMMR) or microsatellite instability and none of the profiled tumors had a high tumor mutational burden (≥ 10 mutations/megabase). **Conclusions:** This data suggests that IDC-P harbors targetable molecular alterations in DDR genes (*BRCA1/2* and *CDK12*) with approved targeted agents (e.g. PARP inhibitors). These findings should underscore the importance of germline and somatic mutation testing when IDC-P is identified. We also found enrichment of oncogenic *FOXA1* mutations in IDC-P which are associated with prostate cancer progression, castrate-resistance and an unfavorable prognosis. Further efforts are ongoing to expand this cohort of IDC-P cases and compare them with a matched cohort of pure adenocarcinoma cases and will include analysis of key RNA expression signatures. Research Sponsor: None.

5023

Poster Session

Clinical analysis of optimized neural network risk models to predict clinically significant prostate cancer and avoid unnecessary prostate biopsies. *First Author: Christopher J.D. Wallis, Division of Urology and Surgical Oncology, Department of Surgery, Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, ON, Canada*

Background: Given the low specificity of the current standard of care diagnostic tests for prostate cancer (PCa), there is an unmet clinical need for higher specificity tests to counter overdiagnosis of grade group (GG) 1 PCa. The aim of the study was to create optimized neural network risk models using PSA, free PSA, and other useful clinical features, and to validate the accuracy of the risk models to predict GG ≥ 2 PCa using real-world samples and data. **Methods:** Men aged 40-75 years with PSA ≥ 3 ng/mL and a biopsy referral were recruited into cohorts from sites in Canada (Kipnes Urology Centre (KUC), Edmonton, AB, and Prostate Cancer Centre (PCC), Calgary, AB) and the United States (Johns Hopkins University (JHU), Baltimore, MD and UCLA, Los Angeles, CA). Risk models to predict all GGs or GG ≥ 2 PCa were fit using data from KUC and JHU (train cohort n = 1037) while fixed models were validated on PCC (n = 401) and UCLA (n = 945). Prediction models were created using neural networks to generate the patient's risk score. To compare the risk model test with PSA, the high-grade cancer detection sensitivity was fixed, and the number of biopsies needed to achieve that sensitivity was evaluated. Threshold values for the training cohort were determined using at least 95% sensitivity and maximum specificity. Threshold values for other clinical features and risk calculator outputs were set to match the test sensitivity when possible. **Results:** The optimized neural network risk models test had the highest area under the curve (AUC 0.81) for predicting GG ≥ 2 PCa on the validation cohorts compared to four other risk calculators; Prostate Cancer Prevention Trial Risk Calculator 2.0 (PCPTRC) with free PSA (0.78, p -value < 0.001), Prostate Biopsy Collaborative Group risk calculator (PBCG, 0.73, p -value < 0.0001), European Randomized study of Screening for Prostate Cancer risk calculator 3 (ERSPC-3, 0.72, p -value < 0.0001), and PCPTRC with no free PSA (0.71, p -value < 0.0001) and PSA (0.66, p -value < 0.0001). At a threshold of 18.6%, this test provided 94% sensitivity, 37% specificity, 49% positive predictive value, and 90% NPV for predicting GG ≥ 2 PCa. If a biopsy was performed only when the tests' risk score prediction was ≥ 17.8 for GG ≥ 2 PCa, 36-44% of unnecessary prostate biopsies could be avoided while missing 4-12% of patients with GG ≥ 2 prostate cancer. **Conclusions:** This neural network risk model is a tool that can be used to inform the physician of a patient's risk of having GG ≥ 2 PCa on prostate biopsy. Using this novel test in the clinic is expected to significantly reduce the number and burden of unnecessary prostate biopsies. Research Sponsor: Alberta Innovates - Alberta Small Business Innovation & Research Initiative (ASBIRI) Program; Bird Dogs - Alberta Cancer Foundation: Prostate Cancer Research Plan; Prostate Cancer Canada.

Biopsies avoided with a grade group (GG) ≥ 2 prostate cancer (PCa) threshold of 18.6.

Validation Sites	GG ≥ 2 PCa found		GG ≥ 2 PCa missed		Biopsies avoided		Unnecessary biopsies avoided	
	n	%	n	%	n	%	n	%
PCC	165	95.4	8	4.6	105	23.8	97	36.1
UCLA	442	87.5	63	12.5	256	27.1	193	43.9

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Poster Session

Prostate cancer public health system database from Brazil: Racial disparities and heterogeneity of treatment interventions to understand evidence-based practice patterns in a large real-world database. *First Author: Daniel Herchenhorn, University of California, San Diego (UCSD), San Diego, CA*

Background: The Brazilian Public National Health System (SUS) provides an opportunity to understand epidemiologic information, treatments, discrepancies in care, and costs of men with prostate cancer (PCa) using a large real-world dataset. This analysis focuses on racial disparities and heterogeneity of specific interventions to understand evidence-based practice patterns in Brazil. Additionally, the dataset can serve as a model for other low-middle income countries (LMIC). **Methods:** Patients included in the database were those with a diagnosis of PCa receiving care in the SUS from 01/01/2008 to 08/31/2022. Data were analyzed using a proprietary Healthcare Data Science platform offered by TECHTRIALS and included information regarding stage, demographics, cancer-related information, treatment-related information, and resources utilized. **Results:** 657,609 PCa pts were diagnosed and treated at SUS during the 14.5-year study period of whom 382,263 (58%) were brown/black (non-white) and 262,820 (42%) white. Median age of the population was 72.6 years, and did not vary with race. 26.16% of the pts were diagnosed with stage IV and this was not impacted by race or localization, including state or type of city (capital or not). Rates of radical prostatectomy and radiation utilization were similar between race categories. Additionally, in patients with stage IV disease, rates of systemic therapy utilization including chemotherapy with docetaxel (7.7%), with a tendency to increase use in the last years, and androgen receptor signaling inhibitors (ARSI) with (0.6%) or enzalutamide (0.08%), were low and similar between race categories. Rates of first-generation anti-androgens and estrogens were higher (56%) The total costs of prostate cancer directed care was R\$4.31 billions (US\$820 millions) and race did not impact total cost of care and cost by procedure or therapy type options. **Conclusions:** This is one of the largest studies using public health-system databases for Prostate cancer with Real World Data ever published. Race had no impact in presenting stage, treatment received and even in the costs involved. Underutilization of chemotherapy (docetaxel) in a scenario of limiting resources and without the use of new hormonal therapies is a matter of concern, together with an overuse of agents without proven survival advantage. Our data highlights the need for increased access to life prolonging agents for patients with metastatic PCa in the SUS. Research Sponsor: None.

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Poster Session

Longitudinal transcriptome profiling of localized hormone-sensitive tumors in treatment-naïve ENACT patients with prostate cancer with and without enzalutamide (ENZA). *First Author: Ashley Ross, Northwestern University Feinberg School of Medicine, Chicago, IL*

Background: The ENACT trial (NCT02799745) randomized men with low- or intermediate-risk prostate cancer to 12 months of ENZA monotherapy followed by active surveillance (AS) for 12 months or to AS alone. Men were followed longitudinally, including by serial genome-wide expression profiling. Of 258 genomic signatures evaluated from baseline samples, increased Decipher genomic classifier score was prognostic for progression on AS; androgen receptor activity (AR-A) and PAM50 subtypes were associated with clinical benefit from ENZA, as previously reported. Here we present transcriptomic changes over time for men undergoing AS and those treated transiently with ENZA. **Methods:** Gene-expression profiling was performed via the Decipher GRID platform (Veracyte, Inc.) on 131 ENACT patient samples (ENZA, n=57; AS, n=74) collected at prespecified time points (screening, 12 months, and 24 months). Predefined GRID signatures were assessed for correlation with biological and clinical characteristics, including immune activity, treatment sensitivity, metastatic risk, and molecular subtypes. Statistical analysis was conducted by Cox proportional hazards models and logistic/linear regression; longitudinal changes were assessed by linear mixed-effects models. **Results:** Analysis of 12-month longitudinal samples showed significant transcriptomic changes in patients treated with ENZA, including markers of AR-A downregulation, decreased regulatory T-cell suppression, and increased immune activation. Many of the transcriptomic signature changes that occurred during ENZA treatment, including immune marker changes, were transient and returned to baseline values by 24 months following ENZA treatment discontinuation at 12 months. **Conclusions:** This exploratory biomarker analysis provides valuable data on transcriptomic changes in patients undergoing AS and those exposed to ENZA followed by cessation of treatment. Longitudinal analysis data provided insights into progression of early disease in the AS arm and possible strategies for extending ENZA activity beyond progression. Immune modulation with ENZA treatment may provide further insights for exploration of immunotherapy strategies. Clinical trial information: NCT02799745. Research Sponsor: This study was funded by Astellas Pharma Inc. and Pfizer Inc., the co-developers of enzalutamide, and by Veracyte, Inc.

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Poster Session

Building a predictive model for outcomes with ¹⁷⁷Lu-PSMA-617 in patients with metastatic castration-resistant prostate cancer using VISION data: Preliminary results. *First Author: Ken Hermann, Department of Nuclear Medicine, West German Cancer Center, University Hospital Essen, University of Duisburg-Essen, Essen, Germany*

Background: ¹⁷⁷Lu-PSMA-617 is approved in adults with PSMA+ metastatic castration-resistant prostate cancer (mCRPC). This analysis of VISION data sought to build predictive models for clinical outcomes after ¹⁷⁷Lu-PSMA-617. **Methods:** In VISION, adults with PSMA+ mCRPC received ¹⁷⁷Lu-PSMA-617 (7.4 GBq every 6 weeks, ≤6 cycles) plus protocol-permitted standard of care (SoC) or SoC alone. In this *post hoc* analysis, 29 baseline parameters were assessed for prognostic and predictive value on overall survival (OS), radiographic progression-free survival (rPFS) and PSA response (≥50% reduction; PSA50). Parameters associated with outcome regardless of treatment were prognostic, and those associated with outcome after treatment with ¹⁷⁷Lu-PSMA-617+SoC vs SoC were predictive. Cox proportional hazards (OS and rPFS) or logistic regression (PSA50) models were used in univariate analyses for parameter selection and to build statistical models. Here, univariate analyses are presented. Multiplicity was corrected by use of q values (α = 0.05). **Results:** Data from 831 adults were analyzed. In initial univariate analyses, 76%, 69% and 38% of parameters assessed were prognostic for OS, rPFS and PSA50, respectively; fewer were predictive of better outcomes after ¹⁷⁷Lu-PSMA-617+SoC vs SoC (subset shown). **Conclusions:** Baseline prognostic and predictive parameters were identified for OS, as well as for rPFS and PSA50, in adults with mCRPC in VISION receiving ¹⁷⁷Lu-PSMA-617+SoC or SoC alone. For clinical application, select parameters will be reassessed categorically, and multivariate predictive models will be developed using identified parameters and parameter shrinkage. Research Sponsor: Advanced Accelerator Applications, a Novartis company.

A subset of parameters in univariate analyses of outcomes in VISION.

	Prognostic for OS	Predictive for OS	Prognostic for rPFS	Predictive for rPFS	Prognostic for PSA50	Predictive for PSA50
ECOG performance status (0/1 vs 2) [†]	q < 0.05	q = 0.99	q < 0.05	q < 0.05	q = 0.97	q = 0.98
PSMA+ liver metastases (yes vs no) [†]	q < 0.05	q = 0.99	q < 0.05	q = 0.13	q < 0.05	q = 0.74
Alkaline phosphatase (U/L) [†]	q < 0.05	q = 0.83	q < 0.05	q = 0.81	q < 0.05	q < 0.05
Aspartate aminotransferase (U/L) [†]	q < 0.05	q = 0.99	q < 0.05	q < 0.05	q < 0.05	q = 0.85
⁶⁸ Ga-PSMA-11 tumor SUV _{mean} [†]	q < 0.05	q = 0.41	q < 0.05	q = 0.12	q < 0.05	q < 0.05
Lymphocyte count (cells/μL) [†]	q < 0.05	q = 0.99	q < 0.05	q = 0.38	q < 0.05	q = 0.79
Neutrophil-to-lymphocyte ratio [†]	q = 0.70	q < 0.05	q = 0.57	q < 0.05	q = 0.71	q = 0.59
Pan-immune-inflammation value [†]	q = 0.77	q < 0.05	q = 0.57	q = 0.38	q = 0.71	q = 0.79

Parameter treated as "categorical or" continuous.
For prognostic parameters, symbols denote correlation of higher/positive values with worse outcome ("−") or with better outcome ("+").
For predictive parameters, symbols denote correlation of higher/positive values with decreased ("−") or increased ("+") effect of ¹⁷⁷Lu-PSMA-617 vs SoC.

5027

Poster Session

AI-enabled analysis of H&E-stained prostate cancer tissue images: Assessing risk for metastasis prior to apalutamide (APA) treatment of patients with non-metastatic castration-resistant prostate cancer (nmCRPC). *First Author: Pooya Mobadersany, Janssen Research & Development, Cambridge, MA*

Background: Most prostate cancer patients (pts) treated with androgen deprivation therapy (ADT) for progressive disease will experience progression to CRPC. APA has been approved for the treatment of nmCRPC and metastatic castration sensitive prostate cancer (mCSPC). AI-enabled tools developed to predict oncological outcomes from digitized whole-slide images (WSIs) of H&E-stained tissues are a practical alternative to costly genomic testing tools that require sufficient tumor material. PathomIQ has developed the AI-enabled prognostic test PRAD-DX that predicts risk of metastasis from WSIs of H&E-stained core biopsies or radical prostatectomy specimens. It has been validated as a research tool on more than 2000 tissue samples across multiple institutions. The objective of this study is to evaluate PRAD-DX on predicting risk of metastatic progression using archived primary tumor samples from a randomized, double-blind, phase 3 trial in nmCRPC pts [1]. **Methods:** WSIs were collected from 471 pts (APA+ADT (n=315); placebo+ADT (n=156)), de-identified and anonymized prior to the AI analysis. Patient outcomes were blinded to the PathomIQ team. 35 pts were excluded due to lack of tumor or poor image quality; PRAD-DX scores were generated for 436 (93%) pts. The PRAD-DX test generated a risk score for each patient between 0 and 1, with higher values representing increased risk of metastasis. A pre-determined cut-off of 0.55 was previously developed to provide the best predictive accuracy and stratification with respect to time-to-metastasis on multiple clinical cohorts and was applied to this dataset. Kaplan-Meier analysis was performed on Metastasis-free-survival (MFS). **Results:** All pts receiving APA+ADT had improved outcomes compared with pts receiving ADT alone, independent of PRAD-DX risk score category. 53% of pts had high PRAD-DX scores and significantly benefited from treatment with APA+ADT compared to placebo+ADT with regard to MFS (hazard ratio, 0.19; 95% CI, 0.1 – 0.37; P<0.005). 47% were assigned low PRAD-DX risk; also in this cohort, treatment with APA+ADT resulted in a significantly improved MFS (hazard ratio, 0.39; 95% CI, 0.17 – 0.86; P=0.02). **Conclusions:** These results indicate that PRAD-DX score derived from AI-powered image analysis could be used as a biomarker to identify pts at highest risk of metastatic progression in the nmCRPC setting. Although, there are limitations related to sample size, this may have significant impact in identifying pts for informed clinical trial patient selection based on their individual risk profile for development of novel therapies. 1) Smith MR, Saad F, Chowdhury S, et al. *N Engl J Med.* 2018;378(15):1408-1418. doi:10.1056/NEJ-Moa1715546. Research Sponsor: Janssen R&D.

5029

Poster Session

The performance of prostate specific antigen (PSA) testing in the population based NPCC cohort. *First Author: Jan Oldenburg, Department of Oncology, Akershus University Hospital (Ahus), Lørenskog, Norway*

Background: Prostate cancer (PCa) screening using prostate-specific antigen (PSA) is controversial. Benign prostate hyperplasia increases PSA in aging men independent of PCa such that PSA's test performance differs between younger and older men. Age-specific cut-off values might therefore be advisable. The large Norwegian Prostate Cancer Consortium (NPCC) database might be able to contribute with clinically relevant information on age-specific PSA cut-off values. **Methods:** The Norwegian Prostate Cancer Consortium (NPCC) collected 8 857 761 PSA tests from 1.291.151 men. Results were linked with the date of diagnosis and grade of PCa. Analyses were restricted to men aged 45-75 years. PSA results were grouped into two groups: PCa negative vs PCa positive. The PCa negative group comprised PSA measurements from 2005 to 2015 men being alive and without PCa diagnosis five years after PSA measurement, in total 1 775 986 PSA measurements from 533 216 men. The PCa positive group comprised PSA measurements from 2005 to 2020 of men diagnosed with PCa during this period. PCa diagnoses at autopsy, as incidental finding at cystectomy, with metastases or with PSA > 50 ng/ml were excluded, in total 242 874 PSA measurements from 48 659 men with PCa. Sensitivity, specificity, area under the curve (AUC) as well as top decile and proportion of PCa in the top decile were calculated. **Results:** For men of 50 years of age, PSA at a threshold of 3 ng/ml yielded a sensitivity and specificity of ~ 95%. In 70-74-year-old men, a 3 ng/ml PSA threshold resulted in a 95% sensitivity but declining specificity of 70%. Maintaining specificity requires increasing PSA cut-off values to 4.5, 6, 7 and 8 ng/ml for men aged 55-59, 60-64, 65-69 and 70-74 years, respectively. The increasing cut-off values for the top PSA decile as well as the decreasing proportion of PCa within the top decile are in line with a declining AUC in older men. **Conclusions:** PSA test performance declines with increasing age. PCa screening in well-informed men should take into account age adjusted PSA cut-off values. Research Sponsor: None.

Age, years	# Prostate Cancer negative	# Prostate Cancer positive	Sensitivity (95%) PSA, ng/ml	Specificity (95%) PSA, ng/ml	AUC	Top Decile PSA, ng/ml	Percent of Cancers in the Top Decile
45-49	65,870	743	2.07	2.40	0.970	>1.80	98%
50-54	98,385	2 476	2.60	3.30	0.962	>2.35	98%
55-59	106,115	6 536	3.11	4.55	0.951	>3.21	96%
60-64	107,346	11 620	3.26	5.96	0.931	>4.20	94%
65-69	95,969	15 159	3.03	7.00	0.907	>5.05	89%
70-74	59,531	17 776	2.30	7.90	0.867	>5.77	77%

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Poster Session

Predicting absolute benefit in risk of metastasis of androgen deprivation therapy added to radiation therapy in patients with newly diagnosed prostate cancer using Prolaris. *First Author: Jonathan David Tward, Hunstman Cancer Institute at the University of Utah, Salt Lake City, UT*

Background: Most patients would defer using androgen deprivation therapy (ADT) with radiation therapy (RT) when the number-needed-to-treat (NNT) exceeds 25 persons to prevent 1 from developing metastasis, corresponding to an absolute benefit of 4%.¹ However, no tools for estimating personalized NNT or absolute benefit from ADT exist. We aimed to quantify personalized absolute benefit and NNT for persons receiving ADT added to single modality RT. **Methods:** The clinical cell-cycle risk (CCR) score combines the University of California, San Francisco's Cancer of the Prostate Risk Assessment and the cell cycle progression molecular score to accurately assess prostate cancer aggressiveness. The effect of ADT added to RT was modeled using a 10-year risk of metastasis as a function of continuous CCR score for patients treated with RT alone. The relative benefit of ADT added to RT to reduce distant metastasis was modeled using published data from The Meta-Analysis of Randomized trials in Cancer of the Prostate (MARCAP) which utilized several prospectively randomized RT±ADT trials.² The average absolute benefit was calculated for patients with CCR scores above and below a prespecified multimodality treatment threshold (MTT) using the distribution of scores in a cohort of patients commercially tested by Myriad Genetics. **Results:** The commercially tested cohort consisted of 56,485 patients spanning all National Comprehensive Cancer Network risk categories (33.7% very low/low risk, 29.8% favorable intermediate risk, 25.6% unfavorable intermediate risk, 11.0% high/very high risk), with 87.2% having CCR scores at or below the MTT and 12.7% with CCR scores above the threshold. The average absolute benefit of ADT treatment was 0.86% (NNT=116) for patients with CCR scores below the MTT and 8.2% (NNT=12) for patients with CCR scores above the MTT. Patients with CCR scores at precisely the MTT had a predicted absolute benefit of 3.7% (NNT=27). **Conclusions:** The Prolaris test can accurately predict an individual's benefit of adding ADT to RT, and the risk threshold is consistent with patient attitudes about when to use or omit ADT. 1. Spratt DE, Tward JD: JROBP 108:899-902, 2020. 2. Kishan AU, Sun Y, Hartman H, et al. Lancet Oncol 23:304-316, 2022. Research Sponsor: Myriad Genetics.

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Poster Session

Sequential metastasis-directed therapy (MDT) for oligometastatic prostate cancer (Oligo PCa) assessed by PET-based imaging. *First Author: Alberto Carretero-González, Medical Oncology Department, Hospital Universitario 12 de Octubre, Madrid, Spain*

Background: Prostate specific membrane antigen (PSMA) and F-18-Fluciclovine PET imaging have high sensitivity for the detection of prostate cancer (PCa) metastases. MDT with stereotactic body radiation therapy (SBRT) to PET-detected Oligo PCa has been shown to improve progression free survival (PFS) and delay androgen deprivation therapy (ADT). However, in those patients (pts) who ultimately develop oligoprogressive disease following MDT, the utility of subsequent courses of MDT has not been well defined. **Methods:** A single institution retrospective review was undertaken to describe outcomes following ≥2 courses of PET-guided SBRT in pts with Oligo PCa. Pts included in this analysis had undergone initial SBRT for ≤5 PCa lesions detected on PSMA or Fluciclovine PET, and subsequently underwent ≥1 additional course of SBRT at progression. Baseline data collected included stage, PSA level, Gleason Score, tracer type, and concurrent systemic therapy. Endpoints collected for each SBRT course included PSA decline ≥50% (PSA50), PFS, and systemic therapy change free survival (RxFs) (initiation of ADT, or for pts already on ADT, addition of an androgen signaling inhibitor). Association of factors with PFS after SBRT2 were analyzed using multivariable Cox proportional-hazards models. **Results:** 34 pts underwent ≥2 courses of MDT (SBRT1, SBRT2). At SBRT2, progression was identified by PSMA-PET in 26 (77%) pts, and by Fluciclovine-PET in 8 (23%). With SBRT2, 18 (53%) had a concurrent systemic therapy change; 10 (29%) did not receive any systemic therapy. 12 pts subsequently underwent SBRT3. Progression was detected by PSMA PET in 9 (75%) and Fluciclovine PET in 3 (25%). Clinical outcomes are summarized in the table. In the multivariable analysis, predictors associated with PFS following SBRT2 were 1) PSA decline at SBRT1 (HR 1.10, 95% CI 1.05-1.16, P<0.001) and 2) PSA doubling time (PSADT) <12 months at the time of SBRT2 (HR 11.52, 95% CI 1.36-97.38, P=0.025). Overall, from SBRT1 to last follow-up (median 25.2 months), 23 (68%) pts remained ADT-free (14 after SBRT2; 9 after SBRT3). **Conclusions:** Serial MDT for Oligo PCa detected on PSMA or Fluciclovine PET is feasible and results in PSA declines, independent of change in systemic therapy. There is a persistent but diminishing benefit of MDT over successive courses. Overall, 2/3 of pts were able to postpone the use of ADT. PSA decline at SBRT1 and PSADT at SBRT2 may be biomarkers for SBRT2 benefit. Despite the retrospective nature of this study and cohort heterogeneity, these data provide a rationale for serial SBRT in Oligo PCa, and the need for larger, prospective studies of this strategy. Research Sponsor: None.

	% patients with CRPC at SBRT	PSA50	PFS	RxFs
SBRT1	21%	28/34 (82%)	19.9 mo	40.9 mo
SBRT2 (n = 34)	35%	22/34 (65%)	10.1 mo	9.2 mo
SBRT3 (n = 12)	42%	8/12 (67%)	6.3 mo	8.9 mo

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Poster Session

Prevalence of mismatch repair deficiency in a large prospective prostate cancer cohort. *First Author: Ciara S. McNevin, St James Hospital, Dublin 8, Ireland*

Background: Mismatch repair (MMR) deficiency and microsatellite instability (MSI) are predictive biomarkers for immunotherapy response. The best approach to identify patients with such tumors is unclear in prostate cancer. **Methods:** This study included men diagnosed with primary prostate cancer during prospective follow-up of the Health Professionals Follow-up Study (HPFS) and Physicians' Health Study (PHS). The highest-grade/index lesions of tumor tissue from radical prostatectomy (95%) or transurethral resections of the prostate were mounted in triplicate on tissue microarrays. Immunohistochemistry for the MMR proteins MLH1, MSH2, MSH6, and PMS2 was performed, with scoring as MMR-deficient requiring a visible staining in a non-tumor internal positive control of the same case. For validation, a polymerase chain reaction-based MSI assay (Idylla MSI Test, Biocartis) was performed on tumor DNA of MMR-deficient cases and a selection of MMR-intact cases. **Results:** The study included 1016 men with prostate cancer. Tumor stage was predominantly pathologically localized (71% stage pT1/2, 18% T3a/b) with a full distribution of Gleason scores, including 20% Gleason score 6 (grade group 1), 36% 3+4 (grade group 2), 23% 4+3 (grade group 3), 8% 8 (grade group 4) and 13% 9-10 (grade group 5). MMR tumor scoring could be performed for MLH1 in 747 cases (75% of those with tumor tissue), for MSH2 in 903 cases (90%), for MSH6 in 708 cases (74%), and for PMS2 in 703 cases (72%). The remaining tumors were unevaluable due to lack of non-tumor tissue necessary as an internal positive control. Of the 903 tumors evaluable for MSH2 protein loss, 4 tumors had loss of MSH2 (prevalence 0.4%, 95% confidence interval [CI] 0.2-1.1%), and 3 of 708 evaluable tumors had concomitant loss of MSH6 (prevalence 0.4%, 95% CI 0.1-1.2%). No tumor had loss of MLH1 or PMS2. The MMR-deficient tumors had Gleason scores of 3+4, 8 (two cases), and 9-10. Tumor DNA of 1 of the 4 MMR-deficient tumors met the manufacturer's cut-off for MSI-high; two additional MMR-deficient cases had non-zero repeats, with good reproducibility between tumor cores and technical replicates. One MSH2-deficient tumor and 6 DNA samples from 3 MMR-intact cases had repeat scores of zero. **Conclusions:** In this nationwide prospective study, MMR deficiency was rare in primary, surgically treated prostate cancer. This low prevalence contrasts with hospital-based studies of MMR deficiency and MSI that may have represented tumors with certain clinical features. The low prevalence and the need for an internal positive control for reliable scoring calls into question to what extent immunohistochemistry-based screening for MMR deficiency on limited tissue specimens, such as prostate biopsies, is routinely feasible. Research Sponsor: U.S. National Institutes of Health.

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Poster Session

Prevalence of intra-patient inter-metastatic heterogeneity in mCRPC patients based on triple-tracer PET imaging: The 3TMPO study. *First Author: Frederic Pouliot, Laval University and CHU De Quebec, Quebec, QC, Canada*

Background: Intra-patient inter-metastatic heterogeneity (IIH) has been demonstrated in metastatic castration resistant prostate cancer (mCRPC) patients based on genomic and imaging studies, most often after several lines of therapies. IIH is of utmost importance for PSMA radioligand therapy (RLT) eligibility, biopsy-based precision medicine and/or treatment intensification decision-making. The Triple-Tracer strategy against Metastatic Prostate cancer (3TMPO) study (NCT04000776) is a prospective multicenter PET imaging study that was designed to determine the prevalence of IIH in mCRPC patients and to determine candidacy for RLT. **Methods:** 3TMPO is a PET-imaging trial including mCRPC patients showing at least 3 metastases on conventional imaging with evidence of biochemical or radiographic progression, at least 3 months after initiation of the last systemic therapy. ⁶⁸Ga-PSMA-617 and ¹⁸F-FDG PET/CT scans were performed within 10 days and analyzed quantitatively. A third scan with ⁶⁸Ga-Octreotate was done when a PSMA-/FDG+ lesion was found. For all tracers, positivity of a lesion was defined as its SUV_{peak} being 1.5 times higher than the SUV_{mean} of the liver. Lesions smaller than 1 cc and likely benign foci of uptake were excluded. IIH prevalence was the primary outcome, defined as the percentage of patients having at least two lesions with discordant features on PET imaging. **Results:** We included 98 patients in the final analysis. Patients had a mean age of 69 years and a median PSA of 51.1 ng/mL. Number of metastases were <5 in 46.9% and ≥10 in 33.7% of patients and 10.2, 20.4, 18.4 and 51.0% had received 0, 1, 2 or >2 lines of systemic therapies for mCRPC, respectively. Prevalence of IIH was 83.7% based on pre-specified PET criteria. Overall, seven different combinations of lesion phenotypes were found among patients based on FDG and PSMA PETs, and at least one PSMA-/FDG+ lesion was found in 46 patients (46.9%). Of the 44 patients who underwent Octreotate PET, six (13.6%) had at least one Octreotate-positive lesion. In this FDG/PSMA/Octreotate-imaged subgroup, 11 different combinations of phenotypes were observed between metastases of individual patients. Overall, 52.0% (IC95: 41.7-62.2) of patients were found to be candidate for PSMA RLT, but none for Octreotate RLT. **Conclusions:** The majority of mCRPC patients showed IIH. Based on a multi-tracer approach, up to 11 lesion phenotype combinations were found amongst patients. Correlation of these imaging phenotypes with genomics and treatment response will be highly relevant for optimized precision medicine, especially with respect to PSMA-RLT. Clinical trial information: NCT04000776. Research Sponsor: Fonds de recherche du Québec - Santé, ONCOPOL (co-funding); Merck; Cancer Research Society.

Imaging phenotypes based on FDG and PSMA tracer PET/CT in mCRPC patients.					
Phenotype	Prevalence N(%)	FDG-/PSMA-	FDG+/PSMA-	FDG-/PSMA+	FDG+/PSMA+
1	1 (1.0)	Only			
2	6 (6.1)		Only		
3	5 (5.1)			Only	
4	4 (4.1)				Only
5	19 (19.4)		Yes		Yes
6	42 (42.9)			Yes	Yes
7	21 (21.4)		Yes	Yes	Yes

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Poster Session

Genetic ancestry associations with somatic mutations in a real-world cohort of over 3,000 patients with prostate cancer. *First Author: Francisco M De La Vega, Tempus Labs, Inc., Chicago, IL*

Background: Disparities in incidence and outcomes of prostate cancer among racial groups have been reported. Black men have a higher incidence of prostate cancer compared to White men and are more likely to be diagnosed at a later stage, resulting in poorer outcomes. These differences are likely due to a combination of genetic, socio-economic, and healthcare access factors. Furthermore, evidence has revealed racial differences in molecular profiles of prostate cancer, such as a higher incidence of *ERF* mutations and increased transcriptional activation of the androgen receptor signaling and inflammatory pathways in tumors derived from Black men compared to White men, suggesting that underlying biology may contribute to these disparities. Here, we aimed to identify differences in the mutational profiles of prostate cancers by race and genetic ancestry in a de-identified real-world cohort of 3,804 patients that underwent the Tempus xT 648-gene NGS tumor profiling test. **Methods:** We used 654 ancestry-informative markers to estimate continental ancestry likelihoods for five regions: Africa (AFR), Americas (AMR), East Asia (EAS), Europe (EUR), and South Asia (SAS). We imputed Asian (ASN, n=122), Hispanic/Latino/Native American (HLN, n=300), Non-Hispanic Black (NHB, n=619) and Non-Hispanic White (NHW, n=2,679) categories using genetic ancestry thresholds based on literature and validated with available metadata. Associations between either race/ethnicity categories or continental ancestry proportions and somatic variants (copy number alterations (CNAs), small nonsynonymous, OncoKB L1/2 & R1, and predicted driver somatic mutations) were assessed for 109 prostate cancer-related genes using logistic regression models. Likelihood ratio tests were used to compare models with and without race/ethnicity or ancestry terms, and the Benjamini-Hochberg method was used to adjust p-values and control the FDR at 5%. **Results:** NHB and ASN men had lower odds of having a *PTEN* CNA compared to NHW men (OR=0.58 and 0.40, p=0.0001 and 0.009, respectively). Confirming this finding was a positive association between EUR ancestry and *PTEN* CNAs (OR=1.07 per doubling of EUR ancestry proportion, p=0.0007). NHB men were also less likely to have actionable OncoKB somatic mutations in the *PIK3CA* gene when compared to NHW men (OR=0.48, p=0.03). Increased AFR ancestry was associated with the presence of nonsynonymous predicted driver mutations in *SPOP* (OR=1.04, p=0.04), while both EAS and SAS ancestries were associated with fewer such mutations in *TP53* (OR=0.95 in both cases, p=0.02 and 0.003). **Conclusions:** Analysis of a large real-world cohort leveraging genetic ancestry inferred from NGS data confirms previously known associations between the presence of somatic alterations in prostate cancer genes and race/ethnicity, and identifies novel associations of potential precision therapeutic relevance. Research Sponsor: None.

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Poster Session

HERCULES: A prostate cancer (PC) sequencing panel for parallel analysis of circulating tumor DNA (ctDNA) and circulating tumor cells (CTCs). *First Author: Daniel Bsteh, Division of Medical Oncology, Department of Medicine, Keck School of Medicine and Norris Comprehensive Cancer Center, University of Southern California, Los Angeles, CA*

Background: In metastatic PC, tracking genomic alterations over time and with treatment can predict disease outcomes, guide treatment, and identify novel therapeutic targets. Analysis of peripheral blood ctDNA offers a non-invasive liquid biopsy for genomic profiling, but ctDNA often comprises a small portion of total cell-free DNA (cfDNA) in the blood, requiring high depth of sequencing which may still miss PC-relevant variants. We and others have shown that single CTCs captured from the same blood sample yield additional PC-relevant genomic data when combined with ctDNA profiling, but currently there is no assay that can be applied uniformly to both analytes. Here, we present a new amplicon-based sequencing panel capable of detecting PC-relevant variants in both cfDNA and single CTCs. **Methods:** PC-relevant genes were curated by overlapping reviews of cBioPortal for cancer genomics, the catalogue of somatic mutations in cancer (COSMIC), and PC-relevant genomic literature. HERCULES targets 36 genes with 258 amplicons covering PC-associated mutations and copy number variations. AmpliSeq HD targeted sequencing technology was applied for analysis of both cfDNA and CTCs. Analytical validation was performed sequentially, first using AcroMatrix and Seracare DNA control samples, then single and pooled LNCap and PC3 PC cells and cfDNA, then 8 patient peripheral blood samples of matched plasma cfDNA and single CTCs captured using the RareCyt platform from participants in SWOG S1802, an ongoing CTEP/CIRB-approved phase 3 trial for men with metastatic PC. **Results:** In DNA control samples with allele frequencies of 1%, 0.25%, and 0.1%, HERCULES displayed sensitivity of 100%, 75%, and 50%, respectively. In matched single cells and cfDNA from cell lines, HERCULES detected 100% of database-annotated somatic variants in cfDNA and in pools of 2 or more cells, and it identified >90% of variants in single cells. In 16 matched patient samples of cfDNA and single CTCs, with read coverage depths of >50,000x for 20ng cfDNA and >1,500x for single CTCs, HERCULES detected shared variants (mean N per sample = 6.1) as well as unique somatic variants (mean of 1.1 CTC variants not called in the cfDNA, and 4.1 cfDNA variants not called in the CTCs). **Conclusions:** HERCULES is, to our knowledge, the first PC-specific targeted sequencing panel capable of parallel genomic profiling of both ctDNA and CTCs. In our preliminary analytical validation, it detected somatic variants with high sensitivity in matched cfDNA and CTC samples. With additional validation, HERCULES has the potential to augment conventional ctDNA profiling by illuminating both cell-free and cellular genomic evolution during PC treatment and progression. Research Sponsor: U.S. National Institutes of Health; Hope Foundation; Thermo Fisher Scientific.

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Poster Session

Digital histopathology-based multimodal artificial intelligence scores predict risk of progression in a randomized phase III trial in patients with nonmetastatic castration-resistant prostate cancer. *First Author: Felix Y Feng, Helen Diller Family Comprehensive Cancer Center, San Francisco, CA*

Background: The addition of apalutamide (APA) to androgen deprivation therapy (ADT) improved metastasis-free survival (MFS) and second progression-free survival (PFS2) among patients (pts) with nonmetastatic castration-resistant prostate cancer (nmCRPC) [1]. We applied a previously-reported digital histopathology-based multimodal AI (MMAI) algorithm developed based on 5 phase III randomized trials, validated, and accepted to NCCN guidelines for localized prostate cancer, to evaluate whether MMAI could define risk of progression among nmCRPC pts treated with APA or placebo in the SPARTAN trial. **Methods:** Pts enrolled in the SPARTAN trial with available H&E-stained biopsy slides from their primary diagnosis were included. H&E slides were digitized. Baseline clinical parameters to generate MMAI scores were Gleason score, age, T stage, and PSA. MMAI scores for distant metastasis (DM) were generated, ranging from 0 to 1. Pts were further categorized into MMAI non-high-risk and high-risk groups using a previously established score cutoff. Kaplan Meier estimates were calculated for PFS2 and MFS; comparisons were performed using log-rank test and Cox proportional-hazards regression for treatment arms and MMAI risk groups. Two-way ANOVA was used to evaluate the interaction between treatment arms and risk groups. **Results:** The study included 471 pts with 1051 biopsy pathology slides: 311 pts treated with APA, and 156 with placebo. 55 pts were excluded due to missing treatment (n=4) or clinical data (n=49) and inadequate H&E images (n=2), resulting in 273 evaluable APA-treated and 147 placebo-treated pts. 63% of pts were MMAI high risk and 37% MMAI non-high risk. MMAI high risk pts demonstrated significant improvement in MFS with APA (HR 0.19 (95% CI: 0.12-0.29, p<0.005)), but not in PFS2 (HR 0.76 (95% CI: 0.45-1.28, p=0.30)). There was a significant interaction between MMAI risk group and treatment for MFS (p=0.02). Among the placebo-treated cohort, MMAI high risk status was associated with shorter MFS (HR 2.98 (95% CI: 1.72-5.18, p<0.005)) and PFS2 (HR 1.83 (95% CI: 1.09-3.09, p=0.02)). For APA-treated pts, MMAI risk group was not associated with MFS and PFS2. **Conclusions:** These findings suggest that MMAI may provide prognostic risk stratification for nmCRPC pts and that MMAI high-risk pts may benefit most from treatment with APA. The current results represent the first evaluation of this MMAI classifier in the nmCRPC setting. Prospective validation is warranted. [1] Smith MR, Saad F, Chowdhury S, et al.; SPARTAN Investigators. Apalutamide treatment and metastasis-free survival in prostate cancer. *N Engl J Med.* 2018;378(15):1408-1418. Clinical trial information: NCT01946204. Research Sponsor: Janssen.

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Poster Session

Association of plant-based diet index with quality of life in patients with prostate cancer. *First Author: Stacy Loeb, New York University and Manhattan Veterans Affairs, New York, NY*

Background: Plant-based diets have many health benefits including a lower risk of fatal prostate cancer. Less is known about the relationship between diet and functional outcomes among prostate cancer survivors. We hypothesized that greater consumption of plant-based food after prostate cancer diagnosis is associated with improved quality of life (QOL). **Methods:** This prospective cohort study included 3,505 participants in the Health Professionals Follow-up Study with non-metastatic prostate cancer (1986-2016). Overall and healthful Plant-based Diet Indices were calculated from food frequency questionnaires with cumulative updating. QOL scores were calculated using the Expanded Prostate Cancer Index Composite. Generalized estimating equations were used to examine associations between Plant-based Diet Indices and 5 QOL domains, adjusted for clinical and demographic factors. **Results:** Higher Plant-Based Diet Index was associated with improved scores for sexual function, urinary irritation/obstruction, and urinary incontinence among men with prostate cancer. Consuming more healthful plant-based foods was also associated with better scores for bowel function and hormonal/vitality in the age-adjusted models. Results were similar in sensitivity analyses excluding patients with pre-existing erectile dysfunction or lower urinary tract symptoms, and adjusting for use of sexual or urinary medications. A limitation is that no participants followed a strict vegan diet. **Conclusions:** This prospective study suggests that greater consumption of healthful plant-based foods is associated with modest improvements in QOL domains among patients with prostate cancer. Research Sponsor: New York State Department of Health; NYU Perlmutter Cancer Center.

Generalized estimating equation models for 5 quality of life domains, including mean differences between dietary index highest (Q5) and lowest quintile (Q1), and p-trend across quintiles.

	Plant Diet Index Diff Q5-Q1 (95% CI), p-trend	Healthful Plant-Diet Index Diff Q5-Q1 (95% CI), p-trend
Sexual		
Model 1	-0.76 (-1.08, -0.44), p<0.0001	-0.78 (-1.09, -0.46), p<0.0001
Model 2	-0.36 (-0.73, 0.00), p=0.02	-0.60 (-0.94, -0.26), p<0.0001
Urinary Irritation/Obstruction		
Model 1	-0.07 (-0.25, 0.10), p=0.17	-0.17 (-0.35, 0.02), p=0.07
Model 2	-0.21 (-0.41, -0.01), p=0.01	0.01 (-0.20, 0.21), p=0.82
Urinary Incontinence		
Model 1	-0.15 (-0.40, 0.09), p=0.13	-0.41 (-0.66, -0.15), p<0.0001
Model 2	-0.26 (-0.54, 0.02), p=0.03	-0.20 (-0.48, 0.07), p=0.2
Bowel		
Model 1	0.0 (-0.19, 0.20), p=0.56	-0.41 (-0.60, -0.22), p<0.0001
Model 2	-0.12 (-0.36, 0.11), p=0.54	-0.20 (-0.41, 0.00), p=0.1
Hormonal/Vitality		
Model 1	-0.13 (-0.29, 0.03), p=0.08	-0.29 (-0.45, -0.13), p<0.0001
Model 2	-0.13 (-0.32, 0.06), p=0.12	-0.08 (-0.25, -0.10), p=0.46

Model 1 is adjusted for age and time. Model 2 is also adjusted for PSA, grade, stage, body mass index, physical activity, calories, smoking, alcohol, diabetes, heart disease, stroke and hypertension.

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Poster Session

The impact of household income on prostate cancer diagnosis, treatment, and outcomes. *First Author: John Panzone, SUNY Upstate Medical University, Syracuse, NY*

Background: Financial difficulties can lead to cancer patients delaying or deferring necessary care, resulting in later presentation with more advanced disease and worse clinical outcomes. **Methods:** A cross-sectional study was conducted assessing 488,853 prostate cancer patients from the Surveillance, Epidemiology, and End Results (SEER) Program between the years of 2010 and 2018. The association between annual household income (HHI) and diagnosis and outcomes of prostate cancer were examined using ANOVA and Chi-square analyses comparing clinical measures based on categorical HHI groupings. **Results:** Sociodemographic data and univariate analyses are displayed. The average age across all HHI classifications was 66.63 years. ANOVA analysis demonstrated that patients with a lower HHI had higher PSA levels upon diagnosis (12.10 vs. 10.90, 10.61, and 10.37 for $\leq 35k$, 35-55k, 55-75k, and $\geq 75k$, respectively, $p < 0.001$). Patients with lower HHI also demonstrated lower rates of undergoing surgical treatment (31.9%, 36.9%, 37.6%, and 35.1% for $\leq 35k$, 35-55k, 55-75k, and $\geq 75k$, respectively, $p < 0.001$) and the highest rate of disease metastasis to bone upon diagnosis (6.3%, 5.6%, 5.7%, and 5.8% for $\leq 35k$, 35-55k, 55-75k, and $\geq 75k$, respectively, $p < 0.001$). Lastly, patients with lower HHI demonstrated progressively higher rates of cancer-specific mortality (8.4%, 6.8%, 6.5% and 5.1% for $\leq 35k$, 35-55k, 55-75k, and $\geq 75k$, respectively, $p < 0.001$), as well as higher overall mortality (21.2%, 18.0%, 15.0%, and 11.9% for $\leq 35k$, 35-55k, 55-75k, and $\geq 75k$, respectively, $p < 0.001$). **Conclusions:** In conclusion, these data suggest that prostate cancer patients with lower household income are diagnosed with more aggressive disease, tend to undergo surgery at lower rates, develop more advanced disease, and endure worse clinical outcomes than those in higher income brackets. Healthcare providers should be made aware of the clear associations between lower income and more aggressive disease at diagnosis, lower rates of surgical treatment and worse cancer-specific and overall mortality. Research Sponsor: None.

Sociodemographic data and univariate analyses stratified by household income.

	Household income (dollars)				p-value
	<35,000 (n=7,577)	35,000-55,000 (n=112,951)	55,000-75,000 (n=219,382)	75,000+ (n=148,943)	
Mean age (years)	66.72	66.65	66.58	66.67	$p = 0.10$
Cancer specific mortality (n, %)	638 (8.4%)	7,690 (6.8%)	14,253 (6.5%)	7,574 (5.1%)	$p < 0.001$
Overall mortality (n, %)	1,605 (21.2%)	20,311 (18.0%)	33,003 (15.0%)	17,790 (11.9%)	$p < 0.001$
Received Surgical treatment (n, %)	2,416 (31.9%)	41,725 (36.9%)	82,459 (37.6%)	52,348 (35.1%)	$p < 0.001$
Bone metastasis on diagnosis (n, %)	476 (6.3%)	6,345 (5.6%)	12,515 (5.7%)	8,612 (5.8%)	$p < 0.001$

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Poster Session

A single-arm, phase II study of durvalumab (D) and tremelimumab (T) for relapsed/refractory germ cell tumors (GCT). *First Author: Samuel A Funt, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Patients (pts) with GCT and progressive disease (PD) after salvage high-dose chemotherapy (HDCT) have dismal outcomes with median progression free survival (PFS) and overall survival (OS) of 1.0 and 4.7 months (mo), respectively (Feldman et al. Cancer 2012). Immune checkpoint blockade (ICB) has resulted in durable benefit in multiple tumor types. We tested D (anti-PD-L1) + T (anti-CTLA-4) for pts with relapsed/refractory GCTs in a phase II trial (NCT03158064). **Methods:** Eligible pts were ≥ 18 years old with GCT of any primary site who had PD after first-line chemotherapy and HDCT or were not candidates for HDCT or other curative options. Pts received D (1500 mg) and T (75 mg) every 4 weeks (wks) for 4 cycles followed by D (1500 mg) every 4 wks for up to 1 year (schedule 1). The study was later amended to one cycle of D (1500 mg) and T (300 mg) followed by D (1500 mg) every 4 wks for up to 1 year (schedule 2). The primary endpoint was initially overall response rate (ORR) in a Simon's two-stage design with null and alternate rates of 5% and 20%, respectively. The study was then amended to use a primary endpoint of 16-wk PFS in a new Simon's two-stage design with null and alternate rates of 5% and 25%. The regimen would be considered promising if 16-wk PFS was achieved in ≥ 3 of 20 pts. Secondary endpoints included PFS, OS, safety, and association of PD-L1 staining with outcome. **Results:** Between July 2017 and Jan 2022, 29 pts were treated, the last 7 (24%) on schedule 2. Median age was 37 (range, 21-70). Histology was non-seminoma in 25 pts (86%), and primary sites were testis in 20 (69%), mediastinum in 7 (24%), ovary in 1 (3%), and unknown in 1 (3%). Six (21%) pts had late relapse and 21 (72%) received prior HDCT. Median AFP was 310 ng/mL (range, 1-18,087) and HCG 471 mIU/mL (range, 3.3-62,302). Ten pts were treated with the ORR primary endpoint with no responses in stage 1, but 2 pts had tumor reductions of 20% and 22% with PFS of 9.9 and 10.4 mo, respectively, and 1 patient with elevated AFP but no RECIST measurable disease had a PFS of 5.7 mo. Of 19 pts treated with the 16-wk PFS primary endpoint, one had an ongoing partial response (59% tumor reduction) with 33 months follow-up; all others had PD in < 16 wks (17 with PD and 1 with stable disease). Thus, the study did not meet its primary endpoint. Among 29 treated pts, the 16-wk PFS was 13.8% (range, 4.3-28.6), and median PFS and OS were 1.4 (95% CI: 4.1, 7.1) and 7.3 mo (95% CI: 3.2, 10.9), respectively. PD-L1 expression data was available for 20/29 pts - 3/13 (23%) with low/negative and 1/7 (14%) with high expression achieved PFS > 16 wks. Six (21%) pts had grade 3-4 treatment-related adverse events, 3 (10%) of whom required high-dose steroids. **Conclusions:** D+T had limited antitumor activity in pts with relapsed/refractory GCT, failing to meet protocol-defined success. However, some pts did appear to benefit, including one exceptional responder. Additional correlative studies are ongoing. Clinical trial information: NCT03158064. Research Sponsor: AstraZeneca.

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Poster Session

^{64}Cu -SAR-bisPSMA (PROPELLER) positron emission tomography (PET) imaging in patients with confirmed prostate cancer. *First Author: Eva Lengyelova, Clarity Pharmaceuticals, Eveleigh, NSW, Australia*

Background: Prostate cancer (PC) is the second most frequent malignancy in men globally. Prostate-specific membrane antigen (PSMA) is a type II transmembrane glycoprotein that is overexpressed in PC. Recently, several new ^{68}Ga - and ^{18}F -based PSMA-targeted PET agents have been approved by the FDA to detect PC, which offer improved sensitivity and specificity compared to traditional imaging. **Methods:** PROPELLER (NCT04839367) investigated ^{64}Cu -SAR-bisPSMA in 30 men with untreated, histopathologically proven, primary PC with intermediate- to high-risk features. At screening, patients completed ^{68}Ga -PSMA-11 PET/CT at 1h post dose. Following enrollment, patients received either 100MBq, 150MBq or 200MBq of ^{64}Cu -SAR-bisPSMA, followed by PET/CT at 2-4h post dose. Safety was evaluated before and after ^{64}Cu -SAR-bisPSMA dosing. The ^{68}Ga -PSMA-11 and ^{64}Cu -SAR-bisPSMA PET/CT scans were evaluated by 2 independent, blinded central readers for image quality, PC detection, and intensity of tracer uptake in lesions (SUVmax and Tumor-to-Background Ratio [TBR]). **Results:** A single, Grade 1 ^{64}Cu -SAR-bisPSMA-related AE was reported in the 200MBq cohort. Both readers scored 200MBq of ^{64}Cu -SAR-bisPSMA as the dose providing the highest image quality. In this cohort, ^{64}Cu -SAR-bisPSMA and ^{68}Ga -PSMA-11 was able to detect primary PC in 100% and 77.8% of patients for Reader 1 and 85.7% and 83.3% of patients for Reader 2, respectively. In the 200MBq cohort, Reader 1 identified 41 lesions with ^{64}Cu -SAR-bisPSMA vs 36 lesions with ^{68}Ga -PSMA-11, while Reader 2 identified 31 lesions with ^{64}Cu -SAR-bisPSMA vs 22 lesions with ^{68}Ga -PSMA-11. In the 200MBq cohort, ^{64}Cu -SAR-bisPSMA consistently showed higher uptake compared to ^{68}Ga -PSMA-11 (SUVmax: Reader 1 median [IQR]: 31.40 [27.45] vs 10.08 [13.92], $p < 0.001$, Reader 2 median [IQR]: 41.00 [46.09] vs 14.58 [14.98], $p < 0.001$); TBR: Reader 1 median [IQR]: 49.07 [67.69] vs 21.91 [35.71], $p = 0.0015$, Reader 2 median [IQR]: 76.34 [66.37] vs 23.90 [33.05], $p < 0.001$). **Conclusions:** ^{64}Cu -SAR-bisPSMA was safe and effective for detecting PSMA-expressing lesions. 200 MBq of ^{64}Cu -SAR-bisPSMA was determined as the optimal dose for future trials. ^{64}Cu -SAR-bisPSMA PET/CT showed a greater number of lesions and lesions exhibited significantly higher uptake when compared to ^{68}Ga -PSMA-11 in men being with intermediate- to high-risk PC. Further studies to evaluate ^{64}Cu -SAR-bisPSMA as an imaging agent in patients with biochemical recurrence of PC are underway. Clinical trial information: NCT04839367. Research Sponsor: Clarity Pharmaceuticals.

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Poster Session

Prognostic factors for relapse in patients with clinical stage I testicular seminoma: A nationwide, population-based cohort study. *First Author: Thomas Wagner, Department of Oncology, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark*

Background: Approximately 20% of patients with clinical stage I testicular seminoma will relapse after orchiectomy. No robust prognostic factors for relapse exist which challenges risk assessment and counselling for patients. Previous studies have been hampered by selection bias and variable pathology reporting that limit interpretation and generalization of results. We therefore assessed prognostic factors for relapse in a large unselected nationwide population-based setting with centralized pathology review. **Methods:** Patients with clinical stage I seminoma diagnosed in Denmark between 2013 and 2018 were identified in the prospective Danish Testicular Cancer database. By linkage to the Danish National Pathology Registry, microscopic slides from the orchiectomy specimens were retrieved and reviewed blinded to the clinical outcome. Clinical data were obtained from medical records with follow-up until July 2022. The association between prespecified clinical and histopathological prognostic factors and relapse were assessed by use of Cox regression analysis. Potential prognostic factors included age, pre-orchiectomy values of β -human chorionic gonadotropin (β -hCG) and lactate dehydrogenase (LDH), tumor size, tumor multifocality, tumor necrosis, lymphovascular invasion, pagetoid rete involvement, and invasion of rete testis, hilar soft tissue, epididymis, spermatic cord, tunica albuginea, and tunica vaginalis. **Results:** In total, 924 patients were included. During a median follow-up of 6.3 years, 148 (16%) patients relapsed. Invasion of the testicular hilum (rete testis and hilar soft tissue), lymphovascular invasion, and elevated pre-orchiectomy levels of β -hCG and LDH were independent predictors of relapse. The estimated 5-year risk of relapse ranged from 6% in patients with no risk factors, to 64% in patients with all four risk factors with tumor extension into the hilar soft tissue of the testicular hilum. After internal model validation, the model had an overall concordance statistic of 0.70. **Conclusions:** The provided prognostic factors allow a long-awaited opportunity to make more informed treatment decisions about post-orchiectomy management in patients with clinical stage I seminoma. These should replace current risk factors in guidelines and be used in future studies investigating risk-adapted follow-up and treatment strategies. Research Sponsor: The Danish Cancer Society, The Danish Cancer Research Foundation, The Preben and Anna Simonsen's Foundation, and The Valdemar Beck's Foundation.

Results of the final multivariable Cox model.

	Hazard ratio, 95% CI	p-value
Testicular hilum invasion		
Rete testis invasion -	1 (Reference)	-
Rete testis invasion +	1.80 (1.18-2.74)	0.0061
Hilar soft tissue invasion -		
Rete testis invasion +	2.90 (1.87-4.49)	< 0.0001
Hilar soft tissue invasion +		
Lymphovascular invasion (present vs absent)	1.85 (1.24-2.75)	0.0024
β -hCG (elevated vs normal)	1.91 (1.36-2.67)	0.0002
LDH (elevated vs normal)	1.66 (1.18-2.33)	0.0034

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Poster Session

Hospital Anxiety and Depression Scale (HADS) score trends among testicular cancer survivors: A longitudinal study. *First Author: Khalid Y. Alkhatib, University of Pennsylvania, Philadelphia, PA*

Background: The rarity of testicular germ cell tumors, in conjunction with the young age of its patients, makes it challenging to study its long-term adverse effects. We sought to investigate the changes in Hospital Anxiety and Depression Scale (HADS) scores over time in our institutional cohort of testicular cancer (TC) survivors, hypothesizing that anxiety and depression indices will improve over time, and specifically after treatment completion. **Methods:** A longitudinal analysis of TC survivors at the University of Pennsylvania between 2013 and 2020, quality of life metrics were measured annually during routine clinic visits. A validated HADS score was utilized to calculate indices of anxiety and depression. Multivariable linear mixed-effects regression models adjusted for pathology type, stage, treatment type, age, marital status, education, income, insurance, employment status, living situation, and time from diagnosis to first survey administration were used to calculate the mean predicted HADS, HADS-Anxiety, and HADS-Depression scores. ANOVA was used to test for parallelism and changes between survey scores. Each item is rated on a 4-point scale (ranging from 0 = no not at all, to 3 = yes definitely), for a total score ranging from 0-21 for each sub-scale with a cut-off point of 8/21 for anxiety or depression. **Results:** A total of 353 patients were included in the study. Baseline mean scores were 7.3, 4.9, and 2.4 for HADS overall, HADS-Anxiety, and HADS-Depression, respectively. Mean scores did not change over time, ANOVA testing of $p=0.84$, $p=0.78$, and $p=0.0.65$ for overall HADS, HADS-Anxiety, and HADS-Depression, respectively. Stratification by pathology, stage, or treatment did not show any significant interaction. **Conclusions:** Our data demonstrates that there was no significant change over time in HADS scores, thus considering the risks associated with depression and anxiety, such as suicide, it is essential to consider early referrals to psychiatric services. Our results are from a single institution, limited by a small sample size, and data lacks granularity, including mental health history. Nonetheless, our findings serve as a framework for future prospective studies of TC survivors. Research Sponsor: None.

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Poster Session

Penile squamous cell carcinoma (PSCC) with elevated tumor mutational burden (TMB): A genomic landscape study. *First Author: Rebecca A Sager, SUNY Upstate Medical University, Syracuse, NY*

Background: TMB has emerged as a novel biomarker of immune checkpoint inhibitor (ICPI) response in a wide variety of malignancies, but not yet in PSCC. **Methods:** 397 clinically advanced PSCC underwent hybrid capture based comprehensive genomic profiling (CGP) to evaluate all classes of genomic alterations (GA). TMB was determined on up to 1.1 Mb of sequenced DNA and categorized into three groups: <10 mutations/Megabase [mut/Mb] (low), 10-19 muts/Mb (high), and >20 muts/Mb (very high). MSI was determined on 114 loci. Genome-wide loss of heterozygosity (gLOH) was determined using validated pipelines and PD-L1 expression by IHC (TPS and Dako 22C3). Statistical comparisons utilized the Bonferroni correction method. **Results:** There were 339 (85.4%) TMB low, 40 (10.1%) TMB 10-19 and 18 (4.5%) TMB very high PSCC cases. The mean age of PSCC with very high TMB at 70.1 yrs was older than TMB low at 63.4 yrs ($p=.08$). The GA per tumor frequencies ranged from 5.4 to 5.5 in the 3 groups. There were no significant differences in genomic ancestry among the 3 groups. The TMB 10-19 and TMB very high tended to feature an APOBEC genomic mutational signature more than the TMB low PSCC cases (74 and 76% vs 44%). MSI high status was absent in the TMB low PSCC, but was present in 7.5% in the TMB 10-19 and 11.8% in the TMB very high cases. gLOH levels above 16% were similar in all 3 groups and ranged from 6.2 to 9.4%. GA associated with differences in TMB status in the PSCC cases included higher *PIK3CA* GA in TMB 10-19 (40.0%) vs TMB low (18.3%; $p=.035$) and TMB very high (66.7%) vs low ($p=.0002$). *CDKN2A* GA were higher in TMB low (45.7%) than the combined TMB 10-19 + very high (25.9%; $p=.049$). GA in *KMT2D* were higher in the combined TMB 10-19 + very high (29.3%) than TMB low (7.7%; $p=.0002$). *FGFR3* GA were similar in all 3 groups. In total, 6.5% of all GA were predicted to be of germline nature. The highest proportions of germline GA were seen for HRR genes *ATM* and *CHEK2* (both 40%) and *BRCA2* (37.5%) and *PMS2* (40%) linked to Lynch syndrome. PD-L1 expression was not significantly different among the 3 groups with TMB low (78.3%), TMB 10-19 (64.2%) and TMB very high (54.5%). HPV identification was more frequent as TMB increased: 28.3% for TMB low, 50.0% for TMB high and 58.8% for TMB very high groups. **Conclusions:** The evaluation of PSCC by CGP based on TMB levels reveals significant differences in biomarkers for the near 15% of cases that have TMB ≥ 10 muts/Mb. TMB and MSI status can also serve as biomarkers of response to SOC anti-PD1 based on the current FDA indications. These data may be useful to provide rationale for inclusion of PSCC in basket or umbrella trials testing novel monotherapies or combination therapies. Research Sponsor: None.

	TMB-low (n=339)	TMB-int+high (n=58)	P-value
Mean age	63.4	67.7	0.091
CDKN2A	45.7%	25.9%	0.050
KMT2D	7.7%	29.3%	<.0001
PIK3CA	18.3%	48.3%	<.0001
MSI-high	0.0%	8.8%	<.0001
Mean TMB	3.6	17.6	<.0001
APOBEC	44.1%	73.6%	0.052
PD-L1 low + (1-49%)	41.4%	32.0%	NS
PD-L1 high + ($\geq 50\%$)	36.9%	28.0%	NS

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Poster Session

Phase II study of the efficacy of retifanlimab (Rf) (INCMGA00012) in penile squamous cell carcinoma (PSqCC): ORPHEUS final analysis. *First Author: Xavier Garcia del Muro, Medical Oncology. Institut Català d'Oncologia (ICO) L'Hospitalet del Llobregat, Barcelona, Spain*

Background: PSqCC is a rare tumor with poor prognosis. The standard of care for advanced disease (AD) has been palliative platinum-based chemotherapy (CT). Most PSqCC patients (pts) have high levels of programmed death-ligand 1 (PD-L1). ORPHEUS has evaluated the efficacy and safety of Rf—a PD-1 antagonist—in pts with unresectable locally advanced or metastatic PSqCC. **Methods:** ORPHEUS (NCT04231981) is an international, multicenter, open-label, single-arm phase II trial. The study enrolled pts aged ≥ 18 years with locally advanced or metastatic PSqCC who had not received any previous treatment with PD-1 or PD-L1/2 agents. Pts received Rf 500 mg intravenously on day 1 of each 28-day cycle until progressive disease, unacceptable toxicity, discontinuation or death. The primary endpoint was investigator-assessed objective response rate (ORR) as per RECIST v.1.1. Secondary endpoints included clinical benefit rate, progression-free survival (PFS), duration of response (DoR), time to response (TTR), disease control rate (DCR), overall survival (OS) and safety evaluated as per NCI-CTCAE 5.0. The design was planned to attain an 80% power at 5% one-sided α level (H0: ORR $\leq 5\%$; H1: ORR $\geq 25\%$). **Results:** Between Jul 7, 2020, and Aug 26, 2021, 18 men were enrolled at 8 sites from Italy and Spain. Median age was 64.2 years (range 42-81), 13 (72.2%) pts had an AD at first diagnosis, 15 (83.3%) had a previous surgical procedure for penile cancer (lymphadenectomy in 7 pts), 10 (55.6%) had previously received platinum-based CT (TPF/TIP in 8 pts) and 7 (38.9%) were naïve to AD treatment. At data cutoff (Aug 26, 2022), with a median follow-up of 7.2 months, no pts remained on therapy. ORR (3 partial responses) was 16.7% (95% CI 5.8%-39.2%) with a median DoR and TTR of 3.3 (range 1.8-8.5) and 1.9 (range 1.7-2.4) months, respectively. DCR was (33.3%) (1 stable disease ≥ 6 months). Median PFS was 2.0 months (95% CI 1.6-3.3) and median OS with 17 events was 7.2 months (95% CI 3.0-9.8). Most common non-hematological treatment emergent adverse events (TEAEs) of any grade (G) were fatigue (27.8%; 5.6% G ≥ 3), cellulitis, groin infection and Pseudomonas infection (11.1%; 5.6% G ≥ 3), respectively. Treatment related (TR) TEAEs were fatigue (22.2%; 5.6% G ≥ 3), rash (5.6%; 0% G ≥ 3) and decreased appetite (5.6% G ≥ 3). Anemia (11.1%; 0% G ≥ 3) was the most frequent hematological TEAE. Serious unrelated TEAEs occurred in 5 pts (27.8%). Two (11.1%) pts discontinued treatment due to unrelated non-hematological TEAEs; 1 case of infected lymphocele (G3) and 1 case of skin neoplasm bleeding (G3). No TR deaths were reported. **Conclusions:** Rf in monotherapy showed signals of clinical activity in advanced or metastatic PSqCC pts. Safety profile was consistent with previous data. These results along with identification of suitable biomarkers could help to develop novel immunotherapy combination strategies in this orphan genitourinary tumor. Clinical trial information: NCT04231981. Research Sponsor: Incyte Biosciences International Sàrl.

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Poster Session

Effects of [¹⁷⁷Lu] Lu-PSMA-617 on overall survival in TheraP versus VISION randomized trials: An exploratory analysis. *First Author: Yu Yang Soon, NHMRC Clinical Trials Centre, The University of Sydney, Australia; Department of Radiation Oncology, National University Cancer Institute, Singapore, Singapore*

Background: Observed effects on overall survival (OS) differed in the first two randomized trials (RCTs) of [¹⁷⁷Lu] Lu-PSMA-617 (LuPSMA) in metastatic, castration-resistant prostate cancer. TheraP randomized participants to LuPSMA or Cabazitaxel (CBZ). In TheraP, the CBZ group (n = 101) included 20 participants who crossed over to LuPSMA, and the LuPSMA group (n = 99) included 32 who crossed over to CBZ. VISION randomized participants to treatment with or without LuPSMA, plus physicians' choice among protocol-defined treatments, excluding CBZ. Thirty-eight percent of control group participants in VISION had received CBZ prior to randomization. This study investigated explanations for differences in these RCTs in the observed effects of LuPSMA on OS. **Methods:** Individual participant data (IPD) on survival time from VISION was extracted from published survival curves for comparison with IPD from TheraP. Rank-preserving structural failure time (RPSFT) and inverse probability of censoring weighting (IPCW) were used in TheraP to estimate treatment effects on OS in counterfactual analyses assuming crossover had not occurred in either group, or in both groups. **Results:** OS was longer in the comparator group of TheraP than the comparator group of VISION (HR: 0.57, 95% CI 0.43 - 0.75) while OS was similar in the LuPSMA groups of VISION and TheraP (HR: 0.92, 95% CI 0.70 - 1.19). No significant differences in OS between the LuPSMA and CBZ groups of TheraP were apparent using counterfactual analyses assuming crossovers had not occurred (No crossover from CBZ: RPSFT HR 0.97, 95% CI 0.62 -1.52, IPCW HR 0.92, 95% CI 0.65-1.32; No crossover from LuPSMA: RPSFT HR 0.97, 95% CI 0.60-1.58, IPCW HR 0.82, 95% CI 0.55-1.24; No crossover from LuPSMA or CBZ: RPSFT HR 0.97, 95% CI 0.53-1.74, IPCW HR 0.82, 95% CI 0.53-1.27). **Conclusions:** The difference in observed effects of LuPSMA on overall survival in TheraP and VISION are better explained by the use of different comparator treatments in their control groups than by crossovers in TheraP from Cabazitaxel to LuPSMA, or LuPSMA to Cabazitaxel. Clinical trial information: NCT03392428, NCT03511664. Research Sponsor: None.

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Poster Session

Tumor dosimetry of [¹⁷⁷Lu]-Lu-PSMA-617 for the treatment of metastatic castration-resistant prostate cancer: Results from the VISION trial sub-study. *First Author: Bernd J. Krause, Rostock University Medical Center, Rostock, Germany*

Background: In VISION, lutetium (¹⁷⁷Lu) vipivotide tetraxetan ([¹⁷⁷Lu]-Lu-PSMA-617; ¹⁷⁷Lu-PSMA-617) plus protocol-permitted standard of care (SoC) significantly improved overall survival and radiographic progression-free survival compared with SoC alone, in patients with prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer. In a VISION dosimetry sub-study, ¹⁷⁷Lu-PSMA-617 had a good safety profile with low radiotoxicity in at-risk organs. Here, we estimated the dosimetry of tumors after administration of ¹⁷⁷Lu-PSMA-617. **Methods:** The VISION sub-study was performed in a separate cohort of 29 non-randomized participants at four sites in Germany. Eligible patients received ¹⁷⁷Lu-PSMA-617 (7.4 GBq every 6 weeks, ≤ 6 cycles) plus SoC. Patients underwent single-photon emission computed tomography/computed tomography (SPECT/CT) scans at approximately 2, 24, 48 and 168 hours after the first administration of ¹⁷⁷Lu-PSMA-617 (Cycle 1). Up to five tumors in each patient were selected according to tumor size and relative activity uptake. Tumor delineation, volume and morphology were determined using positron emission tomography (PET)/CT images. Kinetic (time-activity) data was determined using SPECT images and the application of phantom derived recovery coefficients. Tumor dosimetry was estimated using the standard Medical Internal Radiation Dose/Radiation Dose Assessment Resource (MIRD/RADAR) method for internal dosimetry. S-values were determined using CT-derived tumor volumes and tissue type as input to the Internal Dose Assessed by Computer (IDAC-Dose) 2.1 program. Tumor dosimetry estimates were reported as absorbed dose per unit activity (Gy/GBq) and cumulative estimated absorbed dose (Gy) over all 6 cycles (44.4 GBq cumulative activity). **Results:** In total, 104 tumors were analyzed after administration of ¹⁷⁷Lu-PSMA-617 in Cycle 1. Tumor sites included bone (n = 84), lymphatic tissue (n = 18), lung tissue (n = 1) and soft tissue (n = 1). Mean tumor mass by site was 14.6 (standard deviation [SD], 29.8; range, 0.49–224) g for bone and 12.5 (15.9; 0.68–60.7) g for lymphatic tissue. The mean radiation-absorbed dose for all tumors was 6.5 (SD, 8.4; range, 0.13–55) Gy/GBq, and the median absorbed dose was 4.4 Gy/GBq. The mean radiation-absorbed dose by tumor site was 5.4 (SD, 6.0; range, 0.13–45) Gy/GBq for bone and 9.7 (12; 0.99–55) Gy/GBq for lymphatic tissue. The 6-cycle cumulative estimated absorbed dose for all tumors was 287 (SD, 373; range, 5.7–2432) Gy. The 6-cycle cumulative estimated absorbed dose by tumor site was 240 (SD, 268; range, 5.7–2010) Gy for bone and 429 (549; 44–2432) Gy for lymphatic tissue. **Conclusions:** Tumor dosimetry estimates after administration of ¹⁷⁷Lu-PSMA-617 in the VISION sub-study patient population were consistent with previously published estimates. Clinical trial information: NCT03511664. Research Sponsor: Advanced Accelerator Applications, a Novartis Company.

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Poster Session

Bone biomarkers and subsequent survival in men with bone-metastatic hormone sensitive prostate cancer (HSPC): Results from the phase III SWOG S1216 trial of androgen deprivation +/- orteronel. *First Author: Primo N Lara, University of California Davis Comprehensive Cancer Center, Sacramento, CA*

Background: We previously reported that circulating serum biomarkers of bone metabolism were significantly associated with overall survival (OS) in men with advanced prostate cancer, either in the hormone sensitive (Lara, et al. ASCO 2022) or castration resistant state (Lara, et al. JNCI 2016). In S1216, we showed that elevated bone biomarkers were significantly associated with an increased risk of death in HSPC regardless of bone metastases (mets). We also identified three risk groups (low, intermediate, and poor) with differential OS outcomes (median OS: 8.2, 5.1, and 2.1 years, respectively) based on combinations of bone biomarkers in these patients. Here we report the association of bone biomarkers with OS in men with HSPC and documented skeletal mets as part of a planned analysis of S1216. **Methods:** Bone resorption [C-telopeptide (CTX) and Pyridinoline (PYD)] and bone formation markers [C-terminal collagen propeptide (CICP) and bone alkaline phosphatase (BAP)] were assessed from patient sera. Patients were randomly divided into training (n=238) and validation (n=475) sets. In the training set, recursive partitioning that maximizes discrimination of OS was used to identify the dichotomous cut-point for each biomarker and for a combination of biomarker split points to define prognostic groups. In the validation set, Cox proportional hazards models were used to assess the impact of biomarkers on OS, adjusted for patient and tumor characteristics. **Results:** Of 1,279 men in S1216, 713 had both baseline bone mets and evaluable bone biomarkers. Patient characteristics were similar between the overall population and the subset with bone mets. Elevated levels of CICP, CTX, and PYD were strongly prognostic for OS, but not for BAP. Hazard ratios (95% CI) for OS adjusted for treatment arm and baseline clinical variables were: BAP – 1.31 (0.93, 1.84), p=0.12; CICP – 1.58 (1.09, 2.29), p<0.02; CTX – 1.55 (1.12, 2.15), p=0.008; and PYD – 1.66 (1.27, 2.217), p=0.0002. There was no evidence of interaction between elevated biomarkers and treatment (all p>0.2). Recursive partitioning algorithms identified four groups of patients with differential OS outcomes based on bone biomarkers, adjusted for baseline clinical variables, with median OS ranging from 2.3 years (highest risk group) to 7.5 years (lowest risk group). **Conclusions:** In this subset analysis of men with HSPC and bone mets in S1216, elevated serum markers of bone metabolism were significantly associated with worse OS. Bone biomarker levels alone and in combination with patient and tumor characteristics identify unique subsets of men with differential OS outcomes. Clinical trial information: NCT01809691. Research Sponsor: U.S. National Institutes of Health; Millennium/Takeda; Jerry and Susan Knapp.

5047

Poster Session

Concurrent chemo-hormonal therapy of enzalutamide (ENZ) and cabazitaxel (CAB) in patients (Pts) with metastatic castration-resistant prostate cancer (mCRPC): Final analysis of objective response rate (ORR), radiographic progression-free survival (rPFS), and overall survival (OS). *First Author: Alexandra Sokolova, OHSU Knight Cancer Institute, Portland, OR*

Background: We previously reported the PSA response rate and toxicity data of a phase 1/2 single-arm, multi-institutional trial to examine the efficacy and safety of co-administration of ENZ + CAB in mCRPC without prior chemotherapy given in the mCRPC setting. We found that full doses of ENZ (160 mg daily) and CAB (25 mg/m²) were tolerable and that 80% of pts had PSA decline ≥50%. Here, we report the final analysis of ORR, rPFS and OS. **Methods:** We calculated the ORR (CR/PR) and 95% confidence intervals using the Clopper-Pearson Exact Method. We determined response according to RECIST 1.1 for measurable disease and Prostate Cancer Working Group 2 criteria for non-measurable (bone) disease. We estimated median rPFS (time from the study entry to the time of confirmed progression (radiographic or clinical) or death) and OS (time from the study entry to death) with 95% confidence intervals using the Kaplan-Meier method; data cutoff was 6/1/22. Statistical analysis was performed using R: A language and environment for statistical computing. **Results:** 37 pts consented and 35 were included in the efficacy analyses (1 withdrew consent, 1 was lost to follow up before efficacy assessment); 7/35 (20%) had prior exposure to chemotherapy given for mHSPC and 9/35 (25%) had prior exposure to abiraterone (ABI), including 2/35 (25.7%) with prior exposure to chemotherapy and ABI. 28 pts had at least one on-study trial imaging study and were evaluable for ORR. After a median follow-up of 23.7 (range: 4.9 to 62.4) months (mo), median OS was 25.1 mo (95%CI 19.4 - 37.6 mo). Median PSA PFS was 11.9 mo (95%CI 9.2 - 15.4), and median rPFS was 22.2 mo (95%CI 13.6 - 25.2). PK assessments revealed that ENZ decreased CAB levels: CAB (monotherapy) Cmax 178.9ng* h/ml vs CAB (in the presence of ENZ) Cmax 85.5 ng* h/ml (p<0.05). **Conclusions:** The combination of ENZ+CAB in this heterogeneous mCRPC population, which included about a quarter of pts with prior chemotherapy and ABI exposure, resulted in an OS of 22.5 mo comparing favorably with the OS of 25.2 mo seen in the FIRSTANA trial of single agent CAB in docetaxel naïve men, 15.1 mo post chemotherapy in the TROPIC trial, and 13.6 mo in the post-docetaxel, post-ABI in the CARD trial. Of note, the rPFS in this trial was 22.2 months compared to 5.1 months in FIRSTANA suggesting improved efficacy; however cross-trial comparisons are discouraged due to several confounders. Chemo-hormonal therapies and prognostic/predictive biomarkers warrant further study in mCRPC. Clinical trial information: NCT02522715. Research Sponsor: PCF YIA; SPORE, DoD; SPORE.

Radiographic Best Response (n=28)	Pts N (%)	Lower 95%CI	Upper 95%CI
Complete response	3 (10.7%)	2.3%	28.2%
Partial response	11 (39.3%)	21.5%	59.4%
Stable disease	12 (42.9%)	24.5%	62.8%
Progressive disease	2 (7.1%)	0.9%	23.5%
ORR	14 (50%)	30.6%	69.4%

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Poster Session

Impact of synchronous (sync) vs metachronous (meta) metastasis at the presentation on survival in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) treated with androgen receptor signaling inhibitors (ARSI). *First Author: Georges Gebrael, Huntsman Cancer Institute at the University of Utah, Salt Lake City, UT*

Background: Pts with sync metastatic castration-sensitive prostate cancer (mCSPC) appear to have worse survival outcomes and earlier time to developing castration resistance than pts with meta mCSPC (PMID: 33914595). However, the impact of the initial timing of metastasis on survival in the mCRPC setting is less clear. Herein, our objective was to assess the correlation between the sync/meta metastatic disease presentation and survival in real-world newly diagnosed mCRPC pts. **Methods:** In this IRB-approved study, patient-level data were collected retrospectively. Eligibility: confirmed diagnosis of mCRPC, treatment with ARSI (abiraterone or enzalutamide) as first-line (1L) therapy for mCRPC, and no prior exposure to ARSI in the mCSPC or localized states. The disease was considered sync if distant metastasis was diagnosed within 90 days of the initial prostate cancer diagnosis. Study endpoints: progression-free survival (PFS) was defined from the start of therapy for 1L mCRPC to progression (per PCWG-2) or death from any cause. Overall survival (OS) was defined from the start of therapy for 1L mCRPC to the date of death from any cause or censored at the last follow-up. A multivariate analysis using the Cox proportional hazards model was used, adjusting for potential confounders. **Results:** 323 pts (144 sync and 179 meta) were eligible and included in the analysis. Sync and meta pts had respectively similar baseline characteristics: median PSA (19.6 vs 20.8 ng/ml), liver metastasis (9 vs 12.3%), median alkaline phosphatase (97 vs 95 IU/L), and ECOG performance > 1 (9 vs 3.9%). The difference in median PFS was not statistically significant (8.2 vs. 10.7 months, HR 1.13, 95% CI 0.85-1.49, p=0.4 for sync and meta, respectively). Median OS was significantly shorter in pts with sync compared to meta (26 vs. 38.7 months, HR 1.51, 95% CI 1.11-2.08, p=0.01). In the multivariate analysis, the initial timing of metastasis remained an independent prognostic factor. **Conclusions:** For the first time, we report the impact of the initial timing of metastasis on mCRPC prognosis in a real-world patient population with sync disease being associated with having a poor prognosis. Initial timing of metastasis may be worth accounting for in future mCRPC clinical trials to explore its prognostic value further. These hypothesis-generating data need external validation. Research Sponsor: None.

Variable	PFS	OS
	HR (95% CI, P-value)	HR (95% CI, P-value)
Sync vs Meta	1.13 (0.85 – 1.49, p = 0.4)	1.51 (1.11 – 2.08, p = 0.01)
Baseline Log PSA	1.15 (1.07 – 1.23, p < 0.001)	1.12 (1.04 – 1.21, p = 0.005)
Liver Metastasis (yes vs no)	1.86 (0.87 – 3.99, p = 0.11)	1.88 (0.82 – 4.29, p = 0.14)
ECOG (≤1 vs >1)	0.86 (0.51 – 1.47, p = 0.59)	1.35 (0.73 – 2.34, p = 0.34)
Alkaline Phosphatase (continuous)	1.00 (1.00 – 1.00, p = 0.002)	1.00 (1.00 – 1.00, p = 0.08)

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Poster Session

Real-world safety and effectiveness of radium-223 (²²³Ra) in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) treated in the US: The non-interventional REASSURE study. *First Author: Daniel Y. Song, Department of Radiation Oncology and Molecular Radiation Sciences, Johns Hopkins University School of Medicine, Baltimore, MD*

Background: ²²³Ra improved overall survival (OS) and quality of life and demonstrated a favorable safety profile in pts with mCRPC in the phase 3 ALSYMPCA trial. REASSURE (NCT02141438) is a global, prospective, single-arm, observational study of ²²³Ra use in pts with mCRPC and bone metastases in routine clinical practice. Here, we present clinical outcomes from the second planned interim analysis of REASSURE for pts treated in the US. **Methods:** This analysis included pts with confirmed mCRPC with bone metastases scheduled to receive ²²³Ra in the US. All pts received ≥1 dose of ²²³Ra. Primary endpoints are short- and long-term safety, including incidence of bone marrow suppression and second primary malignancies (SPM). Secondary endpoints included OS and pt-reported pain (Brief Pain Inventory – Short Form [BPI-SF] scores). A clinically meaningful pain response was defined as a decrease from baseline of ≥2 points in BPI-SF worst pain item. **Results:** Pts were enrolled from 2014–2017. Overall, 498 pts were included in this analysis. At the data cut-off (20 March 2019), the median duration of observation was 11.9 months (0.4–41.3). Most pts (81%) had bone metastases only; 69% of pts received 5–6 ²²³Ra injections. Overall, 77% of pts had received ≥1 prior life-prolonging therapies: abiraterone (45%), enzalutamide (48%), docetaxel (25%), cabazitaxel (6%), or sipuleucel-T (24%). Concomitant enzalutamide was received by 31% of pts, and 47% received concomitant bone health agents. After ²²³Ra, 31% of pts received ≥1 life prolonging therapies. During treatment, 208/358 (58%) pts with a baseline BPI-SF ≥2 had a clinically meaningful pain response. Any-grade and grade ≥3 drug-related treatment-emergent adverse events (TEAEs) occurred in 32% and 10% of pts, respectively. Drug-related TEAEs resulted in ²²³Ra discontinuation in 4% of pts. Treatment-emergent and drug-related serious AEs (SAEs) occurred in 21% and 6% of pts, respectively. The most common (>5% of pts) any-grade drug-related TEAEs were diarrhea (10%), fatigue (9%), anemia (8%) and nausea (7%). Overall, 4% of pts had fractures; 2% of pts developed bone disorders. Eleven SPMs occurred in 10 pts (2%). In total, 60% of pts died during study follow-up. Median OS was 17.8 months (95% CI 15.6–19.4). **Conclusions:** Within the current treatment landscape in routine clinical practice in the US, median OS after ²²³Ra treatment was close to 18 months. A majority of pts completed 5–6 ²²³Ra injections. The known safety profile of ²²³Ra was confirmed with no new safety signals. Over half of pts with pain at baseline had a clinically meaningful pain response during ²²³Ra treatment. Clinical trial information: NCT02141438. Research Sponsor: Bayer AG.

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Poster Session

A novel abiraterone acetate oral suspension for patients with metastatic prostate cancer: An open-label, phase 3, randomized trial. *First Author: Imanol Martinez, Jiménez Díaz Foundation University Hospital, Madrid, Spain*

Background: Abiraterone acetate (AA) is a first-line oral hormone therapy for metastatic prostate cancer (mPC), but the licensed formulation is limited by large tablet size, requirement to take on an empty stomach, and pharmacokinetic variability. TAVT-45, a novel formulation of AA granules for oral suspension, offers improved oral bioavailability (allowing dose reduction), decreased food effect, and may provide an option for the ~20-30% of patients with dysphagia. This Phase 3, open-label global study (NCT04887506) aimed to establish therapeutic equivalence between TAVT-45 granules and reference AA tablets (R-AA). **Methods:** Patients with castrate-resistant or castrate-sensitive mPC (mCRPC or mCSPC) were randomized 1:1 to receive TAVT-45 (1 sachet of AA granules [250 mg] in water or juice, twice daily) or R-AA tablets (2 x 500 mg once daily ≥1 h before or ≥2 h after food), plus prednisone (5 mg once [mCSPC] or twice [mCRPC] daily) for 84 days. Efficacy (serum testosterone and prostate-specific antigen [PSA]) and safety were assessed. Average serum testosterone concentrations on Days 9 & 10 (primary endpoint, analyzed via analysis of covariance) were compared to show therapeutic equivalence. The key secondary endpoint was PSA-50 response (patients with ≥50% decrease in PSA from baseline at any time). mCRPC was the primary analysis population. Preliminary results are presented. **Results:** Of 107 randomized patients, 103 received TAVT-45 (n=54) or R-AA (n=49). The TAVT-45 and R-AA groups were well matched (mean [SD] age: 74.5 [8.45] and 74.9 [8.40] years; mCRPC: 61.1% and 61.2%). In mCRPC, serum testosterone concentrations fell rapidly from mean (SD) baseline of 9.7 (5.19) for TAVT-45 and 10.6 (7.32) ng/dL for R-AA, with all <1 ng/dL by Day 9. Therapeutic equivalence between TAVT-45 and R-AA at Days 9 & 10 was also shown in the full study population: Days 9 & 10 average rounded-up least-squares mean serum testosterone levels were comparable (TAVT-45 [n=52]: 1.004 ng/dL; R-AA [n=47]: 1.015 ng/dL), and the geometric mean ratio between groups was 0.990 (90% CI: 0.978-1.002), with the 90% CI falling within 80.0–125.0% equivalence limits. No statistical difference between TAVT-45 vs R-AA was demonstrated for PSA-50 (mCRPC 85% vs 70%; mCSPC 90% vs 95%). The frequency of treatment-emergent adverse events (TEAEs) was similar between groups; most were mild or moderate. Serious TEAEs occurred in 5 TAVT-45 and 3 R-AA patients. There were two deaths in treated patients due to cardiorespiratory arrest (TAVT-45) and prostate cancer (R-AA); neither was considered related to study drug. **Conclusions:** This Phase 3 study demonstrates that TAVT-45, a novel AA formulation with improved bioavailability, yields similar testosterone/PSA responses and a comparable safety profile to R-AA, and as an oral solution, may be suitable for mPC patients with dysphagia. Clinical trial information: NCT04887506. Research Sponsor: TAVANTA Therapeutics.

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Poster Session

The effect of a reduced dose of enzalutamide on fatigue and cognition. *First Author: Joanneke Overbeek, Department of Pharmacy, Radboud University Medical Center, Nijmegen, Netherlands*

Background: Enzalutamide (ENZA) is a highly effective treatment for patients (pts) with metastatic prostate cancer, but central nervous system (CNS)-associated side effects occur frequently and may hamper the quality of life. These side effects are addressed with dose reductions, while they potentially can be prevented by starting at a reduced dose, since androgen receptor saturation is already observed at dose levels above 60 mg once daily (OD) and ENZA plasma concentrations > 5 mg/L. We hypothesized that a lower starting dose of ENZA can reduce the risk of CNS side effects in frail pts while preserving efficacy. In this study (NCT03927391) the effect of a reduced dose of ENZA on fatigue and cognitive side effects is determined. **Methods:** This randomized multi-center trial compared the ENZA standard dose of 160 mg OD to the reduced dose of 120 mg OD in frail prostate cancer pts. At baseline, and 6, 12, and 24 weeks after start of ENZA, fatigue and cognitive side effects were measured by the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) and Functional Assessment of Cancer Therapy–Cognition (FACT-Cog) questionnaires. A change in scores of 3.0 for the FACIT-F and 7.0 for the FACT-Cog was considered clinically relevant. Linear mixed effects models were used to study within and between-group differences in fatigue and cognitive side effects over time. Furthermore, ENZA plasma concentrations were measured after 6, 12, and 24 weeks of treatment and PSA response (>50% PSA decline) was compared between the two dosing regimens. **Results:** A total of 51 pts were included (25 reduced dose, 26 standard dose). Completion rates for the questionnaires were high throughout the study (>90%). Pts treated at the reduced dose showed no significant changes in FACIT-F and FACT-Cog scores over time. Pts treated at the standard dose showed increasingly worse FACIT-F and FACT-Cog scores. This resulted in clinically relevant and statistically significant better FACIT-F and FACT-Cog scores for pts treated at the reduced dose compared to pts treated at the standard dose after 24 weeks (table). All pts had therapeutic ENZA concentrations (>5 mg/L) throughout the study. PSA response did not differ between both groups (87% for 120mg OD vs 80% for 160mg OD, p=0.796). **Conclusions:** By starting with a reduced dose of ENZA of 120mg OD CNS side effects can be prevented, which might beneficially affect the quality of life of frail prostate cancer pts, without any indication of interference with efficacy endpoints. Clinical trial information: NCT03927391. Research Sponsor: Dutch health insurance company VGZ.

Difference in change from baseline between the reduced dose vs standard dose (95%CI).				
		6 weeks	12 weeks	24 weeks
FACIT-F score	Standard dose	Ref	Ref	Ref
	Reduced dose	2.0 (-2.8, 6.8)	3.0 (-2.0, 8.0)	6.4 (1.1, 12)*
FACT-Cog score	Standard dose	Ref	Ref	Ref
	Reduced dose	3.8 (-5.6, 13)	1.1 (-8.7, 11)	11 (0.24, 22)*

Higher scores represent less fatigue and cognitive side effects. * Significant p<0.05.

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Poster Session

Talazoparib (TALA) plus enzalutamide (ENZA) in metastatic castration-resistant prostate cancer (mCRPC): Safety analyses from the randomized, placebo (PBO)-controlled, phase 3 TALAPRO-2 study. *First Author: Arun Azad, Peter MacCallum Cancer Centre, Melbourne, Australia*

Background: The phase 3 TALAPRO-2 study demonstrated a clinically meaningful and statistically significant improvement in radiographic progression-free survival for 1st-line TALA + ENZA versus PBO + ENZA in men with mCRPC, unselected for homologous recombination repair gene alterations (all-comers population). Here, we detail the safety profile of TALA + ENZA. **Methods:** In this double-blind, randomized, PBO-controlled trial, men received TALA 0.5 mg or PBO, plus ENZA 160 mg once daily (QD). Patient (pts) were ≥18 yrs of age, had Eastern Cooperative Oncology Group performance status ≤1, were receiving ongoing androgen deprivation therapy, and had no prior systemic therapy for mCRPC. Treatment-emergent adverse events (TEAEs) were evaluated: type, severity, timing, and associated dose modifications/discontinuations. **Results:** The all-comers safety population included 398 pts in the TALA + ENZA arm. Data cutoff was August 16, 2022. The median treatment duration of TALA was 19.8 months. All-cause any-grade TEAEs were observed in 98.5% of pts. Overall, 19.1% of pts discontinued TALA due to TEAEs. The 3 most common hematologic all-cause TEAEs and associated dose modifications are reported. To ensure optimal dosing of TALA at the individual level, the protocol did not require dose modification of TALA until anemia was grade (G) ≥3. Median time to onset of first G≥3 anemia was 3.3 months. At study entry, 49.0% had G1–2 anemia. 43.2% had anemia leading to dose reduction (with or without transfusion) and 8.3% discontinued TALA due to anemia. Despite dose reduction, the relative dose intensity of talazoparib remained >80% (approx. 0.4 mg/day). The 3 most common nonhematologic TEAEs were fatigue (33.7%; 4.0% G3), back pain (22.1%; 2.5% G3), and decreased appetite (21.6%; 1.3% G3). **Conclusions:** TALA 0.5 mg QD + ENZA 160 mg QD was generally manageable, with dose modifications of TALA and/or standard supportive care. Anemia was the most common TEAE and led to discontinuation of TALA in 8.3% of pts. G≥3 hematologic AEs typically occurred within 6 months of starting therapy and resolved in <1 month. A detailed understanding of the onset, duration, and severity of AEs, as well as the impact of dose adjustments in the TALAPRO-2 study, will optimize the management of pts receiving TALA + ENZA for mCRPC. Clinical trial information: NCT03395197. Research Sponsor: Pfizer Inc.; Astellas Pharma Inc. provided enzalutamide.

TALA + ENZA (N=398)	Any G					G≥3 median time to onset/ duration (mo, d) ^a	Led to TALA dose interruption/ reduction/ discontinuation (%) ^a
	G1 (%)	G2 (%)	G3 (%)	G4 (%)	G5 (%)		
Anemia	6.0	13.3	43.2	3.3	65.8	3.3/16	44.2/43.2/8.3
Neutropenia	3.0	14.3	17.1	1.3	35.7	2.3/12	13.6/15.1/3.3
Thrombocytopenia	10.3	7.0	5.0	2.3	24.6	2.3/19	7.8/5.0/0.5

^aCluster terms used for anemia, neutropenia, and thrombocytopenia.

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Poster Session

Final results of a pilot study of docetaxel and carboplatin for treatment of patients with mCRPC containing biallelic inactivation of genes in the homologous recombination DNA repair pathway. *First Author: Ruben Raychaudhuri, Fred Hutchinson Cancer Center, Seattle, WA*

Background: Inactivating mutations in genes important in homologous recombination DNA repair (HRD) are present in the tumors of ~25% of patients with metastatic castration resistant prostate cancer (mCRPC). These alterations are associated with more aggressive disease but may also predict vulnerability to DNA damaging agents. We previously reported promising interim results from a single arm, Phase 1/2 trial studying the combination of the DNA damaging agent carboplatin with docetaxel for patients with mCRPC containing HRD mutations. Here we report final results after completing accrual and two additional years of follow up. **Methods:** We assessed response to the combination of docetaxel 60mg/m² and carboplatin AUC 5 IV q21 days in patients with mCRPC whose tumors had evidence of biallelic inactivation of genes involved in HRD and who had progressed on any prior treatment, including docetaxel and/or PARP inhibitor (PARPi). The primary endpoint was the proportion of patients who achieved ≥50% PSA decline from baseline (PSA₅₀). With H0 of PSA₅₀ of 26%, 14 patients provided 80% power to conclude H1 of PSA₅₀ of 60% based on Simon's 2-stage design with 1-sided α = 5%. The secondary endpoints included PSA₃₀, response duration, progression-free survival (PFS), and overall survival (OS). **Results:** The trial opened in Jan 2016 and completed in Sep 2021. A total of 16 patients were treated on study, including 6 who had previously received PARPi and 5 who had received docetaxel. 11/16 patients (69%) achieved PSA₅₀. 7/9 patients (78%) with biallelic inactivation of *BRCA2* (7), *BRCA1* (1), or *PALB2* (1) achieved PSA₅₀. Other biallelic inactivated HRD-related genes were *ATM* (1), *CHD1* (1), *CDK12* (3), *MRE11A* (1), and *NBN* (1). Of these patients, 4/7 (57%) achieved PSA₅₀. Notably, 3/6 patients (50%) previously treated with PARPi therapy achieved PSA₅₀. The median PFS was 8.4 months, and the median OS was 2 years. 6/16 patients (38%) had grade 3 AEs, most commonly thrombocytopenia (25%) and anemia (13%). One patient (6%) had a grade 4 AE (thrombocytopenia). **Conclusions:** The addition of carboplatin to docetaxel significantly improved response rates in patients with mCRPC with biallelic inactivation in genes involved in the HRD pathway. Responses were also seen in patients who had previously received PARPi. The combination was relatively safe and well-tolerated. The encouraging activity and favorable toxicity profile observed here merits further investigation. Additional work is ongoing to further refine biomarkers predictive of treatment response and resistance. Clinical trial information: NCT02598895. Research Sponsor: Prostate Cancer Foundation and the Institute for Prostate Cancer Research; U.S. National Institutes of Health.

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Poster Session

Use of circulating tumor DNA (ctDNA) to complement tumor tissue homologous recombination repair (HRR) gene alteration testing in TALAPRO-2, a phase 3 study of talazoparib (TALA) + enzalutamide (ENZA) versus placebo (PBO) + ENZA as first-line (1L) treatment in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC). *First Author: Arun Azad, Peter MacCallum Cancer Centre, Melbourne, Australia*

Background: In TALAPRO-2 (NCT03395197), pts unselected for tumor genetic alterations in DNA damage repair pathways, directly or indirectly involved with HRR, received TALA + ENZA (n=402) or PBO + ENZA (n=403) as 1L treatment for mCRPC. HRR status was informed by tumor tissue for 804 pts (99.9%), by tumor tissue and ctDNA for 114 (14.2%), and by ctDNA only for 1 (0.1%). TALA + ENZA demonstrated statistically significant and clinically meaningful improvements in imaging-based progression-free survival over standard of care PBO + ENZA regardless of HRR gene alteration status (presented by Agarwal N at ASCO-GU 2023). Here we assessed the overall agreement of solid tissue vs ctDNA-based testing in assessing tumor HRR gene alteration status. **Methods:** HRR status for pts randomized in TALAPRO-2 was determined prospectively by testing for the presence of HRR gene alterations using FoundationOne CDx and/or FoundationOne Liquid CDx. Pts were considered HRR-deficient if they had ≥1 alteration in ≥1 of 12 HRR genes by either test. Plasma samples collected at screening were retrospectively tested using FoundationOne Liquid CDx to examine retrospective test performance and to support exploratory resolution of pts with unknown prospective HRR status. Results were reported as HRR-deficient, non-HRR-deficient, or unknown. **Results:** In prospective testing, high concordance in HRR status was observed between ctDNA and tumor tissue sample results: 95% agreement (90/95) between tests was observed in pts evaluable as either HRR-deficient or non-HRR-deficient by both tests. Retrospective ctDNA test results were reported for 739 pts (207 [28%] with a status of HRR-deficient, 480 [65%] non-HRR-deficient, and 52 [7%] unknown; 66 pts had samples not collected or reported). There was high concordance in pt-level alteration status between prospective molecular profiling (mainly based on solid tumor tissue per above) and retrospective ctDNA testing: the agreement was 84% (438/519) between tests for pts evaluable as HRR-deficient or non-HRR-deficient both prospectively and retrospectively (421/501 [84%] for prospective tumor tissue only vs retrospective ctDNA). **Conclusions:** Results show 95% agreement between prospective tissue and ctDNA-based HRR status using FoundationOne, consistent with tumor vs ctDNA results recently reported (Tukachinsky. *Clin Cancer Res.* 2021;27:3094–3105). The high agreement between prospective test results based primarily on tumor tissue and retrospectively assessed ctDNA collected at screening is supportive of exploratory retrospective testing of ctDNA to inform the HRR status of pts whose alteration status is unknown based on prospective testing. Clinical trial information: NCT03395197. Research Sponsor: Pfizer Inc.; Astellas Pharma Inc. provided enzalutamide.

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Poster Session

PSMA expression and response to 177Lu-PSMA-617 (LuPSMA) in men with vs. without DNA damage repair (DDR) mutations. *First Author: Ruben Raychaudhuri, Fred Hutchinson Cancer Center, Seattle, WA*

Background: LuPSMA, a radioligand targeting the cell surface protein PSMA, is approved for men with PSMA-positive metastatic castration resistant prostate cancer (mCRPC) following an androgen receptor (AR)-signaling inhibitor (ARSI) and docetaxel. DNA damage repair gene (DDR) mutations are common in mCRPC, and given that ionizing radiation induces DNA damage, we hypothesized that the presence of these alterations could associate with improved clinical outcomes to LuPSMA. Data also suggests that the presence of DDR mutations may correlate with PSMA expression, providing further motivation to evaluate if DDR alterations are associated with the clinical activity of LuPSMA. **Methods:** We abstracted retrospective data from all patients at our center who received at least one cycle of LuPSMA per the FDA label and who had panel-based sequencing performed (e.g. UW-OncoPrint, Foundation One). Patients with somatic or germline alterations in a DDR gene were assigned to the DDR deficient cohort, while patients with somatic testing negative for a DDR gene mutation were assigned to the DDR intact cohort. Mutations in any DDR gene were considered for the purpose of stratifying between genomic subgroups. Differences in baseline PSMA SUVmean and PSA₅₀ responses (i.e. ≥50% decline in PSA) were compared between cohorts. **Results:** Of 91 patients who received ≥1 cycle of LuPSMA, 54 had genetic testing. 35 (64%) received ≥2 lines of prior ARSI therapy, 30 (56%) received ≥2 lines of prior chemotherapy and 15 (28%) received prior PARP inhibitor. 21 patients had alterations in a DDR gene and the remaining 33 patients had somatic testing without an identifiable DDR mutation. PSMA SUVmean was similar between groups: 8.04 (95% CI: 6.95 - 9.12) (DDR intact) vs. 7.32 (95% CI: 6.23 - 8.41) (DDR deficient), p = 0.37. 7/33 (21%) patients in the DDR intact group achieved PSA₅₀ response compared to 11/21 (52%) in the DDR group (p = 0.018). Survival data is immature but will be presented at the meeting. Rapid autopsy (RA) was performed in one subject with a *BRCA2* mutation (baseline PSMA SUVmean 5.6) and immunohistochemistry analysis revealed profound loss of PSMA following progression on LuPSMA. **Conclusions:** Mutations in DDR genes were associated with a higher PSA₅₀ response rate following LuPSMA compared to patients without a DDR mutation. There was no difference in baseline PSMA expression based on DDR mutational status, suggesting that higher response rates in the DDR cohort may have been mediated primarily by increased sensitivity to ionizing radiation. Evaluation for associations between DDR mutational status and survival endpoints is needed and will require a larger sample size and longer follow up. RA post-LuPSMA revealed loss of PSMA expression, suggesting that antigen loss may be a relevant resistance mechanism. Research Sponsor: U.S. National Institutes of Health.

DDR gene	N	PSA50 Response, n (%)
CDK12	6	1 (17%)
ATM	6	5 (83%)
BRCA1/2	4	2 (50%)
PALB2	2	1 (50%)
RAD51	1	0 (0)
MSH2	2	2 (100%)

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Poster Session

Tumor heterogeneity and treatment response assessment using next generation imaging and liquid biopsy in patients with metastatic castration resistant prostate cancer receiving abiraterone (ANGELA): A single-center prospective observational trial. *First Author: Yao Zhu, Fudan University Shanghai Cancer Center, Shanghai, China*

Background: Metastatic castration resistant prostate cancer (mCRPC) is a disease of intra-patient tumor heterogeneity which poses obstacles in treatment and response evaluation. With the development of next generation imaging (NGI) and liquid biopsy, precise assessment of heterogeneity has entered a new era. In this study, we used longitudinal NGI (⁶⁸Ga-PSMA and ¹⁸F-FDG PET/CT) and circulating tumor DNA (ctDNA) testing to assess tumor heterogeneity and treatment response in mCRPC patients receiving abiraterone. **Methods:** ANGELA is a single-center prospective observational trial (NCT05188911). We recruited mCRPC patients who received abiraterone as initial hormonal treatment. Eligible patients should have a life expectancy >12 months. CtDNA testing and NGI were performed at baseline and after 12 weeks of abiraterone (Week 13). Conventional imaging and PSA testing were performed at Week 1 and every 12 weeks. Primary end-point of this study is intra-patient lesion heterogeneity evaluated by 3 dimensions: (1) Imaging heterogeneity: defined as at least 1 lesion with FDG+/PSMA- phenotype at baseline and/or Week 13; (2) Genomic heterogeneity: quantified by ctDNA fraction increase and mutational changes per gene between baseline and Week 13; (3) Response heterogeneity: defined as at least 1 new tumoral lesion with either PSMA or FDG abnormal uptake at Week 13. Secondary end-points are correlations of heterogeneity with conventional-evaluated progression-free survival (PFS) and 2-year overall survival (OS). **Results:** Between May 20, 2020 and Feb 02, 2021, we included 33 eligible patients in our study. FDG+/PSMA- tumoral lesion was observed in 7/33 (21.2%) and 8/33 (24.2%) of patients at baseline and Week 13, respectively. Notably, 5 of 8 patients with imaging heterogeneity at Week 13 had no FDG+/PSMA- lesion at baseline. For genomic heterogeneity, we detected ctDNA fraction increase in 4/33 patients (12.1%). In addition, we found new gene mutations detected in Week 13 ctDNA testing in 5/33 patients (15.2%), 2 of 5 had ctDNA fraction increase. For response heterogeneity, we observed 15/33 patients (45.5%) patients developed at least 1 new tumoral lesion (FDG+ or PSMA+) at Week 13. We correlated heterogeneity factors with prognosis, and found that detection of new mutated genes (P=0.005 and P<0.001), new PSMA+ lesion (P<0.001 and P<0.001), and new FDG+ lesion (P=0.008 and P<0.0001) at Week 13 were significant predictors of shorter PFS and decreased 2-year OS. Detailed biomarker study for response analysis is still in process. **Conclusions:** Intra-patient tumor heterogeneity was common among mCRPC patients receiving abiraterone. Combining liquid biopsy with NGI can monitor changes in tumor heterogeneity and indicate early combination therapy. Clinical trial information: NCT05188911. Research Sponsor: None.

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mFAST-SeqS based aneuploidy score in circulating cell-free DNA and role as early response marker in patients with metastatic prostate cancer treated with androgen receptor signaling inhibitor. *First Author: Khrrstany T. Isebia, Erasmus MC Cancer Institute, Rotterdam, Netherlands*

Background: Several treatment modalities in metastatic castration resistant prostate cancer (mCRPC) are available to prolong progression-free and overall survival. With the arrival of additional treatment modalities, the need for accurate monitoring of treatment response is becoming more eminent and research for biomarkers pivotal. Cell-free circulating tumor DNA (ctDNA) has emerged as a promising prognostic and predictive biomarker. Several techniques have been employed for the detection and characterization of ctDNA within the total pool of cell-free DNA (cfDNA), one of which is the modified Fast Aneuploidy Screening Test-Sequencing System (mFAST-SeqS). This affordable and robust assay enables the quantitation of a sample's ctDNA using a genome-wide aneuploidy score (GWA). Our aim was to investigate whether estimation of the GWA by mFAST-SeqS can be used to evaluate early response to treatment and predict response to treatment at baseline in patients with mCRPC. **Methods:** We prospectively enrolled mCRPC patients before start of treatment with androgen receptor signaling inhibitor (ARSI) abiraterone or enzalutamide. Blood samples were collected at baseline before start of treatment (BL, $n=134$) and at an early treatment time point during treatment (ET, $n=20$). We isolated cfDNA from plasma collected at both time points using the QiaSymphony or Maxwell system, and performed mFAST-SeqS on 1 ng cfDNA by amplifying and sequencing long interspaced nuclear elements (LINE-1) throughout the genome. The GWA-scores were calculated by taking the summed square of individual Z scores per chromosome arm relative to healthy controls. GWA-score was dichotomized in high (GWA^{high}) and low (GWA^{low}), based on the previously described cut-off of 5. Clinical outcome, defined as treatment duration with ARSI, was compared for patients with a GWA^{high} and GWA^{low} score at baseline and at an early time point. In addition, conversion of GWA score from baseline to early time point was explored. **Results:** Median age at start of treatment was 68.5 years (interquartile range (IQR): 63-73). Median time between start treatment and blood draw at BL and ET was 3 (IQR: 0-10 days before treatment) and 28 (IQR: 18-62 days during treatment) days, respectively. Median number of prior therapy lines was 1 (IQR: 0-10). Treatment duration was significantly shorter in the GWA^{high} group versus the GWA^{low} group both at BL and at ET in patients treated with ARSI (BL: $p<0.001$, log-rank test, median 221 and 82 days; ET: $p<0.01$, log-rank test, median 123 and 42 days). **Conclusions:** The genome-wide aneuploidy score, based on mFAST-SeqS of cfDNA, is a useful tool to predict response to ARSI in patients with mCRPC. The current dataset will be extended to 199 samples at baseline and 78 samples at early time point, and also include mCRPC patients treated with taxanes. Clinical trial information: NCT01855477, NTR732. Research Sponsor: KWF-CPCT alpe project (NKI2014-7080).

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Poster Session

The impact of circulating tumor cell HOXB13 RNA detection in men with metastatic castrate-resistant prostate cancer (mCRPC) treated with abiraterone or enzalutamide. *First Author: Siyuan S Guo, Duke University, Durham, NC*

Background: It has been shown that HOXB13 is an important androgen receptor (AR) coregulator. The primary objective of this analysis was to correlate HOXB13 expression with clinical outcomes in men with mCRPC. **Methods:** We conducted a retrospective analysis of the multicenter prospective PROPHECY trial of mCRPC men ($n=118$) treated abiraterone (abi) or enzalutamide (enza). CTC detection and specific HOXB13 cDNA detection and expression was measured using a modified Adnatest using appropriate controls. CTC HOXB13 status was categorized into 3 groups: undetectable CTCs (CTC=0 based on CTC PSMA & PSA=0); CTC+ but HOXB13 CTC negative (<4 copies) or positive (≥ 4 copies) where the HOXB13 cutoff point was determined by the maximally selected rank statistic for prognostic associations. The association between HOXB13 and overall survival (OS) and radiographic progression-free survival (rPFS) were explored using the proportional hazards model. We also explored the association between the two endpoints and multigroup of HOXB13 at cutoff 0 and CellSearch CTC at cutoff 1 and 5. **Results:** 102 men who had sufficient CTC cDNA sample for HOXB13 detection. Of those men with detectable CTCs, 19% ($n=19$) had no detectable HOXB13, while the majority of men at 67% ($n=58$) had both CTC and HOXB13 detection. The proportion of patients with CTC=0, CTC+ HOXB13-, and CTC+ HOXB13+ using the optimal HOXB13 threshold were 25%, 31% and 44%, respectively. Men with HOXB13- CTCs were more likely to have low PSA (median 3 vs 79 copies), low CTC PSMA (0 vs 99 copies), low AR-FL (47 vs. 89 copies) and CTC AR-V7 (5.9 vs. 42 copies), and more likely to have liver/lung metastases (41% vs 25%). Median OS were 25.7, 25 and 12.1 months while the median rPFS of the three groups were 9.0, 7.2 and 4.7 months, respectively. Compared to CTC=0, men with HOXB13- CTCs did not have a worse hazard rate for OS (HR: 0.9, 95% CI: 0.4-1.9), while HOXB13+ CTC patients had a worse hazard for OS (HR: 2.0, 95% CI: 1.0-3.9), adjusting for prior abi/enza treatment and Halabi clinical risk score. The positive HOXB13 had also statistically significant increased hazard for progression/death (HR: 2.31, 95% CI: 1.24-4.30). Compared to the group with both HOXB13=0 and CellSearch CTC=0, men with HOXB13 >0 and CellSearch CTC ≥ 5 had increased hazard on both OS and rPFS (OS: HR:2.39, 95% CI: 1.06-5.4; rPFS: HR: 2.78, 95% CI: 1.38-5.59). **Conclusions:** Higher CTC HOXB13 expression is associated with AR dependent biomarkers in CTCs and is adversely prognostic in the context of potent AR inhibition in men with mCRPC, and this assay could be useful to select for patients appropriate for AR or future HOXB13 targeted therapies. Clinical trial information: NCT02269982. Research Sponsor: Pfizer; Astellas.

Characterizing the molecular landscape of early onset and average onset prostate cancer. *First Author: Ifeanyichukwu Ogbuoro, University of Miami Miller School of Medicine, Miami, FL*

Background: Prostate cancer (PC) has a median onset age of 66, however, recent evidence suggests an increase in incidence of PC diagnosis in males <55 years of age. Family history and increased mutational burden has been associated with early onset PC (EOPC), nonetheless, comprehensive molecular and immune signatures that cluster in EOPC and average onset PC (AOPC) is poorly understood. Here, we characterized EOPC and AOPC, and their association with molecular and immune signature. **Methods:** 5,305 PC samples (<55 yrs, $n=575$; ≥ 65 yrs, $n=4730$) were tested by NGS (592, NextSeq; WES, NovaSeq), WTS (NovaSeq) (Caris Life Sciences, Phoenix, AZ). PC Patients with age <55 and ≥ 65 was classified as EOPC and AOPC, respectively. Microsatellite-instability (MSI) was tested by IHC and NGS. Tumor mutational burden (TMB) totaled somatic mutations per tumor (high ≥ 10 mt/MB). Androgen receptor (AR) signature and Neuroendocrine Prostate Cancer (NEPC) score was calculated based on expression of a list of previously defined genes (Hieronimus *et al.* 2006, Beltran *et al.* 2016). Pathway enrichment determined by Gene Set Enrichment Analysis (Broad Inst). Immune cell fractions were calculated by deconvolution of WTS: Quantiseq. Statistical significance was determined using chi-square and Mann-Whitney U test ($p<0.05$) along with FDR-corrected p-values ($q<0.05$). **Results:** EOPC had higher frequency of *TPMRSS2* (35.8% vs 29.7%), *ETV1* (5.2% vs 2.8%), *ETV4* (3.4% vs 1.6%), and *BRAF* (1.9 vs 0.7%) fusions, but lower frequency of APC (4% vs 8%), CTNNB1 (2.4% vs 4.6%), RB1 (2.3% vs 4.7%) and AR (1% vs 4.9%) mutation, TMB high (2.1% vs 4.6%) and dMMR/MSI-H (2.1% vs 4%) compared to AOPC (all $p<0.05$). EOPC had pathway enrichment of myogenesis (NES: 1.5, $q<0.01$), but no difference in hedgehog signaling (NES:1.3, $q=0.09$) and epithelial mesenchymal transition (NES: 1.3, $q=0.09$) pathways compared to AOPC. EOPC had higher median NEPC score (0.359 vs 0.353, $q=0.04$), higher MAPK pathway activity score (MPAS) (3-fold, $q=0.02$) but no difference in median AR signature ($q=0.39$) compared to AOPC. In addition, EOPC had higher expression of PSA (1.2-fold, $q<0.01$) and immunomodulatory genes (*IL12A*, *CTLA4*, FC:1.2, $q<0.05$) with reduced AR expression (1.3-fold, $q<0.01$), however there was no difference in IHC-AR ($q=1$) and PD-L1 ($q=0.57$). Analysis of inferred immune cell infiltrates showed that EOPC had increased infiltration of NK cells (4.5% vs 4.1%, $q<0.01$) and dendritic cells (1.9% vs 1.8% $q<0.05$) compared to AOPC. **Conclusions:** Our data suggest that EOPC is enriched in fusion events including *TPMRSS2*, *ETV1*, *ETV4* and *BRAF*. Distinct transcriptomic features seen in EOPC included neuroendocrine differentiation, MAPK activations, immunomodulatory gene expression, and increased infiltration of NK cells and dendritic cells, suggesting inherent molecular differences and differential tumor immune microenvironment in EOPC and AOPC. Research Sponsor: None.

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Poster Session

Associations between androgen-directed treatments and AR mutational landscapes in the circulating tumor DNA of a real-world metastatic prostate cancer cohort. *First Author: Elisa M. Ledet, Tulane University, New Orleans, LA*

Background: AR alterations evolve under the selective pressure of testosterone suppression and AR targeted agents. In metastatic, castration-resistant prostate cancer (mCRPC) AR's mutational landscape and therapeutics targeting is still an unexplored area. Here we evaluate AR mutations in the circulating tumor DNA (ctDNA) of patients treated with AR targeted agents such as abiraterone (abi), enzalutamide (enza) and in combination (abi + enza) setting in a large Tempus real-world mCRPC cohort. **Methods:** De-identified records of patients with mPC who underwent Tempus xF next-generation sequencing (NGS) ≥ 6 months after treatment initiation of abi, enza, or abi + enza were selected for analysis. If patients had multiple NGS samples, the most recent sample was used. The assay is a targeted liquid biopsy panel that detects single-nucleotide variants and insertions and/or deletions in 105 genes, copy number variants in six genes, and chromosomal rearrangements in seven genes. **Results:** The cohort included 1,122 patients treated with abi only ($n=483$), enza only ($n=374$), or prior exposure to abi + enza ($n=265$). Pathogenic/likely pathogenic mutations were detected in 15% ($n=71$) of patients treated with abi, 15% ($n=56$) treated with enza, and 27% ($n=71$; $P<0.001$) treated with both. The most frequent AR alterations were *L702H* (18%, 32%, and 25%) and *T878A* (34%, 3.6%, and 21%) and *H875Y* (7%, 12%, and 8.5%) in abi, enza, and abi + enza, respectively (Table). *L702H* and *T878A* alterations were found in an additional 8.5%, 3.6% and 9.9% of patients treated with abi, enza, or abi + enza, respectively. Alterations in *L702A* and *H875T* were found in 2.8%, 8.9% and 9.9% of patients treated with abi, enza, and abi + enza respectively. Approximately 4.2%, 1.8% and 1.4% (abi, enza, abi + enza) of treated patients had alterations in *T878A* and *H875Y*. Other single-hit alterations included 6 patients with *W742C* and 4 patients with *F877L*. **Conclusions:** AR mutations have implications for clinical decision making and drug development in patients treated with abiraterone and/or enzalutamide. Research Sponsor: None.

	Overall, N = 198 ¹	abiraterone, N = 71 ¹	enzalutamide, N = 56 ¹	abi + enza, N = 71 ¹
AR Alteration				
Other	56 (28%)	18 (25%)	21 (38%)	17 (24%)
L702H	49 (25%)	13 (18%)	18 (32%)	18 (25%)
T878A	41 (21%)	24 (34%)	2 (3.6%)	15 (21%)
H875T	18 (9.1%)	5 (7.0%)	7 (12%)	6 (8.5%)
L702H + T878A	15 (7.6%)	6 (8.5%)	2 (3.6%)	7 (9.9%)
L702H + H875T	14 (7.1%)	2 (2.8%)	5 (8.9%)	7 (9.9%)
T878A + H875T	5 (2.5%)	3 (4.2%)	1 (1.8%)	1 (1.4%)

¹ n (%).

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Poster Session

Phase I trial of enzalutamide (Enz) plus the glucocorticoid receptor antagonist relacorilant (Rela) for patients with metastatic castration resistant prostate cancer. *First Author: Kunal Desai, University of Chicago Medical Center, Chicago, IL*

Background: Resistance to androgen receptor (AR) targeted therapies is common in mCRPC. Glucocorticoid receptor (GR) expression increases with AR inhibition in patients (pts) and blockade of GR signaling inhibits CRPC growth in preclinical models when combined with AR blockade. We thus conducted a phase I study of the combination of rela and enz in patients with mCRPC. **Methods:** The study used a 6+3 design to assess safety and pharmacokinetics (PK) of the 2-drug combination. The starting dose of rela 100mg/day was chosen based on current clinical studies indicating this dose was both safe for daily dosing and pharmacologically active and the starting dose for Enz was 120mg based on anticipated drug-drug interactions. Escalating doses of rela were combined with Enz 120 using pre-specified dose escalation profiles. An additional 12 patients were to be assessed at the MTD to refine safety and PK profiles. Primary endpoint was safety of the combination and to establish safe and pharmacologically active doses of both agents. Key secondary endpoints were tumor response per RECIST 1.1 criteria and progression-free survival (PFS; defined as either PSA progression, radiographic progression or death). PSA was measured after 12 weeks or at the last time at which PSA data was available, including times <12 weeks. **Results:** 35 pts were enrolled. Pts had a median age of 74 (range 62–85) and baseline PSA of 89.5 (range 7.3–2391). 100% had prior potent AR signaling inhibitor (abi or enz) with 89% receiving prior enz, 94% prior abi, 83% prior both. 69% of pts received prior docetaxel. Median PSA change was 0.1%. Enz 120mg + Rela 100mg and Enz 120mg+Rela 150 were found to be safe and tolerable and achieved desirable Enz PK. DLTs were noted in 3 pts at the 200mg Rela dose, which was deemed to have exceeded the MTD, which was thus defined as 150mg Rela+120mg Enz. Most common ≥ grade 3 treatment related adverse events (TRAEs) were fatigue (11% of pts), anemia (9%), abdominal pain (6%) and pericardial effusion (6%). Median PFS was 2.5 months for 21 of 35 evaluable pts. Best response per RECIST 1.1 were Not Evaluable (40%), SD (34%) & PD (26%). No CR or PR were noted. Most common reasons for discontinuation from trial included progressive disease/hospice (82%), AEs (12%), physician discretion (3%) & death (3%). 2 pts remain on trial as of data cutoff (12/31/22). **Conclusions:** The combination of enzalutamide and relacorilant was safe & largely well tolerated. The majority of pts were discontinued from trial due to progressive disease or hospice. Further analyses of secondary & correlative endpoints such as translational/endocrine biomarkers, GR target gene expression and circulating tumor cells are ongoing. Clinical trial information: NCT03674814. Research Sponsor: U.S. National Institutes of Health; University of Chicago.

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Poster Session

Early changes of PSMA PET signal after initiation of androgen receptor signaling inhibitors in mCRPC: An international multicenter retrospective study. *First Author: Lena Unterrainer, Ahmanson Translational Therapeutics Division, Department of Molecular and Medical Pharmacology, David Geffen School of Medicine, UCLA, Los Angeles, CA*

Background: Androgen receptor signaling inhibitors (ARSi) play a relevant role in the treatment of prostate cancer. A potential influence of ARSi on PSMA expression has been described. We evaluated early changes of PSMA-expression by PET in mCRPC patients. **Methods:** This retrospective study included 5 international sites. Patients with mCRPC undergoing ⁶⁸Ga-PSMA-11 PET/CT prior to (PET1) and early after ARSi (PET2 within 29 days maximum) were included. Whole-body (WB) PSMA-positive tumor volume (PSMA-TV) was evaluated using a liver-specific semi-automatically threshold (Affinity 3.0.2, Hermes Medical Solutions). WB PSMA-TV, SUV_{mean} and SUV_{max} and their respective changes (%) were analyzed. PSA changes between PET1 and PET2 were evaluated. Median values and ranges are provided. **Results:** 54 patients were included in the analysis. ARSi was initiated 1 day (range 0–28) after PET1 while PET2 was performed 14 days (range 7–29) after ARSi initiation. PSA at PET1 and PET2 was 9.5 ng/ml (range 0.2–490.0) and 8.7 ng/ml (range 0.1–732.0), respectively (p = 0.035); -33.0% (range -98%–+496%). The WB PSMA-TV at PET1 and PET2 was 89.9 ml (0.0–3097.0) and 112.2 ml (0.0–3133.0) ml, respectively (p = 0.016; change of +6.0% (range -88%–+260%). WB PSMA SUV_{mean} and SUV_{max} at PET1 and PET2 was 9.0 (range 5.0–43.7) and 9.3 (range 0.0–42.5) and 26.5 (range 0.0–125.0) and 28.5 (range 0.0–212.0), respectively (p = 0.194 and p = 0.353); % change of +3 % (-85%–+71%) and 0% (-55%–+232%). Four of 7 patients with PSA increases at PET2 had an increasing PSMA-TV, 6/7 showed an increasing SUV_{mean} and 5/7 presented with an increased SUV_{max}. Decreasing WB-PSMA-TV in 18/54 (33%) patients was accompanied by decreasing SUVs in 10 of them (56%). Percent PSA change was unrelated to changes in PSMA-TV, SUV_{mean} and SUV_{max}. **Conclusions:** PSMA-PET performed early after ARSi revealed slight increases in the WB-PSMA-TV, stable WB-PSMA SUVs while serum PSA decreased in most of the patients. We conclude that ARSi does not have a strong effect on PSMA expression within 30 days after treatment initiation. Research Sponsor: None.

	PET1	PET2	Change in %	Significance (p-value)
PSA (ng/ml)	9.5 (0.2–490.0)	8.7 (0.1–732.0)	-33 (-98–496)	0.035*
PSMA-TV (ml)	89.9 (0.0–3097.0)	112.2 (0.0–3133.0)	+6 (-88–260)	0.016*
SUV _{mean}	9.0 (5.0–43.7)	9.3 (0.0–42.5)	+3 (-85–71)	0.194
SUV _{max}	26.5 (0.0–125.0)	28.5 (0.0–212.0)	0 (-55–232)	0.353

All values are displayed as median (range). * Statistically significant.

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Poster Session

Circulating tumor cells (CTCs) in patients with metastatic castration resistant prostate cancer (mCRPC) treated with olaparib plus ¹⁷⁷lutetium-prostate specific membrane antigen-617 (¹⁷⁷Lu-PSMA-617) in the LuPARP trial. *First Author: Hamid, Department of Medical Oncology, Peter Mac-Callum Cancer Centre and University of Melbourne, Melbourne, Australia*

Background: LuPARP (NCT03874884) is evaluating the safety and efficacy of olaparib in combination with ¹⁷⁷Lu-PSMA-617 in patients (pts) with mCRPC who have progressed on an androgen receptor pathway inhibitors and docetaxel. We aim to identify potential prognostic and predictive biomarkers from serial CTC profiling. **Methods:** Twenty-six pts with high PSMA expression on PSMA-PET received 7.4 GBq of ¹⁷⁷Lu-PSMA-617 every 6 weeks (wk) together with an escalating dose-schedule of olaparib (50mg BD–300mg BD, days 2 to 14 or days -4 to 14) for up to 6 cycles. For CTC analysis, 10 mls of blood was collected at baseline, 12-weekly for 48 wk, and thereafter every 24 wk and at disease progression. CK+, CD45-, and DAPI+ CTCs were enumerated from 3 mls of blood and immunoassayed for PSMA expression using the Epic Sciences platform. Correlations between total and PSMA+ CTC counts and PSA50 response (PSA reduction of ≥ 50%) were evaluated. Low pass whole genome sequencing (lpWGS) was performed on baseline and longitudinal CTC samples to identify copy number alterations. **Results:** At baseline, 23 of 26 pts (88%) had detectable CTCs (median 2.9 CTC/ml, range 0–30), and of these 23 pts, 17 (74%) had detectable PSMA+ CTCs (median 0.9 CTC/ml, range 0.3–27), indicating heterogeneity of PSMA expression in CTCs. The CTC positivity rates (% of cases ≥ 1 CTC) at week (w) 12, w24, w36, w48 and at disease progression were 57%, 58%, 75%, 36% and 100%, and the PSMA positivity rates (% of cases ≥ 1 PSMA+ CTC) were 38%, 36%, 22%, 50% and 56%, respectively. Fifteen of 20 (75%) evaluable pts with paired baseline and w12 CTCs had a ≥ 50% decline in total CTC count, of which 9/15 (60%) pts also achieved a PSA50 response. Five of these 9 (56%) pts had 100% CTC clearance at w12. In terms of PSMA+ CTCs, 14/15 (93%) evaluable pts had ≥ 50% PSMA+ CTC decline with 13 pts (93%) achieving complete CTC clearance by w12. Six of the 13 pts with complete PSMA+ CTC clearance at w12 also achieved a PSA50 response. Beyond PSMA expression, genomic heterogeneity was evident in baseline and on-treatment CTCs, including recurrent loss of *PTEN*, *TP53*, *BRCA2*, *ATM*, and *RB1*, and gain of *AR* and *MYC*. lpWGS in 10 baseline samples identified 5 cases with *BRCA2* loss and 5 cases with *ATM* loss. Two pts with *BRCA2* loss and 3 pts with *ATM* loss had a PSA50 response by w12. **Conclusions:** We observed high rates of total and PSMA+ CTCs in PSMA-expressing mCRPC. Total and PSMA+ CTCs decline with combined olaparib and ¹⁷⁷Lu-PSMA-617 treatment. Early declines in total and PSMA+ CTCs including 12w CTC clearance paralleled PSA responses. Notably, total and PSMA+ CTCs rise again in the setting of disease progression. Serial CTC profiling may assist in tracking response to ¹⁷⁷Lu-PSMA-617 therapy. Clinical trial information: NCT03874884. Research Sponsor: Prostate Cancer Foundation.

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Poster Session

Deutenzalutamide, an oral deuterated androgen receptor inhibitor, vs placebo for patients with mCRPC who have experienced treatment failure with abiraterone and docetaxel: Results of the HC-1119-04 phase 3 trial. *First Author: Ding-Wei Ye, Fudan University Shanghai Cancer Center, Shanghai, China*

Background: Deutenzalutamide (HC-1119) is a novel deuterated derivative of enzalutamide with a different metabolic profile while maintaining biologic activity at a lower dose. Abiraterone and docetaxel are widely used in mCRPC, however, resistance mechanisms eventually occur. **Methods:** The HC-1119-04 (NCT03851640), a multicenter, randomized, double-blind phase 3 trial in China enrolled patients with mCRPC who have failed abiraterone, or failed or were not eligible for docetaxel. Patients were randomized 2:1 to deutenzalutamide (80 mg orally daily) or placebo. Stratification factors included lesion site (visceral/non-visceral), prior docetaxel treatment (yes/no). The primary endpoint was investigator-assessed radiographic PFS. Secondary endpoints included: OS, independent radiologic review committee (IRC)-assessed rPFS, ORR, and PSA response. The hazard ratio (HR) and its 95% confidence interval (CI) between the two groups were calculated using a stratified Cox proportional hazards model. **Results:** The HC-1119-04 study enrolled 417 subjects between April 2019–Nov 2021, with 276 randomized to deutenzalutamide and 141 to placebo. Demographics and disease characteristics were well-balanced across treatment arms. All subjects were previously treated with abiraterone. Most of the subjects received docetaxel (68.8% vs. 68.1%); visceral lesions accounted for 27.9% in the deutenzalutamide and 27.7% in the placebo group. The study met its primary endpoint with a 42% reduction in the risk of progression or death in the deutenzalutamide arm (HR = 0.58 [95% CI: 0.439, 0.770]; P = 0.001. The median rPFS (95% CI) was 5.55 (4.830, 7.360) months for deutenzalutamide vs 3.71 (2.860, 5.490) months for placebo. Results in the pre-specified subgroups, including visceral metastases, and prior docetaxel were consistent with the overall outcome. The median OS (95% CI) was 14.98 (9.560, -) months and 11.24 (9.890, 15.510) months in the deutenzalutamide and placebo group, respectively, with an HR (95% CI) of 0.88 (0.577, 1.331). Common treatment-related adverse events (TEAE) (> 10%) with deutenzalutamide vs placebo included: weight decreased (23.4% vs 18.6%), platelet count decreased (12.8% vs 10.7%), lymphocyte count decreased (10.2% vs 7.9%), and hypercholesterolemia (10.9% vs 4.3%), mostly grade 1/2. The overall incidence of ≥ Grade 3 study drug related TEAEs in the deutenzalutamide group was not significantly different from placebo, except anemia (6.6% vs 2.9%) and hypertension (2.2% vs 0.7%). **Conclusions:** Deutenzalutamide demonstrated a statistically significant improvement of PFS vs placebo in a randomized phase 3 study in patients with mCRPC who have failed abiraterone, and who failed or were intolerant to docetaxel. Deutenzalutamide was well tolerated and has the potential as additional treatment option. Clinical trial information: NCT03851640. Research Sponsor: Hirona Pharma.

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Poster Session

Enzalutamide vs abiraterone in patients with prostate cancer with and without type 2 diabetes mellitus. *First Author: Amy L Shaver, Department of Medical Oncology, Thomas Jefferson University, Philadelphia, PA*

Background: Estimations are that 8-18% of newly diagnosed cancer patients have Type 2 Diabetes Mellitus (T2DM). Current guidelines offer no clarification on the choice of therapy for prostate cancer (PCa) patients with T2DM. Since the comorbid PCa—T2DM population is increasing and these patients face unique challenges from adverse events requiring acute care utilization (ACU) it is important to ascertain which medication poses less of a threat of adverse events. The objective of this study was to describe the SEER-Medicare T2DM-PCa population in terms of those with and without complications and determine if T2DM influences ACU and PCa medication choice. **Methods:** We identified men with primary PCa treated with abiraterone (ABI, 2011) or enzalutamide (ENZ, 2012) with comorbid T2DM using the Surveillance, Epidemiology, and End Results (SEER)-Medicare database (1999-2019). Patients with a missing date of diagnosis, those diagnosed at death, having HMO or no continuous A and B coverage 12 months before diagnosis and 6 months continuous part D coverage before starting treatment as well as 6 months following treatment or until death were excluded. T2DM was identified using ICD-9 and ICD-10 codes. ACU was calculated utilizing the CMS Research Data Assistance Center definition focusing on emergency room visits resulting in in-patient hospitalization during the 6 months following treatment initiation. Differences in emergency room in-patient visits were evaluated using negative binomial models adjusted for age, race, SEER region, marital status, state-buyin, education, income, and modified Charlson Comorbidity Index (excluding T2DM). **Results:** The sample of 11,163 men included 61.8% treated with ABI and 38.2% with ENZ. We identified 3,044 (27.3%) men with T2DM, of which, 59.1% were treated with ABI and 40.8% with ENZ. Compared to those without T2DM those with T2DM had more ACU, regardless of medication, with a higher rate in the ABI than ENZ group, see table. Among diabetics, those with complications related to T2DM compared to those without also experienced a higher rate of ACU. The rate of ACU was 43% higher among those treated with ABI compared to ENZ (IRR 1.43; 95% CI 1.28, 1.61). Overall mortality (15.7% vs 10.1%, $p<0.01$) and PCa-specific mortality (8.2% vs 5.3%, $p<0.01$) were worse in those with T2DM treated with ABI compared to ENZ. **Conclusions:** Outcomes for PCA patients with T2DM are worse than for those without. ACU is higher in men treated with ABI compared to ENZ regardless of T2DM status. Given the worse outcomes for comorbid T2DM patients, further study to evaluate comorbidity management in this population is warranted. Research Sponsor: U.S. National Institutes of Health; PA CURE: 4100088563.

Crude acute care utilization per person-days by T2DM among those treated with abiraterone and enzalutamide.		
	Abiraterone (n=6,900)	Enzalutamide (n=4,263)
Overall	0.38	0.28
Type 2 Diabetes Mellitus (T2DM)		
No T2DM	0.34	0.26
T2DM without complications	0.43	0.26
T2DM with complications	0.56	0.45

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Poster Session

Genomic alterations and self-reported Agent Orange exposure in United States veterans with metastatic prostate cancer. *First Author: JJ Haijing Zhang, David Geffen School of Medicine at University of California Los Angeles (UCLA), Department of Urology, Los Angeles, CA*

Background: Agent Orange has been posited as an environmental risk factor for prostate cancer among United States Veterans. Prior studies have shown that Veterans with Agent Orange exposure are diagnosed at a younger age and at more advanced clinical stages. It is unknown if there are differences in somatic alterations among Veterans exposed to Agent Orange. **Methods:** Genomic alterations were identified from clinical tumor testing conducted from 2019 – 2022 in a large cohort of Veterans with metastatic prostate cancer diagnosed from 2001 – 2022. Primary prostate and metastatic carcinoma tissue specimens were submitted for Foundation Medicine tumor-only sequencing. Baseline demographics, clinical, and genomic alterations data were stratified by Veteran self-reported exposure to Agent Orange in accordance with an institutional review board approved protocol. **Results:** Of the 2673 Veterans with metastatic prostate cancer who underwent tumor-only genomic testing, 629 reported exposure to Agent Orange and 2044 were not exposed. After verification of military service records of Veterans with self-reported Agent Orange exposure to include only Veterans who served in the Vietnam War between 1962 – 1975 and Korean War between 1967 – 1971, 603 patients with self-reported Agent Orange exposure (22.8%) and 2044 without exposure (77.2%) were included in the analysis. On univariate analysis, *TPMRSS2-ERG* fusions were significantly more frequent in men who reported exposure to Agent Orange (35.3% vs 28.8%, $p<0.01$) after multiple hypothesis testing with Benjamini-Hochberg. Agent Orange exposure also correlated to higher rates of androgen receptor (*AR*) alterations (12.4% vs 9.5%, $p=0.04$) and *FGFR1/2/3/4* alterations (3.2% vs 1.7%, $p=0.02$). There were no significant differences in alterations in Agent Orange exposure in *TP53*, *CDK12*, *ERBB2*, *EGFR*, *BRCA*, and genes implicated in the DNA damage response and repair (*DDR*), mismatch repair (*MMR*), and *PTEN/PI3K/AKT* pathways. On multivariable analysis controlling for race, age at diagnosis, smoking, secondary malignancies, and environment, only alterations in *AR* (OR 1.43, $p=0.02$) remained more frequent in Veterans exposed to Agent Orange. As expected, age at diagnosis (OR 0.98, $p<0.001$) and Black/African-American race (OR 0.33, $p<0.001$) were associated with decreased odds of *TPMRSS2-ERG* alterations. **Conclusions:** Agent Orange exposure may contribute to tumor somatic alterations in Veterans with prostate cancer. These findings hold potential prognostic and therapeutic implications for U.S. Veterans with metastatic prostate cancer. Research Sponsor: None.

Genomic alterations associated with Agent Orange exposure.						
Genomic Alteration	Univariable			Multivariable		
	Odds Ratio	95% CI	p-value	Odds Ratio	95% CI	p-value
TPMRSS2-ERG	1.35	1.12 - 1.64	0.002**	1.18	0.91 - 1.53	0.2
AR	1.35	1.01 - 1.79	0.04*	1.43	1.06 - 1.92	0.02*
FGFR 1/2/3/4	1.87	1.06 - 3.29	0.03*	1.72	0.97 - 3.06	0.06

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Poster Session

Determinants of widespread metastases and of metastatic tropism in patients with prostate cancer: A genomic analysis of primary and metastatic tumors. *First Author: Edward Christopher Dee, Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: A growing body of evidence suggests that metastatic cancer is better described as a spectrum of disease rather than a binarily defined state, ranging from oligometastatic cancer to widespread metastases. Widespread metastases represent the most common cause of cancer-related death among patients with prostate cancer. Therefore, a greater understanding of the genomic features that determine the extent and location of metastatic spread may inform risk stratification, treatment, and monitoring. We identify genomic alterations from primary prostate tumors that are predictive of widespread metastatic potential. **Methods:** Genomic and clinical data for 1,312 patients with primary prostate adenocarcinomas were extracted from the MSK-MET cohort through cBioPortal. Metastatic site counts and overall survival (OS) data were publicly available for all patients. All samples from primary tumors were profiled using the MSK-IMPACT targeted sequencing platform. Our study focused on 58 genes frequently altered in prostate cancer. Cox proportional hazard analyses defined hazard ratios (HRs) and 95% confidence intervals (CIs) for overall mortality in patients with different metastatic outcomes. Patterns of genomic alterations of the primary tumor associated with metastatic extent and location were compared. **Results:** Out of 1,312 patients, 939 (71%) developed metastases, and 113 (8.6%) had metastases to 5 or more distinct anatomical sites (defining wide-spread metastases, WSM). Bone was the most common site of metastasis (36%), and 80% of patients with liver metastases had 4 or more additional sites of metastasis. Among patients with metastases, increasing number of metastatic sites was associated with increased risk of death (HR:1.8, 95% CI:1.63-1.99, $p<0.001$). To define genomic determinants of WSM, we characterized genomic alterations in 58 prostate cancer related genes. Alterations in the following genes were enriched in tumors from patients with WSM vs others: TP53 mutation (40% vs 20%, $p<0.0001$), FOXA1-amplification (8% vs 3%, $p=0.02$), AR-amplification (4.4% vs 1%, $p=0.01$), RB1-deletion (5.3% vs 0.7%, $p=0.001$), and BRCA2-deletion (4.4% vs 0.7%, $p=0.01$). In a univariable survival analysis, all these alterations were predictive of OS ($p<0.05$). However, on multivariable analysis, only TP53 mutations, and FOXA1 and AR amplifications were independent prognostic factors. Amplifications of FOXA1 ($n=37$) and AR ($n=13$) were mutually exclusive (0 overlap), and we found that patients who have either AR or FOXA1 amplifications experienced very poor OS (HR:3.57, 95%CI:2.26-5.6, $p<0.001$). **Conclusions:** We identified genomic alterations (TP53 mutations, FOXA1 and AR amplification, RB1 and BRCA2 deletions) from primary prostate tumors that are predictive of wide-spread metastases and poor outcomes. Research Sponsor: U.S. National Institutes of Health.

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Poster Session

Association of dynamic changes in serological markers with survival in de novo metastatic hormone-sensitive prostate cancer. *First Author: Soumyajit Roy, Rush University Medical Center, Chicago, IL*

Background: Prognostic association of serological markers of systemic inflammatory response have been demonstrated in metastatic castrate resistant prostate cancer. However, it remains unknown whether dynamic changes in these markers over time are prognostic earlier in the disease process, namely in metastatic hormone sensitive prostate cancer (mHSPC). We performed a secondary analysis of LATITUDE trial to determine if dynamic changes in hemoglobin (Hb), neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), and lymphocyte to monocyte ratio (LMR) are predictive of prostate cancer-specific survival (PCSS), and overall survival (OS). **Methods:** We used a joint model approach to determine the association of the dynamic change in the marker levels with PCSS, and OS. For the time-to-event submodel, a multivariable Cox regression model was constructed with treatment arm, skeletal lesion number, liver or lung metastasis, ECOG performance status, and age. For the longitudinal submodel, a linear mixed-effects model was built with an interaction term for treatment arm and time of evaluation in addition to treatment arm, time of evaluation, and baseline value of the serological markers. The two submodels were linked through a shared random effect. **Results:** Overall 1172 patients were eligible - 580 from the abiraterone plus ADT arm and 592 from the ADT alone group. Median follow-up for surviving patients was 52 months (IQR 47-57). Median number of post-baseline assessments was 16 (IQR 10-28). On univariate joint models, every 10 g/L dynamic increase in Hb was associated with superior PCSS (HR 0.71 [0.67-0.75]) and OS (HR 0.74 [0.68-0.79]) while every 5 points dynamic increase in LMR was associated with a superior PCSS (HR 0.38 [0.26-0.53]) and OS (HR 0.41 [0.29-0.56]). In contrast, dynamic increase in NLR was associated with inferior PCSS (HR 1.29 [1.22-1.36]) and OS (HR 1.29 [1.23-1.36]) while every 10-point dynamic increase in PLR was associated with a small but significant deterioration in PCSS (HR 1.05 [1.04-1.06]) and OS (HR 1.05 [1.04-1.06]), respectively. On multivariate joint modeling, dynamic increase in Hb was also associated with superior PCSS (HR per 10g/L increase 0.74 [0.69-0.79]) and OS (HR per 10g/L rise 0.75 [0.71-0.80]). When dynamic changes in Hb, LMR, NLR, and PLR were included in the same multivariate model with dynamic change in PSA, dynamic increase in Hb continued to show association with significantly superior PCSS (HR per 10g/L rise 0.80 [0.75-0.86]), and OS (HR per 10g/L rise 0.81 [0.75-0.86]), respectively. **Conclusions:** Our findings suggest that dynamic increase in hemoglobin can predict for superior PCSS, and OS in men with de novo mHSPC treated with ADT with or without abiraterone. These findings need additional validation before implementing routine use of hemoglobin as a prognostic biomarker in de novo mHSPC. Research Sponsor: None.

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Poster Session

Assessing PSA levels as prognostic of overall survival (OS) in men with metastatic hormone-sensitive prostate cancer (mHSPC). *First Author: Susan Halabi, Duke University Medical Center, Durham, NC*

Background: Prior data have shown that prostate specific antigen (PSA) ≤ 0.2 ng/dL at 6-7 months with androgen deprivation therapy (ADT) with testosterone suppression (TS) alone is prognostic of OS. We hypothesized that PSA ≤ 0.1 ng/dL at 7 months would be a stronger prognostic for OS in men with mHSPC treated with TS alone. This hypothesis was investigated by the STOPCAP M1 collaborators. **Methods:** Individual patient data from 13 eligible randomized trials comparing treatment regimens (TS or TS + docetaxel in the control or research arms in mHSPC trials) were utilized. Landmark survival analyses were performed at 7 months after ADT initiation. Overall survival was computed as the time from 7 months after start of initial TS to death or date of last follow for patients who started TS prior to randomization or 7 months after randomization to death or date last follow-up for patients who started TS after randomization. PSA measurements between 4-7 months after ADT were selected and cut off-points of PSA ≤ 0.2 , 0.2-4, and >4 ng/dL or PSA ≤ 0.1 , 0.1-0.2, 0.2-4, and >4 ng/dL were considered. The proportional hazards model was utilized to explore the prognostic significance of PSA levels in predicting OS adjusting for treatment in all patients and patients who were enrolled on docetaxel trials. **Results:** IPD from 5,438 patients randomized 1994-2012 from 13 trials were pooled. At 7 months, the proportion of patients who had PSA ≤ 0.1 and PSA ≤ 0.2 were 18.1% and 26.1%. The median OS in patients who experienced PSA ≤ 0.1 and PSA ≤ 0.2 and in patients enrolled on docetaxel trials are presented in the table below. The hazard ratios (HR) for death for PSA ≤ 0.1 and PSA ≤ 0.2 vs. those PSA >4 at 4-7 months were 0.26 and 0.27, respectively. In patients enrolled on docetaxel, HRs for death for PSA ≤ 0.1 and PSA ≤ 0.2 vs. those PSA >4 at 7 months were 0.35 and 0.34, respectively. **Conclusions:** PSA ≤ 0.1 and PSA ≤ 0.2 at 7 months have similar prognostic value of OS in men with mHSPC treated with weak ADT (TS alone) without and with docetaxel. Clinical trial information: NCT00309985; NCT00268476; NCT00104715; NCT00079001; NCT00002651; NCT00685646. Research Sponsor: Prostate Cancer Foundation; U.S. National Institutes of Health.

	PSA Levels (ng/dL)				
	≤ 0.1 (n=986)	0.1-0.2 (n=435)	≤ 0.2 (N=1,421)	0.2-4 (n=2,270)	>4 (n=1,747)
All Trials					
Median OS, years in 13 units* (5,348 pts; 95% CI)	6.59 (6.06-7.13)	6.52 (5.55-7.17)	6.59 (6.06-7.08)	4.33 (4.05-4.56)	1.81 (1.71-1.95)
HR of PSA level vs. Ref (95% CI)	0.26 (0.23-0.29)	0.30 (0.26-0.35)	0.27 (0.25-0.30)	0.44 (0.40-0.47)	Ref
Docetaxel trials					
4 units* (2,378 pts)					
Median OS, years (95% CI) ADT	NE (5.14-NE)	7.14 (5.64-NE)	7.14 (6.01-NE)	4.25 (3.86-4.65)	1.98 (1.77-2.26)
Median OS, years (95% CI) ADT+Docetaxel	5.79 (5.25-7.56)	7.08 (5.55-NE)	6.70 (5.57-7.65)	4.56 (4.10-5.02)	2.52 (1.99-3.05)
HR of PSA level vs. Ref (95% CI) in ADT	0.22 (0.16-0.31)	0.25 (0.18-0.36)	0.23 (0.18-0.30)	0.43 (0.37-0.50)	Ref
HR of PSA level vs. Ref (95% CI) ADT+Docetaxel	0.35 (0.27-0.46)	0.32 (0.23-0.43)	0.34 (0.27-0.42)	0.5 (0.40-0.67)	Ref

*Units= Number of comparisons; NE=not estimated, Ref=referent.

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Poster Session

Early results from CASCARA: A phase 2 study of cabazitaxel/carboplatin plus abiraterone in high-volume metastatic castrate-sensitive prostate cancer (mCSPC). *First Author: Charles J. Ryan, Prostate Cancer Foundation, Santa Monica, CA*

Background: Best treatment of mCSPC involves doublet therapy (ADT + novel hormonal agent) or triplet therapy (ADT + novel hormone + docetaxel); however, opportunity remains for further improvement. Studies show that homologous recombination repair (HRR) gene mutations are enriched in metastatic prostate cancer, and may portend resistance to docetaxel. CASCARA tested quadruplet therapy (ADT + cabazitaxel/carboplatin + abiraterone) in high-volume mCSPC, aiming to enhance PSA responses and decrease progression at 1 year. **Methods:** This phase 2 study enrolled 61 mCSPC patients with high-volume disease who received ADT plus cabazitaxel (20 mg/m² q21d x 6) and carboplatin (AUC=4 q21d x 6) followed by abiraterone (1000 mg, plus prednisone 5 mg). Primary endpoint was freedom from PSA/radiographic progression at 1 year. Other endpoints included PSA₅₀ response, freedom from PSA progression, and safety. Archival biopsies were retrospectively evaluated for HRR (*BRCA1/2*, *ATM*, *CHEK2*, *CDK12*, *BRIP1*, *RAD51B*) mutations at a CLIA-certified lab. A sample size of 61 was determined using a Simon two-stage design (stage 1: 32 men, stage 2: 29 men) with a null hypothesis of a 1-year PSA/radiographic progression-free rate of 0.80 against a one-sided alternative of 0.92. **Results:** From 11/2019 to 06/2022, 61 men enrolled at 7 sites. Median age was 64 (range, 45–76) years; 21% were African American. Median baseline PSA was 8.9 (range, 0.1–1021) ng/mL. 44% of men had ECOG=1. 91% had Gleason sum 8–10. Prevalence of DNA alterations (50 evaluable pts) was 18% for HRR mutations, 38% for *TP53* muts, 22% for *ERG* fusions, 10% for *SPOP* muts. Freedom from PSA/radiographic progression at 1 year was 77% (95% CI, 63–87%), and freedom from PSA progression at 1 year was 81% (95% CI, 67–90%). The PSA₅₀ rate response was 97%. PSA ≤ 0.2 ng/mL at month-7, a surrogate for survival in other mCSPC studies, was 61%; PSA ≤ 4 ng/mL at month-7 was 82%. Outcomes according to mutation status are shown. AEs included 7% grade (Gr)-3/4 myelosuppression, 8% Gr-3/4 infections, 10% Gr-3 GI disorders, and 3% Gr-3 fatigue. There were 4 treatment-related discontinuations. **Conclusions:** Quadruplet therapy with ADT + cabazitaxel/carboplatin + abiraterone was well tolerated. At 1 year, 77% of pts were progression-free. PSA ≤ 0.2 ng/mL at month-7 was 61%, exceeding the historical month-7 PSA ≤ 0.2 ng/mL rate of 45% in CHAARTED-docetaxel arm. Further exploration of this quadruplet strategy in randomized phase III studies is warranted. Clinical trial information: NCT03934840. Research Sponsor: Sanofi-Genzyme.

	HRR status N (%)	TP53 status N (%)	ERG fusion N (%)	SPOP status N (%)
Freedom from PSA/radiographic progression at 1 yr	HRRm – 6 (67%) HRRwt – 34 (83%)	TP53m – 14 (77%) TP53wt – 26 (84%)	ERGm – 11 (100%) ERGwt – 29 (74%)	SPOFm – 5 (100%) SPOFwt – 35 (78%)
PSA ≤ 0.2 ng/mL at month 7	HRRm – 3 (38%) HRRwt – 27 (66%)	TP53m – 12 (67%) TP53wt – 18 (60%)	ERGm – 9 (82%) ERGwt – 21 (55%)	SPOFm – 4 (100%) SPOFwt – 26 (58%)

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Poster Session

Enzalutamide, docetaxel and androgen deprivation (ENZADA trial) for metastatic castrate sensitive prostate cancer (mCSPC). *First Author: Earle F Burgess, Levine Cancer Institute, Atrium Health, Charlotte, NC*

Background: The use of contemporary androgen receptor signaling inhibitors (ARSI) in combination with docetaxel (Doc) and androgen deprivation therapy (ADT) has shown improved outcomes in recent trials. Prostate specific antigen (PSA) serologic complete response (CR) has correlated with improved overall survival (OS) in prior studies. In the E3805 study, the 12-month PSA CR rate was 28% for the ADT + Doc arm. In this study, we hypothesized the combination of androgen deprivation therapy with Doc and enzalutamide (Enz) would improve the 52-week PSA CR rate compared to the historical control with ADT + Doc in newly diagnosed patients with mCSPC. **Methods:** The ENZADA trial is a single institution phase II study in patients with mCSPC. Patients received ADT, Doc 75 mg/m² IV every 3 weeks for up to 6 cycles and Enz 160mg daily until radiographic progression. The primary endpoint was 52-week PSA CR. Secondary endpoints included safety/toxicity, best PSA response, time to castration resistance (TTCR) and overall survival (OS). Patients were stratified by radiographic volume of disease by E3805 criteria. The study was designed with 90% power and 1-sided alpha 0.1 to show an improvement in the 52-week PSA CR from 25% to 45%, with rejection of the null hypothesis if 14 of 39 evaluable subjects achieved a 52-week PSA CR. **Results:** Between Sep 2017 and Aug 2021, 40 subjects were enrolled, and 36 were evaluable for the primary endpoint. At the data cut-off of 9/2/22, median follow up was 42.6 months. Thirty subjects (75%) had high volume disease, and 32 (80%) subjects presented with de novo metastatic disease. Median age was 64.5 years; 65% (N=26) were identified as White and 35% (N=14) were identified as Black or African American (AA). Median pretreatment PSA was 129.5 ng/mL. 67.5% (27/40) of subjects received six cycles of Doc. 10% (4/40) of subjects had Enz dose modifications. 52-week PSA CR occurred in 22/36 (61.1%) patients (P<0.001). 13/23 (56.5%) White subjects and 9/13 (69.2%) Black or African American subjects experienced 52-week PSA CR (P=.50). Median TTCR was not reached; castrate resistance at 2 and 4 years was 62.4% and 53.5%, respectively. Eleven deaths occurred (3/14 Black or AA and 8/26 White); median OS was not reached. OS at 2 and 4 years was 83.2% and 63.1%, respectively. OS at 2 and 4 years was 85.7% and 78.6%, respectively, in Black or AA subjects and 82.4% and 50.9%, respectively, in White subjects (P=.26). Treatment-related Grade 3-5 adverse events occurred in 17/40 (42.5%) patients, including 3 episodes of febrile neutropenia. **Conclusions:** ADT+Doc+Enz improved 52-week PSA CR compared to historical control with ADT+Doc. These results are consistent with the recent ARASENS and PEACE1 studies and support the use of triplicate regimens combining ADT+Doc+ARSI in newly diagnosed mCSPC patients. No detectable difference in outcome by race has been observed to date in the study cohort. Clinical trial information: NCT03246347. Research Sponsor: Astellas Pharma Global Development, Inc./Pfizer, Inc.

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Poster Session

The relationship between a priori defined prognostic risk groups and overall survival (OS) in men with metastatic hormone sensitive prostate cancer (mHSPC). *First Author: Susan Halabi, Duke University Medical Center, Durham, NC*

Background: Prior analyses have shown that men who present with high volume (HV) disease and *de novo* metastases have shorter OS compared with other mHSPC subgroups. The objective of this analysis was to determine the prognostic relationship between *a-priori* defined 4-prognostic groups and OS in men with mHSPC and in a subset of trials in patients treated with androgen deprivation therapy (ADT) + docetaxel. This hypothesis was investigated by the STOPCAP M1 collaborators. **Methods:** We obtained individual patient data (IPD) from 13 randomized trials comparing treatment regimens (ADT or ADT + docetaxel in the control or research arms) in mHSPC. OS was defined as the time between date of randomization and date of death/or last follow-up. Patients (pts) were classified into 4 mutually exclusive groups. Poor prognostic risk-group was defined as HV (presence of visceral metastases, and/or >4 bone metastases) or presence of bone metastases beyond pelvic or vertebral bones) plus synchronous diagnosis (SYN); whereas intermediate risk groups were patients with HV and metachronous (MET; intermediate A) or low volume plus SYN (intermediate B); and lastly good risk group had LV plus MET. The proportional hazards model was used to estimate the hazard ratio (HR) and assess the prognostic significance of risk groups in predicting OS adjusting for treatment. **Results:** Of 6041 pts included in this analysis, 60% (3622 pts) had died. Median follow-up time=5-years. Overall 11%, 8%, 47% and 34% were in the good, intermediate A, intermediate B and poor risk groups, respectively and for trials including docetaxel (n=2627 pts) 9%, 5%, 39% and 47% respectively. HRs for risk groups are shown in the table. **Conclusions:** Differences in OS across the risk groups were observed. Further work is needed to investigate if more precise prognostic groups can be defined such as better characterization of patients' groupings of extent of bone metastases and visceral metastases. Clinical trial information: NCT00309985; NCT00268476; NCT00104715; NCT00079001; NCT00002651; NCT00685646. Research Sponsor: Prostate Cancer Foundation.

	Good (LV+MET) (n=686)	Intermediate A (HV+MET) (n=465)	Intermediate B (LV+SYN) (n=2852)	Poor (HV+SYN) (n=2038)
Median OS in 6,041 pts, units*=12 (years; 95% CI)	6.4 (5.8-7.4)	5.1 (4.8-5.8)	4.8 (4.5-5.0)	3.6 (3.5-3.8)
HR for risk group vs ref (95% CI)	0.53 (0.47-0.60)	0.76 (0.71-0.82)	0.73 (0.64-0.82)	Ref
Median OS in 2,627 pts, units*=4 (years; 95% CI)	NE (8.2-NE) 6.9 (5.8-NE)	4.3 (2.9-5.2) 5.5 (3.1-6.2)	4.7 (4.2-5.4) 6.0 (5.4-6.5)	2.9 (2.7-3.1) 3.8 (3.4-4.0)
ADT				
ADT + Docetaxel				
HR for risk group vs ref ADT (95% CI)	0.21 (0.15-0.30)	0.78 (0.57-1.06)	0.51 (0.44-0.59)	Ref
HR for risk group vs ref ADT+Docetaxel (95% CI)	0.41 (0.30-0.55)	0.73 (0.54-0.99)	0.57 (0.48-0.66)	Ref

*Units= number of trial comparisons; Ref=referent; HR=hazard ratio, CI=confidence interval, NE=not estimated.

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Prostate-specific antigen value at 3 & 7 months (PSA-3mo, PSA-7mo) and overall survival (OS) in metastatic hormone-sensitive prostate cancer (mHSPC) treated with androgen deprivation (ADT) with or without orteronel (SWOG S1216). *First Author: Mamta Parikh, University of California Davis Comprehensive Cancer Center, Sacramento, CA*

Background: Analysis of phase 3 studies of patients (pts) with mHSPC in the era of ADT, including in combination with docetaxel and/or androgen receptor axis targeted therapies have established PSA-7mo as a key prognostic marker. Our objective was to evaluate the association between PSA-3mo, PSA 7-mo and OS measured in the phase 3 S1216 trial in mHSPC comparing ADT + orteronel (treatment arm) vs ADT + bicalutamide (control arm) [NCT01809691]. **Methods:** Pts enrolled in the S1216 trial with available PSA-3mo & PSA-7mo were included in this analysis. PSA responses were defined as complete response (CR) if PSA $\leq$ 0.2 ng/mL, partial response (PR) for PSA $>$ 0.2 and $\leq$ 4ng/mL, and no response (NR) as PSA $>$ 4 ng/mL at month 3 or 7. Landmark OS was measured and Cox regression model applied adjusting for stratification (performance status, extent of disease, early vs late start of treatment, treatment arm). **Results:** 1251 pts were alive and evaluable for PSA-3mo and 1231 pts were evaluable at 7 mo, out of a total of 1279 pts. The median age was 67 (range: 43-92), 10% of patients were black, 96% had a Zubrod performance status of 0-1. Median PSA at baseline was 29 ng/ml (range: 2-6710). Of pts on treatment vs control arm, PSA-3mo CR, PR, and NR occurred in 52% vs 35%; 31% vs 42%, and 17% vs 23%, respectively. Of pts on treatment vs control arm, PSA-7mo CR, PR, and NR occurred in 61% vs 46%, 20% vs 26%, and 19% vs 29%, respectively. CR or PR at either timepoint led to significantly better outcomes than those with NR. No interaction between treatment arm and PSA response was observed in terms of OS. **Conclusions:** PSA-3mo and PSA-7mo are strong prognostic markers for pts with mHSPC. More pts on ADT with orteronel achieved CR at 3 and 7 mo. In addition to its use in counseling patients in the clinic, PSA-3mo and PSA-7mo may be used as parameters for designing future trials in pts with mHSPC, utilizing the next generation of intensification or de-intensification treatment regimens. Clinical trial information: NCT01809691. Research Sponsor: U.S. National Institutes of Health; Millenium Pharmaceuticals (Takeda Oncology Company).

Response	Hazard Ratio	95% CI	2-sided p-value	5-year OS post PSA response at 3 months	
3-month				Treatment	Control
CR	0.34	(0.27,0.42)	<0.0001	72%	73%
PR	0.60	(0.49,0.73)	<0.0001	51%	54%
NR	1.0 (ref)	–	–	31%	31%
5-year OS post PSA response at 7 months					
7-month				Treatment	Control
CR	0.20	(0.16,0.24)	<0.0001	75%	78%
PR	0.51	(0.42,0.63)	<0.0001	39%	47%
NR	1.0 (ref)	–	–	24%	23%

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Comparing the efficacy of abiraterone and enzalutamide in United States veterans with metastatic castration-sensitive prostate cancer (mCSPC) by estimating rates of tumor growth (g-rate). *First Author: Harshraj Leuva, University of Nebraska Medical Center, Omaha, NE*

Background: The choice of 1st line novel hormonal therapy in mCSPC is often based on comorbidities/physician preference due to the lack of data comparing abiraterone (Abi) and enzalutamide (Enza) in clinical trials and in real-world settings; especially in Black American (BA) patients. We have developed a novel method to estimate rates of tumor growth (g-rate) and have shown that the g-rate is a robust biomarker of drug efficacy and overall survival in prostate cancer (Wilkerson, 2017; Leuva, 2019). We performed a 1:1 matched analysis to compare Abi and Enza outcomes in 1st line mCSPC, using g-rate and median overall survival (mOS) estimates. **Methods:** All patients with mCSPC diagnosis in national VA Corporate Data Warehouse were eligible for comparison. The cohort date range was from 7/2017 to 6/2022. Drug efficacy was established by estimating g-rates using PSA values while on therapy via the TUMGr package for R. For the matched analyses, we created 1:1 comparison cohorts for Abi and Enza, matched on age ($\pm$ 10 years), race, total number of therapies received ($1\geq 2$), drug start year ($<2020\geq 2020$), PSA at diagnosis ($<20\geq 20$), Gleason score (GS) ($<8\geq 8$), Charlson comorbidity index excluding cancer diagnosis ($<5\geq 5$) and therapy setting (urban/rural). **Results:** We identified a total of 1712 and 464 Veterans with mCSPC who received Abi and Enza as 1st line, with median follow-ups of 19 and 12 mo, respectively. Fewer Veterans and shorter duration of follow up with Enza than Abi reflect Abi's earlier approval in mCSPC. The Abi and Enza cohorts had similar median g-rates 0.000114/d and 0.000110/d, respectively (p=0.76). The mOS was 43 mo for Abi versus not reached (NR) for Enza (p=0.33). Our cohort had 425(25%) and 119(26%) BA veterans who received Abi and Enza, respectively. Compared to Caucasians, mOS was similar with Abi (42.7 vs 41.9 mo, HR=0.96, p=0.6) and Enza (NR, HR=0.85, p=0.4) for BA. In 1:1 matched analysis, the Abi and Enza arms had 391 patients and both had median follow-ups of 13 mo. We did not observe a statistically significant difference in median g-rate and mOS for either the whole matched cohort or BA subgroup when comparing Abi to Enza. The matched cohort had 203 (52%) with GS $\geq$ 8 and 228 (58%) Veterans with PSA $\geq$ 20 at diagnosis; there was no significant mOS difference in these subgroups. **Conclusions:** Real-world data from 2176 Veterans show comparable efficacy for Abi and Enza as 1st line for mCSPC, with similar g-rates and mOS, even when matched on various factors, including comorbidities, and in aggressive/high volume matched cohorts. BA patients also had similar g-rates and mOS. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology.

Matched analysis	Abi (n=391)	Enza (n=391)	p value
Median g	0.000110/d	0.000112/d	0.93
mOS	43.9 mo	NR	0.84
GS $\geq$ 8 group	54 mo	NR	0.63
PSA $\geq$ 20 group	40.7 mo	NR	0.57
Matched Black American	n=90	n=90	
Median g	0.000117/d	0.000110/d	0.08
Median OS	NR	NR	0.09

Differential tumor gene expression profiling of obese and non-obese patients (pts) with prostatic adenocarcinoma (PC). *First Author: Vinay Mathew Thomas, Huntsman Cancer Institute at the University of Utah, Salt Lake City, UT*

Background: Increased baseline body mass index (BMI) has been linked to poorer prostate cancer outcomes, including recurrence, reduced quality of life, and mortality (PMID: 21325564, 17211863). Herein, we sought to interrogate and validate the corresponding differences in tumor gene expression profiles of obese (Ob) vs. non-obese (N-Ob) pts with PC. **Methods:** In this IRB-approved retrospective study, eligibility criteria included histologically confirmed PC and available RNA sequencing results from treatment naïve primary prostate tissue from a CLIA-certified lab (either Tempus or Caris Life Sciences). Tempus cohort was used for interrogation and Caris for validation. Pts in each cohort were categorized into two groups: obese (BMI $\geq$ 30) and non-obese (BMI $<$ 30). BMI at the time of diagnosis of PC was used for analysis. The DESeq2 pipeline was used to analyze differentially expressed genes between the groups. The data included the Log2 fold change, Wald-Test p-values, and Benjamini-Hochberg adjusted p-values for each differentially expressed gene. These results were subjected to Gene Set Enrichment software analysis (GSEA) to identify pathways enriched in each cohort. All bioinformatic analysis was undertaken using R v4.2. **Results:** Tempus cohort: n=60 (Ob =22, N-Ob=38); Caris cohort: n=50 (Ob=17, N-Ob=33). Both Tempus and Caris showed that Ob pts had an increased expression of the heme metabolism, androgen response, protein secretion, fatty acid, and bile metabolism pathways. N-Ob pts had a significantly higher expression of genes involved in the inflammation pathways (interferon-alpha & TNF alpha pathways). Normalized enrichment scores are reported in the table. Differential gene set expression analysis in Ob vs. N-Ob pts with PC. **Conclusions:** Our study showed an upregulation of distinct genomic pathways in Ob pts with prostate cancer. For example, Ob pts with PC have tumors that depend more on androgen signaling, and N-Ob pts' tumors express increased inflammatory pathway genes that promote PC growth, invasiveness, and metastasis. After external validation, these hypothesis-generating data may provide the rationale for personalized therapy in men with PC. Research Sponsor: None.

Tempus			Caris		
Pathway	Normalized Enrichment Score	q-values	Pathway	Normalized Enrichment Score	q-values
Heme Metabolism	2.32	<0.01	Heme Metabolism	2.32	<0.01
Protein Secretion	1.76	<0.01	Protein Secretion	1.76	<0.01
Fatty Acid Metabolism	1.66	<0.01	Fatty Acid Metabolism	1.66	<0.01
Bile Acid Metabolism	1.52	<0.01	Bile Acid Metabolism	1.51	<0.01
Androgen Response	1.47	0.01	Androgen Response	1.47	0.01
MYC Targets	-1.89	<0.01	MYC Targets	-1.89	<0.01
Interferon- α	-2.35	<0.01	Interferon- α	-2.35	<0.01
TNFA signaling via NFKB	-2.51	<0.01	TNFA signaling via NFKB	-2.52	<0.01

Positive NES = upregulation in Ob pts, and negative NES = downregulation in Ob pts.

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Poster Session

Depth of PSA nadir and subsequent PSA progression-free survival in patients (pts) with high-risk biochemically relapsed prostate cancer: Results from the phase 3 PRESTO study (AFT-19). *First Author: Rahul Raj Aggarwal, University of California, San Francisco, San Francisco, CA*

Background: In the phase 3 PRESTO study, intensified androgen deprivation therapy (ADT) with apalutamide (Apa) with or without abiraterone acetate plus prednisone (AAP), administered for a finite treatment period of 52 weeks, prolonged prostate-specific antigen progression-free survival (PSA PFS) in pts with high-risk biochemically relapsed prostate cancer (BRPC). We evaluated the association between PSA nadir within 3 months of treatment initiation with subsequent PSA PFS in this study. **Methods:** PRESTO is a randomized phase 3, open-label trial in pts with BRPC following radical prostatectomy (RP) and PSA doubling time (PSADT) $\leq$ 9 months, without distant metastases on conventional imaging (NCT03009981). Pts were randomized 1:1:1 to receive a finite 52-week treatment course with ADT, ADT + Apa, or ADT + Apa + AAP, stratified by PSADT ($<$ 3 vs 3–9 months), with post-treatment follow-up. The association between PSA nadir within the first three months on treatment with subsequent PSA PFS was analyzed in a post hoc fashion. **Results:** 504 pts were randomized to ADT alone (N = 167), ADT + Apa (N = 168) or ADT + Apa + AAP (N = 169). 463 pts were evaluable for PSA nadir at 3 months. Across the three treatment arms, a PSA nadir of less than 0.1, between 0.1 – 0.2, and $\geq$ 0.2 ng/mL within the first three months of treatment was observed in 86.3%, 4.4%, and 9.3% of patients, respectively. A PSA nadir of $<$ 0.2 ng/mL was reached within 3 months of treatment initiation in 79.8%, 96.9%, and 95.0% of pts randomized to the ADT, ADT + Apa, and ADT + Apa + AAP arms, respectively. The association between time to PSA nadir and subsequent PSA PFS was -0.30 (standard error = 0.03, Kendall's tau modified for bivariate censoring), and median time to PSA nadir was 2.0 months (interquartile range 1.12 – 4.76 months). Failure to reach a PSA nadir $<$ 0.2 ng/mL within the first three months of treatment was associated with a significantly shorter PSA PFS compared to pts with a PSA nadir $\leq$ 0.1 ng/mL (median PSA PFS of 13.9 vs. 22.8 months from 3 months post-treatment initiation; hazard ratio = 5.60, 95% CI: 3.58 – 8.75, p $<$ 0.0001). There was also a significant difference in PSA PFS in those with a three-month PSA nadir between 0.1 – 0.2 vs $\leq$ 0.1 ng/mL (median PSA PFS 17.4 vs 22.8 months, HR = 2.63, 95% CI: 1.49 – 4.63, p = 0.0008). **Conclusions:** Using a landmark analysis at 3 months, a failure to reach PSA nadir less than 0.1 ng/mL within three months following initiation of ADT in BRPC is associated with shorter time to subsequent progression following treatment discontinuation. Follow-up is ongoing to integrate genomic profiling of primary prostate cancer tissues and whole blood RNA in pts with suboptimal PSA nadir to identify potential markers of relative androgen pathway inhibitor resistance. Clinical trial information: NCT03009981. Research Sponsor: Janssen.

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Poster Session

Assessing racial differences in time to treatment escalation following androgen-deprivation therapy among veterans with prostate cancer. *First Author: Nadine Adriana Friedrich, Department of Urology, Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles*

Background: Androgen deprivation therapy (ADT) is standard care first-line (1L) systemic treatment for advanced and metastatic prostate cancer (PC). Currently, there are no population-level studies assessing the duration of 1L ADT and time to treatment escalation (chemotherapy [CT], novel hormonal therapy [NHT], or non-steroidal antiandrogen [NSAA]). **Methods:** We performed a retrospective population-level analysis to assess the association between race and time to treatment escalation after ADT in the Veterans Affairs Health Care System. From 2001-2021, 164,477 patients (pt) diagnosed with PC and treated with ADT alone were identified. Baseline demographic and clinical characteristics were sorted by race: Non-Hispanic White (NHW), Non-Hispanic Black (NHB), Hispanic, Other and compared among groups using chi square tests for categorical variables and Kruskal-Wallis tests for continuous variables. The primary outcome was time from ADT to treatment escalation, defined as receipt of NHT, NSAA, or CT. Men with no evidence of treatment escalation were censored at time of death or most recent visit. We estimated 5-year event rates by race using Kaplan-Meier (KM) analyses. Univariable and multivariable Cox proportional hazards models were used to test the association between race and time to treatment escalation with time of ADT as time zero. Multivariable models were adjusted for age, year, time from PC diagnosis to ADT, Charlson Comorbidity Index and BMI at ADT start along with PSA, testosterone level, and receipt of radiation therapy (RT) prior to ADT. **Results:** NHB were youngest ($p < 0.001$), started ADT in more recent years ($p < 0.001$), had the highest pre-ADT PSA ($p < 0.001$) and testosterone levels ($p < 0.001$), the most comorbidities ($p < 0.001$), and the highest rate of RT prior to ADT ($p < 0.001$) relative to other groups. During a median (Q1, Q3) follow-up of 55.2 (25.0, 102.4) months, 31,288 pt (19%) had treatment escalation, of which 12,093 (39%) were NHTs, 14,842 (47%) were NSAAs, 3,895 (12%) were CT and 458 (2%) were other 2nd line therapies. Compared to NHW, NHB had significantly lower rate of treatment escalation in univariable (HR=0.89, 95% CI=0.87-0.92) and multivariable analysis (HR=0.82, 95% CI=0.80-0.84). KM estimates at 5-year for the percent free from escalation was 80.5 (80.2-80.8%) in NHW vs. 83.0 (82.6-83.4%) in NHB. Rate of treatment escalation was similar for Hispanics and other races compared to NHW, with 5-year KM estimates of 81.0 (80.3-81.7%) and 81.0 (80.0-82.0%) for Hispanics and other races, respectively. **Conclusions:** This study assessing racial differences in time to treatment escalation of men receiving 1L ADT found that NHB had a significantly lower rate of treatment escalation. Whether this decreased rate of treatment escalation among NHB men represents improved outcomes (i.e. lower risk of progression) or undertreatment requires further study. Research Sponsor: Myovant Sciences, Inc.; U.S. National Institutes of Health.

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Poster Session

Baseline circulating tumor cell (CTC) count as a prognostic marker of overall survival (OS) in metastatic hormone sensitive prostate cancer (mHSPC): Results from SWOG S1216, a phase III randomized trial of androgen deprivation plus orteronel (cyp17 inhibitor) or bicalutamide. *First Author: Amir Goldkorn, Division of Medical Oncology, Department of Medicine, Keck School of Medicine and Norris Comprehensive Cancer Center, University of Southern California, Los Angeles, CA*

Background: Biomarkers are needed to predict clinical outcomes in mHSPC. We previously reported that baseline CTC counts in S1216 were prognostic of PSA response and disease progression (ASCO 2020; CCR 2021). However, the trial's primary overall survival (OS) endpoint was not yet mature at that time. Here we present the final results of S1216 using all available samples to assess the prognostic value of CTC counts for response, progression, OS, and treatment arm interactions. **Methods:** In S1216, peripheral blood was drawn with informed consent at registration (baseline) and at progression to metastatic castrate resistant prostate cancer (mCRPC). CTCs were enumerated on the FDA-cleared CellSearch platform (Menarini). CTC counts were evaluated for associations with 3 pre-specified trial endpoints: 7-month PSA (7mPSA) ≤ 0.2 ng/ml vs. 0.2-4.0 vs. > 4.0 using a generalized logit model; and progression-free survival (PFS) and OS using Cox regression. **Results:** From 2014 to 2021, 503 evaluable samples were collected at baseline and 93 at progression. Baseline CTC count was ≥ 5 in 11.9% of samples, 1-4 in 19.3%, and 0 in 66.8%. Comparing men with 0 vs. ≥ 5 CTCs at baseline, those with 0 CTCs were significantly more likely to attain a complete PSA response and had significantly lower risk of a PFS event and death after adjusting for clinical covariates (disease burden, bone metastases, age, race, alkaline phosphatase, hemoglobin, PSA, treatment arm). These associations were not modified by treatment arm. Progression CTCs < 5 vs. ≥ 5 also were prognostic of OS (logrank $p = 0.001$), consistent with prior findings in mCRPC. Same-patient CTC counts in matched baseline-progression pairs ($n = 61$) were highly correlated (Spearman $p < 0.001$). **Conclusions:** CTC count at the start of treatment for mHSPC was highly prognostic of PSA response, PFS, and OS; associations that held in both treatment arms. Moreover, baseline CTC count strongly correlated with progression count, suggesting that mild vs. aggressive disease phenotypes may persist from mHSPC to mCRPC. This evidence from a large prospective phase 3 trial suggests that baseline CTC count is a valuable prognostic marker in men initiating therapy for mHSPC, discriminating those likely to experience favorable vs. unfavorable response and OS. Research Sponsor: U.S. National Institutes of Health; Millennium Pharmaceuticals (Takeda Oncology Company).

	Baseline CTCs 0 vs. ≥ 5
Likelihood of 7mPSA ≤ 0.2	OR = 3.85 (95% CI 1.85, 8.33; $p < 0.001$)
Risk of progression	HR = 0.41 (95% CI 0.29, 0.57; $p < 0.0001$)
Risk of death	HR = 0.31 (95% CI 0.21, 0.45; $p < 0.0001$)

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Poster Session

Treatment and survival of de novo metastatic hormone sensitive prostate cancer among African American US Veterans. *First Author: Rigoberto De Jesus Pizarro, Washington University School of Medicine, St. Louis, MO*

Background: Combinations of androgen deprivation therapy (ADT) plus docetaxel (DOC) or androgen signaling inhibitors (ASIs: abiraterone, enzalutamide, etc.) have revolutionized treatment of metastatic hormone sensitive prostate cancer (mHSPC), particularly for high volume disease. However, little is known about the use of and outcomes of combination therapy in African Americans (AA) with de novo mHSPC, due to their lack of representation in clinical studies. This study evaluates the patient characteristics, treatment, and survival in a cohort of US veterans with mHSPC with equal access to treatment under the Veterans Affairs Health System (VA). **Methods:** Veterans with mHSPC were identified from 2014-2022 in the VA using the initial pathological diagnosis of prostate cancer with SEER stage 'distant' and first ADT initiated within 1 month prior and 3 months after diagnosis. Therapies including DOC or ASIs were collected if initiated from 1 month prior to 4 months after ADT. Additional information at the time of diagnosis was collected including Prostate Specific Antigen (PSA), race from VA enrollment, and Charlson Comorbidity Index (CCI). Median survival was obtained for each group and stratified by PSA level > 100 ng/mL. Chi-square and ANOVA testing were used to assess differences in survival (OS) were assessed by log-rank testing. **Results:** 4,248 veterans with de novo mHSPC were identified, 1,138 (26.8%) were AA and 3,110 (73.2%) white. Black veterans were younger (70.8 vs. 74.8, $p < 0.001$) and had higher median PSA (183 vs. 86.3, $p < 0.001$) with similar mean CCI (4.4 vs. 4.4, $p = 0.78$). AA veterans were likely to have a PSA > 100 ng/mL at diagnosis (61.6% vs. 46.1%, $p < 0.001$) and to receive combination therapy than white veterans (36.8% vs. 32.7%, $p = 0.01$). The median OS among AA and white veterans was similar (32.5 months vs. 32.1, $p = 0.75$). In 1,210 veterans with PSA > 100 ng/mL (a surrogate for higher volume disease), AA veterans were more likely to receive combination therapy (39.5% vs. 32.9%, $p = 0.003$) without differences in survival in AA veterans compared to white (31.0 vs. 26.9 months, $p = 0.18$). **Conclusions:** In an equal access health care system, AA veterans had similar survival to white veterans despite having double the PSA levels, reflecting higher risk disease. AA presented 4 years younger and are likely treated with doublet therapy. The differences in the age of onset and burden of disease highlight persistent differences in populations with mHSPC. Further investigations to understand environmental, social, and tumor factors are warranted to explain these disparities. Research Sponsor: Department of Defense grant W81XWH-22-1-0602 and a Prostate Cancer Foundation Young Investigator Award.

	2014-2021		2014-2021 PSA > 100 ng/mL	
Race	Black n=1138	White n=3110	Black n=697	White n=1423
Age (mean years)	70.8	74.2	71.2	75.9
Median PSA (ng/mL)	184	86.3	441	348
Charlson Comorbidities	4.4	4.4	4.2	4.3
ADT alone	63.2%	67.3%	60.5%	67.1%
ADT + docetaxel	14.9%	10.4%	16.1%	10.8%
ADT + ASI	22.3%	21.9%	23.4%	22.1%
Overall Survival (months)	32.5	32.1	31.0	26.9

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Poster Session

Cost-effectiveness analysis (CEA) of seven treatment regimens in metastatic hormone-sensitive prostate cancer (mHSPC): A public payer perspective using network meta-analysis. *First Author: Manish Kohli, Huntsman Cancer Institute at the University of Utah, Salt Lake City, UT*

Background: Recently several new drug treatment regimens have been approved in mHSPC state, building on using androgen deprivation therapy (ADT) alone. These include docetaxel + ADT (DA), Abiraterone Acetate + Prednisone + ADT (AAP), Apalutamide + ADT (AAT), Enzalutamide + ADT (ET), Darolutamide + Docetaxel + ADT (DAD) and AAP + ADT + Docetaxel (AAD). At present, there are no predictive biomarkers for choosing a specific drug regimen over the other. The goal of this study was to conduct an economic evaluation of FDA-approved standard of care drug regimens in the current management of mHSPC state to determine a cost-effective optimal treatment from the US public sector (Veterans Affairs-VA) perspective with a 10-year time horizon. **Methods:** We developed a partitioned survival model in which mHSPC patients (pts) transitioned between three health states (progression free, progressive disease to castrate resistance state, and death) at monthly intervals based on Weibull survival model estimated from published Kaplan-Meier curves using a network meta-analysis. A Bayesian network meta-analysis of seven randomized clinical trials included 7,208 mHSPC pts. The effectiveness outcome in our model was quality-adjusted life-years (QALYs) with utility values obtained from published literature. Costs in our model included those associated with treatment regimens, subsequent therapies, terminal care, and for managing grade 3-4 drug related adverse events. Costs were obtained from the Federal Supply Schedule and published literature. Incremental cost-effectiveness ratios (ICERs) were calculated for nondominated treatments. **Results:** Average 10-year costs ranged from \$32,697 (ADT) to \$649,622 (DAD). Mean QALYs ranged from 3.25 (ADT) to 4.57 (ET). Treatment with DAT, EAD, and DAD were eliminated due to dominance (i.e. they were more costly and less effective than other treatments). AAT was the most cost-effective strategy at a willingness-to-pay threshold of \$100,000/QALY (ICER = \$70,150/QALY). Results from our analysis for all regimens are shown. **Conclusions:** Our CEA simulation model found AAT is an optimal cost-effective first-line treatment strategy in mHSPC state from a public (VA) payer perspective. Research Sponsor: None.

Results from cost-effectiveness analysis of treatment regimens for mHSPC.			
Treatment strategy	Cost (\$)	Effectiveness (QALYs)	ICER(\$/QALY)
Androgen Deprivation Therapy (ADT)	\$32,697	3.25	
Abiraterone Acetate-Prednisone + ADT (AAP)	\$45,512	3.83	\$22,299
Apalutamide + ADT (AAT)	\$68,503	4.16	\$70,150
Enzalutamide + ADT (ET)	\$488,061	4.57	\$1,017,538
Docetaxel + ADT (DA)	\$51,093	3.79	Dominated
Enzalutamide + ADT + Docetaxel (EAD)	\$396,809	3.99	Dominated
Darolutamide + ADT + Docetaxel (DAD)	\$649,622	4.29	Dominated

Outcomes were discounted at an annual rate of 3% to reflect present value; All costs were in 2022 US dollars.

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Poster Session

Landscape and impact of germline pathogenic variants (PVs) in metastatic hormone sensitive prostate cancer (mHSPC): Ancillary study of E3805 CHAARTED. *First Author: Anis Hamid, University of Melbourne, Parkville, Australia*

Background: Enrichment of germline PVs in metastatic castration resistant prostate cancer (mCRPC), compared to localized disease, has directly informed genetic testing guidelines. The prevalence and prognostic/predictive associations of such variants are not well characterized in the mHSPC state, in particular the effect of susceptibility mutations related to DNA damage and repair (DDR) pathways. **Methods:** We performed whole exome sequencing of germline DNA derived from whole blood available from patients (pts) in the phase III CHAARTED trial (NCT00309985) of androgen deprivation therapy (ADT) versus ADT plus docetaxel (ADT+D). After filtering for low coverage, variant annotation and effect prediction, PVs from a curated list of 588 prostate cancer-associated genes were reviewed. The prognostic effect of PVs was evaluated within each treatment arm. Endpoints of time to CRPC (ttCRPC), time to clinical progression (ttClinPD), and overall survival (OS) were estimated by Kaplan-Meier method. Hazard ratios (HRs) and 95% confidence intervals (95% CIs) were estimated by Cox models evaluating association of endpoints with biomarkers/arm. Multivariable analysis adjusted for metastatic timing and volume. **Results:** Of 137 pts, 135 had unique germline exomes that passed downstream analysis. Most pts had synchronous (66.7%) and high-volume (62.2%) disease. This biomarker cohort showed benefit of adding docetaxel to ADT (ttCRPC: HR 0.55, 95% CI 0.37-0.82; OS: HR 0.68, 95% CI 0.44-1.07). In total, 61 PVs were detected; 49 pts (36.3%) harbored at least 1 PV in 41 different genes. The most frequently-mutated gene was *BRCA2* (6.67%). In addition, PVs were found in DDR-associated genes including *PALB2* (1.48%), *CHEK2* (1.48%), *BRCA1* (0.74%) and *PMS2* (0.74%) for an overall prevalence of 11.1% (15/135). Pts with *BRCA2* PV on ADT alone had shorter ttCRPC compared with men without the PV (UVA: HR 2.67, 95% CI 0.93-7.63, log rank p=0.057; MVA: HR 2.59, 95% CI 0.91-7.39, p=0.074). There was no evidence of a difference in the ADT+D arm (UVA: HR 1.00, 95% CI 0.31-3.25, log rank p=0.1). Supportive data was observed for ttClinPD in ADT arm (HR 2.85, 95% CI 1.01-8.08, log rank p=0.04). Metastatic volume and timing were not significantly associated with germline *BRCA1/2* or DDR PVs. **Conclusions:** The prevalence of germline *BRCA1/2* and DDR PVs in mHSPC is similar to mCRPC and *BRCA2* PV may confer worse outcomes on ADT alone. This supports the need for genetic testing at diagnosis of mHSPC. Research Sponsor: U.S. National Institutes of Health.

Median survival (mos, 95% CI) by arm and <i>BRCA2</i> status.			
	ttCRPC	ttClinPD	OS
ADT: <i>BRCA2</i> -wt	10.3 (6.18-18.92)	14.9 (11.56-22.01)	42.5 (29.04-52.8)
ADT: <i>BRCA2</i> -mt	4.5 (1.84-NA)	4.5 (1.84-NA)	30.5 (22.64-NA)
ADT+D: <i>BRCA2</i> -wt	19.8 (14.95-29.4)	29.8 (23.62-41.92)	52.1 (43.99-69.62)
ADT+D: <i>BRCA2</i> -mt	23.1 (8.87-NA)	29.4 (14.62-NA)	37.0 (29.44-NA)

wt: wild-type; mt: mutated.

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Poster Session

CABIOS trial: A phase Ib study of cabozantinib and nivolumab in combination with abiraterone in patients (pts) with metastatic hormone sensitive prostate cancer (mHSPC). *First Author: Jesse Meir Zaretsky, Washington University School of Medicine, Department of Medicine, Division of Oncology, St. Louis, MO*

Background: Androgen deprivation therapy (ADT) combined with novel hormonal agents +/- docetaxel is a standard of care treatment for mHSPC. The combination of tyrosine kinase inhibitors (TKI) and immune checkpoint blockade (ICB) is FDA approved in renal cell carcinoma, and shows promising efficacy in preclinical models of prostate cancer by favorably altering the tumor immune microenvironment. There are currently ongoing trials of TKI + ICB in metastatic castration resistant prostate cancer. Here we present interim safety results from an ongoing phase Ib single-arm trial of cabozantinib + nivolumab + abiraterone/prednisone (cabo, nivo, abi/pred) in pts with newly diagnosed mHSPC (NCT04477512). **Methods:** Eligible pts had de-novo or recurrent mHSPC with up to 12 weeks ADT prior to enrollment, ECOG 0-1, and adequate organ function. Prior abi and docetaxel were excluded. Pts received cabo 20 mg or 40 mg daily (3+3 dose escalation in 2 cohorts) combined with nivo 480mg IV q4 weeks, and abi/pred 1,000mg/5mg daily until progression or unacceptable toxicity. The primary endpoint is safety and tolerability. Secondary endpoints include overall response rate (ORR) by RECIST 1.1, overall survival (OS), progression free survival (PFS), and PSA response. Exploratory analyses include CyTOF of peripheral blood and serum cytokine ELISA. **Results:** As of 19DEC2022, 17 pts were enrolled, 3 at 20mg and 14 at 40mg cabo with no dose-limiting toxicity (DLTs) observed. Median age was 65 yrs, 4/17 pts are Black, 11 had de-novo and 6 recurrent disease, with median baseline PSA 78ng/mL. Most had bone (n=16), lymph node (6), or lung (1) mets, and 11 (64.7%) had high-volume disease. With median follow-up 12.8 months, 9 pts (53%) remain on study. 1 withdrew, 3 discontinued due to disease progression (with 1 death), and 4 stopped due to toxicity. Grade $\geq$ 3 adverse events (AEs) include encephalitis (n=1, grade 4 likely nivo-related after 1yr on therapy), diarrhea (n=2), elevated AST/ALT (n=4), wound infection/dehiscence, adrenal insufficiency, hypertension, elevated lipase, and proteinuria (grade 3, n=1 each). No other AEs were reported outside the current safety labels for the study agents. Of 15 response evaluable pts, 7 had RECIST-measurable lesions; 4 had partial response and 3 had stable disease as best response at data cutoff. 9/14 (64.3%) evaluable had PSA <0.2ng/mL at 7 months. Immune correlative studies are ongoing. **Conclusions:** Here we present the initial safety and preliminary efficacy results of the first trial of cabo + nivo in mHSPC patients receiving SOC ADT + abi. To date, the combination has a safety profile consistent with known AEs for these agents, no DLTs, and evidence of clinical benefit. Further follow up will be required to fully assess clinical safety, efficacy and immune responses. Future, larger studies could compare this combination to SOC ADT + abi. Clinical trial information: NCT04477512. Research Sponsor: Exelixis, Bristol-Myers Squibb.

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Poster Session

Development and independent validation of a predictive gene expression signature based on RB1, PTEN, and TP53 in patients with metastatic hormone-sensitive metastatic prostate cancer (mHSPC). *First Author: Oscar Reig Torras, Department of Medical Oncology, Hospital Clinic of Barcelona, Barcelona, Spain*

Background: Alterations on the tumor suppressor genes (TSG) RB1, PTEN and TP53 are associated with treatment resistance and aggressive clinical evolution of prostate cancer patients (pts). Here, we developed and validated a TSG gene expression signature in mHSPC pts. **Methods:** This is a multicenter retrospective biomarker study in mHSPC pts. Mutations on TSG were assessed by targeted sequencing, mRNA expression by nCounter platform and protein by IHC in FFPE tumor samples. Expression data of the training cohort were used to establish the cut-off applied to the other cohorts. TSGlow was considered when $\geq$ 2 out of 3 TSG presented low expression and TSGwt in the remaining cases. CHAARTED trial pts with microarray data (Hamid, Ann Oncol, 2021) were analyzed as an independent validation cohort. TSG signature was correlated with castration resistance-free survival (CRPC-FS) (primary endpoint) and overall survival (OS) by Kaplan Meier and multivariate Cox analysis. **Results:** 218 pts were included: 125 treated with ADT + docetaxel (ADT+D) and 93 with ADT. 160 pts from the CHAARTED dataset were analyzed (84 with ADT+D and 76 with ADT). ADT+D pts with available TSG gene expression and targeted sequencing were considered as the training cohort (n=54). Pts with low *PTEN* and *RB1* gene expression had lower IHC expression (p<0.01). Low *PTEN* pts had a higher frequency of *PTEN* mutations (p<0.05). TSGlow (25.9%) pts had a worse CRPC-FS (14.3 vs 21.7 months (m); HR 2.2 (95% CI, 1.1 – 4.4) p=0.022). In the internal validation cohort of ADT+D-treated pts (n=71), TSGlow (9.9%) correlated with a worse CRPC-FS (11.7 vs 20 m, p=0.027) and OS (27.6 vs 58.1 m, p=0.012). TSGlow was independently associated with CRPC-FS (HR 2.7 (95% CI, 1.2 – 6.1) p=0.02) and OS (HR 3.7 (95% CI, 1.3 – 10.1) p=0.012). In the ADT cohort (TSGlow 21.5%), no differences in either CRPC-FS or OS were observed. When analyzed together the ADT+D and ADT cohorts, we observed that TSGwt pts treated with ADT+D had the largest CRPC-FS (21.6 m; p=0.014) and OS (58.1 m; p=0.029), while TSGlow pts receiving ADT+D had a CRPC-FS and OS similar to ADT-treated pts. Similarly, in the CHAARTED dataset, TSGlow (20.2%) pts treated with ADT+D had a worse CRPC-FS (14.8 vs 29.4 m, HR 2.2 (95% CI, 1.1 – 4.3) p=0.023) and OS (32.9 vs 57.4 m, HR 2.2 (95% CI, 1 – 4.5) p=0.04). TSGlow (35.5%) was not predictive of either CRPC-FS or OS in ADT-treated pts. Analyzing together ADT+D and ADT pts, TSGwt pts treated with ADT+D had the best CRPC-FS and OS (p<0.01). **Conclusions:** Our results suggest that a TSGlow expression may predict the lack of benefit to taxanes in mHSPC pts, which may be useful to personalize the treatment. Research Sponsor: Janssen; Instituto de Salud Carlos III (Spain).

	ADT + D (Training)	ADT + D (Validation)	ADT
Age (median, years)	67.8	65.8	66.1
Stage IV at diagnosis (%)	96.3	90.1	52.7
Gleason $\geq$ 8 (%)	83.3	80.3	60.2
High volume (%)	85.2	73.2	54.8
Median follow-up (months)	36.9	35.7	45.8

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Poster Session

An analysis to inform the timing of docetaxel use leveraging data from the United States Veterans Administration on patients with metastatic castration-sensitive prostate cancer (mCSPC). *First Author: Mengxi Zhou, Columbia University Medical Center, New York, NY*

Background: Every oncologist caring for patients(pts) with a diagnosis of mCSPC at some point finds themselves deciding whether to use docetaxel (DOCE) in 1st line or later, a difficult selection often based on perceived tolerability. In 1st line mCSPC, both novel hormonal therapies (NHTs) and DOCE have been shown effective, with direct comparisons lacking. We conducted the present analysis to help address this issue. **Methods:** All pts with mCSPC diagnosis in the VA Corporate Data Warehouse (CDW) who received either DOCE or NHT (abiraterone or enzalutamide) in the mCSPC setting and the converse after disease progression to castrate-resistant prostate cancer (mCRPC) were eligible for comparison. The cohort date range was from 7/2015 to 6/2022. We then created two arms — DOCE 1st and DOCE later — matched 1:1 exactly for age, race, total lines of therapy received, PSA at diagnosis, Gleason score (GS), Charlson comorbidity index (CI) excluding cancer diagnosis, and rurality. **Results:** 580 pts met study eligibility, with two 147 patient cohorts identified for matched analysis. Median age was 69 (64-73) and 70 (65-73) for the DOCE 1st and DOCE later cohorts, respectively. In both cohorts, 66%/31% were white/black. Starting PSA was <20/ $\geq$ 20 in 36%/64%. 60% had GS $\geq$ 8. CI was <5/ $\geq$ 5 in 80%/20%. 2/ $\geq$ 3 total lines of therapy had been given to 32%/68%. Urban/rural distribution was 74%/26%. Median follow up of 30.2/23.7 months for DOCE 1st/DOCE later, reflects DOCE approval in mCSPC two years before approval of NHTs. Median OS were 37.9/31.6 months for DOCE 1st/DOCE later, [HR 0.65 (0.48-0.89), p=0.012], with HRs when comparing those from each cohort with GS $\geq$ 8 or with starting PSA $\geq$ 20, of 0.7 (0.47-1.05), p=0.018 for GS $\geq$ 8, and 0.48 (0.32-0.73) p=0.001 for starting PSA $\geq$ 20, both in favor of DOCE 1st. Duration of abiraterone treatment was greater in DOCE later with values of 284 (160-460) and 153 (90-286) days, p<0.0001 for DOCE later and DOCE 1st, respectively. Durations of DOCE treatment was statistically insignificant between cohorts at 135 (94-141) and 93 (51-177) days, p=0.35 for DOCE 1st and DOCE later, respectively. Surprisingly, time to mCRPC, defined as time from diagnosis to 1st mCRPC therapy, was longer but not statistically significant for DOCE later than for DOCE 1st, with durations of 23.7 and 20.3 months, respectively, p=0.23. **Conclusions:** Our data in US Veterans suggest the strategy of using DOCE upfront in those with mCSPC followed by a NHT on progression results in superior OS compared with DOCE later in mCRPC, especially in men with PSA $\geq$ 20 as a surrogate for high volume disease. Concordant with data from CHAARTED and STAMPEDE arm C where single agent ADT was the reference and ADT + DOCE emerged as the SOC for high volume or high-risk disease, the 6.3-month survival difference between strategies in this analysis argues for consideration of a prospective comparative study. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology.

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Poster Session

Androgen-deprivation therapy and risk of dementia in patients with prostate cancer: Clinical outcomes from real-world data. *First Author: Dina Elantably, MetroHealth Medical Center, Case Western Reserve University, Cleveland, OH*

Background: Androgen deprivation therapy (ADT) is the cornerstone for the treatment advanced prostate cancer. However, there has been growing concerns regarding increased risk of dementia with ADT. Previous studies of dementia risk following ADT were controversial and inconclusive. **Methods:** Data was collected from an electronic health record database (TriNetX LLC., Cambridge, MA) which includes over 89 million patients from 56 healthcare systems in the United States. We identified males over the age 50 years who were diagnosed with any stage of prostate cancer between 2005 and 2022. Patients receiving ADT were 1:1 propensity score-matched with non-exposed controls for demographics and risk factors for dementia; diabetes mellitus, hypertension, hyperlipidemia, obesity, depression, cerebrovascular disease, tobacco use, alcohol dependence and benzodiazepine use. Patients with prior dementia, stroke, or TIA were excluded. **Results:** In a cohort of 627,025 men with prostate cancer, 73,933 patients (mean age of 70.8 years) received ADT and 57,005 patients (mean age of 70.4 years) did not. ADT exposure was associated with a diagnosis of dementia (Alzheimer's disease, vascular dementia, or unspecified dementia); HR 1.6; 95% CI (1.49, 1.73). Subgroup analysis by dementia subtype is highlighted in (table). Compared to non-ADT group, exposure to ADT was associated with a statistically higher risk of dementia among whites (78.6% vs. 77.7%, $P < 0.001$), whereas there was no significant difference among African Americans. The risk of dementia with different ADT regimens is shown. **Conclusions:** This is the largest real-world study describing the association between ADT and the risk of dementia, including over 600 thousand prostate cancer patients. The risk of dementia was significantly higher in patients on ADT, with a 60% increased risk. The highest risk was witnessed with GnRH antagonists (degarelix), with a 92% increased risk. Interestingly, the increased risk of dementia in ADT groups was observed only among whites but not in African Americans. Possible causes of this discrepancy include socioeconomic disparities, bias that resulted in underdiagnosis, or biological differences. Research Sponsor: None.

Association between androgen deprivation therapy and the risk of dementia.				
	ADT group (reference), n pts with dementia (%)	Non-ADT group, n pts with dementia (%)	Adjusted HR (95% CI),	p-value
All ADT categories	1571 (3.12%)	1102 (2.19%)	1.60, (1.49, 1.73), S	
GnRH analogues	1612 (3.33%)	1055 (2.12%)	1.69, (1.56, 1.83), S	
GnRH antagonists	130 (2.75%)	100 (2.11%)	1.92, (1.47, 2.52), S	
Antiandrogens	1216 (3.27%)	859 (2.30%)	1.63, (1.49, 1.78), S	
Alzheimer's disease	470 (0.93%)	343 (0.68%)	1.54, (1.34, 1.77), S	
Vascular dementia	250 (0.50%)	209 (0.42%)	1.37, (1.14, 1.64), 0.0008	
Unspecified dementia	1295 (2.58%)	904 (1.80%)	1.61, (1.48, 1.76), S	

P-value of < 0.0001 is noted as S.

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Poster Session

The role of volume of disease for treatment selection in patients with metastatic castration sensitive prostate cancer (mCSPC): A living meta-analysis. *First Author: Syed Arsalan Ahmed Naqvi, Mayo Clinic, Phoenix, AZ*

Background: Previous evidence suggests that there may be no additional benefit of triplet therapy in low volume disease based on limited data. Therefore, we investigated the efficacy of triplet therapy as compared to docetaxel (D) and androgen pathway inhibitor (API) doublets by volume of disease using the most up to date results from the ARASENS trial. **Methods:** Phase III randomized controlled trials (RCTs) assessing treatment intensification with API, and/or D in patients with mCSPC were included. Precomputed hazard ratios (HR) with 95% confidence intervals (CI) for OS were pooled using an inverse-variance approach. A DerSimonian-Laird random-effects meta-analysis was conducted to assess the efficacy of triplet therapy compared to D doublet therapy. P-value of interaction was computed to assess difference between high (HV) and low volume (LV) disease subgroups ($P_{int} < 0.1$ - statistical significance). Additionally mixed treatment comparisons were computed using network meta-analysis (NMA) to assess the comparative effectiveness of triplet therapy compared to API doublets by volume of disease. **Results:** Pairwise meta-analysis included a total of 3 RCTs (ARASENS, PEACE-1, ENZAMET) with 2518 patients (HV: 1820; LV: 698) as shown. In patients with HV disease, 385 (43%) and 484 (53%) deaths were observed with triplet therapy, and D doublet, respectively. Triplet therapy significantly improved OS as compared to D doublet in HV (HR: 0.73; 95% CI: 0.64-0.84). In patients with LV disease, 73 (20%) and 94 (28%) deaths were observed with triplet therapy, and D doublet, respectively. Triplet therapy significantly improved OS as compared to D doublet in LV (HR: 0.71; 95% CI: 0.52-0.97). There was no statistically significant interaction by volume of disease for triplet therapy vs. D doublet (P_{int} : 0.86). NMA including 10 clinical trials and over 11500 patients updated as of 13th Feb 2023 showed that in HV mCSPC, triplet therapy was ranked as potentially the most efficacious treatment option and may improve OS compared to API doublet therapy (HR: 0.83; 95% CI: 0.66-1.03). In LV mCSPC, API doublet therapy was ranked as potentially the most efficacious treatment followed by triplet therapy. There was no significant difference between triplet therapy and API doublet therapy (HR: 1.12; 95% CI: 0.74-1.12). **Conclusions:** These results underscore that triplet therapy may be preferred in mCSPC patients with HV disease whereas API doublet therapy may be preferred in LV disease. Research Sponsor: None.

Subgroup	Overall Survival		Anticipated absolute effects	
	Participants (trials)	Hazard ratio (95% CI)	Risk of death with D doublet	Risk difference with triplet therapy
Volume of disease				
High volume	1820 (3 trials)	0.73 (0.64 to 0.84)	530 deaths per 1,000	106 fewer per 1,000; (147 fewer to 60 fewer)
Low volume	698 (3 trials)	0.71 (0.52 to 0.97)	280 deaths per 1,000	72 fewer per 1,000; (123 fewer to 7 fewer)

5087

Poster Session

Phase 2 study of olaparib (without ADT) in men with biochemically recurrent prostate cancer (BCR) after prostatectomy. *First Author: Catherine Handy Marshall, Johns Hopkins University, Baltimore, MD*

Background: The natural history of BCR after prostatectomy is variable and current treatment approaches include observation, salvage radiation, or androgen deprivation therapy (ADT), although many men wish to defer such therapy. We hypothesized that olaparib, now approved for use in certain men with metastatic castration resistant prostate cancer, might be an alternative option for men with high-risk BCR. **Methods:** This was a single arm, phase 2 trial (NCT03047135) conducted at 4 US sites. Subjects with biochemically recurrent (MO) prostate cancer, post prostatectomy, with a PSA doubling time of ≤ 6 months and an absolute PSA of ≥ 1.0 ng/mL were eligible. Patients were NOT selected based on the presence of homologous recombination repair (HRR) mutations. 51 patients were treated with olaparib 300mg twice per day, until radiographic or symptomatic progression, PSA doubling from baseline value, or drug-related toxicity. The primary endpoint was PSA50 response (50% PSA decline from baseline). Secondary endpoint was PSA progression free survival (PFS). Patients were required to undergo tissue-based next generation sequencing on the radical prostatectomy specimen to determine the presence of mutations in HRR genes (*ATM*, *BARD1*, *BRCA1/2*, *BRIP1*, *CDK12*, *CHEK1/2*, *FANCA/E/L*, *PALB2*, *AD51B/C/D*). A prespecified endpoint was to assess PSA responses in HRR[+] and HRR[-] cohorts separately. **Results:** Mean age was 64 years (SD 7), and 92% (47/51) of patients were White. Mean baseline PSA doubling time was 2.9 (SD 1.5) months. 55% (28/51) of pts had Gleason 6-7, 14% (7/51) had Gleason 8, and 31% (16/51) had Gleason 9-10. 86% (44/51) of patients had previously received salvage radiation. 27 patients harbored HRR mutations, the most common of which were *BRCA2* (n=11), *CHEK2* (n=6), and *ATM* (n=6). The overall PSA50 response rate was 24% (12 of 51) (95% CI 0.13, 0.38), with no responses in the HRR[-] group and 44% (12/27) PSA50 responses in the HRR[+] group (95%CI 0.26, 0.65). All 11 of the participants with a *BRCA2* mutation achieved a PSA50 response. The median PSA PFS was 22 months in the HRR[+] group and 13 months in the HRR[-] group (HR 0.71; 95% CI 0.31, 1.63). Most AEs were low grade. The most common all-grade AEs were fatigue, nausea, leukopenia, anemia, and dysgeusia. Grade-3 AEs were leukopenia (9.8%), ALT/AST increase (3.9%), and anemia (2.0%). There were no grade 4-5 AEs. **Conclusions:** Olaparib, in the absence of ADT, can be safely administered and demonstrated activity in men with BCR prostate cancer and HRR mutations, especially for *BRCA2* mutations. Additional studies to further evaluate olaparib in these patients are indicated. Clinical trial information: NCT03047135. Research Sponsor: Astra Zeneca; U.S. National Institutes of Health.

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Poster Session

Early findings from the GARUDA trial: The impact of a genetic signature of late radiation toxicity on prostate cancer treatment decision making. *First Author: Joanne B. Weidhaas, UCLA Radiation Oncology, Los Angeles, CA*

Background: GARUDA (Germline DNA-Based Radiosensitivity Biomarker Influence on Toxicity Following Prostate Radiotherapy) was a single center phase II prospective study evaluating the impact of sharing results from a germline genetic signature (PROSTOX) characterizing patients as having a low or high risk of developing late > 2 genitourinary (GU) toxicity from stereotactic body radiation therapy (SBRT) on decision making and toxicity. The goal of this early analysis was first to see if this information changed treatment choice, and second to see if patients categorized as genetically "low-risk" would have less late GU toxicity than those categorized as genetically "high-risk." **Methods:** PROSTOX is a test of germline mutations run in the MiradX CLIA-certified laboratory. Results were reported to the ordering physician and their patient for joint decision-making before proceeding with treatment selection. To be enrolled on the study patients could choose SBRT or moderately hypofractionated radiation therapy (MHFRT) for treatment of their prostate cancer. 279 men were screened for the GARUDA study between November 2020 and May of 2022. 71 withdrew for a variety of reasons, primarily choosing another location for treatment or form of treatment. 208 patients remained on the protocol and are included in this exploratory analysis. Statistical comparisons of stratified proportions are based on Gaussian approximations to Binomial probabilities. **Results:** The average age for the cohort was 72.12 with the majority being non-Hispanic and Caucasian. Overall, 85.15% (177) of patients were classified as low-risk and 14.9% of patients (31) were classified as high-risk for late grade > 2 GU toxicity by PROSTOX. There was not a significant difference in predicted toxicity risk by age (72.45 vs 70.2), ethnicity or race. Regarding treatment choice based on toxicity score, in patients determined to be low-risk, 1.2% chose MHFRT, and 98.8% chose MRI- or CT-guided SBRT. In patients who were classified as high-risk, 44.8% chose MHFRT, and 55.2% chose MRI- or CT-guided SBRT. The difference in treatment choice was significant ($p < 0.001$). In an early analysis of physician scored late > 2 GU toxicity in patients with > 18 months of follow-up (n = 57), 8.8% of patients had toxicity - 4.8% of those predicted to be low-risk, and 27.3% of those predicted to be high-risk ($p = 0.015$). **Conclusions:** In this exploratory analysis, predicting toxicity risk with PROSTOX significantly impacted patient and physician radiation treatment choice in localized prostate cancer. Early results also suggest that these changed treatment decisions lowered overall toxicity, which remained significantly different between patients classified as low-risk and high-risk. Analysis is ongoing to include patient reported outcomes and toxicity rates depending on treatment choice for those identified as high-risk. Clinical trial information: NCT04624256. Research Sponsor: U.S. National Institutes of Health.

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Poster Session

Pre-surgical ⁶⁸Ga-PSMA-11 PET for biochemical recurrence risk assessment: A surrogate of pelvic lymph node dissection? Follow-up analysis of a multicenter prospective phase 3 imaging trial. *First Author: Loic Djaïleb, UCLA Ahmanson Translational Therapeutics Division, LOS Angeles, CA*

Background: To compare the prognostic value of presurgical PSMA-PET and pelvic lymph nodes invasion (pN1) for biochemical recurrence (BCR) free-survival (FS) in patients with intermediate-risk to high-risk prostate cancer (PCa) treated with radical prostatectomy (RP) and pelvic lymph node dissection. **Methods:** This is a follow-up study of the surgery cohort included in the multicenter prospective phase 3 imaging trial (n=277; NCT03368547, NCT02611882, NCT02919111). Each ⁶⁸Ga-PSMA-11-PET scan was read by three blinded independent readers. Local histopathology risk score (CAPRA-S (Cancer of the Prostate Risk Assessment) score without pN data), PSMA-PET extra-prostatic disease (N1/M1), and pN were used to assess risk of BCR. Patients were followed up after RP by the local investigators using electronic medical records. BCR was defined by a prostate-specific antigen (PSA) level ≥ 0.2 ng/ml after RP or an initiation of PCa specific secondary treatment (>6 months after surgery). Univariate, multivariate Cox model, and c-statistic index were performed to assess the prognostic value of PSMA-PET, LNI and its added value to Local histopathology risk score. **Results:** From December 2015 to December 2019, 277 patients underwent surgery after PSMA-PET. Clinical follow-up was obtained in 240/277(87%) patients. Median follow-up from surgery was 32.4 (IQR 23.3-42.9) months. Ninety-one/240 BCR events (38%) were observed. PSMA-PET N1/M1 and pN1 were found in 41/240 (17%) and 67/240 (28%) patients respectively. Local histopathology risk score, PSMA-PET and pN were significant univariate predictors of BCR. Only Local histopathology risk score and PSMA-PET were significant in multivariate analysis (HR [95% CI] 1.4 (1.2-1.5) $p < 0.0001$ and (1.7 (1-2.9) $p = 0.03$). Prognostic value of model combining local histopathology and PSMA-PET was not significantly different than model combining local histopathology and pN (c-statistic 0.74 (0.69-0.79) vs 0.73 (0.68-0.78); $p = 0.69$). In patient group with low-risk Local histopathology score and PSMA-PET NO-M0 only 4/109 (5%) were pN1. In patients with high-risk local histopathology score, a PSMA-PET N1/M1 was associated with a significant lower BCR-FS than a PSMA-PET NO-M0 (median survival (95% CI) 32.7 (14.9-NR) vs 8 (3.2-15.5) $p = 0.001$). pN1 was found in respectively 25/34 (74%) and 34/90 (38%). **Conclusions:** Combination of pre-surgical PSMA-PET and Local histopathology was not statistically different than the reference standard, i.e. local histopathology and pN to predict BCR-FS. Interestingly rate of discrepancy with pN was low among patient with low histopathology risk and PSMA-PET (NO-M0) and patient with high histopathology risk and PSMA-PET (N1/M1). Clinical trial information: NCT03368547. Research Sponsor: None.

5092

Poster Session

Socio-demographic, clinical, and genetic predictors of low versus high Gleason score among men with prostate cancer in the Detroit Research on Cancer Survivorship (ROCS) cohort. *First Author: Samantha Goodenow, Wayne State University School of Medicine, Detroit, MI*

Background: Black men with prostate cancer typically present with a higher Gleason Score (GS) and more aggressive disease than White men. The purpose of this project is to describe the relationship between socio-demographic, clinical and genomic variability with GS categories among 599 men with prostate cancer in the Detroit Research on Cancer Survivorship (ROCS) cohort. **Methods:** Detroit ROCS is a cohort of Black cancer survivors based in the Detroit Metropolitan area. Patient data was obtained from a self-administered questionnaire, cancer registry and biologic samples were collected through at home phlebotomy or mailed saliva kits. The primary analysis focused on clinical and genetic differences between men with GS ≤ 6 vs. ≥ 7 . Germline data was compiled into the multi-ethnic genotyping array (MEGA) data panel and 21 genes were chosen for analysis (2,393 SNPs) based on their clinical applicability. Eight tools were used in ANNOtate VARIation (ANNOVAR) to determine whether a genetic variant was pathogenic. The determination of pathogenicity was defined by at least seven of the tools indicating variant pathogenicity. We assessed the rate of pathogenic variants for each GS category. Multivariable models of predictors of GS categories were conducted using logistic regression. **Results:** The categories across GS in the ROCS cohort included: ≤ 6 (21.2%), 3+4 (40.4%), 4+3 (20.2%) and ≥ 8 (18.2%). Variables associated with increased GS (≥ 7 vs. ≤ 6) included age (for each 10-year increase the OR was 1.71, 95% CI 1.26-2.34) and body mass index (for each 5 unit increase the OR was 1.27, 95% CI 1.06-1.54). Higher vs. lower education (some college education or higher vs less than or equal to a high school education) was associated with lower GS, OR 0.58, 95% CI 0.37-0.96. Out of a total of 2,393 SNPs analyzed, 880 (36.8%) were polymorphic, of which 684 had a minor allele frequency (MAF) >0.001 , and 282 had a MAF >0.05 . Overall, 16.2% of the men were carriers of a pathogenic variant, the most common of which were *ATR* (9.3%), *FANCL* (3.5%), and *ATM* (1.7). Men with GS 6 had a lower rate of pathogenic variants (8.7%), than those with GS 3+4 (18.2%), GS 4+3 (16.5%), and GS 8 (20.2%). Men with a pathogenic variant in *ATR* were 2.87 (95% CI 1.08- 7.65) times more likely to have GS ≥ 7 vs. ≤ 6 . Higher GS was specifically associated with SNP rs33972295 in the *ATR* gene. **Conclusions:** The relationship between older age, higher BMI, and less educational background suggests that socio-demographic risk factors should be accounted for when assessing risk for higher grade prostate cancer. Identification of genomic differences associated with aggressive prostate cancer may provide insight into new targeted therapy options. Research Sponsor: None.

5091

Poster Session

PSMA PET findings in an “EMBARC-like” cohort of patients with high-risk non-metastatic hormone-sensitive prostate cancer: A single center post-hoc retrospective analysis. *First Author: Wesley Robert Armstrong, UCLA-Caltech Medical Scientist Training Program, Los Angeles*

Background: The EMBARK trial is a phase 3, randomized, study evaluating use of enzalutamide with or without concomitant leuprolide in non-metastatic castrate sensitive prostate cancer patients. Eligibility status for the trial relied upon conventional imaging which under detects metastatic disease in comparison to PSMA-PET imaging. The aim of this post-hoc retrospective analysis was to describe the PSMA-PET findings in a patient population representative of the EMBARK trial. **Methods:** This was a post-hoc, retrospective analysis of 5 prospective studies of PSMA PET conducted at UCLA from 2016 to 2021 that included patients with recurrent PCa following RP, RT or SRT. Patients were included if they met eligibility for enrollment in the EMBARK trial at the time of their PSMA scan defined as the following: Rising PSA at a level above 1.0ng/mL (post RP and SRT) or 2.0ng/mL $>$ nadir (post-RT), PSA doubling time ≤ 9 months, Serum testosterone ≥ 150 ng/dL. Exclusion criteria constituted: distant metastatic disease as assessed by radiographic imaging, prior hormonal therapy or systemic therapy for prostate cancer. PSMA PET findings (PROMISE mITNM stage, number of lesions) were collected from the clinical imaging reports. Descriptive statistics were used (median, range). **Results:** From 2002 patients screened, 146 patients were included in the analysis. Median time from primary therapy to PSMA PET was 39 (2.1-261) months. Median pre-scan PSA levels and PSA doubling time in patients who underwent RP (n=85), dRT (n=22), post-RP SRT (n=39) and overall (n=146) were 2.4 ng/mL (1-72.1), 8.3 ng/mL (2.37-202), 2.58 ng/mL (1.1-32.3), 2.7 ng/mL (1-202), and 3.5 months (1-9), 3.3 months (1-9), 4.4 months (1-9), 3.7 (1-9) months, respectively. PSMA-PET was positive in 80%, 41%, 85%, 83% of the RP, dRT, RP + SRT and overall populations, respectively. Poly-metastatic disease (≥ 5 lesions) was found in 19%, 32%, 21% and 21% of cases, respectively. PSMA-PET detected disease only localized to the prostate fossa (miT+NOMO) in 7%, 32%, 0% and 9% respectively. PSMA-PET detected pelvic nodal disease (miTxN1M0) in 40% 18% 28% and 34% respectively. PSMA PET detected any distant metastatic disease (miTxNxM1) in 33%, 41% 56% and 40% respectively. PSMA-PET detected metastatic nodal only disease (N1 and/or M1a) in 58% 32% 74% and 39% and osseous disease (M1b) in 19% 23% 31% and 23% cases respectively. **Conclusions:** In this “EMBARC-like” cohort of patients with high-risk nmCS PCa and PSA DT < 9 months, PSMA PET was positive in 83% of patients, detected M1 disease in 40% of patients and over one-fifth of cases presented with 5 or more lesions. PSMA-PET provides novel additional risk stratification for patients with high-risk nmCS PCa without distant metastasis based on conventional imaging. Further studies are needed to assess its independent prognostic value and use for treatment guidance. Clinical trial information: NCT03582774. Research Sponsor: None.

5093

Poster Session

Racial differences in the utilization of MRI-guided biopsy before prostate cancer diagnosis. *First Author: Grace L. Lu-Yao, Division of Population Science, Department of Medical Oncology, Sidney Kimmel Medical College, Sidney Kimmel Cancer Center at Jefferson Health, Philadelphia, PA*

Background: Most low-risk prostate cancer (PCa) patients undergo active surveillance (AS). Compared with Whites, Blacks are more likely to opt for AS and suffer a higher risk of cancer progression while on AS. A primary concern of AS is the likelihood of missing clinically significant cancer. Transrectal ultrasound-guided biopsy is the most common method for diagnosing and grading PCa; however, this method often misses anterior PCa. Magnetic resonance imaging (MRI) allows clinicians to identify better and detect PCa; however, current guidelines on MRI-guided biopsy (MRI-GB) are inconsistent. This population-based study aimed to examine the utilization of MRI-GB 6 months before PCA diagnosis over time by race in the US. **Methods:** We used SEER-Medicare data to identify men diagnosed with PCa between January 1, 2012, to December 31, 2017, and excluded patients missing the date of diagnosis, being diagnosed at death, enrolled in HMO, or having no continuous A and B coverage six months before diagnosis. We used the CPT codes to identify prostate biopsy and MRI use. Multivariable logistic regression was used to evaluate racial disparity in MRI use six months before PCa. The model included covariates age, race, SEER region, marital status, state buy-in for Medicare (a poverty indicator), education, income, Charlson comorbidity index, and procedure (MRI) year. **Results:** Among 38,612 eligible men, MRI use six months before PCa diagnosis increased from 2012 to 2017 (3.2% to 24.3% among Whites, 1.8% to 14.2% among Blacks). Compared with Whites, Blacks were 38% less likely to receive pre-diagnosis MRI (OR=0.62, 95% CI 0.52-0.74). Besides race, having state buy-in for Medicare (OR=0.44; 95% CI 0.30-0.65) and geographic regions (Central vs. West OR=0.40; 95% CI 0.34-0.45) were strong predictors of lower utilization of MRI. **Conclusions:** The gap in the utilization of MRI may exacerbate racial disparities in PCa. Future studies are needed to identify potential barriers to adopting MRI for PCa workups. Research Sponsor: U.S. National Institutes of Health; Pennsylvania Department of Health.

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Poster Session

Basal-luminal subtyping of localized high-risk prostate cancer and benefit of adding docetaxel to definitive radiotherapy with androgen suppression in the NRG Oncology/RTOG 0521 phase III trial. *First Author: Ryan Phillips, Mayo Clinic, Rochester, MN*

Background: In prior studies, basal vs. luminal differentiation portends differential response to a) androgen suppression (AS) duration for high-risk prostate cancer (PCa) (NRG-GU-TS006) and b) docetaxel chemotherapy (CT) and AS for metastatic hormone-sensitive disease (CHAARTED). In NRG-GU-TS006, basal tumors appeared to benefit the most from longer duration of AS while those with luminal subtype did not whereas, in CHAARTED, luminal subtype had greater benefit from addition of CT. Herein, we examined basal-luminal subtyping to predict differential response to the addition of CT in the setting of high-risk PCa treated with AS and definitive radiotherapy (AS + RT) in NRG/RTOG 0521. **Methods:** Per pre-specified and approved NCI analysis plan (Navigator #1061), we obtained available NRG biobank biopsy specimens from patients enrolled on the NRG/RTOG 0521 phase III trial, which randomized patients to AS + RT +/- CT. The highest-grade tumors were profiled on clinical-grade whole-transcriptome arrays (Veracyte, San Diego, CA). Basal-luminal subtypes were generated using a 215-gene PCa subtyping classifier (PSC), a second generation PAM50 basal-luminal model. Treatment effects in Luminal Proliferating (LP) and non-LP subtypes were examined with Cox (for overall survival, OS, and metastasis-free survival, MFS) and Fine & Gray (for distant metastasis, DM) multivariable (MVA) models adjusted for age and trial risk stratification, as well as with restricted mean survival times (RMST). **Results:** Of 183 samples available for analysis (91 from control and 92 from the CT arm), 52 (28%) were classified as LP subtype. Median follow-up for OS was 9.9 years. No significant differences in clinical or pathological variables were observed between LP and non-LP subtypes. In MVA, we did not detect any significant LP subtype-by-CT treatment interaction but observed evidence of non-proportional hazards (Grambsch-Therneau test, $p < 0.05$). In unselected patients, 5- and 10-year RMST difference between the arms was 0.9 (95% CI [-1.5, 3.4], $p = 0.46$) and 5.7 (95% CI [-2.5, 13.9], $p = 0.17$) months of OS. Stratifying by tumor subtype, at 5 years the RMST difference in months was 3.8 (95% CI [0.3, 7.2], $p = 0.03$) for LP and -0.2 ([-3.4, 2.9], $p = 0.89$) for non-LP. The RMST difference in months at 10-years was 13.7 (95% CI [-0.2, 27.5], $p = 0.053$) for LP and 2.5 ([-7.6, 12.5], $p = 0.63$) for non-LP. **Conclusions:** In pre-treatment biopsy samples from a Phase 3 trial cohort of localized high-risk men, luminal-basal subtyping of tumors demonstrated differential response to docetaxel CT. Similar to results from the CHAARTED trial of metastatic disease, LP tumors may derive greater benefit from addition of CT. Validation of these findings may enable effective earlier use of CT in men with PCa. Research Sponsor: U.S. National Institutes of Health; Sanofi.

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Poster Session

Post radical prostatectomy (RP) PSA outcomes following 6 vs 18 months of perioperative androgen deprivation therapy (ADT) in men with localized high risk prostate cancer (LHRPC): Results of Part 2 of a randomized phase 2 trial. *First Author: Rana R. McKay, University of California San Diego, La Jolla, CA*

Background: Patients with LHRPC have an increased risk of relapse following RP. We previously reported on Part 1 of a phase 2 trial testing neoadjuvant apalutamide, leuprolide, and abiraterone acetate plus prednisone (ALAAP) or leuprolide and abiraterone plus prednisone (LAP) for 6 months followed by RP (McKay, J Urol, 2021). We demonstrated favorable pathologic responses (tumor < 5 mm) at RP in 20.3% of patients ($n = 24/118$). Herein, we report the results of Part 2 testing adjuvant ALAAP (NCT02903368). **Methods:** Eligible patients had a Gleason score $\geq 4+3$, PSA > 20 ng/mL, or T3 disease (by DRE or MRI) and lymph nodes < 20 mm. At Part 2, patients were randomized 1:1 to ALAAP for 12 months (Arm 2A) or observation (Arm 2B), stratified by neoadjuvant therapy and pathologic T stage ($< y pT3$ or $\geq y pT3$). The primary endpoint was biochemical progression-free survival (bPFS) at 3 years post-RP. bPFS was defined as the time from randomization to progression (PSA ≥ 0.2 ng/mL, local/distant disease on CT/MRI or bone scan, or receipt of post-RP therapy or radiation for rising PSA) or death. The Kaplan-Meier estimate of bPFS at 3 years was compared between arms using a Chi-square test (Klein, Stat Med, 2007). Secondary endpoints included safety and time to testosterone recovery (> 200 ng/dL). **Results:** Overall, 82/118 (69%) of patients enrolled to Part 1 were randomized to Part 2. Median follow-up was 47 months post-RP. Patient preference was the main reason for non-randomization in Part 2. In the intent-to-treat analysis, the 3-year bPFS estimate was 80% (95% CI: 65-90%) for Arm 2A and 72% (95% CI: 56-84%) for Arm 2B, which was not statistically significant (2-sided $p = 0.39$). Patients who achieved pathologic responses ($n = 14$) had longer bPFS than non-responders (log-rank test 2-sided $p = 0.03$; 3-year bPFS 100% vs 72%). In per-protocol population, of 36 patients receiving Arm 2A treatment with available data, 83% had testosterone recovery and median time to recovery from therapy end was 8.7 months. For patients on observation ($n = 42$), 95% had testosterone recovery, and median time to recovery from RP was 4.0 months. No new safety signals were observed. **Conclusions:** Neoadjuvant ADT in LHRPC resulted in favorable pathologic responses and 3-year bPFS in a subset of patients. As 30% of patients declined an additional 12 months of adjuvant treatment, the study was underpowered to detect a difference between 6 months vs. 18 months of treatment. Subsequent analyses will evaluate predictors of improved bPFS. Clinical trial information: NCT02903368. Research Sponsor: Investigator initiated study funded by Janssen.; Prostate Cancer Foundation.

	Arm 2A N=42	Arm 2B N=40	Not Randomized* N=31
At Part 1			
NCCN high-risk	39 (93%)	37 (93%)	30 (97%)
At Part 2			
y pT3	24 (57%)	24 (60%)	13 (42%)
pCR/MRD	08 (19%)	06 (15%)	10 (32%)
Part 1 APL	23 (55%)	22 (55%)	14 (45%)

pCR=pathologic complete response; MRD=minimum residual disease. *Agreed to be followed per Arm 2B.

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Poster Session

Testosterone recovery following androgen suppression and prostate radiotherapy (TRANSPORT): Updated individual patient data meta-analyses from the MARCAP consortium. *First Author: Wee Loon Ong, Odette Cancer Centre, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, ON, Canada*

Background: Time to testosterone recovery (TR) following androgen deprivation therapy (ADT) and radiotherapy for prostate cancer varies following cessation of ADT. We aimed to quantify the association between time to TR and duration of ADT and patient age. **Methods:** We identified prospective randomized trials of prostate radiotherapy and ADT in the Meta-Analysis of Randomized trials in Cancer of the Prostate (MARCAP) consortium for which prospectively collected serial testosterone values were available. The time to non-castrate TR (NCTR) (> 1.7 ng/mL), non-hypogonadal TR (NHTR) (> 8.0 ng/mL) and full TR (FTR) (> 10.5 ng/mL) were estimated from the end date of prescribed ADT using the Kaplan Meier method. Cox regression was used to evaluate the differences in time to TR for men aged < 65 years and ≥ 65 years for each duration of ADT. Interaction effects between ADT duration and patient age on TR were evaluated. **Results:** 2628 men from 5 trials (TROG 9601, TROG 0304, PCSIII, PCSIV, and Ottawa-01) met the inclusion criteria for analysis. Of these, 236, 1485, 731, and 176 men had 3-, 6-, 18-, and 36-months of ADT respectively. 1502 (57%) men had baseline (pre-ADT) testosterone data available, of which 99% (1494/1502) had non-castrate testosterone (> 1.7 ng/mL), and 78% (1178/1502) had normal testosterone (> 10.5 ng/mL) at baseline. At last follow-up, there were 96% (2522/2628), 77% (2035/2628) and 65% (1700/2628) of men who had NCTR, NHTR and FTR respectively. The median time (range) to NCTR was 1.9 (0.2-60), 6.2 (0.0-92), 6.3 (0.0-92), and 15.7 (0.1-75) months for men who had 3-, 6-, 18- and 36-months of ADT, respectively. The median time (range) to NHTR was 2.5 (0.4-73), 11.2 (0.1-93), 17.7 (0.2-92), and 53.4 (5.3-76) months for men who had 3-, 6-, 18- and 36-months of ADT, respectively. The median time (range) to FTR was 5.8 (0.4-72), 16.7 (0.3-95), and 26.0 (0.2-90) for men who had 3-, 6-, and 18-months of ADT, respectively, while the median time to FTR was not reached in men who had 36-months of ADT. In men who had 6-months of ADT, men aged ≥ 65 years were 35% (95% CI=26-43%) less likely to have FTR compared to men aged < 65 years, while for those who had 18-months of ADT, men aged ≥ 65 years were 52% (95% CI=41-60%) less likely to have FTR compared to men aged < 65 years. There was no statistically significant interaction between the effect of ADT duration and age on the time to FTR (interaction $P = 0.07$ for the entire cohort). **Conclusions:** In this updated individual patient-data meta-analysis of prospectively collected serial testosterone data from 5 randomized trials, substantial delay in FTR in men who had longer duration of ADT was observed, consistent with prior analyses. Approximately 1-in-3 men did not have FTR, which may have life-long impacts on their quality of life. Research Sponsor: RANZCR-TROG Research Grant.

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Poster Session

Comparative real-world (RW) evidence on darolutamide (Daro), enzalutamide (Enza), and apalutamide (Apa) for patients (Pts) with nonmetastatic castration-resistant prostate cancer (nmCRPC) in the United States: DEAR. *First Author: Alicia K. Morgans, Dana-Farber Cancer Institute, Boston, MA*

Background: Novel androgen receptor inhibitors (ARIs) are recommended for pts with nmCRPC. Daro has a distinct structure with low blood-brain barrier penetration which may lead to a lower risk of central nervous system-related adverse events (AEs) and minimal risk of AEs commonly associated with ARIs. DEAR is the first study comparing RW utilization, outcomes, and AEs between daro and enza/apa in nmCRPC pts. **Methods:** This retrospective chart review cohort study uses electronic medical records from the PPS network of US urology practices. Eligible pts had nmCRPC, no prior novel hormonal therapy, and initiated first ARI treatment (index date) between 8/2019-3/2022. We describe the % of pts who discontinued initial ARI treatment (DISC), % who progressed to metastasis (PROG), and % with AEs. A comparative analysis was performed between daro and enza/apa using Cox proportional hazards models for time to DISC/time to PROG, adjusting for observed baseline (BL) factors. **Results:** 870 pts were included (daro/enza/apa, $n = 362/382/126$). Median age (80/79/80 y), median BL prostate-specific antigen (PSA) doubling time (6.8/6.4/7.4 mo), other BL characteristics, and median follow-up (22.2/22.7/23.3 mo) were similar for daro/enza/apa. A lower % of pts had a DISC event on daro vs enza/apa (30.4 vs 40.8/46.0) or a PROG event (17.7 vs 28.3/27.8) during the study period. Multivariate analyses adjusting for BL factors showed that pts on daro had a lower risk of DISC and PROG over time vs enza/apa. A lower % of pts on daro had AEs vs enza/apa (24.9 vs 29.3/30.2). **Conclusions:** Overall, a lower % of pts discontinued initial ARI treatment, progressed to metastasis, or had AEs on daro vs enza/apa. In analyses adjusting for observed BL factors, pts on daro had considerably lower risk of DISC and PROG vs enza/apa. This study confirms daro's strong efficacy and favorable tolerability profile in a RW setting. The longer treatment duration seen with daro may be associated with a lower risk of progression to mCRPC vs enza/apa. Research Sponsor: Bayer AG.

Outcomes.

Adjusted Cox proportional hazards model, ^a HR (95% CI)	Daro (n=328) vs Enza (n=341)	Daro (n=328) vs Apa (n=122)
Time to DISC ^b	0.73 (0.56-0.94)	0.61 (0.44-0.85)
Time to PROG ^c	0.59 (0.43-0.82)	0.65 (0.42-0.99)

^aAdjusted for age at index, race, insurance coverage, index yr, BL PSA, BL PSA doubling time, time from CRPC to index date, and Gleason score. ^bDISC was defined as occurrence of any of the following: initial ARI treatment stop/switch to another ARI/death. ^cPROG was defined as evidence of bone, visceral/soft tissue, or distant nodal metastases, such as secondary neoplasm diagnosis codes or codes associated with a PC-related claim, manual data entry in patient charts, and/or initiation of mCRPC treatment (abiraterone, sipuleucel-T, docetaxel, cabazitaxel, mitoxantrone, or radium-223).

TPS5098

Poster Session

Whole-food plant-based diet (WFPBD) to control weight and metabo-inflammation in overweight/obese men with prostate cancer (PC) receiving androgen deprivation therapy (ADT): A multi-center randomized control trial.

First Author: Nicole Jacobs, Weill Cornell Medicine, New York, NY

Background: Obesity promotes a chronic inflammatory state that is associated with PC progression. ADT can cause significant side effects including weight gain, accumulation of body fat, insulin resistance, and an increased risk of diabetes and cardiovascular disease. A WFPBD has been shown to promote weight loss, decrease chronic inflammation, and shift gut microbial profiles to a microbiome that promotes insulin sensitivity. We hypothesize that a WFPBD and behavior intervention will promote weight loss and a reduction in adiposity in overweight/obese patients with PC on ADT and will decrease biomarkers of metabo-inflammation; and that a WFPBD, which is enriched in fiber, will modulate the fecal microbiota and metabolites, and alter study participants' serum metabolome. Correlative studies will offer insight into the impact of nutrition on metabolic pathways that are known to be affected by PC, ADT and/or excess body fat, including steroid metabolism, ketogenesis, and fatty acid metabolism. **Methods:** Key eligibility criteria include pts with PC with a BMI ≥ 27 receiving ADT with an LHRH/GnRH analogue for >24 weeks pre-study (+ androgen receptor pathway inhibitor for >3 mos) with anticipation of >26 more weeks of ADT. 60 patients randomized 1:1 between two cohorts. Cohort 1: pts receive 12 prepared meals (provided by *Plantable*) per weeks 1-4 and 6 meals weeks 5-8 plus *Plantable* coaching, nutritional counseling and education to assist in self-prepping plant-based meals (weeks 9-26); Cohort 2 (control): pts receive general nutritional counseling from a Registered Dietician weekly for 8 weeks, then monthly x 4. Collection of baseline and serial measurements (pre-intervention, weeks 4, 8 and 26) including weight, serum carotenoid levels (to monitor dietary compliance), dual energy x-ray absorptiometry (DXA) scans, MnSOD polymorphisms, and biomarkers of inflammation and metabolism. The primary comparison is weight loss at 4 weeks (with an 80% power to detect an effect size 0.74 standard deviations with a 2-sided significance level of 0.05 using a two-sample t-test). Secondary objectives will assess and compare changes in: a) biomarkers of metabolic disorders (Hemoglobin A1c, fasting insulin/glucose) and cardiovascular risk (LDL cholesterol, HDL cholesterol, triglycerides); b) pro-inflammatory markers (IL-6, hsCRP) and adipokines (leptin, adiponectin); c) fecal microbiota; and d) quality of life measurements. Exploratory objectives will assess the effects of a WFPBD on serum and fecal metabolomics and on clonal hematopoiesis. Trial is open at Weill Cornell Medicine (WCM), John Hopkins University and Columbia University. First pt enrolled at WCM September 2022. Funding support from the Prostate Cancer Foundation; PC Clinical Trials Consortium c22-301. Clinical trial information: NCT05471414. Research Sponsor: Prostate Cancer Foundation.

TPS5100

Poster Session

CLIMATE: Assessing the clinical utility of miR-371a-3p as a marker of residual disease in stage 1 testicular germ cell tumour (TGCT) following orchiectomy: ANZUP 1906. *First Author: Ciara Conduit, Personalised Oncology, Walter and Eliza Hall Institute of Medical Research, Parkville Victoria, Australia*

Background: There is impetus to identify biomarkers in TGCT to help select those at high-risk of relapse following orchiectomy and target interventions to prevent over-treatment. miR-371 has been shown to reliably predict presence of active malignancy with higher accuracy than currently available biomarkers. More clinical evidence is required to ascertain its clinical utility as a marker of microscopic disease to guide treatment recommendations in stage 1 TGCT and other settings. **Methods:** CLIMATE ANZUP1906 (ACTRN12622000247774) is a prospective, single-arm, non-interventional cohort study recruiting adults with clinical stage 1 TGCT entering active surveillance. Eligible participants are recruited within six weeks of orchiectomy and are willing to undergo active surveillance in accordance with the Australian and New Zealand Urogenital and Prostate (ANZUP) Cancer Trials Group Surveillance Recommendations (or similar), without adjuvant treatment. Participants with metastases, non-testicular primaries, or history of contralateral TGCT are ineligible. Serum, plasma, and buffy coat samples are collected at consent and every three months until 24 months (and at relapse, if applicable). miR-371 will be assessed using established protocols. Clinical data, including treatment(s), surveillance, and relapses are captured in Australia's national TGCT registry, iTestis. Archival tissue from diagnosis $\pm$ relapse is identified for future translational research. The primary endpoint for CLIMATE is 12-month relapse-free survival of miR-371 positive/negative groups. Key secondary endpoints include miR-371 during surveillance and at relapse, concordance between serum/plasma miR-371 and archival tissue, and health economic analyses. Prior studies suggest ~20% of post-orchidectomy miR-371 samples are positive. A sample size of 200 participants will result in 20 relapses, 160 non-relapses and 20 individuals lost to follow-up, and will permit description of the primary endpoint. Patient-level data from CLIMATE will contribute to a joint analysis of parallel trials evaluating miR-371 in this setting, COG AGCT1531 and SWOG1823. The first participant was recruited to CLIMATE in February 2022. 9/12 study sites in Australia and New Zealand have been activated and 47/200 (24%) have been enrolled. Recruitment is expected to take 36 months, followed by a further 24 months follow-up. Clinical trial information: ACTRN12622000247774. Research Sponsor: ANZUP.

TPS5099

Poster Session

GUIDE: A randomized non-comparative phase II trial of biomarker-driven intermittent docetaxel versus standard-of-care docetaxel in metastatic castration-resistant prostate cancer (ANZUP 1903). *First Author: Ciara Conduit, Australian & New Zealand Urogenital and Prostate (ANZUP) Cancer Trials Group, Camperdown, Australia*

Background: Docetaxel improves survival in people with metastatic castration resistant prostate cancer (CRPC) but is associated with toxicities which impact tolerability, particularly for patients who may be older and often with multiple comorbidities. Biomarker-driven de-escalation of docetaxel chemotherapy may allow improved balance of cancer control and quality of life against toxicity. In patients with metastatic CRPC receiving docetaxel, a reduction to undetectable levels in circulating promoter methylated glutathione S-transferase Pi-1 (*mGSTP1*) DNA after 2 cycles of chemotherapy is associated with improved overall survival¹. This study aims to determine the efficacy and safety of intermittent docetaxel chemotherapy guided by the presence or absence of circulating *mGSTP1* DNA in patients with metastatic CRPC. **Methods:** GUIDE (NCT04918810) is a randomized, two-arm, non-comparative phase 2 trial recruiting 120 patients at eight Australian centres. Patients with Prostate Cancer Working Group-3 defined metastatic CRPC who are commencing docetaxel 75mg/m² q3w will be pre-screened for detectable *mGSTP1* at baseline +/- following two cycles of treatment. Those with detectable plasma *mGSTP1* at baseline that becomes undetectable after two cycles of chemotherapy will be eligible for GUIDE. Prior to Cycle 4 of docetaxel, these patients are randomized 2:1 to one of two treatment arms: Arm A (cease docetaxel and reinstitute if *mGSTP1* becomes detectable) or Arm B (continue docetaxel 75mg/m² q3w in accordance with clinician's usual practice) (Figure 1). The primary endpoint is radiographic progression-free survival (rPFS). Secondary endpoints include time on treatment holidays, safety, patient-reported outcomes, overall survival, health resource use and cost associated with treatment. This study is powered to detect a rPFS curve with at least 50% rPFS at 12 months using a one-sided log-rank test with 2.5% alpha and 90% power. 3 of planned 120 patients have been enrolled. This novel study is the first to prospectively test the clinical utility of a circulating epigenetic biomarker (*mGSTP1*) in clinical decision-making in prostate cancer, building upon existing data supporting analytical and clinical validity. We anticipate that this novel biomarker will safely guide treatment de-escalation and improve the quality of survival for a group of patients with metastatic CRPC. Clinical trial information: NCT04918810. Research Sponsor: Chris O'Brien Lifehouse Philanthropic Fund; ANZUP Discretionary Funding Initiative and ANZUP Below the Belt Research Fund.

TPS5101

Poster Session

A study of prospective monitoring of patients with recurrent prostate cancer using serial PSMA imaging (18F-DCFPyL). *First Author: Mohammad O. Atiq, Genitourinary Malignancies Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD*

Background: 18F-DCFPyL PSMA PET imaging is now FDA approved for patients with high-risk prostate cancer and those with biochemically recurrent prostate cancer (BCR). BCR has been traditionally defined as a rising PSA after definitive surgery and/or radiation have not been curative in patients without tumor findings on a CT or Tc99 bone scan. There are an estimated 25,000-50,000 new cases of BCR in the US annually. BCR patients are usually managed conservatively, often with surveillance since there is no data demonstrating interventions improve survival. Although 18F-DCFPyL will be able to detect disease at the micrometastatic/subclinical level, there is limited prospective data on how these patients should be managed. While great enthusiasm exists to utilize radiation or ADT-based regimens extrapolated from a more advanced disease state, the natural history of subclinical disease seen on 18F-DCFPyL remains unclear (Madan RA et al. J Clin Oncol 2022). **Methods:** The primary objective of this study is to monitor patients with recurrent prostate cancer to learn about the natural history of 18F-DCFPyL PET positive disease in this patient population. Eligible patients include those who have had prior definitive surgery or radiation, current PSA ≥ 0.50 ng/mL, testosterone > 100 ng/mL, no evidence of soft tissue disease on CT scan/MRI and no bone lesions on bone scan. Patients will undergo initial imaging with 18F-DCFPyL scans. Those with negative findings on the initial scan will have annual repeat 18F-DCFPyL scans. Patients with positive initial scans will be scanned every 6 months. All patients will have PSA testing every 3 months and will undergo annual CT and Tc99 bone scans. Up to 250 patients will be followed for 5 years or until off-study criteria is met (including new findings on CT/bone scans consistent with metastatic disease or continuous systemic prostate cancer therapy for more than 6 months). In addition to monitoring the imaging changes, we will evaluate patterns of progression on 18F-DCFPyL scans over time, analyze PSA doubling time in context of 18F-DCFPyL changes and evaluate circulating biomarkers. ClinicalTrials.gov Identifier: NCT05588128. Clinical trial information: NCT05588128. Research Sponsor: U.S. National Institutes of Health.

TPS5102

Poster Session

P3BEP (ANZUP 1302): An international randomized phase 3 trial of accelerated versus standard BEP chemotherapy for male and female adults and children with intermediate and poor-risk metastatic germ cell tumours (GCTs). *First Author: Danka Sinikovic Zebic, NHMRC Clinical Trials Centre, The University of Sydney, Camperdown, NSW, Australia*

Background: Bleomycin, etoposide, and cisplatin (BEP) given 3-weekly x 4 remains standard 1st line chemotherapy for intermediate or poor risk metastatic GCT. Accelerating standard regimens by shortening the cycle length to 2-weekly improved cure rates in other cancers. P3BEP will determine effects of accelerated versus standard BEP in this setting. This is the first international, randomized trial of chemotherapy for intermediate and poor-risk metastatic GCT to include adults and children of both sexes. **Methods:** This open label, randomized, phase 3 trial is conducted seamlessly in 2-stages. The primary endpoint for stage 1 (n = 150) was favourable response; and for stage 2 (n = 500) is progression free survival at 2 years (PFS2y). These sample sizes provide > 80% power with a 2-sided type I error rate of 5% to detect an absolute improvement of 21% in the favourable response rate (stage 1) and of 7% in the PFS2y (stage 2). The target population is males and females aged 11 to 45 with intermediate- or poor-risk metastatic GCT of the testis, ovary, retroperitoneum, or mediastinum. Participants are randomized (1:1) to 4 cycles of standard BEP (q3w) or accelerated-BEP (q2w) with cisplatin 20mg/m² D1-5, etoposide 100mg/m² D1-5, bleomycin 30 KIU weekly x 12, and pegylated G-CSF D6 or filgrastim daily (Figure 1). Study assessments occur at 30 days after completing chemotherapy, 6 months from randomisation, and after completion of all post-chemotherapy treatments (e.g. surgery). Tumour and blood samples are collected for translational substudies. Progress - As of Jan 2023, 241 participants have been recruited from 22 ANZ sites, 16 UK sites (led by Cambridge Clinical Trials Unit), and 55 USA sites (led by Children's Oncology Group). The first planned interim analysis for safety (n = 76) identified no safety concerns. The stage 1 analysis of safety and activity (response rate) for the 1st 150 patients was reviewed by the IDSMC, which recommended continuation of the trial as per protocol. Clinical trial information: NCT02582697. Research Sponsor: Cancer Australia; Clinical Trials Awards and Advisory Committee (UK) and National Cancer Institute (USA).

TPS5103

Poster Session

SWOG S1823/CCTG GCC1: Translational observational investigational study of the liquid biomarker microRNA 371a-3p in newly diagnosed germ cell tumours—Real-world trial design, rapid accrual, and robust secondary use of data opportunities. *First Author: Antoine Morin Coulombe, BCCancer, Vancouver, BC, Canada*

Background: With the discovery of the very promising, germ cell malignancy (GCM) specific, liquid biomarker microRNA 371a-3p (miR371), the investigative trajectory has markedly accelerated. With its outstanding, previously-reported specificity and positive predictive value, miR371 likely will become a powerful tool for clinical decision-making. The primary objective of SWOG S1823/CCTG GCC1 [NCT03067181] is to define the operating characteristics of plasma miR371 expression at the time of clinical relapse for low/moderate risk non-seminoma GCM patients on active surveillance. **Methods:** S1823 is a prospective, observational, adult GCM translational trial which is actively accruing. Broad eligibility includes all newly diagnosed adult GCM patients. Patients are assigned to low (<25% risk of relapse), moderate (25-90% risk of relapse) or high (≥90% risk of harboring active GCM) risk groups. Pragmatic logistics include using Streck tubes and centralized processing for miR371 sample processing and analytics. Research samples were drawn at the time of routine blood draws minimizing patient burden. Source documents are submitted along with case report forms. This data-gathering model gives an important data quality-control check. S1823 began in July 2020 and has since accelerated its accrual to consistently predicted new enrollments of 20-30 cases/month. As of January 2023, the study enrolled 389 low-risk, 114 moderate-risk and 146 high-risk patients (657 total). Interim analysis is planned at the time 40 non-seminoma GCM patients have relapsed and is anticipated in late 2023 to early 2024. 404 centers have opened S1823. 3 Canadian centers have enrolled >10 patients (range 11-51). 17 USA institutions have enrolled >10 patients (range 11-112). In North America, 9 of the 12-storied GCM clinical research programs have had robust participation. The leading accruing organization was the Kaiser Permanente system where 112 patients have been enrolled. In Canada, all population centers contributed proportionally. In the USA, the dominant enrollment comes from the west coast and mid-west. Proportional enrollments have been seen in Hispanic and Asian populations. The entire study provides rich opportunities for a variety of secondary use and patterns of care projects that will begin to roll out over the next year. Clinical trial information: NCT03067181. Research Sponsor: Hope Foundation for Clinical Research.

S1823 enrollment by race, sex and ethnicity.

	Hispanic & Female (n=1)	Hispanic & Male (n=109)	Non-Hispanic & Female (n=3)	Non-Hispanic & Male (n=496)	Unknown & Male (n=48)
RACE					
White	1	75	3	422	17
Black	0	0	0	5	0
Asian	0	2	0	41	1
Pacific Islander	0	1	0	5	1
Native American	0	6	0	5	0
Multi-Racial	0	0	0	3	2
Unknown	0	25	0	15	27

TPS5104

Poster Session

AGCT1531: Evaluating the utility of circulating microRNA in the management of children, adolescents, and adults with malignant germ cell tumors. *First Author: Furqan Shaikh, Division of Haematology/Oncology, The Hospital for Sick Children, Toronto, ON, Canada*

Background: Conventional serum tumor markers for malignant germ cell tumors (MGCTs) have limited performance characteristics, especially in non-secreting histologies such as embryonal carcinoma or seminoma. Growing evidence has shown circulating microRNAs (miRNA), particularly miR-371a-3p, to be a more sensitive biomarker, elevated across all MGCT subtypes except teratoma. However, studies to date have been retrospective or non-randomized. If confirmed in prospective clinical trials, circulating miRNA may have the potential to become a universal MGCT biomarker, aiding in diagnosis, prognostication, relapse detection, and prediction of viable disease after chemotherapy. One of the key objectives of AGCT1531 is to test the performance characteristics of circulating miRNA in children, adolescents, and young adults (AYAs) with low-risk and standard-risk MGCTs. AGCT1531 is unique among MGCT trials for including patients across all ages, genders, sites, histologies, and treatments. **Methods:** AGCT1531 is a prospective clinical trial sponsored by the Children's Oncology Group (COG), co-designed with United Kingdom, Japan, and India, and supported by all NCTN groups. It has three strata for low-risk tumors, defined as stage I tumors treated with surgery followed by active surveillance: non-seminomatous tumors of any site; testis seminomas; and ovarian immature teratomas. Patients of any age are eligible. Target accruals are 432, 277, and 212 patients, respectively. Key endpoints include overall and event-free survival and longitudinal measurements of circulating miRNA. Serum is collected at intervals aligned with NCCN follow-up guidelines to minimize testing burden. For patients over 11 years old with stage I non-seminomatous tumors, serum is collected at enrollment, months 4, 8, 12, 18, and 24; and (if applicable) at relapse. The trial also has two strata for standard-risk MGCTs: SR1 for children under age 11 years and SR2 for AYAs age 11-25 years. Target accruals are 518 and 595 patients, respectively. Both strata are randomized trials of cisplatin-based versus carboplatin-based regimens, with carboplatin used at doses higher than those previously tested in adult MGCTs. Serum collection is recommended at enrollment, months 6, 12, 18, 24, and (if applicable) at relapse. AGCT1531 was activated in August 2017. The low-risk seminoma stratum was added on November 2021. The trial is currently open at 466 sites across seven countries. For adults with testicular GCTs, data from AGCT1531 can contribute to joint analyses of parallel trials evaluating circulating miR-371a-3p in this population: SWOG1823, ANZUP1906 (CLIMATE), and ANZUP P3BEP. Together, this suite of trials will help validate the utility of circulating miRNA and set the stage for future investigations where miRNA is used to influence real-time management decisions for patients with MGCTs. Clinical trial information: NCT03067181. Research Sponsor: U.S. National Institutes of Health.

TPS5105

Poster Session

A phase (Ph) I/II trial of abiraterone acetate in combination with tildrakizumab (anti-IL23 monoclonal antibody) in patients with metastatic castration-resistant prostate cancer (mCRPC). *First Author: Christina Guo, Institute of Cancer Research, London, United Kingdom*

Background: Tumor-infiltrating inflammatory myeloid cells promote prostate cancer (PC) growth and therapeutic resistance. Myeloid inflammatory cells release interleukin-23 (IL-23) to fuel tumor growth via JAK2-STAT3 signalling and facilitate tumor-promoting T helper 17 (T_H17) differentiation in PC models *in vivo*. IL-23 blockade reverses resistance to AR-targeting *in vivo*; we hypothesise that targeting IL-23 can be an effective therapeutic strategy for CRPC. Tildrakizumab, an anti-IL-23 (p19) monoclonal antibody, is FDA/EMA approved for treating moderate-severe psoriasis. In progress is the first clinical trial to combining IL-23 and AR signalling blockade in humans. **Methods:** This is an open-label, single-arm, Ph I/2, dose-escalation and expansion study evaluating safety and tolerability of tildrakizumab and abiraterone acetate combination therapy in patients with mCRPC. Eligible patients must have progressed on androgen deprivation therapy, plus abiraterone and/or enzalutamide. The Ph 1 trial will adopt a one-stage Bayesian Continual Reassessment Method design exploring escalating doses of 4-weekly, IV tildrakizumab (100 mg, 300 mg, and 600 mg), in combination with standard fixed doses of abiraterone acetate and methylprednisolone, with the aim of determining the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D). Depending on the number of responses observed, tolerable dose levels may be expanded up to 10 patients after review by the Safety Review Committee (SRC). The RP2D and MTD determination will be based on the rate of toxicity and efficacy, reviewed by the SRC. Once RP2D is determined, the Ph 2 study will enrol up to 25 response-evaluable patients using a Simon's two-stage design. Primary endpoint of the Ph 2 trial is overall response rate. Adverse events are assessed according to CTCAE v5. Tumor response is determined according to RECIST v1.1, confirmed PSA decline of at least 50%, and/or CTC conversion. PK analyses is being performed for both drugs to identify potential drug-drug interactions. PD analyses is being performed on archival and serial tumour biopsies and blood samples to investigate putative predictive biomarkers and confirm on-target and downstream effector modulation. The trial began enrolling in January 2021 in the United Kingdom and Switzerland. As of January 22th 2023, 12 patients were included in the study. Clinical trial information: NCT04458311. Research Sponsor: Prostate Cancer Foundation; Sun Pharmaceuticals; Prostate Cancer UK, CRUK, National Institute of Health and Research (NIHR) Biomedical Research Centre.

TPS5106

Poster Session

The Maverick trial: A phase 2 study of abivertinib in patients (pts) with metastatic castration resistant prostate cancer (mCRPC). *First Author: Rana R. McKay, University of California San Diego, La Jolla, CA*

Background: Abivertinib is a potent, small molecule third-generation tyrosine kinase inhibitor (TKI) of epidermal growth factor receptor (EGFR), Bruton tyrosine kinase (BTK) receptor, and bone marrow tyrosine kinase gene on chromosome X (BMX). Abivertinib irreversibly binds to the BTK receptor, preventing the phosphorylation of the receptor, and also BMX. The adrenal-permissive HSD3B1(1245C) allele, which is present in upwards of 50% of men with prostate cancer, encodes a 3 β HSD1 enzyme missense that up-regulates the rate-limiting step of androgen biosynthesis from androgen precursor steroids and promotes poor clinical outcomes. 3 β HSD1 must be phosphorylated by BMX for androgen biosynthesis. Preclinical studies suggest BMX inhibition blocks 3 β HSD1, androgen biosynthesis and CRPC in xenograft models. These provide the rationale for use of the combination of abivertinib and abiraterone to block residual androgen synthesis that escapes abiraterone inhibition. **Methods:** The Maverick Trial is a multicenter, open-label phase 2 study within the US Dept of Defense Prostate Cancer Clinical Trials Consortium (DOD PCCTC) of abivertinib with abiraterone in pts with mCRPC harboring the adrenal-permissive HSD3B1(1245C) allele (germline heterozygous or homozygous). HSD3B1 status will be confirmed centrally prior to enrollment via CLIA testing at the Cleveland Clinic. The study includes two cohorts: abiraterone-naïve and abiraterone-progressing. There will be cap of 50% of accrual in each cohort for pts heterozygous for the HSD3B1(1245C) allele. An interim futility analysis is embedded in each cohort, and toxicity rates will be continuously monitored for early stoppage according to predefined rules. Pts receive continuous treatment with abivertinib 200 mg BID with abiraterone 1000 mg QD + prednisone 5 mg BID until radiographic progression, unacceptable toxicity, intercurrent illness, or other reason, such as subject withdrawal. The primary endpoint is 6-month rPFS defined as percent of subjects alive and without progression by RECIST version 1.1 for measurable disease and PCWG3 criteria for bone metastases. Secondary and exploratory endpoints include objective response rate, duration of response, PSA progression, pharmacokinetics, pharmacodynamic tissue changes, and mechanisms of response and resistance to therapy via sequential tissue and blood sampling. The study is currently open at 1 site and will activate at 9 additional sites. It is sponsored by Sorrento Therapeutics, Inc, and managed by the Prostate Cancer Clinical Trials Consortium. Trial Registration: NCT05361915 Funding Source: Sorrento Therapeutics, Inc, the trial's sponsor who is funding the trial. Clinical trial information: NCT05361915. Research Sponsor: Sorrento Therapeutics, Inc.

TPS5108

Poster Session

HB-300, a novel arenavirus-based cancer immunotherapy in patients with metastatic castration-resistant prostate cancer. *First Author: David D. Chism, Thompson Cancer Survival Center, Knoxville, TN*

Background: Prostate cancer is the most frequent type of malignant neoplasia in men. Immunotherapy targeting self-antigens in prostate cancer is evolving and requires overcoming multiple mechanisms that mediate immune tolerance. Sipuleucel-T, a cell-based therapy recognizing prostatic acid phosphatase (PAP) protein, is approved for treatment of patients with metastatic castration-resistant prostate cancer (mCRPC) and induced PAP-specific T cell responses correlating with overall survival (OS). Poxvirus vectors encoding prostate-specific antigen (PSA) increased PSA-specific T cell levels and were associated with OS benefit, although not confirmed in a Phase 3 study. Arenaviral vectors used in preclinical tumor models could overcome self-tolerance by inducing strong self-antigen specific CD8 T cell responses. In humans, arenaviral vectors encoding HPV16 E7E6 fusion protein (HB-200) induced unprecedented E6E7-specific CD8 T cell levels in patients with recurrent/metastatic HPV16+ cancers. Preliminary clinical activity and favorable safety and tolerability were observed in these heavily pre-treated, checkpoint inhibitor-resistant patients (ref: Fu et al. ASCO 2022; NCT04180215). It is therefore hypothesized that HB-300, a live-attenuated arenaviral vector therapy encoding the self-antigens PAP and PSA, will induce substantially stronger T cell responses in prostate cancer patients than previously tested active immunization approaches. **Methods:** This is a Phase 1/2 open-label clinical study of HB-300 in ~ 70 patients with advanced mCRPC. A 3+3 Dose Escalation will be followed by a dose-expansion to confirm the recommended Phase 2 dose (RP2D). HB-300 consists of HB-302 (Pichinde virus based) alternating with HB-301 (LCMV based) vectors, administered IV every 3 weeks (Q3W) for 5 doses then Q6W. The program's entry into the clinic with a mini dose-escalation was supported by the submission of a data master file along with the HB-300 Investigational New Drug application, based on arenavirus vector platform data collected in the HB-200 program. Trial inclusion criteria include male participants age $\geq$ 18; documented mCRPC (adenocarcinoma without neuroendocrine or small cell features); receipt of at least 1 androgen deprivation therapy and no prior chemotherapy regimens (docetaxel in the castration-sensitive setting is allowed); $\geq$ 1 measurable lesion; ECOG PS 0-1. Exclusions are uncontrolled pain or symptoms; active auto-immune disease; immunosuppression; active central nervous system or liver metastasis; and active infection. Phase 1 primary objectives include safety/tolerability and determination of RP2D, secondary objectives include preliminary efficacy, and exploratory assessments include antigen-specific T cell response and circulating tumor cell analysis. Clinical trial# NCT05553639. Clinical trial information: NCT05553639. Research Sponsor: Hookipa Pharma Inc.

TPS5107

Poster Session

A randomized phase II study of apalutamide with or without carotuximab (ant-CD105) in metastatic, castration-resistant prostate cancer. *First Author: Edwin Melencio Posadas, Cedars-Sinai Cancer, Cedars-Sinai Medical Center, Los Angeles, CA*

Background: CD105 (endoglin) is a co-receptor for the transforming growth factor-beta (TGF- β) receptor family. TGF- β signaling is activated in response to castration and is a determinant of PCa epithelial cell death in response to castration. In prostate cancer, silencing of TGF- β receptor type 2 (Tgfr2) in cancer-associated fibroblasts (CAF) potentiates tumor progression and castrate resistance primarily by paracrine signaling mechanisms mediated by the bone morphogenic protein (BMP)-SMAD axis. Upregulation of CD105 is observed in the face of progression through AR suppression and can drive pro-survival, pro-metastatic pathways BMP-SMAD signaling. This is accompanied with an increase in neural differentiation and the generation of AR-splice variants. In model systems, suppression of CD105-mediated signaling reversed these behaviors and resorted sensitivity to AR suppression. Carotuximab is a humanized monoclonal antibody that potentially inhibits CD105-mediated signaling. It was originally developed for clinical use as an anti-angiogenic agent and was found to have an acceptable toxicity profile. Given our previous work, we hypothesized that use of CD105 will restore sensitivity to AR inhibition in men who have developed early resistance to an AR signaling inhibitor (ARSI) that would result in a synthetic lethality from combination treatment that will manifest as an extension of progression free survival when compared to ARSI therapy alone. **Methods:** This study (NCT05534646) is open to men with metastatic, castration-resistant prostate cancer who have progressed on previous ARSI therapy. Patients with recent thrombotic and/or cardiovascular events are excluded. Patients are allowed to have had prior docetaxel only in the setting of castration sensitive disease. The study includes a safety lead-in of 10 patients on combination therapy based on our previous work with carotuximab with other ARSI in NCT03418324. This will ensure that the probability of starting the phase 2 dose with a safe dose is sufficiently high. The study then proceeds to a (1:1) randomized study of apalutamide with or without carotuximab (n = 90). Patients randomized to apalutamide alone are permitted to cross over to combination therapy at the time of radiographic progression. The primary endpoint of the study is radiographic progression free survival (rPFS) and is designed to detect a 45% difference in rPFS in the two arms with 81% power and two-sided alpha of 0.10. This study also includes extensive correlative studies focusing on circulating tumor cells and extracellular vesicles which will be enriched and studies using novel nanotechnology enabled methodologies from our group as well as cell free DNA studies which will be used identify those patients with the greatest benefits from this form of therapy to expedite the development of this therapeutic approach. Clinical trial information: NCT05534646. Research Sponsor: Enviro Therapeutics, Inc.

TPS5109

Poster Session

First-in-class oral innate immune activator BXCL701 combined with pembrolizumab, in patients with metastatic castration-resistant prostate cancer (mCRPC) of small cell neuroendocrine (SCNC) variant: Randomized phase 2b trial. *First Author: Rahul Raj Aggarwal, University of California, San Francisco, San Francisco, CA*

Background: BXCL701 (talabostat), oral small molecule inhibitor of dipeptidyl peptidases (DPP)—primarily DPP8/9 & DPP4—triggers inflammasome to alert and prime immune cells, leading to induction of IL-18 & IL-1 β , bridging innate & adaptive immunity. BXCL701 + pembrolizumab evaluated in a Phase 2 study, in mCRPC patients with SCNC. SCNC is highly proliferative and aggressive with limited duration of response to platinum-based chemotherapy. Final results of Phase 2a presented at ASCO GU 2023 (abstract #176) after enrollment of 28 evaluable SCNC patients. 7 (25%) patients achieved a composite response, primary endpoint of trial. In patients with measurable disease (n = 25), RECIST 1.1-defined partial response (PR) observed in 5 (20%) patients (4 confirmed PR + 1 uPR). Disease control rate (complete response + PR + stable disease) was 48% (12 patients). Median duration of response for both composite responses and RECIST-defined PRs was 6+ months as of data cutoff on 19-DEC-22. 6 / 34 patients (18%) in safety population experienced serious adverse events (SAEs) possibly related to BXCL701 or pembrolizumab, and 6 (18%) patients discontinued any drug due to an AE. No evidence found that BXCL701 potentiates immune-related AEs related to immune checkpoint inhibitors. DPP9 overexpression was identified as a potential predictive biomarker for BXCL701 response; biomarker evaluation is ongoing and additional findings will be presented at an upcoming medical meeting. Since SCNC cohort showed encouraging efficacy in Phase 2a, the Phase 2b portion of study was initiated to evaluate SCNC variant in a potential registration randomized study. **Methods:** Patients with any SCNC histopathological features, either *de novo* or treatment-emergent including mixed SCNC, are randomized 2:1 to receive BXCL701 + pembrolizumab (n = 40) or BXCL701 monotherapy (n = 20). Patients are required to have progression by PCWG3 on $\geq$ 1 prior line of cytotoxic chemotherapy (patients who either have refused chemotherapy or are considered unsuitable for chemotherapy also permitted entry with prior approval by sponsor). Patients receive pembrolizumab (200 mg IV q3week Day 1) + BXCL701 or BXCL701 alone (0.2 mg BID Days 1-7 with step-up to 0.3 mg BID Days 8-14, and 0.3 mg BID Days 1-14 of subsequent 21-day cycles). Primary endpoint is response rate defined by RECIST 1.1 criteria. Secondary objectives are $\geq$ 50% decline in PSA from baseline, OS, duration of response, rPFS, and PSA PFS. Exploratory biomarkers and changes in relevant immune effector cells are also evaluated. Phase 2a activity threshold for accrual was met. ClinicalTrials.gov Identifier: NCT03910660. Clinical trial information: NCT03910660. Research Sponsor: BioXcel Therapeutics, Inc.

TPS5110

Poster Session

A phase 1/2 study of combination olaparib and radium-223 in men with metastatic castration-resistant prostate cancer with bone metastases (COM-RADE): A trial in progress. *First Author: Chinmay Jani, Mount Auburn Hospital, Harvard Medical School, Cambridge, MA*

Background: Radium-223, an α -emitting radioisotope inducing DNA double-stranded breaks leading to cell death has demonstrated improvement in overall survival (OS) in men with metastatic castration-resistant prostate cancer (mCRPC) with bone metastases. PARP inhibitors prevent the repair of DNA single-stranded breaks and have demonstrated clinical efficacy as monotherapy in mCRPC patients harboring alterations in the homologous recombination repair (HRR) pathway and in combination with androgen receptor signaling inhibitors irrespective of DNA repair mutation status. In preclinical models, PARP inhibitors have shown efficacy as radio sensitizing agents. We designed a phase 1/2 trial to identify the recommended phase 2 dose (RPD2) of olaparib and radium-223 and test the hypothesis that radium-223 + olaparib will demonstrate anti-tumor activity in mCRPC irrespective of homologous recombination repair deficiency (HRD) status (NCT03317392). **Methods:** This open-label, multi-center, phase 1/2 study evaluates the dosing, safety and efficacy of olaparib with radium-223 in men with mCRPC with bone metastases. The phase 1 component used a 3+3 dose escalation design to determine the olaparib recommended phase 2 dose (RP2D) + fixed dose radium-223 (55 kBq/kg IV every 4 weeks x 6). The phase 1 portion has completed accrual (n = 12) and demonstrated that the RP2D of olaparib is 200 mg by mouth twice daily when combined with standard dose radium-223. The phase 2 component of the study which was activated in 1/2021 is an open-label, randomized trial (1:1) evaluating olaparib + radium-223 compared to radium-223 alone. The inclusion criteria include patients with mCRPC with any number of prior therapy lines for mCRPC and ≥ 2 bone metastases by imaging and at least 1 lesion which has not been treated with prior radiation. Patients with visceral metastases or malignant lymphadenopathy (> 4 cm in short diameter) are excluded. The primary endpoint for phase 2 is radiographic progression-free survival (rPFS) per PCWG3 guidelines for bone metastases and RECIST v1.1 for non-bone disease. The integrated biomarker is Oncopanel assay to determine HRR status. A key secondary endpoint will evaluate rPFS in biomarker positive and negative patients. Other secondary endpoints include time to PSA progression, PSA response, time to subsequent therapy, time to first skeletal event, and OS. Exploratory endpoints include WES/WTS of baseline biopsy tissue, assessment of RAD51 IHC and correlation with outcomes, ctDNA assessment and correlation with responses, evaluation of changes in the tumor immune microenvironment, and quality of life assessment. Target accrual is 133 patients. Clinical trial information: NCT03317392. Research Sponsor: U.S. National Institutes of Health.

TPS5112

Poster Session

Open-label study of darolutamide plus androgen-deprivation therapy (ADT) vs ADT in metastatic hormone-sensitive prostate cancer using an external control arm (ARASEC). *First Author: Neal D. Shore, Carolina Urologic Research Center, Myrtle Beach, SC*

Background: Darolutamide (DARO) is a structurally distinct and highly potent androgen receptor inhibitor. In the phase 3 ARASENS study (NCT02799602) in patients (pts) with metastatic hormone-sensitive prostate cancer (mHSPC), DARO + ADT + docetaxel significantly reduced the risk of death by 32.5% vs ADT + docetaxel (hazard ratio 0.68; 95% confidence interval 0.57–0.80), with a favorable tolerability and safety profile. In the global (excluding US), phase 3 ARANOTE study (NCT04736199), DARO + ADT vs ADT alone is being evaluated in pts with mHSPC. ARASEC (NCT05059236) will complement ARANOTE by assessing DARO + ADT in US pts. As ADT alone is no longer an acceptable comparator in the US, the external control arm will be derived from the historical US CHAARTED study (NCT00309985). A real-world analysis of electronic health record data from pts with mHSPC (TIMES) indicated that there was minimal risk of historical time bias associated with the use of the external ADT alone arm from CHAARTED as a comparator for ARASEC (Shore N, et al. *J Clin Oncol* 2022;40(28 Suppl):Abstract 403). **Methods:** ARASEC is a phase 2, open-label, single-arm study enrolling pts with confirmed mHSPC and no prior systemic therapy. Pts will receive DARO 600 mg orally twice daily + ADT (luteinizing hormone-releasing hormone agonist/antagonist or orchiectomy). The external control arm will be derived from 394 pts with mHSPC treated with ADT alone in CHAARTED. To remove biases in evaluating outcomes that could arise due to differences in baseline profiles between arms, pts will be matched 1:1 using a propensity score (PS) summarizing baseline characteristics relevant to disease outcomes. Baseline variables will include age (< 70 vs ≥ 70 years), Eastern Cooperative Oncology Group performance status (0–1 vs 2), CHAARTED-defined extent of disease (low vs high volume + bone metastases only vs high volume + visceral metastases $\pm$ bone metastases), and prior therapy (yes vs no; as a proxy for recurrent vs *de novo* disease). Matching patients with scores within a narrow window across the cohorts will ensure that pts in CHAARTED are representative of pts in the DARO + ADT arm. The primary endpoint is progression-free survival (PFS), as defined in CHAARTED. Secondary endpoints include overall survival, radiographic PFS, time to CRPC, undetectable prostate-specific antigen response rate (< 0.2 ng/mL) at 6 months, and safety. Target enrollment for the DARO + ADT arm is 200 pts at 30 sites. The study will continue until either the event count threshold triggering the primary endpoint analysis has been met (161 PFS events) or all pts have been followed for ≥ 2 years, whichever occurs later. As of January 2023, 121 pts have been enrolled. A per-protocol, predefined matching exercise on the first 100 pts enrolled will be conducted to ensure that the planned sample size is adequate. Clinical trial information: NCT05059236. Research Sponsor: Bayer and Orion Corporation.

TPS5111

Poster Session

A phase 2, randomized, open-label study comparing the effects of darolutamide versus enzalutamide monotherapy on serum testosterone levels in patients with hormone-naïve prostate cancer: ARAMON study. *First Author: Xin Gao, Massachusetts General Hospital Cancer Center and Harvard Medical School, Boston, MA*

Background: Darolutamide is a structurally distinct and highly potent androgen receptor inhibitor with low blood–brain barrier penetration. In the phase 3 ARAMIS study (NCT02200614) of patients with nonmetastatic castration-resistant prostate cancer, treatment with darolutamide significantly improved metastasis-free survival and overall survival versus placebo, with a favorable safety profile. The incidences of central nervous system adverse events (AEs; e.g. falls, memory impairment, and depression) showed a $\leq 2\%$ difference between the darolutamide and placebo groups. Fatigue was the only AE with an incidence of $> 10\%$ for darolutamide (13.2% vs 8.3% for placebo). In a separate neuroimaging study of healthy volunteers, cerebral blood flow was not altered in patients treated with darolutamide but was significantly reduced in brain areas related to cognition in patients treated with enzalutamide. Furthermore, it is postulated that the low blood–brain barrier penetration of darolutamide may result in lower serum testosterone elevations than those seen with enzalutamide, with the potential of leading to fewer associated feminizing AEs. The objective of ARAMON (NCT05526248) is to compare the effect of darolutamide and enzalutamide monotherapy on post-treatment testosterone levels in patients with hormone-naïve prostate cancer experiencing biochemical recurrence after definitive treatment for localized disease. **Methods:** ARAMON is a two-stage, open-label, phase 2 study of patients with histologically or cytologically confirmed adenocarcinoma of the prostate who have biochemical recurrence after radical primary prostatectomy or radiation therapy, with a prostate-specific antigen (PSA) doubling time of ≤ 20 months, baseline serum testosterone > 150 ng/dL, and Eastern Cooperative Oncology Group performance status 0/1. During a 52-week lead-in phase, 25 patients will receive darolutamide 600 mg twice daily. If criteria based on serum testosterone increase from baseline to Week 12 are met, the study will proceed to a 52-week randomized phase in which the effects of darolutamide (600 mg twice daily, n = 20) will be compared with the effects of enzalutamide (160 mg once daily, n = 20). The primary endpoint of both phases is the change in serum testosterone level from baseline to Week 12. Secondary endpoints of the randomized phase include the change in serum testosterone levels from baseline to Weeks 24 and 52; PSA at Weeks 4, 12, 24, 36, and 52; changes in blood levels of markers for glucose, lipid metabolism, and endocrine function related to sex hormones; safety; and quality of life. Safety will be assessed through AE monitoring. The first of the 25 planned patients in the lead-in phase was enrolled on January 13, 2023. Clinical trial information: NCT05526248. Research Sponsor: Bayer and Orion Corporation.

TPS5113

Poster Session

A feasibility study of ^{177}Lu -PSMA radioligand therapy alternated with radium-223 in patients with bone-metastatic, oligo-metastatic, hormone-sensitive prostate cancer after curative therapy: The DUET study. *First Author: André Vis, Amsterdam UMC, location VUMC, Amsterdam, Netherlands*

Background: Previous randomized clinical trials have shown an improvement in overall survival in patients with metastatic castration resistant prostate cancer (mCRPC), who have already failed other therapies, treated with ^{177}Lu -PSMA radioligand therapy (RLT). Although ^{177}Lu -PSMA RLT has shown exciting treatment responses in men with mCRPC and suggests a low toxicity profile, it has not been widely investigated in patients with metastatic hormone-sensitive prostate cancer (HSPCa). As of today, treatment with systemic drugs is proof of concept in advanced or metastatic HSPCa, as well as in other cancer types, and leads to improved oncological outcome, potentially by eradicating micro-metastatic disease. As a bone-seeking calcium mimetic, Radium-223 (Ra-223) is incorporated into new bone stroma, predominantly within sclerotic metastatic deposits. The high-energy of the alpha-particle radiation generates double-stranded DNA breaks, offering a potent and highly localized cytotoxic effect in the target areas. In a phase 3, randomized, double-blind, placebo-controlled study, Ra-223 has proven to significantly improve overall survival (by a treatment comprising 1 injection per month, at a dose of 50 kBq per kilogram of body weight intravenously), as compared with placebo. The optimal therapy in patients with oligometastatic bone HSPCa after previous curative treatment has not yet been defined. **Methods:** This is a single center, interventional, one-arm phase I-II study that prospectively investigates if a treatment strategy in which two types of cytotoxic RLT, i.e., an alpha-emitter and a beta-emitter, alternatively offered to patients with oligometastatic HSPCa, is feasible and safe. Eight patients with low volume, PSMA expressing, radiological progressive HSPCa (minimal 2 bone metastases, maximal 5, and at 0 to 3 lymph node metastases) will be recruited. In these patients, loco-regional radiotherapy or surgery is not an option anymore. The PSA doubling time in participating patients should be less than 6 months. **Primary endpoint:** To assess the feasibility and safety in patients with bone metastatic, oligometastatic HSPCa, treated by Ra-223 RLT alternated with ^{177}Lu -PSMA RLT. **Secondary endpoints:** Toxicity and (serious) adverse events will be monitored and reported in concordance with the NCI CTCAE v5.0; Assessment of the xerostomia inventory; Prostate-specific antigen (PSA) levels on follow-up at 3, 6 and 12-months; **Investigative Treatment:** Patients enrolled in the trial will receive three intravenous applications of Radium-223, in a dose of 5.5 kBq/kg body weight at t = 0 weeks, t = 4 weeks and t = 8 weeks (± 1), and two intravenous applications of 7.4 GBq ^{177}Lu -PSMA RLT at t = 6 weeks and t = 12 weeks (± 1). Clinical trial information: NL81658.029.22. Research Sponsor: Bayer B.V.

TPS5114

Poster Session

ProSperA: Phase I study to evaluate safety, tolerability and preliminary efficacy of a bispecific PSMAxCD3 antibody in men with biochemical recurrence of prostate cancer. *First Author: Christopher Hackenbruch, University Hospital Tübingen, German Cancer Consortium (DKTK), Department of Internal Medicine, Clinical Collaboration Unit Translational Immunology, Tübingen, Germany*

Background: Bispecific antibodies (bsAbs), like CAR T cells, are not yet successful in solid tumors. Recently we developed a PSMAxCD3 bsAb termed CC-1 in an IgG-based format mediating fully target cell-restricted T cell activation and potent antitumor activity (Zekri *et al*, EMBO Mol Med, 2020). In prostate cancer (PC), PSMA is not only expressed on the malignant cells themselves, but also on tumor vessels. Targeting the latter improves accessibility of the tumor site for immune effector cells, a critical prerequisite for success. CC-1 is under evaluation in a First in Human trial enrolling patients with castration resistant prostate carcinoma (NCT04104607) and, in combination with checkpoint inhibition, in a phase I trial enrolling patients with squamous cell carcinoma of the lung (NCT04104607). On the basis of the meanwhile available very favorable safety and preliminary efficacy data, CC-1 is now being evaluated as first line treatment in patients with biochemical recurrence (BCR) of PC (NCT05646550), where tumor burden is low and accordingly further reduced side effects and sustained efficacy are expected. **Methods:** This is an ongoing open label, single center phase I clinical trial evaluating CC-1 without androgen deprivation therapy as first line treatment in men with BCR of PC. Key eligibility criteria include low risk of disease progression (PSA-Doubling time > 1 year after prostatectomy or interval to BCR > 18 months after radiation; ISUP grade < 4; PSA ≥ 0.2 ng/ml and < 5 ng/ml) and no androgen deprivation therapy except in a neoadjuvant/adjuvant setting. The clinical trial consists of (i) a dose escalation part (24-42 patients) using a 3+3 design to determine overall safety, tolerability as well as maximum tolerated dose (MTD) and (ii) a dose expansion part, in which 14 patients are treated at the MTD. CC-1 is applied twice-weekly over 21 days as three-hour infusion in up to six 28-day cycles. In the first cycle, step dosing (day 1: 10µg, day 2: 28µg, day 3 and thereafter: target dose) is performed, and 7 patient cohorts receiving dose levels from 78µg to 600µg are evaluated. Premedication includes acetaminophen, dimetindene and cortisone to minimize the risk of infusion reactions and cytokine release syndrome (CRS). The primary objectives are definition of MTD and recommended phase II dose. Assessment of safety is based on the frequency of adverse events according to CTCAE v5.0. Dose limiting toxicities are defined as ≥ 3° adverse drug reactions (e.g. CRS) with predefined exceptions (e.g. temporary laboratory abnormalities). Efficacy is determined by serial PSA-measurements (PSA-response: ≥50% decrease compared to baseline). Furthermore, percentage of patients with no clinical relapse, no salvage and no subsequent antineoplastic therapy will be assessed. Clinical trial information: NCT05646550. Research Sponsor: AKF program of the University Tübingen; Else-Kröner Fresenius Stiftung.

TPS5116

Poster Session

PSMAAddition: A phase 3 trial to compare treatment with ¹⁷⁷Lu-PSMA-617 plus standard of care (SoC) and SoC alone in patients with metastatic hormone-sensitive prostate cancer. *First Author: Scott T. Tagawa, Weill Cornell Medicine, New York, NY*

Background: Lutetium (¹⁷⁷Lu) vipivotide tetraxetan (¹⁷⁷Lu-PSMA-617) plus protocol-permitted standard of care (SoC) significantly improved radiographic progression-free survival (rPFS) and overall survival (OS) in patients with prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer, previously treated with at least one androgen receptor pathway inhibitor (ARPI) and one or two taxanes. Androgen deprivation therapy (ADT) and ARPIs may alter PSMA expression and radiosensitivity. PSMAAddition will assess the efficacy and safety of ¹⁷⁷Lu-PSMA-617 plus SoC versus SoC alone in adults with metastatic hormone-sensitive prostate cancer (mHSPC). **Methods:** PSMAAddition (NCT04720157) is an international, prospective, open-label, randomized, phase 3 trial, with crossover, in adults with mHSPC. Eligible patients are treatment-naïve or minimally treated candidates for hormonal therapy, with PSMA-positive disease (determined by ⁶⁸Ga-PSMA-11 PET/CT), ECOG performance status of 0 to 2 and adequate major organ function. Patients are excluded if they have rapidly progressing tumors that require chemotherapy. Approximately 1126 patients will be randomized 1:1 to receive ¹⁷⁷Lu-PSMA-617 (7.4 GBq every 6 weeks for a maximum of 6 cycles) plus SoC or SoC alone (an ARPI and ADT). Stratification factors are tumor volume (high/low), age (≥ 70 / < 70 years), and previous/planned prostatectomy or radiation treatment of the primary prostate tumor (yes/no). Recruitment for a China extension cohort (40–60 patients) will follow after completion of main study recruitment. The primary endpoint is rPFS, as assessed by blinded independent centralized review. Upon centrally confirmed radiographic progression, participants in the SoC-only arm can cross over to the ¹⁷⁷Lu-PSMA-617 arm. The planned sample size provides 95% power to detect a hazard ratio of 0.7 for rPFS after 418 events with an overall one-sided significance level of 0.025. The key secondary endpoint is OS, others include the proportion of patients with a prostate-specific antigen (PSA) decline of ≥ 90% from baseline, time to development of metastatic castration-resistant prostate cancer, composite PFS (radiographic, clinical or PSA progression), safety and tolerability, and health-related quality of life. Imaging and biospecimen (tissue and blood) collection is embedded for correlative analysis. Participants who have received ¹⁷⁷Lu-PSMA-617 will have the option to enroll in a separate long-term safety follow-up study. Updated from previous presentation at the 2021 European Society for Medical Oncology Congress, FPN 3035, with permission. Clinical trial information: NCT04720157. Research Sponsor: Novartis.

TPS5115

Poster Session

APPROACH trial: Multimodal approach in patients with mHSPC: A pragmatic, randomized, phase 3 trial of androgen-deprivation therapy (ADT) plus apalutamide (APA) versus ADT plus apalutamide (APA) and local treatment—Meet-URO 29 study. *First Author: Valentina Guadalupi, Department of Medical Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy*

Background: it is reasonable to offer radiotherapy (RT) to improve outcomes for patients with newly diagnosed M1 prostate cancer with < 5 bone metastases (HRRAD) or low volume disease (STAMPEDE) (Burdett, S *et al.*, Eur. Urol. 2019). Data from clinical randomized trials evaluating feasibility and overall benefit of cytoreductive radical prostatectomy (cRP) in oligo-metastatic hormone sensitive patients are not available. The rationale for performing cytoreductive radical prostatectomy is to eliminate lethal clones of castration-resistant intraprostatic PCa, which can favor the process of metastasis (A Heidenreich *et al.* Current Opinion in Urology 2020), in order to improve OS and PFS and to prevent local progression and correlated events. **Methods:** APPROACH is an Italian multicenter study, which is enrolling ~566 pts with oligometastatic hormone sensitive prostate cancer who are candidates to receive treatment with apalutamide. After 6 months from the start of treatment, patients will be randomized 1:1 to receive local treatment or not in addition to apalutamide (investigator's choice between primary radiotherapy and cytoreductive prostatectomy). Primary end point: To determine whether treatment with apalutamide plus ADT for 6 months followed by locoregional treatment with radiotherapy or radical prostatectomy has better efficacy than treatment with apalutamide plus ADT alone in terms of radiographic progression-free survival (rPFS). Secondary end points: To evaluate tumor shrinkage after locoregional approach and to evaluate short and long-term side effects after locoregional surgery or RT, time to PSA progression, time to castration resistance, cancer specific survival, overall survival and quality of life according to EPIC-26 and EQ-5D-5L questionnaires. Clinical trial information: NCT05649943. Research Sponsor: Janssen.

TPS5117

Poster Session

Phase 1/2a study of PRL-02, a long-acting intramuscular (IM) depot injection of abiraterone decanoate, in patients (pts) with advanced prostate cancer. *First Author: Neal D. Shore, Carolina Urologic Research Center, Myrtle Beach, SC*

Background: PRL-02 is a long-acting IM depot injection of abiraterone decanoate, a novel prodrug of abiraterone delivered through the lymphatic system. PRL-02 potentially blocks androgen production with minimal increases in mineralocorticoids or decreases in glucocorticoids through preferential inhibition of Cytochrome P450 (CYP)17 lyase versus CYP17 hydroxylase. Phase 1 is a standard 3+3 design intended to identify a recommended Phase 2 dose (RP2D). PRL-02 is administered every 84 days (1 cycle). As of 9/8/22, 17 pts (6 mCRPC, 11 mCSPC) were treated across 5 dose cohorts (180, 360, 720, 1260, 1800mg). At 720mg and above, 9 of 11 had a 90% reduction in testosterone (T), including 2 pts with T ≤ Lower Limit of Quantitation (LLOQ) of 0.1ng/dL. A PSA decline of ≥50% from baseline (PSA50) was observed in 8 of 10pts. PRL-02 was very well tolerated. Only minimal and transient changes in 'upstream' steroids (e.g., progesterone) were observed at doses of 1260 mg (the RP2D) and lower. **Methods:** Phase 2a is an A'Hern single-stage design. Group 1 includes pts with mCSPC divided into 2 groups (1A: previously untreated high-volume disease and 1B: previously untreated, low-volume disease). Group 2 includes pts with mCRPC. Enrollment of 66 pts is planned across 30 sites in the U.S. (Clinical Trial information: NCT04729114). Patient populations, interventions and study design are described below. Clinical trial information: NCT04729114. Research Sponsor: U.S. National Institutes of Health; Propella Therapeutics, Inc.

Patient population, primary endpoints, hypothesis testing and rationale.			
Group	1A	1B	2
Patient Population	mCSPC, previously untreated high-volume disease	mCSPC, previously untreated, low-volume disease	Chemotherapy-naïve, mCRPC
Treatment	PRL-02 + dexamethasone (Dex) + docetaxel + Androgen Deprivation Therapy (ADT)	PRL02 + Dex + ADT	PRL02 + Dex + ADT
Primary Endpoint	Undetectable PSA (≤0.2ng/mL) at 8 months	Undetectable PSA (≤0.2ng/mL) at any time	PSA50 confirmed by a second consecutive PSA at least 3 weeks later
HO and Ha Rationale/Precedent	0.51, 0.70 PEACE-1 trial (NCT01957436) (Mescam 2022; Klaassen 2022), which showed a strong correlation between undetectable PSA at 8 months and clinical benefit. (overall survival and Radiographic progression-free survival) The combination of abiraterone + prednisone + docetaxel + ADT had a 51% rate of undetectable PSA at months	0.51, 0.70 Null hypothesis based on the LATITUDE study (NCT01715285) (Fizazi 2019; Tran 2019) in which the undetectable PSA rate at any time was 0.55	0.50, 0.75 Null hypothesis based on the activity of the ACIS study control arm abiraterone + prednisone (NCT02257736) (Saad 2021)

TPS5118

Poster Session

Phase III study of local or systemic therapy intensification directed by PET in prostate cancer patients with post-prostatectomy biochemical recurrence (INDICATE): ECOG-ACRIN EA8191. *First Author: Neha Vapiwala, Abramson Cancer Center, Philadelphia, PA*

Background: Salvage radiation therapy (sRT) to the prostate bed and pelvic nodes with short-term androgen deprivation therapy (STAD) is considered a standard of care (SOC) salvage therapy (ST) paradigm for prostate cancer (PC) patients (pts) with post-prostatectomy (RP) biochemical recurrence (BCR). PET imaging with recently FDA-approved agents in this setting (18F-Fluciclovine, 18F-DCFPyL and 68Ga-PSMA-11), have shown improved accuracy for detection of metastases not identified with conventional imaging (CIM). Given the greater sensitivity and specificity of PET, its findings are being increasingly but variably applied to justify modification or omission of SOC therapies without high-level evidence of clinical benefit. PET may help identify candidates for different treatment intensification approaches. In metastatic prostate cancer, metastasis-directed RT (MDT) has been used to avoid or delay systemic therapy in men with oligometastatic disease. Apalutamide (Apa) is an androgen receptor signaling inhibitor that has been shown to improve outcomes when added to ADT in mCSPC. This study will evaluate whether patients with PET-detected lesions outside the pelvis will benefit from addition of MDT to treatment intensification with STAD/Apa, and whether patients with no PET-detected lesions outside the pelvis will benefit from addition of Apa to standard sRT/STAD. **Methods:** PC pts with post-RP BCR (PSA > 0.5ng/mL; > 0.2ng/mL if first detectable within 12 mos of RP) and no extrapelvic metastases on CIM who are candidates for SOC ST (sRT to prostate bed and pelvic nodes with STAD) are eligible. Pts will undergo SOC baseline PET using a FDA-approved tracer. Based on institutional clinical interpretation of the SOC PET, pts will be placed in Cohort 1 (PET-negative) or 2 (PET-positive for extra-pelvic metastases). Cohort 1 will be randomized to SOC ST +/- Apa for 6 months and Cohort 2 will be randomized to SOC ST and Apa +/- MDT to PET-positive lesions. The primary endpoint is PFS, defined as time from randomization to radiographic progression on CIM, symptomatic disease or death, whichever occurs first. Primary objectives are to evaluate whether addition of Apa to SOC ST and addition of MDT to SOC ST and Apa could prolong PFS in Cohorts 1 and 2, respectively. For Cohort 1, 480 pts will be randomized with 85% power to distinguish a 5-year PFS rate of 90% (Apa arm) vs. 80% (SOC arm) using one-sided stratified logrank test with type I error of 0.025. For Cohort 2, 324 pts will be randomized with 85% power to distinguish a 5-year PFS rate of 76.5% in the experimental arm from 61.5% in the control arm. Secondary endpoints include overall and event-free survival, toxicity, PET progression and quality of life. Clinical trial registry number: NCT04423211. Clinical trial information: NCT04423211. Research Sponsor: U.S. National Institutes of Health; Janssen.

TPS5120

Poster Session

Exercise to enhance cardiovascular health among Black patients with prostate cancer with androgen deprivation therapy: The POWER trial. *First Author: Dong-Woo Kang, Dana-Farber Cancer Institute, Boston, MA*

Background: Large racial disparities persist in prostate cancer (PCa) incidence and mortality in the US. Among all races, Black men have the highest rates of PCa incidence and mortality, where they are 1.7 and 2.1 times more likely to develop and die of PCa compared to non-Hispanic White men, respectively. Androgen deprivation therapy (ADT) is one of the most recommended treatments for intermediate and advanced PCa. However, men receiving ADT have a higher risk of developing cardiovascular disease (CVD) by 65% compared to patients not receiving ADT, which is likely linked to ADT-induced cardiovascular and metabolic toxicity. Moreover, Black men with PCa receiving ADT have a higher risk of CVD-related death and a higher prevalence of comorbid conditions. Therefore, prevention and management of CVD risk factors in this population is an important unmet clinical need. Exercise is an effective way to lower CVD risk factors in many clinical settings; however, Black men with cancer are underrepresented in exercise oncology research, and no studies to date have focused on Black men with PCa on ADT. We designed a randomized controlled trial, entitled "Exercise to Enhance Cardiovascular Health among Black Prostate Cancer Patients with Androgen Deprivation Therapy: POWER Trial." The objective of the POWER Trial is to examine the effects of a tailored exercise intervention on CVD risk factors in Black men with PCa undergoing ADT. **Methods:** The POWER trial is a two-arm, multi-center, randomized controlled trial, recruiting 62 Black men with localized or metastatic PCa who are receiving ADT at Dana-Farber Cancer Institute or Beth Israel Deaconess Medical Center, Boston, MA. Participants are randomly assigned to either exercise training or usual care at a 1:1 ratio. Participants in the intervention group are asked to complete a culturally tailored, home-based, virtually supervised exercise training program thrice weekly for 16 weeks. Aerobic exercise is high-intensity interval training and performed on a stationary bike, alternating 1-min high-intensity (75-95% of VO_{2peak}) and 1-min recovery (40% of VO_{2peak}) intervals. Resistance exercises are performed on large muscle groups using dumbbells with 2-3 sets of 15-20 repetitions at 60-75% of the 1-repetition maximum. Participants in the usual care group are asked not to change their baseline exercise behavior and then may cross over to the exercise program after the initial 16 weeks. The primary outcome is the CVD risk assessed by the Framingham Risk Score (i.e., age, sex, blood cholesterol, blood pressure, and smoking). The secondary and exploratory outcomes include cardiorespiratory fitness, muscular strength, body composition, patient-reported outcomes, and treatment-related symptoms. To date, five out of the planned 62 patients have been enrolled. This trial is registered in clinicaltrials.gov (NCT05327465). Clinical trial information: NCT05327465. Research Sponsor: CDMRP.

TPS5119

Poster Session

Prime-boost immunotherapeutic trial in men with biochemical recurrence after definitive local therapy for prostate cancer. *First Author: Mark N. Stein, Department of Medicine and Division of Hematology/Oncology, Columbia University Medical Center, New York, NY*

Background: VTP-850 is a heterologous prime-boost immunotherapeutic consisting of 2 nonreplicating viral-vectored components: ChAdOx1-PCAQ, based on an adenoviral vector, and MVA-PCAQ, based on a modified vaccinia virus Ankara (MVA) vector. Both components encode the same 4 prostate cancer antigens: prostate-specific antigen (PSA), prostatic acid phosphatase (PAP), six transmembrane epithelial antigen of prostate 1 (STEAP1), and 5T4, an oncofetal antigen. Preclinical studies in inbred, outbred, and HLA-A2 transgenic mice show that VTP-850 is highly immunogenic. Immune responses were measured in splenocytes using IFN- γ ELISpot assay, multiparameter flow cytometry, and targeted in vivo killing assays. The results indicate that VTP-850 can elicit T cell responses to each of the 4 encoded antigens, with the responses to PSA of greatest magnitude in all mouse strains studied. Intravenous administration of the boost resulted in a 6-fold increase in the magnitude of antigen-specific T cells induced and increased in vivo killing relative to the intramuscular boosting route. **Methods:** This is a first-in-human multicenter Phase 1/2 trial to evaluate safety, PSA response rate and duration, and immunogenicity of VTP-850 in men with biochemical recurrence of prostate cancer after definitive local therapy. Phase 1 (15-18 participants) will follow a 3+3 design to determine the recommended phase 2 regimen; dose level of both ChAdOx1-PCAQ and MVA-PCAQ, and route of administration of MVA-PCAQ (IM or IV). Phase 2 will consist of 2 stages. In Stage 1, 19 additional participants will be enrolled at the chosen Phase 2 regimen. If 4 or more of the 25 participants (including the 6 Phase 1 participants who received the same regimen) have a PSA response (defined as $\geq 50\%$ reduction in serum PSA compared to baseline at any time, measured twice consecutively, at least 2 weeks apart), Stage 2 will enroll 100 additional participants. Participants will be followed for 6 months or until start of new therapy (e.g. ADT) or until development of metastatic disease. Participants who have a PSA response during the 6 months follow up will be followed for up to an additional 18 months. Patients who have undergone primary therapy for prostate cancer and have biochemical recurrence are eligible. Patients must have nonmetastatic (M0) disease; serum PSA of > 0.3 ng/mL for participants with prior radical prostatectomy or serum PSA of 2 ng/mL above nadir for participants with prior external beam radiation or brachytherapy; PSA doubling time ≤ 12 months; and testosterone > 75 ng/dL. They cannot have received ADT within 6 months prior to Day 1 and cannot have received prior chemotherapy, immunotherapy or experimental agent for prostate cancer. The trial is open in the USA, with sites in Spain and Italy planned to open later in 2023. 1. Vardeu A et al 2022. Clinical trial information: NCT05617040. Research Sponsor: Vaccitech.

TPS5121

Poster Session

A multi-center natural history study of precision-based genomics in prostate cancer (PC). *First Author: Himisha Beltran, Dana-Farber Cancer Institute, Boston, MA*

Background: With genomic-based therapies approved for advanced PC, there has been a substantial rise in the clinical use of genomic sequencing. In addition to identifying actionable targets, there is a long list of less common 'tail' alterations in metastatic PC with unclear prognostic or predictive significance. We hypothesize that integrative clinico-genomic studies of uncommon subgroups of PC, defined based on a molecular biomarker of low-prevalence or based on an exceptional clinical outcome to therapy, can lead to the identification of new predictive and resistance biomarkers and will accelerate the development of precision medicine strategies for patients with PC. **Methods:** This is a multi-institutional prospective observational study for longitudinal collection of clinical and genomic data from participants (prts) with distinct molecular alterations of interest and/or exceptional phenotypes. The primary objectives are: 1) to define the natural history of men with select molecular alterations and/or exceptional clinical responses, 2) to establish a biospecimen repository for extensive molecular analyses to study the biology of PC and mediators of therapeutic response and resistance. Exploratory objectives include: 1) understanding the impact of co-occurring genomics alterations and other molecular alterations on the natural history of PC in these defined subsets, 2) identifying biologic mechanisms of exceptional response, primary and secondary resistance, and tracking evolutionary patterns that occur during acquired resistance. Eligible prts have a diagnosis of PC with known germline and/or somatic variants in *PIK3A*, *PIK3CB*, and/or *AKT*, *PALB2*, *BRIP1*, *RAD50*, *RAD51*, *RAD54*, *RB1*, *SPOP*, Wnt/B-catenin pathway, MMR genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*), *EPCAM* and/or TMB-high (as defined by TMB ≥ 10 mut/Mb). Any platform for genomic testing is acceptable and data is collected centrally. Prts deemed exceptional responders (with or without mutational aberrations) are defined as those with a complete response or a confirmed partial response of any duration of time to systemic therapies or any response of exceptional duration (particularly with therapies targeting PARP, the androgen receptor, and/or immunotherapies). Data including demographic, disease characteristics, treatment outcomes including response to therapies, and survival are collected along with other pathologic, radiographic, and molecular/genomic data. Correlative sample collection includes archival primary and metastatic biopsy specimens and prospective collection of blood for future analyses. This study will provide insights into the significance of individual and co-occurring alterations and will help establish a path forward for the expansion of drug indications for PC patients with rare variants. 37 prts have been accrued with an accrual ceiling of 2000 prts. Clinical trial information: NCT04706663. Research Sponsor: U.S. National Institutes of Health.

5500

Oral Abstract Session

KEYNOTE-826: Final overall survival results from a randomized, double-blind, phase 3 study of pembrolizumab + chemotherapy vs placebo + chemotherapy for first-line treatment of persistent, recurrent, or metastatic cervical cancer. *First Author: Bradley J. Monk, Division of Gynecological Oncology, HonorHealth Research Institute, University of Arizona College of Medicine, Phoenix and Creighton University School of Medicine, Phoenix, AZ*

Background: The first interim analysis of KEYNOTE-826 (NCT03635567) showed that first-line pembrolizumab (pembro) + chemotherapy (chemo) provided statistically significant and clinically meaningful improvements in OS and PFS vs placebo (pbo) + chemo in patients (pts) with recurrent, persistent, or metastatic cervical cancer across all prespecified populations (PD-L1 combined positive score [CPS] ≥ 1 , all-comer, and CPS ≥ 10). Here, we present the protocol-specified final OS analysis results of KEYNOTE-826. **Methods:** Eligible adults with persistent, recurrent, or metastatic cervical cancer not previously treated with systemic chemo (prior radiosensitizing chemo allowed) and not amenable to curative treatment (surgery or radiation) were randomized 1:1 to pembro 200 mg or placebo Q3W for up to 35 cycles + chemo (paclitaxel 175 mg/m² + cisplatin 50 mg/m² or carboplatin AUC 5), $\pm$ bev 15 mg/kg. Pts were stratified by metastatic status at diagnosis (yes/no), planned bev use (yes/no), and PD-L1 CPS (< 1 , 1 to < 10 , or ≥ 10). Dual primary end points were OS and PFS per RECIST v1.1 assessed by investigator review, each tested sequentially in the PD-L1 CPS ≥ 1 , all-comer, and CPS ≥ 10 populations. **Results:** From Nov 2018 to Jan 2020, 617 patients were randomized (pembro + chemo, n = 308 [63.6% with bev]; pbo + chemo, n = 309 [62.5% with bev]); 548 (88.8%) pts had PD-L1 CPS ≥ 1 and 317 (51.4%) had CPS ≥ 10 . At the Oct 3, 2022 data cutoff, median follow-up was 39.1 mo. Pembro + chemo significantly improved OS and PFS in the CPS ≥ 1 , all-comer, and CPS ≥ 10 populations (Table). The pembro + chemo benefit was seen regardless of bev use. Grade ≥ 3 AE incidence was 82.4% in the pembro + chemo arm and 75.4% in the placebo + chemo arm. The most common grade ≥ 3 AEs were anemia (30.3% vs 27.8%), neutropenia (12.4% vs 9.7%), and hypertension (10.4% vs 11.7%). **Conclusions:** The addition of pembro to chemo $\pm$ bev significantly reduced the risk of death by 40% in the PD-L1 CPS ≥ 1 population, by 37% in the all-comer population, and by 42% in the CPS ≥ 10 population, and had a manageable safety profile. These data are consistent with the earlier results and provide further support for pembro + chemo $\pm$ bev as a new standard of care for first-line treatment of persistent, recurrent, or metastatic cervical cancer. Clinical trial information: NCT03635567. Research Sponsor: Merck & Co., Inc.

	PD-L1 CPS ≥ 1		All-Comer		PD-L1 CPS ≥ 10
Pembro Chemo n = 273	Pbo + Chemo n = 275	Pembro + Chemo n = 308	Pbo + Chemo n = 309	Pembro + Chemo n = 158	Pbo + Chemo n = 159
OS, median, mo	28.6	16.5	26.4	16.8	29.6
24-mo OS rate, %	53.5	39.4	52.1	38.7	54.4
OS, HR (95% CI)	0.60 (0.49-0.74); P < 0.0001		0.63 (0.52-0.77); P < 0.0001		0.58 (0.44-0.78); P < 0.0001
PFS, median, mo	10.5	8.2	10.4	8.2	10.4
12-mo PFS rate, %	45.6	33.7	44.7	33.1	44.7
PFS, HR (95% CI)	0.58 (0.47-0.71); P < 0.0001		0.61 (0.50-0.74); P < 0.0001		0.52 (0.40-0.68); P < 0.0001

5502

Oral Abstract Session

Incorporation of triapine (T) with cisplatin chemoradiation (CRT) for locally advanced cervical and vaginal cancer: Results from NRG-GY006, a phase III randomized trial. *First Author: Charles A. Leath, O'Neal Comprehensive Cancer Center at the University of Alabama at Birmingham School of Medicine, Birmingham, AL*

Background: Definitive cisplatin-based chemoradiation (CRT) plus brachytherapy for locally advanced cervical cancer (FIGO IB3-IVA) results in sustained survival for 60-70% of patients. Recent studies integrating anti-PD-1 checkpoint immunotherapy (CALLA, NCT03830866) or consolidation chemotherapy (OUTBACK, ACTRN12610000732088) have not demonstrated a survival benefit over CRT. Intrinsic overexpression of ribonucleotide reductase may enhance DNA damage repair due to CRT. We report on the efficacy and tolerability of adding the ribonucleotide reductase inhibitor, triapine, to CRT. **Methods:** NRG GY006 is a randomized, open-label phase III clinical trial. Eligible patients had FIGO 2009 locally advanced cervical (stages IB2, II, IIIB or IVA without radiographic evidence of para-aortic nodal involvement) or stages II-IV vaginal cancer. Patients were randomly assigned to receive cisplatin (40 mg/m² weekly) with RT 45 Gy + lymph node boost alone (CRT) or CRT in combination with 15 total infusions of triapine (25 mg/m² IV) Mon/Wed/Fri (CRT + T). Both image guided IMRT or 3D RT were allowed but needed to be specified and pass a rigorous credentialing process. All RT plans had a pre-treatment review with expert planning feedback to the sites. The primary endpoint was overall survival (OS); secondary endpoint was progression-free survival. Exploratory endpoints included rate of complete metabolic response on post treatment PET/CT imaging at 3 months and knowledge-based planning for image guided IMRT. The target sample was 450 with 127 OS events. The design was to provide 80% power to detect a 10% improvement in OS at 3 years over the control (or HR = 0.6) at 2.5% significance level including one interim futility analysis at 50% information time. **Results:** Between 1/15/16 and 9/22/22 448 eligible patients were randomized to CRT (n=224) or CRT+T (n=224). The database was locked on 10/18/22 with 69 deaths. Median age was 47 years (range 23-85 years). The majority had cervical cancer (93.3%) and squamous cell carcinoma (82%). 52% had FIGO stage II disease. Racial/ethnic distribution included non-Hispanic white (53.8%), Hispanic/Latina (22.5%), and black (15.2%). IMRT was used in (74.3%) and HDR brachytherapy (98.2%) of cases. No differences in Grade 3-5 toxicities were observed: CRT =52% and CRT +T= 49% with Two G5 toxicities (cardiac arrest and acidosis) in the CRT+T arm. 343 patients have completed all protocol directed therapy. With a median follow-up of 28 months (IQR 15-45 months), the median PFS and OS for both arms were not reached yet. HR for death was 1.018 (95% CI 0.634-1.635), the conditional power was 15% to detect a HR = 0.6 at 100% information time. **Conclusions:** The addition of triapine to CRT did not improve OS. Clinical trial information: NCT02466971. Research Sponsor: U.S. National Institutes of Health.

5501

Oral Abstract Session

In situ immune impact of nivolumab + ipilimumab combination before standard chemoradiation therapy (RTCT) for FIGO IB3-IVA in patients (pts) with cervical squamous carcinoma: COLIBRI trial, a GINECO study. *First Author: Isabelle Laure Ray-Coquard, Centre Léon Bérard, University Claude Bernard Lyon 1, Lyon, France*

Background: We report the results of a window-of-opportunity phase 2 trial using neoadjuvant nivolumab + ipilimumab followed by standard chemoradiation therapy (RTCT) in cervical squamous cell carcinoma pts using the CD8⁺/FOXP3⁺ ratio as a surrogate marker of immune checkpoint blockade (ICB) *in situ* effect. Association with better clinical outcome after neoadjuvant chemotherapy and higher CD8⁺/FOXP3⁺ ratio was described in cervical cancer pts. However, immune modulation after ICB and correlation with treatment response needs to be characterized. **Methods:** The primary objective was to explore the changes in the ratio of CD8⁺/FOXP3⁺ in tumor biopsies performed before and after ICB (prior to standard RTCT) by multiplex-immunofluorescence (mIF) analyzing densities of CD8 effector T cells (CD8⁺: CD3⁺CD8⁺FOXP3⁻) and CD4 regulatory T cells (FOXP3⁺: CD3⁺CD8⁻FOXP3⁺). To normalize the distribution of the values, mIF data were log-transformed (log10). Targeted gene expression profiling of 2,549 genes using HTG technology allowed us to evaluate the 27-gene based 'HOT' score reported to be associated with immunologically active tumors (Foy J-P. *et al.*, 2022, Eur J Can). **Results:** Pts received 1 cycle of nivolumab 3 mg/kg (D1D15) + ipilimumab 1 mg/kg (D1) before starting RTCT + brachytherapy. After RTCT, pts could continue nivolumab in maintenance 480 mg total dose every 28 days for 6 months. Forty pts were treated (including 50% FIGO III-IV). There were no new or unexpected toxicity. Grade ≥ 3 AEs related to ICB occurred in 3 pts. mIF data of the 28 evaluable pts revealed an increase of total CD8⁺ cells (Wilcoxon, p=0.009), proliferating CD8⁺ cells (p=0.002) and CD8⁺/FOXP3⁺ ratio (p=0.03) between baseline and before RTCT. In the 37 pts evaluable by HTG, a significant increase of expression of the *CD8A* gene (paired t-test, p=2.2e-05) and the 'HOT' score (paired t-test, p=3.1e-06) was observed after ICB. The Objective Response Rate on primary tumor before, after, at the end of treatment (EOT) is reported in table. Correlation between CD8⁺/FOXP3⁺ ratio, the 'HOT' score and response to treatment will be presented. **Conclusions:** These data indicate that neoadjuvant nivolumab + ipilimumab is safe and orchestrates *de novo* immune responses in cervical squamous cell carcinoma. The 82.5% CR rate on primary tumor 6 months post RTCT suggests favorable clinical outcomes. Clinical trial information: NCT04256213. Research Sponsor: Bristol-Myers Squibb.

Primary tumor responses.			
Primary tumor response (RECIST)	Before RTCT (After ICB induction) (%)	After RTCT (at 4W) (%)	EOT (at 24W) (%)
Total cohort (N=40)			
CR	0	25 (62.5)	33 (82.5)
PR	6 (15.0)	14 (35)	4 (10.0)
SD	32 (80.0)	1 (2.5)	0
PD	2 (5.0)	0	2 (5.0)
NE	0	0	1 (2.5)*

CR, complete response; EOT, end of treatment; ICB, immune checkpoint blockade; NE, not evaluable; PD, progressive disease; PR, partial response; RTCT, radiochemotherapy; SD, stable disease; W, weeks. *no MRI done.

5503

Oral Abstract Session

Dostarlimab for primary advanced or recurrent (A/R) endometrial cancer (EC): Outcomes by blinded independent central review (BICR) of the RUBY trial (ENGOT-EN6-NSGO/GOG-3031/RUBY). *First Author: Matthew A. Powell, National Cancer Institute sponsored NRG Oncology, Washington University School of Medicine, St Louis, MO*

Background: RUBY (NCT03981796) evaluated the efficacy and safety of the anti-programmed death 1 (PD-1) dostarlimab + standard of care (SOC) carboplatin paclitaxel (CP) versus CP alone in A/R EC. The primary endpoint of PFS by investigator assessment (INV) per RECIST v1.1 was significantly longer with dostarlimab+CP than placebo (PBO)+CP in the mismatch repair deficient/microsatellite instability-high (dMMR/MSI-H; HR 0.28; 95% CI 0.162-0.495) and overall populations (HR 0.64, 95% CI 0.507-0.800). Here we present secondary efficacy endpoints by BICR. **Methods:** RUBY is a phase 3, global, randomized, double-blind, multicenter, PBO-controlled study. Patients (pts) with primary advanced stage III or IV or first recurrent EC were randomized 1:1 to receive dostarlimab 500 mg, or PBO, plus carboplatin AUC 5 and paclitaxel 175 mg/m² Q3W (6 cycles), followed by dostarlimab 1000 mg, or PBO, monotherapy Q6W for up to 3 y. Secondary endpoints by BICR assessment per RECIST v1.1 were PFS, ORR, DOR, and DCR in the overall and dMMR/MSI-H populations. **Results:** 494 pts were randomized (245:dostarlimab+CP; 249:PBO+CP); 47.8% had recurrent disease, 18.6% and 33.6% had primary stage III and IV disease, respectively. PFS by BICR was longer with dostarlimab+CP than PBO+CP in the dMMR/MSI-H (HR 0.29; 95% CI 0.158-0.543) and overall populations (HR 0.66; 95% CI 0.517-0.853; Table). Consistent benefits were seen with dostarlimab+CP for ORR, DCR, and DOR by BICR in the dMMR/MSI-H and overall populations (Table). Safety was previously reported. **Conclusions:** Dostarlimab+CP showed clinically meaningful improvement in BICR-assessed PFS in the dMMR/MSI-H and overall populations compared with CP alone. The HRs for PFS per BICR and per INV were consistent, which supports the reliability of PFS by INV in EC trials. Benefits were seen in all BICR-assessed endpoints, which were consistent with INV. Dostarlimab+CP represents a new SOC for pts with primary A/R EC. Clinical trial information: NCT03981796. Research Sponsor: GSK.

	dMMR/MSI-H		Overall	
	Dostarlimab +CP N=53	PBO+CP N=65	Dostarlimab +CP N=245	PBO+CP N=249
PFS by INV, HR (95% CI)	0.28 (0.162-0.495) P<0.0001		0.64 (0.507-0.800) P<0.0001	
PFS by BICR, HR (95% CI)	0.29 (0.158-0.543) P<0.0001		0.66 (0.517-0.853) P<0.0001	
Probability of PFS by BICR at 24 mo, % (95% CI)	66.3 (50.8-77.9)	26.0 (13.5-40.5)	42.5 (35.2-49.6)	25.4 (18.9-32.4)
ORR by BICR, % (95% CI; n/N)* CR, % (n)	77.1 (62.7-88.0; 37/48)	63.3 (49.9-75.4; 38/60)	68.2 (61.6-74.2; 152/223)	59.4 (52.7-65.8; 136/229)
DCR, % (95% CI; n/N)*	22.9 (11)	13.3 (8)	20.6 (46)	14.8 (34)
mDOR (95% CI), mo*	58.2 (26)	50.0 (30)	47.5 (106)	44.5 (102)
	91.7 (80.0-97.7; 44/48)	91.7 (81.6-97.2; 55/60)	88.3 (83.4-92.2; 223)	86.9 (81.8-91.0; 229)
	NE (13.1-NE)	6.9 (5.5-10.1)	12.9 (8.2-NE)	6.7 (5.7-8.3)

*Assessed in pts with evaluable disease at baseline. CR, complete response; PR, partial response; NE, not estimable. *no MRI done.

5504

Oral Abstract Session

Patient-reported outcomes (PROs) in primary advanced or recurrent endometrial cancer (pA/REC) for patients (pts) treated with dostarlimab plus carboplatin/paclitaxel (CP) as compared to CP in the ENGOT-EN6/GOG3031/RUBY trial. *First Author: Mansoor Raza Mirza, Rigshospitalet, Copenhagen University Hospital, Nordic Society of Gynaecological Oncology—Clinical Trial Unit, Copenhagen, Denmark*

Background: In RUBY, a phase 3, global, randomized, double-blind, placebo (PBO)-controlled trial, dostarlimab+carboplatin/paclitaxel demonstrated significant and clinically meaningful improvement in PFS compared with PBO+CP in pts with pA/REC. PROs are reported here. **Methods:** 494 pts with pA/REC were randomized 1:1 to dostarlimab (D)+CP or PBO+CP Q3W for 6 cycles followed by D or PBO monotherapy Q6W $\leq$ 3 yrs or to disease progression. EORTC QLQ-C30 and EN24 were prespecified secondary endpoints. PROs were administered on Day 1 of each treatment (tx) cycle (C), end of tx (EOT), and at safety and survival follow-ups and reported here for C7, the end of chemotherapy (chemo) and C13, and the end of 1 yr of study. Change (chg) from baseline (BL) to C7/C13 was calculated for all scales assessed. Mixed model for repeated measures analysis was conducted to generate least-squares means (LSM), adjusting for correlations across multiple time point assessments within a pt and controlling for the BL value for the global, pain, fatigue, and physical function (PF) scores. **Results:** PRO outcomes were similar for D+CP and PBO+CP through the chemo period (C7). The table shows selected scores at C7 and C13 for mean (SD) and chg from BL. Further, no differences across the 3 yr period between the 2 arms were reported; LSM (standard error) for global QoL was 0.5 (1.42; $P=0.72$), PF was -0.7 (1.39; $P=0.63$), fatigue was 0.2 (1.75; $P=0.91$) and pain was -1.0 (1.99; $P=0.62$). Mean chg from BL to EOT showed improvement in back/pelvic pain for D+CP and deterioration in global QoL/GHS, social functioning, body image, and chg in taste for pts on PBO+CP. **Conclusions:** Dostarlimab + CP significantly improved PFS while maintaining HRQoL, further supporting its use as a standard of care in pA/REC. Clinical trial information: NCT03981796. Research Sponsor: GSK.

Domain:	D + CP BL Mean (SD)	D + CP BL to C7 Mean chg (SD)	D + CP BL to C13 Mean chg (SD)	PBO + CP BL Mean (SD)	PBO + CP BL to C7 Mean chg (SD)	PBO + CP BL to C13 Mean chg (SD)
Global QoL/GHS	67.7 (21.63)	-1.8 (22.79)	3.3 (23.51)	69.7 (21.15)	-2.3 (23.10)	-0.9 (19.25)
Physical Function	77.7 (20.83)	-6.9 (22.82)	2.4 (20.64)	76.2 (21.92)	-6.8 (21.09)	-0.1 (18.22)
Role Function	73.9 (28.77)	-6.9 (34.88)	4.6 (33.46)	77.5 (28.89)	-8.4 (32.94)	-0.2 (26.17)
Emotional Function	76.2 (18.40)	2.0 (18.75)	5.4 (20.16)	78.6 (19.41)	2.5 (22.64)	4.0 (19.85)
Cognitive Function	87.4 (16.96)	-4.8 (19.78)	-3.2 (16.95)	88.7 (16.86)	-6.8 (21.70)	-4.6 (21.73)
Social Function	79.7 (24.70)	-3.8 (31.55)	3.8 (25.90)	83.0 (23.75)	-4.5 (27.08)	1.8 (21.93)
Pain*	-2.4 (19.40)	-3.6 (30.85)	-2.4 (34.02)	25.2 (27.68)	1.1 (26.34)	2.1 (22.52)
Fatigue*	31.1 (22.57)	10.3 (26.67)	-1.2 (22.73)	30.2 (23.84)	9.0 (26.78)	-2.4 (19.40)
EN24 back/pelvic pain*	29.0 (28.81)	-10.1 (31.89)	-5.6 (35.72)	28.6 (31.25)	-6.3 (30.62)	-3.0 (25.90)

*Lower scores indicate reduced symptom severity.

LBA5506

Oral Abstract Session

Durvalumab with paclitaxel/carboplatin (PC) and bevacizumab (bev), followed by maintenance durvalumab, bev, and olaparib in patients (pts) with newly diagnosed advanced ovarian cancer (AOC) without a tumor BRCA1/2 mutation (non-tBRCAM): Results from the randomized, placebo (pbo)-controlled phase III DUO-O trial. *First Author: Philipp Harter, Department of Gynecology and Gynecologic Oncology, Kliniken Essen-Mitte, and AGO, Essen, Germany*

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2023, issue of the *Journal of Clinical Oncology*.

5505

Oral Abstract Session

Randomized controlled phase III trial of weekly paclitaxel $\pm$ ofranergene obadenovex (VB-111) for platinum-resistant ovarian cancer (OVAL Study/GOG 3018). *First Author: Rebecca Christian Arend, University of Alabama at Birmingham, Birmingham, AL*

Background: Ofranergene obadenovex (ofra-vec, VB-111) is a nonreplicating adenoviral vector with a murine pro-endothelin 1 (PPE-1-3X) promoter and pro-apoptotic Fas-tumor necrosis factor receptor 1 (TNFR1) chimeric transgene thought to have a dual mechanism of action: vascular disruption and immune activation. **Methods:** This is a randomized, placebo-controlled, double-blind, multi-center randomized phase III trial (ClinicalTrials.gov identifier: NCT03398655) of ofranergene obadenovex combined with paclitaxel vs paclitaxel with placebo for the treatment of patients with recurrent platinum resistant ovarian cancer (PROC). Patients were randomly assigned 1:1 to receive IV VB-111 1×10^{13} viral particles (VPs) every 8 weeks with weekly IV paclitaxel 80 mg/m² or placebo with paclitaxel until disease progression. The dual primary endpoints were overall survival (OS) and progression free survival (PFS) as assessed by Blinded Independent Central Review (BICR). **Results:** Between December 2017 and March 2022, 409 patients were randomized at 86 clinical sites in US, Israel, Spain, Poland and Japan. The median PFS was 5.29 months in the VB-111 arm and 5.36 months in the control arm; hazard ratio (HR) 1.03 (CI: 0.83-1.29, $p = 0.7823$), and median OS with was 13.37 months vs. 13.14 months HR 0.97 (CI: 0.75-1.27 $p = 0.8440$). Objective response rates (ORR) were similar in both arms: RECIST 1.1 ORR was 28.9% with VB-111 vs. 29.6% with control (CA-125 ORR 41.1% vs 49.4%). In both treatment arms response to CA-125 was a substantial prognostic factor for both PFS and OS. In the VB-111 arm, the HR in CA-125 responders compared to non-responders was for PFS HR 0.2428 (CI: 0.1642-0.3588), and for OS HR 0.3343 (CI: 0.2134-0.5238). Safety profile was consistent with the known safety profile of ofra-vec and was characterized by common transient flu like symptoms such as fever and chills. **Conclusions:** The addition of ofranergene obadenovex to paclitaxel did not improve PFS or OS. Clinical trial information: NCT03398655. Research Sponsor: VBL Therapeutics.

5508

Oral Abstract Session

Luveltamab tazevivulin (STRO-002), an anti-folate receptor alpha (FolR α) antibody drug conjugate (ADC), safety and efficacy in a broad distribution of FolR α expression in patients with recurrent epithelial ovarian cancer (OC): Update of STRO-002-GM1 phase 1 dose expansion cohort. *First Author: Ana Oaknin, Vall d'Hebron Institute of Oncology (VHIO), Vall d'Hebron University Hospital, Barcelona, Spain*

Background: Luveltamab tazevivulin (luvelta) is a novel FolR α -targeting ADC with a stable cleavable linker and a 3-aminophenyl hemiasterlin warhead (DAR of 4) that induces cytotoxic and immunologic cell death. Using site-specific conjugation technology, luvelta is designed to target a broad range of FolR α expressing OC. STRO-002-GM1 is a global phase 1 study evaluating luvelta in patients with relapsed OC. We provide updated data from the initial ovarian expansion cohort. **Methods:** The study enrolled advanced OC pts who had progressive platinum resistant (PROC) after 1-3 prior lines or platinum sensitive disease after 2-3 prior lines of platinum chemotherapy. Pts were randomized 1:1 to received luveltamab at 4.3 or 5.2 mg/kg given IV every 3 weeks until disease progression. Prophylactic corticosteroid eyedrops were not required/administered. FolR α expression was not required for study entry but was analyzed retrospectively in archival tissue using the FOLR1 IHC assay (Ventana Medical Systems). The scoring paradigm assessed percentage of cells with any intensity expression (TPS). TPS $>25\%$ was selected for further analysis. **Results:** 44 pts were enrolled (23 pts at 4.3 mg/kg and 21 pts at 5.2 mg/kg). For pts with a TPS $>25\%$ ($n=35$), the median prior lines of therapy was 2.5 (range 1-3), 69% had prior bevacizumab treatment, and 83% prior PARP inhibitor treatment. Investigator assessed efficacy data for pts with a TPS $>25\%$ are presented in the table. The most common grade ≥ 3 treatment emergent adverse events (TEAEs) included neutropenia (70.5%), arthralgia (18.2%), and anemia (13.6%). G3/4 neutropenia had a higher incidence at 5.2 mg/kg than 4.3 mg/kg (76% vs 65%); most notable for G4 neutropenia (52% vs 22%). 1 pt at each dose level had febrile neutropenia. TEAEs led to dose delay in 80% of pts with a higher incidence at 5.2 mg/kg (95% vs. 65%). TEAEs led to dose reduction in 61% of pts with a higher incidence at 5.2 mg/kg (76% vs. 48%). 1 pt had a G5 sepsis with G4 neutropenia. Neutropenia, arthralgia and anemia were managed with standard medical treatment and dose reductions. **Conclusions:** These dose expansion data confirm activity of luvelta at starting doses ranging from 4.3-5.2 mg/kg in recurrent OC with FolR α expression as low as TPS $>25\%$ and supports further clinical study in this population. The global phase 2/3 REFRAme registration study will evaluate luvelta in PROC pts with TPS $>25\%$. Clinical trial information: NCT03748186. Research Sponsor: Sutro Biopharma, Inc.

Efficacy data for subjects with FolR α TPS $>25\%$.				
Population	Endpoint	All	4.3 mg/kg	5.2 mg/kg
RECIST Evaluable		N=32 pts	N=16 pts	N=16 pts
	ORR (95% CI)	37.5% (21.1, 56.3)	31.3% (11.0, 58.7)	43.8% (19.8, 70.1)
	mDOR (95% CI)	5.5m (2.5, 11.0)	13m (4.5, NE)	5.4m (2.4, 6.1)
Enrolled		N=35 pts	N=19 pts	N=16 pts
	mPFS (95% CI)	6.1m (4.1, 7.0)	6.1m (4.0, 8.3)	6.6m (2.9, 7.6)

5509

Clinical Science Symposium

Final survival analysis of the phase III OVHIPEC-1 trial of hyperthermic intraperitoneal chemotherapy in ovarian cancer after ten year follow-up. *First Author: Lot Aronson, The Netherlands Cancer Institute - Antoni van Leeuwenhoek, Amsterdam, Netherlands*

Background: The randomized, phase 3 OVHIPEC-1 trial (NCT00426257) investigated the addition of hyperthermic intraperitoneal chemotherapy (HIPEC) to interval cytoreductive surgery in patients with stage III epithelial ovarian cancer who were ineligible for primary cytoreduction. OVHIPEC-1 previously demonstrated improved recurrence-free and overall survival after 4.7 years of follow-up. Here, we report the final survival outcomes after ten years of follow-up. In addition, we report new data on the subsequent anti-cancer treatments given after disease progression. **Methods:** Patients were randomized to receive interval cytoreductive surgery with or without HIPEC, after receiving three cycles of neo-adjuvant carboplatin and paclitaxel. Randomization was performed at the time of surgery when either complete (no visible disease) or optimal cytoreduction (residual tumor measuring <10mm in diameter) was anticipated. All patients received an additional three cycles of adjuvant systemic chemotherapy. We analyzed survival according to the intention-to-treat principle using stratified log-rank tests and Kaplan-Meier methods. Subsequent lines of therapy were compared between arms. **Results:** At a median follow-up of 10.1 years, 114 of 123 patients (92.7%) who underwent surgery alone and 109 of 122 patients (89.3%) who had surgery-plus-HIPEC experienced recurrence, progression, or death from any cause. Median recurrence-free survival was 10.7 months in the surgery group compared to 14.3 months in the surgery-plus-HIPEC group (HR, 0.63; 95% confidence interval [CI], 0.48-0.83; stratified P<0.001). One hundred and eight patients (87.8%) in the surgery group have died as compared to 100 patients (82.0%) in the surgery-plus-HIPEC group. Median overall survival was 33.3 versus 44.9 months (HR, 0.70; 95% CI, 0.53-0.92; stratified P=0.011), respectively. Subsequent anti-cancer therapies, including chemotherapy (platinum and non-platinum based), secondary surgery, poly (ADP-ribose) polymerase (PARP) inhibitors and bevacizumab, were received by 104 patients (84.6%) in the surgery group and 100 patients (82.0%) in the surgery-plus-HIPEC group. The median number of subsequent systemic treatment lines was 2 (IQR 1-3) in both arms. **Conclusions:** This study provides the first long-term survival analysis of HIPEC in ovarian cancer and confirms the benefit of HIPEC in patients with primary stage III epithelial ovarian cancer undergoing interval cytoreductive surgery. No imbalance in subsequent therapy after disease recurrence was found that could explain the improved overall survival after HIPEC. Clinical trial information: NCT00426257. Research Sponsor: Dutch Cancer Society (NKI 2006-4176).

LBA5511

Clinical Science Symposium

An international randomized phase III trial comparing radical hysterectomy and pelvic node dissection (RH) vs simple hysterectomy and pelvic node dissection (SH) in patients with low-risk early-stage cervical cancer (LRESCC): A Gynecologic Cancer Intergroup study led by the Canadian Cancer Trials Group (CCTG CX.5-SHAPE). *First Author: Marie Plante, Division of Gynecologic Oncology, Université Laval, CHU de Quebec, Quebec, QC, Canada*

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2023, issue of the *Journal of Clinical Oncology*.

5510

Clinical Science Symposium

Hyperthermic intraperitoneal chemotherapy in platinum-sensitive relapsed epithelial ovarian cancer: The CHIPOR randomized phase III trial. *First Author: Jean-Marc Classe, Institut de Cancérologie Ouest, Nantes, France*

Background: Standard treatment for patients with first platinum-sensitive relapse of epithelial ovarian cancer (EOC) is based on surgery and second-line systemic chemotherapy (CT). The role of hyperthermic intra-peritoneal chemotherapy (HIPEC) remains uncertain. **Methods:** The CHIPOR multicentric randomized phase III trial (NCT01376752), conducted in 31 institutions, enrolled patients with a first platinum-sensitive relapse (platinum-free interval of ≥6 months) of EOC. Patients were treated with 6 cycles of platinum and taxane based CT ± bevacizumab, and those amenable to a complete cytoreductive surgery at the end of CT were enrolled and randomly assigned to receive HIPEC (cisplatin 75 mg/m² at 41°C for 60 min) or not. Randomization was performed during complete cytoreductive surgery, stratified by center, surgical outcome (no residual disease vs residual <0.25 cm), chemotherapy-free interval before relapse, and PARP inhibitor use (yes vs no). The primary endpoint was overall survival (OS). The target sample size was 404 evaluable patients, providing 80% power at 5% alpha after 268 deaths. Secondary endpoints included progression-free survival (PFS), peritoneal PFS, patient-reported outcomes, safety, and postoperative morbidity and mortality (≤60 days after surgery). **Results:** Between May 11, 2011, and May 14, 2021, 415 patients were randomized. Baseline characteristics were balanced between treatment arms. At the data cutoff (Jan 8, 2023), with a median follow-up of 6.2 years, 268 patients (65%) had died. Efficacy results are summarized below. **Conclusions:** HIPEC significantly improves OS and peritoneal PFS of women with first platinum-sensitive relapse of EOC treated with second-line platinum-based CT followed by secondary complete cytoreductive surgery. Ongoing analyses, including patient reported outcome, BRCA status, bevacizumab exposure, and subsequent therapy, will be presented. Clinical trial information: NCT01376752. Research Sponsor: The trial was supported by R&D UNICANCER, by a Clinical Research Hospital Program grant from the French Ministry of Health/Institut National du Cancer and by French national Ligue against cancer.

Endpoint	HIPEC (n=207)	No HIPEC (n=208)
OS	Events, n (%) Median, months (95% CI) HR (95% CI)* 126 (61) 54.3 (41.9-61.7) 0.69 (0.50-0.94), p=0.020	142 (68) 45.6 (39.9-54.2)
Global PFS	Events, n (%) Median, months (95% CI) HR (95% CI)* 180 (87) 10.2 (9.3-12.1) 0.82 (0.64-1.06)	184 (88) 9.8 (8.8-11.9)
Peritoneal PFS	Events, n (%) Median, months (95% CI) HR (95% CI)* 151 (73) 13.1 (10.7-16.3) 0.71 (0.54-0.94)	157 (75) 12.2 (9.8-13.1)
Postoperative adverse events, n (%)	Grade 3/4 Grade 3/4 renal toxicity Grade 5 32 (15) 8 (4) 0	22 (11) 1 (<1) 3 (1)
Gastrointestinal stoma, n (%)	20 (10)	10 (5)

*Stratified on stratification factors. HR = hazard ratio.

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Poster Discussion Session

Randomized phase 2 study of gemcitabine with or without ATR inhibitor berzosertib in platinum-resistant ovarian cancer: Final overall survival (OS) and biomarker analyses. *First Author: Panagiotis A. Konstantinopoulos, Dana-Farber Cancer Institute, Boston, MA*

Background: The multicenter, open-label, randomized phase 2 NCI-9944 study (NCT02595892) demonstrated that addition of ATR inhibitor (ATRi) berzosertib to gemcitabine increased progression-free survival (PFS) compared to gemcitabine alone (HR = 0.57, one-sided log-rank p = 0.044, which met the one-sided significance level of 0.1 used for sample size calculation). Final overall survival (OS) and corresponding biomarker analyses are reported here. **Methods:** Patients (pts) with platinum-resistant high-grade serous ovarian cancer and unlimited previous lines of cytotoxic therapy in the platinum-sensitive setting but no more than one line of cytotoxic therapy in the platinum-resistant setting, were randomized 1:1 to gemcitabine/berzosertib versus gemcitabine alone. Randomization was stratified based on platinum free interval (PFI), PFI ≤3 months versus > 3 months. Crossover from gemcitabine to gemcitabine/berzosertib was allowed upon disease progression by RECIST 1.1. OS was a secondary endpoint while preplanned exploratory correlative studies included assessment of DNA repair pathways and replication stress (RS) alterations by targeted gene sequencing and/or immunohistochemistry (IHC). **Results:** Seventy pts were randomly assigned to treatment with gemcitabine/berzosertib (34 pts) or gemcitabine alone (36 pts); 15 pts crossed over from gemcitabine to gemcitabine/berzosertib. At the final OS analysis (92.9% maturity), median follow-up was 53.2 weeks in the gemcitabine/berzosertib and 43 weeks in the gemcitabine alone groups. Median OS in the intent-to-treat (ITT) population was 59.4 weeks in the gemcitabine/berzosertib group versus 43.0 weeks in the gemcitabine alone group (HR 0.79, 90% CI 0.52-1.2, one-sided p = 0.18). However, when patients who crossed over to gemcitabine/berzosertib were excluded from analysis, a significant OS benefit was observed with gemcitabine/berzosertib (HR 0.60, 90%CI 0.37–0.97); HR was 0.26 (90% CI 0.1–0.7) in pts with PFI ≤3 months and 0.89 (90%CI 0.50–1.59) in pts with PFI > 3 months. Furthermore, significant OS benefit was observed in pts with RS-low tumors (HR 0.39, 90%CI 0.17–0.91, defined as tumors harboring no genomic RS alterations related to loss of RB pathway regulation and/or oncogene-induced RS) but not in pts with RS-high tumors (HR 0.74, 90%CI 0.35–1.56). Additional targeted gene sequencing and IHC analyses as well as analyses adjusting for patient crossover will be reported at the meeting. **Conclusions:** In the ITT population, gemcitabine/berzosertib did not significantly improve OS versus gemcitabine alone. Pts with PFI ≤3 months and pts with RS-low tumors may derive a survival advantage from addition of berzosertib to gemcitabine in the platinum-resistant setting. Clinical trial information: NCT02595892. Research Sponsor: U.S. National Institutes of Health.

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Poster Discussion Session

Correlation of cyclin E1 expression and clinical outcomes in a phase 1b dose-escalation study of azenosertib (ZN-c3), a WEE1 inhibitor, in combination with chemotherapy (CT) in patients (pts) with platinum-resistant or refractory (R/R) epithelial ovarian, peritoneal, or fallopian tube cancer (EOC). *First Author: Joyce F. Liu, Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA*

Background: Azenosertib (ZN-c3) is a novel, selective, and orally bioavailable WEE1 inhibitor demonstrating single-agent antitumor activity. Azenosertib may inhibit CT-induced DNA damage repair and provide benefit in pts with platinum R/R EOC. Cyclin E1 amplification/overexpression is present in $\geq 35\%$ of metastatic ovarian cancer. High expression/amplification of Cyclin E1 is a poor prognostic marker and predictive of lack of response to platinum-based CT. Ovarian models overexpressing Cyclin E1 have exquisite sensitivity to azenosertib *in vitro* and *in vivo*; forced Cyclin E1 overexpression sensitizes cell lines with low endogenous Cyclin E1 to azenosertib. **Methods:** This open-label, multicenter study (NCT04516447) assessed azenosertib + paclitaxel (PAC), carboplatin (Carbo), gemcitabine (GEM), or pegylated liposomal doxorubicin (PLD) in pts with metastatic high-grade serous EOC after ≤ 2 lines of CT including platinum CT. Primary endpoint is safety and identification of RP2D of each combination. Secondary endpoints include clinical activity. Azenosertib was given continuously or intermittently QD in 21 or 28D cycles until PD or unacceptable toxicity. **Results:** 103 pts were enrolled; at data cut-off, 94 were efficacy evaluable. 26.6% had a partial response (PR) and median progression free survival (PFS) = 9.03 mo (95%CI: 5.52-11.01). Azenosertib + PAC demonstrated the highest ORR [9/18 (50%)], followed by Carbo [9/27 (33.3%)]; ORR for azenosertib + PLD or + GEM was 14.3% (5/35, 2/14 respectively). 80 pts had available Cyclin E1 expression data by IHC; higher Cyclin E1 (H-score > 50) correlated with higher ORR and longer PFS (ORR = 31.3% vs 7.7%; PFS = 10.35 vs 3.25 mo, HR=0.3; Table). Frequent Grade ≥ 3 TEAEs (%) were neutropenia (44.4), thrombocytopenia (30.3), anemia (12.1), leukopenia (11.1), fatigue (10.1), diarrhea (6.1), nausea (5.1), and vomiting (5.1). **Conclusions:** Azenosertib + CT is well tolerated and has encouraging clinical activity, with durable responses in pts with platinum R/R EOC. Pts with Cyclin E1 overexpressing tumors, a subgroup with suboptimal benefits from CT, demonstrated significant improvements in ORR and PFS vs pts with tumors having low expression. These data support a planned trial of azenosertib + CT vs CT alone in Cyclin E1 overexpressing platinum R/R EOC. Clinical trial information: NCT04516447. Research Sponsor: Zentalis Pharmaceuticals.

	Azenosertib + PAC (n=18)	Azenosertib + Carbo (n=27)	Azenosertib + GEM (n=14)	Azenosertib + PLD (n=35)	Total (n=94)
ORR, %	50.0	33.3	14.3	14.3	26.6
Pts with IHC Available (N)	15	23	13	29	80
ORR by Cyclin E1 (n/N; %)					
High	8/15; 53.3	7/18; 38.9	2/11; 18.2	4/23; 17.4	21/67; 31.3
Low	0/0; 0	0/5; 0	0/2; 0	1/6; 16.7	1/13; 7.7
mPFS, mo	7.36	4.24	NE	9.03	9.03
mPFS by Cyclin E1, mo					
High	7.36	10.35	NE	11.01	10.35
Low	NE	2.14	NE	3.75	3.25
HR	NE	0.1	NE	0.4	0.3

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Poster Discussion Session

A phase II trial of palbociclib combined to letrozole after progression on second-line chemotherapy for women with ER/PR-positive high-grade serous or endometrioid ovarian, fallopian tube, or peritoneal cancer: LACOG 1018. *First Author: Fernanda Bronzon Damian, Hospital São Lucas da PUCRS, Porto Alegre, Brazil; Hospital Fêmima - Grupo Hospitalar Conceição, Porto Alegre, Brazil; Brazilian Gynecologic Oncology Group (EVA), Brazil; Latin American Cooperative Oncology Group (LACOG), Porto Alegre, Brazil*

Background: Treatment options for patients with high-grade ovarian serous (HGSC) or endometrioid carcinoma (HGEC) who progress after receiving chemotherapy for recurrence are limited. **Methods:** LACOG 1018, a phase II, single-arm, multicenter trial evaluated the efficacy of letrozole 2.5mg/day po continuously plus palbociclib 125mg/day po for 21 days in 28-day cycles in patients with histologically proven ovarian HGSC or HGEC, fallopian tube or peritoneal cancer who had progressed on prior chemotherapy for locoregional recurrence or metastatic disease (at least one platinum-based regimen). Patients had centrally confirmed ER and/or PR positivity ($> 10\%$ by immunohistochemistry) and ECOG PS 0-2. The primary endpoint was progression-free survival (PFS) at 12 weeks by RECIST 1.1. Secondary endpoints were overall survival (OS), overall response rate (ORR), clinical benefit rate (CBR) and safety. Tumor evaluations were performed every 6 weeks until week 24. Sample size was calculated as 31 patients for the primary endpoint (90% power to detect a two-sided significance level of 5%, 45% PFS at 12 weeks) and 39 patients for secondary endpoints considering 10% drop-out. NCT03936270. **Results:** A total of 41 eligible patients were included in five Brazilian centers between Feb2020-Jan2022 (table). The PFS-week12 rate was 63.4% (95%CI 46.8 – 76.1). At the time of analysis (cut-off date Jan 18th, 2023) median follow-up was 18.1 months (95%CI 12.9 – 24.3), and 37 PFS events had occurred. Median PFS was 4.2 months (95%CI 2.7 – 5.5) and median OS was 13.4 months (95%CI 10.4 – 20.1). The ORR was 7.7% (N=3 PR) and the CBR was 71.8%. Treatment-related adverse event rates of any grade and grade 3-4 were 95.1% and 51.2%, respectively. Grade 3-4 neutropenia was reported in 17 (41.5%) patients, and febrile neutropenia in 1 (2.4%). Only one patient (2.4%) discontinued the treatment due to toxicity. At the cut-off date, three patients remained on treatment. **Conclusions:** Palbociclib combined to letrozole demonstrated a significant efficacy in terms of PFS rate at 12 weeks (63.4%) and CBR (71.8%), with no new safety concerns in women with recurrent advanced and metastatic hormone receptor-positive ovarian cancer. These results warrant further investigation of palbociclib plus letrozole in high-grade ovarian cancer. Clinical trial information: NCT03936270. Research Sponsor: Pfizer.

Characteristic	N (%)
Age, median (range) - years	60.8 (42.6-82.8)
ECOG 0-1	40 (97.6%)
Previous line of systemic chemotherapy	
2	23 (56.1%)
3	15 (36.6%)
4	3 (7.3%)
Platinum-resistant	13 (31.7%)
Ca125 $\geq$ UNL	33 (84.6%)
BRCA mutated	4 (9.7%)

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Poster Discussion Session

Initial efficacy and safety results from ENGOT-ov60/GOG-3052/RAMP 201: A phase 2 study of avutometinib (VS-6766) $\pm$ defactinib in recurrent low-grade serous ovarian cancer (LGSOC). *First Author: Susana N. Banerjee, The Royal Marsden NHS Foundation Trust and Institute of Cancer Research, National Cancer Research Institute (NCRI), London, United Kingdom*

Background: LGSOC is a RAS/MAPK pathway driven cancer that constitutes $\leq 10\%$ of ovarian cancer. There are no FDA approved treatments specifically for LGSOC. Avutometinib is a novel small molecule RAF/MEK clamp. Focal adhesion kinase (FAK) activation is a resistance mechanism to RAF/MEK inhibition, and defactinib, a small molecule inhibitor of FAK, has shown synergistic antitumor activity with avutometinib in preclinical models. The combination of avutometinib and defactinib has demonstrated a high rate of confirmed and durable responses (overall response rate [ORR] = 46%) in recurrent LGSOC (Banerjee S, ESMO 2021). **Methods:** A registration-directed phase 2, adaptive, multicenter, randomized study was initiated to evaluate avutometinib $\pm$ defactinib in patients with *KRAS* mutant (mt) and *KRAS* wild-type (wt) recurrent LGSOC to identify the optimal regimen based on confirmed ORR by blinded independent central review (Part A) and determine the efficacy of the optimal regimen (Part B) (NCT04625270). Pts were randomized to avutometinib 4 mg orally (PO), twice weekly, 3 weeks on, 1 week off (mono) or avutometinib 3.2 mg PO twice weekly + defactinib 200 mg PO BID 3 weeks on, 1 week off (combo). Key inclusion criteria include histologically confirmed recurrent LGSOC, known *KRAS* status and prior systemic therapy with platinum chemotherapy. Unlimited additional prior lines, including prior MEK inhibitor, were permitted. Here we present efficacy results from Part A (evaluable patients, N=59) and safety data from all pts enrolled (N=121). **Results:** In Part A, the median number of prior systemic regimens was 3 for mono, and 4 for combo. In evaluable patients, a confirmed ORR of 7% (2/30) was observed for mono (13% *KRAS* mt, 0% *KRAS* wt), and an ORR of 28% (8/29) was observed for combo (27% *KRAS* mt, 29% *KRAS* wt). Two of 4 patients previously treated with a MEK inhibitor showed a confirmed partial response (PR) on the combination arm. A high disease control rate (PR or SD ≥ 8 weeks) was observed for both mono (90%) and combo (93%). The majority of treatment related adverse events (AEs, any grade) for combo (N=57) were mild to moderate. The most common Grade ≥ 3 AEs for combo were blood CPK increase (15.8%), fatigue (5.3%), diarrhea (3.5%), dermatitis acneiform (1.8%), and rash (1.8%). A similar AE profile was observed for mono (N=64). Most AEs were manageable/reversible. On the combo arm, 90.6% ($\pm 20\%$) of planned doses were given and 9% (n=5) of pts discontinued due to AEs (asymptomatic elevated blood CPK (n=3) and fatigue (n=2)). **Conclusions:** The interim data support avutometinib + defactinib as an active go-forward regimen in heavily-pretreated recurrent LGSOC, regardless of *KRAS* status. No new safety signals were observed, and most AEs were mild to moderate. Enrollment continues in Part B for the combination of avutometinib and defactinib. Clinical trial information: NCT04625270. Research Sponsor: Verastem Oncology.

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Oral Abstract Session

Camrelizumab plus apatinib in patients with advanced or recurrent endometrial cancer after failure of at least one prior systemic therapy: A single-arm phase II trial. *First Author: Huaying Wang, Department of Gynecologic Oncology, Fudan University Shanghai Cancer Center; Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, China*

Background: The first stage results of a Simon's two-stage single-arm phase II trial showed promising antitumor activity and manageable safety of camrelizumab (a humanized anti-PD-1 monoclonal antibody) plus apatinib (a highly selective VEGFR2 inhibitor) in patients with advanced or recurrent endometrial cancer after failure of prior systemic therapy. Here, we report the primary results of this trial. **Methods:** This open-label, single-arm, phase II trial used a minimax Simon's two-stage design. Patients with advanced or recurrent endometrial cancer that had progressed after at least one prior systemic therapy were treated with camrelizumab (200 mg, intravenously, every two weeks) and apatinib (250 mg, orally, daily) on a four-week cycle until disease progression or intolerable toxicity. The primary endpoint was the objective response rate per Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1. Other assessed endpoints were disease control rate, time to response, duration of response, time to treatment failure, progression-free survival, overall survival, and treatment-related adverse events. **Results:** Between January 20, 2020 and October 14, 2022, 36 patients (median age: 60 [range: 29, 76] years; 17 [47.2%] had Eastern Cooperative Oncology Group [ECOG] performance status 1; 15 [41.7%] had received at least two prior systemic therapies) were enrolled. At the date of data cutoff (December 31, 2022), the median follow-up time was 13.9 (interquartile range: 5.8-23.2) months. All 36 patients were evaluable for efficacy, the confirmed objective response rate was 44.4% (95% CI: 27.9%, 61.9%) and the confirmed disease control rate was 88.9% (95% CI: 73.9%, 96.9%), with two complete response, 14 partial response, and 16 stable disease. The median progression-free survival was 6.4 (95% CI: 5.2, 13.0) months. The treatment-related adverse events of grade 3 or greater occurred in 19 (52.8%) patients, with increased gamma-glutamyltransferase (8 [22.2%]), hyperglycemia (4 [11.1%]), hypertension (4 [11.1%]) and increased direct bilirubin (4 [11.1%]) being most common. Reactive cutaneous capillary endothelial proliferation occurred in 6 (16.7%) patients and all were grade 1 or 2. No treatment-related death occurred. **Conclusions:** Camrelizumab plus apatinib show promising antitumor activity and manageable toxicity in patients with advanced or recurrent endometrial cancer after failure of prior systemic therapy and warrant further investigation. Clinical trial information: ChiCTR2000031932. Research Sponsor: National Natural Science Foundation of China (No. 82002758).

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Poster Discussion Session

A phase II basket trial of dual anti-CTLA-4 and anti-PD-1 blockade in rare tumors (DART) SWOG S1609: The vulvar cancers. *First Author: Young Kwang Chae, Northwestern University, Chicago, IL*

Background: Dual checkpoint inhibition with Anti-PD-1 and anti-CTLA4 checkpoint inhibitors have proven to be effective in several malignancies but their potential role in various rare solid cancers is yet to be established. The efficacy of immunotherapy in vulvar cancer patients has not been explored. This study presents the first results of ipilimumab and nivolumab in vulvar cancers (cohort 35) of the SWOG S1609 Dual Anti-CTLA-4 & Anti-PD-1 blockade in Rare Tumors (DART) trial. **Methods:** DART is a prospective, open-label, multicenter/multi-cohort phase 2 clinical trial of ipilimumab (1mg/kg intravenously every 6 weeks) plus nivolumab (240mg intravenously every 2 weeks). The primary endpoint was objective response rate (ORR) (RECIST v1.1) (confirmed complete (CR) and partial responses (PR)); progression-free survival (PFS), overall survival (OS), stable disease (SD) > 6 months, and toxicity are secondary endpoints. **Results:** Sixteen evaluable patients (median age, 55.5 years) were analyzed. 14 cases were of squamous cell carcinoma histology and 2 were of poorly differentiated carcinoma. ORR was 18.8% (3/16, 25% when including one unconfirmed PR). There was 1 CR (SCC; PFS of 465 days) and 2 PR (both SCC; one with 57% regression with PFS of 1022 days, another with 53% regression with PFS of 501 days). Of note, there was one SCC patient with unconfirmed PR that showed 69% regression with PFS of 209 days. Overall clinical benefit rate (CBR; no progression > 6months) was 31.3% (5/16). The median PFS was 2.2 months, 6-month PFS 33%, 1-year PFS 20%. The median OS was 7.6 months, 6-month OS 62%, 1-year OS 44%. The most common adverse events were diarrhea, fatigue, pruritus, anorexia, and nausea (25%, n = 4 each). Grade 3-4 adverse events occurred in 25% of patients (n = 4). There was 1 grade 3-4 adverse event (6.7%) that led to discontinuation, and 1 (6.7%) grade 5 death adverse event. **Conclusions:** Ipilimumab plus nivolumab in vulvar cancers resulted in an ORR of 18.8% and CBR of 31.3%, with durable responses seen. Correlative studies to determine response and resistance markers are ongoing. Expanded prospective studies exploring the role of immunotherapy in vulvar cancers are warranted. Clinical trial information: NCT02834013. Research Sponsor: U.S. National Institutes of Health; Bristol-Myers Squibb.

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Poster Discussion Session

Neoadjuvant camrelizumab plus chemotherapy for locally advanced cervical cancer (NACI study): A prospective, single-arm, phase II trial. *First Author: Jing Chen, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China*

Background: First-line treatments for locally advanced cervical cancer (LACC) have limited efficacy and neoadjuvant chemotherapy (NACT) is an emerging approach, however, two-thirds of patients (pts) respond to it and pts without response benefit little. PD-1 inhibitors have shown promising role in recurrent or metastatic cervical cancer. This study aims to evaluate the efficacy and safety of preoperative PD-1 inhibitor camrelizumab combined neoadjuvant therapy for LACC. **Methods:** The study is designed as a multicenter, open-label, single-arm, prospective phase II study. Pts are enrolled if they had previously untreated LACC (2018 FIGO staged IB3, IIA2 and IIB/IIIC1r (tumor size > 4cm). Eligible pts will receive neoadjuvant chemo-immunotherapy (NACIT), defined as one cycle of cisplatin (75-80 mg/m², iv) plus nab-paclitaxel (260 mg/m², iv) NACT and subsequent two cycles of camrelizumab (200mg, iv) combined NACT. Either surgery or concurrent chemoradiotherapy are conducted according to the response as per the Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1. The primary endpoint was objective response rate (ORR), and the secondary endpoints were pathological complete remission (pCR) rate, rate of postoperative adjuvant treatment, event-free survival, overall survival and safety. **Results:** From Dec 1, 2020 to Feb 1, 2023, 83 pts were enrolled, and 78 pts were evaluated for response. The ORR was 100% (95%CI, 95.38 to 100), with 14 (17.95%) complete response (CR) and 64 (82.05%) partial response. Regarding the pathological findings of 76 pts who underwent radical surgery, 30 (39.47% (95%CI, 28.44 to 51.35)) pts achieved pCR, while 17 (22.37%) needed postoperative adjuvant treatment as indicated in NCCN guideline, of who 14 had positive pelvic nodes, positive surgical margin, and/or positive parametrium and the other three met Sedlis criteria. RECIST CR was significantly associated with pCR (P = 0.016). Pre-treatment PD-L1 expression (Combined Positive Score) was a predictive biomarker for RECIST CR (P = 0.036) but not for pCR (P = 0.078) in these evaluated patients. Grade 3 or 4 treatment-related adverse events occurred in 35 (44.87%) pts during NACIT; the most common were lymphocytopenia (25.64%), neutropenia (12.82%) and leucopenia (8.97%). **Conclusions:** NACIT for LACC demonstrated extremely high ORR and pCR rate with manageable toxicity profile, and greatly reduced the need of postoperative adjuvant therapy. Clinical trial information: NCT04516616. Research Sponsor: Jiangsu Hengrui Medicine, Lianyungang, China; Chinese Clinical Medical Research Center for Obstetrical and Gynecological Diseases.

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Poster Discussion Session

Efficacy and final safety analysis of pre- and co-administration of nivolumab (Nivo) with concurrent chemoradiation (CCRT) followed by Nivo maintenance therapy in patients (pts) with locally advanced cervical carcinoma (LACvCa): Results from the phase I trial, GOTIC-018. *First Author: Kazuto Nakamura, Department of Gynecology, Gunma Prefectural Cancer Center, Ota, Japan*

Background: LACvCa is associated with a poor prognosis, and CCRT is the standard treatment for LACvCa pts. Anti-PD1 monoclonal antibodies are associated with increased survival in recurrent or persistent CVCa pts; thus, Nivo may enhance antitumor immune responses. We previously reported that the addition of pre- and co-administration of Nivo was safe and feasible in the acute phase in pts with LACvCa who were treated with CCRT (GOTIC-018; JMA-IA00425). Herein, we report the efficacy and final safety of GOTIC-018. **Methods:** The GOTIC-018 study was a multicenter, multi-cohort phase I study of Nivo plus CCRT in pts with LACvCa. The treatment plan in cohort A was co-administration of Nivo (240 mg/body once every 2 weeks) with CCRT followed by Nivo maintenance therapy for 52 weeks. The treatment plan in cohort B was pre-CCRT (two doses of Nivo before CCRT) followed by co-administration of Nivo with CCRT followed by Nivo maintenance therapy. Efficacy was evaluated using the RECIST v1.1. Tumor biopsies were obtained before treatment in each cohort and after two doses of Nivo in cohort B. **Results:** 30 pts (15 in each cohort) were enrolled between May 2019 and June 2021. There were one stage IVA, 11 stage IIIB, 16 stage II, and two stage IB2 tumors based on FIGO 2008. 28 squamous cell and 2 adenocarcinomas were included. 27 of the 30 tumors were positive for high-risk HPV, 14 were positive for PD-L1 TPS, and all tumors were microsatellite stable. The median follow-up was 15.2 months. The median number of Nivo cycles was 30 and 32 for cohorts A and B, respectively. 26 pts completed the study protocol, two discontinued Nivo due to AEs, and two withdrew their consent during the maintenance phase. Ten and eight pts in cohorts A and B, respectively, required Nivo interruption. The best overall response rates were 100% and 93.3% in cohorts A and B, respectively. A total of 73.3% of the pts achieved a complete response in each cohort. The 12-months progression-free survival rate was 100% of the evaluable 29 pts for each cohort. The most common grade ≥ 3 AEs were neutropenia (60.0 and 26.7% in cohorts A and B, respectively), followed by diarrhea (13.3 and 26.7%, respectively), and anemia (13.3 and 16.7%, respectively). Grade ≥ 3 irAEs were observed in two (13.3%) and one (6.7%) pts in cohorts A and B, respectively. The most common grade ≥ 3 irAEs were increased serum lipase levels in two pts. In addition, 6 of the 12 tumors that were PD-L1 TPS negative turned positive after two doses of Nivo in cohort B. **Conclusions:** The addition of pre- and co-administration of Nivo followed by Nivo maintenance therapy appears safe and shows encouraging efficacy in pts with LACvCa treated with CCRT. Pre-CCRT administration of Nivo may affect the tumor microenvironment. Clinical trial information: JMA-IA00425. Research Sponsor: Ono.

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Poster Discussion Session

Toxicity profile and discordance between patients/physicians regarding niraparib maintenance in recurrent ovarian cancer (ROC) patients: Lessons from the NIQOLE real-life study—GINECO study. *First Author: Florence Joly, Department of Medical Oncology, Centre François Baclesse, Caen, France*

Background: Niraparib (NI) maintenance is a standard of care in platinum-sensitive ROC. Based on pivotal randomized trials, toxicity profile appears manageable through adapted drug dosing. However, data on tolerance and feasibility for unselected patients (pts) are missing, especially regarding pts' reported adverse events (AE). **Methods:** NIQOLE study is a real-life longitudinal multicenter, phase IV study in ROC pts treated with NI maintenance. NI starting dose was adapted to pts' weight and platelet count. The primary endpoint was to describe physicians' reported AE (NCI-CTC-AE, grading from 0 to 5) leading to treatment modifications (TM), defined by dose reduction or treatment interruption/discontinuation from baseline to month 3 and delay of first TM. Secondary endpoints included duration of treatment and pts' reported AE. Progression rates were exploratory endpoints. Owing to a digital device, pts provided remoted weekly AE (NCI PRO-CTC-AE, grading from 0 to 3) which were accessible to investigators. Concordance between the main symptomatic AEs reported by pts and those reported by physicians was analyzed. **Results:** 139 pts were treated: median age 70 [44-88], high-grade serous histology 91%, BRCA mutation 5%, first relapse 72%, prior bevacizumab 71%. The median delay from platinum-based regimen and NI was 49 days [15-109]. NI starting dose was 200 mg in 80% of pts and the median treatment duration was 5.6 months [0.2-21]. Progression rates at 3 and 6 months were 19 and 45%, respectively. At 3 months, 60% (n=84%) of pts had at least one TM, of whom 47% (n=66) were treatment-related AEs: dose reduction in 17/66 (26%), interruption in 53/66 (80%) and discontinuation in 11/66 (17%). The first AE inducing TM occurred at 22 days (median) [2 -91]. Thrombocytopenia was the main AE leading to TM (70% of cases). 24% of AEs were grade 3-4. Remoted PRO-CTC-AEs were acknowledged by physicians in 59% of cases of whom 31% led to adaptation of pts' care. During the 3 months, 98% of pts reported symptomatic AEs (including nausea, constipation, fatigue, dry mouth and insomnia), of which 66% were grade 3. There was a very poor correlation (<0.20) between symptomatic AEs reported by the pts vs by the physicians (table). **Conclusions:** In real life, despite initial individual dosing, NI maintenance requires frequent TM during the first 3 months of treatment. There is a strong discrepancy between symptomatic AEs regularly captured by pts and those reported by physicians during clinics. Next generation of clinical trials should integrate pts' perspective to better assess toxicity and manage treatment course. Clinical trial information: NCT03752216. Research Sponsor: GSK.

Main symptomatic Aes	Patients (%)		Physicians (%)	
	All	Severe*	All	Severe**
Fatigue	93	32	43	2
Nausea	73	12	26	0
Constipation	86	40	26	2
Dry Mouth	78	22	9	0
Insomnia	90	22	12	0

*Grade 3 according to PRO-CTC-AE, ** Grade 3 and 4 according to CTC-AE.

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Poster Discussion Session

The Normal Risk Ovarian Screening Study (NROSS): Twenty-one year update. *First Author: Chae Young Han, The UT MD Anderson Cancer Center, Houston, TX*

Background: The Normal Risk Ovarian Screening Study (NROSS) tested a two-stage screening strategy in post-menopausal women at conventional hereditary risk where significantly rising CA125 prompted transvaginal sonography (TVS) and abnormal TVS prompted surgery to detect ovarian cancer. **Methods:** A total of 7,856 healthy postmenopausal women were screened annually for a total of 50,596 women-years in a single arm study (NCT00539162). Serum CA125 was analyzed with the Risk of Ovarian Cancer Algorithm (ROCA) each year. If risk was normal ($< 1:2000$), women returned in a year. If risk was elevated ($> 1:500$), TVS was undertaken immediately and if risk was intermediate, CA125 was repeated in 3 months, risk recalculated, and the participant re-triaged. An average of 2% of participants were referred to TVS annually. **Results:** Thirty-four patients were referred for operations detecting 15 ovarian cancers and 2 borderline tumors with 12 in early stage (I-II). In addition, 7 endometrial cancers were detected with 6 in early stage. Thus, the positive predictive value (PPV) of the NROSS trial was 50% (17/34) for detecting ovarian cancer and 74% (25/34) for any cancer, far exceeding the minimum acceptable study endpoint of 10% PPV. As 4 ovarian cancers and 2 borderline tumors were diagnosed within a year of each participant's last normal risk, the sensitivity for detecting ovarian and borderline cancer was 74% (17/23) and 70% of ROCA-detected cases (12/17) were in stage I-II. NROSS screening reduced incidence of late stage (III-IV) disease by 34% compared to the United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) control arm and by 30% compared to US SEER values. Results of our NROSS trial contrast dramatically with those of the recently reported UKCTOCS that showed only a modest 14% early-stage shift, underlying a lack of reduction in mortality. Across multiple randomized trials of mammography, those trials that demonstrated at least a 20% late-stage incidence reduction had a significant mortality reduction, whereas those with less of a stage shift did not. **Conclusions:** An elevated ROCA, characterized by a significantly rising CA125, prompted referral of 2% of participants to TVS each year and required only 2 operations to detect each case of ovarian cancer, indicating that CA125 used in this way is adequately specific for effective screening. While the NROSS trial was not powered to detect reduced mortality, the high specificity, PPV and marked stage shift support further development of this strategy. Clinical trial information: NCT00539162. Research Sponsor: U.S. National Institutes of Health; Cancer Prevention Research Institute of Texas; UT MD Anderson Moon shot; Concord (MA) Detect Ovarian Cancer Early Fund.

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Poster Session

Active bone marrow-sparing to reduce the incidence of grade 3+ acute hematologic toxicity in patients with locally advanced cervical cancer who receive chemoradiotherapy: A single-center prospective randomized controlled trial. *First Author: ShanBing Wang, Department of Oncology, the Second People's Hospital of Yibin City, Yibin, Sichuan, China*

Background: Acute hematologic toxicity is the most common side effect of chemoradiotherapy in patients with locally advanced cervical cancer. We aim to test the efficacy of single-photon emission computed tomography-defined active bone marrow-sparing volumetric-modulated arc therapy in reducing grade 3+ acute hematologic toxicity (HT) in locally advanced cervical cancer patients treated with chemoradiotherapy. **Methods:** This was a prospective, single-center, open label, randomized clinical trial that enrolled locally advanced cervical cancer patients. Participants were randomized to the ^{99m}Tc sulfur colloid SPECT-defined ABMS VMAT (ABMS group) or control group, who received weekly cisplatin concurrently with volumetric-modulated arc therapy followed by high-dose-rate intracavitary brachytherapy. The ABMS group additionally received SPECT-defined ABM dose constraints. The primary endpoint was the incidence of grade 3+ acute hematologic toxicity. Secondary objectives included acute gastrointestinal toxicity, planning Target Volume (PTV) coverage, dosimetric parameters of organs at risk (OARs), progression-free survival (PFS), overall survival (OS). **Results:** A total of 192 FIGO stage IB-IIIB patients were randomized treated (96 each in the ABMS control groups). The median follow-up was 24.0 months. The incidence of grade 3+ acute hematologic toxicity in the ABMS group was significantly lower than that in the control group (32.3% vs 53.1%, $p < 0.01$). The number of patients completing five cycles of cisplatin was 88.5% in the ABMS group and 75% in the control group, and the difference was significant ($p = 0.02$). There were no significant differences in the mean dose to 95%, 97% and 99% of the PTV between the ABMS group (45.1 Gy, 44.6 Gy, and 43.3 Gy, respectively) and the control group (45.4 Gy, 44.8 Gy, and 43.6 Gy). There were no differences in dosimetric parameters of OARs, acute gastrointestinal toxicity, 2-year PFS or 2-year OS between the two groups. Patients in the control group had nonsignificantly worse 2-year distant metastasis than patients in the ABMS group (17.8% vs. 11.1%, $p = 0.19$). **Conclusions:** ABMS VMAT significantly reduced grade 3+ acute HT and improved chemotherapy delivery compared with the control treatment. We found weak evidence of the effect of ABMS VMAT on distant metastasis. Clinical trial information: ChiCTR-IOR-16010214. Research Sponsor: This study was supported by the Sichuan Medical Association youth innovation project (NO. Q16082.NO.Q21022) and the health commission of Yibin City (NO.2019yw029).

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Poster Discussion Session

The effects of the Covid-19 pandemic on practice patterns and outcomes in patients diagnosed with gynecologic malignancies in the United States. *First Author: Adrian Kohut, City of Hope National Comprehensive Cancer Center, Duarte, CA*

Background: The Covid-19 pandemic caused historic disruptions in the United States healthcare system due to many factors, including a lack of medical equipment and pharmaceutical availability, over-capacitated hospital censuses, and limited essential workers. The short- and long-term effects on patients diagnosed with gynecologic malignancies during this time have yet to be delineated. **Methods:** The National Cancer Database (NCDB) was queried for patients diagnosed with ovarian, uterine, and cervical malignancies from 2019 (pre-covid) to 2020 (covid). Descriptive statistics of practice patterns and outcomes were performed and compared using IBM SPSS Statistics (version 29.0). **Results:** Within the NCDB, 10,261 patients were diagnosed with ovarian cancer in 2019 compared to 8,501 in 2020. A significantly higher proportion of ovarian cancer patients were diagnosed with stage IV disease at diagnosis in 2020 (32.7%) compared to 2019 (30.9%), $p = 0.007$. Patients were less likely to undergo primary debulking surgery during covid (37.7%) compared to pre-covid (40.5%), $p < 0.001$. There was no significant difference in time from diagnosis to initiation of treatment (median: 9 vs. 9 days), nor was there a difference in the proportion of patients undergoing cytoreductive surgery to no gross residual disease (54.3 vs. 54.3%). 42,828 patients were diagnosed with uterine cancer in 2019 compared to 37,431 in 2020. A significantly higher proportion of uterine cancer patients were diagnosed with stage IV disease at diagnosis in 2020 (8.7%) compared to 2019 (8.2%), $p = 0.016$. The median time from diagnosis to initiation of treatment was 28 days in 2020 compared to 30 days in 2019, $p < 0.001$. The proportion of uterine cancer patients receiving primary radiation was higher during covid (1.7% vs. 0.5%), $p < 0.001$. Additionally, the proportion of uterine cancer patients receiving primary hormonal management was also higher during covid (2.5% vs. 2.1%, $p < 0.001$). 9,289 patients were diagnosed with cervical cancer in 2019 compared to 7,661 in 2020. A significantly higher proportion of cervical cancer patients were diagnosed with stage IV disease at diagnosis in 2020 (16.6%) compared to 2019 (14.9%), $p = 0.0021$. The median time from diagnosis to initiation of treatment was 31 days in 2020 compared to 32 days in 2019, $p = 0.005$. **Conclusions:** We identified significant variations in practice patterns and outcomes in patients diagnosed with gynecologic malignancies in the United States in 2020 (covid) compared to immediately before covid (2019). Notably, we found a significantly higher proportion of patients presenting with advanced disease stages in all queried ovarian, uterine, and cervical cancer patients. Long-term follow-up and survival outcomes are currently pending. Research Sponsor: None.

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Poster Session

Neoplastic and blood-based biomarkers of response in patients with advanced endometrial cancer: Results from NRG GY012. *First Author: Helen Mackay, Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto, ON, Canada*

Background: NRG GY012 is a randomized, 3-arm phase II study, comparing olaparib (O) and the combination of cediranib and olaparib (CO) to the reference arm cediranib (C) for metastatic pre-treated, endometrial cancer (EC). The trial found a trend towards benefit for CO and no benefit for O compared to C. Archival tumor and prospective blood samples were collected for biomarker analysis. **Methods:** Targeted next-generation sequencing (BROCA-GO) was used to detect pathogenic variants (PV) and loss of heterozygosity (LOH) in DNA from paired blood and archival cancers. The LOH cut-off was identified at 11% for HRD based on testing ovarian cancers with known HRD. Plasma samples collected at baseline, cycle 2 day 1, and end-of-treatment were analyzed via multiplex ELISA for 25 angiogenic and inflammatory circulating protein biomarkers (Angiome); IL6 was of specific interest. Prognostic associations with PFS and OS were analyzed using proportional hazards models (PhM) stratified by histology and adjusted for treatment assignment. Predictive associations (PFS and OS) were analyzed using PhM stratified by histology and including main effects for both treatment assignment and biomarker group plus an interaction term. **Results:** In 97 patients (pts) with evaluable tumor, BROCA-GO identified 370 somatic PV; TP53 (61%) was the most commonly mutated gene. PV in homologous recombination repair (HRR) genes were identified in 5 cases (5%). Somatic PVs were identified in BRCA2, RAD51B and PALB2. 1 pt had a germline BRCA1 PV. 2 cases had somatic PV that might restore HRR: 1 case with a somatic BRCA2 PV had somatic PVs in CHD4 and TP53BP1; the TP53BP1 frameshift PV was present only in the recurrent and not primary cancer. LOH was available for 45 cases. LOH high occurred in 16 (35.6%) cases and was exclusive to EC with TP53 mutations ($p = 0.0003$). LOH was not associated with outcome in any of the arms. For the circulating biomarker analysis (N=96), median IL-6 was 4pg/ml. IL-6 levels $> 4\text{pg/ml}$ were associated with increased risk of progression (HR: 1.59; 95% CI: (1.04-2.42); $p\text{-value} = 0.032$). In predictive analyses, pts with IL-6 $> 4\text{pg/ml}$ receiving C or C+O had increased PFS (3.8 mo vs 1.9 mo) and OS (11.9 mo vs 5.7 mo) compared to pts receiving O, the interaction p value did not reach statistical significance. **Conclusions:** LOH high status was not associated with outcome to O. There were too few cases with HRR PVs to determine their relationship to PARPi response. The restriction of LOH high to cancers with TP53 mutation may suggest that genomic LOH in ECs correlates better with aneuploidy than with HRR function indicating that at least some biomarkers of PARPi response vary between tumor types. IL-6 levels were prognostic of PFS but were not predictive of either OS or PFS for pts receiving C compared to pts receiving O in this small study. Further analysis of the complete Angiome and integration with the BROCA-GO dataset are ongoing. Clinical trial information: NCT03660826. Research Sponsor: U.S. National Institutes of Health.

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Poster Session

Molecular tumor profiling and therapy selection in advanced gynecological cancers: A retrospective cohort analysis from the Australian Molecular Screening and Therapeutics (MoST) Program. *First Author: Damien Kee, Austin Health and Peter MacCallum Cancer Centre, Melbourne, Australia*

Background: Gynecological (gyne) cancers are highly diverse with distinct sites of origin and histological subtypes that can limit development of evidence-based therapies. Comprehensive genomic profiling (CGP) has an increasing role in characterizing clinically relevant molecular subsets and in identifying actionable biomarkers with potential to guide therapy selection. **Methods:** MoST (ACTRN12616000908437) is an Australia-wide precision oncology program for adult patients (pts) with advanced cancers and limited treatment options. Tumor specimens are analysed by CGP and genomic results tiered by the level of evidence supporting matched therapies (https://topograph.info). Pts are followed for subsequent treatment and survival. Here, we present data for the MoST gyne cancer cohort. **Results:** Between Sept 2016 and Oct 2022, 533 gyne tumors were sequenced, with included pts having a minimum 4 months (mo) follow-up. Key histotypes included: ovarian serous (n=162) and non-serous (n=46) epithelial tumors; uterine carcinomas (n=99) and sarcomas (n=108); cervical carcinomas (n=51); germ cell and sex-cord stromal tumors (n=18); carcinosarcomas (n=33); and vulva/vaginal tumors (n=16). The median number of reported variants was 3 (IQR 2-5) and tumor mutational burden 3.1 mut/Mb (IQR 1.3–5.5, Range 0–284); 9 (2%) tumors were microsatellite unstable; and 22 (4%) had high level loss-of-heterozygosity (confirmed on validated genome-wide assays). The most common pathways involved in this pan-gyne cohort were: p53 (n=287, 54%), PI3K/AKT (n=227, 43%), cell cycle (n=182, 34%), and mitogen-activated protein kinase (n=91, 17%). Pathogenic mutations in *BRCA1/2* were identified in 29 tumors (5%; 18 in ovarian serous cancers), whereas 81 tumors (15%) had alterations in other homologous recombination genes, most commonly uterine sarcomas (n=32, 30%). Actionable genomic biomarkers matched to a clinically active treatment (TOPOGRAPH tier 1-3) were identified in 207 (39%) tumors. In 19 pts (3.5%) who received Tier 1-3 matched therapy after CGP, a trend towards longer survival was observed (median OS 22.3 mo, 95% CI 17.3 to not reached) compared to those receiving unmatched therapy (n=65, median OS 14.9 mo, 10.2 to 22.1, p=0.052) following CGP. No OS difference was seen in pts who received matched investigational therapy (Tier 3B/4, n=31, median OS 17.0 mo, 8.1 to NR) versus only unmatched therapy (n=118, median OS 14.0 mo, 11.3 to 22.5; HR 0.97, 0.57 to 1.64; p=0.91). **Conclusions:** CGP identified actionable genomic results in nearly half of advanced gyne cancers, with enrichment in particular histotypes that supports testing above current standard of care. Trends in prolonged OS with subsequent matched therapies may be better realized with earlier testing and improved drug/clinical trial access. Research Sponsor: Australian Government.

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Poster Discussion Session

Advanced cervical cancer therapy: Comparison of contemporary expert and healthcare professional recommendations from an online treatment decision tool. *First Author: Lauren S. Prescott, Vanderbilt University Medical Center, Nashville, TN*

Background: Practice patterns for the management of advanced cervical cancer are rapidly evolving given the emergence of novel treatment options. We developed an online Interactive Decision Support Tool (IDST) for advanced cervical cancer to provide expert guidance to healthcare professionals (HCPs). **Methods:** With input from 5 experts, an IDST was developed for patient scenarios with newly diagnosed (ND) and recurrent/second-line (2L) advanced cervical cancer. The IDST included expert insights on 352 scenarios based on criteria such as adenopathy, disseminated disease status, previous therapy, and actionable biomarkers (PD-L1, MMR/MSI, TMB). Users were asked to enter specific patient criteria and their intended management approach. The IDST then showed the 5 expert recommendations for that specific scenario and HCPs were asked to indicate whether the recommendations changed their intended treatment plan. Expert recommendations vs user-selected therapy for different scenarios were analyzed. We present self-reported practice patterns in this disease setting and the impact of expert recommendations on treatment choice. **Results:** At this interim analysis, 141 unique learners used the IDST, entering 232 unique patient scenarios. Data from the IDST also showed areas of consensus and controversy in treating patients with advanced cervical cancer. For locally advanced, ND, no adenopathy and no metastases, all experts recommended pelvic chemoradiation with or without brachytherapy vs only 61% of HCPs; 16% and 3% of those entering cases for the locally advanced ND setting indicated expert recommendation changed their treatment choice and that barriers impeded the recommendations, respectively. For advanced ND, with adenopathy, metastatic, PD-L1–positive cervical cancers, all experts vs 50% of HCPs chose an immunotherapy-containing platinum-based chemotherapy regimen with/without bevacizumab; 9% of those indicated barriers to implementing expert recommendations. In 2L recurrent disease, all experts chose either single-agent immunotherapy (if PD-L1 positive) or tisotumab vedotin (if PD-L1 negative) vs 45% and 40% of HCPs, respectively; 19% of those selecting 2L therapy in the recurrent setting said the expert recommendations had changed their intended choice. **Conclusions:** Analysis from this IDST indicates differences in practice patterns between experts and HCPs for various case scenarios of advanced cervical cancer. Online decision support tools may increase the number of HCPs making optimal treatment decisions for advanced cervical cancer, particularly when new data, indications, and guideline updates must be considered. Updated and detailed analyses from the IDST will be presented. Research Sponsor: Clinical Care Options.

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Poster Session

Association of HRD ovarian cancer by RAD51 with hot immune microenvironment: Translational analyses of MITO 16A/MaNGO-OV2 trial. *First Author: Benedetta Pellegrino, University of Parma, Parma, Italy*

Background: Homologous recombination repair (HRR)-deficient Ovarian Cancer (OvC) is sensitive to PARP inhibitors and platinum salts. Genomic HRR-deficiency (HRD) tests (i.e. Myriad MyChoice) are currently used to guide treatment selection in the maintenance setting. However, they are showing a limited predictive value, they are expensive and static, i.e. unable to capture the restoration of the HRR functionality, as a mechanism of drug resistance. **Methods:** We performed the functional and dynamic RAD51 test on 164 patients with high-grade serious OvC, enrolled in the MITO16A/MANGO OV2 trial and treated with first-line therapy containing carboplatin, paclitaxel, and bevacizumab. The RAD51 assay included the immunofluorescence of gH2AX (as a marker of Double Strand Breaks DNA damage), BRCA1 and RAD51 nuclear foci. Stromal Tumor Infiltrating Lymphocytes (TIL) by Immunohistochemistry, and gene expression profile were performed on the same samples. **Results:** RAD51 assay was informative on 70% (115/164) of the samples. On evaluable samples, median gH2AX score was 57%. BRCA1 foci by immunofluorescence were detected on 55% (49/112) of the samples; 45% (63/112) of the tumors did not show BRCA1 foci likely due to germline or somatic BRCA1 mutations, or BRCA1 promoter hypermethylation. RAD51 identified 69% (79/115) of all tumors as HRD, with a median RAD51 score of 8.8%. HRD tumors presented a statistically significantly higher TIL content than HRR-proficient ones (p = 0.03). **Conclusions:** Our preliminary results confirmed the feasibility of the RAD51 functional assay on primary untreated OvC. The association between HRD by RAD51 and TIL content encouraged to investigate the efficacy, in clinical trials, of the combination of PARPi and immune-checkpoint inhibitors on selected patients (i.e. HRD by RAD51 and TIL high). Gene expression profile and comparison of the HRD status by RAD51 and genomic HRD (both Myriad MyChoice and academic) and correlations with clinical outcomes will be available for the meeting. Research Sponsor: Associazione Italiano Ricerca sul Cancro (AIRC).

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Poster Session

SHR-1701 in combination with platinum-based chemotherapy and BP102 (a bevacizumab biosimilar) for persistent, recurrent, or metastatic cervical cancer: Data from a phase 1b/3 study. *First Author: Jihong Liu, Department of Gynecologic Oncology, Sun Yat-sen University Cancer Center, Guangzhou, China*

Background: Platinum-based chemotherapy (chemo) ± bevacizumab is the standard first-line therapy for cervical cancer, regardless of PD-L1 expression. SHR-1701 is a novel bifunctional fusion protein targeting PD-L1 and TGF-βRII, and shows promising efficacy and controllable safety in pretreated patients (pts) with cervical cancer. This ongoing phase 1b/3 study aims to assess the addition of SHR-1701 to standard first-line therapy. **Methods:** In the phase 1b part, eligible pts had persistent, recurrent, or metastatic squamous-cell carcinoma, adenocarcinoma, or adenosquamous cell carcinoma of the cervix not previously treated with systemic chemo for recurrence or metastasis and not amenable to curative treatment. Prior chemoradiotherapy was permitted for recurrence, if mono-chemo was used as sensitizer. Pts were given SHR-1701 (30 mg/kg), paclitaxel (175 mg/m²), cisplatin (50 mg/m²) / carboplatin (AUC 5), and BP102 (15 mg/kg) every 3 weeks. The primary endpoints were safety and ORR. **Results:** From Feb 26 to Aug 12, 2022, 31 pts were enrolled. Median age was 55 years (range, 27-71). 24 (77.4%) had squamous-cell carcinoma, and 7 (22.6%) had adenocarcinoma. 20 (64.5%) had metastatic disease, 7 (22.6%) had recurrent cervical cancer, and 4 (12.9%) had persistent cervical cancer. Grade ≥3 treatment-related adverse events (TRAEs) were reported in 25 (80.6%) pts, with the most common being decreased neutrophil count (n=16, 51.6%), decreased white blood cell count (n=12, 38.7%), and anemia (n=8, 25.8%). TRAEs led to discontinuation of any study agent in 8 (25.8%) pts; of note, only 2 (6.5%) pts discontinued SHR-1701 due to TRAEs (grade 3 infusion reaction and grade 3 immune-mediated rash). No treatment-related deaths occurred. Efficacy outcomes are summarized in Table. ORR was 77.4%, with 4 CRs and 20 PRs; responses were ongoing in all 24 responders. DCR was 93.5%. Shrinkage in target lesions was observed in 30 (96.8%) pts. PFS rate at 6 months reached 93.5%. **Conclusions:** SHR-1701 plus platinum-based doublet chemo and BP102 provided a manageable safety profile and potent antitumor activity in pts with persistent, recurrent, or metastatic cervical cancer, supporting the subsequent randomized, double-blind, placebo-controlled phase 3 part. Clinical trial information: NCT05179239. Research Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

Efficacy outcomes.	
	All pts (n=31)
Best overall response, n (%)	
CR	4 (12.9%)
PR	20 (64.5%)
SD	5 (15.1%)
PD	2 (6.5%)
ORR, % (95% CI)	77.4% (58.9-90.4)
DCR, % (95% CI)	93.5% (78.6-99.2)
6-month PFS rate, % (95% CI)	93.5% (76.6-98.3)

CR, Complete response; PR, partial response; SD, stable disease; PD; progressive disease; ORR, objective response rate; DCR, disease control rate; PFS, progression-free survival; pts, patients.

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Poster Session

Efficacy and safety of combining PD-1 blockage and human papillomavirus vaccine for patients with relapsed/refractory advanced cervical cancer. *First Author: Bu hai Wang, Cancer Institute of Northern Jiangsu People's Hospital, Yangzhou, China*

Background: The prognosis for patients with relapsed/refractory advanced cervical cancer is dismal with a 5-year survival rate of 17%. Limited treatment options were available including platin based therapy, antiangiogenic therapy and immune therapy. Immune checkpoint blockage with anti-programmed cell death 1 (PD-1) antibodies had an overall response rate of 17% among a minority of patients. Recently a phase II study showed human papillomavirus (HPV) 16 vaccination amplified PD-1 antibodies in incurable HPV16 positive cancer with an ORR of 33%. But the study enrolled majority were oropharyngeal cancer patients (92%). Here, we designed and conducted phase II clinical trial to assess the efficacy and safety of combining anti-PD-1 antibody and HPV vaccination for patients with relapsed/refract cervical cancer. **Methods:** In this single-arm, single-center phase II clinical trial, patients with relapsed/refract cervical cancer were registered (NCT04096911) and enrolled from Dec, 2019 to Dec, 2022 in Department of Oncology, Northern Jiangsu People's Hospital, Yangzhou, China. All patients received prior radiation therapy and had at least one or more lines of therapies. Duration of follow up for censored patients was 36 months. The recombinant human papillomavirus quadrivalent vaccine (0.5ml) was given subcutaneously on day 0, third month, and 6th month. Anti-PD-1 antibody, 200mg was given intravenously every 3 weeks starting on day 1 for up to 2 years. **Results:** As of Dec 21, 2022, thirteen patients were enrolled in the trial. The median age was 55 years (range, 52 to 83 years). The overall response rate was 69.2%. Disease control rate was 84.9%. Median duration of response was 7.07 months (95%CI, 1.94 to 15.8 month). Six patients achieved complete response. Median overall survival was 13.96 month. No grade 3 and 4 toxicity occurred. **Conclusions:** Our study was the first clinical trial using HPV vaccine as therapeutic agent in advance cervical cancer treatment. Up to date, immunotherapy along in cervical cancer had limited response rate less than 20% and the combination therapies was less than 40%. In our study, the overall response of 69.2%, disease control rate of 84.9% and median overall survival of 13.96 months were significantly higher compared with anti-PD-1 antibody alone or any current available regimen combinations in relapsed/refract advance cervical cancer patients. We also found synergistic effect of T cell and B cell plays an important role in our study. It appears neoantigen associated with tumor was easier to initiate immune response in cervical cancer patients. This is the first time to show employing combined immune therapeutic agents only is a novel effective clinical strategy in relapsed/refract advance cervical cancer. Clinical trial information: NCT04096911. Research Sponsor: None.

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Poster Session

A confirmatory trial of modified radical hysterectomy for patients with FIGO stage IB1 cervical cancer with tumor diameter preoperatively estimated at 2 cm or less: Japan Clinical Oncology Group study, JCOG1101. *First Author: Takahide Arimoto, Toranomon Hospital, Tokyo, Japan*

Background: The standard surgery for Stage IB1 uterine cervical cancer is radical hysterectomy (RH, Piver class III hysterectomy). However, RH is highly invasive, and there is a need to establish less invasive techniques. We conducted a single-arm confirmatory trial (JCOG1101) to evaluate the efficacy and safety of modified radical hysterectomy (MRH) in patients with tumor diameter $\leq$ 2 cm Stage IB1 cervical cancer (jRCT: jRCTs031180167). **Methods:** From January 2013 to August 2017, 240 patients were enrolled from 40 institutions in Japan. Eligibility criteria included: (1) FIGO 2008 Stage IB1 cervical cancer; (2) histologically proven squamous cell carcinoma, adenocarcinoma (mucinous or endometrioid) or adenosquamous carcinoma; (3) tumor diameter $\leq$ 2 cm (measured by MRI or conization specimen); and (4) neither distant LN metastasis nor distant metastasis in CT. In case that the cancer could be microinvasive, conization was required to exclude Stage IA cases. The protocol surgery involved cutting the anterior layer of the vesicouterine ligament of the uterus and dissecting regional lymph nodes. Only laparotomy was permitted; laparoscopy and robotic surgery were not allowed. Postoperative irradiation was administered in cases where pelvic LN or parametrial invasion was positive, depth in the cervical wall invasion was $\geq$ 2/3, or surgical margin was $<$ 1 cm by pathological findings. The primary endpoint was 5-year overall survival (OS). We set the expected 5-year OS of MRH at 95.8% (5-year OS of RH in JCOG0806A, retrospective observational study) and the threshold 5-year OS at 90.8%. **Results:** Among 225 eligible patients, 193 (85.8%) were pT1b1 (UICC 7th), and 184 (81.8%) had pathological maximal tumor diameter $\leq$ 2 cm. Parametrial involvement, lymph node metastasis, $\geq$ 2/3 stromal invasion and $<$ 1 cm surgical margin were observed in 3 (1.3%), 16 (7.1%), 30 (13.3%) and 11 (4.9%) patients, respectively. Thirty-nine patients (17.3%) underwent adjuvant (chemo)radiation. Median follow-up was 77.7 months. Five patients (2.2%) died, and 5-year OS was 98.2% (90% CI: 96.0-99.2, $>$ 90.8%). Thirteen patients (5.8%) relapsed (8 local recurrence and 5 distant recurrence), and 5-year relapse-free survival was 94.7% (95% CI: 90.8-96.9%). Self-urination was observed in all patients, and residual urine disappearance up to 56 days after urethral catheter removal was observed in 213 patients (94.7%). Median time to disappearance of residual urine after urethral catheter removal was 1 day. There was no treatment-related death. Grade 3/4 non-hematological adverse events were observed in 17 patients (7.6%), including 8 infection and 4 hemorrhage. **Conclusions:** In this study, MRH was as effective as RH and less invasive. MRH can be considered a standard surgery for tumor diameter $\leq$ 2 cm Stage IB1 uterine cervical cancer. Clinical trial information: UMIN000009726, jRCTs031180167. Research Sponsor: Labour and Welfare of Japan, Japan Agency for Medical Research and Development (AMED); The National Cancer Center of Japan Research and Development Funds.

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Poster Session

The efficacy and safety of tislelizumab plus bevacizumab and chemotherapy as first line therapy in patients with persistent, recurrent, or metastatic cervical cancer: A multicenter, phase II study. *First Author: Jianqing Zhu, Cancer Hospital of the University of Chinese Academy of Sciences (Zhejiang Cancer Hospital), Hangzhou, China*

Background: Patients (pts) with persistent, recurrent, or metastatic cervical cancer are at high risk of progression after first line standard treatment with platinum-doublet chemotherapy $\pm$ bevacizumab. The addition of programmed death-1 (PD-1) inhibitor to this standard treatment has shown improved survival profiles in pts with PD-L1 positive. This study aims to investigate the efficacy and safety of PD-1 inhibitor (tislelizumab) plus bevacizumab and platinum-doublet chemotherapy as the first line therapy in pts regardless of the PD-L1 expression status. **Methods:** Pts with persistent, recurrent, or metastatic cervical cancer were enrolled and received tislelizumab 200 mg + bevacizumab 7.5 mg/kg + cisplatin 50 mg/m² or carboplatin AUC5 + paclitaxel 175 mg/m² IV D1 Q3W. This study comprised two parts: safety run-in (Part 1) and cohort expansion (Part 2). In Part 1, a total of 6 pts were enrolled and underwent safety assessment during the first treatment cycle (21 days). If no more than 2 of 6 pts were observed with dose-limiting toxicity (DLT), pts will be allowed to continue treatment and additional 43 pts will be enrolled (Part 2). The primary endpoint was progression-free survival. A one-sample log-rank test with a total sample size of 49 pts with one sided alpha of 5%, achieved 85% power to detect a difference in PFS between the investigated treatment and historical control. The secondary endpoints were objective response rate (ORR), disease control rate (DCR), duration of response (DOR) and safety and tolerability. **Results:** We report the preliminary results of this study. No DLT was observed among the first 6 pts in Part 1 stage and the study proceeded to the Part 2. Until Oct 28, 2022, a total of 24 pts were enrolled with the median age of 56.0 years. 6 (25.0%) pts were diagnosed with stage IV disease at the study entry and 21 (87.5%) were with squamous cell carcinoma. At the data cutoff time of Nov 30, 2022, among the 19 efficacy evaluable pts, the unconfirmed ORR was 73.7% (14/19, 95% CI: 48.8%-90.8%), and the DCR was 100% (19/19, 95% CI: 82.3%-100.0%). With the median follow up time of 3.8 months, DOR was not reached. The incidence of treatment related adverse events (TRAEs) of any grade was 79.2% (19/24), and grade $\geq$ 3 TRAEs occurred in 45.8% (11/24) pts. Most common TRAEs ($\geq$ 20%) of any grade were anemia (58.3%, 14/24), decreased platelet count (37.5%, 9/24), alopecia (29.2%, 7/24), decreased white blood cell count (25.0%, 6/24), and weight decreased (20.8%, 5/24). Immune related adverse events were all grade 1-2 (16.7%, 4/24). Severe adverse events were reported in 4 (16.7%) pts. **Conclusions:** Tislelizumab plus bevacizumab and chemotherapy showed preliminary promising efficacy and was well-tolerated as the first line therapy in pts with persistent, recurrent, or metastatic cervical cancer. Clinical trial information: NCT05247619. Research Sponsor: BeiGene (Beijing) Co., Ltd.

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Poster Session

Patient-reported outcomes during pelvic radiation therapy: A secondary analysis on sexual function from NRG-RT0G 1203. *First Author: Kelsey L Corrigan, Department of Radiation Oncology, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: NRG-RT0G 1203 reported that intensity-modulated radiation therapy (IMRT) reduced patient-reported GI and GU toxicities in cervical/endometrial cancer patients receiving adjuvant RT, as compared to standard whole field pelvic RT (WPRT). We conducted a secondary analysis of patient-reported sexual function (PR-SF) to compare this endpoint among treatment groups and identify factors associated with sexual dysfunction. **Methods:** Patients on NRG-RT0G 1203 were randomly assigned to WPRT vs. IMRT and completed the PRO-CTCAE for GI toxicity and the cervical cancer FACT-Cx at baseline, week 5 of RT, and at 4-6 weeks, 1-year, and 3-years post-RT. Patient responses to FACT-Cx sexual function questions were analyzed. The between arm frequency and severity of responses were tested using chi-square. PR-SF was compared with PRO-CTCAE GI toxicity using chi-square. A repeated measures logistic regression model was used to determine the impact of clinical/treatment factors on sexual function by dichotomizing the responses. **Results:** Of the 279 patients included for primary analysis, 236 (85%) completed PR-SF questions; 125 (53%) in the WPRT arm and 111 (47%) IMRT. There were no significant differences in PR-SF between treatment groups ($p > 0.05$). PR-SF improved for both groups post-RT, except responses to "my vagina feels too narrow or short" worsened (Table). Women without abdominal pain interference at 4-6 weeks post-RT were less likely to fear sex (74.2% vs. 25.8%, $P = 0.03$) and more likely to like their body appearance at 1 year (95.7% vs. 4.3%, $P < 0.01$) compared to women with interference. Women liked the appearance of their body less during RT vs. at baseline (OR 1.95, 95% CI 1.04-3.64, $P = 0.04$). Women were less interested in sex during RT in both arms (WPRT: OR 3.61, 95% CI 1.40-9.34; IMRT: OR 3.96, 95% CI 1.02-15.34) and at 4-6 weeks post-RT for IMRT (OR 3.16, 95% CI 1.14-8.72) vs. at baseline. **Conclusions:** PR-SF was similar between treatment groups. PR-SF during and post-RT was not significantly reduced compared to baseline with the exception of patients with abdominal pain interference, who had significantly worse PR-SF at 4-6 weeks and 1-year post-RT. Clinical trial information: NCT01672892. Research Sponsor: U.S. National Institutes of Health.

Longitudinal change in the percent of women reporting "very much" or "quite a bit"

	Baseline	During RT	4-6 Weeks Post-RT	1-Year Post-RT	3-Years Post-RT
"I am bothered by discharge/bleeding from my vagina"	(n=201) 3.1%	(n=203) 1.5%	(n=201) 0.5%	(n=179) 1.1%	(n=49) 0%
"I am afraid to have sex"	(n=192) 14.9%	(n=184) 19%	(n=192) 12.5%	(n=174) 12.6%	(n=48) 6.3%
"My vagina feels too narrow/short"	(n=190) 6%	(n=183) 8.2%	(n=190) 8.9%	(n=171) 11.1%	(n=47) 10.6%
"I feel sexually attractive"	(n=190) 25.2%	(n=189) 21.7%	(n=190) 18.9%	(n=173) 24.9%	(n=47) 23.4%
"I am interested in sex"	(n=192) 24.3%	(n=192) 14.1%	(n=192) 20.8%	(n=172) 22.1%	(n=47) 19.1%
"I like the appearance of my body"	(n=198) 29.9%	(n=197) 22.8%	(n=198) 26.8%	(n=178) 27.0%	(n=48) 29.2%

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Poster Session

A peptide-based human papillomavirus therapeutic vaccine, PepCan, or *Candida* adjuvant alone in treatment of cervical intraepithelial neoplasia 2/3 (CIN2/3). First Author: Mayumi Nakagawa, University of Arkansas for Medical Sciences, Little Rock, AR

Background: A non-surgical alternative for treating CIN2/3 would be desirable for women of childbearing age due to a risk of cervical incompetency in subsequent pregnancies following surgical treatments. PepCan consists of four current good manufacturing-grade HPV 16 E6 peptides and a *Candida* skin testing reagent (Candin, Nielsen Biosciences), because of *Candida*'s ability to regress common warts in humans, and to promote T cell proliferation and interleukin-12 secretion *in vitro*. **Methods:** In this single-center, randomized, double-blind Phase II study (NCT02481414), women with biopsy-confirmed CIN2/3 were treated with PepCan or *Candida* (1:1). Four intradermal injections were given 3 weeks apart which were followed with two visits 6 months apart. Histological responses (primary endpoint) were assessed using quadrant biopsies, and those whose lesions regressed to no CIN were considered to be responders. Regression rate of each treatment group was compared to that of a historical placebo group following the same treatment schedule. A sample size of 35 per arm had 93% power to test the null hypothesis that $\pi = 0.29$ (historical control placebo rate) and detect a difference of 0.31 with a two-sided type I error of 5%. Adverse events (AEs) were assessed using Common Terminology Criteria for Adverse Events Version 4. **Results:** Of 99 subjects screened, 81 (81.8%) qualified for vaccination, and 80 received at least one vaccination. No dose-limiting toxicity was observed. With the intention-to-treat analysis, PepCan showed 30.8% efficacy (12 of 39, $p=0.16$) while *Candida* demonstrated 47.6% efficacy (20 of 42, $p=0.0004$). Likewise, with the per-protocol analysis, PepCan showed 45.8% efficacy (11 of 24, $p=0.06$) and *Candida* showed 62.1% efficacy (18 of 29, $p=0.0002$). There was no difference between efficacy of PepCan and *Candida*. **Conclusions:** PepCan and *Candida* treatments are safe. Only *Candida* was effective in inducing histological regression in the intention-to-treat and per-protocol analyses. *Candida* could become a new treatment for CIN2/3 by eliciting general immune stimulation similar to checkpoint inhibitors. Clinical trial information: NCT02481414. Research Sponsor: U.S. National Institutes of Health; University.

Comparisons of histological responses between each treatment and a historical placebo group.

	PepCan	<i>Candida</i>	Historical Placebo*
Intention-to-treat			
No. patients	12/39	20/42	34/149
Percentage of patients	30.8	47.6	22.8
90% CI (19.3, 45.0)		90% CI (34.2, 61.3)	
P value--	0.16	0.0004	
Per-protocol			
No. patients	11/24	18/29	34/117
Percentage of patients	45.8	62.1	29.1
90% CI (28.2, 64.2)		90% CI (54.4, 88.1)	
P value--	0.06	0.0002	

*Myers et al., J Natl Cancer Inst, 1994; ~binomial test.

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Poster Session

Surgical resection based on ontogenetic cancer field theory for cervical cancer: 10-year updated results of the MMR study. First Author: Laura Weydandt, University of Leipzig Medical Center, Department of Gynecology, Leipzig, Germany

Background: Previously published findings from our center suggest that carcinoma of the cervix propagates within ontogenetic cancer fields, tissue compartments defined by staged morphogenesis. In the MMR study we aimed to determine whether surgical treatment that accounts for stage-associated, ontogenetic cancer fields and their associated lymphoid tissues results in locoregional tumor control without the need for adjuvant radiotherapy. **Methods:** The Leipzig School Mesometrial Resection Study (MMR study) is an ongoing, prospective, single-center, observational cohort study including patients with primary cervical cancer. All study participants undergo either total or extended mesometrial resection (TMMR or EMMR) and therapeutic lymph node dissection. Because this treatment strategy enables surgical removal of all locoregional at-risk tissues, no adjuvant radiotherapy is necessary, even in the presence of established risk factors. The trial is registered at the German Clinical Trials Register, number DRKS00015171. For this updated analysis, we identified patients in our institutional study database with primary cervical cancer staged IB1 – IIA2 according to the 2009 International Federation of Gynecology and Obstetrics staging system. Using the Kaplan-Meier estimator, we calculated recurrence free and overall survival. **Results:** Between October 16, 1999, and December 16, 2020, 420 patients were treated per protocol and followed up for a median of 136 months (IQR 77–190). The median age was 42 years (IQR 36–51). 329 patients (78.3%) had stage IB1, 58 (13.8%) stage IB2, 24 (5.7%) stage IIA1 and 9 (2.1%) stage IIA2 disease. Patients had either squamous cell ($n = 297$, 70.7%), adenocarcinoma ($n = 104$, 24.8%), adenosquamous ($n = 18$, 4.3%) or other ($n = 1$, 0.24%) histology. The nodal status was pN0 in 349 (83.1%) patients and pN1 in 71 (16.9%) of the cases. Clinically occult parametrial involvement was present in 47 (11.2%) patients. 10-year overall survival was 90.2% (95% confidence interval [CI] 87.1–93.4) and recurrence-free survival was 90.6% (95% CI 87.8–93.6). Stratified for lymph node status 10-year overall survival was 91.7% (95% confidence interval [CI] 88.5–95) for pN0 and 83.2% (95% confidence interval [CI] 74.6–92.9) for pN1. Recurrence-free survival was 93.8% (95% CI 91.2–96.5) for pN0 and 75.4% (95% CI 65.9–86.3) for pN1. **Conclusions:** Despite dispense of adjuvant radiotherapy, patients treated with total or extended mesometrial resection with therapeutic lymph node dissection have excellent survival outcomes. Additional multicenter studies are needed to further investigate and confirm our results. Clinical trial information: DRKS00015171. Research Sponsor: None.

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Poster Session

Association between serum folate and vitamin B12 and cervical high-risk human papillomavirus (HPV) infection. First Author: Josephine Peitz, University of Maryland School of Medicine, Baltimore, MD

Background: Serum concentration of folate (vitamin B9) and vitamin B12 were inversely associated with cervical intraepithelial neoplasia and cervical cancer in some studies. The association between folate and vitamin B12, and human papillomavirus (HPV) infection has not been well elucidated. We evaluated whether low serum level of folate and vitamin B12 was associated with high-risk HPV (hrHPV) infection. **Methods:** The study population was 6,452 women, aged 18–59 years old, enrolled in the National Health and Nutrition Examination Survey (NHANES), from 2003 to 2016, in the United States. In this cross-sectional study, odds ratios (ORs) of hrHPV were calculated, by quintiles of low folate and vitamin B12 combined, using logistic regression models. **Results:** The mean age (standard deviation) of the women was 36.98 (12.19) years. Women in the lowest quintile had less than 20.6 nmol/L of folate and less than 248 pmol/L of vitamin B12. Some of the women, 23% (1,509/6,452), were hrHPV positive. In age-adjusted models, low folate and vitamin B12 was significantly associated with hrHPV infection. The ORs and 95% confidence intervals (CI) was (OR: 0.704, 95% CI: 0.509 - 0.975, $p = 0.034$) for the second, (OR: 0.671, 95% CI: 0.479 - 0.940, $p = 0.020$) third, (OR: 0.534, 95% CI: 0.370 - 0.770, $p = 0.0008$) fourth and (OR: 0.476, 95% CI: 0.33 - 0.679, $p < 0.0001$) fifth quintiles, compared to women in the lowest quintile. The association remained statistically significant after the models were further adjusted for smoking status and income level; women in the highest quintile were less likely to have hrHPV infection compared to those in the lowest quintile (OR: 0.541, 95% CI: 0.343 - 0.855, $p = 0.008$). **Conclusions:** This study supports an association between low serum levels of folate and vitamin B12, and hrHPV infection, among women in the United States. Research Sponsor: American Cancer Society Research Scholar Grant RSG-22-079-01-CSCT.

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Poster Session

Efficacy and safety of camrelizumab in combination with radiation and chemotherapy for recurrent or metastatic cervical cancer. First Author: Zhongjie Chen, Tianjin Medical University Cancer Hospital & Institute, Tianjin, China

Background: Cisplatin-based concurrent chemoradiation regimens have been suggested to be beneficial in recurrent or metastatic cervical cancer. Immunotherapy has also shown good therapeutic efficacy in recurrent or metastatic cervical cancer. Among them, Pembrolizumab in combination with chemotherapy has been used for first-line treatment of advanced PD-L1-positive cervical cancer. Meanwhile, Camrelizumab has shown good anti-tumor activity and manageable toxicity in patients with locally advanced cervical cancer. The primary objective of this study is to evaluate the efficacy and safety of Camrelizumab in combination with concurrent chemoradiation in patients with recurrent or metastatic cervical cancer. **Methods:** Patients diagnosed with recurrent or metastatic cervical cancer received Camrelizumab combined with concurrent chemoradiotherapy, radiotherapy: External beam radiotherapy (EBRT) 1.8–2.15 Gy/f, a total of 28 fractions; Brachytherapy: high-risk CTV using image guidance 28 Gy in 4 fractions (18 Gy in 3 fractions for posthysterectomy recurrent patients); chemotherapy regimen used TP regimen (paclitaxel: 175 mg/m², cisplatin: 75 mg/m², Q3W 6 cycles); Camrelizumab 200 mg Q3W 6 cycles. The primary endpoint of this trial was objective response rate (ORR), and secondary endpoints were progression-free survival (PFS), overall survival (OS), disease control rate (DCR), and incidence of adverse reactions. **Results:** From September 16, 2020 to September 30, 2022, a total of 29 patients were recruited. 27 of these patients completed 6 cycles of planned treatment. 27 patients had a median age of 53 years (33–73 years), ECOG PS 0 ($n = 8$), ECOG PS 1 ($n = 14$), ECOG PS 2 ($n = 1$). The ORR rate was 96.30% (26/27), including 17 patients with CR, 9 patients with PR, and 1 patient with SD. Treatment-related AEs were mainly lymphocyte count decreased, anemia, and white blood cell count decreased, with overall safety manageable and no treatment-related deaths. **Conclusions:** Camrelizumab combined with concurrent chemoradiation in patients with recurrent or metastatic cervical cancer has good efficacy, low side effects and acceptable toxicity. Clinical trial information: NCT04884906. Research Sponsor: None.

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Poster Session

The spectrum of homologous recombination deficiency in cervical cancer: Is it also a cervical issue? *First Author: Muhammad Danyal Ahsan, Weill Cornell Medicine - Qatar, Doha, Qatar*

Background: Tumors deficient in homologous recombination DNA damage repair (HR-DDR) demonstrate sensitivity to therapeutic agents targeting the HR-DDR pathway, such as poly-ADP ribose phosphate (PARP) inhibitors. The landscape of homologous recombination deficiency (HRD) is not well-characterized for cervical cancer; thus, we sought to analyze the prevalence of somatic pathogenic gene variants (PGVs) in HRD genes in cervical cancers. **Methods:** The American Association for Cancer Research's (AACR) Project Genomics Evidence Neoplasia Information Exchange (GENIE) database version 13.0 was queried for all cervical cancer tumors via cBioPortal (<http://genie.cbioportal.org>). This is a publicly available, multi-institutional database of next-generation sequencing (NGS) genomic profiles of multiple tumors. PGV frequencies of 27 genes involved in HR-DDR were descriptively reported for cervical cancer tumors, with histologic stratification: *ATM*, *ARID1A*, *ATRX*, *BRCA1*, *BRCA2*, *BARD1*, *BRIPI*, *BLM*, *BAP1*, *CHEK1*, *CHEK2*, *FANCA*, *FANCC*, *FANCD2*, *FANCE*, *FANCF*, *FANCG*, *FANCL*, *MRE11*, *NBN*, *PALB2*, *RAD50*, *RAD51*, *RAD51B*, *RAD51C*, *RAD51D*, *WRN*. **Results:** A total of 857 cervical tumors from 817 patients were included for analysis. At least one somatic PGV in an HRD gene was found in 16.5% of all tumors (141/857). When stratified by histological subtypes with at least 25 tumors sequenced, highest frequencies of ≥ 1 PGV in HRD genes were observed in mucinous cervical cancer (13/66, 19.7%), cervical adenocarcinoma (48/262, 18.3%), squamous cell cervical cancer (53/349, 15.2%), adenosquamous cervical cancer (6/43, 14.0%) and neuroendocrine cervical cancers (5/42, 11.9%). Substantial rates of PGVs in HRD genes were also observed in histological subtypes with fewer than 25 sequenced tumors. Across all tumors, HRD genes with the highest frequencies of PGVs were *ARID1A* (9%), *BAP1* (3%), *ATM* (1.6%) and *BRCA1* (1.6%). **Conclusions:** NGS data demonstrate a substantial rate of somatic PGVs in HRD genes in cervical cancers, including among HPV related subtypes. These data suggest the need to expand routine functional HRD status assessment to cervical cancers in order to further characterize the landscape of HRD in these tumors. Furthermore, genetically driven clinical trials are warranted to evaluate the efficacy of HRD-targeted therapies such as PARP inhibitors, ataxia telangiectasia, and Rad-3 related kinase (ATR) inhibitors. Research Sponsor: None.

Tumor Histology (n = tumors sequenced for ≥ 1 HRD gene)	Frequency of tumors with ≥ 1 HRD PGV	HRD gene with highest PGV frequency*
Squamous Cell (349)	15.2%	<i>BAP1</i> , 6.5%
Adenocarcinoma (262)	18.3%	<i>ARID1A</i> , 11.2%
Mucinous (66)	19.7%	<i>ARID1A</i> , 11.6%
Adenosquamous (43)	14.0%	<i>ARID1A</i> , 8.8%
Neuroendocrine (42)	11.9%	<i>ARID1A</i> , 16.1%
Serous (22)	13.6%	<i>ARID1A</i> , 8.8%
Endometrioid (21)	9.5%	<i>ARID1A</i> , 12.5%
Clear Cell (19)	42.1%	<i>ARID1A</i> , 37.5%
Mesonephric (10)	20.0%	<i>ARID1A</i> , 8.0%, <i>NBN</i> , 8.0%
Rhabdomyosarcoma 3	33.3%	<i>CHEK2</i> , 50.0%

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Poster Session

Correlating expression of NaPi2b and FRa in high grade serous ovarian cancer (HGSOC). *First Author: Debra L. Richardson, Stephenson Cancer Center/University of Oklahoma Health Sciences Center and Sarah Cannon Research Institute, Oklahoma City, OK*

Background: Biomarker driven therapies are increasingly being used for gynecologic cancers, with mirvetuximab soravtansine, a Folate Receptor alpha (FRa) targeting antibody drug conjugate (ADC) being a recent FDA approved agent for patients with FRa positive PROC. Uptifitambic rilosodotin (UpRi) is a late-stage, first in class NaPi2b-targeting ADC with a novel scaffold-linker-payload that enables high drug to antibody ratio and a controlled bystander effect. Approximately 29% of HGSOC patients have FRa positive tumors (Roche VENTANA FOLR1 (FOLR-2.1) Rx Dx Assay, USPI 2022); ~59% have NaPi2b positive tumors (Okeke et al, USCAP 2022). With the high unmet medical need in PROC and the evolving landscape of available treatments, understanding biomarker expression and correlation between FRa and NaPi2b is critical. Here we evaluate NaPi2b and FRa RNA expression correlation in HGSOC. **Methods:** Tumor samples (N=84) from the Ph1b UpRi expansion (EXP) cohort were analyzed via Nanostring (770 immune-focus genes from IO 360 panel + 30 customized ADC-related genes) to evaluate the association between NaPi2b and FRa expression. The cutoff for NaPi2b RNA positive or negative was based on approximately 60% of HGSOC patients having NaPi2b positive tumors (top 60% of samples based on expression deemed NaPi2b positive; bottom 40% NaPi2b negative) and FRa RNA cutoff assumed that ~30% of samples were FRa positive. To correlate the NaPi2b expression level between RNA and IHC, the N=84 samples with known expression levels via IHC were analyzed via Nanostring. **Results:** When evaluating NaPi2b and FRa RNA expression correlation, 21% (N=18) of samples had both NaPi2b positive and FRa positive expression. 38% (N=32) samples were NaPi2b positive and FRa negative. No statistically significant association was observed (Chi-squared test, p=0.129). NaPi2b RNA and IHC expression was evaluated; a statistically significant association was observed (Kappa statistic, p=0.001). Results are in the Table below. **Conclusions:** Based on this analysis of a limited sample size, there does not appear to be an association between FRa and NaPi2b expression, with the majority of NaPi2b positive samples not being FRa positive. Additionally, general NaPi2b prevalence and the correlation of expression between RNA and IHC suggest that NaPi2b may be a rational biomarker to integrate in RNA tumor panel testing. This research underscores the importance of early, comprehensive testing of all relevant biomarkers to guide therapy selection, and suggests that additional research is needed to evaluate the potential association between FRa and NaPi2b expression via IHC. Research Sponsor: Mersana Therapeutics.

N (% of total)	NaPi2b RNA	
	Positive (upper 60%)	Negative (lower 40%)
FRa RNA	Positive (upper 30%) Negative (lower 70%)	18 (21.4%) 32 (38.1%)
N (% of total)	Positive (upper 60%)	7 (8.3%) 27 (31.2%)
NaPi2b IHC	Positive (TPS > 75) Negative (TPS < 75)	14 (16.7%) 20 (23.8%)

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Poster Session

Phase 1 dose escalation study of SL-172154 (SIRP α -Fc-CD40L) in platinum-resistant ovarian cancer. *First Author: Nehal J. Lakhani, START Midwest, Grand Rapids, MI*

Background: SIRP α -Fc-CD40L is a hexameric, bi-functional fusion protein consisting of SIRP α linked to CD40L via an inert Fc linker. This molecule competitively inhibits CD47 to enhance tumor cell phagocytosis and activates CD40 to increase antigen processing and cross-presentation by antigen presenting cells (APCs) to CD8 T cells, thus bridging innate and adaptive immunity. **Methods:** This first-in-human, Phase 1 dose escalation study evaluated SL-172154 in patients (pts) with advanced platinum resistant ovarian, fallopian tube and primary peritoneal cancers (PROC). SL-172154 was administered intravenously across 5 dose levels (0.1, 0.3, 1.0, 3.0, 10mg/kg). Dose escalation followed a modified toxicity probability interval 2 design. Objectives included evaluation of safety, dose-limiting toxicity (DLT), recommended phase 2 dose, pharmacokinetic and pharmacodynamic (PD) parameters, and antitumor activity per RECIST 1.1. **Results:** As of 3 Jan 2023, 27 pts (median age 66 years [range 33-85]; median of 4 prior systemic therapies [range 2-9]) with ovarian (70%), fallopian tube (15%) or primary peritoneal (15%) cancer were dosed. Treatment-emergent AEs (>15% regardless of grade (G) included infusion related reaction (IRR) (67%), fatigue (44%), nausea (33%), back pain (26%), constipation, diarrhea (both 22%), decreased appetite and pruritus (both 19%). There was one DLT of G3 ALT increased at 10mg/kg requiring dose interruption for resolution. A maximum tolerated dose was not reached. G3/4 treatment-related AEs (>1pt) were AST increased (G3) and lymphopenia (G4), each in 2 pts (7%); all were fully resolved with no dose modifications. There were no fatal AEs, no AEs that led to drug discontinuation and no events of cytokine release syndrome. The frequency of IRR events increased with increasing dose, and slowing the rate of infusion was utilized for mitigation. SL-172154 Cmax and AUC increased with dose with greater than proportional exposure noted at 3 and 10mg/kg potentially due to target saturation. These findings were supported by dose-dependent target engagement of CD47 and CD40 on CD4 T cells and B cells respectively, approaching 100% by 3 mg/kg. Rapid dose-dependent egress of CD40+ B cells was maximal at ≥ 3 mg/kg. SL-172154 induced dose-dependent responses in IL-12, CXCL-8, CXCL-10, IL-10, CCL2, CCL20, and CCL22, which also approached a plateau at ≥ 3 mg/kg. Analysis of peripheral and tumor immunophenotypes and anti-drug antibodies in response to SL-172154 is ongoing and will be presented. Best response was stable disease in 6/27 response evaluable (22%) pts. **Conclusions:** SL-172154 is well tolerated in heavily pretreated PROC pts. IRRs were readily manageable. Maximal CD47 and CD40 target engagement and CD40-dependent PD effects were observed with ≥ 3 mg/kg SL-172154. 3mg/kg is a safe, tolerable, and pharmacologically active dose for evaluation in combination studies in pts with PROC. Clinical trial information: NCT04406623. Research Sponsor: Shattuck labs.

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Poster Session

Systematic high-throughput combination drug screen to enhance poly (ADP-ribose) polymerase (PARP) inhibitor efficacy in ovarian cancer. *First Author: Katherine Foster, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: PARP inhibitors currently offer the greatest benefit to patients with loss-of-function *BRCA1* or 2 mutations or other causes of homologous recombination deficiency (HRD). We hypothesized that combination therapy, possibly by augmenting or inducing an HRD phenotype, would enhance the efficacy of PARP inhibition in epithelial ovarian cancer. **Methods:** We performed a high-throughput screen of an informer set containing FDA-approved drugs, clinical candidates, and small-molecule probes to identify synergistic partners with olaparib in representative HRD and non-HRD human epithelial ovarian cancer cells. Single agent activity was described by area under the curve of the Hafner growth rate index (AUC_GRI) and synergy was ranked by cumulative difference from Bliss (Δ_{Bliss}). Analysis of the drug screen was performed using algorithms developed by the Gulf Coast Consortia's Combinatorial Drug Discovery Program at the Texas A&M Institute of Bioscience and Technology. MTT assays were then independently performed to verify and characterize synergy between CT7439, an agent selected following the drug screen, and olaparib. MTT data were analyzed using the SynergyFinder Plus web application. **Results:** In an initial single agent screen, we identified 62 compounds with a mean AUC_GRI <0.75, indicating inhibitory activity. Prioritizing more potent agents and those of mechanistic interest, we selected 40 hits to validate and advance to a combination screen. Diverse mechanisms of action were represented among the hits, including many small molecule inhibitors of various cell cycle pathways. Following a combination screen with olaparib, the compounds selected for final validation were: AZD 7762 (CHK1/2 inhibitor), dinaciclib (pan-CDK inhibitor), onalespib (HSP90 inhibitor), and SN-38 (topoisomerase 1 inhibitor). The Δ_{Bliss} for these agents are presented in the table. Due to mechanistic rationale and concern for overlapping toxicities among the other candidates, we focused further study on CDK inhibitors. In MTT assays, we identified robust synergy between olaparib and CT7439, a next-generation oral CDK12/13 inhibitor, with a mean Bliss synergy score of 1.31 and scores as high as 22.03 at certain concentrations in the non-HRD model OVCAR-5. These findings were recapitulated in the HRD cell lines OVCAR-4 (mean Bliss synergy score 1.56) and OVCAR-8 (mean Bliss synergy score 5.69). Results from an *in vivo* model will be presented as well. **Conclusions:** Pairing a PARP inhibitor and CDK inhibitor, a strategy identified by a high-throughput drug screen and known to impair homologous recombination, resulted in robust synergy in both HRD and non-HRD ovarian cancer models. Clinical translation of this combination may enhance the efficacy of PARP inhibitors in patients with ovarian cancer. Research Sponsor: MD Anderson Ovarian Cancer Moon Shot; CPRIT Grant #RP200668.

Compound	Mean Δ_{Bliss}
AZD 7762	6.62
Dinaciclib	1.93
Onalespib	1.83
SN-38	6.70

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Poster Session

The impact of adjuvant platinum-based chemotherapy in early adult granulosa cell tumor of the ovaries: A meta-analysis of comparative studies. *First Author: Dinesh Keerty, LSUHSC-S, Feist-Weiller Cancer Center, Shreveport, LA*

Background: Adult granulosa cell tumors (AGCT) are the most common type of malignant ovarian sex chord stromal tumors but only comprise 2 to 5 percent of all malignant ovarian neoplasms. Most granulosa cell tumors have an indolent growth pattern, and prognosis depends on the disease stage at diagnosis and the presence of residual disease after surgery. Though these tumors have metastatic potential, their tendency for late relapses is well documented. Despite the lack of supporting data, the National Cancer Centers Network recommends platinum-based adjuvant chemotherapy (AC) for Stage I with intermediate and high-risk features. Most studies have failed to show any benefit of AC with disease-free or overall survival. However, several of these studies were small, and some had short median follow-ups. Others included advanced stages and the juvenile variant of the disease. Therefore, we conducted this meta-analysis to evaluate the impact of AC on disease recurrence in a stage I enriched AGCT. **Methods:** A review of the medical literature was conducted using online databases. Inclusion criteria consisted of English language, diagnosis of AGCT, studies with a preponderance of stage I, comparative studies of AC versus none, and studies that reported recurrence rates. Studies that had a preponderance of advanced stages or juvenile variants were excluded. A meta-analysis using the fixed effects and random effects models was conducted. **Results:** Seven retrospective comparative studies with a total of 500 patients were included. The average median age was 47 years, and the average median follow-up was 58 months. Approximately 79% of the sample were stage I, and 79% of stage I were IC. Most AC regimens used were BEP and EP, though it varied among the regions. Platinum-based AC in early-stage AGCT failed to impact recurrence rates compared to clinical observation (HR=1.39, 95%CI 0.86-2.25, $I^2=48\%$, $p=0.18$). **Conclusions:** This is the first meta-analysis to show that adding platinum-based adjuvant chemotherapy to surgery does not improve the recurrence rate in early AGCT. Therefore, in the absence of evidence supporting any benefit of AC in this disease, recommendations to use AC should be re-evaluated, especially since the risk of platinum-based AC with or without Bleomycin is well-documented and carry potentially serious side effects. Research Sponsor: None.

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Poster Session

Utility of surgically documented minimal residual disease as a therapeutic target and early surrogate of frontline treatment outcomes in ovarian cancer. *First Author: Anne Knisely, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Cure rates for patients with advanced stage ovarian cancer have not changed over the last four decades likely due to inability to eradicate residual cancer cells after frontline therapy. Identifying clinically undetectable minimal residual disease (MRD) after frontline therapy by second look laparoscopy (SLL) has potential to a) uncover mechanisms of chemoresistance, b) identify MRD-specific therapeutic targets, and c) allow for earlier intervention with investigational therapies. The objective of this study is to describe the initial safety and feasibility of SLL and illustrate clinical pathologic correlates. **Methods:** This IRB-approved observational, single-center study includes patients with epithelial high-grade ovarian cancer with complete CA-125 and radiologic response after frontline treatment who underwent SLL from 4/2017-12/2022. Patients were subsequently offered standard of care or investigational maintenance therapy options based on homologous recombination deficiency (HRD) and MRD status. Summary statistics described the study population, chi-square tests compared categorical variables, and progression free survival (PFS) based on MRD status was estimated using Kaplan-Meier method and compared using log rank test. **Results:** 64 patients underwent SLL with a median of 8 biopsies (range 1-16). The majority of patients had stage III-IV disease (89%), and high-grade serous histology (89%). Approximately half (52%) of patients underwent neoadjuvant chemotherapy (NACT) with interval tumor reductive surgery (TRS). MRD was present in 28 patients (44%), and the presence of MRD was associated with a worse PFS (HR 3.1, 95% CI 1.5-6.3; 9.2 vs 24.6 months; $P=0.002$). MRD was more frequent among NACT recipients compared to those who underwent primary TRS (61% vs 26%, $P=0.005$), those with HRD negative tumors (63% vs 22%, $P=0.003$), and those with R1 versus R0 resections (71% vs 35%, $P=0.012$). Of patients with MRD, 20 patients (71%) received bevacizumab until progression as part of a clinical trial (NCT02884648), 3 (11%) received bevacizumab off trial, 4 (14%) received a PARP inhibitor (all HRD positive) and 1 received other therapy. There was one (1.6%) intraoperative complication requiring conversion to laparotomy. **Conclusions:** SLL is feasible, overall safe, and detected MRD in 44% of ovarian cancer patients who were in radiologic and CA-125 remission after frontline therapy. MRD rates were higher in patients who received NACT and HRD negative patients, and PFS was significantly longer in patients without residual disease. MRD rate by SLL may have utility as an early surrogate for efficacy in trials evaluating novel frontline investigational therapies. Knowledge of MRD status in this patient population enables interventional, observational, and translational investigations, as well as personalized prognostic counseling. Research Sponsor: MD Anderson Cancer Center Support Grant; Break Through Cancer.

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Poster Session

Nivolumab plus ipilimumab (N+I) in patients (pts) with ovarian cancer (OC) with BRCA1/2 mutation (mut): Results from the Targeted Agent and Profiling Utilization Registry (TAPUR) study. *First Author: Charles Drescher, Swedish Cancer Institute, Seattle, WA*

Background: TAPUR is a phase II basket study evaluating antitumor activity of commercially available targeted agents in pts with advanced cancers with genomic alterations. Results in a cohort of pts with OC with *BRCA1/2* mut treated with N+I are reported. **Methods:** Eligible pts had advanced OC, measurable disease, ECOG performance status (PS) 0-2, adequate organ function, and no standard treatment (tx) options. Genomic testing was done in CLIA-certified, CAP-accredited labs. PD-L1 status was not routinely reported. Pts received I at 3 mg/kg every 3 wks for 4 doses with N at 1 mg/kg IV every 3 weeks (wks) for 4 doses. N alone was then continued at 240 mg every 2 wks or 480 mg every 4 wks until disease progression. Primary endpoint was disease control (DC) per investigator defined as complete or partial (PR) response per RECIST v. 1.1, or stable disease of at least 16+ wks duration (SD16+). CA-125 levels were not routinely reported. Simon 2-stage design tested the null DC rate of 15% vs. 35% (power = 0.85; $\alpha = 0.10$). If ≥ 2 of 10 pts in stage 1 have DC, 18 more pts are enrolled; otherwise, the cohort is closed. If ≥ 7 of 28 pts have DC, the null DC rate is rejected. P-value calculated based on 2-stage design. Secondary endpoints were progression-free survival (PFS), overall survival (OS), and safety. **Results:** 33 pts with OC and *BRCA1* (n=20), *BRCA2* (n=10), or both mut (n=3) were enrolled from Sept 2017 to Oct 2019. 6 pts were not evaluable for efficacy analysis; 1 pt was found to be ineligible after enrolling, 5 pts discontinued tx before the post-baseline tumor evaluation due to an adverse or serious adverse event (SAE). Table shows demographics and efficacy outcomes. 6 pts with PR were observed for an OR rate of 22% (95% CI: 9% to 42%) and a DC rate of 27% (90% CI: 13% to 36%); the null hypothesis of a 15% DC rate was not rejected ($p=0.17$). 3 pts with PR had *BRCA1* mut only, 2 pts had *BRCA2* mut only and 1 pt had both *BRCA1* and *BRCA2* mut. Of the 6 pts with PR, 4 had microsatellite (MS) stable (MSS) tumors and MS status was not reported in 2. Of the 4 with MSS, 3 had a tumor mutational burden (TMB) ≤ 10 mutations per megabase and 1 had TMB of 11. 11 pts had at least 1 tx-related SAE, including acute kidney injury, ALT/AST increase, colitis, dehydration, diarrhea, E. coli, electrolyte disorder, fever, nausea/vomiting and pneumonitis. **Conclusions:** N+I did not meet prespecified criteria to declare a signal of activity in pts with OC and *BRCA1/2* mut. However, given 22% of pts had PR (2 with >1 year duration) in this heavily pretreated cohort, additional study may be warranted to further evaluate efficacy. Clinical trial information: NCT02693535. Research Sponsor: Bristol Myers Squibb; AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly and Company, Genentech, Merck, Pfizer, Seagen.

Demographics (N=33) and efficacy outcomes (n=27).

Median (Med) age, years (range)	59 (47-86)
ECOG PS, %	0 25 (76)
	1 7 (21)
	2 1 (3)
Prior systemic regimens, %	0-2 3 (9)
	≥ 3 30 (91)
DC rate, % (OR and SD16+) (90% CI)	27 (13, 36)
OR rate, % (95% CI)	22 (9, 42)
Med PFS, wks (95% CI)	8.1 (8.0, 8.3)
Med OS, wks (95% CI)	45 (20, 133)

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Poster Session

Efficacy of subsequent therapies in patients (pts) with advanced ovarian cancer (AOC) in the phase III PAOLA-1/ENGOT-ov25 trial according to whether disease progression occurred during or after the end of olaparib (ola) maintenance. *First Author: Philipp Harter, Kliniken Essen-Mitte, and AGO, Essen, Germany*

Background: In the PAOLA-1/ENGOT-ov25 trial (NCT02477644), maintenance ola (a PARP inhibitor) + bevacizumab (bev) led to prolonged progression-free and overall survival vs placebo (pbo) + bev in AOC pts, specifically those with homologous recombination-deficient (HRD+) tumors (Ray-Coquard et al. ESMO 2022, LBA29). Here, we explore the efficacy of subsequent chemotherapy (CT) in pts after progression on first-line (1L) treatment in PAOLA-1. **Methods:** The efficacy of subsequent CT was explored by analyzing the median time from first subsequent therapy (FST) to second subsequent therapy (SST). Efficacy was compared by FST type, HRD status, and timing of progression (during/after ola). A multivariate Cox model was used in ola + bev pts to identify prognostic factors influencing time from FST to SST, including HRD status, platinum-free interval (PFI), clinical risk based on disease stage and surgical status, timing of progression, and response to 1L CT. All P values are exploratory. **Results:** In total, 544/806 (67.5%) pts progressed and received subsequent CT: 338/537 (62.9%) ola + bev pts and 206/269 (76.6%) pbo + bev pts. In the overall population and in the subgroup who received platinum-based combination therapy (PBC), time from FST to SST was shortest in pts who progressed during ola (Table). Pts who progressed after ola had similar outcomes to pbo + bev pts (Table). Efficacy was broadly consistent regardless of HRD status (Table). The multivariate analysis confirmed that progression after (vs during) ola prolonged time from FST to SST (hazard ratio [HR] 0.65, 95% confidence interval [CI] 0.50-0.84; $P=0.0011$) independently of other known prognostic factors, such as PFI ≥ 12 vs <12 months (HR 0.38, 95% CI 0.29-0.51; $P<0.0001$) or lower vs higher clinical risk (0.58, 0.42-0.81; $P=0.0015$). **Conclusions:** In this post hoc exploratory analysis of PAOLA-1, the efficacy of subsequent CT at relapse appeared dependent on whether progression occurred during or after the end of ola treatment. Efficacy was reduced when relapse occurred during ola but was comparable between pts who progressed after ola vs pbo + bev pts. Clinical trial information: NCT02477644. Research Sponsor: This work was supported by ARCA Research, AstraZeneca, Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, and F. Hoffmann-La Roche.

Time from FST to SST.

FST	Progression during ola	Progression after ola	Pbo + bev
Any CT	6.1 (4.9-7.3) n=192*	11.4 (10.2-13.2) n=145*	11.9 (10.8-12.9) n=206
HRD+	7.2 (5.5-9.6) n=55	12.7 (10.2-15.5) n=66	13.9 (11.4-17.0) n=100
HRD-	6.0 (4.4-7.7) n=98	10.6 (9.7-15.4) n=53	10.8 (9.5-12.5) n=66
PBC	7.3 (5.7-8.4) n=157	12.0 (10.3-14.8) n=132	12.9 (11.8-14.1) n=162
HRD+	7.3 (6.3-9.6) n=46	12.7 (10.2-15.5) n=64	14.3 (12.4-19.0) n=85
HRD-	6.6 (4.6-8.6) n=81	11.9 (10.3-17.2) n=46	11.8 (10.6-13.2) n=47

*1/338 pts not treated. Kaplan-Meier estimates; median months with 95% CIs. HRD+ defined as tumor *BRCA* mutation and/or genomic instability score ≥ 42 (Myriad MyChoice HRD Plus assay)

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Poster Session

Real-world data from a multi-center study: Insights to the efficacy and safety in patients with ovarian cancer (OC) received niraparib as first-line (1st-L) maintenance therapy (MT). *First Author: Minmin Zhao, Department of Obstetrics and Gynecology, Zhongda Hospital Southeast University, Nanjing, China*

Background: Niraparib has significantly extended PFS as 1st-L MT OC in PRIMA/PRIME. Due to the more complex in treatment and status of the patients (pts) in clinical practice, more real-world data is needed to verify the efficacy and safety of Niraparib. Meanwhile, exploring the link between clinical characters and PFS, may to establish a clinical model to predict Niraparib benefits. **Methods:** This is a retrospective multicentric study recruiting OC pts received Niraparib as 1st-L MT from fourteen hospitals throughout China from Jan. 2019 to Dec. 2021. The database lock-time was on Dec. 31st, 2022. The pts' basic characters, especially biomarkers, KELIM scores, etc. were recorded. Survival analyses were conducted using the Kaplan-Meier method and log-rank test, and 95% CI were calculated. The primary endpoint was PFS, and secondary endpoints included time to treatment discontinuation (TTD), time to first subsequent therapy (TFST) and safety. The exploratory endpoint was to establish a clinical prediction model of Niraparib benefits. **Results:** 199 pts' data were analyzed. The median(m) follow-up at the time of the data cutoff was 14.93 months (mos) (12.17, 39.47). Baseline characteristics were shown in Table. MPFS was not reached (NR) (29.80 to not be estimated, NE), with maturity 29.64%, and PFS rate at 6, 12, 18, 24mos was 89.4%, 79.5%, 68.3%, 64.5% respectively, showing the efficacy of Niraparib. MPFS (95% CI) in subgroups were as follows: BRCAwt 23.83mos (23.83 to NE); HRD negative 15.63mos (12.6 to NE); KELIM < 1 NR (15.33 to NE); BRCA1/2m, HRD positive and KELIM≥1 subgroups all NR yet, due to the no longer enough follow-up time and low data maturity. Multivariate analysis found that pts with <65 years, BRCA1/2m, HRD positive, KELIM > 1, and R0 after primary cytoreductive surgery were likely to have longer PFS. The rate of grade ≥3 thrombocytopenia was 19.1%. Treatment discontinuation occurred in 11 (5.5%) pts due to TEAEs. The clinical prediction model for probability of progression was established from 149 pts (training dataset): Score = 0.612 Age_{> 65} + 0.3889 BMI_{≥ 23.90} + 0.097 FIGO_{IV} + 0.191Chronic_N + 1.398 Surgery result_{R1/R2} + 2.552 BRCA_{wt}. The probability of disease progression received Niraparib in 6, 12 and 18m can be obtained by mapping the score to the nomogram. **Conclusions:** The efficacy and safety of Niraparib in this study are consistent with the results in PRIME. The clinical predictive model established in this database needs more data to be matured and verified. Research Sponsor: Beijing Science & Technology Innovation Fund (KC2021-JX-0186-143).

Some baseline characteristics.		
Characteristics	Number	%
Age (years), medium (range)	57.00 (51.00, 63.50)	
BMI, medium (range)	23.05 (21.09, 25.12)	
BRCA mutational status		
BRCAm		20.1
BRCAwt	40	
Unknown	131	65.8
HRD status	28	14.1
HRD status		
Positive	66	33.2
Negative	52	26.1
Unknown	81	40.7
KELIM score		
> 1	55	27.6
≤ 1	23	11.6
Unknown	121	60.8

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Poster Session

Circulating tumor DNA (ctDNA) as a marker of residual disease and recurrence in resected stage I-IV epithelial ovarian cancer (EOC). *First Author: Sumitra Ananda, Peter MacCallum Cancer Centre, Epworth Healthcare, Western Health, Walter and Eliza Hall Institute, University of Melbourne, Melbourne, VIC, Australia*

Background: The management of EOC remains challenging, with a high risk of relapse despite surgery, chemotherapy and maintenance therapy. Detection of ctDNA after surgery and adjuvant chemotherapy (CT) may identify patients (pts) at highest risk of recurrence suitable for treatment escalation. Our primary aim was to investigate the use of ctDNA as a marker of residual disease following both surgery and adjuvant CT that might predict later recurrence. **Methods:** In this multi-centre observational study, we collected blood samples post-op and 6-8 weeks post-CT completion from pts with debulked stage I-IV EOC planned for adjuvant CT. Pre-cycle 1 CT and pre-op blood was also collected from some pts who received neoadjuvant CT. We used a tumor-informed approach for ctDNA analysis with whole exome sequencing of tumor tissue followed by detection of up to 50 variants in the plasma with the SaferSeqS assay. The primary outcome was recurrence-free survival (RFS), calculated using the Cox proportional-hazards model. **Results:** 81 pts who had post-op ctDNA results were included. 84% had high grade serous histology and 23% had BRCA mutations. Median number of tumor-informed variants analyzed in the plasma was 44 (range 3-60). Overall, post-operative ctDNA was detected in 63 of 81 (78%) of pts, 18 of 26 (69%) in Stage I-II and 45 of 55 (82%) in Stage III-IV. Pts who were ctDNA negative post-surgery had longer RFS versus who were ctDNA positive (HR 3.28, 95% CI 1.39 to 7.72, p = 0.007). Estimated RFS at 2 years was 78% among pts who were ctDNA negative post-surgery and 44% among the ctDNA positive group. Pts with BRCA mutations were less likely to have positive post op ctDNA (OR 0.12, 95% CI 0.036 to 0.39, p < 0.001). For post-CT ctDNA, estimated RFS at 2 years was 74% in the ctDNA negative pts versus 43% in the ctDNA positive group but this was not statistically significant (HR 1.64, 95% CI 0.84 to 3.18, p = 0.15). Pts with zero residual disease were more likely to be ctDNA negative post-surgery (OR 12.36, 95% CI 1.54 to 99.4, p = 0.018). Post-op ctDNA outperformed post-op CA-125 in predicting recurrence; pts with elevated CA-125 post-surgery had shorter RFS compared to those with normal CA-125 post-surgery (HR 1.99, 95% CI 1.15 to 3.42, p = 0.013). Of 18 pts who had neoadjuvant CT, pre-treatment ctDNA was detected in 17 (94%). Only two pts had clearance of ctDNA post neoadjuvant CT and both had zero residual disease at surgery. For the pts that maintained positive ctDNA results post-op, 7/15 (47%) pts had zero residual disease. **Conclusions:** ctDNA detection after ovarian cancer cytoreduction identifies pts at very high risk of recurrence. Pts with BRCA mutations were more likely to have negative ctDNA post-op. The role of ctDNA in guiding neoadjuvant and adjuvant therapy to improve outcomes, warrants further investigation. Clinical trial information: ACTRN12617001119381. Research Sponsor: Marcus Foundation; Epworth Medical Foundation Grant.

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Poster Session

Venous thromboembolism prophylaxis during neoadjuvant chemotherapy for patients with ovarian cancer. *First Author: Hannah Dysinger McLaughlin, University of Michigan Hospital, Ann Arbor, MI*

Background: The primary objective was to assess the rate of venous thromboembolism (VTE) in patients with ovarian cancer who received neoadjuvant chemotherapy (NACT) following a quality improvement (QI) intervention of routine pharmacologic VTE prophylaxis compared to patients that did not receive prophylaxis. **Methods:** This is a retrospective cohort study of patients with pathologically confirmed ovarian cancer that received NACT between January 2009 to December 2021 from a single institution. Patients were excluded if VTE was diagnosed prior to initiating NACT. Routine pharmacologic VTE prophylaxis during NACT started in January 2017 following a QI initiative. VTE events were diagnosed by doppler scan of extremities or computed tomography of the chest ordered for symptomatic patients or diagnosed incidentally on routine treatment imaging. Patient factors and perioperative variates of interest were investigated for their association with VTE events through univariate and multivariate models. **Results:** A total of 290 patients with ovarian cancer received NACT and were included, with 106 of 290 patients (36.5%) receiving pharmacologic prophylaxis during NACT. Rate of VTE prophylaxis prior to the QI intervention was 3.68% (n=5) compared to 65.58% (n=101) after. The rate of VTE during NACT was 11.41% (n=21) without prophylaxis and 2.83% (n=3) with prophylaxis (p=0.013) (Table). The rate of any VTE event from the start of NACT through adjuvant chemotherapy was 20.11% (n=37) without prophylaxis and 4.72% (n=5) with prophylaxis (p<0.01). There was no difference in adverse bleeding events in those that received prophylaxis to those that did not (0% vs 1.32%, p=0.239). On univariate analysis, VTE prophylaxis was associated with a decreased risk of VTE during NACT (OR 0.23; 95% CI: 0.06-0.78) and any VTE during primary treatment (OR 0.19; 95% CI 0.07-0.52). On multivariate analysis, VTE prophylaxis remained significantly associated with reduced VTE rates during NACT and during primary treatment (p=0.02 and p=0.001, respectively). **Conclusions:** Routine administration of pharmacologic VTE prophylaxis during NACT for patients with ovarian cancer is associated with reduced risk of VTE during NACT and throughout primary treatment and is not associated with adverse bleeding events. Research Sponsor: None.

VTE events with and without VTE prophylaxis during NACT.			
Characteristics	No VTE Prophylaxis N=184 (63.4%)	VTE Prophylaxis N=106 (36.5%)	p-value
Total VTE Events	37 (20.11%)	5 (4.72%)	<0.01
NACT VTE	21 (11.41%)	3 (2.83%)	0.013
VTE within 30 days of surgery	7 (3.80%)	1 (0.94%)	0.265
Adjuvant Chemotherapy VTE	11 (5.98%)	1 (0.94%)	0.062

NACT: neoadjuvant chemotherapy; VTE: venous thromboembolism.

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Poster Session

Safety and efficacy of PIPAC in patients with ovarian cancer with peritoneal metastases: A first-in-US phase I study. *First Author: Rosemary Senguttuvan, City of Hope National Medical Center, Duarte, CA*

Background: Epithelial ovarian cancer (EOC) is characterized by chemoresistant recurrences primarily confined to the intraperitoneal cavity, frequently leading to malignant small bowel obstructions. Intraperitoneal (IP) chemotherapy has been incorporated in EOC, but only in the first-line setting. Pressurized intraperitoneal aerosolized chemotherapy (PIPAC) is a novel IP drug delivery method that optimizes tissue penetration depth and drug distribution, to treat recurrent peritoneal malignancies. Recent trials outside the U.S. demonstrated partial to stable response following PIPAC in recurrent EOC. To date, no clinical trials have been completed investigating the role of PIPAC in EOC in the United States. **Methods:** We performed a multicenter prospective phase I trial using IP cisplatin 10.5 mg/m² and doxorubicin 2.1 mg/m² via PIPAC at 6-week intervals. Patients were eligible if they had recurrent disease with peritoneal metastasis; extraperitoneal metastasis was allowed. The primary endpoint was dose-limiting toxicity (DLT). Secondary endpoints included progression free survival, PCI scoring, RECIST measurements, and quality of life (QoL). The patients with gastric and uterine cancers' toxicity data were used but given inherent prognostic differences the treatment efficacy for these patients were not used in this analysis. Adverse event (AE) monitoring was graded using CTCAE spanning 18 weeks. Following completion of treatment (≥2 PIPACs) patients were followed up every 12 weeks. QoL was measured using patient-reported assessments at 0, 6, 12, and 18 weeks. Baseline demographics were summarized. Mean change in PCI was calculated between cycle (C) 1 and 2, and cycle 2 and 3. Toxicities attributed to the surgery or PIPAC were reported with highest grade for each patient. **Results:** Nine heavily pretreated, recurrent patients were enrolled in the trial: 7 with platinum-resistant recurrent EOC, 1 with uterine cancer, and 1 with gastric cancer. PIPAC completion rate was 71.4%. Median age of participants was 65 years. Median prior lines of chemotherapy were 4 (range 2 - 10). No surgical complications occurred in the cohort. Two patients came off study: one for G3 abdominal pain and the other for G3 anorexia. For the EOC cohort, the median PCI reduction was -1.4% (C1 to C2) and -2.8% (C1 to C3). One low-grade serous EOC patient demonstrated a partial response based on RECIST criteria and received 6 cycles. Two EOC patients showed an initial response based on PCI reduction, but progressed following Cycle 2. Overall, QoL was stable. **Conclusions:** PIPAC with cisplatin/doxorubicin in platinum-resistant ovarian cancer is well tolerated. Intraperitoneal responses were seen in a subset of low-grade serous ovarian cancer patients, which may warrant further study. Heavily pretreated, platinum-resistant high-grade EOC patients derived limited intraperitoneal control from PIPAC monotherapy. Clinical trial information: NCT04329494. Research Sponsor: Internal Funding.

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Poster Session

Analyses of tumor microenvironment affecting the survival in patients with ovarian cancer receiving intraperitoneal chemotherapy: Translational research from the phase 3 trial of intraperitoneal therapy for ovarian cancer with carboplatin (TRiPocc). *First Author: Aiko Ogasawara, Aichi Cancer Center Research Institute, Nagoya, Japan*

Background: The iPocc trial is a randomized, global phase (P) 3 study of intraperitoneal (IP) versus intravenous (IV) carboplatin with dose-dense paclitaxel chemotherapy in epithelial ovarian cancer (EOC) patients that demonstrated an improved progression-free survival (PFS) but not overall survival (OS) in the former. IP chemotherapy induces an antitumor immune response and increases survival in a murine xenograft model. This study aimed to assess whether immunological background affected the clinical outcomes of patients receiving IP chemotherapy. **Methods:** Fresh frozen tumor samples at the time of primary surgery were obtained from 116 patients who joined the iPocc P3 trial for microarray analysis. Cell-type deconvolution was performed using MCP counter. Single sample Gene Set Enrichment Analysis was performed to evaluate the tumor immune microenvironment. Clinical data were obtained from the iPocc P3 trial. We stratified 116 patients according to the high or low values of each factor determined by the median values. The Kaplan-Meier method and log-rank test were used to analyze PFS and OS. **Results:** A total of 116 patients were assigned to either the IP (n=59) or IV (n=57) group. The most common histologic type was serous (58.6%), followed by endometrioid (17.2%) and clear cell (12.1%). The patients who received IP therapy had longer OS than those who received IV therapy in the group with a high infiltration of T cells, NK cells, or cytotoxic lymphocytes in the MCP counter (median OS: not reached (NR) vs 75.0 months, $P=0.041$, NR vs. 75.0 months, $P=0.042$, NR vs 65.2 months, $P=0.031$), but not in the group with a low infiltration. Similarly, the IP therapy improved OS in the patients with high expression of immune-related genes such as *CD8A*, *FOXP3* or *PDCD1* (median OS; NR vs 65.2 months, $P=0.035$, NR vs 65.2 months $P=0.030$, NR vs 53.1 months, $P=0.016$), but not in the patients with low expression of those genes. In addition, a multifaceted evaluation was conducted because of the limitations of evaluating the interaction between cancer and immunity using a single factor. When the patients were divided into two groups, "Immune Hot" and "Immune Cold" based on the hierarchical clustering analysis with 4 parameters representing "Innate immunity," "T cells," "Interferon gamma response" and "Inhibitory molecules," the IP therapy increased both PFS and OS compared to the IV therapy in the "Immune Hot" group (median PFS; 35.5 vs 23.4 months, $P=0.024$, median OS; NR vs 75.0 months, $P=0.040$), but not in the "Immune Cold" group. **Conclusions:** IP therapy may improve the survivals in EOC patients with a high immunological background. Further studies are warranted to validate this hypothesis and to clarify the impact of IP therapy on the tumor immune microenvironment. Clinical trial information: NCT01506856 / GOTIC-001/JGOG3019. Research Sponsor: None.

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Poster Session

The role of innate immune system in modulating CHK1 inhibitor (CHK1i) response in BRCA wild-type (BRCAwt), platinum-resistant high-grade serous ovarian cancer (PR-HGSOC): Exploratory analysis from a phase II study of CHK1i prexasertib. *First Author: Elena Giudice, Women's Malignancies Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD*

Background: Immune checkpoint blockade, e.g., anti-PD-1/PD-L1, demonstrated limited efficacy in HGSOC despite high levels of tumor-infiltrating lymphocytes, suggesting the innate, rather than adaptive, immune system may play a prominent role in anticancer response. Preclinical studies suggest CHK1i modulates the innate immune milieu. We previously showed clinical activity of prexasertib in BRCAwt, PR-HGSOC patients (pts). Here, we investigated the association of innate immunogenic features with CHK1i response. **Methods:** Prexasertib was given at 105 mg/m² IV every 14 days in a 28-day cycle. Baseline (BL) fresh core biopsies were collected from pts enrolled in the biopsy (Bi) cohort for RNA sequencing. Computational immunogenomic analysis (CIBERSORT) was used for immune cell fractions quantification. Blood samples (BS) were obtained at BL and cycle 1 day 15 (C1D15) from pts enrolled in both Bi and non-Bi (nBi) cohorts for multiparametric flow cytometry (FC) analysis to evaluate dynamic changes in immune cell subsets. Mann-Whitney and Wilcoxon tests were used to compare unpaired and paired data, respectively. **Results:** 49 BRCAwt, PR-HGSOC pts were enrolled in the Bi cohort (n=25) and nBi cohort (n=24). 39 were evaluable per RECIST v1.1. 18/39 pts (46.2%) had a clinical benefit (CB), defined as progression-free survival ≥ 6 months. Transcriptomic profiles of BL biopsies (n=15) met the quality control and assurance (Gene Similarity Index, Principal Component Analysis) for further *in silico* analysis. CIBERSORT analysis did not exhibit any differences in the immune cell fractions between CB and non-CB (NCB) groups at BL. FC analysis on paired BS (BL and C1D15) showed an increase of immunosuppressive monocytic myeloid-derived suppressor cells (M-MDSCs, $p<0.001$) and classical monocytes (CM, $p=0.003$) in the NCB group (18 paired BS). In the CB group (19 paired BS), CD141+ and CD1c+ dendritic cells (DCs) express higher rates of CD83, a marker of maturity and functionality ($p<0.001$ and $p<0.001$, respectively), despite no increase in the absolute number of DCs. At C1D15, a higher rate of M-MDSCs (median 7.8% vs. 5.52%; $p=0.03$) and CM (median 40.7% vs. 31.7%; $p=0.03$) were found in the NCB group (n=18) compared to the CB group (n=19); also, CM showed lower expression of HLA-DR in the NCB group (median 19.25% vs. 27.8%; $p=0.02$). **Conclusions:** Collectively, our data suggest the possible involvement of innate immunity in modulating CHK1i response. Increasing peripheral immunosuppressive cells and lower immunocompetence of the innate immune system may contribute to CHK1i resistance, whereas the functionality of DCs may be involved in the response. Enhancing innate immunity may represent a strategy to increase CHK1i response in this hard-to-treat population. Clinical trial information: NCT02203513. Research Sponsor: U.S. National Institutes of Health.

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Poster Session

Pegylated liposomal doxorubicin and carboplatin versus paclitaxel and carboplatin as first-line treatment for Chinese patients with ovarian cancer: A multi-center, randomized, open-label trial. *First Author: Yuanming Shen, Women's Hospital School of Medicine Zhejiang University, Hangzhou, Zhejiang, China*

Background: Paclitaxel combined with carboplatin is a standard first-line chemotherapy regimen for ovarian cancer. This study was designed to evaluate the efficacy and safety of pegylated liposomal doxorubicin (PLD) plus carboplatin (CD) compared with paclitaxel plus carboplatin (CP) as first-line treatment for epithelial ovarian cancer (EOC). **Methods:** Patients with stage IC to IV EOC, fallopian tube cancer, or primary peritoneal cancer were eligible for enrolment in this open-label, randomized controlled trial at 20 centers in China. Patients were randomly assigned 1:1 to CD group (carboplatin area under the curve [AUC] 5 plus PLD 30 mg/m²) or CP group (carboplatin AUC 5 plus paclitaxel 175 mg/m²) every 3 weeks for 3-6 cycles. The primary end point was progression free survival (PFS); secondary end points were overall survival (OS), objective response rate (ORR), disease control rate (DCR) and safety. **Results:** Between March, 2019 to December, 2021, 395 patients were enrolled, of whom 391 patients were analyzed (195 assigned to CD, 196 to CP). Baseline characteristics were balanced between the two treatment groups. The median follow-up was 21.6 months for the CD group and 22.5 months for the CP group. There was no significant difference in PFS between the two arms ($P=0.516$); the median PFS was 28.1 months and 30.1 months in the CD and CP arms, respectively. OS data were immature at data cutoff, with a total of 26 deaths in the two treatment groups. In patients with at least one measurable lesion at baseline, ORR was 65.5% in the CD arm and 66.2% in the CP arm ($P=0.941$); DCR was 74.1% and 73.8% in the CD and CP arms, respectively ($P=0.971$). Among patients who were evaluable by GCIG CA125 criteria, CA125 response was obtained in 86.0% and 88.5% of patients in the CD and CP arms, respectively ($P=0.560$). More frequent grade 1 to 3 alopecia (32.1% vs 12.3%) and neurotoxicity (20.4% vs 0%) were observed in the CP arm; more hand-foot syndrome (grade 1 to 3, 10.8% vs 2.6%), and oral mucositis (grade 1-3, 12.8% vs 5.1%) in the CD arm. **Conclusions:** The efficacy of CD regimen is comparable to that of CP, with less alopecia and neurotoxicity. CD may be an alternative first-line treatment for EOC. However, survival data are not yet mature, and longer follow-up is needed. Clinical trial information: NCT03794778. Research Sponsor: CSPC Ouyi Pharmaceutical Group Co., Ltd.

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Poster Session

DNA methylation patterns between tissue and blood samples in ovarian cancer. *First Author: Hao Wen, Department of Gynecological Oncology, Fudan University Shanghai Cancer Center, Shanghai, China*

Background: Altered DNA methylation pattern, with functional consequences in the activity of key carcinogenic pathways, has been shown to be involved in the carcinogenesis of ovarian cancer. Tumor DNA is released into the blood via apoptosis or necrosis. Therefore, cell-free DNA (cfDNA) methylation alteration can also be detected in blood, which has shown promising performance in ovarian cancer early detection and prognostication. However, the difference of DNA methylation patterns between the tissue and blood samples of ovarian cancer is still unclear. **Methods:** PERCEIVE-I study (NCT04903665) is a prospective study aimed at the early detection of gynecological malignancies. Blood and paired tissue samples from this study were collected at the Fudan University Shanghai Cancer Center. Blood samples from age-matched non-cancer controls were also collected. All the blood and paired tissue samples were sequenced by a target methylation panel covering ~490,000 CpG sites. Finally, The ovarian cancer methylation patterns were analyzed based on 11 paired cancer-adjacent tissue samples and 170 blood samples (cancer, n=48; non-cancer control, n=122). **Results:** In total, 7,225 differentially methylated blocks (DMBs) were identified by comparing cancer and adjacent tissues, with 5,093 hypomethylated and 2,132 hypermethylated. By contrast, there were 5,853 hypomethylated and 8,685 hypermethylated DMBs in cancer blood samples compared with non-cancer controls. Among the 7,225 DMBs in tissues, 3,962 (54.8%) blocks were also observed to be altered in blood samples, including 2,354 hypomethylated blocks and 1,114 hypermethylated blocks. GO analysis revealed that these hypomethylated blocks were mainly associated with functions such as regulation of synaptic membrane and DNA-binding transcription activator activity, while the hypermethylated blocks were mainly enriched in the pattern specification process, transcription factor complex, and the DNA-binding transcription activator activity. The alteration of the above 3,962 DMBs in tissue were highly correlated with the alteration in blood (correlation coefficient of 0.71, 0.50, 0.73 and 0.73 for stage I-IV, respectively). Furthermore, in patients carrying germline *BRCA1/2* mutations (n=11), most of the above DMBs were not significantly different from those without germline *BRCA1/2* mutations (n=37). **Conclusions:** In this study, we demonstrated that blood DNA methylation alteration was highly consistent with tissue DNA methylation alteration in ovarian cancer, indicating the sustained release of DNA methylation signals from the primary cancer sites. These results suggest that cfDNA methylation can be used as reliable biomarkers for the early detection of ovarian cancer. Clinical trial information: NCT04903665. Research Sponsor: None.

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Poster Session

BRCA1 and RAD51 methylation impact on outcome in patients with advanced ovarian cancer: A PAOLA-1 ancillary study. *First Author: Helene Blons, APHP, European Georges Pompidou Hospital, Department of Biochemistry, Pharmacogenetics and Molecular Oncology, Paris Cancer Institute CARPEM, Paris, France*

Background: The PAOLA-1/ENGOT-ov25 trial showed that adding olaparib (ola) to maintenance bevacizumab (bev) after first-line therapy led to a progression-free and overall survival benefit in advanced ovarian high-grade carcinoma (AOC) patients with homologous recombination deficiency (HRD) (Myriad MyChoice[®] Genomic Instability Score) or *BRCA1/2* mutations (*BRCAmut*). Here, we address the impact of *BRCA1* and *RAD51C* epimutations to improve our understanding of GIS beyond *BRCAmut*. **Methods:** *BRCA1* and *RAD51C* methylation analysis was assessed and quantified in pre-treatment biopsies (66%), after neo-adjuvant chemotherapy (NACT) (20%) or unknown (14%) from bisulfite converted DNAs using fluorescent methylation specific PCR and methylation specific droplet digital PCR (ddPCR). Methylation status was correlated to clinical data, *BRCA1/2* mutations, GIS and HRD scores, PFS (PFS1, PFS2) and OS. R (r-project.org) was used for statistical analysis. **Results:** Among the 537 patients randomized to maintenance ola + bev and 269 to placebo (pbo) + bev, 348 and 171 were available for methylation analysis. Their baseline molecular and clinical characteristics were well balanced with those of the entire cohort. Promoter methylation was identified in 67 (12.9%) samples for *BRCA1* and 25 (4.8%) for *RAD51C* (4 were methylated on both genes). Methylation and *BRCAmut* were mutually exclusive except for 3 samples. Mean GIS scores were 62.5 [59.6-65.5]; 59.4 [57.2-61.5]; 54.2 [50.5-57.8]; 23.4 [21.6-25.2] for *BRCA1* or *RAD51C* methylated (*met-tumors*), *BRCAmut*, *non-mut/non-met* HRD+ (*b-/m-HRD+*) and HRP (proficient) tumors respectively. Among *met-tumors* 92% (66/72) were GIS positive (>42). The mean GIS score of *Met-tumors* were significantly higher than that of *b-/m-HRD+* samples (p=0.009). Benefit of adding ola maintenance to bev was in a similar between patients with *met* AOC and those with *b-/m- HRD+* tumors (*table*). **Conclusions:** Methylated *BRCA1/RAD51C* tumors are HRD+ and provide to ovarian cancer patients a similar clinical benefit of ola+bev as patients with *b-/m- HRD+* tumors. Methylation assessment represents a rapid and cost effective tool; which coupled with *BRCA1-2* somatic testing allows the identification of the majority (81%) of HRD+ AOC. Clinical trial information: NCT02477644. Research Sponsor: Fondation ARC pour la recherche sur le cancer.

	BRCAmut		met		b-/m- HRD+		HRP	
	Olaparib	placebo	Olaparib	placebo	Olaparib	placebo	Olaparib	placebo
N	106	50	59	26	31	20	152	75
Median PFS1	66.3	22.0	29.8	17.4	57.1	16.6	16.7	15.1
HR	[42.6-75.2] [16.6-26.3]		[22.0-42.1] [11.1-27.7]		[18.7-NR] [11.8-24.9]		[15.3-18.8] [14.0-18.7]	
	0.42 [0.27-0.66]		0.49 [0.29-0.84]		0.34 [0.17-0.67]		0.9 [0.73-1.34]	
Median OS	NR	66.8	64.3	65.4	NR	54.4	36.6	42.1
	[55.6-NR]		[53.3-NR]		[38.5-NR]		[30.5-44.9]	
5-years survival	75%	54%	56%	52%	54%	44%	28%	35%
HR	0.52 [0.30-0.92]		0.76 [0.42-1.50]		0.78 [0.35-1.76]		1.2 [0.86-1.71]	

(NR: Not reached)

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Poster Session

Cell-free DNA in plasma and ascites as a biomarker of bevacizumab response: A translational sub-study of the REZOLVE (ANZGOG-1101) clinical trial. *First Author: Bonnita Werner, UNSW, Sydney, Australia*

Background: The REZOLVE clinical trial investigated the effect of administering bevacizumab via the intraperitoneal route to reduce re-accumulation of ascites in patients with ovarian cancer who were not suitable for further chemotherapy. Plasma and ascites were collected throughout for translational research. Ascites contains cell-free DNA (cfDNA), a large proportion of which is tumour derived (ctDNA). There is increasing interest in cfDNA in plasma, yet little is known of it in ascites. Objectives: To compare cfDNA in ascites and plasma in terms of total concentration, tumour proportion and endothelial-cell derived (ec-cfDNA) proportion and investigate their association with clinical outcomes (paracetesis-free interval, overall survival) and CA125 level. **Methods:** Longitudinal plasma and ascites samples were collected from 20/24 participants and stored at -70°C for up to 8.5 years. cfDNA was extracted from 0.3-1 mL fluid using conventional protocols. Standard and methylation-specific PCR was used to measure total cfDNA, ctDNA and ec-cfDNA. Values were correlated with time to paracetesis pre- and post-bevacizumab treatment (the primary trial outcome) as well as overall survival, using log-rank tests. Relationships with clinical CA125 levels were tested by Pearson's correlation coefficient. Comparisons between plasma and ascites used non-parametric analyses. **Results:** cfDNA was detected in all samples, with higher yield in ascites (average 669 ng/mL) than plasma (average 75 ng/mL, p<0.0001). ctDNA was detected in 30/32 (94%) ascites samples and 37/56 (68%) plasma samples. ctDNA was detected in plasma and/or ascites from each patient at at least 1 time point. ctDNA proportion was higher in ascites than plasma (p<0.0001) and ec-cfDNA proportion was higher in plasma than ascites (p=0.002). High ctDNA (>75%) in ascites at baseline was associated with significantly shorter paracetesis-free interval (median interval 47.5 versus 84 days, hazard ratio (HR) 2.21, 95% confidence interval (CI) 0.85 to 5.73, p=0.039). ctDNA presence in plasma at baseline was unfavourable for survival (median survival 56 versus 242 days, HR 3.21, 95% CI 1.15 to 9.00, p=0.008). A significant positive correlation was observed between ctDNA proportion in plasma and CA125 level measured within 7 days (p=0.0006). No difference in total cfDNA, ctDNA nor ec-cfDNA was observed between participants who were bevacizumab responders and non-responders in the trial. **Conclusions:** Sufficient cfDNA was obtained from plasma and ascites to perform qPCR for three biomarkers. Ascites was found to contain proportionately more ctDNA, while plasma contained more ec-cfDNA. The early evidence presented here supports the potential value of cfDNA biomarkers in plasma and ascites, however incorporation of their collection in future clinical trials will allow further investigation. Research Sponsor: Philanthropic.

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Poster Session

Randomized phase 2 trial of personal dendritic cell (DC)-autologous tumor antigen (ATA) vaccines in newly diagnosed advanced ovary cancer. *First Author: Bradley Corr, University of Colorado Cancer Center, Aurora, CO*

Background: Advanced ovarian cancer has a high recurrence rate and poor overall survival (OS). The addition of DC-ATA AV-OVA-1, a personal vaccine consisting of autologous DC pulsed with ATA, was investigated to pursue improving OS. **Methods:** A multi-center, 2:1 double-blind randomized phase 2 trial was designed for patients with newly diagnosed stage 3 or 4 epithelial ovary cancer to determine feasibility of manufacturing study product, and to compare safety and efficacy between DC-ATA and autologous monocytes (MC). Primary endpoint was OS from randomization. Following completion of debulking surgery and chemotherapy, about 6 to 7 months after initial tumor collection, patients were screened and eligible for randomization if a short-term cell line was established from resected tumor, sufficient numbers of MC were collected by leukapheresis, and ECOG status was 0 or 1. Intent was to enroll 99 patients stratified by whether they had residual cancer. MC were differentiated into DC by incubating with IL-4 and GM-CSF. DC-ATA was produced by incubating DC with an ATA lysate prepared from irradiated self-renewing tumor cells. Just prior to each treatment, DC-ATA or MC was admixed in 500 mg GM-CSF and injected s.c. at weeks 1, 2, 3, 8, 12, 16, 20 and 24 (up to 8 doses). Interferon-gamma elispot assays were performed on cryopreserved mononuclear cells obtained from heparinized blood collected prior to each of the first 3 injections. Patients were monitored for adverse events (AE), immune response, OS, and progression-free survival (PFS). Analysis was planned after 44 deaths. **Results:** During the SARS-CoV-2 pandemic the sponsor terminated accrual and long-term follow up. 70/72 tumors yielded a successful cell line. 20/70 patients did not proceed with leukapheresis. Sufficient MC were collected from 47/50 patients. 45 patients were randomized: 29 to DC-ATA, 16 to MC. Study arms did not differ in patient age, cancer stage, use of neoadjuvant therapy, ECOG status, or residual cancer. Injections were well-tolerated. No patient stopped therapy because of toxicity. Mean number of injections were 7.7 and 7.3. Study arms did not differ in type, proportion or severity of AE, which typically were mild to moderate, short-lived, and self-limited. Number of interferon-gamma elispots were unchanged after MC (p=0.256), but more than doubled after DC-ATA (p<0.0012). The 45 patients were followed for 1 to 31 months from randomization. Median PFS (24 events) was 16.9 months (95% CI 9.2 to 18.7); median OS was not reached (8 deaths). 1-yr OS was 91% (95% CI 78.9, 96.9), 2-yr was 80% (95% CI 49.7, 93.7). There was no difference between study arms in PFS (p=0.837) or OS (p=0.790). **Conclusions:** Manufacturing DC-ATA was feasible and treatment well-tolerated. There were no differences in AE, PFS or OS between study arms, but survival analyses were severely underpowered. An enhanced immune response was detected after DC-ATA. Clinical trial information: NCT02033616. Research Sponsor: AIVITA Biomedical Inc.

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Poster Session

Efficacy and safety of niraparib maintenance therapy in patients with newly diagnosed advanced ovarian cancer who had measurable residual disease: A post-hoc subgroup analysis of the PRIME study. *First Author: Beihua Kong, Qilu Hospital of Shandong University, Jinan, China*

Background: Niraparib maintenance therapy significantly prolonged progression-free survival (PFS) versus placebo in patients with newly diagnosed advanced ovarian cancer (aOC), but its antitumor activity remains unclear in those with measurable residual disease (MRD) after first-line platinum-based chemotherapy (1LCT). This study aims to report the efficacy, including antitumor activity, and safety of niraparib maintenance therapy in patients with MRD after 1LCT from the phase 3 PRIME trial (NCT03709316). **Methods:** In PRIME, adults with newly diagnosed aOC who had received cytoreductive surgery and responded to 1LCT were randomized 2:1 to receive niraparib or placebo with stratification by receipt of neoadjuvant chemotherapy, response to 1LCT, status of germline *BRCA* mutations, and tumor homologous recombination deficiency status. Tumor assessment was conducted at baseline and every 12 weeks thereafter by blinded independent central review (BICR) according to RECIST, version 1.1. Between 29 June 2018 and 11 November 2019, 384 patients were randomized (255 niraparib, 129 placebo). The data cut-off date was 30 September 2021. This *post-hoc* analysis reports BICR-assessed objective response rate (ORR) and PFS in patients with MRD at baseline. An initial response was confirmed $\geq$ 4 weeks later. **Results:** In total, 73 (19.0%) patients (47 niraparib, 26 placebo) had MRD at baseline. Baseline characteristics were well balanced between the two MRD groups. Complete and partial responses, both confirmed, were observed in 12 (25.5%) and 15 (31.9%) niraparib-treated patients and 3 (11.5%) and 5 (19.2%) placebo-treated patients, respectively, leading to a confirmed ORR of 57.4% with niraparib and 30.8% with placebo (odds ratio, 3.20; 95% confidence interval [CI], 1.11–9.11). ORRs by biomarker status are provided in the table. Median PFS (95% CI) was 22.3 (8.7–not estimable) months with niraparib versus 8.3 (5.6–11.0) months with placebo (hazard ratio, 0.36; 95% CI, 0.19–0.71). Treatment-emergent adverse events (TEAEs) of grade $\geq$ 3 occurred in 28 (59.6%) niraparib-treated patients and 7 (26.9%) placebo-treated patients. TEAEs led to treatment discontinuation in three (6.4%) niraparib-treated patients and one (3.8%) placebo-treated patient. **Conclusions:** In patients with newly diagnosed aOC who had MRD after 1LCT, niraparib maintenance therapy tended to induce additional antitumor activity and led to a clinically meaningful increase in PFS versus placebo. Clinical trial information: NCT03709316. Research Sponsor: This study was funded by Zai Lab (Shanghai) Co., Ltd and partially supported by the National Major Scientific and Technological Special Project for Significant New Drugs Development in 2020, China [grant number 2020ZX09101-014].

ORRs by biomarker status.

ORR, % (CR/PR/N)	Niraparib	Placebo
Germline <i>BRCA</i> mutations		
Yes	69.2 (2/7/13)	37.5 (0/3/8)
No	52.9 (10/8/34)	27.8 (3/2/18)
Homologous recombination status		
Deficient	61.3 (10/9/31)	29.4 (2/3/17)
Proficient	50.0 (2/6/16)	33.3 (1/2/9)

CR, complete response; ORR, objective response rate; PR, partial response.

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Poster Session

Ex vivo tumor testing platform for predicting clinical response to platinum-based therapy in patients with high grade serous ovarian cancer. *First Author: P. B. Ottevanger, Radboud University Medical Center, Nijmegen, Netherlands*

Background: Precision medicine for cancer patients has brought effective novel therapy options over the past decades. However, treatment for high-grade serous ovarian cancer (HGSOC) is still based on platinum-containing therapy. Around 30% (Morgan 2020) of primary disease patients do not respond to this treatment, and non-response rates in residual disease are higher still. We present an ex vivo 3D tumor testing platform that predicts patient-specific response to standard of care therapy using the CA125 half-life, the primary ovarian cancer marker (Charkhchi, 2020). **Methods:** Patients with HGSOC, eligible for platinum-based neoadjuvant chemotherapy (NACT), were included in the study between 2019 and 2022 in the Netherlands (IRB P18.032). Clinical data was collected including CA125 levels at baseline and after 2-4 courses of NACT. Tumor clusters enriched from ascites were embedded in hydrogel and exposed to first-line (carboplatin, paclitaxel) and second-line therapies (doxorubicin, gemcitabine, topotecan and olaparib). Screening plates were imaged in a high content screening 3D platform. Morphological features were extracted after image analysis and fitted as dose-response (Hill)-curves. A Bayesian linear regression model was trained on the AUCs of carboplatin and paclitaxel to predict the CA125 half-life. The result was classified according to clinical standards: insensitive (IN, progressive and stable disease), moderate response (MR), or strong response (SR). In addition, for each second-line treatment the top 25% strongest responding samples were classified as *sensitive* while the bottom 25% were classified as *resistant* samples. **Results:** The model was trained using 30 patients. The correlation coefficient between the predicted and actual CA125 half-life is 0.739 ($R^2 = 0.55$). This results in a classification accuracy of 87% (insensitive: 100% (n = 2), MR: 80% (n = 14), SR: 80% (n = 14)). The percentage of samples, per response class, responding to at least one of the alternative chemotherapies is as follows: SR: 58% (8/14), MR: 29% (4/14) and IN 50% (1/2). For olaparib the equivalent results are SR: 36% (5/14), MR: 21% (3/14) and IN: 0% (0/2). When sufficient tumor content is received, the assay has a technical success rate of 89%. Results are delivered in two weeks. **Conclusions:** The presented platform for ex vivo tumor testing predicts clinical response to platinum-based NACT in HGSOC patients. The same platform measured patient specific patterns of relative sensitivity to other chemotherapies. The platform enables better stratification of responders vs non-responders, and can support informed treatment decisions for first-line and second-line therapies. The value of integration of this predictive tool in the clinical routine will be assessed in an ongoing prospective trial for patients with suboptimal response and recurrent disease. Clinical trial information: P18.032. Research Sponsor: VitroScan BV; Subsidy: EUREKA Eurostars.

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Poster Session

Germline variants in non-*BRCA1/2* homologous recombination-related genes and ovarian cancer: Analysis of tumor phenotype and survival. *First Author: Ryan M. Kahn, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: *BRCA1/2*-associated ovarian cancer (OC) exhibits homologous recombination (HR)-deficiency (HRD) and a better prognosis than *BRCA1/2*-wildtype (WT) OC. However, it is unclear if patients with germline pathogenic variants (gPV) in other HR-related genes have a similar tumor phenotype. We sought to define OC molecular features from patients with gPV in other HR genes and analyze survival compared to patients with *BRCA1/2* and WT OC. **Methods:** We identified patients with OC treated at our institution who underwent tumor-normal sequencing using MSK-IMPACT targeting 341-505 cancer-related genes with germline analysis of ≥ 76 genes from 7/2015-12/2020. Biallelic inactivation was inferred via assessments of loss of heterozygosity (LOH) at gPV in non-*BRCA1/2* HR-related genes (*ATM*, *BARD1*, *BRIP1*, *FANCA*, *FANCC*, *NBN*, *PALB2*, *RAD50*, *RAD51B*, *RAD51C*, and *RAD51D*). Clinical characteristics were compared to patients with *BRCA1/2*-associated and WT OC using non-parametric tests. Progression-free (PFS) and overall-survival (OS) were calculated from date of pathologic diagnosis using the Kaplan-Meier method. Left truncation at date of MSK-IMPACT consent was applied. Whole-exome sequencing (WES) was performed in a subset of OCs. **Results:** Of 882 patients with OC, 56 (6.3%) had gPV in non-*BRCA1/2* HR-related genes compared to 95 (10.8%) patients with *BRCA1*-associated OC (58 germline, 37 somatic) and 59 (6.7%) patients with *BRCA2*-associated OC (40 germline, 19 somatic). Patients with a deleterious genetic alteration were diagnosed with OC at younger age and more likely to have high-grade serous histology compared to the WT group ($p < 0.01$). High rates of biallelic alterations were observed amongst gPV in *BRIP1* (11/13), *PALB2* (3/4), *RAD51B* (3/4), *RAD51C* (3/4), and *RAD51D* (8/10), and WES was performed in a subset ($n = 27$) of tumors from these patients with adequate tumor purity ($>30\%$). We observed a higher tumor mutational burden (TMB), median 2.5 (1.1-6.0) vs. 1.2 (0.6-2.6) mut/Mb, and enrichment of HRD mutational signatures in tumors associated with *PALB2* and *RAD51B/C/D* compared with *BRIP1* ($p < 0.01$), although markers of telomeric-allelic imbalance (TAI), large-scale state transitions (LST) and fraction of genome altered (FGA) were similar. PFS and OS varied by gene group with best survival in *BRCA1/2*-associated OC, even after adjustment for clinical covariates in multivariable models ($p < 0.01$). Although we observed heterogeneity in PFS and OS for those with gPV in other HR-related genes by biallelic status and HRD phenotype, none had significantly better survival than those with WT OC. **Conclusions:** OCs associated with gPV in non-*BRCA1/2* HR-related genes represent a heterogeneous group. OCs in those with gPV in *PALB2* and *RAD51B/C/D* preferentially harbored biallelic alterations and displayed an HRD phenotype. Research Sponsor: U.S. National Institutes of Health; MSKCC.

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Poster Session

Phase 2 trial of TRC102 (methoxyamine HCl) with temozolomide (TMZ) in patients with granulosa cell ovarian cancer. *First Author: Sarah Shin, Developmental Therapeutics Clinic/Early Clinical Trials Development Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute, Bethesda, MD*

Background: TRC102 is a novel small molecule that binds to reactive aldehyde created in apurinic/apyrimidinic (AP) sites, inhibiting base excision repair (BER), which is implicated as a pathway of resistance to alkylating agents. In preclinical studies, TRC102 demonstrated synergistic anti-tumor activity when TRC102 was combined with the alkylating agent temozolomide (TMZ) and the phase 1 trial of this combination reported 4 patients with partial response, two of which were of granulosa cell ovarian cancer (GCOC) histology. Here we report the phase 2 results of the combination TRC102 and TMZ in the GCOC cohort (NCT01851369). **Methods:** We conducted an open-label, single center Simon 2-stage trial including patients (pts) with GCOC who received $\geq$ one line of therapy in the metastatic setting. TRC102 was dosed at 125 mg (100 mg for BSA < 1.6) and TMZ was dosed at 150 mg/m² orally on day (D) 1-5 in 28-day cycle (C). Restaging CT scans every 2 Cs were evaluated by RECIST v1.1. Mandatory paired biopsies (C1D1 pretreatment and C1D4 3-4 hours after drug administration) and optional blood samples for circulating tumor cells (CTC) were collected at set time points for pharmacodynamic analyses. **Results:** Nine pts with GCOC (7 adult, 2 juvenile histology) were enrolled as of 12/23/2022. Median age was 53 years (range 21-79) and median prior lines of therapy was 6 (range 3-9). Most common grade (G) 1 and G2 treatment-related adverse events (trAE) were fatigue, myelosuppression, nausea, and vomiting. One pt had G3 trAE of vomiting. No toxicity-related treatment discontinuations and no treatment-related deaths were reported. The median PFS for the 8 evaluable pts was 3.7 months. One pt exited the study after one C per pt's choice with no restaging available. Four pts had stable disease (SD) as their best response. Of those who had SD, one pt completed 26 Cs prior to progression, one pt completed 11 Cs as of data cut-off but continues on study, two pts completed 6 Cs (one pt went off study for PD and one by pt choice). MGMT analysis was performed for 3 pts, including the pt still on study after 11 Cs with SD. MGMT immunohistochemistry (IHC) of pretreatment biopsies were positive for protein expression, consistent with unmethylated MGMT status. No significant induction in the levels of the DNA damage response markers γ H2AX, pNbs1, and RAD51 was detected in 5 evaluable post-treatment biopsy samples as compared to the pre-treatment timepoint. **Conclusions:** TRC102 combined with TMZ was well-tolerated and demonstrated durable disease control in 4 pts, which is promising in this heavily pretreated GCOC cohort. MGMT analysis suggests that unmethylated MGMT status and protein expression does not preclude response to TRC102/TMZ combination therapy. Analysis of CTCs and biopsy samples are ongoing to further elucidate possible biomarkers of response. Funded by NCI Contract No. HHSN261201500003I. Clinical trial information: NCT01851369. Research Sponsor: U.S. National Institutes of Health.

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Poster Session

Anastomotic leakage following bowel resection in radical cytoreductive surgery for ovarian cancer: A subgroup analysis of the prospective AGO-OVAR.OP3/LION. *First Author: Bastian Czogalla, Department of Obstetrics and Gynecology, University Hospital, Ludwig-Maximilians-Universität München, Munich, Germany*

Background: Anastomotic leakage (AL) is an important and severe complication following bowel resection in cytoreductive surgery (CRS) for ovarian cancer (OC). Identifying patients (pts) at risk for AL could improve clinical management and reduce frequency and severity of complications. **Methods:** AGO-OVAR.OP3/LION intraoperatively randomized 647 pts with advanced OC (FIGO IIB-IV) following complete cytoreduction with unsuspected lymph nodes to either undergo systematic pelvic and paraaortic lymphadenectomy (LNE) or not. All pts who underwent bowel resection were included in this analysis. Potential prognostic impact of AL was analyzed by Kaplan-Meier method and log-rank tests regarding progression-free (PFS) and overall survival (OS). Risk factors for AL in a subset of clinicopathological parameters were evaluated by calculating odds ratio (OR) with 95% confidence interval (CI) in univariate and multivariate logistic regression models. A stepwise variable selection algorithm using the Akaike Information Criteria (AIC) for identification of the final logistic regression model was applied. *P* values presented were two-tailed, and $P < 0.05$ was considered as statistically significant. **Results:** Among all 647 randomized pts, AL was noted in 24 (3.7 %) pts. The AL rate of the 336 pts with bowel surgery during CRS (median age 61.3 years; 316 large bowel, 94 small bowel resections) was 7.1% (24/336 pts). Pts following stoma formation had an AL rate of 5.5% (3/55 pts) compared to 7.5% (21/281 pts) in pts without stoma. Median PFS was 18 months in pts with AL versus 19 months in the no-AL-group (hazard ratio (HR) 0.86; 95% CI 0.5 to 1.4, $P=0.53$), median OS was 31 months in the AL group and 58 months in the no-AL-group (HR 0.69; 95% CI 0.4 to 1.2, $P=0.17$). The clinicopathological characteristics "volume of blood loss" (OR 1.05 per 100cc; 95% CI 1.01-1.10) and "LNE vs non-LNE" (OR 4.10; 95% CI 1.60-12.62) were identified as factors potentially predictive for AL in univariate analysis, and both factors (volume of blood loss [OR 1.04 per 100cc, 95% CI 1.0001-1.09], LNE vs non-LNE [OR 3.67, 95% CI 1.41-11.39]) remained a significant independent factor in multivariate analysis. **Conclusions:** Considering the high surgical complexity in this large prospective surgical trial, the overall rate of AL following bowel surgery was relatively low and had no significant impact on PFS or OS. While protective stoma formation was not identified as protective factor in this cohort, volume of blood loss and LNE procedure were clinical parameters associated with higher risk of AL. Being potential surrogates for extensive surgery, these factors should be considered in perioperative management in pts with advanced OC. Further specific factors predicting AL were not identified. Clinical trial information: NCT00712218. Research Sponsor: Deutsche Forschungsgemeinschaft; Austrian Science Fund.

Proactive assessment of patient reported outcomes in patients with ovarian cancer. *First Author: Ainhoa Madariaga, 12 de Octubre University Hospital, Madrid, Spain*

Background: Patient reported outcome (PRO) measures are key instruments to provide an evaluation of health outcomes from the patient's perspective. Assessment of PROs may help identify the nature, severity, and time course of symptoms of concern in patients with ovarian cancer. The ability to access this information in real-time, including changes over time, could improve patient safety and decision-making. **Methods:** This systematic review evaluated the proactive or real-time assessment of PROs in patients with ovarian cancer undergoing systemic therapy. Medline, Embase, and Cochrane databases were searched (up to February 2022), and prospective ovarian cancer studies (experimental or observational) that incorporated PROs (including quality of life) were included. Conference abstracts were excluded. Primary objective was to assess the frequency of studies incorporating proactive use of PROs. A secondary objective was to describe PRO reporting. Descriptive statistics were used. **Results:** 3,071 articles were screened, with 117 included in the final analysis. Studies were published between 1990-2022 and contained 35,735 patients (median 140 patients per study; inter-quartile range 58-415). Median time from patient enrollment initiation to study publication was 7 years (range 1-15). Most studies were experimental/clinical trials (n=93, 79%), followed by observational (n=23, 20%) and not reported (n=1; Table). Among experimental studies, 56% (52/93) were phase III, 35.5% (33/93) phase II, 6.5% (6/93) phase I or I/II trials and it was not reported in two. Therapeutic strategies were assessed in 98% (91/93) of experimental studies, being the most frequent one chemotherapy (n=53, 58%), followed by antiangiogenics and PARP inhibitors (n=8, 9%, each). Types of observational studies were descriptive 43.5% (10/23), cohort 26% (6/23), cross-sectional 22% (5/23), or other 9% (2/23). PROs were the primary objective in 7.5% (7/93) and 83% (19/23) of experimental and observational studies respectively. The table describes PRO reporting standards per type of study. PROs were assessed in real-time in 0.8% (1/117) of studies. **Conclusions:** Completion of PRO and quality of life questionnaires involve time and effort for patients with ovarian cancer. PRO questionnaire responses were only assessed in real-time in <1% of analyzed studies. Efforts should be made to incorporate proactive assessment of PROs to optimize patient care and safety. Research Sponsor: None.

Summary of PRO reporting information provided in the study publication.			
	Observational or not reported n=24	Experimental n=93	Overall n=117
	% (n)	% (n)	% (n)
Questionnaire type	100% (24)	97% (90)	97% (114)
Questionnaire number/frequency	96% (23)	85% (79)	87% (102)
Missing data	46% (11)	69% (64)	64% (75)
Collection method (e.g. paper, electronic)	21% (5)	5% (5)	8.5% (10)
Minimally important difference	12.5% (3)	20% (19)	19% (22)
Real-time assessment	0%	1% (1)	0.8% (1)

CD47 expression in ovarian cancer: Dynamic correlation with lymphocyte and macrophage features as well as thrombospondin-1 (TSP-1) under neo-adjuvant chemotherapy. *First Author: Alexandra Leary, Gustave Roussy Cancer Center, INSERM U981, and Groupe d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens (GINECO), Villejuif, France*

Background: To date, the results of immunotherapy strategies to treat ovarian cancer (OC) have been unfulfilling. A more comprehensive knowledge of the intricate immune tumor microenvironment (iTME) as well as the effects of chemotherapy on immune features may reveal novel immune targets. CD47 is overexpressed in OC and correlates with shorter survival and immune evasion via interaction with circulating ligands such as TSP-1. Little is known about how the CD47 receptor or its ligand TSP-1 changes under chemotherapy or their association with other features of iTME. In the randomized CHIVA trial, we therefore investigated CD47 expression in OC patients at diagnosis and after neoadjuvant chemotherapy (NACT) and assessed its relationship to other iTME features, including circulating level of thrombospondin-1 (TSP-1). **Methods:** Tumour samples were collected from 105 patients from the CHIVA trial, a GINECO-GINEGEPS study. CD47 expression was assessed by IHC in paired samples before and after NACT and scored by H-score: staining intensity (0, +1, +2, +3) x % cells positive (0-300). At baseline, we defined a CD47^{high} (highest quartile, score above 240) and CD47^{low} population (lowest quartile, score under 150). CD4⁺, CD8⁺, CD68⁺, CD163⁺, FoxP3⁺ cells were assessed by IF and scored as number of positive cells. The Pearson correlation coefficient (r) was used to determine the linear correlation between CD47 expression and other immune markers. Circulating TSP-1 was quantified by ELISA on paired plasma samples pre- and post-NACT. **Results:** While CD47^{high} does not correlate with CD4 and CD8 expression at baseline, a correlation with CD8 (r=0.59, p=0.02) and a trend with CD4 (r=0.49, p=0.05) is observed after NACT. These linear correlations do not exist in the CD47^{low} population. In addition, NACT induces a 2-fold decrease in FoxP3⁺ cells, but only within the CD47^{high} group (p=0.028). Thus, both the CD4⁺/FoxP3⁺ (p=0.001) and CD8⁺/FoxP3⁺ (p=0.005) ratios were increased by 2-fold under NACT, exclusively in OC patients with CD47^{high} expression. Interestingly, these correlations appear to be T-cell specific as no correlation exist when considering CD68 and CD163 before or after NACT, neither for CD47^{high} nor CD47^{low}. In parallel, we determined that the plasma level of TSP-1, a preferential CD47 agonist, was very high (>1500 ng/mL) in OC patients and decreased by about 2-fold after NACT. Interestingly, a pattern emerges in which the highest level of circulating TSP-1 is associated with the CD47^{low} population. **Conclusions:** Our data suggest that OC patients with the highest CD47 expression profile at baseline have greatest lymphocyte influx post-NACT and may be most likely to benefit from post-operative immunotherapy. Whether blocking the immune-suppressive CD47:TSP1 interaction in this subset would provide an alternative strategy merits investigation. Clinical trial information: NCT01583322. Research Sponsor: French National Cancer Institute (INCa).

The effect of maintenance hormone therapy on overall survival in advanced-stage low-grade serous ovarian carcinoma: A risk-set matched retrospective study. *First Author: Syem Barakzai, Massachusetts General Hospital, Boston, MA*

Background: Low-grade serous ovarian carcinoma (LGSOC) is a rare malignancy often treated similarly to high-grade serous ovarian carcinoma (HGSOC) despite differences in clinical behavior and carcinogenesis. Observational studies suggest that, among patient with advanced-stage LGSOC, maintenance hormonal therapy (HT) following primary treatment is associated with improved progression free survival. We conducted a multi-institutional observational study to investigate whether HT is associated with an overall survival advantage in this setting. **Methods:** We included patients with histologically confirmed stage III or IV LGSOC diagnosed between Jan 1, 2004, and Dec 31, 2019, treated in Commission on Cancer accredited cancer programs in the US. Patients who received HT within 6 months of diagnosis were matched to controls who did not initiate HT during this timeframe. The primary outcome was risk of death from any cause, within five-years of initiation of HT or observation. For each treated patient, we employed risk-set propensity score matching to identify a control in a manner that avoided the introduction of immortal-time-bias, and balanced groups with respect to year of diagnosis, upfront treatment strategy, age, stage, race/ethnicity, comorbidity index, insurance status, zip-code median income, and cancer program type. **Results:** There were 296 patients who initiated HT within 6 months of diagnosis, and 2,805 potential controls. Patients who received HT were more often treated in academic medical centers (55% vs 44%), diagnosed later in the study period (62% vs 23% diagnosed in 2018-2019), and received upfront chemotherapy less frequently (55% vs 83%). After risk set and propensity score matching, we identified 204 patients treated with HT and 204 untreated controls, who were otherwise similar with respect to measured covariates. In the matched cohort, maintenance HT was associated with a reduction in the risk of death (hazard ratio 0.61; 95% CI 0.37-0.99), corresponding to a 60-month survival of 71% compared with 61%, and an improvement in 5-year life expectancy of 3.6 months (95% CI 0.004-7.2). **Conclusions:** Maintenance hormone therapy following primary management of LGSOC is associated with an overall survival benefit compared with observation. Research Sponsor: None.

Trends in ovarian cancer incidence and incidence-based mortality: A 15-year population-based analysis. *First Author: Sahana Somasegar, Stanford University School of Medicine, Palo Alto, CA*

Background: The predicted incidence and incidence-based mortality (IBM) of ovarian cancer (OC) in 2023 is lower than prior years. OC encompasses a range of heterogeneous cancers with subtypes categorized on histology and site of origin. Given differences in survival and treatment paradigms, we aim to characterize trends in OC incidence and IBM based on histology and site of origin to determine what factors are responsible for the decline. **Methods:** Patients with OC from 2000-2019 were identified from the US Surveillance, Epidemiology, and End Results 17 registry database. Using ICD-O-3 codes, patients with epithelial, stromal, and germ cell cancers of the ovary, fallopian tube, and peritoneum were included. Incidence and IBM were reported as age-adjusted rates and stratified by cancer subtype. Using Joinpoint 4.9.1.0, we characterized piecewise log-linear time trends to identify inflection points in the rates' annual percentage change (APC). **Results:** The incidence of epithelial OC decreased significantly from 2004-2019 (APC -1.24%). When stratified by disease stage, this trend was seen in distant disease (APC -2.11%) and unknown/unstaged disease (APC -3.40%); however, there was a significant increase in incidence of local disease (APC +0.83%). There was no significant change in the incidence of germ cell and stromal OC from 2004-2019 in all stages. (APC -0.30% and +0.33%). Among all OC subtypes, there was a significant decline in incidence from 2000-2019 (APC -1.57%) with a sharper decline from 2015-2019 (APC -3.41%). Among all cancer subtypes, the incidence trended down from 2000-2019, with a significant decline from 2015-2019 (APC -2.37%). Similar trends are observed in IBM. Among all stages of epithelial OC, there was a significant decrease in IBM from 2006-2019 (APC -2.02%). When stratified by disease stage, there was a decline in IBM in local disease (APC -7.19%, 2014-2019) and distant disease (APC -2.44%, 2010-2019). There were no changes in IBM of germ cell and stromal OC from 2004-2019 (APC +0.78% and -0.20%). Among all cancers, IBM significantly decreased from 2006-2019 (APC -2.28%). When stratified by disease stage, there was no change among local disease and an increase in regional disease from 2006-2019 with the increase from 2006-2010 (APC +14.35%) compared to 2010-2019 (APC +1.45%). Conversely, there was a significant decrease in IBM for distant disease (APC -2.51% from 2010-2019) and unknown/unstaged disease (APC -3.27% from 2006-2019). **Conclusions:** There has been an overall decline in incidence and IBM of OC over a 15-year period, primarily driven by the epithelial histology. Over the past 20 years, OC has been increasingly diagnosed at earlier stages with a corresponding improvement in survival. While stage migration and improved survival may contribute to these trends, they do not entirely explain them. As new treatments become available, the incidence and IBM of OC may further decline. Research Sponsor: None.

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Poster Session

Mechanisms of resistance to bispecific T-cell engager therapy for ovarian cancer. *First Author: Syem Barakzai, Massachusetts General Hospital, Boston, MA*

Background: Patients with recurrent ovarian cancer (OC) invariably develop multidrug resistance and have poor prognoses. Bispecific T-cell engager (BiTE) immunotherapy represents an innovative therapeutic modality where cytotoxic T-cells are activated and recruited to tumor cells using a predefined tumor-associated antigen. Clinical trials evaluating BiTEs in OC are currently in progress with promising results, and exploration of potential mechanisms of resistance to BiTEs could provide meaningful insight into disease biology and combination strategies. **Methods:** After obtaining informed consent, experiments were performed on patient samples collected under an IRB-approved tissue-banking protocol. Samples were collected before patients started clinical trials and at disease progression. Serum, peripheral blood mononuclear cells (PBMCs), and malignant ascites were collected when available for translational analysis. Immune cell subsets were evaluated for activation and exhaustion via flow cytometry, and tumor cells were subjected to western blot analysis and IHC. Ex vivo cytotoxicity assays were performed using BiTEs, patient tumor samples, OC cell lines (immortalized), and patient-derived and healthy donor PBMCs. Patient serum samples were analyzed by multiplex ELISA to determine cytokine and chemokine signatures. **Results:** Serum and PBMC samples from 10 patients and ascites from 2 patients were used for these analyses. Cells derived from patient ascites after progression on BiTEs were primarily comprised of tumor cells and myeloid-derived suppressor cells (MDSCs). These tumor cells had lost expression of the target antigen recognized by the BiTE and upregulated markers as N-cadherin and vimentin with concordant down-regulation of E-cadherin consistent with epithelial to mesenchymal transition (EMT). Ascites immune subset analysis showed a predominance of CD11b+, CD163+, and PD-L1+ cells. Compared to PBMCs from healthy donors, patient PBMCs showed higher frequencies of CD4+ TIM3+ LAG3+ cells consistent with T-cell dysfunction. Compared with healthy donors, serum from patients revealed higher levels of myeloid recruiting and activating chemokines and cytokines (CCL3, CXCR3, CXCL10, and IL18) and low immunostimulatory cytokines (IL-7 and IFN- α). Coculture of patient tumor cells with BiTEs and T-cells ex vivo showed diminished cytotoxicity, consistent with the loss of target antigen expression. Patient PBMCs retained cytotoxicity against OC cell lines ex vivo, suggesting preserved cytotoxic capacity. Finally, T-cells cocultured in the presence of patient serum displayed suppressed cytotoxicity against OC cell lines. **Conclusions:** Resistance to BiTE therapy is multifactorial, primarily involving tumor-associated antigen loss, EMT, and an immunosuppressive tumor microenvironment. Combination treatment approaches to mitigate these factors might increase response rates. Research Sponsor: Nile Albright Research Foundation; Julie Fund, Mary Margaret Darling Flatley Foundation, Worden Fund.

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Poster Session

Impact of cytoreductive surgery on survival outcomes for recurrent adult-type granulosa cell tumors of the ovary. *First Author: Jeffrey How, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Adult-type granulosa cell tumor of the ovary (aGCT) is a rare tumor that often relapses and the optimal management strategy is not known. Cytoreductive surgery (CRS) offers an attractive option for disease confined to the abdomen/pelvis. However, few studies have evaluated the role of CRS compared to systemic therapy alone. Thus, the study objective was to determine the impact of secondary, tertiary, and quaternary CRS on survival outcomes for patients with relapsed aGCT. **Methods:** This was an IRB-approved retrospective cohort study that evaluated all patients with relapsed aGCT who were enrolled in the Rare Gynecologic Malignancy Registry at MD Anderson. Study inclusion criteria were patients who had histology-proven aGCT, were above 18 years of age, had at least one documented relapse, and had received treatment or treatment planning at MD Anderson. Progression-free survival (PFS) endpoints were the outcomes of interest and were defined as follows: PFS2 was defined from first recurrence to subsequent progression or death (PFS2), PFS3 was defined as second relapse/progression to third relapse/progression or death, and PFS4 was similarly defined. PFS2, PFS3, and PFS4 were estimated with methods of Kaplan and Meier and were modeled via cox proportional hazards regression. Analyses were performed among those with resectable disease at time of disease progression. **Results:** Among the 369 aGCT patients identified from January 1970 to October 2022, 162 met the study inclusion criteria for analysis. The mean age of diagnosis was 44.4 years old and the majority were initially diagnosed with stage 1 disease (72.8%). The median follow-up time for all patients was 5.86 years (range 0.09 – 34.27). At the first relapse, there were 151 patients who had resectable disease with 128 who underwent secondary CRS. PFS2 was significantly improved among those who underwent CRS compared to those who did not (HR 0.50, 95% CI 0.30 – 0.81; $p = 0.005$) with the median PFS2 difference being 18.24 months ($p = 0.006$). At the second relapse/progression, there were 120 patients with resectable disease with 52 who underwent tertiary CRS. PFS3 was significantly improved among those who underwent CRS compared to those who did not (HR 0.57, 95% CI 0.39 – 0.84; $p = 0.004$) with the median PFS3 difference being 6 months ($p = 0.01$). At the third relapse/progression, there were 96 patients with resectable disease with 46 who underwent quaternary CRS. There was a trend towards improved PFS3 among those who underwent CRS compared to those who did not (HR 0.69, 95% CI 0.45 – 1.06; $p = 0.09$). The use of systemic or hormonal therapy did not confer additional PFS benefit among those who underwent CRS. **Conclusions:** For relapsed, resectable aGCT, CRS may offer a beneficial impact on PFS. Future studies should evaluate the role of CRS on survival outcomes. Research Sponsor: None.

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Poster Session

Patterns of ovarian cancer care in an elderly population in Australia: A prospective cohort study from the National Gynaecology Oncology Registry (NGOR). *First Author: Mahendra Naidoo, Monash University School of Public Health and Preventive Medicine - Cancer Research Program, Melbourne, VIC, Australia*

Background: Elderly women with ovarian cancer are often undertreated in comparison to best practice. The National Gynaecology Oncology Registry (NGOR) is Australia's first country-wide clinical quality registry (CQR) measuring compliance with optimal care defined by a set of clinical quality indicators (CQIs). **Objectives:** To assess compliance with a predefined set of CQIs for elderly women with newly diagnosed ovarian cancer aged > 75 compared to non-elderly women aged < 75 years of age from the NGOR sites. **Methods:** All women with newly diagnosed ovarian cancer from May 2017 – July 2022 were eligible for inclusion. Data were collected from medical records and relevant hospital linked databases by expert data managers. **Results:** A total of 1590 women were eligible for inclusion from 21 hospitals across 5 Australian states. The CQI data were subsequently aggregated and are summarised in the table. The proportion of elderly women receiving first-line chemotherapy with a platinum and taxane doublet was significantly lower compared to non-elderly (60% vs 89%, $p < 0.001$). The proportion of women with sub-optimally debulked or Stage IV cancer who received first-line chemotherapy with a platinum/taxane doublet and bevacizumab was significantly lower in elderly women compared to non-elderly (10% vs 30%, $p < 0.001$). Enrolment in clinical trials or translational research was significantly lower in elderly women compared to non-elderly (13% vs 21%, $p = 0.002$). The remaining CQIs showed no significant differences between the age groups. **Conclusions:** In this cohort, most measures of best practice were not significantly different between elderly and non-elderly women, with the exception of elderly women receiving less first line doublet chemotherapy, less doublet chemotherapy with bevacizumab in sub-optimally debulked or Stage IV cancer, and less likely to be enrolled in clinical trials or translational research. While these 3 CQIs represent a minority of the overall list of CQIs, such lack of compliance may result in significant differences in quality of life and overall survival for elderly women with ovarian cancer. Subsequent investigation is therefore warranted to confirm and explain these findings. Research Sponsor: MRFF.

Clinical Quality Indicators by age group.

CQI	Women aged < 75 (n = 1307)	Women aged > 75 (n = 283)	p-value
Presented at a multi-disciplinary team meeting	98 %	98 %	0.7
Histological or cytological diagnosis confirmed prior to receiving first-line neoadjuvant chemotherapy.	88 %	91 %	0.3
Primary surgery (no macroscopic residual disease)	57 %	50 %	0.4
Interval surgery (no macroscopic residual disease)	46 %	40 %	0.4
1st line chemotherapy with a platinum/taxane doublet	89 %	60 %	< 0.001
1st line chemotherapy with a platinum/taxane doublet and bevacizumab in sub-optimally debulked or Stage IV cancer	30 %	10 %	< 0.001
Enrolled in clinical trial/translational research	21 %	13 %	0.002

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Poster Session

A phase 1 study of the SYK inhibitor fostamatinib and weekly paclitaxel for recurrent platinum-resistant ovarian cancer. *First Author: Stephanie Gailard, Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD*

Background: Response to chemotherapy in patients (pts) with recurrent platinum-resistant ovarian cancer (PROC) is generally $< 15\%$. Spleen tyrosine kinase (SYK) is overexpressed in PROC and is a key mediator of paclitaxel resistance in ovarian cancer cells. Fostamatinib (Fos), an orally available inhibitor of SYK, is currently FDA approved for the treatment of idiopathic thrombocytopenic purpura. The active form of Fos (R406) was shown to synergistically enhance taxane-mediated cytotoxicity in preclinical ovarian cancer models. This phase 1 study aimed to identify the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) of Fos when combined with standard weekly paclitaxel (wPac) for pts with PROC. **Methods:** Pts with PROC, defined as progression ≤ 6 months of last platinum, were eligible. A modified toxicity probability interval (mTPI) dose escalation design was used to determine the MTD/RP2D and response was assessed using RECISTv1.1 criteria. All pts received paclitaxel (wPac) 80mg/m² intravenously on Days 1, 8, and 15, of a 28-day cycle. Fos was administered orally twice a day (BID) on a continuous schedule. Three dose levels (DL) were planned: DL1 - 100mg, DL2 - 150mg, and DL3 - 200mg. MTD was determined based on cycle 1 dose-limiting toxicities (DLTs) and responses were assessed every 2 cycles. A dose expansion cohort to further assess adverse events (AEs) and tolerability was performed. **Results:** 27 eligible pts, median age 62 years (range 35-79 years) with high-grade serous (n = 18), clear cell (n = 4), carcinosarcoma (n = 3), or other (n = 2) histology were treated at 3 centers. Twelve pts were treated in the dose escalation cohort (DL1 = 6, DL2 = 3, DL3 = 3). Common AEs at least possibly attributed to Fos, wPac, or both included diarrhea (70%), fatigue (52%), anemia (44%), neutropenia (33%), nausea (33%), hypertension (30%), and dysgeusia (30%). Treatment-emergent grade 3-4 AEs were neutropenia (37%), anemia (26%), and thromboembolic event (22%). During DL1, updated toxicity management guidelines not consistent with the original protocol were released and 2 of the 3 pts treated prior to the amendment were not considered evaluable for DLT. Thus 3 more pts were enrolled to DL1 after the amendment. Of the 10 pts evaluable for DLT in dose escalation, no DLTs were reported on any of the 3 DLs (DL1 = 4, DL2 = 3, DL3 = 3). DL3 was selected for dose expansion. One of 15 pts in the dose expansion cohort had a DLT (neutropenia) and one patient had a grade 5 infection. Of 18 pts treated at DL3, 7 (39%) had partial or complete response (95% CI: 17.3, 64.3%). Overall, 27 patients received a median of 3 cycles (range 0-10). Analysis of pharmacokinetic and correlative molecular studies of target expression are ongoing. **Conclusions:** The RP2D of Fos will be 200 mg orally BID when combined with wPac. AE profile of the combination was as expected and the combination demonstrated promising efficacy in pts with recurrent PROC. Clinical trial information: NCT03246074. Research Sponsor: U.S. National Institutes of Health; Alleghany Health Network; Johns Hopkins.

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Poster Session

Anlotinib combined with carboplatin/paclitaxel and maintenance anlotinib as front-line treatment for newly diagnosed advanced ovarian cancer: A phase II, single-arm, multicenter study (ALTER-GO-010). *First Author: Yi Jiang, Jiangsu Province Hospital, Nanjing, China*

Background: Several studies have shown that antiangiogenic drug combined with chemotherapy as first-line treatment, followed by antiangiogenic drug maintenance therapy significantly improve outcomes for patients with ovarian cancer. Anlotinib, a highly effective VEGFRs, FGFRs, PDGFRs and c-kit multi-target tyrosine kinase inhibitor, has been approved for multiple tumor types in China. The aim of this single arm, multicentric, phase II study is to investigate the efficacy and safety of using anlotinib combined with carboplatin/paclitaxel as front-line treatment for advanced ovarian cancer patients. **Methods:** Eligible patients with FIGO stage III–IV primary epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer and ECOG PS 0–1 undergo primary cytoreductive surgery or interval debulking surgery, will receive 6–8 cycles of chemotherapy (paclitaxel 175 mg/m² + carboplatin area under the curve [AUC] 5 q3w) and anlotinib (12 mg po qd, days 1–14, 21 days per cycle, anlotinib will be omitted from the first treatment cycle to prevent delayed wound healing). After chemotherapy finished, anlotinib continues as maintenance monotherapy until disease progression, unacceptable toxicity, or death. Patients with prior anti-angiogenic therapy or major surgical procedure within 28 days before starting anlotinib therapy will be excluded. The primary endpoint is progression free survival (PFS). Key secondary endpoints include overall response rate, disease control rate per RECIST1.1, overall survival, safety. **Results:** From 9 Sep 2021 to 30 Jan 2023, 30 pts were enrolled, including 96.7% (29/30) high-grade serous carcinoma (HGSC) and 3.33% (1/30) endometrioid carcinoma (EC). The median age was 56 years old, with 96.7% (29/30) patients in FIGO stage III and 3.33% (1/30) in stage IV. Median follow-up was 5.36 (95% CI: 3.68, - 7.98) months. PFS rates at 6 months and 9 months were both 100%. Twenty-nine patients (96.7%) experienced adverse events (AE) of any level. The most common AEs include white blood cell decreased, neutrophil count decreased, anemia, platelet count decreased, lymphocyte count decreased and hypertension. There was no treatment-related death during the study. **Conclusions:** Preliminary results of anlotinib combined with carboplatin/paclitaxel have shown favorable efficacy and tolerated safety profile in newly diagnosed advanced ovarian cancer patients. Clinical trial information: NCT04807166. Research Sponsor: Chia Tai Tianqing Pharmaceutical Group Co., Ltd.

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Poster Session

First-in-human, phase I study of CBP-1008, a bi-specific ligand drug conjugate, in patients with advanced solid tumors. *First Author: Jifang Gong, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Department of Gastrointestinal Oncology/Early Drug Development Center, Peking University Cancer Hospital & Institute, Beijing, Beijing, China*

Background: Folate receptor α (FR α) and vanilloid subfamily member 6 of transient receptor potential channels (TRPV6) are overexpressed in many solid tumors including ovarian cancer hence could be promising therapeutic targets. CBP-1008 is a first-in-class bi-specific ligand drug conjugate targeting FR α and TRPV6 carrying monomethyl auristatin E (MMAE) as payload. **Methods:** CBP-1008 was administered by intravenous infusion. Phase Ia study included a dose-escalation period initiated by accelerated titration (0.015, 0.03mg/kg d1,15; q28d) and then switched to 3–3 scheme (0.12, 0.15, 0.17, 0.18mg/kg d1,15; q28d) and a dose expansion period. Phase Ib clinical expansion study included 3 cohorts, platinum-resistant ovarian cancer (PROC), metastatic triple negative breast cancer (TNBC) and other solid tumors. The primary objective was to assess the safety and preliminary efficacy. **Results:** As of September 30, 2022, 178 patients received at least one dose of study drug were enrolled (phase Ia: n=35; phase Ib: n=143) and received median 3 prior regimens. Included tumor species were PROC (n=101), TNBC (n=25), ER+/Her2+ breast cancer (BC) (n=17), colorectal cancer (n=6), pancreatic cancer (n=12) and others (n=17). In phase Ia study, DLTs were observed in 3 patients (0.12, 0.15, 0.18mg/kg, n=1 each), including grade 4 hypophosphatemia, neutropenia, febrile neutropenia, and grade 3 hyperglycemia, alanine aminotransferase (ALT) elevation. MTD was not yet reached. Majority of adverse events were mild to moderate. Grade 3/4 treatment-emergent adverse events (TEAEs) occurred in $\geq 3\%$ subjects were neutropenia (n=85), decreased leukocyte count (n=49), anaemia (n=10), AST elevation (n=7), ALT elevation (n=7). Drug-related death was observed in 1 patient. A total of 82 PROC patients at dose of 0.15mg/kg or above were evaluable for efficacy assessment. There were 21 patients achieved partial response (PR) and 30 patients achieved stable disease (SD). The objective response rate (ORR) and the disease control rate (DCR) were 25.6% and 62.2%, respectively. The median progression-free survival (mPFS) was 3.7 months (95% CI: 2.7–5.1). In 34 PROC patients with FR α expression $\geq 25\%$ and ≤ 3 prior treatment regimens, ORR was 32.4% and mPFS was still 3.7 months (95% CI: 3.3–7.3). Given the small sample size, efficacy data of breast cancer and other solid tumors will be analyzed after recruiting more patients. **Conclusions:** The current result showed that CBP-1008 has manageable safety profile. Antitumor activity was observed in PROC patients at dose of 0.15mg/kg or above, especially in PROC patients with FR α expression $\geq 25\%$ and ≤ 3 prior treatment regimens. Jifang Gong, Jian zhang and Ning Li contributed equally to this work. Xichun Hu, Lin Shen and Lingying Wu are the corresponding authors. Clinical trial information: NCT04740398. Research Sponsor: Coherent Biopharma (Suzhou) Co., Ltd.

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Poster Session

Understanding differences in the rates of BRCA/HRD testing and treatment in 1st line maintenance in patients with ovarian cancer treated by gynecologic oncologists compared to other providers: A quality initiative by Integra Connect (IC) PrecisionQ. *First Author: Fred J. Kudrik, South Carolina Oncology Associates, West Columbia, SC*

Background: The role of PARPi in the treatment of advanced ovarian cancer (aOC) has expanded in recent years. In this context, South Carolina Oncology Associates (SCOA) partnered with Integra Connect (IC) on a quality initiative (QI) to evaluate the rate of BRCA and HRD testing in newly diagnosed OC patients and the use of maintenance therapy in the 1st line (1L) setting in aOC. Patients with aOC at SCOA are typically managed by gynecologic oncologists. **Methods:** Using the IC Precision Q real-world database of over 1 million cancer patients across 275 sites of care, we assessed newly diagnosed OC patients evaluated via medical chart curation from 1/1/2020 to 6/30/2022 for BRCA and HRD testing at SCOA (N = 81) and other oncology practices (N = 1,045). We also studied the use of maintenance therapy in patients with stage II–IV OC who completed platinum-based chemotherapy from 1/1/2020 to 6/30/2022 at SCOA (N = 75) and other oncology practices (N = 899). SCOA was compared to other oncology practices in terms of provider specialty treating the patient, rates of HRD and BRCA testing, and use of 1L maintenance treatment in patients with or without BRCA or HRD mutations. Descriptive analyses were used. Proportions were compared using a two tailed two sample z-test. **Results:** Among newly diagnosed patients at SCOA, 95% of patients with OC were primarily managed by a gynecologic oncologist compared to 5% at other practices. The rate of BRCA testing at SCOA was 81% (66 of 81) compared to 75% (788 of 1045) and HRD testing was 60% (49 of 81) compared to 39% (403 of 1045) at other oncology practices in the IC database. The difference in HRD testing was significant ($p < 0.01$). The use of 1L maintenance regardless of biomarker status was 64% (48 of 75) at SCOA compared to 50% (449 of 899) at other practices. The difference in 1L maintenance use was significant ($p < 0.05$). PARPi were used at SCOA for maintenance therapy in 82% (38 of 46) of patients compared to 74% (314 of 427) at other practices. The use of maintenance in BRCA or HRD positive patients was 84% (21 of 25) at SCOA compared to 75% (151 of 201) for other practices. **Conclusions:** In this real-world study, treatment by gynecologic oncologists was associated with higher rates of BRCA and HRD testing and higher use of 1L maintenance treatment in patients with aOC compared to other practices. These findings underscore the importance of gynecologic oncologists in the management of aOC to ensure optimal testing and adherence to treatment guidelines. Research Sponsor: None.

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Poster Session

Response to subsequent platinum-based chemotherapy post PARP inhibitor in recurrent epithelial ovarian cancer. *First Author: Genevieve MacAulay Vacheresse, University of Ottawa, Ottawa, ON, Canada*

Background: Maintenance therapy with PARP inhibitors (PARPi) can increase progression free survival (PFS) for recurrent or metastatic platinum-sensitive epithelial ovarian cancer (EOC). Little is known about disease trajectory following treatment with these agents, though some evidence suggests a decreased response to subsequent platinum-based chemotherapy. This retrospective cohort study assessed real-world response rates to platinum-based chemotherapy for recurrent high grade EOC following treatment with a PARPi. **Methods:** All patients prescribed a PARPi as maintenance therapy for recurrent or metastatic EOC at the Ottawa Regional Cancer Center (ORCC) from September 2017 to May 2022 were included. PFS following penultimate therapy (line of therapy preceding PARPi initiation) as well as the PFS following subsequent platinum-based chemotherapy in patients with disease progression more than 6 months after penultimate therapy were calculated. Incidence of platinum resistance in patients with disease progression following PARPi therapy was determined. **Results:** 91 patients were included in the analysis including 54 patients on niraparib and 36 patients on olaparib. Follow-up after initiation of PARPi ranged from 4.6 months to 62.0 months with a median of 16.3 months. 54 (59.3%) of patients experienced disease progression after initiation of PARPi therapy, including 10 (11.0%) who progressed within 6 months of their penultimate therapy. Of the 44 patients who experienced disease progression more than 6 months following penultimate therapy, 32 (72.7%) were rechallenged with platinum-based chemotherapy. Of these, 16 (50.0%) experienced further disease progression with 14 (43.8%) progressing within 6 months of their platinum rechallenge. Median PFS following platinum rechallenge was 4.4 months (from 0.8 months to 34.9 months), significantly lower than previous reports. **Conclusions:** Patients who experienced disease progression following PARPi therapy showed a poor response to subsequent platinum-based chemotherapy, even when progression occurred more than 6 months after completion of their penultimate platinum-based chemotherapy. This supports the theory that PARPi resistance may be a surrogate for platinum resistance and raises concern for possible contribution of PARPi in the induction of platinum resistance in recurrent EOC. Research Sponsor: University of Ottawa Department of Obstetrics & Gynecology.

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Poster Session

Molecular and immune profiling of TP53-mutated ovarian cancers with non-BRCA1/2 homologous recombination gene alterations. *First Author: Kyle C. Strickland, Labcorp Oncology; Duke University Medical Center, Duke Cancer Institute, Department of Pathology, Durham, NC*

Background: Molecular alterations in homologous recombination (HR) pathway genes lead to HR deficiency (HRD) in ~50% of high grade serous ovarian carcinomas (HGSOC). The immune microenvironment of BRCA1/2-mutated HGSOC has been extensively characterized, in contrast to tumors with mutations in other HR genes. We evaluated a cohort of epithelial ovarian cancers (EOC) enriched for HGSOC and compared molecular and immune signatures of tumors with BRCA1/2 mutations (BRCAm) to those with non-BRCA1/2 HR gene mutations (NBHRD). **Methods:** We characterized 173 EOC by comprehensive genomic and immune profiling (CGIP) using panel-based next-generation DNA (523 genes) and RNA sequencing (384 genes), respectively. We enriched for HGSOC by selecting for TP53 mutations and excluding tumors with non-serous histology or any mutation in POLE, MLH1, PMS2, MSH2, MSH6, or nucleotide excision repair genes. Tumors lacking BRCA1/2-mutations were classified as NBHRD if a reportable mutation was present in canonical HR genes. Mutational burden (TMB, mut/Mb) was estimated from detected SNV/indels. We calculated immune-related expression signatures, including tumor immunogenicity score (TIGS), cellular proliferation (CP), and cancer testis antigen burden (CTAB). PD-L1 expression was assessed by tumor proportion score (TPS) following 22C3 immunohistochemistry. Differences in TMB, TIGS, CP, CTAB, PD-L1 and gene expression rank were tested for using Wilcoxon rank-sum test. **Results:** Of 173 EOC, 84 cases had complete CGIP, including 11 (13%) BRCAm, 7 (8%) NBHRD (Table), and 66 (79%) lacking HR gene alterations. On average, NBHRD tumors harbored lower TMB (4.1±2.3 vs. 6.6±2.3 vs. p=0.03) and elevated TIGS (59.1±16.2 vs. 41.7±16.2 p=0.044) compared to BRCAm tumors. We found no difference in PD-L1 (p=0.21), CP (p=0.26), or CTAB (p=0.48). Expression changes were identified in 32 immune genes, of which 31 (97%) were substantially up-regulated (1.3-3.3 fold) in NBHRD compared to BRCAm tumors. **Conclusions:** Our findings showed our cohort of NBHRD tumors were more immunogenic but less mutagenic than BRCAm tumors, implying enhanced immunogenicity unrelated to neoantigen load. Given that immune checkpoint inhibitors have shown limited efficacy in ovarian cancer, our data suggest NBHRD tumors may have stronger and possibly distinct immune escape mechanisms compared to BRCAm tumors. Research Sponsor: Labcorp.

NBHRD mutations		
NBHRD Case	Gene(s)	Mutation(s)
1	ATM	3085dupA (T1029fs)
2	BRIP1	517C>T (R173C)
3	FANCA	3494T>G (L1165*)
4	BRIP1	1871C>A (S624*)
5	BRIP1	2010dupT (E671*)
6	FANCF	388dupC (Q130fs)
7	BRIP1	1489delG (V497fs)
	CHEK2	1100delC (T367fs)

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Poster Session

Trends in the use of neoadjuvant chemotherapy for low-grade serous ovarian cancer in the United States. *First Author: Jason Silberman, Massachusetts General Hospital, Boston, MA*

Background: Following the publication of randomized trials demonstrating its noninferiority, the use of neoadjuvant chemotherapy (NACT) for the treatment of advanced stage epithelial ovarian cancer has increased substantially in the United States. However, low-grade serous ovarian cancers (LGSOC) respond poorly to chemotherapy compared with high-grade serous carcinoma. For LGSOC, clinical guidelines favor surgical resection prior to adjuvant therapy. This study seeks to describe patterns and temporal trends in the use of NACT for LGSOC. **Methods:** This cohort study identified women treated for stage III or IV LGSOC in a Commission on Cancer accredited cancer program between January 1, 2004, to December 31, 2020. We fit Poisson regression models to evaluate temporal trends in the use of NACT and cytoreductive outcomes, and to identify factors associated with receipt of NACT. We considered age, race/ethnicity, Charlson Comorbidity Index, year of diagnosis, insurance status, income, facility type, census region, and stage as potentially associated with NACT. Due to the high rate of missingness in data describing cytoreductive outcomes after surgery, we undertook both multiply imputed and complete case analyses. **Results:** A total of 3,343 patients received treatment for LGSOC during the study period. The mean age at diagnosis was 54.8 year (SD 15.5) and most patients (82%) were white. The most commonly observed upfront treatment strategies were cytoreductive surgery followed by adjuvant chemotherapy (63.7%) and surgery without chemotherapy (19.2%). Treatment with NACT followed by interval cytoreductive surgery (13.0%) or chemotherapy alone (4.1%) were less common. The proportion of patients who received NACT increased from 9.5% in 2004 to 25.9% in 2020, corresponding to a statistically significant annual percent change (APC) of 7.2% (95% CI 5.6-8.9). Increasing decade of age (risk ratio [RR] 1.15; 95% CI 1.09-1.23), increasing calendar year of diagnosis (RR 1.07; 95% CI 1.05-1.08) and stage IV disease (RR 2.66; 95% CI 2.3-3.07) were associated with a higher probability of receiving NACT. Other variables were not associated with receipt of NACT. Among patients who underwent cytoreductive surgery, the proportion who achieved no gross residual disease remained stable over the course of the study period in both complete case (APC 0.5%; 95% CI -1.8 to 0.9) and multiply imputed (APC -0.1%; 95% CI -1.6 to 1.3) analyses. **Conclusions:** The use of NACT for patients with LGSOC increased substantially from 2004 to 2020. Despite increased utilization of NACT, the rate of complete cytoreduction has not improved over the study period, possibly calling into question the effectiveness of NACT in reducing tumor burden in this setting. Research Sponsor: None.

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Poster Session

Exploring the significance of PARP inhibitor therapy after first-line chemotherapy in patients with homologous recombination proficient ovarian cancer: An extracted individual patient data and trial-level meta-analysis. *First Author: Mateus Trinconi Cunha, Instituto do Câncer do Estado de São Paulo, University of São Paulo, São Paulo, SP, Brazil*

Background: The use of poly (ADP-ribose) polymerase inhibitors (PARPi) as maintenance therapy in advanced epithelial ovarian cancer (EOC) patients (pts) has shown to delay cancer progression among patients with mutated BRCA (mBRCA) or homologous recombination deficiency (HRD), with debatable and divergent benefit among the subgroup of patients with homologous recombination proficiency (HRP). We aimed to further clarify the efficacy of PARPi after first-line chemotherapy (1L CT) in patients with HRP EOC. **Methods:** A systematic literature search of PubMed, Embase, The Cochrane Library until February 9th was conducted to identify articles or presentations of phase III clinical trials (P3CT) evaluating PARPi maintenance therapy after 1L CT in ovarian cancer. Individual patient data was reconstructed from Kaplan-Meier plots of progression-free survival (PFS) among pts with mBRCA, HRD and HRP through WebPlotDigitizer and R package IPDfromKM and further combined. We also performed trial-level meta-analysis with a random effects model. Comparisons were made with Cox proportional hazards. Clinical benefit for each sub-group was accessed with the ESMO Magnitude of Clinical Benefit Formulary 2b (ESMO MBCS). **Results:** The literature search resulted in 513 items. After screening, 6 P3CT (SOLO1, PRIMA, VELIA, PAOLA, PRIME, and ATHENA-MONO) were selected, and the longer follow-up data of each trial was used. A total of 3205 pts were included in the analysis (2090 in PARPi arms, 1115 in control arms). HRP was associated with worse PFS regardless of the treatment arm (HRP vs mBRCA in PARPi arms: HR 1.92, 95% CI 1.62 - 2.21, P < 0.001). Compared to control treatment arm, PARPi therapy was associated with a improved PFS in all subgroups, although the magnitude of benefit decreased from mBRCA to HRD and HRP (Table). Trial-level meta-analysis yielded similar results. PARPi therapy summed 4 out of 4 possible points at ESMO MBCS for mBRCA and HRD, but only 2 points among HRP pts, confirming a lower clinical benefit in this subgroup. **Conclusions:** This meta-analysis included additional P3CT recently presented and new data of subgroup analysis of previous studies. Results confirm a statistically significant benefit of PARPi maintenance after 1L CT for HRP EOC. Nevertheless, the relative and absolute gain in PFS is modest (9% in 2 years), while mBRCA and HRD subgroups have a substantial benefit. The worse prognosis of HRP pts, in addition to the small clinical benefit of PARPi therapy, highlights the need for new treatment strategies for this subgroup. Research Sponsor: None.

	Median PFS (PARPi vs control)	2-year PFS (PARPi vs control)	HR	95% CI	P
mBRCA	45.5 vs 16.6 mo	69% vs 38%	0.41	0.35 - 0.49	< 0.001
HRD	23 vs 15.6 mo	49% vs 32%	0.62	0.51 - 0.75	< 0.001
HRP	13.9 vs 10 mo	28% vs 19%	0.80	0.69 - 0.92	0.002

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Poster Session

Distinguishing primary mucinous ovarian tumors from metastases of non-gynecologic mucinous cancers: Can we leverage next-generation sequencing? *First Author: Muhammad Danyal Ahsan, Weill Cornell Medicine - Qatar, Doha, Qatar*

Background: Primary mucinous ovarian cancers (MOC) are histopathologically challenging to differentiate from ovarian metastases of non-gynecologic origin, with this distinction being critical for appropriate management and prognosis. We compared the somatic gene variant landscape of MOC to that of non-gynecologic mucinous tumors. **Methods:** Data were extracted from the American Association for Cancer Research's (AACR) Project Genomics Evidence Neoplasia Information Exchange (GENIE) database version 13.0 via cBioPortal. This publicly available, multi-institutional database provides next generation sequencing (NGS) genomic profiles of tumors. We queried this database for samples of MOC, mucinous colorectal cancer (MCRC), mucinous appendiceal cancer (MAC), mucinous breast cancer (MBC) and gastric type mucinous cancer (GMC). Frequencies of somatic gene variants including mutations, copy number alterations and structural variants were compared using Chi-squared or Fisher's exact tests, using the Benjamini-Hochberg method to control for multiple hypothesis testing with q-values reported. **Results:** A total of 883 tumors were included for analysis: 358 MCRC, 268 MAC, 157 MOC, 59 MBC and 41 GMC samples. Compared to MAC, MOC samples had higher variant frequencies of CDKN2A (33.3% vs 0.4%, q<0.001), CDKN2B (24.0% vs 0.0%, q<0.001), TP53 (64.3% vs 23.5%, q<0.001), ERBB2 (14.3% vs 1.1%, q<0.001) and CDK12 (13.2% vs 0.0%, q<0.001), whereas GNAS variants were more common in MAC (45.5% vs 5.7%, q<0.001). Compared to MCRC, MOC samples had higher variant frequencies of CDKN2A (33.3% vs 2.3%, q<0.001), CDKN2B (24.0% vs 3.7%, q<0.001), TP53 (64.3% vs 42.9%, q<0.001), KRAS (69.4% vs 51.1%, q<0.001) and ERBB2 (14.3% vs 5.3%, q<0.001), whereas MCRC had higher variant frequencies of 57 genes, with the largest differentials among APC (48.8% vs 2.6%, q<0.001), SMAD4 (25.2% vs 5.8%, q<0.001) and TCF7L2 (19.0% vs 0.0%, q<0.001). Samples of MOC had significantly higher rates of KRAS variants compared to GMC (69.4% vs 31.7%, q<0.001) and lower rates of STK11 variants (1.9% vs 22.0%, q<0.001). Compared to MBC, MOC samples had higher variant rates of CDKN2A (33.3% vs 3.4%, q<0.001), TP53 (64.3% vs 10.2%, q<0.001) and KRAS (69.4% vs 0.0%, q<0.001), whereas MBC samples had higher variant frequencies of 11 genes, with the largest differentials among GATA3 (32.1% vs 0.8%, q<0.001), FGF3 (30.4% vs 2.4%, q<0.05) and CCND1 (28.1% vs 1.6%, q<0.001). **Conclusions:** NGS demonstrates that MOCs carry a distinct genetic signature compared to mucinous tumors of non-gynecologic origin, most commonly with significantly higher variant frequencies of CDKN2A, CDKN2B and lower variant frequencies of GNAS, APC, STK11 and GATA3. This provides rationale for prospective studies evaluating genetic signatures as an adjunct to histopathology in the diagnosis of primary MOC. Research Sponsor: None.

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Poster Session

Effectiveness of PARP inhibitor maintenance therapy (mPARPi) in advanced ovarian cancer (OC) by *BRCA1/2* and HRD signature in real-world practice. *First Author: Debra L. Richardson, Stephenson Cancer Center/University of Oklahoma Health Sciences Center and Sarah Cannon Research Institute, Oklahoma City, OK*

Background: mPARPi following surgery and platinum chemotherapy (PCT) is a standard of care treatment for newly diagnosed advanced OC. Clinical trials have demonstrated benefit of mPARPi for patients (pts) with and without *BRCA1/2* mutations (*BRCA*+/-). The degree of benefit of mPARPi for pts without homologous recombination deficiency (HRD) biomarkers detected remains in question. This study aimed to compare the effectiveness of mPARPi in real world practice defined by biomarker status (*BRCA*+/- mutation and a novel HRD signature [HRDsig]). **Methods:** This study included pts with advanced OC who received 1st-line PCT with real-world progression-free survival (rwPFS) of at least 10 months after treatment initiation and received either mPARPi (without bevacizumab) or no maintenance therapy (nm). Pt data was obtained by the US-based de-identified Flatiron Health-Foundation Medicine real-world OC clinico-genomic database, originating from ~280 US cancer clinics (~800 sites of care) between 01/2015 and 09/2022. rwPFS and real-world overall survival (rwOS) were compared between pts +/- biomarkers by Cox models, adjusted for propensity scores accounting for disease stage at diagnosis, ECOG, age, and *BRCA* status (for the HRDsig analysis). HRDsig+ (Foundation Medicine) status was determined using a pre-specified cutoff. **Results:** Of 604 included pts, 128 pts received mPARPi (25.8% *BRCA*+ and 48.4% HRDsig+) and 476 received nm (14.3% *BRCA*+ and 35.5% HRDsig+). *BRCA*+ pts receiving mPARPi vs. nm had more favorable rwPFS (HR 0.44, 95% CI 0.24-0.79, *p* = 0.006), as did *BRCA*- pts (HR 0.7, 95% CI 0.51-0.95, *p* = 0.021). More favorable rwOS was not observed for either group (*p* = 0.7112, *p* = 0.2066 respectively). HRDsig+ pts receiving mPARPi vs. nm had more favorable rwPFS (HR 0.31, 95% CI 0.20-0.48, *p* < 0.001) and rwOS (HR 0.35, 95% CI 0.12-1.05, *p* = 0.061), while no differences were observed for those HRDsig- (rwPFS HR 0.99 0.71-1.40, *p* = 0.976 / rwOS HR 0.86, 95% CI 0.5-1.47, *p* = 0.575). A treatment interaction was observed for HRDsig+ vs. HRDsig- (rwPFS *p* < 0.001 / rwOS *p* = 0.042) but not for *BRCA*+ vs. *BRCA*- (rwPFS *p* = 0.213 / rwOS *p* = 0.596). Among *BRCA*- pts, those HRDsig+ receiving mPARPi vs nm had favorable rwPFS (HR 0.27, 95% CI 0.15-0.49, *p* < 0.001) and rwOS (HR 0.40, 95% CI 0.08-1.98, *p* = 0.216), while no difference was observed for those HRDsig- (rwPFS HR 1.02, 95% CI 0.72-1.44, *p* = 0.923 / rwOS HR 0.86, 95% CI 0.49-1.49, *p* = 0.590), with a treatment interaction observed for rwPFS (*p* < 0.001), but not for rwOS (*p* = 0.120). **Conclusions:** In this analysis of real-world practice, we observed improved outcomes among biomarker positive pts treated with mPARPi. HRDsig+ pts had improved outcomes, even among those who were *BRCA*-, while HRDsig- pts showed no enrichment for benefit with mPARPi, suggesting that a novel HRDsig might be able to predict benefit from mPARPi regardless of *BRCA* status. Research Sponsor: Foundation Medicine Inc.

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Poster Session

The diagnostic landscape of HRD testing based on cross-sectional survey of physicians and molecular biologists conducting testing (INDICATOR ONE). *First Author: Robert L. Coleman, Texas Oncology, Texas, US & Sarah Cannon Research Institute (SCRI), Tennessee, US, Texas, TX*

Background: Homologous recombination deficiency (HRD) occurs in approximately 50% of epithelial ovarian cancer (OC) cases. As HRD-positive tumors are more sensitive to poly(ADP-ribose) polymerase inhibitors (PARPi), HRD testing (determined by BRCAm and genomic instability score) identifies advanced ovarian cancer (AOC) patients who will benefit most from PARPi treatment. The value of these tests is recognized by guidelines to inform PARPi maintenance treatment decisions following first-line chemotherapy. This study characterizes the current testing landscape. **Methods:** This non-interventional, cross-sectional, web-based survey will be repeated in three waves, 9-12 months apart. Reported results are from Survey Wave 1 open from July to November 2022 and conducted among physicians and clinical laboratory heads/molecular biologists in the US and Europe (UK, France, Germany, Austria). Participants were recruited from clinical sites/laboratories known to be conducting HRD testing and via a standing physician panel. **Results:** Responses were received from 287 eligible participants (representing invitees from ~9% sites and < 2% panelists), 265 of whom completed the full survey (Europe: 153, US: 112; 228 physicians, 37 clinical laboratory heads/molecular biologists). Physicians ordered HRD testing for 70% ± 27% (mean ± SD) of newly diagnosed AOC patients. Nearly all physicians ordered the test to inform treatment decisions (*n* = 222; 97%). Physicians were most likely to conduct testing at stage 3 or 4 of OC diagnosis (Europe: *n* = 89, 64%; US: *n* = 63, 71%), followed by OC diagnosis regardless of stage (Europe: *n* = 51, 37%; US: *n* = 51, 57%). When European participants selected all types of tests used MyChoice CDx, Myriad Genetics (*n* = 82, 54%) was most commonly selected, followed by FoundationOne CDx, Foundation Medicine (*n* = 38, 25%). US participants used FoundationOne CDx (*n* = 62, 55%), followed by MyChoice CDx (*n* = 49, 44%), and QIAGEN QIASeq HRD (*n* = 38, 34%). Test costs were often partially (Europe: *n* = 47; 27%; US: *n* = 125; 53%) or fully covered (Europe: *n* = 89; 51%; US: *n* = 48; 21%). Results were received within 10 ± 6 (mean ± SD) working days in the US and 16 ± 11 working days in Europe. Testing guided treatment decisions 'always/often' (Europe: *n* = 117, 84%; US: *n* = 65, 73%) or 'sometimes' (Europe: *n* = 21, 15%; US: *n* = 23, 26%). Most European (*n* = 108, 78%) and US (*n* = 71, 80%) institutions offered genetic counselling. **Conclusions:** Among physicians and molecular biologists known to be conducting HRD testing, most newly diagnosed AOC patients were tested for HRD, and results usually played a role in treatment decisions. Variations in testing between the US and Europe include test types, test cost coverage, and time to receive results. Differences indicate potential areas for improvement in HRD testing to further benefit patients. Research Sponsor: This study was sponsored by AstraZeneca and is part of an alliance between AstraZeneca and Merck & Co., Inc., Kenilworth, NJ, USA.

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Poster Session

Triplet maintenance (olaparib, pembrolizumab, and bevacizumab) in *BRCA* non-mutated patients with platinum-sensitive recurrent ovarian cancer: A multi-center, single-arm phase II study (OPEB-01). *First Author: Yoo Na Kim, Department of Obstetrics and Gynecology, Yonsei University College of Medicine, Seoul, South Korea*

Background: The optimal treatment of *BRCA* 1/2 non-mutated patients with platinum-sensitive recurrent ovarian cancer remains unknown. In this study, we evaluated the efficacy and safety of triplet maintenance therapy in *BRCA* non-mutated patients with platinum-sensitive recurrent ovarian cancer. **Methods:** *BRCA* 1/2 non-mutated patients with platinum-sensitive recurrent epithelial ovarian cancer, showing a complete/partial response after second-line platinum-based chemotherapy, were eligible. Triplet maintenance therapy (olaparib, bevacizumab, and pembrolizumab) was administered until disease progression or unacceptable toxicity. The primary endpoint was the progression-free survival (PFS) rate at six months after therapy initiation. The secondary endpoints were PFS, overall survival, and safety. The translational objectives included biomarker evaluation with respect to survival outcomes. **Results:** Forty-four patients were enrolled (median age 61 years), majority with high-grade serous carcinoma (93.2%) and partial response (75.0%) to second-line chemotherapy. Overall, 54.6% were homologous recombination deficiency (HRD)-positive (genomic instability score ≥ 42) and 63.6% had PD-L1 positive tumors (combined positive score [CPS] ≥ 1). At 6 months, the PFS rate was 88.6% (95% confidence interval [CI] 75.4–96.2). The median PFS has not been reached. The most common ≥ grade 3 treatment-related adverse events (AEs) were anemia (20.5%) and neutropenia (6.8%), but there were no grade 4 AEs. Exploratory analysis demonstrated remarkable survival outcomes regardless of HRD status, whereas patients with PD-L1 CPS ≥ 1 showed improved PFS compared to those with PD-L1 CPS < 1 (*P* = 0.032). Analysis of molecular consensus subtype of the pre-treatment tissue samples showed that patients with mesenchymal subtype demonstrated poor PFS, compared to non-mesenchymal subtypes (*p* = 0.0023). **Conclusions:** This is the first report on triplet maintenance therapy in *BRCA* non-mutated platinum-sensitive recurrent ovarian cancer. The results show that the triplet maintenance therapy is efficacious with manageable toxicity, showing a particular promise for patients with molecular consensus subtype other than mesenchymal. Clinical trial information: NCT04361370. Research Sponsor: MSD supported the study drugs; Korean government.

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Poster Session

Immune features of ovarian tumors with a good response to neo-adjuvant chemotherapy in combination with an anti-PD-L1 alone or with an anti-CTLA4: Data from the randomized IneOV trial (a GINECO study). *First Author: Alexandra Leary, Gustave-Roussy Cancer Campus, Villejuif, and GINECO, Paris, France*

Background: We have shown that chemotherapy may have immunomodulatory properties and prime the tumor microenvironment (TME) by recruiting cytotoxic immune cells. We previously reported that neoadjuvant chemotherapy (NACT) associated with Durvalumab (D) +/- Tremelimumab (T) resulted in encouraging complete resection (70%) and complete pathological response (18%) rates in patients with unresectable ovarian cancer. Here, we aimed to 1) characterize the immune TME at baseline of responders compared to non-responders and 2) describe changes in immune TME in paired tumor samples at diagnosis and after 3 cycles of NACT with D +/- T in the randomized IneOV trial. **Methods:** Tumor samples from IneOV trial (55 at diagnosis, 40 after treatment) were analyzed for CD3+, CD68+ and CD20+ by multiplexed immunohistochemistry. Stromal and intra-epithelial TILs were scored as percentage of positive surface. Patients were classified as good pathological responders (pR) (CRS3) or pathological non-responders (pNR) (CRS1 or 2). Intra-tumoral T cell infiltration was described as High or Low (intraepithelial (ie)CD3+ > median vs <, respectively). Non parametric statistical tests were used. We evaluated the correlation of the markers with each others (Spearman test) and with pathological response rate (Mann-Whitney test). **Results:** At diagnosis, in the intra-epithelial compartment of the TME, the most abundant cells were macrophages (median ieCD68+ = 3.4) compared to T (ieCD3+ = 1.1), B (ieCD20+ ND) ANOVA *p*-value = 0.002 and < 0.0001 respectively. In individual tumors, infiltration by the 3 different immune subsets was poorly correlated suggesting immune TME heterogeneity in OC. Pathological response was evaluable in 64 patients: 19 pR and 45 pNR. At diagnosis, CD3+ (*p* = 0.02) and CD68+ (*p* = 0.006) infiltration was significantly higher in pR tumors compared to pNR. Most of pR (76%) had high intra-tumoral CD3+ infiltration versus 39% in pNR (*p* = 0.011). After treatment, tumors with pR showed significantly greater CD3+ intra-epithelial infiltration compared to pNR (*p* = 0.047). **Conclusions:** Our results suggest that good pathological response to NACT +D+/-T is associated with high levels of both T cells and macrophages in iTME at baseline, and increased intratumoral T cell infiltration post-treatment. Work is ongoing to further characterize the iTME, especially in pNR to identify other strategies to enhance the anti-tumor immune response. Clinical trial information: NCT03249142. Research Sponsor: AstraZeneca.

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Poster Session

Ovarian cancer and bevacizumab: Real-world use across western countries and effect on survival in high-risk subgroups. *First Author: Kristina Lindemann, Department of gynecological oncology, Radiumhospital, Oslo University Hospital & Faculty of Medicine, University of Oslo, Oslo, Oslo, Norway*

Background: Bevacizumab (bev) may be part of first-line treatment for patients with "high-risk" epithelial ovarian cancer (OC) (GOG-Q218 and ICON7 trials). The prevalence of high-risk patient subgroups, including bev use and its effect on survival in a real-world setting is not well studied. **Methods:** The observational multi-country cohort study RESPONSE collected retrospectively medical record data on women with newly diagnosed advanced high-grade serous or endometrioid OC (DOI: 10.1002/cncr.34350). We analysed patients defined as 'high-risk' according to ICON7 definition as either 1) stage IV disease, 2) inoperable stage III disease or 3) sub-optimally debulked (>1 cm residual disease) stage III disease. Unadjusted Cox proportional hazards regression analysis was performed to estimate the association of bev with the risk of death. Follow up time was calculated from time between response assessment at the end of primary chemotherapy and death or 20 months follow-up, whichever occurred first. **Results:** Of 954 patients in total, we identified 386 high-risk patients (40%) treated with platinum-based chemotherapy. Of these, 132 (34%) received bev maintenance treatment. Baseline characteristics did not differ between patients receiving bev or no bev. Bev use was associated with a statistically significant reduction in risk of death with a HR of 0.49 (95%CI: 0.18-0.78, p=0.002) in the total group of high-risk patients. The effect on survival was most evident among inoperable stage III/IV patients (n=151) with a 63% reduction in risk of death (HR 0.37; 95% CI (0.18-0.78, p=0.009). Risk estimates for additional subgroups are given in the table. **Conclusions:** Forty percent of this real-world population are considered high-risk according to ICON7 and a majority of these patients did not receive bev during first-line treatment. In line with ICON 7, this analysis supports the beneficial effect of bev on overall survival in this high-risk population. Patients who do not receive surgery are underrepresented in clinical trials and this real-world study confirms the strong benefit of bev particularly in this subgroup. Any real-world study may be limited by the potential presence of selection bias of patients to receive bevacizumab or not. Research Sponsor: AstraZeneca, part of an alliance between AstraZeneca and Merck Sharp & Dohme Corp, a subsidiary of Merck & Co, Inc (Kenilworth, New Jersey).

Effect estimates on overall survival in patients receiving platinum-based chemotherapy with or without bev.

Analysis set	Chemotherapy with bevacizumab (no. of pts)	Chemotherapy without bevacizumab (no. of pts)	Events N	HR 95% CI	p-value
High-risk*	132	254	102	0.49 (0.31-0.77)	0.002
Inoperable (stage III/IV)	34	117	62	0.37 (0.18-0.78)	0.009
Stage IV	89	150	56	0.50 (0.28-0.91)	0.023
Stage III inoperable	15	68	28	0.33 (0.10-1.10)	0.069
Stage III >1cm residual	28	38	18	0.63 (0.25-1.6)	0.324

*High-risk patients included stage IV disease, inoperable stage III disease or sub-optimally debulked (>1 cm) stage III disease

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Poster Session

Predictors of long-term progression-free survival (PFS) in niraparib-treated patients (pts) from the PRIMA/ENGOT-OV26/GOG-3012 study. *First Author: Whitney Graybill, Medical University of South Carolina, Charleston, SC*

Background: Niraparib was approved as maintenance therapy for pts with advanced ovarian cancer (OC) after complete or partial response (CR/PR) to first-line (1L) platinum-based chemotherapy (CT) based on results from the PRIMA study. In this post hoc analysis, we identified factors associated with long-term PFS. **Methods:** PRIMA is a phase 3, randomized study of pts with newly diagnosed advanced high-grade serous or endometrioid ovarian, primary peritoneal, or fallopian tube cancer at high risk for relapse with CR/PR after 1L platinum-based CT. Pts were randomized 2:1 to niraparib 200 or 300 mg or placebo QD, and stratified by best response to 1L CT (CR/PR), neoadjuvant CT (yes/no), and homologous recombination deficiency (HRD) status (deficient [HRD]/proficient or not determined [HRP/nd]). Investigator-assessed PFS was dichotomized in niraparib-treated pts with progressive disease (PD)/censoring <2 years vs PD/censoring ≥2 years after randomization (data cut, Nov 17, 2021). Logistic regression modeling using backward elimination (significance level=0.15) was used to identify baseline covariates associated with long-term PFS. **Results:** Of 487 niraparib-treated pts, 152 (31%) had PD/censoring ≥2 years after randomization. Odds ratios (OR) for PFS ≥2 years by baseline subgroup are shown (Table). The logistic regression model showed that BRCA mutation and HRD status, International Federation of Gynecology and Obstetrics (FIGO) stage, fallopian tube as the site of the primary tumor, and absence of baseline nontarget lesions were associated with longer PFS. Eastern Cooperative Oncology Group (ECOG) performance score, body mass index, age, time from CT to randomization, number of target lesions, best response after CT, number of CT cycles, type of debulking surgery, and residual disease were not associated with PFS ≥2 years. Safety has been reported previously (*Ann Oncol*. 2022;33 [suppl 7]:S789). **Conclusions:** Results suggest that long-term PFS in pts treated with niraparib may be associated with BRCA/HRD biomarker status, FIGO stage, primary tumor site, and number of baseline non-target lesions. These data are hypothesis generating. Clinical trial information: NCT02655016. Research Sponsor: GSK.

Variable	OR* (95% CI)	P Value
BRCA/HRD status	3.73 (2.191-6.335)	<0.0001
BRCA1/HRd, n=105	10.75 (5.158-22.407)	<0.0001
BRCA2/HRd, n=47	2.49 (1.422-4.372)	0.0014
BRCAwt + HRd, n=95	1.00	
FIGO stage		0.0412
III, n=318	1.62 (1.019-2.568)	
IV*, n=169	1.00	
Primary tumor site	0.53 (0.208-1.332)	0.1755
Primary peritoneal, n=34	0.54 (0.275-1.052)	0.0700
Fallopian tube, n=65	1.00	
Ovarian*, n=388		
Baseline nontarget lesions	4.67 (2.076-10.485)	0.0002
0, n=331	2.20 (0.857-5.649)	0.1010
1, n=90	1.00	
≥2, n=66		

*Reference variable. *Higher OR indicates more likely to remain progression free; eg, OR of 1.63 is 63% more likely to remain progression free for ≥2 years vs reference. wt, wild type.

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Poster Session

Blinded-assessment of a solution to evaluate olaparib maintenance treatment efficacy in patients with ovarian cancer from the GINECO/ENGOT PAOLA-1 trial. *First Author: Adrien Buisson, Department of Biopathology, Centre Léon BÉRARD, Lyon, France*

Background: SOPHiA DDM Dx HRD Solution (SOPHiA GENETICS, SA) combines analysis of genomic instability with mutational status of HRR genes, including *BRCA1/2*, generated through a single genomic workflow in order to predict Homologous Recombination Deficiency (HRD) status in ovarian cancer (OvCa) samples. Previous evaluation of SOPHiA DDM Dx HRD Solution demonstrated its results to be highly concordant with a reference HRD method. As part of the ENGOT HRD initiative, we present updated clinical relevance results of SOPHiA DDM Dx HRD Solution. **Methods:** GINECO/ENGOT-Ov25 PAOLA-1 trial randomized (2:1) 804 patients (pts) to receive after the end of first-line platinum-based chemotherapy either maintenance olaparib+bevacizumab or placebo+bevacizumab for up to 2 years. DNA from a sub-cohort of 384 formalin-fixed paraffin-embedded (FFPE) OvCa pts samples included in the PAOLA-1 clinical trial were analyzed using SOPHiA DDM Dx HRD Solution(*). We combined SOPHiA DDM Dx HRD Solution genomic instability score, with *BRCA* mutational status obtained from a Clinical Decision Support module, and clinical interpretation of Variants of Unknown Significance to establish the pts HRD status and investigated differences in progression-free survival (PFS) in the olaparib+bevacizumab and placebo+bevacizumab arms between pts with HRD positive or HRD negative test. **Results:** We determined the HRD status of 98.4% of pts using SOPHiA DDM Dx HRD Solution. The median PFS time for pts with HRD positive tumors was 35.7 months longer in the olaparib+bevacizumab arm than in the placebo+bevacizumab arm (hazard ratio [HR], 0.36; 95% confidence interval [CI], 0.25-0.51, p< 0.001), confirming the findings of our previous interim analysis. No significant difference in PFS was observed between treatment arms in pts with HRD negative test (HR, 1.02; 95% CI, 0.71-1.48; p= 0.90). **Conclusions:** These clinical relevance results from the SOPHiA DDM Dx HRD Solution evaluation on the PAOLA-1 samples further support the value of combining low-pass whole genome and targeted sequencing in a unique workflow for reliable and cost-effective HRD testing and future patient stratification. (*) Comparison data generated using the CE-IVD pipeline with Clinical Decision Support module for *BRCA* status only available in EU, Switzerland, UK. Research Sponsor: None.

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Poster Session

Phase 1/1b study of PRGN-3005 autologous UltraCAR-T cells manufactured overnight for infusion next day to advanced stage platinum resistant ovarian cancer patients. *First Author: John B. Liao, University of Washington Medical Center, Seattle, WA*

Background: Relapsed or refractory (r/r) ovarian cancer patients (pts) have limited treatment options. PRGN-3005 UltraCAR-T cells express a chimeric antigen receptor (CAR) targeting unshed MUC16, membrane bound IL-15 (mbIL15) and a kill switch with robust activity in preclinical models. UltraCAR-T investigational therapies are manufactured overnight using the proprietary UltraPorator electroporation system at the medical center and administered to patients one day after gene transfer. **Methods:** The Phase 1/1b study of PRGN-3005 evaluates the safety and recommended Phase 2 dose (RP2D) of PRGN-3005 in pts with r/r ovarian cancer (NCT03907527). In Phase 1, pts received PRGN-3005 without lymphodepletion (LD) via Intraperitoneal (IP) infusion (Cohort 1, C1) or Intravenous (IV) infusion (Cohort 2, C2) at Dose level 1-3. Dose level 3, IV infusion was further evaluated in pts treated with cyclophosphamide LD (60mg/kg/day on days -4 to -3 (IV LD)). As of the February 6, 2023 data cut-off, 25 evaluable pts have been treated in C1 (n = 12), C2 (n = 6), and IV LD (n = 7). Pts had a median age of 64 years (38-76) and were heavily pre-treated with a median of 8 prior regimens (4-11). Pts treated in C1 received 1 to 65.5 x 10⁵ cells/kg, pts treated in C2 received 0.1 to 50 x 10⁵ cells/kg and pts treated in IV LD received 0.1 to 39 x 10⁵ cells/kg. **Results:** PRGN-3005 was well tolerated at up to 65.5 x 10⁵ cells/kg. There have been no deaths, dose-limiting toxicities, neurotoxicity, grade ≥3 Cytokine Release Syndrome (CRS), or unexpected on-target/off-target toxicities related to PRGN-3005, and no use of the kill switch as of data cut-off. Grade 1 CRS occurred in 3/7 IV LD pts and one pt had transient grade 2 CRS, which resolved in < 24 hours. Plasma levels of IL-15 did not increase with treatment confirming mbIL15 is not shed. A dose dependent increase in PRGN-3005 was observed in peripheral blood of patients even in the absence of LD, and *in vivo* persistence of PRGN-3005 could be observed in some patients for up to 9 months post infusion. Response was evaluated per RECIST 1.1, and 20% of all subjects experienced a response in at least 1 target lesion. In the IV LD pts, the disease control rate (DCR) was 85.7% at first restaging, with a decreased target tumor burden in 4/7 (57%), and a 27.4% average decrease in CA125. One pt had a 28% decrease in target tumor burden after receiving a second infusion of PRGN-3005 after 12 months. **Conclusions:** PRGN-3005 UltraCAR-T targeting MUC16 has been well tolerated with minimal toxicity. PRGN-3005 demonstrated a dose-dependent expansion and persistence in blood with or without LD. Encouraging DCR rates and a reduction in overall tumor burden have been observed in heavily pretreated, ovarian cancer pts treated with LD. The study continues to enroll to the Phase 1b expansion phase and is treating pts at DL3 with LD with an option to receive a second dose. Clinical trial information: NCT03907527. Research Sponsor: Precigen, Inc.

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Poster Session

The role of Chemotherapy Response Score (CRS) in the decision making process for patients with advanced high grade serous ovarian cancer undergoing neoadjuvant chemotherapy. *First Author: Claudia Marchetti, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy*

Background: The role of chemotherapy response score (CRS) in predicting PARP inhibitors (PARPi) response for high grade serous Advanced Ovarian Cancer (AOC) patients undergoing Neoadjuvant Chemotherapy (NACT) has never been investigated. Also, the correlation between CRS and Homologous Recombination status (HRs) is unclear. **Methods:** In this observational retrospective study, we collected data from patients with high grade serous AOC, FIGO stage III-IV, undergoing NACT and subsequent Interval Debulking Surgery (IDS) from 2017 to 2021. KELIM score, CRS and BRCA status were considered; additionally, HRs (Foundation test) was reported when available. Primary endpoint was Progression Free Survival (PFS) according to CRS (CRS 1/2 vs 3) in patients receiving PARPi. **Results:** We enrolled 309 patients; 102 had CRS3 and 193 had CRS1/2 (14 were undetermined). Patients with CRS3 and PARPi maintenance showed the best prognosis, compared to all other subgroups (median PFS Not Reached, $p=0.014$); additionally, in the BRCA wild type population, CRS3 was predictive of longer survival (median PFS for the CRS3+PARPi BRCAwt population 24 months compared with 15 months for the CRS1/2+PARPi BRCAwt patients, $p=0.041$). Furthermore, among the 44 patients with known HRs, 59.1% of HR Deficiency (HRD) positive patients had CRS3, conversely 22.7% of HRD negative ones had a CRS3 ($p=0.048$). Finally, we found out that a favorable KELIM was significantly associated with CRS3 in the all-comers patients ($p=0.007$) and in the BRCAwt ($p=0.04$), but it was not predictive of PARPi response. **Conclusions:** Our findings suggested that the higher the CRS at the interval cytoreduction, the better the subsequent PARPi response. CRS correlates with PARPi response, as the HRD test does in other clinical trials and it may be considered as a surrogate of HRD status. We have planned to retrospectively perform HR test on a total sample size of 77 patients who received PARPi to corroborate this hypothesis. Research Sponsor: Fondazione Policlinico Universitario Agostino Gemelli IRCCS.

	Patients (N)	Median PFS (months, CI 95%)	p value
All-Comers			
CRS 3 + PARPi	47	NR	-
CRS 1/2 + PARPi	106	26	0.014
CRS 3 - NO PARPi	23	18	<0.001
CRS 1/2- NO PARPi	61	13	<0.001
BRCA-wt population			
CRS 3 + PARPi	24	24	-
CRS 1/2 + PARPi	53	15	0.041
CRS 3 - NO PARPi	19	18	0.161
CRS 1/2 + No PARPi	48	13	0.001

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Poster Session

Gynecologic-cancer analysis of ARID1A alterations detected in tissue and liquid biopsies. *First Author: Natalie Danziger, Foundation Medicine, Inc., Cambridge, MA*

Background: The tumor suppressor gene *ARID1A* is an emerging target for new cancer treatment strategies including ATR inhibition. This study aimed to describe the landscape of *ARID1A* alterations (*ARID1A*mut) in gynecologic malignancies. **Methods:** Patients (pts) with a diagnosis of ovarian (OC) or uterine cancer (UC) of different histologies and comprehensive genomic profiling (CGP) by Foundation Medicine Inc. were included in this study. CGP of solid tissue biopsies (Tbx; FoundationOneCDx) included evaluation of genomic loss of heterozygosity (gLOH; gLOH-high as $\geq 16\%$ as validated in OC), microsatellite instability (MSI), and tumor mutational burden (TMB; high as ≥ 10 mutations/Megabase). CGP of peripheral whole-blood liquid biopsies (Lbx; FoundationOneLiquidCDx) included evaluation of MSI and tumor fraction (TF), a measure of the relative quantity of circulating tumor DNA (ctDNA). TF was calculated by measures of aneuploidy and allele frequency and binned as TF $< 1\%$, TF 1 to $< 10\%$, or TF $\geq 10\%$. **Results:** Tbx Cohort: 5,778/30,212 (19.1%) cases were *ARID1A*mut. Pts had a median age of 63 (range 21-89) years. *ARID1A*mut were observed across many subtypes and most frequently in endometrial endometrioid ($n = 3,052$, 57.7%) and ovarian clear cell ($n = 982$, 57.6%) but rarely in serous (OC, $n = 12,258$, 2.8%; UC, $n = 2,682$, 8.9%). Pts frequently harbored more than one *ARID1A*mut (2,360/5,778, 40.8%). Of the 8,484 observed *ARID1A*mut, 97.6% were short variants (SV), 0.5% were deletions, and 1.9% were inactivating rearrangements. SV were primarily frameshifts (68.5%) and nonsense mutations (27.6%). The most frequent alterations observed were frameshifts at the D1860 codon. SV were predicted to be homozygous in 11.9%, heterozygous in 65.3%, or unknown zygosity in 22.8%. Overall, 16.6% of *ARID1A*mut cases with SV had at least one homozygous alteration. 6.6% of pts with homozygous *ARID1A*mut were MSI-high (MSI-H), while 39.4% of pts with only heterozygous or unknown zygosity *ARID1A*mut were MSI-H ($p < 0.0001$). Overall, 1,905 (33.0%) of *ARID1A*mut cases were MSI-H, and 2,183 (37.8%) were TMB high. For *ARID1A*mut cases with evaluable gLOH ($n = 4745$), the median gLOH was 2.7%, and 5.9% pts were gLOH-high. The most frequently altered co-occurring genes were *PTEN* (62.2%), *PIK3CA* (54.2%), and *TP53* (27.6%). 8.7% of *ARID1A*mut also harbored a *BRCA* alteration. Lbx Cohort: 59/967 (6.1%) cases were *ARID1A*mut. 17 (28.8%) were MSI-H. Frequency of *ARID1A*mut increased as TF increased, with a detected frequency of 1.3%, 6.7%, and 14.0% among Lbx with TF $< 1\%$, TF 1 to $< 10\%$, or TF $\geq 10\%$ respectively. **Conclusions:** *ARID1A*mut are observed across a variety of Gynecological cancer subtypes but are enriched in clear cell and endometrioid histologies and detected in both tissue and liquid biopsies. *ARID1A*mut were not associated with elevated gLOH but were often MSI-H and TMB ≥ 10 mut/Mb. Clinical trials targeting *ARID1A* may wish to consider the context of co-occurring biomarkers. Research Sponsor: Foundation Medicine Inc.

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Poster Session

Real-world overall survival in second-line maintenance niraparib monotherapy vs active surveillance in BRCA wild-type patients with recurrent ovarian cancer. *First Author: Robert L. Coleman, US Oncology Research/Sarah Cannon Research Institute and GOG-Foundation, The Woodlands, TX*

Background: The Phase 3NOVA trial assessed niraparib versus placebo as a maintenance treatment (tx) for patients (pts) with recurrent ovarian cancer (OC) who were platinum-sensitive after ≥ 2 regimens; progression-free survival was the primary endpoint and overall survival (OS) was a secondary endpoint (NCT01847274). The aim of this real-world study was to compare OS in a breast cancer gene wild-type (BRCAwt) population of pts with recurrent OC and who received second-line maintenance (2Lm) niraparib monotherapy or were under active surveillance (AS). **Methods:** This study used the US nationwide Flatiron Health de-identified electronic health record (EHR)-derived database. Pts diagnosed with epithelial OC between 1Jan2011–31May2021 who completed 2L therapy between 1Jan2017–2Mar2022 were eligible for inclusion. Pts were BRCAwt, had an ECOG PS score 0–1, epithelial histology, and platinum-sensitive disease with ≥ 6 months between end of first-line tx and start of 2L tx. Pts were assigned to 2Lm niraparib or AS cohorts based on their management following 2L non-maintenance therapy (≤ 120 days). Follow-up was measured from the index date (end of 2L non-maintenance therapy) until end of study (31May2022), last activity, or death, whichever came first. A target trial emulation cloned inverse probability of censoring weighting (IPCW) methodology was selected *a priori* to minimize bias. IPCW median OS and hazard ratios (HR) for 2Lm versus AS were estimated with Kaplan-Meier curves and Cox regression models. **Results:** Overall, 266 BRCAwt pts were included and received niraparib 2Lm ($N=123$) or were under AS ($N=143$). Across 2Lm and AS cohorts, prior to cloning and IPCW, 23.6% and 34.3% of pts were aged ≥ 75 years, and 26.0% and 16.8% had an EHR value for race as other than White, respectively. The majority of pts were from community practice (80.5% and 90.2%, respectively), had serous OC (79.7% and 81.1%) and had Stage III disease (53.7% and 60.8%). Homologous recombination deficiency status was unknown for 92.7% and 86.0% of pts in 2Lm and AS cohorts, respectively. Median follow-up for 2Lm and AS cohorts was 16.8 (Quartile [Q] 1, Q3: 10.4, 28.7) and 10.2 (Q1, Q3: 4.1, 23.7) months, respectively. IPCW median OS was 28.1 (95% confidence interval [CI]: 22.5, 43.2) and 21.5 (95% CI: 14.7, 27.0) months (HR: 0.63 [95% CI: 0.45, 0.88]) for niraparib 2Lm and AS cohorts, respectively and survival rates at 24 months were 58.2% (95% CI: 47.5, 67.6) and 46.1% (95% CI: 33.6, 57.7). **Conclusions:** This analysis provides real-world data on OS among pts with OC receiving niraparib 2Lm or under AS in the 2L setting following chemotherapy. Funding: GSK study (219306). Editorial support was provided by Fishawack Health, funded by GSK. Research Sponsor: GSK.

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Poster Session

Healthcare access dimensions and uterine cancer survival: A National Cancer Database study. *First Author: Mary Katherine Anastasio, Duke Medical Center, Durham, NC*

Background: Racial disparities persist throughout the continuum of care for Black patients with uterine cancer. Few studies have evaluated how multiple dimensions of healthcare access (HCA) contribute to these disparities in patients who present at an advanced stage and meet criteria for adjuvant therapy. **Methods:** Patients with Stage III-IV uterine cancer between 2004-2015 who received adjuvant therapy with complete sociodemographic and other relevant covariate data were identified in the National Cancer Database (NCDB). Race and ethnicity were defined as non-Hispanic (NH)-Black, Hispanic, and NH-White. Healthcare access dimensions of affordability, availability and accessibility were measured using variables defined in the NCDB. Overall survival was analyzed using Kaplan-Meier curves, log-rank test, and multivariable Cox proportional hazard models. **Results:** The study cohort included 43,134 patients: 78.8% NH-White, 15.3% NH-Black, and 5.9% Hispanic. Compared to NH-White and Hispanic patients, NH-Black patients were more likely to have Type II (75.6% vs. 53.9% and 55.4%) and Stage IV disease (40.8% vs. 30.7% and 32.3%). NH-Black patients were more likely to receive chemotherapy alone (53.5% vs. 43.1% and 46.2%) compared to NH-White and Hispanic patients. NH-Black patients were the most likely to have government funded insurance (58.6% vs. 50.3% and 50.4%) and live in the lowest income quartile (46.4% vs. 14.2% and 29.9%) compared to NH-White and Hispanic patients. NH-Black patients had a significantly higher risk of death than NH-White patients when adjusting for demographic/clinical characteristics and all three healthcare access dimensions (HR 1.29; 95% CI 1.24, 1.34). **Conclusions:** Healthcare access affordability predicts survival but does not fully explain racial disparities in survival rates of patients with advanced stage uterine cancer. NH-Black patients are more likely to have aggressive disease, receive chemotherapy alone, and have worse survival than NH-White patients regardless of pathogenic subtype. Investigating additional healthcare access dimensions may be critical to addressing disparities in uterine cancer. Research Sponsor: None.

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Poster Session

Preliminary antitumor activity of the combination of COM701 + BMS-986207 + nivolumab in patients with recurrent, metastatic MSS endometrial cancer. *First Author: Drew W. Rasco, START San Antonio, San Antonio, TX*

Background: There is a high unmet medical need for the treatment of patients [pts] with microsatellite stable [MSS], recurrent, metastatic, endometrial cancer [EC]. We reported encouraging preliminary antitumor activity with the triple combination of COM701 + BMS-986207 + nivolumab in patients with platinum resistant epithelial ovarian cancer [1]. COM701 is a novel, 1st-in-class immune checkpoint inhibitor [ICI] that binds to PVRIG, a DNAM-1 axis member, leading to activation of T-and NK-cells; BMS-986207 is an ICI of TIGIT. Nivolumab is an ICI of PD-1. We hypothesized that in pts with EC, the triple combination would demonstrate antitumor activity with a favorable safety and tolerability profile. We present encouraging preliminary results. **Methods:** As part of an expansion cohort, we enrolled 9 patients [pts] with EC. All pts received COM701 20 mg/kg + BMS-986207 480 mg + nivolumab 480 mg all IV Q4W. Primary objectives were safety/tolerability, with secondary objective of antitumor activity in pts with EC. Key inclusion criteria: Age $\geq$ 18 yrs, measurable disease, MSS by IHC or genomic testing, $\leq$ 2 prior systemic cytotoxic therapies, prior PD-1/PD-L1 permissible. Key exclusion criteria: prior receipt of anti-PVRIG, anti-TIGIT. Investigator assessed responses were per RECIST v1.1, safety per CTCAE v5.0. **Results:** Median age 71yrs, median of 2 prior lines of therapy, prior PD-1/PD-L1 3/9 [33%]. All pts received prior cytotoxic therapy. Objective response rate (ORR) 2/9 [22%] pts; 2 pts with SD. Disease control rate [CR + PR + SD] 4/9 [44%]. There were 2 pts with confirmed PR; 1 of these pts was refractory to prior receipt of lenvatinib + pembrolizumab [best response assessment of progressive disease]. Treatment related AEs were reported in 6/9 [67%] pts, the majority 4/6 [67%] were Grade 1 [1 pt each with chills, pyrexia, back pain and pruritus, lipase increased]. No new safety signals are reported. **Conclusions:** The combination of COM701 + BMS-986207 + nivolumab demonstrates encouraging preliminary signal of antitumor activity in pts with EC including in a pt refractory to prior exposure to lenvatinib + pembrolizumab. The triplet combination has a favorable safety/tolerability profile. Additional data analyses and pt follow up are ongoing and will be presented at the conference. Data extract 01/24/2023. 1. Moroney JW, Yeku O *et al.* Triple blockade of the DNAM-axis with COM701 + BMS-986207 + nivolumab demonstrates preliminary antitumor activity in patients with platinum resistant OVCA. *Annals of Oncology* (2022) 16 (suppl_1): 100104-100104. 10.1016/j.annonc.2022.100104. Clinical trial information: NCT04570839. Research Sponsor: Compugen Ltd.; Bristol Myers Squibb.

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Poster Session

The effect of megestrol acetate $\pm$ pterostilbene in endometrial cancer: A prospective, randomized, window-of-opportunity clinical trial. *First Author: Rosemary Senguttuvan, City of Hope National Comprehensive Cancer Center, Duarte, CA*

Background: Pterostilbene (3,5-dimethoxy-40-hydroxystilbene) is a potent oral antioxidant found naturally at highest concentrations in blueberries. Its anti-tumor effects in preclinical studies of various solid tumors include carcinogenesis, inflammation, reactive oxygen species (ROS) formation, and antiproliferative effects. In endometrial cancer (EC), *in vitro* and *in vivo* studies demonstrated a synergistic antiproliferative effect of pterostilbene (PT) in combination with megestrol acetate (MA). No clinical trials testing the potential therapeutic benefit of pterostilbene in cancer have been completed. **Methods:** We performed a prospective, window-of-opportunity, randomized phase 2 clinical trial (NCT03671811) in patients with EC. Eligible patients had to be surgical candidates for treatment with hysterectomy and not have received prior therapy. The primary objective was to determine the effect of MA plus PT versus standard treatment of MA alone on tumor proliferation as measured by the Ki-67 index during the preoperative window. Patients were randomized 1:1 to one of two arms: MA+PT PO BID versus MA PO BID, for 3 weeks. The Ki-67 index was measured via hot-spot and H-score methodology in the preoperative tumor and hysterectomy specimen by two blinded pathologists whose measurements were averaged. The net change between pre- and post-operative specimens was calculated for each patient and expressed as a percentage. Toxicity was assessed using CTCAE grading. **Results:** A total of 44 patients with EC of all histologies were recruited to the study and included in the toxicity analysis. Median age was 61.9 years. Baseline demographics were comparable between both arms. Median treatment duration was 21 days (14-56), similar in both arms. One G3 hypertension was encountered in the MA arm; one G3 thromboembolic event in the MA+PT arm. Of 35 patients with sufficient treatment duration (>10 days) and available pre-and post-treatment specimens, 29 patients with endometrioid histology were evaluated for the Ki67 analysis: 14 in the MA arm and 15 in the MA+PT arm. The MA+PT group demonstrated a -41.1% change in Ki-67 index by Hot Spot Score compared to -27.5% in the MA-only group ($p=0.17$). A similar trend was observed for the Ki-67 index by H Score methodology (-41.6% vs -26.7%, MA+PT vs MA, $p=0.17$). **Conclusions:** The combination of MA + PT in preoperative treatment of endometrial adenocarcinoma is well tolerated. The addition of Pterostilbene demonstrates a trend towards decreased Ki-67 index in endometrioid EC patients. Molecular studies are pending to delineate biomarkers associated with response. Clinical trial information: NCT03671811. Research Sponsor: internal funding.

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Poster Session

Pathogenic germline variants in patients with endometrial cancer across diverse ancestries. *First Author: Ying L. Liu, Gynecologic Medical Oncology Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Racial/ethnic disparities in outcomes exist in endometrial cancer (EC), particularly amongst self-reported Black compared to Non-Hispanic White (NH-White) patients. However, the contribution of differences in germline pathogenic variants (gPV) and genetics care to disparities is unknown. We seek to describe the spectrum of gPV in unselected patients with EC by ancestry to characterize variations and describe any differences in subsequent genetic counseling follow-up. **Methods:** Germline assessment of ≥ 76 cancer predisposition genes was performed in patients with EC undergoing clinical tumor-normal MSK-IMPACT sequencing from 1/1/15-6/30/21. Self-reported data on race/ethnicity and Ashkenazi Jewish (AJ) ancestry were used to classify patients into mutually exclusive ancestry groups: AJ, Asian, Black, Hispanic, NH-White, or Unknown. Genetic ancestry was inferred from MSK-IMPACT, and those with single population ancestral fraction >0.8 were assigned to African (AFR), European (EUR), East Asian (EAS), Native American (NAM), South Asian (SAS), and AJ (ASJ) ancestry populations or considered admixed (Mixed). Clinicopathologic variables were reported using summary statistics and compared by ancestry using non-parametric tests. **Results:** Among 1,625 patients with EC, self-reported ancestry [202 AJ (12.4%), 124 (7.6%) Asian, 171 Black (10.5%), 124 Hispanic (7.6%), 927 NH-White (57.1%), and 77 missing (4.7%)] correlated with genetic ancestry. In those identifying as Black, 122 (71%) had $>80\%$ African ancestry, 45 (26%) were considered Mixed, and 4 (3%) had missing data. We observed gPV in 216 (13.3%) patients (73 high, 36 moderate and 107 low/uncertain penetrance), with 15 patients having >1 gPV. Rates of gPV varied significantly by self-reported ancestry [AJ: 40 (19.8%), Asian: 15 (12.1%), Black: 12 (7.0%), Hispanic: 15 (12.1%), NH-White: 129 (13.9%), Missing: 5; $p=0.009$] and genetic ancestry [AFR: 9 (6.4%), AJ: 53 (19.3%), EAS: 9 (11.0%), EUR: 112 (13.3%), NAM: 2 (40%), SAS: 7(20%), Mixed: 17 (8.6%), Missing: 7; $p<0.001$]. Self-reported Black patients had the lowest rate with 13 gPV observed in 12 patients (7.0%); 5 gPV had biallelic inactivation within the tumor (2 *MSH2*, 1 *MSH6*, 1 *BRCA2* and 1 *FANCA*). Biallelic inactivation was observed in 70 (32%) patients overall with highest rates in Black (42%), Asian (40%), AFR (67%) and SAS (71%) populations. In those with new gPV ($n=114$), 102 (89%) overall were seen in genetics clinic for follow-up care, with the lowest rates in patients identifying as Black (75%) and of AFR ancestry (67%). **Conclusions:** Although rates of gPV varied by ancestry, they are drivers of disease in all populations, emphasizing the importance of germline assessment in EC. Differences in gPV and subsequent genetics care may contribute to racial/ethnic disparities in outcomes in EC by affecting treatment and cancer prevention and should be studied further. Research Sponsor: U.S. National Institutes of Health; Robert and Kate Niehaus Center for Inherited Cancer Genomics.

5598

Poster Session

Overall survival and subsequent therapy from a phase II study of sintilimab and anlotinib in patients with advanced or recurrent endometrial cancer. *First Author: Zhen Zeng, Department of Gynecologic Oncology, State Key Laboratory of Oncology in South China, Sun Yat-sen University Cancer Center, Guangzhou 510060, P. R. China, Guangzhou, China*

Background: Although the combination of immunotherapy and antiangiogenic agents has been proved a promising strategy in endometrial cancer, studies in Chinese patients are limited. In the earlier phase II study (NCT04157491), Chinese patients with recurrent or advanced endometrial cancer treated with sintilimab + anlotinib had an objective response rate of 73.9% (95% confidence interval [CI]: 51.6% to 89.8%). Here we further updated overall survival (OS) and subsequent therapy for this study. **Methods:** Patients with endometrial carcinoma progressed after platinum-based chemotherapy were enrolled. Sintilimab 200 mg was supplied intravenously on day one, whereas anlotinib 12 mg was administered orally on day 1 - 14 every three days. **Results:** Twenty-three patients were enrolled in the study. 47.8% of patients received ≥ 2 lines of prior chemotherapy; microsatellite instability-high/mismatch repair deficiency (MSI-H/dMMR) and microsatellite instability stable/mismatch repair proficient (MSS/pMMR) accounted for 39.1% and 60.9% of patients, respectively. We observed a median OS of 17.8 months (95% CI, 9.4 to 26.3 months). Patients with microsatellite instability-high (MSI-H) had superior OS than their counterparts (not available vs. 13.3 months; HR 0.15, 95% CI, 0.33-0.70; $P=0.006$). All patients had dropped out of the cohort [56.5% progression disease (PD), 13.0% adverse events (AE)]. Notably, five patients with partial responses (PRs) obtained pathological or radiography complete responses (CRs) in the follow-up. Pathological CRs were confirmed in three patients with long-lasting PRs who underwent surgery, consistent with PET/CT scans. Two patients with PR continued to have tumor shrinkage following treatment cessation due to AE and achieved CR during follow-up. Three out of four patients with CR experienced recurrences. There were no new grade 3-4 AEs associated with therapy. **Conclusions:** In terms of OS, combining sintilimab and anlotinib had promising therapeutic effects. Pathological CR was observed in patients with long-lasting PR, thus exploratory surgery may be required in selected patients. Clinical trial information: NCT04157491. Research Sponsor: None.

Summary of subsequent therapies (N = 23).

	Sintilimab and anlotinib	Subsequent therapies				Overall survival
		Patients, n	PD-1 inhibitor maintenance	Surgery	Chemotherapy	Other therapy
CR	1	1	Sintilimab	-	-	37.0 m
	1	1	Sintilimab	-	Paclitaxel plus carboplatin	Radiotherapy
	1	1	Sintilimab	-	PD with no subsequent therapy	Olaparib
	3	3	-	Cytoreduction ^a	-	15.5 m
PR	1	1	Sintilimab ^b	Cytoreduction ^a	Paclitaxel plus carboplatin	-
	1	1	Sintilimab	-	Paclitaxel	Pamiparib plus anlotinib
	1	1	Sintilimab	-	NA	-
	6	6	-	No subsequent therapy	-	28.4 m
	1	1	-	-	-	13.8 m
	3	3	-	-	-	3.3 to 37.5 m
SD	1	1	-	-	Paclitaxel	PARPI plus angiogenesis
	3	3	-	-	No subsequent therapy	12.4 to 21.0 m
PD	2	2	-	-	No subsequent therapy	4.0 to 7.1 m

^a After PFS achieved 2 years. ^b After surgery.

5599

Poster Session

Preliminary results of a phase II trial with sacituzumab govitecan-hzyi in patients with recurrent endometrial carcinoma overexpressing Trop-2. *First Author: Alessandro Santin, Department of Obstetrics, Gynecology, and Reproductive Sciences Yale University School of Medicine, New Haven, CT*

Background: Despite recent advances, there remains a significant need for targeted, efficacious treatments for advanced and recurrent endometrial carcinoma (EC). Trop-2 has been demonstrated to be overexpressed in several EC including grade 3 endometrioid adenocarcinoma (96%), and uterine serous carcinoma (65%). Trop-2 overexpression has been found to confer a worse prognosis and predicts disease recurrence. Sacituzumab govitecan-hzyi (SG) is an antibody-drug conjugate comprised of a humanized anti-Trop-2 antibody conjugated with the active metabolite of irinotecan, a topoisomerase-I inhibitor. SG is currently FDA-approved for use in metastatic urothelial cancer and metastatic triple-negative breast cancer. **Methods:** We report results from the stage 1 of an open-label non-randomized phase 2 trial (NCT04251416) established to evaluate the clinical activity of SG in patients with persistent or recurrent EC of epithelial origin with Trop-2 overexpression. Criteria for study participation included radiographically confirmed and measurable persistent or recurrent EC, progression after or during platinum-based chemotherapy, and at least 2+ staining of Trop-2. One target lesion by RECIST v1.1 and adequate bone marrow, renal, and hepatic function were required. Patients were at least two weeks beyond prior treatment, major surgery, or high dose systemic corticosteroid use. Patients were given 10mg/kg of SG administered as an intravenous infusion once weekly on days 1 and 8 of 21-day treatment cycles. This 3-week cycle was continued without rest until disease progression or unacceptable toxicity. **Results:** Twenty-one patients were enrolled into stage 1. Ten patients (48%) had uterine serous carcinoma, seven (33%) had endometrioid adenocarcinoma, three (14%) had carcinosarcoma, and one patient had mixed serous and clear cell histology. All patients received at least one prior line of chemotherapy, (median 3 lines, range 1-6). At the time of submission, 20 patients were response-evaluable (Table); seven (35%) achieved objective response (5 out of 7 confirmed). Eighteen patients were evaluable for durable disease control; 7 (39%) achieved it. Follow-up durations had a median (IQR) of 15.6 (5.7–22.5) months. Median OS was 22.5 months, and median PFS was 5.7 months. The treatment was well-tolerated with no new or unexpected safety signals reported. **Conclusions:** Sacituzumab govitecan shows remarkable clinical activity against some of the most historically challenging and chemotherapy-resistant endometrial pathologies and demonstrates a favorable safety profile. With these promising results, we will begin the stage 2 expansion of this phase 2 trial. Clinical trial information: NCT04251416. Research Sponsor: Gilead.

Overall disease response.		Evaluable		all 21
		too soon	Yes	
Best Response		1	.	1
	N			
Complete Response	N	.	1	1
Progressive Disease	N	.	3	3
Partial Response	N	.	6	6
Stable Disease	N	.	10	10
—All—	N	1	20	21

5601

Poster Session

OATH trial: A phase II clinical trial evaluating the combination of onapristone with anastrozole for women with hormone receptor positive endometrial cancer—Preliminary results. *First Author: Russell J. Schilder, Thomas Jefferson University Hospital, Philadelphia, PA*

Background: Endometrial cancer is the most common gynecologic cancer and is primarily treated with chemotherapy. Many endometrial cancers though express hormone receptors and may respond to hormonal therapy, a potentially attractive non-chemotherapy alternative in such a population of women. The aim of OATH is to investigate the potential of dual hormonal blockade through the combination of antiprogesterone and anti-estrogen therapy via the administration of onapristone extended release (ONA) plus anastrozole (ANA), respectively. OATH is an open-label, multicenter, investigator-initiated, non-randomized, phase 2 study to evaluate the safety and efficacy of ONA + ANA in patients (pts) with endometrial cancer (EC). ClinicalTrials.gov Identifier: NCT04719273. **Methods:** Pts received ONA 50 mg twice daily plus ANA 1 mg once daily and were treated until progressive disease (PD) or unacceptable toxicity. Co-primary endpoints were 4-month progression-free survival (PFS) rate and overall response rate (ORR). A sample size of 25 pts will achieve 80% power to detect an improvement in 4-month PFS estimates from 25% (historical) to 52% and an improvement in response rate from 15% (historical) to 37%, using two-sided exact test at 5% significance level. Secondary endpoints include PFS, disease control rate (DCR), and safety. **Results:** As of January 20, 2023, 14 pts were enrolled. Median age was 67 years (44-80). ECOG performance status was 0 (36%), and 1 (64%). Number of prior chemotherapy regimens was 0 (1 pt, 7%), 1 (9 pts, 64%) and 2 (4 pts, 29%). Seven (50%) pts received radiotherapy and 3 (21%) pts received prior checkpoint inhibitor therapy. Median treatment duration was 4.2 (1.0-19.9) months, and 8 pts remain on treatment. Adverse events were mainly grade 1 and 2. The most common treatment-related adverse events (AEs) and abnormal laboratory values were hot flashes (36%), alanine transferase (ALT) increased (29%), aspartate aminotransferase (AST) increased (29%), nausea (29%), and diarrhea (21%). No treatment-related serious AE, deaths on treatment, or treatment-related drug discontinuations were reported. The 4-month PFS Kaplan-Meier rate was 63.5%. Among 13 pts who had at least one tumor assessment after baseline, the best overall response was: 1 complete response, 1 partial response (response rate: 15.4%), 9 (69%) stable disease, and 2 (15.4%) progressions. Updated results will be presented. **Conclusions:** Preliminary results of dual hormonal blockade using ONA and ANA in heavily pretreated pts with EC suggest that this combination ONA + ANA has promising activity and is well tolerated. Clinical trial information: NCT04719273. Research Sponsor: Thomas Jefferson University; Context Therapeutics.

5600

Poster Session

Racial and ethnic disparities in quality of diagnostic evaluation for uterine cancer among Medicare patients. *First Author: Xiao Xu, Yale University, New Haven, CT*

Background: Uterine cancer is the most common gynecologic malignancy. As there is no routine screening for uterine cancer, appropriate evaluation of presenting symptoms is crucial for early diagnosis. We examined racial/ethnic disparities in the quality of diagnostic evaluation received by Medicare patients with uterine cancer. **Methods:** Using the Surveillance, Epidemiology and End Results (SEER)-Medicare database, we identified patients ≥ 65 years with uterine cancer diagnosed in 2008-2017 who presented with abnormal uterine bleeding (AUB, the most common symptom of uterine cancer). Patients with other cancer or unknown race/ethnicity were excluded. Race/ethnicity was categorized as White, Black, Hispanic, or Other (including American Indian/Alaska Native and Asian/Pacific Islander). Quality of diagnostic evaluation was measured by: 1) not receiving guideline-recommended diagnostic procedures (yes/no), and 2) number of days between AUB presentation and first diagnostic procedure. We compared these measures across racial/ethnic groups using multivariable regressions adjusting for patient sociodemographic characteristics, comorbid conditions, histology, and tumor grade. We further examined racial/ethnic differences in stage at diagnosis before vs. after accounting for these quality indicators. **Results:** The sample included 23,017 patients. Compared to White patients, Black, Hispanic, and Other patients were younger; more likely to reside in a metropolitan area, lack preventive care in the past year, or have comorbidities; and tended to have uterine cancer of non-endometrioid types and higher grade ($p < 0.001$ for all). A larger proportion of Black than White patients did not receive guideline-recommended diagnostic procedures (Black: 9.6% vs. White: 5.0%, $p < 0.001$; adjusted odds ratio [aOR] = 1.45, 95% CI: 1.20-1.74). Time from AUB presentation to first diagnostic procedure was longer for Black than White patients (90th percentile: 34 vs. 21 days, $p < 0.001$; adjusted mean ratio = 1.38, 95% CI: 1.21-1.57). Black patients were more likely than White patients to be diagnosed at regional (aOR = 1.18, 95% CI: 1.04-1.33) or distant stage (aOR = 1.27, 95% CI: 1.06-1.52), rather than localized stage, even after adjusting for other characteristics. Further adjusting for quality of diagnostic evaluation slightly reduced Black-White differences in stage at diagnosis (regional: aOR = 1.16, 95% CI: 1.03-1.32; distant: aOR = 1.23, 95% CI: 1.03-1.48). Hispanic and Other patients also experienced delay in time to first diagnostic procedure, but they did not differ from White patients in receipt of guideline-recommended diagnostic procedures or stage at diagnosis. **Conclusions:** There were racial/ethnic disparities in the quality of diagnostic evaluation received by Medicare patients with uterine cancer, which may partially explain Black-White differences in their stage at diagnosis. Research Sponsor: U.S. National Institutes of Health.

5602

Poster Session

Correlation of cardiovascular disease with racial disparities in endometrial cancer outcomes. *First Author: Mitchell Depke, Medical College of Wisconsin, Milwaukee, WI*

Background: Survival for Black women with endometrial cancer (EC) is shorter than that for non-Hispanic White (NHW) women, with a rate ratio for mortality of 1.98 per the American Cancer Society. Cardiovascular risk factors and disease are also more prevalent in Black women than NHW women. In women with breast cancer, Black patients received less optimal management of comorbidities and experienced increased cardiovascular disease (CVD)-related mortality as compared to White women. Similar to breast cancer, we hypothesize that CVD contributes to EC mortality disparities for Black women. **Methods:** In this retrospective cohort study, SEER and institutional data were utilized to investigate the contribution of CVD to outcomes for Black EC patients. The primary outcome was the contribution of cardiovascular mortality to the overall survival of Black patients. Secondary outcomes included identifying rates of new cardiovascular diagnoses, renal dysfunction, and adequacy of blood pressure control. The SEER cohort was defined using SEER*Stat 8.4.0.1. Uterine cancer patients were identified from the 2020 SEER Research Data. Survival by cause of death and proportion of deaths by cause of death were analyzed. Raw and adjusted hazard ratios for cardiovascular mortality were calculated. Next, institutional data was used to investigate survival, CVD diagnoses, renal dysfunction, and HTN in EC patients. **Results:** The SEER cohort contained 192,465 patients. Of these, 153,878 (80.8%) were White and 19,906 (10.3%) were Black. Black race was associated with decreased survival among patients who died of cardiovascular causes (HR 1.51, 95% CI 1.4 - 1.63, $p < 2 \times 10^{-16}$). When adjusted for age, stage, and histology, the hazard for decreased survival remained elevated for Black patients who died of cardiovascular causes (adjusted HR 1.65, 95% CI 1.52-1.77, $p < 2 \times 10^{-16}$). Our institutional cohort included 1491 patients, 1263 (84.7%) White and 151 (10.0%) Black. Black patients had a relative risk of death of 1.92 (95% CI 1.38 - 2.61) compared with White patients. Among patients with CVD, the hazard for death was 2.02 (95% CI 1.39 - 2.80). Black patients had significantly higher blood pressure, creatinine, and eGFR measurements. **Conclusions:** Racial outcome disparities in EC are multifactorial. CVD management will become increasingly important with the use of targeted therapies including lenvatinib and trastuzumab. Our study highlights an additional area of disparity and suggests possible interventions. Research Sponsor: None.

5603

Poster Session

Association of the Duffy-null allele and endometrial cancer characteristics: An effort to explore racial disparity in Black women with endometrial cancer.*First Author: Emily M. Webster, Weill Cornell Medicine, New York, NY*

Background: Efforts are needed to identify factors that account for the disparately high mortality in Black women with endometrial cancer. The Duffy antigen receptor for chemokines (DARC) is expressed on erythrocytes and endothelial cells and modulates levels of inflammatory chemokines in circulation and in tissues. The African ancestry-specific Duffy-null allele, in which erythrocyte expression and function of DARC is lost, is associated with worse breast cancer phenotypes and survival. Here, we characterize Duffy-null status and associated prognostic and clinical outcomes in patients with endometrial cancer. **Methods:** Patients with endometrial cancer were prospectively consented, and germline DNA was extracted from saliva or blood samples. Duffy-null genotype was determined using an allelic discrimination assay. Associations between Duffy-null genotype status and clinicopathologic characteristics were performed using Fisher's Exact analysis. **Results:** 33 patients were enrolled (Table); 17 (51.5%) were Duffy-null, 5 (15.2%) were Duffy-null allele carriers, and 11 (33.3%) were non-carriers. Compared with non-carriers, Duffy-null patients were more likely to be Black (100% v 9.1%, $p < 0.0001$) and have non-endometrioid histology (64.7% v 10%, $p = 0.0173$). There was a trend towards higher rates of grade 3 histology (70.6% v 36.6%), intact tumor mismatch repair (MMR) (86.7% v 54.6%), estrogen receptor (ER) negative tumor status (25% v 10%), advanced stage (37.5% v 18.2%), and positive lymph nodes (25% v 0%) (Table). Over a minimum of 12 months of follow up, only Duffy-null individuals died from disease (4 v 0, $p = 0.0006$). **Conclusions:** Duffy-null status was associated Black race, aggressive histologic subtypes, intact MMR mechanisms, and worse survival. Further investigation is needed to explore the underlying mechanism of the Duffy-null phenotype on endometrial cancer outcomes to better elucidate risk factors and underlying causes that may contribute to endometrial cancer disparities. Research Sponsor: U.S. National Institutes of Health.

Patient characteristics and Duffy-null status.

Patient Characteristic, n (%)	Duffy-null homozygous	Duffy-null allele carriers	Non-carriers	p-value
Race				<0.0001
Black	17 (100.0)	3 (60.0)	1 (9.1)	
Asian	0	2 (18.2)	2 (18.2)	
White	0	2 (40.0)	8 (72.7)	
Stage				0.1946
I or II	10 (62.5)	2 (40.0)	9 (81.8)	
III or IV	6 (37.5)	3 (60.0)	2 (18.2)	
Grade				0.1831
1	3 (17.7)	1 (20.0)	2 (18.2)	
2	2 (11.8)	0	5 (45.5)	
3	12 (70.6)	4 (80.0)	4 (36.4)	
Histology				0.0173
Clear	2 (11.8)	1 (20.0)	1 (10.0)	
Endometrioid	6 (35.3)	3 (60.0)	9 (90.0)	
Serous	9 (52.9)	1 (20.0)	0	
Tumor ER status				0.1429
Positive	12 (75.0)	2 (40.0)	9 (90.0)	
Negative	4 (25.5)	3 (60.0)	1 (10.0)	
Tumor MMR status				0.0813
Intact	13 (86.7)	5 (100)	6 (54.6)	
Deficient	2 (13.3)	0	5 (45.5)	
Lymph node status				0.2922
Disease	4 (25.0)	1 (25.0)	0	
No disease	12 (75.5)	3 (75.5)	9 (100.0)	
Clinical status				0.0006
Alive	13 (76.5)	4 (100.0)	11 (100.0)	
Deceased	4 (23.5)	0	0	

5605

Poster Session

Laparoscopic versus open-surgery in FIGO stage II endometrioid endometrium cancers: Is there a prognostic effect?*First Author: Daniel Uwe Reimer, Innsbruck Medical University; Department of Obstetrics and Gynecology, Innsbruck, Austria*

Background: Based on two randomized trials (LACE and LAP2) minimal invasive surgery has turned into the surgical standard in early stage endometrial cancer including "high-risk" patients. However, these recommendations are predominantly based on "low-risk" cancers, which are mainly represented in both trial collectives. We herein provide a retrospective study, which focuses on potential differences in clinical outcome in early stage endometrioid endometrial cancers with distinct risk constellations treated by laparoscopy or open surgery. **Methods:** 420 early stage endometrial cancers were retrospectively dichotomized according to the surgical approach and correlated to the recurrence rate and clinical outcome. In addition, subgroup analyses were performed according relevant clinical risk parameters, namely FIGO stage, grading and LVSI. **Results:** The analyzed collective consisted of 73.8% stage IA, 19.5% stage IB, and 6.7% stage II cases. Twenty-three percent of patients exhibit G3 tumors and LVSI was detected in 12.4%. Minimal invasive surgery was performed in 54.5% of study patients. During a median follow-up of 5.0 years, recurrence or death were observed in 8.3% and 6.7%, respectively. Recurrences were predominately located in the vaginal cuff (n = 21; 60.0%), to a minor extent in loco-regional lymph nodes (n = 11; 31.4%), and in three patients (8.6%) in both sides. No distant metastases were detected at first recurrence. Also under consideration of the mentioned clinicopathologic parameters, the surgical approach in FIGO stage I did not influence the recurrence rate and patients' survival. However, in a subgroup analysis of stage II disease, the laparoscopic approach was clearly associated with a significant higher recurrence rate (85.7% vs. 14.3%; $p = 0.013$). All of the recurrences were located in the vaginal cuff, and in one case, additional relapse was found in loco-regional lymph nodes. Moreover, laparoscopic surgery in stage II disease was associated with impaired progression-free and overall survival (HR 8.86 (1.008 – 20.85) and HR 6.36 (1.102 – 28.61), respectively). **Conclusions:** We herein demonstrate that a minimal invasive surgical approach in stage II endometrial cancer is associated with higher recurrence rates and impaired clinical outcome. These data could be interpreted to be in line with the results of the LACC trial in cervical cancer. Although, grounded on a retrospective analysis, these hypothesis-generating results warrants a confirmatory trial, which is ongoing in a much larger collective of stage II endometrial cancer patients. Research Sponsor: None.

5604

Poster Session

The impact of cause of mismatch repair deficiency and other molecular markers on clinical outcomes with the use of durvalumab in advanced endometrial cancer in the phase 2 PHAEDRA trial (ANZGOG1601).*First Author: Daniel D. Buchanan, University of Melbourne, Parkville, VIC, Australia*

Background: In the single arm phase 2 PHAEDRA trial, MMR deficiency (dMMR) was predictive of response to durvalumab (1500mg IV Q4W), with an objective tumor response rate (OTR; defined by iRECIST) of 47% in dMMR compared with 3% in MMR-proficient (pMMR) advanced endometrial cancer (AEC). This substudy of the PHAEDRA trial investigates MMR molecular subtypes and other genomic tumor features and their correlation with treatment outcomes. **Methods:** Testing was performed to determine molecular subtypes of dMMR, including germline pathogenic variants in DNA MMR genes (Lynch syndrome), somatic biallelic MMR gene inactivation through somatic mutation and somatic hypermethylation of the *MLH1* gene promoter. DNA from formalin-fixed paraffin-embedded tumor tissue and matched peripheral blood was available from 41/71 (25 dMMR, 16 pMMR) participants for testing on a custom capture-based 298-gene targeted panel (2.005Mb) including the MMR genes and key somatic AEC driver genes. The derived tumor genomic features included microsatellite instability (MSI), tumor mutational burden (TMB), COSMIC v.3.2 tumor mutational signatures and insertion/deletion (Indel) somatic mutation count. **Results:** Of the 71 patients recruited, 35 were dMMR and 36 were pMMR. Median follow-up was 44 vs 52 months in dMMR vs pMMR participants, respectively. The dMMR molecular subtypes were 4 (11.4%) Lynch syndrome, 4 (11.4%) somatic MMR mutation, 25 (71.4%) *MLH1* methylated and 2 (5.7%) dMMR-uncategorized. The OTR rate was 100% (4/4; 95%CI 40-100%) for Lynch, 75% (3/4; 95%CI 22-99%) for somatic MMR mutations and 40% (10/25; 95%CI 22-61%) for *MLH1* methylated groups. The median TMB (assessed in 41/71) was higher in those with a confirmed radiological response (37, IQR:26-50) vs non-responders (16, IQR:9-25; $p < 0.001$). Within the *MLH1* methylated group, TMB was also higher in responders vs non-responders (40 v 21; $p = 0.03$). Somatic mutations in *KRAS*, *PTEN*, *PIK3CA*, *ARID1A* and *TP53* were not associated with OTR rate. **Conclusions:** dMMR-*MLH1* methylated AEC demonstrated greater heterogeneity in OTR to single agent durvalumab than the dMMR-Lynch and dMMR-somatic MMR mutation molecular subtypes. Higher TMB was seen in responders, and specifically within dMMR-*MLH1* methylated responders, compared to non-responders. Clinical trial information: ANZGOG1601. Research Sponsor: Australia and New Zealand Gynaecological Oncology Group.

5606

Poster Session

Impact of best practice advisory on genetic counseling referral patterns for patients with endometrial cancer.*First Author: Julia M. Nagle, University of Kentucky Medical Center, Lexington, KY*

Background: The National Comprehensive Cancer Network (NCCN) recommends that patients with endometrial cancer under age 50 undergo germline genetic testing. Despite this recommendation, completion rates are suboptimal for patients with gynecologic malignancies. The reasons for failure to complete testing are unknown, but oncology providers may not refer patients to genetic counselors, who frequently order this testing. Best practice advisories (BPAs) in electronic medical records can alert providers of patients who meet guideline-based treatments and testing criteria. It is unknown how oncology providers interact with a BPA indicating patients with endometrial cancer meet NCCN germline testing criteria. The objective of this study is to evaluate genetic counseling referral patterns after implementing a BPA. **Methods:** Our team developed a BPA to prompt oncology providers to order genetic counseling referrals for patients diagnosed with endometrial or uterine cancer under age 50. We reviewed all provider-BPA interactions between go-live (January 2022) and January 2023. Patient demographic, histopathologic, and cancer treatment data were collected. Provider actions, including BPA cancellation and order placement, were collected. The Chi-Square goodness of fit test was used to identify differences in referral rates by patient or disease characteristics. **Results:** The BPA displayed 1121 times for 103 patients. Attending physicians received 535 alerts, fellow physicians – 269, and advanced practice providers (APPs) – 317. The median number of alerts per patient was 7 (range 1-87). Of the 103 patients, 23 were excluded from analysis due to no diagnosis of endometrial cancer, patient declined referral, previously completed, or a lack of provider visits within the study period. Of the 80 eligible patients, 36 (45%) received referrals; 18 were placed by attending physicians, 17 by fellows, and one by an APP. Patients under age 40 versus age 40-49 were more likely to be referred (65% vs. 35%; $p = 0.011$). Patients with active disease were more likely to be referred than those in surveillance (65% vs. 18%; $p < 0.001$). There were no differences in referral rates by primary language, race, body mass index ≥ 40 , fertility-sparing versus definitive treatment, stage I versus stage II-IV disease, or grade 1-2 versus three tumors. **Conclusions:** Despite implementing a BPA, only 45% of eligible patients received indicated referrals. Attending and fellow physicians frequently manage patients with active disease and often order referrals; however, APPs frequently manage patients in surveillance and infrequently place referrals, highlighting an opportunity for education. In addition, patients aged 40-49 are less likely to be referred, suggesting a need for new strategies to improve referral rates. Further research is indicated to identify referral barriers for patients undergoing active treatment. Research Sponsor: None.

5607

Poster Session

Impact of surgical weight loss treatments on care burden among obese endometrial cancer survivors. *First Author: Katia Noyes, University at Buffalo School of Public Health and Health Professions, Buffalo, NY*

Background: Among obesity-related cancers globally, 40% of disability adjusted life years loss are attributed to endometrial cancer (EC). EC patients are more likely to die of obesity-related complications rather than the cancer itself. Metabolic and bariatric surgery (MBS) is an effective weight loss treatment that has been shown to reduce prevalence and severity of many obesity-related chronic conditions. However, there is limited evidence on MBS on EC survivors. We examined the burden of patient healthcare utilization among EC survivors who did and did not undergo MBS. **Methods:** We utilized the SEER-Medicare database to identify 31,437 patients diagnosed with endometrial cancer between 2015 and 2017. We selected 9,229 (29.4%) patients with documented obesity (ICD codes) among whom 75 (0.8%) patients underwent MBS after completing EC treatment (2017-2019). EC survivors with and without a history of MBS were matched on age at EC diagnosis. We examined annualized Medicare inpatient and provider claims payments among EC-MBS (starting 3 months after the surgery, n=66) and EC-no MBS patients (2017-2019) and used Wilcoxon Rank-Sum tests to examine differences in payments in a 1:5 matched sample. **Results:** EC-MBS patients were younger (59.9 years) at the time of cancer diagnosis compared to EC-no MBS patients (68.2 years, $p<0.01$). In an age-matched sample, annualized median inpatient and provider claim payments among EC-MBS patients (\$1,824) were lower than that of EC-no MBS patients (\$2,920, $p<0.01$). **Conclusions:** Surgical weight loss achieves rapid and effective weight loss and has the potential to lower healthcare utilization among EC survivors but less than 1% of eligible patients receive the surgery. Further research is needed to better understand patient, provider, and access barriers to surgical weight loss in patients with obesity-related cancers. Research Sponsor: NYS DOH.

Matched on age	Endometrial Cancer	
	MBS Surgery N = 66	No MBS Surgery N=330
Demographics		
Age at EC Diagnosis	59.9 (10.2)	60.2 (9.3)
Race		
White	59 (89.4)	274 (83.0)
Black	6 (9.1)	43 (13.0)
Other	1 (1.5)	13 (3.9)
Outcomes		
NCH Claim Provider Payment Amount Mean (SD)	2,634.57 (2,960.95)	4,626.66 (8,332.06)
Min	35.92	0
Q1	735.48	1,241.43
Median	1,824.43	2,920.58
Q3	2,989.84	5,289.31
Max	15,629.97	98,045.38
NCH Carrier Claim Submitted Charge Amount Mean (SD)	13,158.50 (18,361.08)	19,659.33 (26,420.96)
Min	92.00	164.68
Q1	2,700.91	5,447.73
Median	6,776.86	12,975.62
Q3	15,771.21	23,664.66
Max	98,302.92	255,705.11

5609

Poster Session

A multicenter, single-arm, phase 2 study of surufatinib plus toripalimab for patients with advanced endometrial cancer. *First Author: Guangwen Yuan, Cancer Hospital Chinese Academy of Medical Sciences, Beijing, China*

Background: Several immunotherapy monotherapies, or combined with anti-angiogenic inhibitors, have shown antitumor efficacy in endometrial cancer (EMC) and been approved by FDA. However, therapeutic options for EMC after failure of first-line treatment remain scarce in China. The open-label, multi-cohort, single-arm phase 2 study was performed to evaluate the efficacy and safety of the combination of surufatinib (a small-molecule inhibitor of VEGFR 1-3, FGFR1 and CSF-1R) with toripalimab (an anti-PD-1 antibody) for Chinese patients (pts) with EMC after failure of one or more prior lines of systemic treatment. **Methods:** Pts with EMC who progressed or were intolerable after at least one prior line of systemic antitumor therapy were eligible and enrolled. They received 21-day cycles of surufatinib 250 mg orally, QD, plus toripalimab 240 mg IV, Q3W, until disease progression or reaching the maximum treatment duration with toripalimab of 24 months, or other protocol-specified criteria. The primary endpoint was objective response rate (ORR) per RECIST 1.1. **Results:** From August 2020 to March 2022, 28 pts were enrolled and received the combination treatment (median duration: 4.6 months). Median age was 58 years (range: 50-71), and 22 (78.6%) pts were endometrioid adenocarcinoma at diagnosis. 9 (32.1%) pts had received ≥ 2 prior lines of therapy. As of 28 Dec 2022, the median follow-up duration was 16.8 months. Microsatellite status was available in 25 pts. 20 with mismatch repair-proficient (pMMR) and 5 with mismatch repair-deficient (dMMR) were determined. All 28 pts were evaluable with at least one post-baseline tumor assessment. Efficacy results were: confirmed ORR, 28.6% (8 partial response [PRs]); DCR, 82.1%; mDoR, 5.7 months; mPFS (95%CI), 5.4 months (2.7, 8.3); 12-month OS rate, 71.0%. Among pts with pMMR, the confirmed ORR was 25.0%; DCR was 85.0%; mDoR was 4.2 months; mPFS (95%CI) was 4.0 months (2.7, 8.3); 12-month OS rate was 75.4%. All pts experienced at least one treatment-emergent adverse event (TEAE), and 19 (67.9%) of them reported grade ≥ 3 TEAEs. The most common ($\geq 5\%$ pts) grade ≥ 3 TEAEs were hypertension (28.6%), aspartate aminotransferase increased (14.3%), alanine aminotransferase increased (10.7%), proteinuria (7.1%), Gamma-glutamyltransferase increased (7.1%) and malignant neoplasm progression (7.1%). No new safety signals were observed. **Conclusions:** Surufatinib plus toripalimab had a promising antitumor activity and a manageable safety profile in pts with EMC after failure of one or more prior lines of systemic therapy. Clinical trial information: NCT04169672. Research Sponsor: HUTCHMED Limited.

5608

Poster Session

Efficacy and safety of anlotinib in overall and disease-specific advanced gynecological cancer: A real-world study. *First Author: Xinyi Hong, Southeast University, Nanjing, China*

Background: Anlotinib is a novel oral small-molecule multi-target tyrosine kinase inhibitor that has been approved for treating non-small cell lung cancer. However, its efficacy and safety among patients with advanced gynecological cancer. We conducted this study to address this issue in the real-world setting. **Methods:** Data from patients treated with anlotinib for persistent, recurrent or metastatic gynecological cancer including cervical, endometrial, and ovarian cancer were collected from 17 centers from August 2018. The database lock-time was on March 2022. Anlotinib was administered orally on days 1-14 every 3 weeks until disease progression, severe toxicity occurred, or death. The outcomes included objective response rate (ORR), disease control rate (DCR), and progression-free survival (PFS). **Results:** A total of 249 patients were analyzed, with a median follow-up of 14.46 months. The overall ORR and DCR were 28.1% (95% CI 22.6% to 34.1%), and 80.7% (95% CI 75.3% to 85.4%), respectively. Specifically, the ORR varied from 19.7% to 34.4% and the DCR differed from 81.7% to 90.0% in disease-specific advanced gynecological cancer. The median PFS was 6.1 months and ranged from 5.6 to 10.0 months in the overall and disease-specific advanced gynecological cancer, respectively. Larger cumulative dosage of anlotinib (>700 mg) was in general associated with longer PFS in the overall and disease-specific advanced gynecological cancer. The most common adverse event related to anlotinib use was pain/arthritis (18.3%). **Conclusions:** In conclusion, anlotinib holds promise in treating patients with advanced gynecological cancer, such as cervical, endometrial, and ovarian cancer, with reasonable efficacy and tolerable safety. Research Sponsor: None.

5610

Poster Session

TROPiCS-03: A phase 2 basket study of sacituzumab govitecan (SG) in patients (pts) with metastatic solid tumors—Early analysis in pts with advanced/metastatic endometrial cancer (EC). *First Author: Alessandro Santin, Yale School of Medicine, New Haven, CT*

Background: Pts with advanced/metastatic EC who progressed on or after platinum (PT)-based and anti-PD-(L)1 therapies have a poor prognosis with limited treatment options. SG is a Trop-2-directed antibody-drug conjugate. In the open-label, phase 1/2 IMMU-132-01 basket study, SG monotherapy resulted in a 22% objective response rate (ORR) with a manageable safety profile in 18 pts with metastatic EC who had relapsed after or were refractory to ≥ 1 prior standard therapeutic regimen (Bardia et al. *Ann Oncol*. 2021). Here, we report early data in pts with advanced/ metastatic disease from the EC cohort of the TROPiCS-03 Ph2 study. **Methods:** TROPiCS-03 (NCT03964727) is a multicohort, open-label, Ph 2 basket study in pts with metastatic solid tumors. Adult pts in the EC cohort progressed after prior PT-based chemotherapy and anti-PD-(L)1 directed therapy [requirement for PD-(L)1 progression added in amendment], had ECOG PS 0-1 and creatinine clearance ≥ 30 mL/min. Pts received 10 mg/kg of SG on D1 and D8 of a 21-D cycle. The primary endpoint was ORR by investigator's assessment per RECIST 1.1. Secondary endpoints included duration of response (DOR), clinical benefit rate (CBR), and progression-free survival (PFS) per investigator's assessment, overall survival, and safety. The safety population included pts who received ≥ 1 dose of SG; the efficacy population included pts receiving ≥ 1 dose of SG and had ≥ 13 weeks of follow-up. **Results:** As of data extraction on October 11, 2022, 28 pts received ≥ 1 dose of SG. Median study follow-up was 5.3 mo (range, 0.4-13.1); median age 69 y (range, 44-83), 57% ECOG PS 1, 14% microsatellite instability high. Pts received a median of 3 prior therapies (range, 1-6); 100% received prior PT-based chemotherapy, 61% prior immunotherapy, 54% prior targeted agents, and 11% prior hormonal therapy. In 20 pts with ≥ 13 weeks of follow-up, ORR was 25% (95% CI, 8.7-49.1). Regarding best overall response, all responses were partial response (PR). In addition, stable disease (SD) was 40% and progressive disease was 15%; CBR (confirmed complete response + PR + SD ≥ 6 mo) was 35% (95% CI, 15.4-59.2). Median PFS was 5.6 mo (95% CI, 2.3 mo-not reached [NR]) and median DOR was NR (95% CI, 2.76 mo-NR; n = 5). Treatment was ongoing for 50% of pts. Grade ≥ 3 treatment-related adverse events (TRAEs) occurred in 64% of pts; most common grade ≥ 3 TRAEs were neutropenia (25%), febrile neutropenia (14%), and diarrhea (14%). Discontinuation rate due to TRAEs was 7%. While on treatment, two deaths occurred due to causes unrelated to SG. **Conclusions:** Preliminary findings showed encouraging efficacy of SG with a manageable toxicity profile in a pretreated population with advanced/metastatic EC. Safety signals were consistent with the known SG safety profile. This early analysis will be updated with the full dataset. Clinical trial information: NCT03964727. Research Sponsor: Gilead Sciences, Inc.

5611

Poster Session

Clinical and genomic landscape of RAS pathway mutations in gynecologic cancers. *First Author: Ji Son, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: We aimed to describe RAS mutations in gynecologic cancers as they relate to clinicopathologic features, subtypes, co-mutations, and implications for therapy. **Methods:** Patients with gynecologic cancers who had next-generation sequencing at our institution between Feb 2010 and Aug 2022 were included. Clinical, histopathologic, and sequencing data were collected and analyzed. Overall survival was estimated using the Kaplan-Meier model. **Results:** Of the 3310 gynecologic cancer patients tested, 522 (15.8%) harbored a RAS mutation. For patients with mutation, median age was 56 (18-87) years, with cancer types including ovarian (43.5%), endometrial (43.4%), cervical (9.2%), and vulvovaginal (2.9%). Most patients (92.2%) had recurrence. The most common histology for each cancer included endometrioid in endometrial (60.8%), low grade serous in ovarian (34.4%), adenocarcinoma in cervical (60.4%), and melanoma in vulvovaginal (66.7%). Mucinous and clear cell differentiations were overrepresented (12.5% each). Median overall survival for all RAS-mutated patients was 69 months (95%CI 59-82), which was significantly better than in wildtype control of 56 months (95%CI 52-59, $p = 0.022$). Mutations observed were in KRAS (85.8%), NRAS (12.8%), and HRAS (3.3%). The most common mutant alleles for each were KRAS G12D (34.5%), KRAS G12V (31.7%), NRAS Q61R (34.3%), and HRAS G12S (17.6%). Of note, the incidence of KRAS G12C was 5.6% (0.8% overall). The most common co-mutations for RAS were PIK3CA (35.7%), PTEN (33.3%), TP53 (32.4%), and ARID1A (20.8%). This trend held for each mutation and cancer type. Of these, 64.7% were potentially actionable alterations, including 91.1% of PIK3CA, 83.7% of PTEN, and 50.0% of ARID1A. RAS pathway targeted therapies were administered to 62 patients (57 MEK, 5 BRAF, 5 KRAS G12C, 4 SHP2). The median overall survival for these patients was significantly improved (101 months, 95%CI 78-160) compared to RAS-mutated patients who did not receive a RAS pathway inhibitor (66 months, 95%CI 53-79, HR 0.7, $p = 0.031$). Of interest, novel KRAS G12C inhibitors showed durable benefit in 3 ovarian (high grade serous, low grade serous, clear cell) and 2 endometrial (mixed endometrioid, clear cell; mixed endometrioid, serous, mucinous) cancers with a clinical benefit rate of 100%, duration of objective response of 22 months, and ongoing responses at 5 and 16 months. **Conclusions:** Gynecologic cancers with RAS mutations have distinct histopathologic distribution and portend improved overall survival. The most commonly actionable co-mutations were PIK3CA, PTEN, and ARID1A, which may aid in combination therapy design. RAS pathway targeted therapy is associated with improved overall survival in this cohort and should be considered. Research Sponsor: None.

RAS-pathway Inhibitor	RAS-mutated GYN Cancer Patients (n)	Median Overall Survival (months, 95% CI)	HR (95% CI)	p
Received	62	101 (78-160)	0.67 (0.47-0.96)	0.031
Not received	460	66 (53-79)		

TPS5613

Poster Session

UPGRADE-A: Phase 1 expansion trial of the NaPi2b-directed antibody drug conjugate (ADC) upifitamb rilsodotin (UpRi) in combination with carboplatin in patients with high-grade serous ovarian cancer (HGSOC). *First Author: John L. Hays, Wexner Medical Center and The James Cancer Hospital, Ohio State University, Columbus, OH*

Background: UpRi is a first in class NaPi2b ADC with a novel scaffold-linker-payload that is designed to enable high drug-to-antibody ratio and controlled bystander effect. NaPi2b is a sodium-dependent phosphate transporter protein broadly expressed in HGSOC, with limited expression in healthy tissues. Interim data from a previous phase 1b study of heavily pretreated HGSOC patients reported clinical activity and tolerability data for UpRi as a monotherapy, most notably in patients with NaPi2b positive tumors (TPS ≥ 75). Based on these emerging single-agent safety and efficacy data, it is hypothesized that UpRi in combination with carboplatin may provide additional clinical benefit for patients in earlier lines of treatment. UPGRADE-A is a Phase 1 dose escalation (DES) and expansion (EXP) study to evaluate UpRi and carboplatin followed by UpRi maintenance in recurrent platinum-sensitive HGSOC. The DES portion of UPGRADE-A has completed enrollment, and the EXP portion is ongoing. **Methods:** The EXP cohort of UPGRADE-A is enrolling patients with recurrent or metastatic PSOC (defined as having achieved a PR or CR to 4+ cycles in their last platinum containing regimen) who have received 1-3 prior lines of therapy. Up to 1 non-platinum based prior chemotherapy regimen is allowed, provided it is not the most recent line of chemotherapy. The primary objective of EXP is feasibility of UpRi + carboplatin at the RP2D, defined as 60% of patients completing at least 4 cycles of UpRi + carboplatin without discontinuing treatment early for reasons other than disease progression. Secondary objectives include the safety/tolerability, pharmacokinetics, and preliminary anti-neoplastic activity of the UpRi + carboplatin combination. Tumor tissue must be provided (archival or fresh sample) for retrospective NaPi2b assessment. UpRi 30mg/m² + carboplatin (AUC 5) will be administered IV every 28 days for up to 6 cycles, followed by UpRi maintenance monotherapy until disease progression or unacceptable toxicity. Up to 30 patients are expected to enroll in EXP, and the trial is currently open for enrollment. NCT04907968. Clinical trial information: NCT04907968. Research Sponsor: Mersana Therapeutics.

TPS5612

Poster Session

ARTISTRY-7: A phase 3, multicenter study of nemvaleukin alfa in combination with pembrolizumab versus chemotherapy in patients with platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer (GOG-3063; ENGOT-OV68). *First Author: Thomas J. Herzog, College of Medicine, University of Cincinnati, Cincinnati, OH*

Background: ARTISTRY-7 will evaluate the novel engineered cytokine nemvaleukin alfa (nemvaleukin, ALKS 4230) in patients (pts) with gynecologic cancers. Ovarian cancer (OC) is the 8th most common cause of cancer mortality in women. OC is an area of high unmet need, as many pts become resistant/refractory to frontline platinum-based chemotherapy. In the platinum-resistant setting, standard of care chemotherapy and anti-PD-1 therapy in clinical trials have modest response rates ranging from ~6% to 20% and ~7% to 12%, respectively. Nemvaleukin was designed to selectively bind to the intermediate-affinity interleukin-2 (IL-2) receptor, preferentially activating antitumor CD8⁺ T and natural killer cells with minimal regulatory T cell expansion. This selectivity may provide enhanced tumor killing and improved safety/tolerability vs high-dose IL-2. In clinical studies, nemvaleukin, as monotherapy and in combination with pembrolizumab, has shown clinical benefit in multiple tumor types, including OC. In ARTISTRY-1, in 14 evaluable patients with OC, 4 responses were observed with nemvaleukin + pembrolizumab, including 2 complete responses and 2 partial responses (ORR 28.6%; DCR 71.4%; median DOR 53.4 wks). Nemvaleukin monotherapy activity was also observed (6 melanoma and 4 renal cell carcinoma responses). **Methods:** ARTISTRY-7 (NCT05092360) is an ongoing phase 3, multicenter, randomized study of nemvaleukin and/or pembrolizumab vs chemotherapy. Eligible pts are women (≥ 18 y) with histologically confirmed epithelial OC (high-grade serous, endometrioid, clear cell), fallopian tube cancer, or primary peritoneal cancer. Pts must have had ≥ 1 prior line of systemic therapy (platinum-sensitive setting), ≤ 5 prior lines (platinum-resistant setting), and prior bevacizumab, with radiographic progression on most recent therapy. Pts with primary platinum-refractory disease (progression on first-line platinum therapy) or primary platinum resistance (progression < 3 months after first-line platinum therapy completion) are excluded. Approximately 376 pts will be randomized (3:1:1:3) to receive nemvaleukin 6 µg/kg IV (days 1-5) + pembrolizumab 200 mg IV (day 1) of each 21-day cycle, pembrolizumab or nemvaleukin monotherapy, or chemotherapy, and stratified by PD-L1 status, histologic subtype, and chemotherapy (paclitaxel vs other). Pts will continue treatment until disease progression or intolerable toxicity (maximum 35 pembrolizumab cycles; nemvaleukin can be continued). The primary endpoint is investigator-assessed PFS (RECIST v1.1) in the nemvaleukin + pembrolizumab vs chemotherapy arms. Secondary/exploratory endpoints include overall survival, other antitumor measures, safety, health-related quality of life, and PK/PD effects. Clinical trial information: NCT05092360. Research Sponsor: Alkermes, Inc.

TPS5614

Poster Session

UP-NEXT (GOG-3049/ENGOT-Ov71-NSGO-CTU): A study of upitfiamab rilsodotin (UpRi), a NaPi2b-directed antibody drug conjugate (ADC), in platinum-sensitive recurrent ovarian cancer. *First Author: Debra L. Richardson, Stephenson Cancer Center/University of Oklahoma Health Sciences Center and Sarah Cannon Research Institute, Oklahoma City, OK*

Background: UpRi is a first-in-class NaPi2b-targeting ADC with a novel scaffold-linker-payload that enables high drug-to-antibody ratio and controlled bystander effect. NaPi2b is a sodium-dependent phosphate transporter protein broadly expressed in high-grade serous ovarian cancer (HGSOC) with limited expression in healthy tissues. It is estimated that the majority of HGSOCs have high NaPi2b expression. Studies are being conducted to evaluate UpRi safety and efficacy in platinum-resistant ovarian cancer (PROC), but there remains an unmet need in the maintenance setting for patients with recurrent platinum-sensitive ovarian cancer (PSOC), particularly for patients who have received prior maintenance therapy, are at high-risk of early relapse, and where close monitoring after platinum-based therapy would generally be considered preferable. **Methods:** UP-NEXT is a Phase 3 study evaluating UpRi monotherapy as post-platinum maintenance treatment in recurrent PSOC, enrolling patients with NaPi2b-positive tumors (defined as TPS ≥ 75). Patients must have received 2-4 prior lines of platinum containing chemotherapy, achieved a partial or complete response in their penultimate platinum regimen, and progressed > 6 months after completion of the last dose of platinum in the penultimate regimen. Patients may be enrolled if their best response to the last line of treatment is no evidence of disease, complete or partial response, or stable disease. Prior PARPi treatment is required for patients with a BRCA mutation. Patients who received bevacizumab in combination with their most recent platinum containing regimen are excluded. Patients are randomized 2:1 to UpRi 30mg/m² or placebo, given IV Q4W. The primary endpoint is PFS assessed by BICR, with key secondary endpoint of OS. UP-NEXT is conducted in collaboration with GOG(3049) and ENGOT(Ov71-NSGO-CTU). Approximately 350 patients will be enrolled globally. NCT05329545. Clinical trial information: NCT05329545. Research Sponsor: Mersana Therapeutics.

TPS5615

Poster Session

A randomized trial of olaparib, durvalumab, and cancer vaccine, UV1, as maintenance therapy in patients with BRCAwt with recurrent ovarian cancer: ENGOT-OV56/NSGO-CTU-DOVACC trial. *First Author: Mansoor Raza Mirza, NSGO-CTU & Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark*

Background: Most ovarian cancers (OC) are diagnosed at an advanced stage and despite initial therapy, the disease will often relapse and require further treatment. Thus, there is a need for novel therapeutic options. PARP inhibitors lead to increasing tumour neoantigen, and modulation of the tumour microenvironment, which may facilitate a more profound antitumour immune response. UV1 is a therapeutic cancer vaccine directed against telomerase. Since telomerase is an essential enzyme and universally expressed by most tumor cells, it represents a unique cancer antigen as a basis for immunotherapy (IO). The rationale for integrating immunotherapy as maintenance therapy following chemotherapy is based on preclinical studies which have shown that chemotherapy induces immunogenic cell death leading to increased recognition of the tumor by the immune system. The proposed study is evaluating the use of the therapeutic cancer vaccine UV1 in combination with olaparib and the PD-L1 inhibitor, durvalumab as maintenance therapy after response to platinum-based chemotherapy. **Methods:** The primary objective is to demonstrate efficacy of UV1-olaparib-durvalumab combination maintenance therapy against olaparib in maintenance after platinum combination therapy for BRCAwt patients with relapsed ovarian cancer. Key eligibility criteria include: histologically confirmed, platinum sensitive recurrent OC in response to last platinum-containing chemotherapy, BRCAwt. Patients may be previously treated with PARPi, however prior IO is not permitted. Patients are stratified by HRD status and previous use of PARPi. 184 patients are randomized to three arms (1:1:2): arm A: olaparib single agent, arm B: olaparib-durvalumab and arm C: olaparib, durvalumab-UV1. Duration of therapy: olaparib until progression of disease; durvalumab for 24 months; intradermal UV1, 8 doses within 5 months. Intradermal sargramostim is used as vaccine adjuvant. Primary endpoint is progression-free survival (PFS) of arm C versus arm A. Key secondary endpoints include PFS arm B versus C, patient reported outcomes, and overall survival. This NSGO-CTU sponsored trial is enrolling patients in 11 countries. The following cooperative groups are participating: NSGO-CTU (DK, FIN, NOR, SWE, LTU), BGOG (BE), HeGOG (GRC, CYP), NOGGO (DE), AGO-A (AUT) & DGOG (NL). Clinical trial information: NCT04742075. Research Sponsor: Ultimovacs; Astra Zeneca.

TPS5617

Poster Session

CRI-CCTG-0003/IND.240: An immunotherapy platform study in platinum-resistant high grade serous ovarian cancer (IPROC). *First Author: Helen Mackay, Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto, ON, Canada*

Background: Identifying new treatments for patients with platinum-resistant high grade serous ovarian cancer (HGSC) is a priority. Although several biological features of HGSC suggest inherent immunogenicity, immunotherapy has had limited efficacy to date. IPROC is an adaptive platform trial designed to evaluate multiple immunotherapy combinations selected and informed by an expert panel. IPROC accommodates both biomarker-agnostic and biomarker-directed combinations. Protocol and sub study specific translational studies are conducted on archived diagnostic tissue and serial prospective blood and tumor sample collection. **Methods:** IPROC is an open-label, multi center, phase II platform trial. Eligibility includes HGSC histology; progression within 6 months of the last platinum regimen; <1 prior line of chemotherapy for platinum resistant disease (unlimited prior lines for platinum sensitive); prior treatment with immunotherapy allowed (provided not discontinued for toxicity), ECOG 0/1. Patients must be willing and able to undergo study procedures. The primary endpoint is ORR (RECIST1.1). Secondary endpoints include iRECIST ORR, RECIST/iRECIST progression free and overall survival and safety. Exploratory objectives include whole exome sequencing and immune profiling of tumor and blood samples to identify biomarkers and new immunotherapy strategies/combinations for future evaluation. Tumor biopsy occurs at baseline, cycle 2 and progression (voluntary) with blood and plasma collected at each cycle and on progression. All sub studies use Simon 2-stage design with 10 patients (pts) enrolled in each stage. At the end of stage 1, in the absence of response, a modified cohort based on biomarker selection may be created through protocol amendment. In each sub study a null hypothesis that the objective response rate (ORR) is $\leq 5\%$ is tested against a one-sided alternative that the ORR is $\geq 25\%$. A combination would be accepted as active if $\geq 4/20$ pts respond with $\alpha=0.02$ and power of 0.76. As of January 19, 2023, 2 sub studies are open and 12 patients have accrued. Sub study A is evaluating the combination of durvalumab and BA3011, a conditionally active anti-AXL humanized monoclonal antibody (IgG1) conjugated to monomethyl auristatin E (MMAE) in AXL overexpressing HGSC. Sub study B is evaluating durvalumab plus BA3021, a CAB anti-receptor tyrosine kinase orphan receptor 2 (ROR2) humanized monoclonal antibody (IgG1) conjugated to MMAE in ROR2 overexpressing HGSC. Further sub studies are planned (NCT04918186). Clinical trial information: NCT04918186. Research Sponsor: Cancer Research Institute.

TPS5616

Poster Session

A phase 1/2 open-label, multicenter, dose escalation and expansion study of AVB-001, an intraperitoneally administered, cell-generated, human IL-2 immunotherapy in patients with platinum-resistant, high-grade, serous adenocarcinoma of the ovary, primary peritoneum, or fallopian tube. *First Author: Shannon Neville Westin, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: The potential of cytokines as cancer therapeutics has been limited by short half-life and severe adverse effects associated with high systemic exposure when delivered intravenously. Many strategies are being explored to overcome these limitations. A locoregional delivery approach to achieve high sustained local concentrations in the tumor microenvironment with minimal systemic exposure could widen the therapeutic window. Early experience with free recombinant human IL2 (rhIL-2) given intraperitoneally (IP) showed meaningful clinical activity in relapsed ovarian cancer. Still, the cumbersome delivery procedure requiring indwelling catheters and need for high volume IP infusions leading to frequent complications and poor patient compliance limited the utility of this approach. To overcome these shortcomings, we developed a clinically translatable localized delivery LOCocyte platform composed of polymer encapsulated allogeneic epithelial cells engineered to produce immune effector molecules for local delivery with temporal regulation. The first product, AVB-001, produces native hIL-2, for the treatment of ovarian cancer and other peritoneal malignancies. IP AVB-001 inhibited tumor growth and improved survival in an *in vivo* ID8 ovarian cancer murine model. Sustained IL-2 production with well tolerated high IP concentrations were achieved, with $>100\times$ differential concentration vs. systemic blood levels in both mice and non-human primates. Strong local and systemic immune activating effects, optimized T cell profile and immune memory were observed without concomitant increase of T regs. The first in human study of AVB-001 in patients with advanced ovarian cancer (NCT05538624) is described here. **Methods:** Part 1 dose escalation exploring 4 ascending dose levels (capsules target production of 0.6, 1.2, 2.4, and 3.6 ug hIL2/kg/d) with a Bayesian Optimal Interval 3+3 design, in patients with recurrent high grade serous adenocarcinoma of the ovary, primary peritoneum, or fallopian tube. A minimum of 12 and up to 24 patients will be enrolled to receive one dose of AVB-001 administered IP. The primary objective is to evaluate safety (Incidence and severity of adverse events per NCI CTCAE v5.0), tolerability, and feasibility of delivering AVB-001 IP, and establish the RP2D. Secondary objectives include assessment of antitumor activity (RECIST v1.1, iRECIST), pharmacokinetics, and pharmacodynamic correlates of immune activation. Part 2 will enroll 20 patients at the RP2D with efficacy as the primary objective. This multicenter study will be conducted at 5 sites, currently two sites are open. The first patient was dosed in December 2022. Recruitment in dose level 1 cohort continues. Clinical trial information: NCT05538624. Research Sponsor: Avenge Bio.

TPS5618

Poster Session

TEDOVA/GINECO-OV244b/ENGOT-ov58 trial: Neo-epitope based vaccine OSE2101 alone or in combination with pembrolizumab vs best supportive care (BSC) as maintenance in platinum-sensitive recurrent ovarian cancer with disease control after platinum. *First Author: Alexandra Leary, Gustave-Roussy Cancer Campus, Villejuif, and GINECO, Paris, France*

Background: Besides PARP inhibitors and bevacizumab, there are no approved maintenance therapies after platinum based chemotherapy for patients with a platinum sensitive relapsed epithelial ovarian cancer (OC). Immune checkpoint inhibitors (ICI) as single agents have limited activity in OC. One attractive strategy is to turn OC from immunogenic "cold" to "hot" tumors via vaccination with tumor-associated antigens (TAAs). OSE2101 is a multiple-neoepitope vaccine restricted to HLA-A*02-positive patients (45% of OC patients) targeting 5 TAAs: TP53, MAGE2, MAGE3, CEA and HER2. These neo-epitopes are modified to increase both major histocompatibility complex and the T cell receptor binding affinity. The proof of concept for this approach was recently demonstrated with OSE2101 improving overall survival in a phase III trial in lung cancer progressing after ICI (Besse *et al.* 2021¹). The combination of OSE2101 with an ICI may most effectively harness anti-tumor immunity. **Methods:** TEDOVA is an international randomized open-label, phase II trial evaluating the benefit of maintenance by OSE2101 alone or in combination with PD1 inhibition (pembrolizumab) after platinum based chemotherapy in relapsed OC, previously treated with bevacizumab (if eligible) and a PARP inhibitor (if eligible). Patients (N=180) with CR/PR/SD at the end of chemotherapy are randomized (1:1:2) to: Observation/BSC (Arm A), OSE2101 alone (Arm B), or OSE2101 in combination with pembrolizumab (Arm C). Experimental treatments are continued until progression, or intolerance, for up to 2 years. The primary endpoint is progression-free survival (PFS). Secondary endpoints include overall response rate, safety, time to subsequent first or second treatment (TTST-1, TTST-2) and overall survival. 180 HLA-A*02 positive patients will be randomized. HLA-A*02 negative patients will be followed in a separate observational cohort. The sample size is calculated to provide 90% power to detect an improvement in PFS for Arm C vs Arm A with a HR of 0.57. Three one-sided Log-rank tests will be considered in a pre-defined sequence: H1: C (OSE2101+pembrolizumab) vs A (BSC); H2: C (OSE2101+pembrolizumab) vs B (OSE2101) and H3: B vs A. The type I error will be $\alpha=5\%$. The type II error will be $\beta=10\%$. Tests will be one-sided. Status: The TEDOVA/GINECO-OV244b/ENGOT-ov58 trial is currently recruiting. Clinical trial information NCT04713514. 1. Besse B, Garcia MR, Cobo MA, Quiox E, Madroszyk A, Felip E, et al. LBA47 - Activity of OSE-2101 in HLA-A2+ non-small cell lung cancer (NSCLC) patients after failure to immune checkpoint inhibitors (IO): Final results of phase III Atalante-1 randomised trial. *Annals of Oncology* 2021;32(suppl_5) : S1283-S1346. Clinical trial information: NCT04713514. Research Sponsor: OSE Immunotherapeutics; Merck Sharp & Dohme Corp.

TPS5619

Poster Session

Uncovering mechanisms of response of pembrolizumab and lenvatinib for the treatment of platinum-resistant high grade serous ovarian cancer. *First Author: Jeffrey How, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Despite initial response to conventional platinum-containing therapies, the majority of high grade serous ovarian cancer (HGSOC) patients will eventually develop treatment resistance. Despite interest for immune checkpoint inhibitor alternatives, pembrolizumab monotherapy is poor with objective response rates (ORR) ranging between 4.1 - 10%. Poor response may be linked to higher expression of immunosuppressive factors (e.g. VEGF, TGF- β) in the tumor microenvironment (TME). In an immunosuppressive TME, monotherapy with PD-1 inhibitors can induce T-cell dysfunction and apoptosis, leading to innate resistance to pembrolizumab. Preclinical studies of other tumors have demonstrated that lenvatinib can improve T-cell activation and reduce the tumor-associated macrophage population and TGF- β /VEGF/FGF-signaling. In HGSOC, mechanisms of resistance to pembrolizumab and whether this resistance can be overcome by the addition of lenvatinib remain unknown. The objective of this investigation is to uncover the immunologic basis and synergistic mechanisms of action underlying clinical efficacy of pembrolizumab and lenvatinib in HGSOC. Specifically, we will evaluate the dynamic changes in proliferative and dysfunctional T-cell populations in the peritoneal TME (p-TME) of HGSOC patients receiving monotherapy with pembrolizumab or lenvatinib followed by combination therapy. **Methods:** All patients will receive a cycle of monotherapy (pembrolizumab 200 mg IV every 3 weeks or lenvatinib 20 mg po daily) followed by combination therapy (both) up to 35 cycles. Enrolled patients will receive intra-peritoneal port placement for serial peritoneal fluid evaluations (cycle 0 day 1, cycle 0 day 8, cycle 1 day 8, cycle 2 day 1, cycle 3 day 1, cycle 5 day 1, then day 1 of every 3rd cycle) for multichannel flow cytometry and single-cell RNA sequencing. Our primary translational objective is to estimate both the individual and combined effects of pembrolizumab and lenvatinib on T-cell dysfunction (PD1+ CD38+) and proliferation (ki67+) in the p-TME using multichannel flow cytometry on the peritoneal fluid. Secondary clinical objective is ORR. Secondary translational objectives include individual and synergistic effects of monotherapy and combination therapy on T-cell effector function, T-cell memory, and myeloid cell subpopulations. Exploratory objectives include evaluating the dynamic changes in immune and non-immune cells in the p-TME for exceptional responders and non-responders using single cell RNA sequencing. Key eligibility criteria include 1) histologic diagnosis of high grade serous ovarian, peritoneal, or fallopian tube cancer 2) platinum-resistant disease and 3) no prior lenvatinib therapy. The trial is open with 10 patients enrolled at the time of submission. Clinical trial information: NCT05114421. Research Sponsor: Merck.

TPS5621

Poster Session

Oregovomab and non-platinum chemotherapy in PARP inhibitor-resistant ovarian, fallopian tube, or primary peritoneal cancer patients not candidates for platinum retreatment: A multicenter, two-cohort, single-arm phase 2 trial (OPERA/KGOG 3065/APGOT-OV6). *First Author: JUNG-YUN LEE, Yonsei University College of Medicine, Seoul, South Korea*

Background: As PARP inhibitors (PARPi) are becoming the standard of care option for epithelial ovarian cancer (EOC), PARPi-resistant patients are increasing. Moreover, non-platinum single agent chemotherapy in these patients has been found to elicit poor survival outcomes. Oregovomab, an investigational murine monoclonal antibody directed against CA-125, has shown promising efficacy in the previous phase II study of combinational front-line adjuvant chemotherapy. The aim of the present study is to investigate the efficacy of oregovomab + non-platinum-based chemotherapy in PARPi-resistant EOC patients not suitable for platinum-based therapy. **Methods:** OEPRA is a multicenter, investigator-initiated, two-cohort, single-arm phase II trial recruiting PARPi-resistant EOC patients from five sites in South Korea. The trial includes patients with recurrent EOC who have experienced disease progression despite treatment with PARPi and who have either received bevacizumab or are not eligible for bevacizumab treatment. Mucinous histology type is excluded. Patients who have received one to three prior lines of chemotherapy are to be assigned to Cohort 1 (oregovomab 2 mg [C1,2,3,5,7 for five doses] + pegylated liposomal doxorubicin [PLD] 40 mg/m² q4w, n = 28), while patients who have received more than three prior lines of chemotherapy are to be assigned to Cohort 2 (oregovomab 2 mg [C1,2,3,5,7 for five doses] + weekly paclitaxel 80 mg/m² [D1,8,15 q4w], n = 28). A total of 56 patients will be recruited and treated with oregovomab + PLD / weekly paclitaxel until disease progression, unacceptable toxicity, or withdrawal of patient consent. The primary endpoint is objective response rate by RECIST 1.1. Accrual is expected to be completed in 2023, followed by presentation of results in 2024. The study is registered with ClinicalTrials.gov (NCT05407584). Clinical trial information: NCT05407584. Research Sponsor: CANARIABIO Inc.; Yonsei University.

TPS5620

Poster Session

First trial of chemotherapy de-escalation in ovarian cancer (OC): A phase III randomized, open label study of niraparib maintenance after carboplatin and paclitaxel in patients with optimally debulked advanced (homologous recombination deficient) HRD high-grade ovarian cancer in first line therapy (N-PLUS/NOGGO-ov53/ENGOT-ov62). *First Author: Elena Ioana Braicu, Charité-Universitätsmedizin Berlin, Department of Gynecology with Center for Oncological Surgery, Campus Virchow Klinikum and North-Eastern German Society of Gynaecological Oncology (NOGGO) and Stanford University, Berlin, Germany*

Background: OC is the fifth most common cause of death from cancer in women. More than 70% of the patients are diagnosed with advanced disease and less than 40% of women with OC are cured. Currently, the standard therapy in HRD OC is surgical debulking followed by 6 cycles of chemotherapy with subsequent maintenance treatment with poly ADP ribose polymerase (PARP) inhibitors. Within the last decades, no focus was set on the benefits of fewer cycles of chemotherapy, even though there is evidence for comparable efficacy and less toxicity in comparison to more cycles. Chemotherapies are usually associated with side effects, which can be severe and even lead to therapy discontinuation. The data available about the needed number of chemotherapy cycles is weak, especially in the context of PARP inhibition. Furthermore, patients with stage III/IV with optimal cytoreduction are underrepresented in previous studies. In the N-PLUS trial, we hypothesize that recurrence-free survival (RFS) in patients receiving 3 cycles of chemotherapy followed by maintenance with niraparib is not inferior to 6 cycles of chemotherapy followed by niraparib in advanced HRD high-grade OC patients with no visible disease following primary tumor debulking. **Methods:** In this multicenter, randomized, open-label study 650 patients with advanced HRD high-grade OC with no residual tumor mass following primary tumor debulking will be enrolled. Patients will be randomized 1:1 to receive either 3 cycles carboplatin + paclitaxel and maintenance therapy with niraparib (Arm A) or 6 cycles carboplatin + paclitaxel and maintenance therapy with niraparib (Arm B) for a maximum of 36 months. Randomization will be performed according to the results of the NGS analysis and stratified either to BRCAm/LOH-independent or BRCAwt/LOHhigh, FIGO stage III vs. IV, and participating countries. The primary endpoint will be RFS, secondary endpoints will be OS, TFST, TWIST, PFS2, Quality of Life and safety assessments. Clinical trial information: NCT05460000. Research Sponsor: GSK.

TPS5622

Poster Session

GLORIOSA: A randomized, open-label, phase 3 study of mirvetuximab soravtansine with bevacizumab vs. bevacizumab as maintenance in platinum-sensitive ovarian, fallopian tube, or primary peritoneal cancer. *First Author: David M. O'Malley, James Gynecologic Oncology Mill Run, Ohio State University, Columbus, OH*

Background: Elevated folate receptor-alpha (FR α) expression is a characteristic of epithelial ovarian cancer (EOC), thereby providing a rational target for antibody drug conjugate (ADC) development in ovarian cancer. Mirvetuximab soravtansine (MIRV) is an ADC comprising a FR α -binding antibody, cleavable linker, and the maytansinoid DM4, a potent tubulin-targeting agent that has received accelerated approval for patients with FR α positive platinum resistant ovarian cancer. MIRV in combination with BEV has demonstrated clinically meaningful activity, along with acceptable tolerability, in patients with FR α expressing ovarian cancer.¹ **Methods:** GLORIOSA is a randomized, open-label, phase 3 study designed to evaluate the efficacy of in combination with bevacizumab compared with bevacizumab alone as maintenance for patients with FR α -positive recurrent platinum-sensitive epithelial ovarian, fallopian tube, or peritoneal cancers who have not progressed after second line platinum-based chemotherapy plus bevacizumab (which may be given on protocol for patients with high FR α tumor expression). Confirmation of high FR α positivity by immunohistochemistry using the Ventana FOLR1 CDx Assay (high expression; $\geq$ 75% of viable tumor cells staining at 2+ intensity) and 1 prior line of therapy is required for inclusion. GLORIOSA is designed to randomize 418 patients, 1:1 receiving intravenous MIRV at a dose of 6 mg/kg adjusted ideal body weight plus bevacizumab 15mg/kg every 3 weeks or receiving bevacizumab 15mg/kg every 3 weeks until disease progression or unacceptable toxicity. Radiological assessments will be conducted every 9 weeks ($\pm$ 2 weeks) for 72 weeks, and subsequently every 18 weeks ($\pm$ 3 weeks) until progressive disease (PD), death, the start of new anticancer therapy, or withdrawal of consent from the study (whichever occurs first). The primary efficacy endpoint is progression-free survival by investigator and will also be assessed as a sensitivity analysis. The secondary endpoints include objective response rate, quality of life, overall survival, and safety and tolerability. GLORIOSA is a global study that opened for enrollment in December 2022. Reference: 1. Gilbert L, Oaknin A, Matulonis UA, et al. Safety and efficacy of mirvetuximab soravtansine, a folate receptor alpha (FR α)-targeting antibody-drug conjugate (ADC), in combination with bevacizumab in patients with platinum-resistant ovarian cancer. *Gynecol Oncol.* 2023; 170: 241–247 Clinical trial information: NCT05445778. Research Sponsor: Immunogen, Inc.

TPS5623

Poster Session

Exactis-03: A phase I trial of the combination of olaparib and navitoclax in women with high grade serous ovarian cancer and triple negative breast cancer. *First Author: Helen Mackay, Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto, ON, Canada*

Background: Identifying new therapeutic options for patients (pts) with high grade serous ovarian cancer (HGSC) and triple negative breast cancer (TNBC) is a priority. For pts with pathogenic variants in *BRCA*, the PARP inhibitor (PARPi) olaparib is used to treat TNBC and as maintenance for HGSC. PARPi can induce a senescence-like phenotype in cancer cells with cell survival dependent on anti-apoptotic proteins. The intrinsic apoptotic pathway is regulated by the Bcl-2 family composed of anti-apoptotic proteins (including Bcl-2, Bcl-xL), pro-apoptotic effectors and the pro-apoptotic BH3-only proteins. Increased expression of Bcl-xL occurs in 88% of HGSC. Olaparib and navitoclax, a Bcl-2/Bcl-xL inhibitor, are synergistic in pre clinical models of HGSC and TNBC. Exactis-03 investigates targeting, olaparib-induced senescence as a treatment strategy for pts with HGSC and TNBC. **Methods:** Exactis-03 is a multi-centre phase I trial determining if olaparib can be safely combined with navitoclax in pts with TNBC who have somatic or germline mutations in *BRCA1/2* or *PALB2* and pts with recurrent HGSC who have progressed ≥ 6 months since their last platinum based chemotherapy. Additional eligibility criteria include: ≥ 3 prior lines of treatment for TNBC (no limit for HGSC); for pts with HGSC prior PARPi is allowed provided there was no progression on or ≤ 6 months since discontinuation of the PARPi; ECOG PS ≤ 2 ; ability to absorb study medication and pts must be willing and able to undergo study related procedures. The primary endpoint is identification of the recommended phase II dose (RP2D) of olaparib combined with navitoclax. Olaparib 200mg bid is administered alone for the first 2 weeks. Tumor biopsies will be performed at baseline and on day 7-12 (prior to navitoclax) to evaluate senescence and apoptosis biomarkers and to create 3D organoids and ex vivo microdissected tumor (MDT) models for functional assessment of drug response. Navitoclax is dose escalated with a fixed dose of olaparib in 28-day cycles with 3 pts initially treated at each dose level. If no dose limiting toxicity (DLT) is observed, the dose level will be escalated until $\geq 1/3$ or $\geq 2/6$ patients experience DLT. The RP2D will be defined as the dose level below the one where $\geq 1/3$ or $\geq 2/6$ patients experience DLT. The 2-week lead-in with olaparib alone and one full cycle of the combination (navitoclax/olaparib) must be completed before dose escalation is permitted. Blood samples are collected for pharmacokinetics and serial evaluation of plasma biomarkers. There is an optional tumor biopsy on progression. Exploratory objectives include determining levels of pro- and anti- apoptotic proteins in biopsy samples and evaluation of cell fate decision biomarkers in biopsy tissue and blood (senescence secretome). Patient-derived organoids and ex vivo MDT will be used to explore drug response and sequencing (NCT05358639). Clinical trial information: NCT05358639. Research Sponsor: Grant from Exactis (Networks of Centres of Excellence (NCE), Canadian Institutes of Health Research (CIHR), Natural Sciences and Engineering Research Council of Canada (NSERC), Social Sciences and Humanities Research Council via Exactis PMT; Philanthropic Donation; Ovarian Cancer Canada (Federal).

TPS5625

Poster Session

FLORA-5/GOG3035: Chemo-immunotherapy (paclitaxel-carboplatin-oregovomab [PCO] vs chemotherapy (paclitaxel-carboplatin-placebo [PCP]) as front-line treatment in patients with advanced epithelial ovarian cancer (EOC)—Phase III, double blind, placebo controlled, global, multinational study. *First Author: Lisa Marie Barroilhet, University of Wisconsin, Madison, WI*

Background: Oregovomab, a murine IgGκ1 monoclonal antibody with high affinity binding to tumor associated antigen CA125, renders the target antigen CA125 more immunogenic or “neoantigen-like”. The proposed mechanism action is enhanced antigen processing and presentation to specific T cells. This phenomenon is hypothesized to bypass tumor-associated immune suppression when oregovomab is combined with chemotherapy. In a randomized phase II study, oregovomab, in combination with paclitaxel and carboplatin, (PC) induced tumor immunity and demonstrated significant improvement in median PFS (41.8 months/m) PCO vs 12.2 m PC, HR 0.46, $p = 0.0027$) and median OS (N.E. PCO vs 43.2 m PCP, HR 0.35, $p = 0.043$) in patients with previously untreated EOC. Patients receiving adjuvant chemotherapy were included. Oregovomab combined with PC had a favorable toxicity profile. FLORA-5/GOG3035, the definitive confirmatory global registration trial, is currently recruiting patients in the front-line setting. **Methods:** In this phase 3, multicenter, double-blind, placebo-controlled trial, optimally debulked patients with FIGO III/IV EOC and serum CA125 ≥ 50 U/ml receiving adjuvant (Cohort 1) or patients receiving neoadjuvant chemotherapy post-interval cytoreductive surgery (Cohort 2) will be randomized to PC + oregovomab or placebo (PCO vs. PCP). Patients with germline *BRCA1/2* mutations are excluded. Chemotherapy will be administered every 3 weeks in both cohorts. Oregovomab/placebo is administered simultaneously at cycles 1, 3, and 5 of chemotherapy with an additional dose at 12 weeks following cycle 5 in Cohort 1. Neoadjuvant patients will be administered oregovomab/placebo after debulking surgery at cycles 4 and 6 with two additional doses at 6- and 18-weeks following cycle 6 in Cohort 2. No other front-line maintenance therapy is permitted. The primary objective is PFS determined by RECIST 1.1. Cohort 1 will recruit 372 patients with a 90% power to detect a difference with an alpha of 0.025 and a hazard ratio of 0.65 when 252 PFS events have been observed. Cohort 2 will be analyzed separately recruiting 232 patients with a 90% power to detect a difference with an alpha of 0.025 and a hazard ratio of 0.60 when 165 PFS events have been observed. An interim futility analysis will be performed. Secondary objectives include OS, frequency and severity of AEs, and QoL. Exploratory objectives include iRECIST, TFS, TSST, PFS2, and evaluation of correlative biomarkers. The study is actively enrolling in the US, Canada, Belgium, Italy, Spain, Czech Republic, Hungary, Poland Korea, Taiwan, Mexico Argentina, India and Chile. 518 of the planned 602 patients were enrolled at the time of submission. Clinical trial information: NCT04498117. Research Sponsor: CanariaBio, Inc.

TPS5624

Poster Session

First-in-human phase 1/2 study of ubamatamab, a MUC16xCD3 bispecific antibody, administered alone or in combination with cemiplimab in patients with recurrent ovarian cancer. *First Author: Kathleen N. Moore, Stephenson Cancer Center, University of Oklahoma Health Sciences Center/Sarah Cannon Research Institute, Oklahoma City, OK*

Background: Mucin-16 is a cell surface glycoprotein that is overexpressed in epithelial ovarian cancer (OC). Ubamatamab (REGN4018) is a mucin-16 x cluster of differentiation 3 (MUC16xCD3) bispecific antibody that promotes T cell-mediated cytotoxicity by facilitating contact between cancer cells and T cells. In mouse model studies, ubamatamab demonstrated dose-dependent antitumor activity against MUC16-expressing OC tumor cells.¹ Cemiplimab is an anti-programmed cell death-1 monoclonal antibody. In a Phase 1 study (NCT03564340) in patients with recurrent OC, ubamatamab monotherapy demonstrated an acceptable safety profile, durable clinical activity across a range of doses between 20 mg and 800 mg intravenous (IV) weekly (as measured by RECIST and cancer antigen 125 [CA-125] response rates), and linear pharmacokinetics up to 800 mg IV weekly.² These clinical data support further evaluation of a once every 3-week (Q3W) regimen of ubamatamab alone and in combination with cemiplimab. The study is currently recruiting patients to combination dose escalation, monotherapy dose expansion, and the randomized Phase 2 cohort. **Methods:** In Phase 2, up to 150 patients with advanced platinum-resistant OC and elevated serum cancer antigen-125 will be randomized to three arms (1:1:1) to receive ubamatamab 250 mg IV Q3W or 800 mg IV Q3W as monotherapy, or ubamatamab 250 mg IV Q3W in combination with cemiplimab 350 mg Q3W. All arms will include weekly step-up dosing of ubamatamab (1 mg week 1, 20 mg week 2, and full dose weeks 3 and 4) to limit risk of cytokine release syndrome prior to proceeding to Q3W dosing. Expansion cohorts will use a Simon 2-stage study design, with an interim analysis after the first 20 patients. Any arm with ≥ 3 objective responses will be expanded to 50 patients. The primary objective of the dose expansion phase is to assess the preliminary efficacy of ubamatamab as monotherapy or in combination with cemiplimab, separately by cohort. Secondary objectives include characterization of the safety profile by cohort, and the pharmacokinetics of ubamatamab alone or in combination with cemiplimab, as well as patient-reported outcomes for all cohorts. In this dose expansion phase the primary endpoint will be the objective response rate for each arm as defined by RECIST 1.1 criteria. Secondary endpoints include evaluation of duration of response and progression-free survival as well as further evaluation of safety and pharmacokinetics. Exploratory endpoints include evaluation of baseline tumor MUC16 immunohistochemistry expression and other biomarkers as predictors of response. The impact of ubamatamab on quality of life and physical functioning will also be assessed. References: 1. Crawford A et al. *Sci Transl Med*. 2019;11:eau7534. 2. *Annals of Oncology* (2022) 33 (suppl. 7): S235-S282. 10.1016/annonc/annonc1054. Clinical trial information: NCT03564340. Research Sponsor: Regeneron Pharmaceuticals, Inc.

TPS5626

Poster Session

A phase II, randomized, double-blind study of the use of rucaparib vs placebo maintenance therapy in metastatic and recurrent endometrial cancer. *First Author: Bradley Corr, University of Colorado Cancer Center, Aurora, CO*

Background: There are currently no approved maintenance therapies for metastatic and recurrent endometrial cancer, which carries a dismal long-term prognosis. The PARP inhibitor drug class has demonstrated significant clinical benefit as a maintenance therapy for patients with germline/somatic *BRCA* mutations or homologous recombination deficiency (HRD) in ovarian cancers. However, *BRCA* mutations are not common in endometrial cancer. Loss of function of the tumor suppressor gene *PTEN* has been demonstrated in greater than 80% of endometrioid endometrial cancers¹. *PTEN* loss of function is well known to lead to activation of the PI3K-AKT-mTOR pathway but has also been shown to lead to defects in homologous recombination (HR) DNA repair of double strand breaks². Specifically, *PTEN* silencing leads to decreased RAD51 foci formation. Based on this mechanism, in vitro data on endometrial cancer cell lines has demonstrated sensitivity to PARP inhibitors. Notably, sensitivity of PARP inhibition in *PTEN* loss of function is independent of microsatellite instability (MSI)³. **Methods:** This is a multi-center phase II, placebo controlled, double-blinded study of the use of rucaparib as maintenance therapy in patients with metastatic or recurrent endometrial cancer. A maximum of 138 patients will be randomized 1:1 to receive rucaparib at starting dose of 600mg BID dosing vs. placebo. Standard dose reductions of known toxicities will be followed based on FDA approved indications of rucaparib. Patients will remain on therapy until progression of disease or toxicity induced discontinuation. Eligible patients will have Stage III/IV or recurrent endometrial cancer and must have received one or two prior lines of chemotherapy. All histologic subtypes, including carcinosarcoma will be included. Treatment arms will be stratified on histology, number of lines of prior therapy, and complete vs partial response to prior line of therapy. The primary endpoint is progression free survival (PFS). Secondary endpoints include overall survival (OS), overall response rate (ORR), and toxicity. To date, 79 patients have been enrolled. 1. Mutter GL, Lin MC, Fitzgerald JT, et al. Altered *PTEN* expression as a diagnostic marker for the earliest endometrial precancers. *J Natl Cancer Inst*. 2000;92(11):924-930. 2. Shen WH, Balajee AS, Wang J, et al. Essential role for nuclear *PTEN* in maintaining chromosomal integrity. *Cell*. 2007;128(1):157-170. 3. Dedes KJ, Wetterskog D, Mendes-Pereira AM, et al. *PTEN* deficiency in endometrioid endometrial adenocarcinomas predicts sensitivity to PARP inhibitors. *Sci Transl Med*. 2010;2(53):53ra75. Clinical trial information: NCT03617679. Research Sponsor: Clovis Oncology.

TPS5627

Poster Session

ENGOT-EN20/GOG-3083/xport-EC-042: A phase 3, randomized, placebo-controlled, double-blind, multicenter trial of selinexor in maintenance therapy after systemic therapy for patients with P53 wild-type, advanced or recurrent endometrial carcinoma. *First Author: Ignace Vergote, University Hospitals Leuven, Leuven Cancer Institute, and BGOG, Leuven, Belgium*

Background: Patients (pts) with first-line metastatic or recurrent endometrial cancer (EC) have a poor prognosis. Selinexor is an oral XPO1 inhibitor, which leads to nuclear accumulation of tumor suppressor proteins, including p53. Selinexor is FDA-approved for use in multiple myeloma and diffuse large B-cell lymphoma, and has shown clinical activity in previously treated, advanced EC. Molecular characterization of EC is critical in directing treatment for advanced and recurrent disease. Of the EC molecular subtypes, TP53 wild type (wt) tumors represent 50% of advanced and recurrent tumors. A recent phase 3 study in maintenance after chemotherapy found that, despite the primary endpoint (PFS) not reaching statistical significance, prolonged PFS of oral once-weekly selinexor versus placebo (13.7 months and 3.7 months, respectively) was observed in a prespecified exploratory subgroup analysis of patients with advanced or recurrent TP53wt EC. **Methods:** XPORT-EC-042 (NCT05611931) is a Phase 3 randomized, double-blind, placebo-controlled study designed to evaluate the efficacy and safety of selinexor as maintenance therapy in pts with TP53wt advanced or recurrent EC, who have achieved a partial response or complete response per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 after completing at least 12 weeks of platinum combination chemotherapy $\pm$ immunotherapy for primary stage IV or recurrent disease. Eligible pts must be $\geq$ 18 years of age, have histologically confirmed EC, and TP53wt disease based on NGS sequencing assessed by Foundation Medicine. Pts will be randomized 1:1 with either selinexor 60 mg or placebo once weekly in 28-day cycles until progressive disease, toxicity, or 3 years if in complete response. A total of 220 pts will be enrolled at sites across the United States, Canada, Europe, and Israel. The primary objective is to compare PFS in pts treated with selinexor compared to placebo based on RECIST v1.1 criteria as assessed by the Investigator. Key secondary objective is overall survival. Other secondary objectives are safety, time to first subsequent therapy, time to second subsequent therapy, time from randomization until the second progression event (PFS2), and PFS by a blinded independent central review. Patient enrollment is ongoing. Clinical trial information: NCT05611931. Research Sponsor: Karyopharm Therapeutics.

TPS5629

Poster Session

A randomized phase II study comparing single-agent olaparib, single-agent cediranib, and the combinations of cediranib/olaparib, olaparib/durvalumab (MEDI4736), cediranib/durvalumab (MEDI4736), and olaparib/AZD5363 (capivasertib) in women with recurrent, persistent, or metastatic endometrial cancer. *First Author: B.J. Rimel, Cedars-Sinai Medical Center, Los Angeles, CA*

Background: Identifying new approaches for the treatment of advanced endometrial cancer (EC) is a priority. A platform study design allows for a faster investigation of novel drug combinations. NRG-GY012 is an ongoing platform study investigating drug combinations with the PARP inhibitor olaparib (O) and the anti-angiogenic agent cediranib (C). Results from the first set of arms established improved PFS for combination cediranib/olaparib over C alone, but did not meet its prespecified statistical significance. In this second set of arms, based on preclinical data, we are investigating the combination of O with an AKT inhibitor (capivasertib), O with durvalumab and C with durvalumab compared to the reference arm of C alone. **Methods:** This is a multicenter randomized four arm study for patients with recurrent, metastatic or persistent EC. Patients are randomized 1:1:1:1 to cediranib PO 30 mg Daily; olaparib 300 mg PO BID and capivasertib 400mg 4 day on/3 off schedule; olaparib 300 mg PO BID and durvalumab 1500mg q28 days; or the combination of cediranib 20 mg PO Daily 5 days on/2 days and durvalumab 1500mg q28. All treatment cycles are 28 days. Primary endpoint is progression free survival (PFS). The study is powered to detect a doubling in median PFS from 3.6 (based on cediranib alone) to 7.2 months with 90% power, using a one-sided test with $\alpha = 0.05$ per comparison. Forty patients will be enrolled per arm, with an interim futility analysis planned at 50% information time. Eligibility includes endometrioid, serous, and mixed histology EC; at least 1 prior line of chemotherapy (no more than 2 lines for metastatic disease), prior endocrine or immunotherapy alone is allowed; prior treatment with lenvatinib and pembrolizumab is excluded. Archival tumor tissue and blood samples are being collected for translational studies. The study is open across the NRG network; 76 of a planned 168 patients are enrolled to date. Safety analysis at the time of 36 patients enrolled did not demonstrate any new safety signals and the study was approved to continue enrollment. Clinical trial information: NCT03660826. Research Sponsor: U.S. National Institutes of Health.

TPS5628

Poster Session

A phase 2, two-stage study of avelumab and axitinib in patients with mismatch repair-proficient (MMR-P) recurrent or persistent endometrial cancer (EC). *First Author: Elizabeth Katherine Lee, Medical Oncology, Dana-Farber Cancer Institute, Boston, MA*

Background: Despite significant strides in understanding the molecular pathogenesis of EC, there remain few effective therapies for recurrent disease. Deeper insight into the roles of disordered tumor vasculature and HIF1 α - and VEGF-mediated immunosuppressive effects on myeloid-derived suppressor cells, T-cells, and PD-L1 expression contributed to the development of new targeted regimens. By inhibiting VEGF receptor (VEGFR) and PD-L1 signaling, immunologically "cold" tumors may become inflamed. The combination of the anti-PD-L1 antibody avelumab with axitinib, an inhibitor of VEGFR 1-3 and PDGFR with more potent IC₅₀ inhibitory activity than lenvatinib, has also shown synergistic activity and is FDA approved as first line treatment for patients with renal cell cancer. We therefore hypothesized that this combination would be well tolerated and efficacious in recurrent MMR-P EC. **Objectives:** This is a non-randomized two-stage phase 2 study in patients with MMR-P EC evaluating the activity of combined avelumab and axitinib, as assessed by the co-primary endpoints of (1) frequency of patients surviving progression-free for at least 6 months (PFS6), and (2) the objective response rate (ORR) as measured by RECIST 1.1. **Methods:** Patients must have MMR-P EC and have received at least one chemotherapeutic regimen, with no upper limit on the number of prior lines received. Prior use of immune checkpoint inhibitors (ICI) is excluded. Eligible patients received avelumab 800 mg IV every 2 weeks and axitinib 5 mg orally twice daily until disease progression or unacceptable toxicity. In the first stage of the study, 16 patients were enrolled; if there were $\geq$ 2 objective responses or $\geq$ 2 PFS6 responses, accrual continued to the second stage with enrollment of an additional 19 patients. The combination of avelumab/axitinib would be considered worthy of further study if overall there were $\geq$ 4 objective responses or $\geq$ 8 PFS6 responses. **Results:** As of the data-cutoff in September 2022, a total of 28 patients had received study treatment; one patient withdrew from the study due to toxicity, prior to her first radiographic assessment. The median number of prior lines was 1 (range 1-4). Median follow-up was 12.7 months. Of the 28 patients receiving study treatment, eleven patients (39.3%, 95% CI 21.5%-59.4%) achieved a PR [11/28; 8 confirmed PR (28.6%) and 3 unconfirmed PR (10.7%)]. An additional 39.3% (11/28) had stable disease as best response. Median PFS was 7.3 months (95% CI 3.9-9.0). PFS6 was 59.3% (95% CI 35.7%-76.7%) and at 6 months, 10 patients were still alive and progression-free. Updated efficacy data and safety data will be reported at the time of the meeting. **Conclusions:** With 8 confirmed PRs and 10 PFS6 responses, the co-primary endpoints were met and the combination of avelumab/axitinib is considered worthy of further study in this population of MMR-P EC. Clinical trial information: NCT02912572. Research Sponsor: Pfizer.

TPS5630

Poster Session

Randomized phase III trial in MMR deficient (MMRd) endometrial cancer (EC) patients comparing chemotherapy (CT) alone versus dostarlimab in first line advanced/metastatic setting: DOMENICA study (GINECO-EN105b/ENGOT-en13 study). *First Author: Florence Joly, Centre François Baclesse, Caen and GINECO, Paris, France*

Background: The standard treatment for advanced EC is still platinum-based combination CT, regardless of the histology, molecular status and the patient's profile. However, EC patients are a particularly frail group of patients, often with co-morbidities. Tolerance of CT can be difficult and induce long-term toxicities. In advanced EC disease, MMRd/MSI-H tumors represent 15 to 20 % of cases. Preclinical data suggest that these tumors are more resistant to platinum. On the other hand, anti-PD1 immunotherapy has shown impressive results among MMRd/MSI-H EC patients after platinum-based CT. The aim of this study is to de-escalate the first line advanced/metastatic treatment of patients with MMRd/MSI-H endometrial cancer with the objective to avoid carboplatin-paclitaxel related toxicities by substituting CT with the PD1 inhibitor dostarlimab. **Methods:** DOMENICA is an ongoing international randomized, open-label, phase III trial. 142 patients with MMRd/MSI-H EC Stage III or Stage IV or first recurrent disease without curative treatment (surgery, radiation therapy, +/- adjuvant CT) will be randomized (1:1) to receive either 4 cycles of dostarlimab 500mg every 3 weeks followed by dostarlimab 1000mg every 6 weeks as maintenance up to 2 years or 6 cycles of carboplatin-paclitaxel. A cross over is allowed from the CT arm to the dostarlimab arm at first progression. The maximum treatment duration with dostarlimab will be 24 months. Stratification factors are prior adjuvant CT, prior pelvic radiotherapy. The primary endpoint is the progression-free survival (PFS). Secondary endpoints include overall survival (OS), PFS2, quality of life, best objective response rate, disease control rate, duration of response rate, safety, tolerability, time to first and second subsequent therapy, efficacy of second systemic therapies, pharmacokinetics description and immunogenicity determination. The study is designed to expect a 17.8-months PFS in dostarlimab arm and a 10-months PFS in the CT arm, translating to a hazard ratio of 0.58. A protocol amendment is submitted to increase patient population (with extended eligibility criteria, PFS hypothesis). Status: The DOMENICA/GINECO-EN105b/ENGOT-en13 trial is currently recruiting, the first patient was randomized in April 2022. Clinical trial information: NCT05201547. Research Sponsor: GlaxoSmithKline.

TPS5631

Poster Session

RT-PACE: Phase I/II study of adjuvant whole pelvic hypofractionated radiotherapy for non-metastatic cervical and endometrial cancer. *First Author: Christina H. Son, University of Chicago, Chicago, IL*

Background: Whole pelvic radiation therapy (WPRT) improves locoregional control in women with high-intermediate and high-risk endometrial cancer. The standard treatment course consists of 25-28 fractions (5-5.5 weeks) of 1.8-2 Gy/fraction, and is delivered using intensity-modulated radiation therapy (IMRT), which allows for superior sparing of normal tissue with a subsequent lower rate of acute and late toxicity compared to less conformal treatment techniques. Moderate hypofractionation (HF, >2 Gy/fraction) has been studied in other disease sites, such as breast and prostate cancer, and is associated with lower or comparable toxicity, improved patient convenience, and greater cost savings compared to standard fractionation. However, HF has not been well-studied in the setting of WPRT for gynecologic cancers. **Methods:** This phase I/II multi-institutional study evaluates the feasibility, safety, and toxicity profile of HF-WPRT in women with non-metastatic cervical or endometrial cancers who have undergone curative hysterectomy and are recommended adjuvant WPRT by their treating physician. Concurrent chemotherapy is not allowed, but can be administered sequentially prior to or after WPRT. Para-aortic radiation or nodal boosts are not allowed, however vaginal brachytherapy boost is permissible. Phase I is a safety study of increasing dose-per-fraction. All treatment regimens have an approximate biologic effective dose of 53 Gy ($\alpha/\beta = 10$). A keyboard design is utilized to identify the maximum tolerated dose-per-fraction (MTD), defined in this study as the regimen that is associated with a CTCAE grade 3+ gastrointestinal/genitourinary toxicity rate of $\leq 10\%$ on the last day of WPRT. There are 3 dose cohorts of increasing dose-per-fraction. Phase II will accrue 64 evaluable patients to HF-WPRT using the MTD determined in phase I. The primary endpoint is to evaluate the change in patient-reported gastrointestinal toxicity from baseline to the last day of WPRT using the EPIC bowel score. The study is powered to compare results to the RTOG 1203 IMRT standard fractionation arm. The phase 1 portion of the study completed accrual; the phase II portion opened in April 2022 with a fractionation of 42.56 Gy in 16 fractions. Secondary endpoints include genitourinary toxicity (EPIC, CTCAE), quality of life (FACT-Cx, PRO-CTCAE), financial toxicity (FACIT-COST), and decision-making (Decision Regret Scale). Pelvic control at 2 years is an exploratory endpoint. Clinical trial information: NCT04683653. Research Sponsor: University of Chicago Comprehensive Cancer Center.

TPS5633

Poster Session

The RAINBO MMRd-GREEN trial (GCIG/DGOG/ENGOT-EN14²): A phase III trial on the addition of adjuvant durvalumab to radiotherapy in patients with high-risk MMRd endometrial cancer. *First Author: Merve Kaya, Leiden University Medical Center, Leiden, Netherlands*

Background: The molecular class of endometrial cancer (EC) is both prognostic and predictive in high-risk EC (HREC). The TransPORTEC research consortium showed that patients with MMRd HREC did not benefit from adjuvant chemotherapy added to radiotherapy. MMRd tumors are particularly sensitive to immunotherapy. We hypothesize that adjuvant durvalumab added to standard radiotherapy will increase recurrence-free survival (RFS) in patients with MMRd HREC. **Methods:** MMRd-GREEN is an international, open-label, randomized phase III trial and part of the RAINBO program (NCT05255653). Eligible patients will be allocated (1:1) to adjuvant durvalumab 1500 mg once every 4 weeks for 1 year combined with radiotherapy or standard radiotherapy alone. The primary endpoint is RFS at 3 years. Secondary endpoints are pelvic, vaginal and distant RFS, EC-specific survival, overall survival, treatment-related toxicity, health-related quality of life and exploratory translational research. Main inclusion criteria include histologically confirmed stage IB/II with (substantial) lymph-vascular space invasion (LVI) or stage IIIA-C MMRd EC, after hysterectomy and bilateral salpingo-oophorectomy (regardless of lymphadenectomy or sentinel lymph node biopsy) without macroscopic residual disease. Molecular classification must be performed according to the WHO 2020 algorithm. The target accrual is 316 patients, accounting for a total drop-out rate of 12%. This sample size yields 80% power to detect a 13% increase in the 3-year RFS (hazard ratio 0.58) as a result of the addition of durvalumab, with an accrual duration of 48 months and follow-up period of 30 months. No interim analysis is planned; an independent data monitoring committee will routinely monitor recurrences and adverse events. Enrollment: Since August 2022, the trial is open for recruitment in the Netherlands and per February 10th 2023, the first 3 patients have been enrolled. Activation of more international centers is ongoing. Clinical trial information: NCT05255653. Research Sponsor: KWF Dutch Cancer Society; AstraZeneca.

TPS5632

Poster Session

CCTG EN10: A phase II study of tailored adjuvant therapy in *POLE*-mutated and p53-wildtype/NSMP early-stage endometrial cancer (EC)—RAINBO BLUE and TAPER. *First Author: Jessica N. McAlpine, BCCA, Vancouver Cancer Centre, Vancouver, BC, Canada*

Background: Molecular classification of EC provides an opportunity to personalize treatment for patients with early disease based on prognosis. We hypothesize that de-escalated adjuvant treatment in patients with early-stage *POLE*-mutated (*POLE*mut) or p53wt/NSMP (p53 wildtype/no specific molecular profile) EC is feasible and associated with favourable disease control, QOL and health economics. **Methods:** EN.10 is a Canadian Cancer Trials Group led phase II trial that enrolls two independent cohorts of patients with early stage EC based on tumour molecular status: *POLE*mut (substudy A) and p53wt/NSMP (substudy B). The primary objective is to estimate the 3-year rate of pelvic recurrence. Secondary objectives include estimated 3-year isolated vaginal recurrence, para-aortic recurrence, distant metastasis, survival (recurrence-free, EC-specific, overall survival) and to describe the patient decisional conflict and fear of recurrence. Tertiary objectives: QOL, economic evaluation and interrogation/discovery of additional prognostic biomarkers. Statistical Design: Registration to Substudy A or B is based on molecular classification. Treatment will be deescalated in both substudies; to surveillance-only (all early stage *POLE*mut, and a proportion of NSMP), or vaginal brachytherapy (proportion of NSMP), with NSMP stratification based on histological grade, and lymphovascular invasion. Substudy A can enroll endometrioid, serous, clear cell, undifferentiated and carcinosarcomas whereas Substudy B is confined to endometrioid histotype. Both arms require ECOG 0-2 and hysterectomy+BSO with nodal assessment required for stage II and grade 3 EC. A total of 120 patients with *POLE*mut (Sub-study A) and 180 with p53wt/NSMP ER+ (Sub-study B) EC will be recruited in 3 years. If the upper 95% confidence limit is less than 5% in either of Substudy A, Cohort A1 and Sub-study B or both, it will be concluded that patients in one or both groups have an acceptable low risk of pelvic recurrence at 3 years with molecularly-tailored de-escalated adjuvant treatment. An additional estimated 25 patients with higher risk *POLE*mut EC will be enrolled for an exploratory analysis. Conduct to Date: Study activation Dec 19 2022. Enrollment January 31, 2023: 36 Supported by Canadian Cancer Society, Canadian Institutes of Health Research, Gynecologic Cancer Initiative, BC Cancer Foundation. Clinical trial information: NCT05640999. Research Sponsor: Canadian Cancer Society, Canadian Institutes of Health Research, Gynecologic Cancer Initiative, BC Cancer Foundation.

TPS5634

Poster Session

AFT-50 EndoMAP: A phase IB/II multi-cohort study of targeted agents for patients with recurrent or persistent endometrial cancer. *First Author: Evelyn Cantillo, 525 East 68th St, New York, NY*

Background: The prognosis for women with recurrent or persistent EC after progressing on first-line chemotherapy is poor, with a median overall survival (OS) of 12 months, highlighting the need for more efficacious therapies for this population. Immune checkpoint inhibitors either as monotherapy or when combined with kinase inhibitors have recently demonstrated encouraging response rates in pts with microsatellite instability-high (MSI-H)/mismatch repair-deficient (dMMR) and MS-stable (MSS)/MMR-proficient (MMRp) EC, respectively. Atezolizumab is a humanized monoclonal anti-programmed cell death ligand 1 (PD-L1) inhibitor that has demonstrated monotherapy antitumor activity with an acceptable safety profile in relapsed recurrent EC. Atezolizumab has shown compelling clinical efficacy for pts with certain solid tumors (e.g., urothelial, NSCLC, triple negative breast cancer) as monotherapy and as part of combination therapy. The AFT-50 EndoMAP trial is a platform trial designed to evaluate the efficacy and safety of Atezolizumab in combination with biomarker-defined targeted agents in pts with recurrent or persistent EC. Recognizing pts may have either progressed through or received a checkpoint inhibitor in a prior line of therapy, a non atezolizumab cohort will also be open to enrollment. **Methods:** This is a phase IB/II non-randomized, multicenter, multicohort, biomarker-driven platform study consisting of two cohorts: A (atezolizumab) and B (non atezolizumab). Eligible pts have recurrent or persistent EC and have received no more than 2 prior lines of therapy. FoundationOne CDx (F1CDx) NGS assay will be used for genomic tumor profiling. In cohort A, pts may be eligible for one of the following doublets: Atezolizumab+ipatasertib (PIK3CA/PTEN/AKT1-altered cancers), Atezolizumab+talazoparib (tumors with genomic loss of heterozygosity (LOH) $\geq 16\%$), Atezolizumab+Trastuzumab emtansine (ERBB2/HER2 mutated and/or amplified tumors), Atezolizumab+Tiragolumab (MSI-H and/or TMB>10 mut/MB), and Atezolizumab+bevacizumab (biomarker unmatched). Pts will receive Atezolizumab in addition to the targeted agent (at the study approved dosing schedule) until progression, unacceptable toxicity, pt or physician decision to withdraw from the study, death, or study termination. Pts in cohort B, will be eligible for inavolisib (PIK3CA/PTEN/AKT1-altered cancers) + letrozole. Each cohort will enroll ~20 pts; however, the exact size of the cohort may be adjusted. The primary endpoint for Cohort A is confirmed overall response rate (ORR) for each cohort, and for Cohort B is progression free survival at 6 months. Secondary endpoints include disease control rate, duration of response, OS, safety and tolerability, 6-month PFS (cohort A). As a platform study, additional arms may be added, as supported by evolving understanding of EC and molecular targets. EndoMAP is actively enrolling at 17 sites in the US with a target of 25 sites nationwide. Clinical trial information: NCT04486352. Research Sponsor: Genentech; Alliance Foundation.

TPS5635

Poster Session

GCIG SB-001/NSGO-CTU-PEACE/ANZGOG 1923/2020: Palliation in gynaecology—Patients' expectations and assessment of care. *First Author: Kristina Lindemann, NSGO-CTU, Denmark & Dep. of Gynaecologic Oncology, Oslo University Hospital & Faculty of Medicine, University of Oslo, Oslo, Norway*

Background: Patients with advanced gynaecological cancers who are approaching end of life (EOL) have a high symptom burden and following several prior lines of therapy, a low likelihood of response to further anti-cancer treatment. Despite this, 20-30% of women with gynecological cancer received chemotherapy in the last 30 days of life, with potentially detrimental effects on health and quality of life. Little is known about patients' and carers' perceptions and preferences in this phase of illness. Eliciting patient's values and preferences for EOL care and shared decision-making are central elements of GCIG SB-001/NSGO-CTU-PEACE with the aim of improving patient-centered EOL care. The primary aim of PEACE is to assess the feasibility of collecting data on patient satisfaction towards EOL. Secondary aims include collecting data on patient and carer satisfaction with care, as well as prospective collection of details of their care. **Methods:** PEACE will prospectively enroll patients in Norway and Australia. Key eligibility criteria include: Patients with gynaecological cancer at an advanced stage with a predicted life expectancy of approximately 4 months. Patients may be on anti-cancer treatment or may be under observation/palliative care. In addition, the patient must be able (both physically and cognitively) to complete patient-reported outcome measures independently. The study will also include an appointed carer (not mandatory). Patient and carer satisfaction with care and the importance of domains of care will be assessed with the CANHELP-Lite individualized (Canadian Health Care Evaluation Project) instrument and FACIT (Functional Assessment of Chronic Illness Therapy). Carer's perception of the bereavement period and the quality of the patient's death will be assessed with the CANHELP lite bereavement and the Quality of Death and Dying questionnaire. The study will prospectively collect data on EOL treatment. Patient and carer satisfaction with care and quality of the dying process will be summarized by standard descriptive statistical measures. A sample size of 65 patients would have at least 80% power with 95% confidence to rule out a 60% completion rate in favour of the more interesting 75% rate. Assuming a 10% drop-out rate, PEACE will enrol 73 patients. Enrolment commenced in December 2022. ClinicalTrials.gov Identifier: NCT05142150 Clinical trial information: NCT05142150. Research Sponsor: Radiumhospitalets Legater; Private Practice Fund, Canberra Hospital.

6000

Oral Abstract Session

Concurrent chemoradiotherapy followed by adjuvant cisplatin-gemcitabine versus cisplatin-5-fluorouracil chemotherapy for N2-3 nasopharyngeal carcinoma: A multicentre, open-label, randomised, controlled, phase 3 trial. *First Author: Lin-Quan Tang, Department of Nasopharyngeal Carcinoma, Sun Yat-sen University Cancer Centre, State Key Laboratory of Oncology in South China, Collaborative Innovation Centre for Cancer Medicine, Guangdong Key Laboratory of Nasopharyngeal Carcinoma Diagnosis and Therapy, Guangzhou, China*

Background: Patients with N2-3 nasopharyngeal carcinoma have a high risk of failures, despite the current practice of concurrent adjuvant cisplatin-5-fluorouracil (PF) regime. Adjuvant PF regimen may not be adequate for tumor control of high risk patients, emphasizing the need for more effective regimen of adjuvant chemotherapy in N2-3 nasopharyngeal carcinoma. **Methods:** We conducted this multicentre, open-label, phase 3, randomised, controlled trial in four centers in China. Patients aged 18–65 years with stage T1–4N2–3 nasopharyngeal carcinoma were randomly assigned (1:1) to receive concurrent cisplatin (100mg/m² intravenously) on days 1, 22, and 43 of radiotherapy followed by either gemcitabine (1 g/m² intravenously on days 1 and 8) and cisplatin (80 mg/m² intravenously on day 1) (GP) once every 3 weeks or 5-fluorouracil (4 g/m² in continuous intravenous infusion over 96 h) and cisplatin (80 mg/m² on day 1 given intravenously) once every 4 weeks for three cycles. Randomisation was by a computer-generated random number code with a block size of six, stratified by treatment centre and nodal stage (N2 or N3). The primary endpoint was 3-year progression-free survival in the intention-to-treat population. This study is registered in ClinicalTrials.gov, NCT03321539. **Results:** From October 30, 2017 to July 9, 2020, 240 were randomly assigned to PF group (n = 120) or GP group (n = 120). After a median follow-up of 40 months (IQR: 32–48), the 3-year progression-free survival was 83.9% (95% CI 75.9–89.4) in GP group and 71.5% (62.5–78.7) in PF group (stratified HR 0.54; 95% CI, 0.32 to 0.93; p = 0.023). Significantly lower cumulative incidence of locoregional relapse (2.6% vs. 12.5%; HR 0.33; 95% CI, 0.12 to 0.90; Fine-Gray p = 0.030) and distant metastasis (10.4% vs. 20.1%; HR 0.50; 95% CI, 0.26 to 0.98; Fine-Gray p = 0.042) were also observed in GP group than PF group. However, there was no effect on early 3-year overall survival (90.7% vs. 94.0%; HR 1.12; 95% CI, 0.50 to 2.55; log-rank p = 0.779). Overall incidence of treatment-related adverse events was not significant different between the two treatment groups in the concurrent phase. In the adjuvant phase, significant higher incidence of grade 3–4 leucopenia (42 [41.2%] vs. 19 [16.8%], p < 0.001), neutropenia (33 [32.0%] vs. 10 [8.9%], p = 0.001) and thrombocytopenia (9 [8.7%] vs. 2 [1.8%], p = 0.044) was observed in GP group than PF group, whereas the frequency of diarrhea (6 [5.3%] vs. 0 [0%], p = 0.030) and mucositis (21 [18.6%] vs. 7 [6.8%], p = 0.010) was higher in PF group than in GP group. **Conclusions:** Concurrent adjuvant GP regimen significantly improved progression-free survival in patients with N2-3 nasopharyngeal carcinoma with acceptable toxicity. Long term follow-up is needed to confirm the ultimate therapeutic ratio. Clinical trial information: NCT03321539. Research Sponsor: National Key Research and Development Program of China, National Natural Science Foundation of China, the Sun Yat-sen University Clinical Research 5010 Program; Guangdong Major Project of Basic and Applied Basic Research, Sci-Tech Project Foundation of Guangzhou City, Innovative Research Team of High-level Local Universities in Shanghai, Natural Science Foundation of Guangdong Province for Distinguished Young Scholar, Postdoctoral Innovative Talent Support Program, the Pearl River S&T Nova Program of Guangzhou, Planned Science and Technology Project of Guangdong Province, Key Youth Teacher Cultivating Program of Sun Yat-sen University, and Fundamental Research Funds for the Central Universities.

LBA6002

Oral Abstract Session

PD-1 blockade with sintilimab plus induction chemotherapy and concurrent chemoradiotherapy (IC-CCRT) versus IC-CCRT in locoregionally-advanced nasopharyngeal carcinoma (LANPC): A multicenter, phase 3, randomized controlled trial (CONTINUUM). *First Author: Jun Ma, Department of Radiation Oncology, Sun Yat-sen University Cancer Center, Guangzhou, China*

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2023, issue of the *Journal of Clinical Oncology*.

6001

Oral Abstract Session

Induction chemotherapy plus radiotherapy alone versus cisplatin-based concurrent chemoradiotherapy in locoregionally advanced nasopharyngeal carcinoma: An open-label, non-inferiority, randomized phase 3 trial. *First Author: MingYuan Chen, Sun Yat-sen University Cancer Center, Guangzhou, China*

Background: Cisplatin-based concurrent chemoradiotherapy (CCRT) has long been regarded as standard treatment for locoregionally advanced nasopharyngeal carcinoma (LA-NPC) due to its favorable local control. However, concurrent platinum is associated with intolerable toxicities and ineffective in preventing distant metastasis. Since IMRT enhances the local control and induction chemotherapy (IC) decreases the risk of distant failure, it is worth exploring whether IC plus IMRT alone regimen could replace CCRT for patients with LA-NPC. **Methods:** This open-label, phase 3, non-inferiority clinical trial was conducted from June 12, 2015 to April 30, 2019. Patients with stage T1–4N2–3 or T3–4N0–1 M0 NPC were randomly assigned (1:1) to receive gemcitabine (1000 mg/m²) and cisplatin (80 mg/m²) IC for 2 cycles followed by IMRT alone or IMRT plus concomitant weekly cisplatin (40 mg/m²) up to 7 cycles. 2-year failure-free survival was set as primary endpoint and non-inferiority margin of 10% was established. Efficacy analysis and safety analysis were dividedly performed in the intention-to-treat and safety population. **Results:** A total of 249 patients were enrolled, including 124 patients in IC group and 125 patients in CCRT group. Median follow-up time was 60 months (IQR, 48–71). 2-year failure-free survival was 90.2% in IC group versus 86.3% in CCRT group, with an HR of 0.818 (95% CI, 0.479–1.397) and absolute difference of 3.9% (1-sided 95%CI, -4.2 to 11.9). No significant differences were observed between groups in overall survival, locoregional relapse, or distant metastasis. Compared with CCRT group, fewer grade ≥3 AEs occurred in IC group (47.5% vs 61.5%, p = 0.015), including leucopenia, anemia, mucositis, nausea and dysphagia. The IC group had significantly better QoL during and short periods after IMRT, including domains of global health status, physical functioning, fatigue, nausea and vomiting, pain, and appetite loss. **Conclusions:** For LA-NPC, gemcitabine and cisplatin induction chemotherapy plus IMRT alone was not inferior in 2-year failure-free survival to concurrent chemoradiotherapy. Clinical trial information: NCT02460887. Research Sponsor: the Key-Area Research and Development of Guangdong Province (2020B1111190001), the National Natural Science Foundation of China (No. 82002857, 82230034, 81874134), Sun Yat-Sen University Clinical Research 5010 Program (No. 2015010, 2018015).

6003

Oral Abstract Session

Results of the multicenter phase II FRAIL-IMMUNE trial evaluating the efficacy and safety of durvalumab combined with weekly paclitaxel carboplatin in first-line in patients (pts) with recurrent/metastatic squamous cell carcinoma of the head and neck (R/M SCCHN) not eligible for cisplatin-based therapies. *First Author: Jerome Fayette, Centre Leon Bérard, Medical Oncology, Lyon, France*

Background: For pts with R/M SCCHN, new standard of care (SoC) has been recently established with pembrolizumab either alone or combined with platinum-5FU (KN 048 – median Overall Survival (OS): 13 months when combined). For pts who need chemotherapy, platinum-5FU-pembrolizumab as first-line treatment appears associated with substantial toxicity that precludes its use in fragile patients. In this context, we investigated the efficacy and tolerance of PDL-1 inhibition with durvalumab combined with weekly carboplatin-paclitaxel as first-line treatment in frail R/M SCCHN pts. **Methods:** This single-arm phase II study enrolled pts in first-line of their R/M SCCHN and not eligible to standard cisplatin-based CT with an ECOG PS of 0 or 1. Pts received 4 cycles of CT (carboplatin AUC2; paclitaxel 80mg/m² both at D1, D8, D15) and durvalumab (D) 1500mg repeated every 4 weeks for a maximum of 12 months. The primary endpoint was OS Rate at 12 months (m). The study used a Fleming A'Hern design (inefficacy boundary: 47% and target efficacy: 65%), requiring 38 successes among 64 pts. Secondary endpoints were Progression-Free Survival (PFS), Time to Treatment Failure (TTF), objective response rate (ORR) and tolerance. **Results:** 64 pts (median age 69.5y; 90.6% males, 62.5% PS1) were included, regardless of their PDL-L1 status. Primary tumors were mainly located in oropharynx (37.5%) and larynx (28.1%) with 37.3% PD-L1 CPS≥20. 54.9% were metastatic. The efficacy rule for OS was met with 40 pts (62.5%, unilateral 95%CI: [51.5%–73.5%]) alive at 12m. With a median follow-up of 27.1 m, median OS was 18.0 m (95% CI [11.9–NR]) and the 24m-OS rate was 45% [32%–57%]. Median PFS was 7.0 m (95% CI [5.4–9.9]) and median TTF was 6.0 m (95% CI [4.7–9]). 44/62 pts (71%) achieved an OR (11.3% complete response and 59.7% partial response). Median duration of response was 5.9 m (95% CI [3.4–9.6]). 20.3% of pts experienced G≥3 adverse events related to D. Toxicity led to permanent discontinuation of D in 3.1% of pts. No D-related death was reported. **Conclusions:** This study performed in fragile patients not amenable to cisplatin-based CT met its primary endpoint on OS and showed a 18 months median OS rate. This combination of durvalumab with weekly carboplatin/paclitaxel was associated with a favorable toxicity profile. Clinical trial information: NCT0372967. Research Sponsor: AstraZeneca.

LBA6004

Oral Abstract Session

Phase 3 randomized study for evaluation of physician choice Rx and triple metronomic as second-line therapy in head and neck cancer (CRSF 2021-HN-001). *First Author: Rushabh Kiran Kothari, Narayana Multispecialty Hospital, Ahmedabad, India*

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2023, issue of the *Journal of Clinical Oncology*.

6005

Oral Abstract Session

Dose expansion results of the bifunctional EGFR/TGFβ inhibitor BCA101 with pembrolizumab in patients with recurrent, metastatic head and neck squamous cell carcinoma. *First Author: Glenn J. Hanna, Dana-Farber Cancer Institute, Boston, MA*

Background: Pembrolizumab (P) is approved to treat patients (pts) with recurrent, metastatic (R/M) head and neck squamous cell carcinoma (HNSCC). BCA101 is a first-in-class bifunctional EGFR antibody fused to a TGFβ immune modulating payload which is well tolerated and has clinical activity as monotherapy and in combination with pembrolizumab in advanced solid tumors (ESMO 2022 731MO). Here we report the results from the interim analysis of an expansion cohort combining BCA101+P as first line therapy in R/M HNSCC. **Methods:** This ongoing single-arm, open-label multicenter dose expansion cohort enrolled pts with R/M HNSCC with a tumor PD-L1 CPS ≥ 1 with no prior systemic therapy for R/M disease, ECOG 0-1, and measurable disease (RECIST v1.1). Pts received BCA101 (1500 mg IV on days 1, 8, 15) with P (200 mg IV on day 1) every 21-days. Primary endpoint: safety; secondary endpoints: overall response rate (ORR), duration of response (DOR), progression-free survival (PFS), overall survival (OS). Exploratory: molecular and immunologic predictors of response. A Simon optimal two-stage design was employed: among 18 evaluable pts in stage 1, >3 pts in response triggered continuation to stage 2 enrolling 21 additional pts targeting an ORR > 35%. **Results:** From 2/2022 to 1/2023, 20 pts enrolled while 18 were evaluable (had first restaging scans) in stage 1. Pts were more often men (n=13, 65%) with a median age of 66 (range: 31-77). Oropharynx (10, 50%) (7/10 (70%) were HPV/p16-pos) and oral cavity (7, 35%) were the most common primary subsites (larynx/hypopharynx: 3). Fifteen (75%) had distant metastatic disease. The ORR in stage 1 was 44% (8 PRs, 4 SD) with a clinical benefit rate (CBR=PR+SD) of 67%; 7/12 (58%) HPV-neg pts achieved a response. Median DOR not reached, but median time on-treatment was 6.7 months (range: 2.7-11.0+) among responders. Ten pts discontinued therapy; all but 1 for PD (n=1 for toxicity). Grade 3+ treatment-related adverse events (TRAEs) were observed in 4 pts (20%, most common: anemia). No treatment-related deaths were observed. Acneiform rash was the most common TRAE of any grade (15, 75%). PFS and OS estimates are forthcoming. Eight (44%) had baseline PD-L1 CPS scores of 0-19, while ten (56%) were ≥ 20. Stage 2 is actively enrolling with completion of accrual expected by the meeting. **Conclusions:** Stage 1 of this dose expansion cohort of BCA101+P shows encouraging anti-tumor activity with additive potential, particularly among HPV-neg pts; and the combination is well tolerated among this R/M HNSCC population. Further investigation is warranted. Study funded by Bicara Therapeutics and conducted in collaboration with Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc. USA (NCT04429542). Clinical trial information: NCT04429542. Research Sponsor: Bicara Therapeutics; Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc. USA.

Efficacy evaluable	PR	SD	PD	ORR	CBR (PR+SD)
HPV-neg (n=12)	7	3	2	7/12 (58%)	10/12 (83%)
HPV-pos (n=6)	1	1	4	1/6 (17%)	2/6 (33%)
Total (n=18)	8	4	6	8/18 (44%)	12/18 (67%)

6006

Oral Abstract Session

Randomised phase III trial of the hypoxia modifier nimorazole added to radiotherapy with benefit assessed in hypoxic head and neck cancers determined using a gene signature (NIMRAD). *First Author: David Thomson, The Christie NHS Foundation Trust, Manchester, United Kingdom*

Background: Tumour hypoxia is an adverse prognostic factor in head and neck squamous cell carcinoma (HNSCC). We assessed whether patients with hypoxic HNSCC benefited from the addition of nimorazole to definitive radiotherapy (RT). **Methods:** NIMRAD was a phase III, multi-centre, placebo-controlled, double-blind trial in patients with HNSCC unsuitable for concurrent platinum chemotherapy or cetuximab with definitive RT (NCT01950689). Patients were randomized 1:1 to receive nimorazole (1.2 g/m² daily, prior to RT) + RT (65 Gy in 30 fractions over 6 weeks) or placebo (taken via the same schedule) + RT. The primary endpoint was loco-regional control (freedom from loco-regional progression, FFLRP) in patients with hypoxic tumours, defined as greater than or equal to the median hypoxia score of the first 50 patients analysed (≥ 0.079), using a validated 26-gene signature. The planned sample size was 340 patients allowing for signature generation in 85%, assumed HR 0.50 for nimorazole effectiveness in the hypoxic group, and requiring 66 loco-regional failures to have 80% power in a two-tail log-rank test at the 5% significance level. **Results:** 338 patients were randomised by 19 UK centres from May 2014 to May 2019, with a median follow-up of 3.1 years (95%CI 2.9-3.4). Hypoxia scores were available for 286 (85%). The median patient age was 73 years (range 44-88); and clinical factors were balanced between the arms, both for the whole population and hypoxic group (Table). There were 36 (25.9%) loco-regional failures in the hypoxic group, where nimorazole + RT did not improve FFLRP (adjusted HR 0.72; 95% CI 0.36-1.44; p=0.35), or overall survival (adjusted HR 0.96; 0.53-1.72; p=0.88) compared with placebo + RT. Similarly, nimorazole + RT did not improve FFLRP or OS in the whole population. In total (n=338), 73% of patients allocated nimorazole adhered to the drug for ≥ 50% of RT fractions. Nimorazole + RT caused more acute nausea compared with placebo + RT (CTCAE v4.0 G1+2: 56.6% vs 42.4%, G3: 10.1% vs 5.3%, respectively; p=0.003), with no differences in other early or late toxicities. **Conclusions:** Addition of the hypoxia modifier nimorazole to RT for locally advanced HNSCC in older and less fit patients did not improve loco-regional control or survival. Clinical trial information: NCT01950689. Research Sponsor: Cancer Research UK.

		Whole population (N=338)	Nimorazole (n=168)	Placebo (n=170)	Hypoxic Group (N=139)	Nimorazole (n=70)	Placebo (n=69)
Site (%)	Oropharynx	207 (61.2)	110 (65.5)	97 (57.1)	71 (51.1)	40 (57.1)	31 (44.9)
	Hypopharynx	51 (15.1)	25 (14.9)	26 (15.3)	29 (20.9)	14 (20.0)	15 (21.7)
	Larynx	80 (23.7)	33 (19.6)	47 (27.6)	39 (28.1)	16 (22.9)	23 (33.3)
HPV positive (%)		142 (42.0)	75 (44.6)	67 (39.4)	42 (30.2)	24 (34.3)	18 (26.1)
Stage AJCC 7 th Edition (%)	II	15 (4.4)	7 (4.2)	8 (4.7)	5 (3.6)	3 (4.3)	2 (2.9)
	III	103 (30.5)	52 (31.0)	51 (30.0)	56 (40.3)	29 (41.4)	27 (39.1)
	IVab	220 (65.1)	109 (64.9)	111 (65.3)	78 (56.1)	38 (54.3)	40 (58.0)

6007

Oral Abstract Session

Neoadjuvant nivolumab, paclitaxel, and carboplatin followed by response-stratified chemoradiation in locoregionally advanced HPV negative head and neck squamous cell carcinoma (HNSCC): The DEPEND trial. *First Author: Ari Rosenberg, University of Chicago, Chicago, IL*

Background: The role of neoadjuvant immunotherapy in curative-intent head and neck squamous cell carcinoma (HNSCC) remains poorly defined. Survival for locoregionally advanced (LA) HPV negative (-) HNSCC remains poor with two-year survival of ~50%, and substantial treatment-related toxicity with standard chemoradiation (CRT). Given the activity of anti-PD1 in recurrent/metastatic HNSCC, we studied neoadjuvant nivolumab with chemotherapy and the feasibility of subsequent response-stratified CRT in HPV(-) LA HNSCC. **Methods:** The DEPEND trial (NCT03944915) is a phase II trial of nivolumab, paclitaxel, and carboplatin followed by response-stratified CRT for previously untreated stage IVA-B (AJCC-8th edition) HPV(-) HNSCC. The ultimate goal is to evaluate radiation volume and/or dose reduction to decrease long-term toxicities. Eligible patients received three 21-day cycles of nivolumab 360mg day 1, paclitaxel 100mg/m² on days 1/8/15, and carboplatin AUC5 day 1. Patients with ≥ 50% reduction by RECIST 1.1 received response-adapted CRT to 66Gy with elimination of elective nodal volumes; < 50% reduction received standard-dose CRT to 70-75Gy. Post-CRT nivolumab 480mg every 4 weeks for 9 months was administered. The primary endpoint was deep response rate (DRR) defined as the proportion of patients with ≥ 50% reduction. Tumor PD-L1 immunohistochemistry was reported as combined positive score (CPS). **Results:** Thirty-six eligible patients started treatment between September 2019 and June 2022. Median age 59 (range 27-77), 22% female, 80% 20PYH smoking, 39% oral cavity, 19% oropharynx, 25% larynx/hypopharynx, 78% T3/4 and 78% N2/3. PD-L1 CPS ≥ 1 in 58%. The DRR with nivolumab/chemotherapy was 54% (95% CI 0.37-0.72), which met our statistical endpoint. The ORR was 89%. CRT stratification was as follows: Response-adapted CRT (n = 19) and standard-dose CRT (n = 16). At a median follow-up of 14 months, 2-year PFS and OS were 64% (95%CI 0.41-0.80) and 76% (95%CI 0.53-0.89), respectively. By CRT stratification, 2-year PFS was 79% and 46% in response-adapted and standard-dose CRT, and 2-year OS was 86% and 67% in response-adapted and standard-dose CRT, respectively. One patient died from disease progression during neoadjuvant therapy. 2-year distant control in response-adapted and standard-dose CRT arms was 100% and 63%, and 2-year locoregional control was 85% and 92%, respectively. PD-L1 CPS ≥ 1 and < 1 demonstrated DRR of 75% and 27%, respectively (p=0.01). **Conclusions:** Nivolumab-based neoadjuvant chemioimmunotherapy led to deep responses, and response-adapted CRT was associated with favorable survival and locoregional control. PD-L1 expression was predictive of deep response to nivolumab-based neoadjuvant therapy. Late toxicity analysis between treatment arms is planned. Clinical trial information: NCT03944915. Research Sponsor: BMS.

6008

Oral Abstract Session

Immuno-chemotherapy as single treatment modality for larynx preservation (ICoLP): Co-primary endpoints and safety results. *First Author: Renata Ferrarotto, Thoracic/Head and Neck Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Optimal treatment of larynx squamous cell carcinoma (LC) maximizes functional outcomes and survival. Surgery and radiotherapy (RT) may lead to significant morbidity, notably dysphonia and dysphagia. Our group published durable pathologic complete response (pCR) with normal function in 33% of patients (pts) with stage II-IV LC treated with single modality chemotherapy. We hypothesized that pembrolizumab (P), cisplatin (C), and docetaxel (D) will cure a subset of LC pts and preserve larynx function. **Methods:** Eligible pts had stage II-III LC measurable per RECIST 1.1. Treatment consisted of P 200 mg, C 75 mg/m² or carboplatin AUC 6, and D 75 mg/m² IV Q3W. After 2 PCD cycles, pts with radiological response (complete [CR], partial [PR], or stable disease [SD]) received 2 additional PCD cycles. After 4 cycles, pts underwent larynx biopsy. Those with pCR received 4 doses of consolidation P; those without pCR received local therapy (LT; RT or surgery). Co-primary endpoints are disease control rate (DCR; CR+PR+SD) after 2 PCD cycles and pCR rate after 4 cycles. Secondary endpoints include safety, laryngeal preservation rate, relapse-free survival, and swallow function. Per Bayesian design (H₀: 65% DCR, 15% pCR; H₁: 85% DCR, 30% pCR), we reject H₀ if of 25 pts, 19 have DCR or > 7 achieve pCR (10% alpha, 88% power). **Results:** 24 pts enrolled from 8/9/19-12/15/22, 62.5% were stage III (54.2% were T3 and 16.7% were N1); 23 were evaluable for the efficacy endpoints. DCR was 100% with 74% (17/23) being objective responses and 52% CR; pCR rate to date is 77.3% (17/22; 1 pt on-treatment). 6 of 17 (35%) pts with pCR developed recurrence, mostly (4/6) within 4 months of pCR, and were salvaged with LT. 5 pCR lasted ≥ 1 y; 2 additional pCR pts unable to perform serial laryngoscopy or imaging due to loss of insurance (n = 1) or moving to another state (n = 1) have not had clinical recurrence for ≥ 2 ys. The median follow-up is 17.2 mos (range: 1.4 – 39.4 mos). One patient who refused LT at early recurrence was lost to follow-up and eventually underwent a total laryngectomy and RT then recurred locally and died of disease. An additional patient who had pCR with early recurrence received definitive RT with CR, but subsequently developed a solitary lung metastasis treated with RT; 2 pts remain on trial treatment. The most common treatment-related adverse events (TRAE) were fatigue (91.6%), anemia (79%), diarrhea (45.8%), and nausea (41.6%). 10 grade 3-4 TRAE were reported in 5 (20.8%) pts with the most common being neutropenia (3/24, 12.5%) and anemia (2/24; 8.3%). 2 pts discontinued PCD treatment due to toxicity. **Conclusions:** The study reached its primary endpoint with a DCR of 100% (23/23) and a pCR in 77.3% (17/22) of evaluable patients; 5 pCR last ≥ 1 y. Recurrences after pCR occurred stressing the importance of close follow-up. Updated efficacy and swallow function results will be presented at the meeting. Clinical trial information: NCT04030455. Research Sponsor: Merck.

6010

Poster Discussion Session

NEOSPACE trial: Neoadjuvant pembrolizumab-gemcitabine-cisplatin followed by concurrent pembrolizumab-chemoradiation and maintenance pembrolizumab for stage IVA nasopharyngeal cancer (NPC). *First Author: Edwin P Hui, Department of Clinical Oncology, Prince of Wales Hospital, Shatin, Hong Kong*

Background: Stage IVA NPC had the worst prognosis despite the current standard of neoadjuvant chemotherapy and concurrent chemoradiation (CRT). There is no safety and efficacy data combining immune checkpoint inhibitor (ICI) and CRT in NPC. **Methods:** We conducted an open label, single arm, multi-site, phase 2 clinical trial in AJCC 8th Edition Stage IVA (T4 and/or N3, M0) WHO type 2/3 Epstein Barr virus (EBV) +ve NPC (Clinical trial register NCT03734809). The experimental treatment consisted of neoadjuvant pembrolizumab (200 mg D1), gemcitabine (1000 mg/m² D1+8) and cisplatin (80 mg/m² D1) q3w x2 followed by concurrent pembrolizumab (200 mg x3 week 1, 4 and 7) and cisplatin (40 mg/m² weekly x7) during intensity-modulated radiation (IMRT), and maintenance pembrolizumab 200 mg q3w x12 from 4 weeks post-RT. By Fleming one-stage design (type I error 0.05, power 0.80, 10% drop out), planned sample size is 46. Primary endpoint is 2-year (yr) progression free survival (PFS). Secondary endpoints include safety and tolerability. Plasma EBV DNA (pEBV DNA) was monitored. **Results:** Accrual was completed with 46 subjects recruited at two study sites from May 2019 to June 2022 in Hong Kong (n=31) and Singapore (n=15). This protocol specified analysis included 37 subjects with >12 months post-treatment follow up (median 26.8 months, 95% CI 21.3-32.9). Patient demographics: mean age 52 (range 27 - 84); M:F 31:6; ECOG 0=23, 1=14; stages: T4N1-2 (16), T1-3N3 (18), T4N3 (3). Overall compliance rate: neoadjuvant cisplatin 98.6%, gemcitabine 97.7%, concurrent cisplatin 73.7%, pembrolizumab 100% (neoadjuvant), 77.5% (concurrent), 77% (maintenance), IMRT 99.7% (69.96 Gy). Treatment related adverse events (≥ grade 3, >10%): dysphagia (32.4%), mucositis (29.7%), neutropenia (29.7%), radiation dermatitis (24.3%), anemia (18.9%), hyponatremia (13.5%), thrombocytopenia (10.8%). No ≥ grade 4 mucositis/dermatitis. The 2-yr PFS was 69.6% (95% CI 53.8 - 88.5%). At the end of neoadjuvant, CRT and maintenance phases, molecular remission (pEBV DNA = 0) was achieved in 24.3%, 70.3% and 70.3% of patients respectively, which strongly correlated with PFS (p=0.0253, 0.0007 and <0.0001 respectively, Table). **Conclusions:** Pembrolizumab incorporated into neoadjuvant, CRT and maintenance protocol is safe with promising results. This strategy of combining ICI with neoadjuvant chemotherapy and CRT is being tested in several ongoing phase 3 trials in advanced NPC. Clinical trial information: NCT03734809. Research Sponsor: Funding for this Investigator-initiated Research was provided by MSD.

Primary endpoint	1-yr rate (%)	2-yr rate (%)
PFS	88.9	69.6
Secondary endpoints		
Overall survival	97.2	88.1
Distant metastasis free survival	94.4	80.8
Locoregional PFS	94.5	87.8
PFS by molecular remission		
pEBV DNA at the end of maintenance		
0	100	91.1
> 0	63.6	21.2
Events	p<0.0001	
Progression	No. of patients	
Death	12	
Second primary cancer (without NPC progression)	5	
	2 (lung, cholangiocarcinoma)	

6009

Poster Discussion Session

Final overall survival analysis of JUPITER-02: A phase 3 study of toripalimab versus placebo in combination with gemcitabine and cisplatin as first-line treatment for recurrent or metastatic nasopharyngeal carcinoma (NPC). *First Author: Hai-Qiang Mai, Department of Nasopharyngeal Carcinoma, Sun Yat-sen University Cancer Center, Guangzhou, China*

Background: There are currently no FDA-approved IO therapies for NPC. Toripalimab in combination with Gemcitabine-Cisplatin (GP) chemotherapy had shown significant improvement over chemotherapy alone in progression-free survival (PFS) as first-line treatment for recurrent or metastatic (r/m) NPC at the interim PFS analysis of JUPITER-02 (NCT03581786) study. The final overall survival (OS) analysis results are summarized here. **Methods:** Patients with r/m NPC (n = 289) were randomized (1:1) to receive toripalimab 240 mg (n = 146) or placebo (n = 143) in combination with GP once every 3 weeks (Q3W) for up to 6 cycles, followed by monotherapy with toripalimab or placebo Q3W until disease progression, intolerable toxicity, or completion of 2 years of treatment. Stratification factors were ECOG performance score (0 vs. 1) and extent of disease (recurrent vs. primary metastatic) at enrollment. The primary endpoint was PFS by an independent review committee. Secondary endpoints included OS and safety. **Results:** By the cutoff date of Nov 18, 2022, when 133 events were reached for the final OS analysis, the median survival follow up was 30.1 months. A significant improvement in OS was observed for the toripalimab arm over the placebo arm: HR = 0.63 (95% CI: 0.45-0.89), two-sided p = 0.0083. The median OS was not reached in the toripalimab arm and was 33.7 months in the placebo arm. The 2-year and 3-year OS rates were 78.0% vs. 65.1%, and 64.5% vs. 49.2% respectively. A consistent effect on OS, favoring the toripalimab arm, was observed in nearly all subgroups, including PD-L1 high and PD-L1 low expression subgroups. No new safety signals were identified in the toripalimab arm since the interim report. The incidence of Grade ≥3 adverse events (AEs) (89.7% vs 90.2%) and fatal AEs (3.4% vs 2.8%) were similar between two arms. However, AEs leading to discontinuation of toripalimab/placebo (11.6% vs 4.9%), immune-related (irAEs) (54.1% vs. 21.7%) and Grade ≥3 irAEs (9.6% vs. 1.4%) were more frequent in the toripalimab arm. **Conclusions:** The addition of toripalimab to GP chemotherapy as 1st-line treatment for r/m NPC provided clinically important and highly significant OS advantage over GP alone with a manageable safety profile. These results support the use of toripalimab with GP chemotherapy as the new standard care for this population. Clinical trial information: NCT03581786. Research Sponsor: Shanghai Junshi Biosciences.

6011

Poster Discussion Session

Dual PD1 and CTLA4 immune checkpoint blockade and hypofractionated radiation in patients with salivary gland cancers. *First Author: Cristina P. Rodriguez, University of Washington, Seattle, WA*

Background: No systemic therapy standard of care exists for recurrent/metastatic malignancies of the salivary glands (SGC) and immune checkpoint inhibitors (ICIs) have low response rates. Preclinical data in solid tumors suggest synergistic antitumor effects of ICIs with hypofractionated radiation (XRT). This study explored the safety and activity of nivolumab (N) and ipilimumab (I) with palliative XRT. **Methods:** This phase I/II open label single arm trial enrolled patients (pts) with incurable SGCs (WHO 2017) with evidence of progression, ECOG 0-1, no prior antiPD1 or CTLA4 directed therapy, RECIST 1.1 measurable disease excluding the XRT site. Pts received N 3mg/kg IV Q 2 weeks x 12 doses followed by 480 mg IV Q4 weeks x 8 doses and I 1 mg/kg IV Q6 weeks x 4 doses. XRT was given to a total dose of 24Gy in 3 fractions every other day over 1 week (wk) and initiated 2 wks after the first dose of N and I. Research blood collection was obtained prior to wks 1, 8 and 16. The primary endpoint was safety and tolerability using CTCAE v. 4, secondary endpoints were objective response rates (ORR) by RECIST 1.1 criteria in non-radiated sites of measurable disease, overall survival (OS) and progression free survival (PFS). The study was approved by the FHCC IRB and registered on clinicaltrials.gov (NCT03749460). **Results:** Between 4/2019 and 5/2022, 20 pts were enrolled, the median age was 58 (range 27-77) years, 10 (50%) were male, 12 (60%) had ECOG 0, and 7 (35%) were Asian. Most common histologies were adenoid cystic 9 (45%) and salivary duct 4 (20%), 15 (75%) had no prior systemic therapy. Ten (50%) had both local and distant disease, 14 (70%) had commercial NGS testing, all had TMB < 10mut/Mb, MSI-stable tumors. All patients completed XRT with the most common XRT site being the lung 13 (65%) and bone 7 (35%). The median number of N doses received was 12 (range 3-20) and I doses 4 (range 1-4). Enrollment was halted until first 6 pts were assessed for dose limiting toxicities during initial 12 wks of treatment, none were observed. Among all pts enrolled, 5 (20%) Grade 3 AEs were observed: adrenal insufficiency, hypokalemia, lung infection, hypotension, and mania. No grade 4/5 toxicities were observed. One pt was not evaluable for RECIST 1.1 due to rapid disease progression: partial responses were observed in 4 (20%: 2 pts with salivary duct, 1 acinic cell and 1 adenoid cystic) with a median duration of 15.5 months (mos) (range 6-16 mos), stable disease in 6 (30%) all lasting 6 mos or greater, and progressive disease in 9 (45%). With a median follow-up of 16 mos, median OS was 25 mos (95% CI: [1.56, 2.59]) and median PFS was 7.2 mos (95% CI: [0.21, 1.56]). Exploratory correlative peripheral blood analysis is ongoing and will be reported. **Conclusions:** Nivolumab/ipilimumab and palliative XRT results in low rates of severe toxicities, modest ORR but durable ORR/SD. Further work is necessary to explore predictors for response. Clinical trial information: NCT03749460. Research Sponsor: Bristol Myers Squibb.

6012

Poster Discussion Session

Safety and efficacy of immune checkpoint inhibitor (ICI) naïve cohort from study of PDS0101 and pembrolizumab in HPV16-positive head and neck squamous cell carcinoma (HNSCC). *First Author: Katharine Andress Rowe Price, Department of Oncology, Mayo Clinic, Rochester, MN*

Background: Up to 70% of oropharyngeal cancers in the US are reported to be HPV-mediated with most caused by HPV16 infection. First line treatment for patients with unresectable, recurrent or metastatic (R/M) disease is pembrolizumab with or without chemotherapy, but most patients eventually experience disease progression. PDS0101 is a novel, investigational HPV16-targeted immunotherapy that stimulates a potent, targeted T cell attack against HPV16-positive cancers. **Methods:** VERSATILE-002 (NCT04260126) is an open-label, non-randomized, Simon 2-stage study evaluating the combination of PDS0101 and pembrolizumab in subjects with HPV16-positive R/M HNSCC in 2 cohorts: ICI-naïve and ICI-refractory. All subjects receive pembrolizumab IV Q3W with PDS0101 SC administered concurrently during Cycles 1, 2, 3, 4, and 12 (max 5 doses). The primary endpoint of the study is confirmed Best Overall Response per RECIST 1.1. Herein we update the safety, PFS, and OS data for the ICI-naïve subjects. **Results:** Forty-eight subjects who received at least one cycle of combination therapy (safety population) had a median age of 62.5 (range 45 – 83), were 93.8% male, 93.8% White, and 62.5% ECOG 0. Among this population, the median overall treatment duration in months was 3.5 (range 0.0 – 19.5). The median number of PDS0101 doses was 4 (range 1 – 5); 56.3% received 4 doses and 22.9% received 5 doses. The median number of pembrolizumab doses was 5 (range 1 – 29); 27.1% received ≥10 doses. Efficacy was evaluated in 34 subjects (47.1% with CPS ≥20) who had assessment of tumor response following treatment (efficacy population). Tumor reduction (maximum percent change from baseline) was seen in 23 (67.6%) subjects. Nine subjects (26.5%) had confirmed response including 1 CR and 8 PR, 15 subjects had SD (44.1%), and 9 subjects had PD (26.5%). One subject was not evaluable (2.9%). The median PFS was 10.4 months (95% CI 4.2, 15.3). Among the safety population, median overall survival was non-estimable due to the ongoing survival status of study subjects. The estimated 12-month OS rate was 87.1%. Thirty-three (68.5%) subjects had mild or moderate (Grade 1 or 2) PDS0101-related TRAE (TRAE); the most common were fatigue and injection site reactions (ISRs). Only 3 subjects (6.3%) had Grade 3 TRAEs: fatigue, ISR, blood alkaline phosphatase increased, and hyperglycemia. No subjects had Grade 4 or 5 TRAE. No subject came off study due to toxicity. **Conclusions:** PDS0101 with pembrolizumab is well tolerated in this ICI naïve R/M HPV-associated HNSCC population. Median PFS was 10.4 months which compares favorably to published median PFS of 2-3 months for approved ICIs when used as monotherapy in patients with similar PD-L1 levels. The estimated 12-month OS of 87.1% is promising compared to published results of about 36-50%. These results justify a confirmatory randomized, controlled study. Clinical trial information: NCT04260126. Research Sponsor: PDS Biotechnology.

6014

Poster Discussion Session

Phase II trial of adjuvant de-escalated radiation + adjuvant nivolumab for intermediate-high risk P16+ oropharynx cancer. *First Author: Heath Devin Skinner, UPMC Hillman Cancer Center, Department of Radiation Oncology, Pittsburgh, PA*

Background: Treatment de-intensification for resected, human papillomavirus (HPV)-associated oropharyngeal squamous cell carcinoma (OPSCC) is an area of active investigation, with a goal of providing a less toxic adjuvant regimen compared to the current standard of care 66 Gy of radiation (RT) combined with concurrent cisplatin defined in recently reported as Arm D of the ECOG3311 trial. Here, the programmed death 1 (PD-1) antibody nivolumab was added to de-intensified RT in high risk, resected HPV+ OPC. **Methods:** Eligible patients included transorally resected pathologic stage III or IVA HPV+ OPSCC using p16 immunohistochemistry, featuring high-risk neck disease factors (gross extracapsular extension >1mm or ≥5 positive lymph nodes) to mirror ECOG3311 Arm D patients accrued. Positive margin status was excluded except by PI approval. Postoperative treatment consisted of accelerated fractionation RT (50 Gy over 4 weeks) concurrent with nivolumab at 240 mg every 2 weeks, followed by 6 months of adjuvant nivolumab biweekly or monthly. The primary endpoint was progression-free survival (PFS). Swallowing and quality of life patient reported outcome (PRO) measures were collected at baseline and defined intervals after treatment. **Results:** Forty-one patients (n=41) were accrued and were analyzed. Forty of 41 patients remain alive with a median follow-up of 30 months (range 1 – 49 months). The probability of 3-year overall survival is 97% (95% CI = 90% - 100%) and the probability of 3-year PFS is 86% (95% CI = 68% - 100%). Two patients developed recurrent disease, one of whom died. One patient developed isolated metastasis while a second developed local, regional, and distant metastasis. The most common adverse grade ≥3 adverse events were lymphocytopenia (n=24), dysphagia (n=2) and oral mucositis (n=2). One grade 4 sepsis/multi-organ failure was reported. Comparison of PRO results with those observed in ECOG3311 trial are underway and will be reported. **Conclusions:** De-intensification of adjuvant treatment adding nivolumab to RT is tolerable and demonstrates favorable clinical outcome for high-risk, resected, HPV+ HNSCC patients. Further targeted immunotherapy combinations are warranted. Clinical trial information: NCT03715946. Research Sponsor: U.S. National Institutes of Health.

6013

Poster Discussion Session

A phase 1 dose-escalation and expansion study of CUE-101, a novel HPV16 E7-pHLA-IL2-Fc fusion protein, given as monotherapy and in combination with pembrolizumab in patients with recurrent/metastatic HPV16+ head and neck cancer. *First Author: Christine H. Chung, Moffitt Cancer Center, Tampa, FL*

Background: Immuno-STATs are modular T cell engagers engineered to selectively activate tumor-antigen specific CD8+ T cells via targeted delivery of cytokines. CUE-101, the first Immuno-STAT in clinical trials, is composed of a human leukocyte antigen (HLA) complex, HLA-A*0201, a peptide epitope derived from the HPV16 E7 protein, and 4 molecules of attenuated human interleukin-2 (IL-2) designed to bind, expand, and activate HPV16-specific CD8+ T cells for the treatment of HPV16+ cancers. **Methods:** CUE-101-01 is an ongoing first-in-human study in HLA-A*0201 patients with HPV16+ recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC). Escalating doses of CUE-101 monotherapy (0.06 mg/kg to 8 mg/kg) and in combination with pembrolizumab (1 mg/kg to 4 mg/kg + 200 mg pembrolizumab) were evaluated, followed by expanded enrollment at the recommended phase 2 dose (RP2D). Patients with R/M HNSCC refractory to ≥ 1 platinum-based or checkpoint inhibitor therapy received CUE-101 monotherapy. Patients with previously untreated PD-L1+ R/M HNSCC received CUE-101 + pembrolizumab as first-line treatment. Therapy was administered every 3 weeks until disease progression or intolerable toxicity. Safety, pharmacokinetics (PK), pharmacodynamics (PD), and anti-tumor activity were assessed. **Results:** As of January 12, 2023, 67 patients were enrolled. A MTD was not established in monotherapy or combination-treated patients; 4 mg/kg of CUE-101, alone or in combination with pembrolizumab, was chosen as the RP2D dose in both cohorts. Monotherapy RP2D enrollment is complete and combination RP2D enrollment is ongoing. Frequent adverse events include fatigue (45%), anemia (34%), chills (27%), infusion related reactions (25%), constipation (22%), lymphopenia (22%) and nausea (22%). CUE-101 PK data demonstrate dose-dependent increases in drug exposure sustained with repeat dosing. PD data demonstrate selective expansion of HPV-16 E7₁₁₋₂₀-specific CD8+ T cells, sustained increase in NK cells and transient increase in Treg cells. Among 19 evaluable monotherapy RP2D patients, 1 PR and 6 durable SD (SD ≥ 12 weeks) were observed, with mOS of 24.4 months (9.1, NA). Among 12 evaluable RP2D combination patients to date, 5 PRs, and 2 durable SDs have been observed, with 71% (5/7) of patients expressing PD-L1 CPS ≤ 20. **Conclusions:** CUE-101 facilitates the targeted delivery of high concentrations of IL-2 to relevant tumor-specific CD8+ T cells. We demonstrate safety and tolerability with encouraging PD signals and antitumor activity with monotherapy and in combination with pembrolizumab in HPV+ R/M HNSCC patients. Enrollment continues in the CUE-101 and pembrolizumab combination cohort. Clinical trial information: NCT03978689. Research Sponsor: CUE Biopharma Inc.

6015

Poster Discussion Session

Correlation of CDKN2A genomic alterations with tumor response to palbociclib given before chemoradiation therapy (CRT) to patients with human papillomavirus (HPV)-negative, locally advanced head and neck squamous-cell carcinoma (LA-HNSCC): A single-arm, phase 2 trial. *First Author: Peter John Oppelt, Washington University School of Medicine, St. Louis, MO*

Background: Cell cycle deregulation is ubiquitous in HNSCC. In HPV-negative disease, the most common genomic alteration of cell-cycling included *CDKN2A* deletions (57%), mutations (27%) or hypermethylation (12%). Selective CDK4/6 inhibition arrested cell cycling and inhibited tumor growth in cell-line and xenograft models of HPV-negative HNSCC, and *CDKN2A* alterations were predictive of response. An exploratory analysis of a double-blind, randomized, phase 2 trial of patients with HPV-negative recurrent/metastatic HNSCC showed that *CDKN2A* alterations were associated with better overall survival (OS) with palbociclib and cetuximab vs placebo and cetuximab (median 9.7 vs 4.6 months, HR 0.38). OS was similar between the two arms in patients without *CDKN2A* alterations. A phase 2 basket trial of patients with *CDKN2A*-altered head and neck cancers observed that palbociclib resulted in a target lesion decrease in 25% of patients. Collectively, these data warrant further studies to delineate predictive biomarkers of response to selective CDK4/6 inhibitors in HPV-negative HNSCC. **Methods:** The primary aims of this single-arm, phase 2 trial were to determine the objective response rate (ORR) of HPV-negative, LA-HNSCC to palbociclib, and to correlate responses to somatic *CDKN2A* alterations. HPV-negative disease was defined as SCC of the larynx, hypopharynx or oral cavity, or SCC of the oropharynx if negative for p16 by IHC and/or high-risk HPV-RNA by ISH. Genome sequencing (FoundationOne CDx/Tempus XT) was performed on tumor tissue obtained before treatment. Patients received palbociclib 125 mg/d orally on days 1-21 of each 28-day cycle. Tumor response was assessed using RECIST 1.1 with CT scans performed pre and post two cycles of palbociclib. Patients then received CRT. A sample size of 24 patients yielded an 80% power if the ORR was ≥38%, using an exact binomial test of one sample proportion comparison with an upper one-sided nominal significance level of 0.05 and null ORR of ≤17%. **Results:** 24 patients enrolled and completed two cycles of palbociclib: primary site (larynx-15; hypopharynx-4; oropharynx-4, oral cavity-1), clinical stage (III-7; IV-17), and smoking history (yes-23; no-1). The ORR with palbociclib was 41.7%. Best tumor response included: CR (1), PR (9), SD (13), and PD (1). *CDKN2A* altered disease was identified in 15 patients (62.5%) [mutation: 8, deletion: 7]. Tumor response to palbociclib occurred in 10 of 15 patients (66.7%) with *CDKN2A* altered disease versus 0 of 9 patients (0%) without *CDKN2A* altered disease (p=0.002, Fisher's Exact Test). **Conclusions:** The primary hypothesis was met: the ORR with palbociclib in HPV-negative, LA-HNSCC was 41.7%. The ORR with palbociclib was significantly higher in *CDKN2A* altered disease. Clinical trial information: NCT03389477. Research Sponsor: Pfizer.

6016

Poster Discussion Session

Olaparib, a poly (ADP-ribose) polymerase (PARP) inhibitor, in combination with pembrolizumab and carboplatin as first-line treatment of recurrent or metastatic head and neck squamous-cell carcinoma (RM-HNSCC): A single-arm, phase 2 trial. *First Author: Jared Cohen, Washington University Siteman Cancer Center, St. Louis, MO*

Background: The homologous recombination deficiency (HRD) phenotype is common in HNSCC and is due to mutation and promoter hypermethylation of DNA repair genes (*BRCA1, BRCA2, ATR, ATM, and FANCD*) and *PTEN*. In pre-clinical models of HNSCC, HRD sensitizes tumor to PARP inhibition and to additive antitumor activity of PARP inhibition in combination with platinum agents. PARP inhibitors also activate the STING pathway and upregulate PD-L1 expression, resulting in synergistic antitumor activity when given with PD-1 inhibitors. Olaparib is a highly selective PARP inhibitor that has been safely combined with pembrolizumab and carboplatin. **Methods:** In this single-arm phase 2 trial, patients with RM-HNSCC, no prior therapy for RM disease, and adequate performance status and organ function received up to six 21-day cycles of olaparib (200 mg bid orally days 1-10), pembrolizumab (200 mg IV day 1), and carboplatin (AUC 5 IV day 1), followed by up to twenty-nine 21-day cycles of olaparib (oral 300 mg bid days 1-21) and pembrolizumab (200 mg day 1). Treatment continued until discontinuation criteria were met. The primary endpoint was objective response, assessed by an independent radiologist using iRECIST. The primary hypothesis was that this regimen would result in a higher objective response rate (ORR) than historically reported with 5-FU, pembrolizumab and a platinum agent in similar patients. A Simon optimal two-stage design tested the null hypothesis (H_0 : ORR $\leq$ 36%) versus the alternative hypothesis (H_1 : ORR=62%) at a type I error rate of 10% and 90% power. In the first stage, up to 13 patients could be accrued. If $\geq$ 6 responses occur, 16 additional patients will be accrued. The null hypothesis will be rejected if $\geq$ 14 responses are observed in these 29 patients. At the end of the first stage, an interim analysis was performed to assess olaparib delivery during cycles 1 and 2 with the goal of 100% delivery in $\geq$ 80% of patients. We report the results of the primary endpoint and olaparib delivery for the first stage of the trial. **Results:** Twelve patients enrolled into the first stage of the trial. Key characteristics included median age 62 years (range 59-74), tobacco history (Y=5; N=7), primary site (oropharynx=7; oral cavity=4; larynx=1), HPV status (positive: 6; negative: 6) and PD-L1 status (CPS $\geq$ 1; 1-19: 4; $\geq$ 20: 7). Tumor response occurred in 8 patients (ORR 67%). The best tumor response to date was CR (1), PR (7), SD (3) and PD (1). Olaparib delivery during cycles 1 and 2 was 100% for all patients. **Conclusions:** Among patients with RM-HNSCC, first-line treatment with olaparib, pembrolizumab and carboplatin resulted in an ORR of 67% during the first stage of the trial. Olaparib delivery was 100%. Enrollment into the second stage is ongoing. Clinical trial information: NCT04643379. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ; Joseph Sanchez Foundation.

6018

Poster Discussion Session

Neoadjuvant nivolumab alone or in combination with relatlimab or ipilimumab in resectable head and neck squamous cell carcinoma (HNSCC). *First Author: Robert L. Ferris, Hillman Cancer Center, Pittsburgh, PA*

Background: PD-1 inhibition using nivolumab (nivo) monotherapy is modestly effective in metastatic HNSCC. Neoadjuvant trials using nivo may permit development of more effective combinations in surgically resectable HNSCC. We evaluated combinations with nivo plus additional immune checkpoints, CTLA-4 (ipilimumab, ipi) and LAG-3 (relatlimab, rela). **Methods:** Phase II randomized trial of neoadjuvant nivo alone (240 mg q2 weeks), or with ipi (1 mg/kg q3 weeks) or rela (160 mg q4 weeks) for 4 weeks prior to surgery. Response was scored using RECIST and standard pathologic response criteria. Patients were stratified by p16, PD-L1, and LAG-3, with staining assessed by immunohistochemistry. Freshly digested tumors were subjected to single cell RNA sequencing (scRNAseq) for T cell receptors and gene pathways to identify biomarkers of response or progression. The Cochran-Armitage trend test was used to explore associations with increasing pathological response efficacy. **Results:** 41 patients (pts) have been enrolled, with 33 evaluable for this analysis. Of these 33, median age is 63 (32-81), primary site oral cavity (n=25), oropharynx (n=5, 3 HPV), larynx (n=3), clinical T2 (n=5), T3 (n=12), T4 (n=13), and cN0/1 (n=22), cN2 (n=9), and PD-L1 CPS $>$ 1 (n=25). There were no serious study drug-related AEs or unexpected surgical delays/complications. Pathologic response (Table) was more frequent with nivo/rela (11/13) vs. nivo/ipi (6/10) or nivo (4/10). Partial ($>$ 50%) or major ($>$ 90%) pathologic responses were more frequent and deeper in the combination arms. Minor ($<$ 50%) pathologic responses were more frequent with nivo/rela, and similar between nivo/ipi and nivo. There was no association between RECIST response, PD-L1, or LAG3 and pathologic response. Combined PD-L1 and LAG3 expression was not associated with pathologic response in the nivo/rela arm, however more patients with combined positivity had a $>$ 50% response (4 vs. 0). Expansion of CD8 $^{+}$ T cells, as well as expanded proportion of CD8 $^{+}$ CXCL13 $^{+}$ T cells in responder tumors were identified in post-treatment specimens using scRNAseq. **Conclusions:** Neoadjuvant nivo/ipi or nivo/rela combinations were safe and associated with promising pathologic responses compared to nivo monotherapy. Anti-tumor CD8 $^{+}$ T cell populations and targetable pathways are emerging in responder patients. The trial continues to enroll and further evaluation of this strategy is warranted. Clinical trial information: NCT04080804. Research Sponsor: U.S. National Institutes of Health.

RECIST and pathologic response.

	RECIST				Pathologic Response			
	PR	SD	PD	None	pmPR (10-49%)	pPR (50-90%)	pMPR ($>$ 90%)	pCR (100%)
Nivo (10)	8	2	6	4	0	0	0	0
Nivo/Ipi (10)	5	5	4	3	2	1	0	0
Nivo/Rela (13)	1	10	2	2	7	2	1	1

6017

Poster Discussion Session

Enfortumab vedotin in the previously treated advanced head and neck cancer (HNC) cohort of EV-202. *First Author: Paul Swiecicki, Department of Internal Medicine, Division of Hematology/Oncology, University of Michigan Medical School, Ann Arbor, MI*

Background: Globally, HNCs accounted for an estimated 932,000 new cases and 467,000 deaths in 2020. Nectin-4 is expressed in a majority of HNCs. Given the poor prognosis (median survival $<$ 1 y) of recurrent/metastatic disease in patients (pts) with head and neck squamous cell carcinoma, effective treatments are needed. Targeting Nectin-4 with an antibody-drug conjugate (ADC) may be a novel strategy. Enfortumab vedotin (EV) is a Nectin-4 directed ADC approved for treatment of adults with locally advanced or metastatic (la/m) urothelial carcinoma previously treated with platinum-containing chemotherapy and PD-1/L1 inhibitor based on survival benefit shown in the phase 3 EV-301 trial. Use of EV for HNC is investigated in EV-202 (NCT04225117). **Methods:** In this multicohort, open-label phase 2 study, pts with previously treated la/m solid tumors not amenable to curative-intent treatment and Eastern Cooperative Oncology Group performance status 0-1 were enrolled into tumor-specific cohorts. For the HNC cohort, pts must have progressed/relapsed/discontinued treatment for toxicity after 1 platinum-based therapy for la/m disease and no more than 2 lines of cytotoxic therapy in the la/m setting. Unless contraindicated, pts must have received a programmed cell death protein 1/ligand 1 (PD-1/L1) inhibitor (based on PD-1/L1 expression). Pts received EV 1.25 mg/kg intravenously on days 1, 8, and 15 of a 28-d cycle until disease progression/discontinuation criteria were met. Primary endpoint was confirmed objective response rate (ORR; per RECIST v1.1) per investigator assessment. Secondary endpoints were duration of response (DOR), disease control rate (DCR), progression-free survival (PFS), overall survival (OS), and safety/tolerability. **Results:** As of April 11, 2022, a total of 46 pts were in the HNC cohort; median follow-up was 9.33 mo. Median age was 65 y, 87% of pts were men, and most had received $\geq$ 2 lines of systemic therapy in the metastatic setting. Histology at diagnosis was squamous cell carcinoma for 45 (97.8%) pts and "other" for 1 pt. ORR was 23.9% (n = 11). Median DOR was not reached. DCR was 56.5% (n = 26). Median time to response was 1.74 mo. Median PFS and OS were 3.94 and 5.98 mo, respectively. Common adverse events (AEs) were fatigue, alopecia, and peripheral sensory neuropathy (28.3% for each; n = 13). Grade $\geq$ 3 AEs occurring in $>$ 1 pt were anemia (n = 3), decreased neutrophil count (n = 2), and malignant neoplasm progression (disease progression of HNC; n = 2). Of treatment-related AEs of special interest for EV, skin reactions occurred in 45.7% of pts, peripheral neuropathy in 32.6%, and hyperglycemia in 4.3%. **Conclusions:** In pts with heavily pretreated HNC, antitumor activity of EV monotherapy and tolerability, with manageable adverse events, was observed, consistent with that in previously studied populations with advanced urothelial carcinoma. Further investigation of EV activity in HNC is warranted. Clinical trial information: NCT04225117. Research Sponsor: Astellas Pharma, Inc. and Seagen Inc.

6019

Poster Discussion Session

Neoadjuvant cemiplimab with platinum-doublet chemotherapy and cetuximab to de-escalate surgery and omit adjuvant radiation in locoregionally advanced head & neck squamous cell carcinoma (HNSCC). *First Author: Winston Wong, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Locoregionally advanced (LA) HNSCC treated with surgery can carry significant functional morbidity, further intensified by adjuvant (adj) radiation (RT) often with concurrent chemotherapy. Although the pathologic response rate of anti-PD1 therapy is modest, combination approaches may provide enhanced clinical benefit. This pilot study evaluates whether the combination of neoadjuvant cemiplimab + platinum-doublet chemotherapy + cetuximab is safe, feasible, and effective in pathologic down-staging to reduce the extent of surgery and justify omission of adj RT. **Methods:** 10 patients (pts) with resectable LA HNSCC who would warrant adj RT per clinical stage were enrolled. Neoadjuvant treatment consisted of cetuximab loading dose with cemiplimab followed by 3 cycles of chemotherapy (cisplatin or carboplatin + docetaxel) with cetuximab and cemiplimab prior to definitive surgical resection. Standard of care adj RT +/- chemotherapy was administered based on pathologic staging. Pts with ypT0-2N0 tumors without adverse features or ypT0-1N1 tumors with minimal residual disease ($<$ 10% viable tumor) were offered 6 months of adj cemiplimab in lieu of RT. Primary endpoint was safety (defined by dose limiting toxicity (DLT) related to the addition of cemiplimab to this combination regimen). Secondary endpoints included feasibility (defined as no surgical delay $>$ 20 weeks from start of neoadjuvant therapy due to treatment toxicity) and pathologic down-staging allowing for omission of adj RT. **Results:** 10 pts completed treatment with no DLTs and surgical delays. 8/10 (80%) pts were clinically staged as T3/T4 and 5/10 (50%) were N2b/c (AJCC 7th Ed). Pathologic down-staging was observed in 9/10 (90%) pts after neoadjuvant therapy. 60% had a major pathologic response and 40% had a complete pathologic response. 6/8 pts and 7/10 pts who would have required a mandibulectomy and free flap, respectively, did not require it following neoadjuvant treatment. Of the 5/10 (50%) pts who were eligible for omission of adj RT, 4 did not undergo RT and 3 received adj cemiplimab. All pts remain disease-free at a median follow-up of 16 months. The most common adverse events (AEs) of any grade (G) were rash (80%), nausea (70%), fatigue (50%), and diarrhea (50%). 2/10 (20%) pts experienced a G3 or G4 immune-related AE attributed to the addition of cemiplimab. One pt developed G3 transaminase elevation prior to surgery and 1 pt experienced G3 myasthenia gravis and G4 myocarditis (resolved) outside the DLT window. **Conclusions:** Neoadjuvant cemiplimab with platinum-doublet chemotherapy and cetuximab has an acceptable toxicity profile, is feasible in pts with LA HNSCC, and led to notable pathologic down-staging allowing for reduction in extent of surgery and omission of adj RT. Further evaluation of this regimen is clearly warranted. Clinical trial information: NCT04722523. Research Sponsor: Regeneron Pharmaceuticals; The Sierra Initiative on the Management of Head and Neck Cancer Side Effects; Investigator Initiated Trial RFA, Department of Medicine, Memorial Sloan Kettering Cancer Center.

6020

Poster Discussion Session

The Quarterback trials: A phase 2 series of sequential studies of induction chemotherapy followed by reduced dose chemoradiation for human papillomavirus positive oropharynx cancer. *First Author: Marshall R. Posner, Division of Hematology and Medical Oncology, The Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY*

Background: Human Papilloma Virus (HPV) oropharynx cancer (HPVOPC) is highly curative. Current standard of care treatment recommendations result in over treatment with chemoradiotherapy (CRT) across all stages of the disease and lead to significant long-term morbidity. The Quarterback (QB) trials (NCT01706939, QB1; NCT02945631, QB2a/2b) applied induction chemotherapy (IC) with modified Taxotere, cis-platinum and 5-fluorouracil (TPF) and reduced dose chemoradiotherapy (rdCRT) in very advanced HPVOPC. The primary endpoints were local regional control (LRC) and progression-free survival (PFS) at 3 years. **Methods:** Patients with locally advanced HPVOPC and High Risk (HR) features (radiographic ECE, T4 primary, $\geq$ N2c disease or non-HPV16 HR genotype) or who were candidates for organ preservation were entered on sequential trials of 3 cycles of TPF IC followed by rdCRT to 5600 cGy with weekly carboplatin. The only variable in IC treatment were 3 sequential reductions of 5-fluorouracil from 800 to 500 mg/M²/day across the trials (QB1, QB2a/2b). Major inclusion criteria were: molecularly documented high risk HPV and $\leq$ 20 pack year smoking history. Patients were eligible for rdCRT if they had a significant clinical response to IC. The hypothesis for non-inferiority was that LRC and PFS at 3 years would be at least 85% and 80%, respectively, based on results from RTOG 1029. Analysis was limited to those patients who received or were randomized (QB1) to rdCRT. **Results:** Of 45 subjects treated with rdCRT, 35 (78%) had HR features. Overall survival (OAS) is 39 (87%), LRC 39 (87%), PFS 35 (78%) with a median follow up of 57m (range: 12-120). Kaplan Meyer 3 year LRC is 88% (95% CI: 79-99), PFS 86% (95 CI 76-97) and OS 93% (95% CI 86-100). 2 subjects (4%) developed an in-field non-HPV, p53 positive squamous cancer and 1 (2%) died. 1 subject (2%) died of non-HPV related disease (SLE); 2 (4%) developed distant metastases; 4 (9%) subjects are alive after recurrence. Disease specific survival is 40/43 (93%). 19 patients signed consent and did not receive rdCRT: 8 were randomized to standard dose (QB1), 2 withdrew consent, 5 had an inadequate response to IC and 4 were screen failures. All 15 treated with IC are alive and disease free. There are no treatment related deaths. **Conclusions:** TPF IC in HPVOPC with HR features, followed by rdCRT met its predetermined statistical goals for LRC, PFS and OAS. Treatment was tolerable and toxicity was manageable. Compared to other Phase 2 and 3 de-escalation trials this approach is reasonable, effective and feasible. QB1 demonstrated improved quality of life in rdCRT with 5600 cGy compared to standard chemoradiotherapy. Randomized trials to establish de-escalation as a standard of care are warranted. Further de-escalation of treatment to further reduce acute and long-term radiation toxicity in HR populations appears feasible. Clinical trial information: NCT01706939; NCT02945631. Research Sponsor: Philanthropy.

6022

Poster Session

Tazemetostat, a selective EZH2 inhibitor, with pembrolizumab as treatment of anti-PD-1 resistant head and neck squamous-cell carcinoma (HNSCC): A phase 1-2 trial. *First Author: Sidharth Puram, Washington University School of Medicine, St. Louis, MO*

Background: EZH2 is the catalytic subunit of PRC2, which catalyzes H3K27me3 of target gene promoters and silences transcription of several cancer-related genes. EZH2 overexpression is common in HNSCC and correlated with methylation of several tumor suppressor genes. EZH2 siRNA downregulated EZH2 mRNA and protein and reduced colony formation in an EZH2-expressing HNSCC cell line. EZH2 inhibitors decreased H3K27me3 in HPV + and - cell lines. Tazemetostat, an EZH2 inhibitor, upregulated expression of HLA class I molecules in anti-PD-1-resistant HNSCC cell lines and mouse models, and increased antigen-specific CD8+ T cell proliferation, IFN- γ production, CXCL10 expression, and tumor cytotoxicity. In an anti-PD-1-resistant HNSCC model, tazemetostat and an anti-PD-1 suppressed tumor growth. The primary aims of this phase 1-2 trial were to establish 1) the recommended phase 2 dose (RP2D) of tazemetostat given with pembrolizumab and 2) the objective response rate of this regimen among patients (pts) with anti-PD-1 resistant, PD-L1 positive HNSCC. We report the results of Phase 1. **Methods:** In phase 1, eligible pts had recurrent/metastatic (RM) HNSCC, adequate performance status and organ function, and ability to swallow study drug. A 3+3 dose-escalation phase 1 design was used to assess 3 dose-levels of tazemetostat (400, 600, and 800 mg orally twice daily) with pembrolizumab (200 mg IV). Cycle 1 was 35 days, with tazemetostat given on days 1-35 and pembrolizumab on day 15. Subsequent cycles were 21 days, with tazemetostat given on days 1-21 and pembrolizumab on day 1. Dose-limiting toxicity (DLT), assessed during cycle 1, was defined as grade 4 neutropenia/thrombocytopenia, grade 3 febrile neutropenia, or study drug-related grades 3-4 non-hematologic adverse events (AEs). Pts must have completed cycle 1 to be evaluable for DLT assessment; otherwise, an equal number of additional pts were enrolled. The RP2D was defined as the highest dose level in which 0 of the first 3 or $<$ 1 of 6 pts experienced a DLT. **Results:** 12 pts enrolled to phase 1: 3 each on the 400 and 600 mg dose-levels of tazemetostat and 6 on the 800 mg dose-level. Key tumor characteristics included primary site (larynx: 4, oral cavity: 3, oropharynx: 3, nasopharynx: 1, cutaneous: 1), HPV status (+: 1, -: 11), and number of lines of prior systemic treatment for RM disease (1-2: 6, $>$ 3: 6). Nine pts were evaluable for DLT; 3 pts on the 800 mg dose-level did not complete cycle 1 and were not evaluable for DLT. DLT events and grade 4-5 AEs did not occur. Grade 3 AEs that occurred after cycle 1 included anemia (2 pts, both at 800 mg dose) and fatigue (1, at 400 mg dose). Across all cycles, the most common AEs included anemia (10 pts), fatigue (9), rash (7), and myalgia (4). **Conclusions:** Among pts with RM-HNSCC, the RP2D of tazemetostat was 800 mg twice daily when given with pembrolizumab. Enrollment to phase 2 is ongoing. Clinical trial information: NCT04624113. Research Sponsor: Epizyme, an Ipsen Company.

6021

Poster Session

Association of neutrophil-lymphocyte ratio (NLR) with clinical outcomes in patients (pts) with recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC) treated with combination of cetuximab and nivolumab (C+N). *First Author: Robin Park, Moffitt Cancer Center, Tampa, FL*

Background: Combination of anti-epidermal growth factor receptor (EGFR) and anti-programmed cell death-1 (PD-1) inhibitors such as C+N is highly efficacious in R/M HNSCC. While PD-1 ligand 1 (PD-L1) combined positive score (CPS) is predictive of anti-PD-1 inhibitor response, there is no predictive biomarker for the combination. NLR is a known prognostic biomarker in HNSCC pts treated with chemotherapy with/without radiation. We evaluated NLR as a potential predictive biomarker in R/M HNSCC pts treated with C+N. **Methods:** The clinical data were obtained from R/M HNSCC pts treated with C+N from a completed clinical trial (NCT03370276) and pts treated with nivolumab or pembrolizumab (N/P) as a standard of care in a retrospective chart review study. NLR were collected at baseline (NLR1) and on-treatment (1-month from the treatment initiation; NLR2). The median NLR was applied as a cut-point. Pts were stratified into NLR-high (H; $>$ median) or -low (L; $<$ median). Time-to-event endpoints were evaluated to assess survival and response at the initiation treatments using the Kaplan Meier and Cox Proportional Hazards Models. Selected variables included in the multivariate (MV) analyses were log2(NLR1 or 2), PD-L1 CPS, p16 and smoking status, and prior exposure to anti-PD-1 inhibitors. **Results:** Total 83 C+N and 40 N/P pts were included. In C+N, the median NLR cut-points were NLR1 6.27 and NLR2 5.98 while they were NLR1 5.87 and NLR2 8.21 in N/P. NLR1-H vs. -L in C+N showed no difference in OS ($p = 0.26$) and progression-free survival (PFS; $p = 0.95$), but NLR2-H had worse OS ($P < 0.001$) and PFS ($P < 0.001$) compared to NLR2-L. Similarly, in N/P, NLR1-H vs. -L did not show difference in OS ($p = 0.23$), but NLR2-H had worse OS ($P < 0.046$) compared to NLR2-L. In C+N, NLR2 (log2(NLR2)) consistently correlated with worse OS [univariate (UV), HR 1.69, CI 1.36-2.12; MV, HR 1.63, CI 1.26-2.11] and PFS (UV, HR 1.63, CI 1.22-2.19; MV, HR 1.70, CI 1.21-2.42). In N/P, PFS and MV analyses were not feasible due to lack of reliable data in the retrospective study. In C+N, NLR2 ($p < 0.001$), but not NLR1 ($p = 0.93$), was correlated with lower best overall response (BOR). Similarly, in N/P, NLR2 ($p = 0.004$), but not NLR1 ($p = 0.12$), was associated with lower BOR. In addition, a significantly larger reduction in NLR on-treatment from baseline (log2(NLR2) - log2(NLR1)) was observed in C+N compared to N/P ($P = 0.005$, Student t-test). **Conclusions:** On-treatment NLR2-H is associated with worse response and survival in pts with R/M HNSCC treated with C+N and N/P. C+N is associated with a greater reduction in NLR compared to N/P, suggesting that the combination enhances a favorable peripheral immunologic response. Further evaluation is warranted to determine the role of NLR as a biomarker of immunotherapy response. Research Sponsor: Lilly Oncology, Bristol Myers Squibb; James and Esther King Biomedical Research Grant (grant no. 7JK02); Junior Scientist Research Program (Moffitt Cancer Center).

6023

Poster Session

Nanoparticle albumin-bound (nab) paclitaxel in combination with nivolumab as treatment of recurrent or metastatic head and neck squamous-cell carcinoma (RM-HNSCC) that progressed on a PD-1 inhibitor: A single-arm, phase 2 trial. *First Author: Jared Cohen, Washington University Siteman Cancer Center, St. Louis, MO*

Background: Drugs bound to albumin selectively target cancer cells with upregulated macropinocytosis, an endocytic nutrient-scavenging process driven by constitutive hyperactivation of the EGFR, RAS, PIK3CA and Syndecan1 signaling pathways that frequently occur in HNSCC. nab-paclitaxel is an active drug in HNSCC and has immunologic effects that can prime an immune response to PD-1 inhibitors, potentially reversing resistance to these agents. These effects include decreased TREGs, increased pro-inflammatory macrophages and differentiation of MDSC to dendritic cells, increased HLA class I expression and antigen presentation, and recruitment of CD8+ CTLs into tumor. **Methods:** In a single-arm phase 2 trial, patients with RM-HNSCC that progressed on a PD-1 inhibitor received 28-day cycles of nab-paclitaxel (125 mg/m² IV days 1, 8, and 15) and nivolumab (480 mg IV day 1). Treatment continued until discontinuation criteria were met. The primary endpoint was objective response, assessed with RECIST1.1 by an independent radiologist. The primary hypothesis was that this regimen would result in a higher objective response rate (ORR) than historically reported with standard chemotherapy or cetuximab in similar patients. A Simon optimal two-stage design tested the null hypothesis (H_0 : ORR $\leq$ 30%) versus the alternative hypothesis (H_1 : ORR = 50%) at the type I error rate of 5% and power 0.80. In the first stage, 15 patients were to be accrued. If $\geq$ 6 responses occurred, 31 additional patients were to be accrued. The null hypothesis will be rejected if $\geq$ 19 responses are observed in these 46 patients. We report the results of the primary endpoint for the first stage of the trial. **Results:** 15 evaluable patients enrolled into the first stage of the trial. Key tumor characteristics and prior treatment history included HPV status (positive: 8; negative: 7), PD-L1 status (CPS 1-19: 7; $\geq$ 20: 8), # of lines of prior systemic treatment for RM disease (1-2: 12; $\geq$ 3: 3), interval (months) from prior PD-1 inhibitor ($<$ 6: 11; $\geq$ 6: 4), duration (months) on prior PD-1 inhibitor (median: 6, range: 1-16), and best response to prior PD-1 inhibitor (PR: 4; SD: 6; PD: 5). Tumor response to nab-paclitaxel and nivolumab occurred in 7 of 15 patients (ORR 47%). The best tumor response was PR (7), SD (5) and PD (3). **Conclusions:** Among patients with RM-HNSCC that progressed on a PD-1 inhibitor, the ORR with nab-paclitaxel and nivolumab was 47% during the first stage of the phase 2 trial. Enrollment to the second stage is ongoing. Clinical trial information: NCT04831320. Research Sponsor: Bristol-Meyers Squibb; Generous support from Gregory Stubblefield and Nancy Apel.

6024

Poster Session

Prognostic value of circulating Epstein-Barr virus DNA level post-induction chemotherapy for patients with nasopharyngeal carcinoma: A recursive partitioning risk stratification analysis. *First Author: Fang-Fang Kong, Department of Radiation Oncology, Fudan University Shanghai Cancer Center, Shanghai, Shanghai, China*

Background: To evaluate the prognostic value of plasma Epstein-Barr virus (EBV) DNA level post-induction chemotherapy (IC) for patients with nasopharyngeal carcinoma (NPC). **Methods:** A total of 893 newly diagnosed NPC patients treated with IC were retrospectively reviewed. The recursive partitioning analysis (RPA) was performed to construct a risk stratification model. The receiver operating characteristic (ROC) analysis was applied to determine the optimal cut-off value of EBV DNA and compare the predictive validity. **Results:** Post-IC EBV DNA levels and overall stage were independent predictors for distant metastasis-free survival (DMFS), overall survival (OS), and progression-free survival (PFS). The RPA model based on post-IC EBV DNA and overall stage categorized the patients into three distinct risk groups: RPA I (low-risk: stage II-III and post-IC EBV DNA < 200 copies/mL), RPA II (median-risk: stage II-III and post-IC EBV DNA ≥ 200 copies/mL, or stage IVa and post-IC EBV DNA < 200 copies/mL), and RPA III (high-risk: stage IVa and post-IC EBV DNA ≥ 200 copies/mL), with 3-year PFS of 91.1%, 82.6%, and 60.2%, respectively ($p < 0.001$). The DMFS and OS rates in different RPA groups were also distinct. ROC analysis showed that the RPA model had superior predictive efficacy than the overall stage. **Conclusions:** Plasma EBV DNA level post-IC was a robust prognostic biomarker for NPC. We developed a risk stratification model that provides improved DMFS, OS, and PFS prediction over the 8th edition of the TNM staging system by integrating the post-IC EBV DNA level and the overall stage. Research Sponsor: None.

6026

Poster Session

A phase Ib/II study of GFH018 in combination with toripalimab in recurrent/metastatic nasopharyngeal carcinoma (R/M NPC). *First Author: Hai-Qiang Mai, Sun Yat-sen University Cancer Center (China), Guangzhou, No, China*

Background: The transformed growth factor beta (TGF- β) signaling pathway is dysregulated in carcinogenesis. In NPC patients, upregulation of TGF- β pathway is correlated with disease stage or phenotype due to Epstein-Barr virus (EBV) infection. GFH018, a novel TGF- β RI inhibitor, can inhibit tumor growth through inhibiting the activity of TGF- β RI kinase to block the signal transduction of TGF- β and modulate the tumor immune microenvironment. Preclinical studies showed that GFH018 in combination with PD-1/PD-L1 monoclonal antibody can significantly inhibit tumor growth synergistically. Here we report the preliminary results of combining GFH018 and Toripalimab treating R/M NPC patients (pts). **Methods:** This is a phase Ib/II study to evaluate the safety and efficacy of the combination of GFH018 and Toripalimab in pts with advanced solid tumors. Patients with RM NPC were enrolled to receive GFH018 80mg twice a day (BID) 14-day-on/14-day-off in combination with Toripalimab 3mg/kg every two weeks. Tumor assessment was performed every 8 weeks per Response Evaluation Criteria in Solid Tumor (RECIST) 1.1. **Results:** As of 31 Dec 2022, 32 pts with R/M NPC who had progressed on at least one prior line therapy were enrolled. Sixteen (50%) had received ≥ 3 lines of prior therapies, and 19 (59.4%) had previously received immune checkpoint inhibitors (ICIs) and platinum-based chemotherapies. The median duration of study drug exposure was 7 weeks. Twenty-five pts (78.1%) experienced treatment-related adverse events (TRAEs) of any grades, and 11 pts (34.4%) had ≥ Grade 3. The most common TRAEs (occurring in ≥ 3 pts) were anaemia ($n = 6$, 18.8%), hyponatraemia ($n = 6$, 18.8%), rash ($n = 6$, 18.8%), fatigue ($n = 4$, 12.5%), white blood cell count decreased ($n = 4$, 12.5%), aspartate aminotransferase increased ($n = 3$, 9.4%), back pain ($n = 3$, 9.4%), decreased appetite ($n = 3$, 9.4%), hypokalaemia ($n = 3$, 9.4%), and hypothyroidism ($n = 3$, 9.4%). As of 18 Jan 2023, among the 27 pts with post-baseline tumor assessments, 8 achieved partial response (PR), and 5 stable disease (SD); the overall response rate (ORR) was 29.6%, and disease control rate (DCR) was 48.1%. Six PR and 2 SD were observed among the 12 pts without prior treatment of ICIs; the ORR was 50%, and DCR was 66.7%. Four pts discontinued treatment without any post-baseline tumor assessments due to AEs or withdrawal of consent, and 1 patient is premature for tumor assessment. **Conclusions:** GFH018 combined Toripalimab was well tolerated and demonstrated preliminary efficacy in pts with R/M NPC. Specifically, in pts who had not previously received ICIs, promising antitumor activity was observed supporting further investigation to this group of pts. Clinical trial information: NCT04914286. Research Sponsor: Zhejiang Genfleet Therapeutics Co., Ltd.

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Poster Session

A phase 1 study of concurrent cabozantinib and cetuximab in recurrent or metastatic head and neck squamous cell cancer. *First Author: Antoine Desilets, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Epidermal growth factor receptor (EGFR) targeting with cetuximab (CTX) is a standard therapy for head and neck squamous cell carcinoma (HNSCC). Resistance to CTX can be mediated by activation of the receptor tyrosine kinase AXL. Cabozantinib (cabo) is a tyrosine kinase inhibitor (TKI) of AXL/c-MET/VEGFR which demonstrated antitumor activity in HNSCC preclinical models. We conducted a phase I trial to assess the safety and efficacy of the cabo-CTX combination in recurrent or metastatic (R/M) HNSCC. **Methods:** Eligibility criteria included RECIST v1.1 measurable disease and incurable R/M HNSCC. Prior treatment with CTX was allowed. Patients received an initial CTX loading dose of 400 mg/m² followed by 250 mg/m² weekly. CTX maintenance dose was later amended to 500 mg/m² biweekly. Cabo was given concurrently on days 1-28 of each 28-day cycle. Primary endpoint was maximally tolerated dose (MTD) of cabo, as identified using a 3+3 dose-escalation design. Tumor responses were assessed every 2 cycles. Secondary endpoints included overall response rate (ORR), progression-free survival (PFS) and overall survival (OS). **Results:** Of 22 patients enrolled between 2018 and 2022, 2 did not start therapy. Among treated patients, median age was 59 (range 33-71) and 90% ($n = 18$) of patients were male. Primary tumor sites included the oropharynx ($n = 13$), oral cavity ($n = 3$), larynx ($n = 2$), hypopharynx ($n = 1$) and unknown primary ($n = 1$). p16 antigenic testing for HPV status was positive in 11 oropharyngeal cancers (85%). Most patients were previously treated with immune checkpoint inhibitors ($n = 19$), chemotherapy ($n = 19$), CTX ($n = 16$), or other TKI ($n = 2$). 12 patients received biweekly CTX dosing at 500 mg/m². Initial cabo dose was 40 mg for the first 11 patients, and 60 mg afterwards (MTD). No dose-limiting toxicity (DLT) was recorded. Common adverse events (AEs) included fatigue (80%), acneiform rash (75%), increased aspartate aminotransferase (AST) (70%), anemia (70%) and hypothyroidism (70%). Grade ≥ 3 AEs occurred in 65% ($n = 13$), including increased AST (45%), increased alkaline phosphatase (15%), increased bilirubin (10%) and erythrocytosis (10%). AEs led to dose reductions in 20% ($n = 4$) and treatment discontinuation in 15% ($n = 3$). In the preliminary efficacy analysis, 4 patients had partial responses (PRs) with an ORR of 20%, including 2 PRs in patients with prior CTX resistance. Disease control rate (DCR) was 75% in the overall population and 75% in those with previous CTX treatment. Median PFS was 3.4 mo and median OS was 8.1 mo. PFS differed according to HPV status, with median PFS 7.1 mo versus 3.1 mo in HPV-positive and -negative patients respectively ($p = 0.03$). **Conclusions:** The cabo and CTX combination showed an acceptable toxicity profile with liver toxicity as a common AE. The regimen showed preliminary efficacy data in patients with R/M HNSCC, including those with prior CTX resistance. Clinical trial information: NCT03667482. Research Sponsor: None.

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Poster Session

Effect of extended treatment with IAP inhibitor xevinapant post radiotherapy (RT) on efficacy and the tumor microenvironment (TME) in preclinical models. *First Author: Tsz Lun Yeung, EMD Serono, Billerica, MA*

Background: Xevinapant is a first-in-class, oral IAP (inhibitor of apoptosis protein) inhibitor designed to restore cancer cell sensitivity to apoptosis, induced by RT and chemotherapy, and enhance antitumor immunity. In a randomized phase 2 study of patients with unresected locally advanced squamous cell carcinoma of the head and neck, xevinapant + chemoradiotherapy (CRT) significantly improved 18-month locoregional control and improved 3-year progression-free survival and 5-year overall survival vs placebo + CRT. A phase 3 confirmatory study (TrilynX NCT04459715) and a phase 3 study to evaluate xevinapant + RT in post-operative, high-risk, cisplatin-ineligible patients (XRAY Vision NCT05386550) are ongoing. In these studies, we investigate 3 additional cycles of xevinapant or placebo monotherapy after completing combination treatment. Based on the role of IAPs in apoptosis, immunity, and stromal activation, continual dosing of xevinapant post RT may have additional therapeutic benefits. **Methods:** MC38 syngeneic tumor-bearing mice were treated with vehicle control, RT alone (3.6Gy once daily [QD], 5 days), or RT + xevinapant (100 mg/kg QD, 1, 2, or 4 weeks). To assess treatment-mediated TME modulation, immune cells in tumors were evaluated by fluorescence-activated cell sorting (FACS)-based immunophenotyping, and tumor-specific T cell responses were investigated by enzyme-linked immunosorbent spot (ELISpot) assays. To understand the effect of xevinapant on RT-induced cancer associated fibroblast (CAF) activation, CAF gene expression was profiled on cell lines and patient-derived primary cultures. **Results:** Xevinapant + RT increased antitumor efficacy compared with vehicle control or RT alone. Moreover, RT in combination with extended dosing of xevinapant for 4 weeks significantly improved therapeutic efficacy and prolonged survival compared with RT + shorter xevinapant dosing durations. FACS analysis demonstrated trends of increased numbers of CD8⁺ T cells, natural killer cells, and dendritic cells and decreased numbers of regulatory T cells in mice treated with xevinapant + RT. FACS and ELISpot further suggested an increase in antigen-specific T cell counts from baseline with combination therapy arm vs vehicle control or RT alone. Xevinapant may also suppress RT-mediated CAF activation, as indicated by downregulation of activation markers and CAF-derived secretory proteins. **Conclusions:** In preclinical models, extended dosing of xevinapant for 4 weeks post RT improved antitumor efficacy. Our data suggest that the effect may be, in part, modulated by TME responses, including enhanced antitumor immunity and suppressed pro-tumorigenic phenotype of CAFs. Based on these results, further evaluation is warranted to determine the mechanisms that underscore the therapeutic benefit offered by extended dosing of xevinapant. Research Sponsor: The healthcare business of Merck KGaA, Darmstadt, Germany.

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Poster Session

Phase 2 study of ISA101b (peltopenimut-S) and cemiplimab in patients with advanced HPV16+ oropharyngeal cancer who failed anti-PD1 therapy. *First Author: Anthony H Kong, King's College London, London, United Kingdom*

Background: ISA101b (peltopenimut-S), a therapeutic vaccine against the HPV-specific E6/E7 oncoproteins, induces specific expansion of HPV16 targeted T-cells when given together with cemiplimab, an anti-PD-1 agent. Previously we showed that ISA101 with nivolumab achieved a higher response rate compared to immune checkpoint inhibitor (ICI) alone in trials for patients with recurrent/metastatic (R/M) HPV16+ oropharyngeal cancer (OPC)^{1,2}. **Methods:** In this single arm phase 2 study, patients with R/M HPV16+ OPC with progressive disease (PD) within 6 months after prior 1st or 2nd line anti-PD-1 ICI were treated with ISA101b (subcutaneously 100µg/peptide on days 1, 29, and 50) with cemiplimab (intravenously 350mg as a 3-weekly regimen) until PD. Patients without PD at 6 months were offered a booster ISA101b injection. HPV16 positive tumor status was confirmed by a central reference laboratory with an established PCR assay. The primary efficacy endpoint was defined as overall response rate (ORR) as per RECIST1.1. An analysis was planned at the end of Stage 1, when 26 patients who had received at least one dose of ISA101b had been followed for 6 months. The cut-off date for this analysis, approved by the DSMB, was 31 January 2023. **Results:** Twenty-six patients (mean age 60.7 ± 12.9 years; 22 (84.6%) male and 4 (15.4%) female) enrolled in Stage 1. Median follow-up was 16.2 weeks (range 1.6-78.8). Three patients were confirmed with partial response (PR) (11.5%); two of the 3 patients with PR never responded to previous ICI treatment. In 13 patients (50.0%) best overall response (BOR) was stable disease (SD); in 8 patients (30.8%) BOR was PD. Two (7.7%) patients did not have a tumor assessment after baseline: one patient died on day 8 due to OPC and one patient withdrew consent shortly after enrolment. The clinical benefit ratio (CBR) was 61.5%. Nine (34.6%) patients received a booster injection. At the time of the booster, 2 patients had PR and 5 patients had meaningful (≥6 months) SD. Time to response ranged between 127 and 307 days. Median duration of study treatment was 13.1 weeks (range 1.1-75.9), with 4 patients still on treatment. There were two grade 3 adverse events (AEs) related to ISA101b: erythema at the injection site and diarrhea. Two patients (7.7%) had grade 3 ICI-related auto-immune events. Grade 4-5 AEs related to study treatment did not occur. Median overall survival was 8.1 months (range 0.3-17.5). **Conclusions:** This treatment appears promising for HPV16+ OPC patients who failed prior anti-PD-1 ICI therapy, with an ORR of 11.5% and a CBR of 61.5%. In this small, ongoing study the combination of cemiplimab and ISA101b was well tolerated with a safety profile resembling anti-PD-1 monotherapy. This is the first study of the combination of ISA101b and cemiplimab in 2nd/3rd line R/M anti-PD-1 refractory OPC patients. ¹Massarelli E. *JAMA Oncol* 2019 ²de Sousa LG. *J Immunother Cancer* 2022. Clinical trial information: NCT04398524. Research Sponsor: ISA Pharmaceuticals; Regeneron Pharmaceuticals.

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Poster Session

Influence of widely targeted quantitative lipidomics on plasma lipid predictors and pathway dysregulation for nasopharyngeal carcinoma. *First Author: Xi Chen, Sun Yat-sen University Cancer Center, Guangzhou, China*

Background: Dysregulation of lipid metabolism is closely associated with cancer progression. We aimed to establish a prognostic model to predict distant metastasis-free survival (DMFS) in patients with locoregionally advanced nasopharyngeal carcinoma (NPC), based on widely targeted quantitative lipidomics. **Methods:** We measured and quantified the plasma lipid profiles of 179 patients with NPC using widely targeted quantitative lipidomics. Then, patients were randomly split into the training (125 patients, 69.8%) and validation (54 patients, 30.2%) sets. To identify distant metastasis-associated lipids, univariate Cox regression was applied to the training set ($p < 0.05$). We employed a deep survival method called DeepSurv to develop our proposed model based on significant lipid species ($p < 0.01$) and clinical biomarkers to predict DMFS. Concordance index and receiver operating curve analyses were performed to assess model effectiveness. We also explored the potential role of lipid alterations in the prognosis of NPC. **Results:** A total of 665 plasma endogenous lipid species consisting of 27 lipid classes and subclasses from 179 patients with NPC were annotated in lipidomics analysis. Forty lipids were recognized as distant metastasis-associated ($p < 0.05$) by univariate Cox regression. The concordance indices of our proposed model were 0.764 (95% confidence interval (CI), 0.682-0.846) and 0.760 (95% CI, 0.649-0.871) in the training and validation sets, respectively. We also calculated the C-index values of the baseline survival model based only on clinical biomarkers, with 0.718 (95% CI, 0.591-0.845) and 0.672 (95% CI, 0.511-0.833) being detected in the training and validation sets, respectively, indicating the outstanding predictive performance of lipid biomarkers. High-risk patients had poorer 5-year DMFS compared with low-risk patients (Hazard ratio, 26.18; 95% CI, 3.52-194.80; $p < 0.0001$). Moreover, the six lipids were significantly correlated with immunity- and inflammation-associated biomarkers and were mainly enriched in metabolic pathways. **Conclusions:** Widely targeted quantitative lipidomics reveals plasma lipid predictors and pathway dysregulation for locoregionally advanced NPC, the prognostic model based on that demonstrated superior performance in predicting metastasis in NPC patients. Research Sponsor: The National Natural Science Foundation of China; the Natural Science Foundation of Guangdong Province, China.

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Poster Session

Final results from TACTI-002 Part C: A phase II study of eftilagimod alpha (soluble LAG-3 protein) and pembrolizumab in patients with metastatic 2nd line head and neck squamous cell carcinoma unselected for PD-L1. *First Author: Bernard Doger de Spéville, Early Phase Clinical Trials Unit, START Madrid Fundacion Jimenez Diaz, Madrid, Spain*

Background: Eftilagimod alpha (E), a soluble LAG-3 protein, acts as an MHC class II agonist triggering activation of antigen-presenting cells (APC) and CD8 T-cells. Using efti to enhance patients' immunity may lead to stronger anti-tumor responses than observed with pembrolizumab (P) alone. We report final results from Part C of the TACTI-002 trial (NCT03625323) where 2nd line metastatic head and neck squamous cell carcinoma (HNSCC) patients (pts) unselected for PD-L1 were treated with E + P. **Methods:** Pts with metastatic HNSCC, unselected for PD-L1 expression with disease progression on or after 1st line platinum-based therapy (± cetuximab) were enrolled. Primary endpoint (EP) was objective response rate (ORR) by iRECIST. Other EPs included tolerability, progression free survival (PFS), duration of response (DoR), and overall survival (OS). Pts received E (30 mg SC Q2W for eight 3-week cycles and then Q3W up to 1 yr) with P (200 mg IV Q3W up to 2 yrs). Imaging was performed Q9W. PD-L1 was retrospectively assessed using the IHC 22C3 kit. The study was approved by ethic committees and institutional review boards. **Results:** 39 pts were enrolled between Mar 2019-Jan 2021 (cut-off Jul 2022) with HNSCC of oropharynx (38%), oral cavity (32%), hypopharynx (19%) and larynx (16%). Median age was 63 yrs (48-84 yrs) and 90% were male. ECOG PS was 0 and 1 in 35% and 65% of pts. Two pts were excluded from efficacy results due to fatal COVID-19 prior to their first post-baseline scan. The primary EP, ORR by iRECIST, was 30% with 14% complete responders (see table). ORR by RECIST 1.1 was comparable (24%). Median PFS by iRECIST was 2.1 mo with 32% of pts progression-free at 6 mo. Median OS was 8.7 mo with 46% alive at 12 mo. Median DoR by iRECIST was not reached with 17 mo min FU. Responses were seen in all PD-L1 subgroups (see table). ORR, 6-mo PFS, 12-mo OS rates for PD-L1 CPS ≥ 20 were 60%, 53%, 73% with a median OS of 15.5 months. Two pts (5%) discontinued due to adverse events (AE) (fatigue and arthralgia [each grade 2]; pneumonitis [grade 3]) that were related to study treatment (efti and/or pembro). The most common (≥ 15%) AEs were hypothyroidism (21%), asthenia (21%), cough (18%), anemia (18%), weight decrease (18%), and fatigue (15%). **Conclusions:** Efti + pembrolizumab is safe, showing encouraging antitumor activity in platinum and partially cetuximab pre-treated, 2nd line HNSCC patients. TACTI-003 (NCT04811027) a randomized study in 1st line HNSCC is currently recruiting. Response by iRECIST: Clinical trial information: NCT03625323. Research Sponsor: Immunet S.A.

	Overall (ITT) N=37	PD-L1 CPS ≥20 N=15	PD-L1 CPS <20 N=17
CR, n (%)	5 (14)	4 (27)	1 (5.9)
PR, n (%)	6 (16)	5 (33)	1 (5.9)
ORR, n (%)	11 (30)	9 (60)	2 (11.8)
DCR, n (%)	14 (38)	9 (60)	4 (23.5)
mPFS, mo	2.1	13.6	2.0
6-mo PFS rate, (%)	32.4	53.3	17.7
mOS, mo	8.7	15.5	7.5
12-mo OS rate, (%)	46.0	66.7	35.3
mDoR, mo	NR	NR	12.0
12-mo DoR rate, (%)	80.0	87.5	50.0

NR: not reached.

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Poster Session

Efficacy and safety of sintilimab plus bevacizumab in metastatic nasopharyngeal carcinoma after failure of platinum-based chemotherapy: An open-label phase II study. *First Author: Nian Lu, Cancer Center, Sun Yat-Sen University, State Key Laboratory of Oncology in South China, Collaborative Innovation Center of Cancer Medicine, Guangzhou, China*

Background: There are limited treatment options for patients with metastatic nasopharyngeal carcinoma (mNPC) after failure of platinum-based chemotherapy. In this trial, we assessed the efficacy and safety of sintilimab plus bevacizumab in mNPC patients where platinum-based chemotherapy has failed. **Methods:** This was a single-center, open-label, single-arm, phase II trial for mNPC patients progressed after at least one line of systemic therapy. Patients were enrolled and received sintilimab (200 mg) plus bevacizumab (7.5mg/kg) intravenously every 3 weeks. The primary end point was objective response rate (ORR) assessed by investigators following the guidelines of RECIST 1.1. Key secondary end points were progression-free survival (PFS), overall survival (OS), duration of response (DOR), and safety. This trial is registered with ClinicalTrials.gov (NCT04872582). **Results:** Thirty-three patients were enrolled. Median age was 46 years (range, 18-64 years), and 63.6% of patients had previously received two or more lines of chemotherapy for metastatic disease. Median follow-up was 7.6 months (range, 4.1-17.5 months). ORR was 54.5% (95% CI, 36.4-71.9%) with 3 complete responses (9.1%) and 15 partial responses (45.5%). Median PFS was 6.8 months (95% CI, 5.2 months to not estimable). Median DOR was 7.2 months (95% CI, 4.4 months to not estimable). Median OS was not reached. The most common potential immune-related AE was grade 1-2 hypothyroidism (42.4%). Treatment-related grade 3 or 4 adverse events (AEs) occurred in 7 patients (21.2%), including nasal necrosis (9%), hypertension (3%), pruritus (3%), total bilirubin increased (3%) and anaphylactic shock (3%). No treatment-related deaths and severe epistaxis occurred. **Conclusions:** This phase II trial showed that sintilimab plus bevacizumab demonstrated promising antitumor activity and manageable toxicities in mNPC patients after failure of platinum-based chemotherapy. Clinical trial information: NCT04872582. Research Sponsor: National Natural Science Foundation of China (KY013113).

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Poster Session

A phase II trial of paclitaxel plus biweekly cetuximab for patients with recurrent or metastatic head and neck cancer previously treated with both platinum-based chemotherapy and anti-PD-1 antibody. *First Author: Taiji Koyama, Department of Medical Oncology and Hematology, Kobe University Hospital, Kobe-Shi, Japan*

Background: An important unmet need in treatment options remains for patients with recurrent or metastatic head and neck squamous cell carcinoma (R/M-HNSCC) previously treated with both platinum-based chemotherapy and anti-PD-1 antibody (PD-1 Ab). Recent retrospective studies suggest that previous treatment with Immune checkpoint inhibitor might augment the efficacy of subsequent chemotherapy. This phase II trial aimed to evaluate the efficacy and safety of paclitaxel plus biweekly cetuximab (PTX+bwCmab) for patients with R/M-HNSCC previously treated with both platinum and PD-1 Ab. **Methods:** This is a single-arm, multicenter phase II trial. Key eligibility criteria were R/M-HNSCC; previous treatment with both platinum-based chemotherapy and PD-1 Ab; ECOG performance status 0 or 1; measurable disease per RECIST v1.1; and adequate organ function. PTX+bwCmab consisted of weekly paclitaxel 100 mg/m² (days 1, 8, 15) and biweekly cetuximab 500 mg/m² (days 1, 15) with a cycle of 28 days. Primary endpoint was objective response rate (ORR). We set a null hypothesis of 10% and alternative of 30% with a one-sided alpha of 0.05 and power of 90%. Secondary endpoints were progression-free survival (PFS), overall survival (OS), disease control rate (DCR), and adverse events (AEs) (CTCAE v5.0). Binominal confidence intervals (CIs) for ORR and DCR were estimated by the exact method. Time-to-event analyses were calculated by the Kaplan-Meier method with 95% CIs. **Results:** Between August 2020 and August 2022, 35 patients were enrolled, of whom 32 were evaluable for response. ORR was 68.7% (95% CI: 49.9-83.8), which met the prespecified criteria for the primary endpoint of ORR. With a median follow-up period for survivors of 16.6 months, median PFS and OS were 5.7 and 13.4 months, respectively. DCR was 93.7% (95% CI: 79.1-99.2). The most common AEs of any grade were skin rash (65%), peripheral nerve neuropathy (45%), neutropenia (40%), fatigue (40%) and paronychia (37%). Grade 3 and 4 adverse events included neutropenia (34%), mucositis (8%), pneumonitis (8%) and febrile neutropenia (5%). These AEs were manageable and no treatment-related death within 30 days was observed. **Conclusions:** PTX+bwCmab showed highly encouraging efficacy and tolerability in R/M-HNSCC patients previously treated with both platinum and PD-1 Ab. Although preliminary, these results suggest that this is a promising treatment option for this hitherto untreatable patient group. Further evaluation is warranted. Clinical trial information: jRCTs051200040. Research Sponsor: None.

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Poster Session

Afatinib in patients with recurrent/metastatic (RM) squamous cell carcinoma of the head and neck (SCCHN) harboring alterations in the HER pathway: Results of the B1 cohort of the EORTC-HNCG-1559 trial (UPSTREAM). *First Author: Rachel Galot, Cliniques Universitaires Saint-Luc, Brussels, Belgium*

Background: Afatinib (A) is an irreversible pan-HER inhibitor that improved PFS in second line RM SCCHN after platinum (LUX-H&N1 trial). In a retrospective biomarker analysis, subgroups of pts with p16 negative, PTEN high or *EGFR* amplification SCCHN seem to benefit the most. Other studies suggest that A has activity in tumors with *HER2* gene activation. **Methods:** The UPSTREAM trial is a biomarker-driven umbrella trial of targeted therapies and immunotherapy for RM SCCHN (post-platinum, ECOG 0-1, measurable disease). The B1 cohort was a phase II, randomized, open-label substudy evaluating the efficacy of afatinib (orally, 40mg/day) vs physician's choice (ctrl) (2:1 ratio) in pts with p16 negative RM SCCHN harboring one of the following biomarkers (fresh biopsy): *EGFR* mutation(mut)/amplification(amp) or *HER2* mut/amp or PTEN high by immunohistochemistry (IHC, H-score > 150). Only *KRAS/HRAS/NRAS* wild type tumors were included. The primary endpoint was progression-free survival rate (PFSR) at 16 weeks after randomization. A 2-stage Simon optimal design was applied to arm A (H1 40%, H0 20%, 1-sided α 10%, power 90%) with 17 and 20 pts enrolled in the first and second stage respectively. Secondary endpoints included ORR, toxicity, PFS, and OS. **Results:** 59 RM SCCHN pts were included in the B1 cohort (A: n = 40, ctrl: n = 19). Out of the 59 patients, *EGFR* amp, *HER2* amp and *HER2* mut were found in 6 pts (10%), 1 pt (2%) and 1 pt (2%), respectively. PTEN (IHC) was high in 97%. 55 pts were evaluable (A: n = 38, ctrl: n = 17) (median age: 62, oral cavity: 29%, oropharynx: 36%, hypopharynx: 24%, larynx: 11%). 69% of pts had received $\geq$ 2 lines of systemic treatment for RM disease. 80% were pretreated with cetuximab. In arm A, 13/38 patients were alive and free of objective progression at 16 weeks (34.2%, 1-sided 90%CI, 23.9 $\pm$ inf), meeting the predefined criteria of success. The PFSR at 16W in ctrl arm was 29.4% (5/17). 4 objective responses were observed in arm A (3 PR and 1 CR) (ORR 11%, 95%CI 2.9-24.8%) and 1 PR in ctrl arm (6%). The median duration of response under A was 5.7 mo (range: 3.7-25.9 mo). All responding patients had previously been treated with cetuximab, were PTEN high but none had *EGFR* or *HER2* alterations. The median PFS and OS were 2.2/2.4 mo and 7.2/5.0 mo in the A/ctrl arms, respectively. Grade $\geq$ 3 drug-related AEs were reported in 31% in arm A and 12% in ctrl arm. The most frequent drug-related AE with A were diarrhea (67%, G3:8%), rash (41%, G3: 3%), fatigue (31%, no G3) and mucositis (23%, G3: 3%). **Conclusions:** The B1 substudy met its primary endpoint of PFSR at 16 weeks. Responses were seen in cetuximab pre-treated pts. However, the clinical activity of A in this biomarker-selected population remains limited. Translational research is ongoing to better define potential biomarkers. Clinical trial information: NCT03088059. Research Sponsor: Boehringer Ingelheim.

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Poster Session

To test, or not to test, that is the question: A real-world analysis of PD-L1 expression testing patterns in recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC). *First Author: Chris M. Black, Merck & Co., Inc., Rahway, NJ*

Background: PD-L1 expression testing plays an important role in identifying patients who benefit from immunotherapy when treating R/M HNSCC. We aimed to understand how PD-L1 expression testing evaluated by Combined Positive Score (CPS) is used in clinical practice and how testing results impact treatment decision-making. **Methods:** A retrospective cohort study was conducted using the Flatiron Health Advanced Head and Neck database. We included adult R/M HNSCC patients who initiated first-line (1L) treatment between 07/01/19 and 12/31/21 with follow-up until 06/30/22. Patients were excluded if they received platinum therapy within 6 months prior to 1L treatment, had other primary cancers before advanced diagnosis, were treated on protocol, or were tested but did not have any record of date of specimen collected, received, or results returned. Multivariable logistic regression was conducted to assess factors associated with PD-L1 testing decisions before 1L therapy start and the association between testing results and choice of 1L treatment. **Results:** A total of 1,762 patients with R/M HNSCC were included, with 32.0% tested for PD-L1 prior to 1L therapy start, 25.6% tested after, and 42.4% never tested. Most patients were tested using the IHC 22C3 pharmDx assay, an FDA-approved companion diagnostic. Among patients tested before 1L treatment initiation, the most prescribed regimens were pembrolizumab or pembrolizumab + platinum + 5-FU for patients with PD-L1(+) (55.9%, 14.2%) and PD-L1(-) tumors (25.3%, 32.0%), respectively. Patients tested after 1L treatment initiation regardless of CPS and patients never tested were most often prescribed platinum monotherapy for 1L. In a multivariable model, patients who were older, treated in academic settings, HPV(+), or had an ECOG $\geq$ 2 were more likely to get PD-L1 testing before 1L treatment initiation. Compared to CPS < 1, CPS $\geq$ 20 and 1 $\leq$ CPS < 20 were associated with a higher likelihood of receiving immunotherapy (OR=3.36, 95% CI, 1.69-6.75, p <0.001; OR=3.11, 95% CI, 1.59-6.14, p <0.001, respectively). **Conclusions:** As an important part of treatment decision-making, PD-L1 testing by CPS should guide 1L single-agent immunotherapy use, but there are many patients not tested before initiating 1L therapy. Age and fitness, clinical practice setting, and HPV status appear to impact testing patterns. Research Sponsor: Merck & Co., Inc., Rahway, NJ, USA.

Patient characteristics by PD-L1 testing patterns.

	Tested before 1L therapy start (N=564)	Tested after 1L therapy start (N=451)	Never Tested (N=747)
Age, median (range)	65 (29 - 85)	64 (20 - 85)	64 (27 - 85)
Community setting	467 (82.8%)	400 (88.7%)	707 (94.6%)
ECOG PS*			
0-1	404 (71.6%)	363 (80.5%)	567 (75.9%)
$\geq$ 2	101 (17.9%)	47 (10.4%)	99 (13.3%)
CPS*			
<1	78 (13.8%)	62 (13.7%)	—
1-19	162 (28.7%)	147 (32.6%)	—
$\geq$ 20	156 (27.7%)	142 (31.5%)	—

* Unknown category was omitted from the table.

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Poster Session

Phase I/IIa clinical trial of a small molecule EBNA1 inhibitor, VK-2019, in patients with Epstein Barr virus-positive nasopharyngeal cancer with pharmacokinetic and pharmacodynamic correlative studies. *First Author: A. Dimitrios Dimitrios Colevas, Stanford Cancer Center, Stanford, CA*

Background: Epstein-Barr Virus (EBV) is associated with a diverse collection of malignancies, including nasopharyngeal carcinoma (NPC). One viral-encoded protein, EBNA1, is consistently expressed in all known EBV-associated malignancies and is critical for the replication and maintenance of the EBV genome in latently infected cells. VK-2019 is a first-in-class, orally bioavailable EBNA1 inhibitor that blocks latent replication and proliferation in preclinical studies. **Methods:** We conducted a Phase I/IIa clinical trial of VK-2019 as a single therapeutic agent in patients with advanced (recurrent or metastatic) NPC. An accelerated titration design allowed dose escalation to proceed rapidly from 60 mg/day to 1800 mg/day. Blood samples for detailed pharmacokinetic analyses were collected after the first and multiple doses. In addition, tumor biopsies were collected from 2 patients at the 1800 mg/day dose level at baseline and during treatment and analyzed for EBV copy number and viral and cellular gene expression. **Results:** A total of 22 advanced NPC patients were enrolled. VK-2019 was well tolerated with mostly grade 1-3 adverse events being reported. VK-2019 is rapidly absorbed with a biphasic distribution and a terminal $T_{1/2}$ of ~12h after single or multiple doses. C_{max} and AUC increases with dose escalation through 920 mg with large variability at 1800mg. Accumulation has been observed with multiple doses up to 460mg. Based on preclinical efficacy models, target exposures are at or above expected activity levels for patients at least on the 920 mg daily dose and above. A partial response (> 30% decrease in tumor size) was observed for one patient. Preliminary results from biopsies from 2 patients show decreases in EBV copy number and viral gene expression (LMP2 and gp150). We also observed decreases in EBER-positive cells in one patient. **Conclusions:** In this study, VK-2019 was well tolerated, exhibiting an excellent safety profile and exposure above in vitro efficacy. An MTD has not been yet established. Preliminary results indicate a decrease in EBV copy number and viral gene expression in latently infected tumor cells in some patients. Alternate dose schedules are justified to determine the clinical efficacy of an EBNA1 inhibitor in patients with advanced NPC. Funded by NCI, R01-CA235633 and Cullinan Oncology. Clinical trial information: NCT04925544. Research Sponsor: U.S. National Institutes of Health; Cullinan Oncology.

Outcomes by time to adjuvant therapy in E3311, a phase II trial of transoral surgery (TOS) followed by pathology-based adjuvant treatment in HPV-associated (HPV+) oropharynx cancer (OPC): A trial of the ECOG-ACRIN Cancer Research Group. *First Author: Robert L. Ferris, Hillman Cancer Center, Pittsburgh, PA*

Background: E3311 is a phase II randomized study of intermediate risk HPV+ OPC patients who underwent TOS by credentialed surgeons and were then treated by pathology-guided, deintensified post-operative treatment. Recent retrospective population data suggest that time to post-operative radiotherapy (PORT) > 6 weeks is associated with worse progression-free survival (PFS). **Methods:** We retrospectively analyzed demographics, pathologic characteristics, and oncologic outcomes in E3311 by time to initiation of PORT (short vs long, exploring both 6 and 7 weeks postop as the cutpoint). Binary and categorical variables were compared using a chi-square test (or a Fisher's exact test for small sample sizes). Ordinal variables were compared using a Wilcoxon rank sum test. PFS and overall survival (OS) were estimated using the Kaplan-Meier method and compared using a log-rank test, which was stratified by intermediate- (Arms B/C) vs high-risk (Arm D). **Results:** Among 321 evaluable patients, the median time to initiation of PORT was 5.1 weeks (range 0.7-15.7); 5.0 (0.7-15.7) for Arm B, 5.1 (2.4-7.0) for Arm C, 5.6 (3.6-7.9) for Arm D. No significant difference in PFS or OS was observed whether PORT commenced by 6 or 7 weeks postoperatively, compared with longer time to initiation of PORT ($p = 0.62$ and 0.65 , $p = 0.30$ and $p = 0.41$, respectively). 3-yr PFS rates were 93.5% (95% CI: 89.4%, 96.0%) among those treated ≤ 6 weeks, and 91.2% (95% CI: 81.4%, 95.9%) among those treated > 6 weeks; 3-yr OS rates were 96.1% (95% CI: 92.7%, 98.0%) among those treated ≤ 6 weeks, and 94.1% (95% CI: 84.9%, 97.8%) among those treated > 6 weeks. No significant differences in outcomes were observed between intermediate risk treatment arms (deintensified (50Gy) or standard dose (60Gy) RT). Additional demographic and pathologic characteristics, including primary site, margin status, histologic grade, stage, and extranodal extension were not significantly different between those with short vs long time to PORT, whether 6 or 7 weeks was used as the cutpoint. There were more T2 tumors in those treated > 7 weeks postop (84% vs. 49%, $p = 0.007$). PS = 1 patients were more numerous among those with shorter time to PORT (10% vs 0%, with the 7 week cutpoint). **Conclusions:** In contrast to retrospective NCDB data, intermediate- and high-risk HPV+ OPC patients enrolled on E3311 had favorable 3-yr PFS and OS rates that were not significantly worse when adjuvant therapy was started > 6 wks or > 7wks. These results argue against a survival advantage for initiation of PORT within 6 or 7 weeks for early-stage HPV+ OPC managed with high-quality transoral resection. The optimal time window to initiate PORT in HPV+ OPC patients remains to be determined. Clinical trial information: NCT01898494. Research Sponsor: U.S. National Institutes of Health.

Efficacy from the ongoing phase I trial Study 1100 with NBTXR3 activated by radiotherapy in combination with nivolumab or pembrolizumab in patients with locoregionally recurrent or metastatic HNSCC. *First Author: Colette Shen, Department of Radiation Oncology, University of North Carolina School of Medicine, Chapel Hill, NC*

Background: Immune checkpoint inhibitors (ICIs) have revolutionized cancer treatment, yet most patients (pts) ultimately develop ICI resistance. Overcoming this resistance is a major clinical challenge. NBTXR3, a novel radioenhancer composed of functionalized hafnium oxide nanoparticles administered by a single intratumoral injection, locally amplifies the RT dose without adding toxicity to surrounding healthy tissue. In preclinical models, NBTXR3/RT has been shown to enhance tumor cell death and tumor antigen release and to effectively expand T-cell repertoire, thus potentially triggering both local and systemic immune responses to help improve ICI treatment. A phase I trial is ongoing to evaluate NBTXR3/RT in combination with anti-PD-1 in pts with advanced cancers. Here we report early outcomes in pts with locoregionally recurrent (LRR) or metastatic (M+) head & neck squamous cell carcinoma (HNSCC). **Methods:** Study 1100 is a phase I dose escalation/expansion trial [NCT03589339] evaluating NBTXR3 activated by stereotactic body radiotherapy (SBRT) followed by anti-PD-1 therapy (nivolumab or pembrolizumab) in 3 cohorts of pts with advanced solid tumors. Pts are either resistant to prior ICI or naïve. Escalation cohorts were defined by site of injection: H&N lesions, lung metastases, or liver metastases. SBRT was delivered as per standard practice. The primary objective of the escalation part was to determine the NBTXR3/RT/anti-PD-1 RP2D for each cohort. Secondary objectives were feasibility, safety, and anti-tumor efficacy (objective responses). **Results:** 16 pts with LRR or M+ HNSCC were treated in the escalation part. 10 pts were resistant to anti-PD-1, 6 were naïve. 8 pts were HPV+, 7 were HPV-, and 1 had HPV status unknown. 13 pts had M+ disease, of which 9 were anti-PD-1 resistant, 4 were naïve. Overall tumor responses were observed in 31.3% (5/16) with mean duration of response (DOR) for these 5 pts of 14.8 (SD ± 7.64) months, at the time of cut-off (4 pts were still responders). Disease control was observed in 75.0% (12/16). Among M+ pts, overall tumor responses were observed in 23.1% (3/13) with mean DOR for these 3 pts of 12.1 (SD ± 5.83) months (2 were still responders). Disease control was observed in 69.2% (9/13) pts with M+ disease. 25.0% (4/16) pts experienced disease progression, and all had M+ disease. All patients who progressed did so with the appearance of a new (non-treated) lesion. **Conclusions:** Promising early signs of efficacy were observed in HNSCC pts treated with NBTXR3/RT/anti-PD-1, including responses in pts resistant to anti-PD-1 and with M+ disease. Disease control was observed in M+ pts, highlighting the potential for NBTXR3 in this difficult to treat population. Overall, these results support evaluation of NBTXR3/RT/anti-PD-1 in the ongoing expansion part. Clinical trial information: NCT03589339. Research Sponsor: Nanobiotix.

Results from two phase II studies of SI-B001, an EGFR $\times$ HER3 bispecific antibody, with/without chemotherapy in patients (pts) with recurrent and metastatic head and neck squamous cell carcinoma (HNSCC). *First Author: Liqiong Xue, Shanghai East Hospital, School of Medicine, Tongji University, Shanghai, China*

Background: SI-B001 is an EGFR $\times$ HER3 bispecific antibody. We present the efficacy and safety results from two ongoing studies of SI-B001, S209 and S206, in recurrent and metastatic HNSCC. **Methods:** S209 included pts with recurrent and metastatic HNSCC progressed on prior anti-PD-1/L1 plus platinum-based chemotherapy (PBC). Pts were treated with SI-B001 16mg/kg IV QW. S206 included pts with recurrent and metastatic HNSCC progressed on prior anti-PD-1/L1 with or without PBC and received no more than two lines of treatment. Pts enrolled in S206 were divided into two groups: Group A, pts without prior exposure to paclitaxel were treated with SI-B001 (12mg/kg IV QW) plus paclitaxel (80mg/m² IV QW); Group B, pts with prior exposure to paclitaxel were treated with SI-B001 (12mg/kg IV QW) plus docetaxel (35mg/m² IV D1D8D15 Q4W). The study endpoints of the two studies were identical. The primary endpoint was objective response rate (ORR) by investigator per RECIST v1.1. Secondary endpoints were ORR by independent central review, progression-free survival (PFS), disease control rate (DCR), duration of response (DOR), overall survival (OS), and safety. **Results:** As of Dec 31, 2022, 11 pts in S209 received SI-B001. Pts had a median of 4 prior lines of therapy. In 9 out of 11 pts who have at least 1 post baseline tumor assessment in S209, ORR (n/N) was 22.2% (2/9), mPFS [95%CI] was 2.7 [1.8-7.9] mo. 29 pts in S206 received SI-B001 plus chemotherapy, including 19 pts in Group A and 10 pts in Group B. In 22 pts who had at least 1 post baseline tumor assessment, ORR was 45.5% (10/22), mPFS was 5.1 [3.7-5.6] mo. 1 nasal sinus cancer pt enrolled had stable disease (SD). 14 out of the 18 pts who have at least 1 post baseline tumor assessment in Group A, ORR was 64.3% (9/14) mPFS was 5.6 [5.1-6.3] mo. 8 out of 10 pts who have at least 1 post baseline tumor assessment in Group B, ORR was 12.5% (1/8), mPFS was 1.9 [1.2-3.7] mo. The most common grade 3 and above treatment-related adverse events (TRAEs) in S209 was Hypomagnesaemia (9%). The most common grade 3+ TRAEs in S206 were rash (16%), anaemia (8%) and white blood cell count decreased (8%). No SI-B001 drug-related deaths occurred in either study. **Conclusions:** SI-B001 plus paclitaxel demonstrated potential improvements in ORR and DCR compared with SI-B001 monotherapy in recurrent and metastatic HNSCC. The toxicity of SI-B001 plus chemotherapy in HNSCC is manageable and tolerable. Clinical trial information: NCT05044897; NCT05054439. Research Sponsor: Sichuan Baili Pharmaceutical Co., Ltd.

	S209 (n=9)	S206 Group A (n=14)	S206 Group B (n=8)	S206 Total (n=22)
Best overall response, n				
cPR	2	4	0	4
PR	0	5	1	6
SD	5	4	4	8
PD	2	1	3	4
ORR, % (95% CI)	22.2% (2.8-60.0)	64.3% (35.1-87.2)	12.5% (0.3-52.7)	45.5% (24.4-67.8)
DCR, % (95% CI)	77.8% (40.0-97.2)	92.9% (66.1-99.8)	62.5% (24.5-91.5)	81.8% (59.7-94.8)

Platinum/taxane/pembrolizumab vs platinum/5FU/pembrolizumab in patients with recurrent/metastatic (r/m) head and neck squamous cell carcinoma (HNSCC). *First Author: Lova Sun, University of Pennsylvania, Philadelphia, PA*

Background: Pembrolizumab +/- chemotherapy is standard of care for patients (pts) with r/m HNSCC. Despite approval of platinum/5FU/pembrolizumab based upon the KN-048 study, a taxane is often substituted for 5FU due to ease of administration and tolerability. No studies have directly compared these approaches. We describe nationwide patterns of taxane vs 5FU chemoimmunotherapy in r/m HNSCC and compare survival and time on treatment between the two. **Methods:** This study used the nationwide Flatiron Health electronic health record (EHR)-derived de-identified database, and included pts treated with frontline pembrolizumab plus platinum-based chemotherapy (either taxane or 5FU) for r/m HNSCC. Demographic, cancer, and clinical outcomes were summarized. Categorical variables were compared using Pearson's chi-square test; continuous variables were compared using T-test. Overall survival (OS) was estimated using Kaplan Meier methodology, and compared using log-rank test. Multivariable Cox regression for overall survival adjusting for age, sex, race, year of diagnosis, ECOG performance status (PS), smoking history, primary tumor site, PD-L1, HPV status, cisplatin use, socioeconomic status, insurance, and practice type was performed, with multiple imputation by chained equations for missing variables. **Results:** Of 444 pts, 321 (72%) received 5FU and 123 (28%) received taxane (108 paclitaxel, 15 docetaxel). Use of cisplatin rather than carboplatin was higher in the 5FU group than the taxane group (16.8% vs 4.9%, $p=0.001$). Taxane use was higher in academic vs community practices (50.7% vs 23.9%, $p<0.001$); within community sites, Northeast states had highest taxane use (27.5%) and Western states had lowest taxane use (16.7%). Pts with Medicare or Medicaid were more likely to receive taxane (35.5%) vs commercial (23.6%) or other (26.7%) insurance. OS did not differ between taxane and 5FU groups (mOS 12.7 vs 13.5 months, $p=0.743$). On multivariable Cox regression, HR for death associated with taxane vs 5FU was 1.01 (95%CI 0.73-1.41). HPV positive status was associated with improved survival (HR 0.58, 95%CI 0.40-0.83). $PS>1$ (HR 1.38, 95%CI 0.96-1.98) and cisplatin use (HR 1.37, 95%CI 0.95-1.98) showed non-significant trends towards worse survival. Taxane-treated pts received more treatment cycles (mean 11.3 vs 8.8 cycles, $p=0.015$) and were on treatment slightly longer (mean 6.9 vs 6.0 months, $p=0.289$) than 5FU-treated pts. **Conclusions:** In US pts with r/m HNSCC undergoing chemoimmunotherapy, rates of taxane vs 5FU use vary by academic setting, geographic region, and insurance status. There was no difference in survival between 5FU and taxane, and taxane-treated pts received more cycles of therapy. Platinum-taxane appears to be a non-inferior alternative to platinum-5FU with pembrolizumab for r/m HNSCC, and should be allowed in clinical trials. Research Sponsor: None.

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Poster Session

Updated results from a phase 2 study of the oral vascular endothelial growth factor receptor 2 (VEGFR2) inhibitor rivocecanib for recurrent or metastatic (R/M) adenoid cystic carcinoma (ACC). *First Author: Hyunseok Kang, University of California, San Francisco, San Francisco, CA*

Background: ACC is a rare tumor that overexpresses VEGF, primarily affecting salivary glands. Often indolent, it can progress, with metastases common in the lungs, liver, and bone. There are no FDA-approved systemic treatments (tx) for R/M ACC. Rivocecanib is an oral tyrosine kinase inhibitor (TKI) that potently and selectively inhibits VEGFR2. **Methods:** In this single-arm, open-label multicenter trial, patients (pts) with R/M ACC with evidence of $\geq 20\%$ progression by RECIST v1.1 or new lesions within the preceding 6 months (mos) were eligible, with no limit on prior tx. Pts received rivocecanib 700 mg daily until disease progression or withdrawal with pre-planned dose reductions for toxicity. Primary endpoint was overall response rate (ORR) per RECIST v1.1 by investigator (INV) and by Independent Review Committee (IRC). Secondary endpoints included duration of response (DoR), progression-free survival (PFS), time to progression (TTP), overall survival (OS), and safety exploratory analysis included disease control rate (DCR) and ORR using Choi criteria by IRC. **Results:** As of 11/2022, 80 pts (72 evaluable) were enrolled in the US and Korea (53% male; median age, 54 yrs), and 6 pts remain on tx. Primary tumor sites: major (34%) and minor (59%) salivary glands and other (8%). 74 pts (93%) had metastatic disease. 61.3% had prior systemic tx (18% prior VEGFR TKI). INV and IRC-assessed efficacy data are listed in the table. ORR by Choi was 52.5% (53.1% VEGFR TKI-naïve and 50% VEGFR TKI treated). mOS was 25.3 mos (28.3 mos VEGFR TKI-naïve and 22.6 mos VEGFR treated). Common adverse events (AEs) were hypertension (66%), fatigue (64%), and nausea (54%). Grade ≥ 3 AEs that occurred in $>5\%$ of pts were hypertension (43%), stomatitis (8%), fatigue and anemia (6% each). There were 4 Grade 5 AEs (2 epistaxis [1 related], 1 acute respiratory failure, 1 respiratory failure). **Conclusions:** Updated results with additional 9-month follow-up data continue to demonstrate that Rivocecanib has clinical efficacy and a manageable safety profile in pts with R/M ACC. Clinical trial information: NCT04119453. Research Sponsor: Elevar Therapeutics.

	Total (N=72)		VEGFR TKI-Naïve (n=59)		VEGFR TKI Prior Tx (n=13)	
	INV	IRC	INV	IRC	INV	IRC
ORR* n, (%)	11 (15.3)	7 (9.7)	11 (18.6)	5 (8.5)	0	2 (15.4)
95% CI	7.9-25.7	4.0-19.0	9.7-30.9	2.8-18.7		1.9-45.4
DoR median (mos)	14.9	7.2	13.5	8.3	17.3	6.3
DCR n, (%)	47 (65.3)	48 (66.7)	37 (62.7)	39 (66.1)	10 (76.9)	9 (69.2)
95% CI	53.1-76.1	54.6-77.3	49.1-75.0	52.6-77.9	46.2-90.9	38.6-90.9
mTTP (mos)	9.2	9.3	9.2	10.8	10.6	8.9
mPFS (mos)	9.1	9.2	9.0	9.3	10.6	8.9
6, 12 mo PFS rate (%)	77.4, 38.9	80.8, 38.6	75.8, 39.3	80.3, 40.4	84.6, 37.6	83.1, 31.2
mOS (mos)**		25.3		28.3		22.6

*all partial responses; ** intention to treat population.

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Poster Session

Evaluation of ICI sensitivity for pembrolizumab in combination with anti-platelet therapy for patients with recurrent or metastatic squamous cell carcinoma of the head and neck (HNSCC). *First Author: Karthik Chakravarthy, The Pelotonia Institute for Immuno-Oncology, The Ohio State University Comprehensive Cancer Center, Columbus, OH*

Background: This study was proposed to elucidate the impact of combining anti-platelet therapy with an immune checkpoint inhibitor (ICI) in altering the CD8⁺ T cell function in patients with head and neck squamous cell carcinoma (HNSCC). With a total enrollment of 15 of out an expected 20 patients, this report characterizes the findings thus far from the ongoing study. **Methods:** This crossover trial consisted of two different treatment regimens for two groups. Regimen A involved treatment with a PD-1 inhibitor pembrolizumab (200 mg iv over 30 min) every 3 weeks in combination of daily aspirin (81 mg orally) and clopidogrel (75 mg orally) for a total of 6 weeks. Regimen B involved pembrolizumab monotherapy (200 mg iv over 30 min) every 3 weeks for two cycles. Thus far, 15 patients with recurrent or metastatic HNSCC were randomized into the two groups, with Group 1 receiving Regimen A followed by Regimen B, while Group 2 received Regimen B followed by Regimen A. In addition to clinical endpoint, in depth analysis of the peripheral blood mononuclear cells (PBMCs) was also implemented using samples obtained prior to treatment, in between regimens, and at the end of treatment. These samples were then analyzed using a spectral flow cytometer panel specific for human CD8⁺ T cells. Given the 75 percent accrual, we performed analysis with the obtained clinical samples and data. **Results:** Of the 15 patients enrolled into the study, 14 remained on study and completed the trial till endpoint. All 14 patients presented with no overtly significant adverse events (AEs). In terms of clinical response, we observed in Group 1 patients (n=7) a total of 1 CR (complete response), 1 PR (partial response), 2 SD (stable disease), and 3 PD (progressive disease), while Group 2 (n=7) presented with 2 PR, 2 SD, and 3 PD. Spectral flow analysis performed on Group 1 patient samples revealed an increase in the Ki67⁺PD1⁺ proliferative subset post combination treatment (p value < 0.05, paired Student's t-test). This finding indicates a potential increase in proliferation among CD8⁺ T cells after antigen stimulation that may pertain to the combination of anti-PD-1 and anti-platelet therapy. In addition, a higher frequency of Ki67⁺TIGIT⁺ CD8⁺ population (p value < 0.05, paired Student's t-test) was also observed after combination therapy compared to pre-treatment; however, this level was not sustained after combination therapy was ceased, implying that ongoing anti-platelet therapy may be necessary for augmenting ICI. **Conclusions:** Combination of anti-PD1 and anti-platelet therapy demonstrates potential for remodeling the immune component pertaining to CD8⁺ T cells without resulting in overt toxicity. Further analysis of the effects of this combination regimen will be essential to better characterize tumor specific impact. Clinical trial information: NCT03245489. Research Sponsor: U.S. National Institutes of Health.

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Poster Session

Evaluation of small extracellular vesicles as biomarkers of efficacy with anti-PD-1 mAb therapy in patients with recurrent/metastatic HNSCC. *First Author: Dan Paul Zandberg, UPMC Hillman Cancer Center, Pittsburgh, PA*

Background: The development of biomarkers that reliably predict response to anti-PD-1 mAb therapy (IO) is a critical need. Small (30-150 nm) extracellular vesicles (sEV), aka exosomes, are "molecular mimics" of their parent cells. In cancer, plasma sEV are mixtures of tumor-derived exosomes (TEX) and vesicles produced by non-malignant cells. We conducted a retrospective study of R/M HNSCC patients treated with IO to evaluate sEV as predictive biomarkers. **Methods:** We evaluated sEV in plasma of R/M HNSCC patients (n = 24) obtained just prior to initiation of IO. Precleared ultrafiltered plasma was used to isolate total plasma sEV by size exclusion chromatography. Total plasma sEV were separated into two subsets, T cell-derived CD3(+) sEV and TEX-enriched CD3(-) sEV by immunocapture with anti-CD3 mAb. On-bead flow cytometry was used to estimate relative levels of proteins carried on the sEV surface. Specifically, the CD3(-) fraction was evaluated for stimulatory (stim; CD40, CD40L, OX40, OX40L, CD80) and suppressive (supp; TGFb, CTLA4, FasL, PD-L1, PD-1) proteins. Differences between responders (CR/PR/SD) and non-responders (PD) were assessed using Wilcoxon-Mann-Whitney test. Multivariate Cox proportional hazards regression was used to evaluate the relationship between the pre-treatment sEV characteristics and outcome. **Results:** Mean age was 62, 46% had oropharynx (82% HPV+), 17% oral cavity and 29% had larynx/hypopharynx primary. Treatment indication for IO was 46% platinum failure, remainder first line. Best response: 17% PR, 29% SD, and 54% PD. Median PFS and OS were 5.3 and 16.2 months, respectively. Total sEV protein level was not associated with efficacy. Total CD3(+) sEV level was low overall and did not correlate with lymphocyte count or neutrophil/lymphocyte ratio. High CD3(+) sEV level was associated with better OS [HR: 0.16 (95% CI 0.04-0.59), P = 0.007] and PFS [HR: 0.16 (95% CI 0.04-0.58), P = 0.005] but not response. While total TEX and levels of individual stim and supp proteins carried by TEX were not predictive of response, an increased supp/stim ratio was (P = 0.02). Importantly, high TEX supp score and stim score were both associated with better OS [HR: 0.19 (95% CI 0.05-0.77), P = 0.02, and HR: 0.26 (95% CI 0.07-0.95), P = 0.04, resp.]. High PD-L1, but not PD-1 on TEX, was associated with better OS [HR: 0.15 (95% CI 0.04-0.56), P = 0.005]; and PFS: HR: 0.33 (95% CI 0.11-0.94), P = 0.04]. **Conclusions:** Evaluation of two sEV subsets, T cell-derived-CD3(+) sEV and TEX-enriched CD3(-) sEV, indicated their potential utility as predictive biomarkers with IO. High T cell-derived sEV, TEX supp/stim ratio, and TEX PD-L1 expression levels were independently associated with significantly increased efficacy with IO. Our study uniquely analyzed the predictive value of plasma sEV subsets in IO treated R/M HNSCC patients, and evaluation in a larger cohort is warranted. Research Sponsor: U.S. National Institutes of Health.

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Poster Session

A phase 1 clinical trial of DB-020 intratympanic injections administered prior to high dose cisplatin chemotherapy to reduce ototoxicity. *First Author: Danny Rischin, Department of Medical Oncology, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia*

Background: Hearing loss with cisplatin (CP) chemotherapy is common. DB-020 is a formulation of thiosulfate for intratympanic (IT) injection being developed to reduce CP ototoxicity. The primary objective of this Phase 1 study was to evaluate the safety and tolerability of repeated IT injections of DB-020. A secondary objective was to compare hearing changes with DB-020 vs. placebo. **Methods:** Subjects scheduled for at least 3 cycles of CP and cumulative exposure of ≥ 280 mg/m² were randomized to blinded, bilateral, IT injection with DB-020 (12% or 25%) in one ear and placebo in the other, once every 3 or 4 weeks, up to 3 hours before receiving CP. Subjects with moderate or severe hearing loss at baseline were excluded. Ototoxicity was defined by American Speech-Language-Hearing criteria: ≥ 20 dB threshold increase at any one test frequency, or ≥ 10 dB threshold increase in any two adjacent frequencies, or loss of response at three consecutive frequencies where responses were previously obtained. Severe ototoxicity was ≥ 20 dB threshold increase in any two adjacent frequencies. A pre-specified interim analysis evaluated safety, ototoxicity (with Mcnemar's test using the last observation carried forward), and average threshold shifts (from air conduction audiometry, analyzed with a mixed model with repeated measures). **Results:** Nineteen subjects were randomized, with mean age of 57 years (84% male and 100% white) and mean cumulative CP dose 248 mg/m². Most (95%) had head and neck cancers (5% had lung cancer). Seventeen subjects had both baseline and follow-up audiometry, and 16/17 had baseline audiograms within 5 dB of the median threshold for age-matched controls. Free CP systemic levels were similar to reference values. Ear pain (15/19 subjects, 78.9%) and tinnitus (8/19 subjects, 42.1%) were common. Ear pain was more common in DB-020 treated ears, and tinnitus was more common in placebo treated ears. There were no tympanic perforations, no serious adverse events in the category of ear and labyrinth disorders, and no deaths. Ototoxicity was significantly more common and more severe in placebo treated ears (Table). As the overall study objectives were met at this interim analysis, no further enrollment was pursued. **Conclusions:** In this initial clinical trial experience there was no significant safety signal, and DB-020 IT injections showed a meaningful reduction in cisplatin ototoxicity. These results warrant further clinical development. Clinical trial information: NCT04262336. Research Sponsor: Decibel Therapeutics.

Assessment	Placebo ears (n=17)	DB-020 ears (n=17)	p-value vs. placebo
Ototoxicity (250 to 8000 Hz)	88.2%	41.2%	0.0047
Ototoxicity (9000 to 16000 Hz)	88.2%	52.9%	0.0143
Severe ototoxicity (250 to 8000 Hz)	64.7%	11.8%	0.0027
Severe ototoxicity (9000 to 16000 Hz)	76.5%	29.4%	0.0047
Acoustic threshold shift (LS mean dB), 250 to 8000 Hz	15.27	4.35	0.001
Acoustic threshold shift (LS mean dB), 9000 to 16000 Hz	18.23	8.45	0.010

Abemaciclib in recurrent/metastatic head and neck squamous cell carcinoma (RM-HNSCC) harboring *CDKN2A* loss, and/or *CCND1* and/or *CDK6* amplification: A phase II multicenter trial. *First Author: Jerome Fayette, Centre Léon Bérard, Lyon, France*

Background: More than half of HPV negative HSNCC harbor genomic aberrations (i.e. *CDKN2A* loss, cyclin D amplification (ampl.)) that activate the cyclin-dependent kinase 4 and 6 (CDK4/6) – retinoblastoma protein (Rb) signalling pathway. Hyperactivated CDK4/6-Rb pathway leads to acceleration of G1/S transition of cell cycle and ultimately to uncontrolled cellular proliferation. We hypothesized that abemaciclib, a CDK4/6 inhibitor, could be a potent targeted strategy by inhibiting this commonly dysregulated pathway in HNSCC. **Methods:** This single arm, multicentre Phase II evaluated the efficacy of abemaciclib (200mg/d orally BID) in molecularly-selected, HPV negative (HPV), RM-HNSCC patients (pts) progressing after at least 1 prior line of platinum and cetuximab. A molecular screening step through centralised CGH-assay was required before treatment start: only pt with tumor harboring CDKN2A loss and/or CCND1 and/or CDK6 ampl. without homozygous deletion of RB1 were eligible to the therapeutic step. The primary endpoint was 8-week non-progression rate (PFR_{8w}) as per central imaging review according to RECIST V.1.1. Secondary endpoints included best overall response rate (BORR), progression free survival (PFS), overall survival (OS) and adverse event (AE) according to NCI-CTCAE V5.0. The study used a Fleming A'Hern design with an inefficacy bound of 15% and a target PFR_{8w} of 40% ($\alpha = 5\%$ one sided, $1-\beta = 90\%$). **Results:** Twenty-six HPV⁺ RM-HNSCC pts (M: 23, F: 3, median age: 59 [range, 42-78], heavily pre-treated [84.6% $\geq$ 2 prior lines]) received at least one dose of abemaciclib. According to central CGH-assay, molecular alterations were *CDKN2A* loss + *CCND1* ampl. + *CDK6* ampl. (n = 1), *CDKN2A* loss + *CCND1* ampl. (n = 10), *CDKN2A* loss (n = 6) or *CCND1* ampl. (n = 9), all with intact Rb. Among the 24 evaluable pts, 7 pts were progression-free at 8 weeks (PFR_{8w}: 29.2% (95% CI 14.6-)). BORR according to central imaging review was stable disease for 7 pts (31.8%) and progressive disease for 11 pts (50%); no objective response was observed. Median PFS and OS were 7.1 weeks (95% CI: 6.9-10.4) and 4.8 months (95% CI: 2.4-7.3), respectively. Most common related AEs ($\geq 20\%$ of pts, all grade) were diarrhea/nausea/vomiting, fatigue and hematological toxicity (anemia, lymphocyte and neutrophil count decreased). Two fatal serious AE potentially related to abemaciclib according to both investigator and sponsor were reported: a case of pulmonary hemorrhage also possibly related to abemaciclib-induced tumor necrosis and a case of myocardial infarction. **Conclusions:** Abemaciclib had limited antitumor activity in RM-HNSCC harboring molecular alteration in CDK4/6 pathway. Clinical trial information: NCT03356223. Research Sponsor: Lilly.

Phase II study evaluating the efficacy of niraparib and dostarlimab (TSR-042) in recurrent/metastatic head and neck squamous cell carcinoma (HNSCC) patients. *First Author: Olga Zamulko, University of Cincinnati Medical Center, Cincinnati, OH*

Background: Patients with recurrent and/or metastatic (R/M) HNSCC have poor overall survival. Immune checkpoint inhibitors (ICIs), specifically programmed death-1 (PD-1) inhibitors, result in durable responses in R/M HNSCC but <20% benefit. Tumor mutational burden (TMB) correlates with ICI response. DNA pathway repair mutations have been reported in 17% of sporadic HNSCC and are associated with higher rates of TMB. Poly (ADP-ribose) polymerase (PARP) inhibition has demonstrated efficacy as a single agent in cancers with a DNA repair defect. We tested the combination of PARP inhibitor (niraparib) with the PD-1 inhibitor (dostarlimab) in R/M HNSCC patients (NCT04313504) with funding support from Tesaro/GSK. **Methods:** Patients with R/M HNSCC who failed at least one line of prior treatment including a PD-1 inhibitor and for whom no surgical or radiation curative options existed were eligible for the study. Patients received niraparib (200 mg daily) beginning one week prior to initiation of dostarlimab (500 mg q3wks x4 followed by 1000 mg q6wks). The primary endpoint was overall response rate (ORR) including complete response (CR), partial response (PR) and stable disease (SD) using RECIST v1.1. Fourteen patients were planned for the first stage and 10 additional patients for the second stage if ≥ 8 patients had a confirmed response. Safety was evaluated by CTCAE v5.0. Tumor PD-L1 immunohistochemistry was performed with 22c3 antibody and reported as combined positive score (CPS). TMB was considered high if ≥ 10 Mut/Mb. **Results:** Ten of 24 planned patients were enrolled. Of the first 10 patients, 8 patients were evaluable by imaging and 1 patient clinically progressed on exam. Of the 9 evaluable patients, there were 0 CR, 1 PR, 1 SD, and 7 with progressive disease (PD). The trial was ended early for futility as it was not possible for at least 8 out of 14 patients to develop response. The patient with a PR remains on treatment past 24 months, was PD-L1 positive, had low TMB and no DDR deficiency. All patients had previously failed a PD-1 inhibitor. One patient had high TMB, 2 patients had a DDR, and 6 patients were PD-L1 positive but 2 patients had insufficient tissue or indeterminate results for sequencing. Grade ≥ 3 adverse events occurred in 70% of patients with most common being hypertension (20%), hyponatremia (20%), and lung infection (20%). **Conclusions:** PARP-1 inhibition and PD-1 inhibition combined does not appear to enhance response over PD-1 inhibitor alone in R/M HNSCC who had previously failed PD-1 inhibitor treatment. However, a more focused population including those with DNA damage response (DDR) mutations and PD-1 treatment naïve may benefit. Clinical trial information: NCT04313504. Research Sponsor: GSK provided funding for this trial; Tesaro.

Molecular breakdown of biomarkers using NGS.	
Biomarker	n (%)
TMB	Total n=8
Low (0-9 mut/Mb)	7 (87.5)
High (≥ 10 mut/Mb)	1 (12.5)
PD-L1 CPS	Total n=8
0	2 (25)
≥ 1 to 20	5 (62.5)
≥ 20	1 (12.5)
DDR	Total n=8
Yes	2 (25)
No	6 (75)

Personalized therapy for head and neck squamous carcinoma (HNSCC) utilizing tissue proteomics profiling. *First Author: Sheeno P. Thyparambil, mProbe Inc., Rockville, MD*

Background: Chemotherapy is widely used in the treatment of HNSCC, yet no biomarkers for chemotherapy are used for selection of the chemo agent in the treatment of HNSCC. We examined 143 HNSCC cancer using targeted proteomics for the protein expression levels of several chemo agents. These include markers of resistance to platinum agents (ERCC1), anti-tubulin inhibitors (TUBB3) and sensitivity markers for topoisomerase inhibitors (Topo1 – irinotecan, topotecan; Topo2A – doxorubicin, etoposide). We also measured markers for several antibody-drug conjugates (EGFR, Her2, Trop2, FR-alpha, Mesothelin). **Methods:** Tumor areas from Formalin-fixed, paraffin-embedded (FFPE) tumor tissues from clinical samples of HNSCC that were received at our CLIA certified laboratory were microdissected and a selected reaction monitoring mass spectrometry (SRM-MS) quantitative proteomic analysis of 72 protein biomarkers were conducted concurrently from 2-3 sections of FFPE tissue. **Results:** Platinum agents are widely agent in HNSCC cancer. ERCC1, a resistance marker for platinum agents was expressed in 44% of HNSCC. Similarly, TUBB3, a resistance marker for Paclitaxel, docetaxel was also expressed in ~45% of HNSCC. These indicate that ~45% of HNSCC could potentially be refractory to platinum and paclitaxel-based therapy. Additionally, ALDH1A1, a marker for resistance of cyclophosphamide, was expressed in 78% of HNSCC. Temozolomide, an alkylating agent used in other cancer type could be beneficial in 14% of HNSCC because of the lack of resistance marker MGMT. On the other hand, 88% of HNSCC expressed Topo1, which is a sensitivity marker for irinotecan or topotecan based therapy. Additionally, Top1 is also the target for the payload of several ADCs (e.g. trastuzumab deruxtecan and sacituzumab govitecan). Similarly, 55% of HNSCC expressed Topo2A, a target for etoposide and doxorubicin. Additionally, 57% of HNSCC expressed hENT1, a transporter of gemcitabine. HNSCC also expressed various targets for targeted and ADC agents. These include EGFR (86% detected with 37x range of distribution), Her3 (11%), IGF1R (16%), MET (13%), Folate receptor- alpha (18%), Mesothelin (13%), and Trop2 (89% with 134x range of distribution). Her2 was overexpressed (> 750 amol/ug) in 11% of HNSCC, however, it was observed in 46% of HNSCC with a 53x range (276 – 14705 amol/ug), indicating that a significant population of HNSCC might be eligible for low Her2 clinical trials. **Conclusions:** Every cancer is unique, and the ability to analyze 72 protein biomarkers from 2-3 FFPE sections simultaneously at the same time provides a wealth of actionable information for clinical treatment or patient stratification for clinical trials. Research Sponsor: mProbe.

TCR-T cells armored with immune checkpoint blockade in EBV-positive nasopharyngeal carcinoma: The first-in-human phase 1/2 trial. *First Author: Qingzhu Jia, Institute of Cancer, Xinqiao Hospital, Chongqing, China*

Background: Nasopharyngeal carcinoma (NPC) refection and metastasis is common, but therapeutics are limited. As adoptive immunotherapy has emerged as effective against other cancers, engineered T cells bearing a transgenic Epstein-Barr virus (EBV)-specific TCR (TCR-T) represent a viable approach to treat EBV-associated NPC. Given PD-1/PD-L1 induced T cell hypofunction, we herein report preliminary findings of a phase I trial of EBV-targeting TCR-T cells armored with secreted PD-1 blockade for patients who failed in two or more lines of standard therapies. **Methods:** Patients with advanced NPC were consented and screened for EBV serotype and HLA haplotype. EBV+ HLA-A*02+ patients were enrolled in a rapid titration setting to escalate the single infusion dose from 5×10^6 to 1.0×10^7 and 5.0×10^7 /kg TCR-T cells. After safety evaluation, the 5.0×10^7 /kg cohort was expanded for further investigation of combining with IL-2 administration. Fludarabine/cyclophosphamide were administered prior to TCR-T cell transfer as pre-conditioning. Patient monitoring and peripheral blood analysis occurred weekly over the first month and then monthly until disease progression or patient withdrawal. The primary objective was to determine safety and a recommended phase 2 dose (RP2D), while the secondary objective was investigator assessed ORR (RECIST v1.1). **Results:** One patient per TCR-T dose was treated, and, as no dose-limiting toxicity (DLT) has been observed, dose level 3 (5.0×10^7 /kg) was expanded with IL-2 administration upon TCR-T cell infusion. As of January 2023, six patients have been treated. One patient (16.7%) exhibited grade 1 CRS (n=6). No grade 4 treatment-related adverse events (TRAEs) have been observed, with leukopenia and fever being the most common AEs. Two patients (33.3%) were assessed as partial response (PR), with one reaching a response duration of 9 months to date. Three patients (50%) were assessed as stable disease (SD). For all patients, pharmacokinetic analysis revealed that levels of TCR-T cells in peripheral blood peak between 3- and 14-days post-infusion, with a maximum duration of 180 days. **Conclusions:** EBV-targeting TCR-T cells armored with PD-1 blockade are well tolerated. Initial results from this ongoing study indicate that EBV proteins may be safe and effective TCR-T targets to achieve superior outcomes in advanced EBV-positive NPC patients. Clinical trial information: NCT04139057. Research Sponsor: Guangdong TCR Cure Biopharma Technology Co., Ltd, Guangzhou, China.

Clinical adverse events and efficacy (5.0x10 ⁷ /kg TCR-T cells, n=6).					
Treatment-Related Adverse Events (TRAEs)				Efficacy	
	All grades	Grade 3	Grade 4		
Leukopenia	6 (100%)	2 (33.3%)	0	Complete response (CR)	0 (0)
Fever	5 (83.3%)	2 (33.3%)	0	Partial response (PR)	2 (33.3%)
Chills	3 (50%)	0	0	Stable disease (SD)	3 (50%)
Anemia	4 (66.7%)	0	0	Progressive disease (PD)	1 (16.7%)
Vomiting	2 (33.3%)	0	0	Disease control rate (DCR)	6 (100%)
Hypoalbuminemia	3 (50%)	0	0		
Hypokalemia	1 (16.7%)	0	0		
Hyponatremia	2 (33.3%)	0	0		

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Poster Session

A phase II study of lenvatinib plus pembrolizumab in patients with progressive, recurrent/metastatic adenoid cystic carcinoma. *First Author: Maliheh Mohamadpour, MSKCC, New York, NY*

Background: Recurrent/metastatic adenoid cystic carcinoma (R/M ACC) is a rare salivary gland cancer (SGC) without standard treatments. The multitargeted, antiangiogenic kinase inhibitor lenvatinib (len) has activity in R/M ACC, but immune checkpoint inhibitor (ICI) therapies lack efficacy. Hypothesizing that VEGFR inhibition can enhance ICI-induced responses, we conducted a phase II trial evaluating len plus the programmed death-1 (PD-1) inhibitor pembrolizumab (pem) in two R/M SGC cohorts: ACC and non-ACC. Here we report results from the completed ACC cohort. **Methods:** Patients (Pts) with R/M ACC were enrolled. RECIST v1.1 measurable disease and evidence of progression on imaging performed within 6 months of enrollment were required; any number of prior therapies was allowed. Pts were treated with len 20 mg orally daily and pem 200 mg intravenously every 3 weeks (21-day cycles). The primary objective was to evaluate best overall response rate (ORR), seeking an ORR improvement with len+pem from 15% (previously reported with len alone) to 35%. In the first stage, > 3 confirmed complete and partial responses (cCRs+cPRs) were required among 17 pts to continue to the second stage; > 8 responses among 32 total pts would have been considered positive (1-sided alpha 0.1, power 0.9). Secondary objectives included evaluating progression-free survival (PFS) and safety/tolerability per CTCAE v5.0 criteria. **Results:** 17 R/M ACC pts were enrolled and evaluable for the primary objective. One pt had a cPR for an ORR of 6%, failing to meet the rule for progression to the second stage. Thirteen (76%) pts had stable disease and 2 (12%) progression of disease as best response; 1 pt did not have response assessed. Thirteen (76%) pts experienced some degree of regression in RECIST target lesions (TLs; -1.9% to -42.8%), including 5 (29%) with > -20% regression. Eleven (65%) pts were progression-free for > 24 weeks. Twelve (71%) pts experienced at least one > Grade 3 adverse event related to study treatment. Sixteen pts had at least one treatment interruption or len dose reduction; 2 pts received only 1 cycle of therapy. Five pts were treated beyond first progression without observation of subsequent response. Quality of life data and correlative tissue studies are ongoing. **Conclusions:** The trial failed to demonstrate that len+pem produces a greater ORR in patients with R/M ACC than what was previously reported with len alone. Further investigation into the biology mediating ICI-resistance and development of novel approaches to augment the efficacy of immune-based therapies in ACC are needed. (Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA provided lenvatinib and pembrolizumab for the study.) Clinical trial information: NCT04209660. Research Sponsor: Merck Sharp & Dohme Corp and Eisai.

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Poster Session

Low-dose fractionated radiotherapy combined with neoadjuvant chemotherapy for T3-4 nasopharyngeal carcinoma patients: Preliminary results of a phase II randomized controlled trial. *First Author: Mei Feng, Department of Radiation Oncology, Sichuan Cancer Hospital and Institution, Sichuan Cancer Center, School of Medicine, University of Electronic Science and Technology of China, Sichuan, China*

Background: Over 70% of NPC patients were local advanced NPC (LANPC). The 5-year local recurrence-free survival rate is only 70% in T3-4 patients. Neoadjuvant chemotherapy (NACT) followed with concurrent chemoradiotherapy (CCRT) was recommended for LANPC patients. Low-dose fractionated radiotherapy (LDFRT), which is < 100cGy, induces enhanced cell killing by the hyper-radiation sensitivity phenomenon and potentiates effects of chemotherapy. The synergy of LDFRT and NACT has not been used in the clinical practice and few studies focused on it. A single arm study found the ORR of primary site was improved to 90% for head and neck squamous carcinoma patients treated with LDFRT and NACT. Our previous study found the ORR of lymph nodes was higher in LDFRT group for high-risk LANPC patients. However, another study showed there was no significant difference between LDFRT and control group for LANPC patients. So, we aimed to investigate the potential efficacy of this novel neoadjuvant therapy for T3-4 NPC patients. **Methods:** 60 pathological confirmed T3-4 (UICC/AJCC8th) NPC patients were prospectively enrolled in our study. They were randomly assigned to two groups. For the LDFRT group, the patients received 3 cycles of NACT (docetaxel 75mg/m² D1, cisplatin 80mg/m² D1) with LDFRT, and followed with CCRT. LDFRT was delivered as 50cGy per fraction twice a day to primary site on D1,2 for each cycle of NACT. The patients in the control group only received NACT and followed with CCRT. All the patients underwent IGRT. RECIST criteria and CTCAE 5.0 was used to evaluate the ORR and toxicity at post-NACT and the completion of CCRT. **Results:** from Feb 2022 to Dec 2022, 60 T3-4 NPC patients were included, and 30 patients for each group. For the primary site, the median volume reduction rate and the ORR after NACT was significantly improved in LDFRT group (69.27% vs 40.10%, p< 0.001; 93.33% vs 73.33%, p=0.038). For the median volume reduction rate of primary site and lymph node, it was also obviously improved in LDFRT group (86.59% vs 55.43%, p< 0.001). Though there was a tendency of ORR improvement in LDFRT group, but no significant difference (96.67% vs 83.33%, p=0.195). After the completion of CCRT, the median volume reduction rate of primary site had an increased tendency in LDFRT group (96.16% vs 88.3%, p=0.065), but the ORR had no statistical significance (LDFRT group: CR 45.8%, PR 54.2%; control group: CR 37.5%, PR 62.5%). For the toxicity, the incidence of grade 3-4 adverse events had no difference between two groups (p=0.786). No grade 5 adverse events occurred. **Conclusions:** LDFRT combined with NACT could obviously improve the median volume reduction rate and ORR of primary tumor for T3-4 NPC patients, and the toxicity was similar and tolerable. The novel treatment could be a promising strategy to improve treatment response, and needed to be confirmed further. Clinical trial information: NCT05503914. Research Sponsor: 2022YFS0047.

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Poster Session

Phase I/II trial of durvalumab plus tremelimumab and stereotactic body radiotherapy for metastatic head and neck carcinoma: Final results. *First Author: Houda Bahig, Centre Hospitalier de l'Université de Montréal, Montreal, QC, Canada*

Background: Anti-PD-1/PD-L1 is now part of first line therapy in metastatic head and neck squamous cell carcinoma (HNSCC). Stereotactic radiotherapy (SBRT) to metastatic lesions can reduce tumor burden and could be immune-stimulatory. The combination of SBRT with dual-checkpoint blockade with Durvalumab (D, anti-PD-L1) and Tremelimumab (T, anti-CTLA-4) has not previously been tested in HNSCC. We report on the safety and efficacy of this triple treatment combination (TTC) consisting of SBRT sandwiched between cycles of D and T in oligometastatic HNSCC. **Methods:** This is a phase I/II single arm multi-institutional study powered for 35 patients with oligometastatic HNSCC (2-10 lesions) (NCT03283605). D (1500 mg) and T (75 mg) were given for 4 monthly cycles, followed by monthly D for 8 monthly cycles. SBRT to 2-5 lesions was administered during cycle 2. The safety of the TTC was the primary endpoint of the phase I and was evaluated through assessment of Grade 3-5 TTC-related adverse events (AE), based on CTCAE (v 4.03). The primary endpoint of the phase II portion was 6-month progression free survival (PFS), with a predetermined 6-month PFS (6moPFS) rate greater than 27% considered as a positive signal to conduct further research on this combination. **Results:** A total of 33 evaluable patients were recruited (study accrual was interrupted by the COVID pandemic). The table describes patients' characteristics. Patients had received 1, 2 and 3 prior systemic therapy lines in 48%, 21% and 9% of the cases, including 6 (18%) patients who had received prior anti-PD-L1 or anti-CTLA-4 therapies. The median prescribed and maximum SBRT doses were 45 Gy (range: 18-50) and 52.3 Gy (range: 28.1-69) in 3-5 fractions, respectively. Fourteen patients (42%) had Grade ≥ 3 AE attributable to D and T. Only 1 patient developed Grade ≥ 3 AE attributable to SBRT. This patient, who had mucosal radionecrosis after re-irradiation and refused surgical debridement and flap reconstruction, specifically developed 2 Grade 3, 1 Grade 4 and 1 Grade 5 AE. Our primary efficacy endpoint, 6moPFS, was 69.7% (95% CI: 55.6-87.3). Median PFS was 11.9 months (6.94-14.5) and median OS was 25.1 months (17.9-28.4). Rates of complete response, partial response, stable disease and progressive disease were 9%, 21%, 33% and 12%, respectively, with 8 (24%) patients with no evaluable non-SBRT treated lesion. **Conclusions:** The addition of SBRT to dual-checkpoint inhibition led to 1 (3%) additional patient developing severe AE. Best response rates were encouraging. Our primary efficacy outcome, 6mo PFS was attained and was higher than what was expected in this patient population. Clinical trial information: NCT03283605. Research Sponsor: Astra Zeneca.

Covariate.	n=33	
Gender (N, %)	Female : Male	5 (15%) : 28 (85%)
Age	Median (Min, Max)	63 (42, 84)
Rx lines prior to entering trial (N, %)	0	7 (21%)
	1	16 (48%)
	2	7 (21%)
	3	3 (9%)
Total number of lesions	Median (Min, Max)	4 (2,8)
SBRT treated lesions (N, %)	1	1
	2	21 (63%)
	3	7 (21%)
	4	2 (6%)
	5	1

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Poster Session

Safety and efficacy of time restricted eating (TRE) in improving response to immunotherapy in patients with head and neck cancer (HNSCC). *First Author: Humaira Sarfraz, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL*

Background: Advanced head and neck cancer continues to have very poor prognosis. Only a fraction of patients respond to immune checkpoint blocker therapy (ICB), with no effective treatment options for non-responders. Gut microbiome composition and diversity have been associated with response to ICB in many cancers including HNSCC. We, therefore hypothesized that modulation of gut microbiota may improve response to ICB. Time restricted eating represents an attractive strategy to favorably alter the microbiome and improve ICB responses. We conducted a phase I/II nonrandomized study to evaluate safety, feasibility and efficacy of TRE in improving response rates in treatment naïve metastatic HNSCC patients receiving single agent ICB. **Methods:** TRE is a form of circadian aligned nightly fast of 14 hours without reduction in calories. Patients were assigned to TRE vs control in 1:2 ratio, with first response evaluation at 12+/- 3 weeks as end point. Compliance to TRE was monitored via an app ("my circadian app") and daily food logs. Blood and stool samples were collected at therapy initiation, at 1st response assessment and at 6 months. We evaluated stool metagenomics, untargeted stool/plasma metabolomics and serum cytokines as correlatives. We focused on microbial metabolites including indoles and short chain fatty acids (SCFA), which are potent aryl hydrocarbon receptor agonist and immunosuppressive. We also evaluated serum cytokines associated with insulin signaling pathways. **Results:** A total of 43 HNSCC patients receiving single agent pembrolizumab were accrued, 15 in the TRE arm and 28 in control arm. TRE was well tolerated without any study dropouts, weight loss or any adverse events attributable to the intervention. TRE was associated with significant improvement in disease control rate (DCR) at 3 months and at 6 months (3 month DCR 85% in TRE vs 50% in the control arm, p<0.0001, 6 month DCR 64% in TRE vs 39% in control arm, p=0.0004). Responders in both TRE and control arm had lower relative abundance of microbial immunosuppressive indole metabolites, butyric acid (NR vs R: 0.67 vs 0.58, p=0.05) and IGF1 (NR vs R: 0.42 vs 0.39, p=0.02). TRE led to a similar change in microbial metabolites including decrease in abundance of 5 Hydroxyindole acetic acid, Indole 3 acetic acid (IAA), Indole Carboxaldehyde, Indole acrylic acid, butyric acid (control vs TRE: 0.68 vs 0.58, p=0.03) and IGF1 (control vs TRE: 0.4 vs 0.3, p=0.03.) **Conclusions:** We report a novel phase I/II study of TRE in HNSCC patients and demonstrate excellent safety, feasibility and marked improvement in efficacy of ICB. The effect of TRE may be mediated via changes in microbial metabolome and insulin signaling pathways. TRE represents an attractive and safe strategy to improve treatment responses to ICB and needs to be explored in phase III expansion studies. Humaira Sarfraz, MD, and Shahla Bari, MD, both 1st authors/equal contributors. Clinical trial information: NCT05083416. Research Sponsor: ACSIRG; Moffitt Advent Health Collaborative Award.

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Poster Session

Association of pretreatment lymphocyte-monocyte ratio with survival outcome in patients with head and neck cancer treated with chemoradiation.
First Author: Brian Yu, Jacobs School of Medicine and Biomedical Sciences, Buffalo, NY

Background: Lymphocyte-monocyte ratio (LMR) from peripheral blood has been suggested as a biomarker to assess the extent of inflammation in several solid malignancies. However, the role of LMR as a prognostic factor in head and neck cancer (HNC) was unclear in several meta-analyses, and there is a paucity of literature including patients in North America. We performed an observational cohort study to evaluate the association of pre-radiation LMR with survival outcomes in North American patients with HNC. **Methods:** A single-institution database was queried for patients with non-metastatic HNC who underwent curative-intent definitive chemoradiation from 6/2007 to 4/2021 at the Roswell Park Comprehensive Cancer Center. Patients were excluded if they underwent induction chemotherapy or postoperative radiation. Primary endpoints were overall survival (OS) and cancer-specific survival (CSS). The association of LMR with OS and CSS was examined using nonlinear Cox proportional hazard model using restricted cubic splines (RCS), Cox multivariable analysis (MVA), and Kaplan-Meier method. LMR was stratified into high and low based on its median. Logistic MVA was performed to identify variables associated with low LMR. Propensity scored matching was used to reduce selection bias. Subgroup analyses were performed among those with available human papillomavirus (HPV) status. **Results:** A total of 476 patients (391 male [82.1%], median [interquartile range] age, 61 [55-67] years) met our criteria. Median follow up was 45.3 months (interquartile range 22.8-74.0). The nonlinear Cox regression model using RCS showed that low LMR was associated with worse OS and CSS in a continuous fashion without plateau and crossed the hazard ratio of 1 at LMR 3.4 for both OS and CSS. On Cox MVA, higher LMR as a continuous variable was associated with improved OS (adjusted hazard ratio [aHR] 0.90, 95% confidence interval [CI] 0.82-1.00, $p = 0.04$) and CSS (aHR 0.81, 95% CI 0.70-0.94, $p = 0.005$). The median value of LMR was 3.8. On logistic MVA, patients with other racial background (adjusted odds ratio [aOR] 0.85, 95% CI 0.74-0.97, $p = 0.02$) and positive HPV status (aOR 0.82, 95% CI 0.72-0.94, $p = 0.005$) were less likely to have low LMR. Higher T staging was associated with low LMR (aOR 1.15, 95% CI 1.04-1.27, $p = 0.005$). A total of 186 pairs were matched with well balanced baseline characteristics. LMR lower than 3.8 remained associated with worse OS (HR 1.60, 95% CI 1.13-2.28, $p = 0.009$) and CSS (HR 1.69, 95% CI 1.07-2.67, $p = 0.03$). In the subgroup of 319 patients (67.0%) with available HPV data, LMR status was not associated with both OS and CSS regardless of HPV status. **Conclusions:** Low LMR was associated with worse OS and CSS. Low LMR was also associated with higher T staging, negative HPV status, and White race. Further studies are warranted to evaluate the role of such prognostic marker to tailor interventions. Research Sponsor: None.

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Poster Session

Association between locoregional failure and NFE2L2/KEAP1/CUL3 pathway mutations in NRG/RTOG 9512: A randomized trial of hyperfractionation vs. conventional fractionation in T2N0 glottic squamous cell carcinoma (SCC).
First Author: Li Guan, Stanford University, Stanford, CA

Background: Radiotherapy (RT) is the primary treatment for patients with T2N0 glottic SCC. ~30% of these patients experience locoregional relapse despite dose escalation. Mutations in the NFE2L2/KEAP1/CUL3 pathway have been linked to radioresistance preclinically and in small retrospective studies. We tested the hypothesis that patients with T2 glottic SCCs having these mutations would show radioresistance and more local (LF) and locoregional failures (LRF) when treated with RT compared to those without, using samples from a phase III trial. **Methods:** Of 250 randomized patients with T2N0 glottic SCC receiving definitive RT in RTOG 9512, 119 had available biospecimens that were subjected to amplicon-based next generation sequencing (appropriate to low-input DNA from biopsy specimens) to assess for presence of NFE2L2/KEAP1/CUL3 mutations without regard to outcomes. The association between binary mutation status and LF, LRF, disease-free survival (DFS), and overall survival (OS) was assessed using (cause-specific) Cox models (2-sided alpha of 0.05). LR/LRF rates were estimated by the cumulative incidence method and DFS/OS rates by the Kaplan-Meier method. **Results:** Nineteen of 119 patients (16.0%; 95% confidence interval [CI] 9.4, 22.6) had mutations in the NFE2L2/KEAP1/CUL3 pathway. Patient and tumor characteristics were similar between those with and without mutation. There were 32 LF, 37 LRF, and 80 DFS events, and 52 deaths. Patients with mutation compared to those without had significantly higher LF and LRF rates (Table). Median DFS was 0.9 years (95% CI 0.4, not reached) for the mutation group compared to 4.2 years (95% CI 3.2, 6.4) for those without. The hazard ratio (HR) for DFS was significantly higher for the mutated compared to the non-mutated group in the first 2 years after randomization but declined thereafter (Table), likely due to limited events after 2 years in the mutation group. There was no significant difference in OS between the two groups (HR = 0.76; 95% CI 0.35, 1.6; $p = 0.48$). **Conclusions:** NFE2L2/KEAP1/CUL3 pathway mutations may predict radiation treatment failure in T2N0 glottic cancer. They may also be a prognostic biomarker for DFS, but the current evidence supports the harmful effect of these mutations only during the first 2 years from randomization. Clinical trial information: NCT00002727. Research Sponsor: This project was supported by grants UG1CA189867 (NCORP), U10CA180868 (NRG Oncology Operations), U10CA180822 (NRG Oncology SDMC), U24CA196067 (NRG Specimen Bank), CTEP from the National Cancer Institute (NCI).

		With Mutation	Without Mutation
LF	2 yr. rate (95% CI)	47.4% (23.5, 68.0)	17.1% (10.5, 25.2)
	HR*, p-value	3.05 (95% CI 1.35, 6.86),	$p = 0.0071$
LRF	2 yr. rate (95% CI)	57.9% (32.0, 77.0)	20.2% (12.9, 28.6)
	HR*, p-value	3.40 (95% CI 1.61, 7.18),	$p = 0.0014$
DFS	2 yr. rate (95% CI)	36.8% (15.2, 58.5)	67.7% (58.5, 76.9)
	HR*, p-value	2.66 (95% CI 1.36, 5.20),	$p = 0.0044$ (≤ 2 years) 0.08 (95% CI < 0.01, 1.42), $p = 0.0851$ (> 2 years)

*Based on multivariable Cox model with treatment arm, age, race, KPS, primary site and T stage.

6053

Poster Session

Evaluation of tumor mutation burden (TMB) in tumor (tDNA) and plasma cell free DNA (cfDNA) in patients (pts) with recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC) treated with a combination of cetuximab and nivolumab (C+N).
First Author: Christine H. Chung, Moffitt Cancer Center, Tampa, FL

Background: High TMB is associated with immune checkpoint inhibitor (ICI) response in many solid tumors. However, obtaining sufficient tumor specimens for testing in a routine clinical setting could be a challenge. We evaluated TMB from whole-exome sequencing (WES) of cfDNA as a surrogate for tDNA TMB in R/M HNSCC pts treated with C+N. **Methods:** Archived formalin fixed paraffin embedded tumors, serially collected plasma (pre-treatment, on-treatment, and time of disease progression/end of treatment), peripheral mononuclear blood cells, and clinical data were obtained from R/M HNSCC pts treated with C+N from a completed clinical trial (NCT03370276). Nucleic acids were extracted using AllPrep DNA/RNA Mini Kit (Qiagen). Libraries were constructed using KAPA HyperPrep Kit with Library Amplification (KK8504) and IDT's duplex UMI adapters. Hybridization and capture were performed using IDT's XGen hybridization kit. Whole exome sequencing was performed using Illumina NovaSeq S4 flowcells (paired 151bp runs). Data preprocessing including point mutation calling, filtering, CNV calling, and purity and ploidy estimation were performed using the Getz Lab CGA WES Characterization pipeline. TMB for each sample was calculated based on the number of mutations with cancer cell fraction > 0.75 as determined by ABSOLUTE and normalized to the 35Mb targeted for exome capture. **Results:** A total of 88 tDNA, 226 cfDNA, and 30 normal DNA (nDNA) from 82 pts were sequenced. To date, sequencing data from 13 matched tDNA/cfDNA/nDNA samples and 34 matched cfDNA/nDNA samples with sufficient tumor purity were available for analyses. The median TMB was 2.4 mut/Mb (range 0.46-17.5) in tDNA and 1.8 mut/Mb (range 1.1-12.6) in cfDNA. There was a high correlation between tDNA/cfDNA pairs in TMB ($r = 0.826$, $p = 1.5 \times 10^{-16}$, Pearson correlation). The median TMBs in tDNA and cfDNA obtained at different time points or treatment course did not differ significantly in 22 patients with at least two cfDNA timepoints ($p = 0.26$ paired t-test of log-transformed TMB). There was no difference between responder (R) vs. non-responder (NR) in cfDNA TMBs (two-sample t-test $p = 0.7$ between 2 R and 12 NR) and tDNA TMBs (two-sample t-test $p = 0.25$ between 6 R and 21 NR). However, tDNA TMB was higher in R compared NR in a subset of pts who did not have prior treatment with ICI (two-sample t-test $p = 0.05$ between 5 R and 2 NR). **Conclusions:** TMB in tDNA and cfDNA is highly correlated and suggests the possible use as a surrogate marker for tTMB. High TMB in cfDNA derived from ICI-naïve patients appears to have a prognostic value. Further evaluation is warranted to determine the role of cfDNA TMB as a biomarker of ICI response. Research Sponsor: Florida Health Department; IBM.

6055

Poster Session

A proteomic signature associated with prognosis in HPV-related locally advanced oropharyngeal squamous cell carcinoma (LA-OPSCC).
First Author: Jia (Jenny) Liu, The Kinghorn Cancer Centre, St Vincent's Hospital, Darlinghurst, NSW, Australia

Background: Although HPV-related LA-OPSCC is associated with better prognosis than HPV-negative disease, ~30% of cases relapse despite curative-intent chemoradiotherapy. New prognostic biomarkers are needed to rationalise curative-intent treatment without compromising efficacy. We aimed to develop a proteomic signature associated with risk of recurrence from diagnostic biopsies of patients with HPV-positive OPSCC. **Methods:** We analysed 139 formalin fixed paraffin embedded archival core biopsy specimens from 124 patients with HPV-related (p16 IHC positive) T1-4N0-3M0 LA-OPSCC tumours. All patients were treated with definitive chemoradiotherapy at the Princess Alexandra Hospital (Brisbane, Australia) between 2007-2019. The cohort included 50 patients with recurrence less than five years from diagnosis and 74 age/performance-status matched patients with no recurrence. Proteomic analysis was performed utilizing data-independent acquisition mass spectrometry (DIA-MS). A proteomic prognostic signature associated with recurrence free survival (RFS) at five years was the primary endpoint of interest. It was developed using a computational pipeline comprising an initial univariate Cox model step, followed by multiple runs of multivariate Cox models with Least Absolute Shrinkage and Selection Operator (LASSO) regularization, and then a final step of recursive feature selection. **Results:** A total of 7,597 proteins were quantified and 665 were differentially expressed proteins between tumour and normal adjacent tissues. There were 5,199 proteins remaining in the tumour samples after filtering. RFS was significantly (q -value < 0.05) associated with 252 proteins, whose functions are enriched in adaptive and innate immunity and MAPK6/MAPK4 signalling pathways. A 16-protein signature associated with RFS stratified patients into low, intermediate, or high-risk groups (C -index = 0.885, $p < 0.0001$). The 16-protein signature outperformed clinico-pathological covariates including age, stage, ECOG and smoking history with the highest area under the receiver operating characteristic curve (AUROC 0.95). **Conclusions:** DIA-MS-based proteomics on core biopsies can be used to risk stratify HPV-related OPSCC patients. A 16-protein signature associated with RFS was successfully identified as a basis for future studies. Validation of this proteomic prognostic signature in independent cohorts is required and may be used to inform future clinical trials to better tailor upfront therapy. Research Sponsor: Australian Cancer Research Foundation, Cancer Institute New South Wales (NSW) Cancer Council NSW (IG 18-01); Ian Potter Foundation, NHMRC; NSW Ministry of Health (CMP-01), ropan Union grant (GNT1170739, a companion grant to support the European Commission's Horizon 2020 Program, H2020-SC1-DTH-2018-1; The University of Sydney, Queensland Head and Neck Cancer Centre.

6056

Poster Session

Single-cell RNA and T cell receptor (TCR) sequencing in patients with HPV-positive head and neck squamous cell carcinoma (HNSCC) after induction CTLA4 and PD-1 immune checkpoint blockade (ICB). *First Author: Xianli Jiang, Department of Bioinformatics and Computational Biology, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Combination CTLA-4 and PD-1 ICB results in durable responses in patients with recurrent and metastatic HNSCC and therefore justifies further investigation in the induction or neoadjuvant setting. **Methods:** We investigated features of the tumor immune microenvironment (TIME) associated with MHR after induction CTLA-4 and PD-1 ICB in patients with newly diagnosed HPV-positive HNSCC. Tumor samples were collected at baseline and on treatment from 31 patients enrolled in a phase 2 trial of a 6-week cycle of CTLA-4 and PD-1 ICB induction followed by dose/volume-adapted IMRT (50-66Gy) concurrent with cycle 2. Tumors were evaluated for histological response and single-cell RNA sequencing (scRNA-seq) and scTCR-seq were performed on the 10X genomics platform. After stringent clustering and annotation of scRNA-seq data, 76,319 CD8⁺ and 78,622 CD4⁺ T cells with paired TCR sequence data were evaluable for transcriptomic, TCR repertoire and clonotype differentiation analysis. **Results:** Percent reduction in tumor viability on histology correlated significantly with reduction in tumor cell proportion in scRNA-seq data ($R^2 = 0.7$). Thirteen (48%) of 27 patients with paired samples (missing data due to COVID) had MHR, defined as $\leq 10\%$ residual tumor viability on ICB treatment. Through TCR tracing, over 100 T cell clonotypes that expanded significantly ($p < 0.05$, Fisher's exact) post-ICB were identified. Highly expanded clonotypes resided mainly in exhausted CD8⁺ T cell clusters and exhibited a tissue resident memory (TRM) phenotype. Examination of their functional states revealed a variety of T cell modulatory trajectories, including reverse transition from exhausted to less exhausted states and from memory to functional states. When compared to patients without MHR, those with MHR had significantly higher ICB-induced TCR clonotype expansion ($p = 0.025$, Wilcoxon), reductions of activated Tregs ($p = 0.003$, Wilcoxon) and terminally exhausted CD8⁺ T cells ($p = 0.003$, Wilcoxon), and increase of polyfunctional CD8⁺ T cells ($p = 0.014$, Wilcoxon). A lasso regression model associated T cell expansion, basal 7-gene TRM and 5-gene effector scores, and on-treatment proliferation score and effector cell proportion with percent reduction in tumor viability ($R^2 = 0.66$). **Conclusions:** In HPV-HNSCC, induction CTLA4 and PD1 ICB lead to extensive reinvigoration of CD8⁺ T cell clonotypes with both an exhausted and TRM phenotype, revealing a high degree of plasticity of distinct T cell clones. Paired RNA and TCR profiling facilitated identification of potentially tumor reactive and ICB-responsive T cells and clonotypes and identified several TIME features associated with tumor cell death. Clinical trial information: NCT03799445. Research Sponsor: Cancer Prevention and Research Institute of Texas.

6058

Poster Session

Association of HPV genotype and phylogenic clade with oropharyngeal cancer outcomes. *First Author: Michael Wotman, MD Anderson Cancer Center, Houston, TX*

Background: Human papillomavirus (HPV) is a causative agent of oropharyngeal squamous cell carcinoma (HPVOPC). There are multiple different HPV genotypes based on variations in the nucleotide sequence of the L1 capsid, with HPV16 being most common in HPVOPC (85%). HPV genotypes can be further classified into phylogenic clades, including alpha-9 (A9) and alpha-7 (A7). HPVOPC is associated with a more favorable prognosis than HPV-negative disease, but the impact of specific HPV genotype and phylogenic clade on patient outcomes is not well understood and has profound implications for de-escalation studies in HPVOPC. **Methods:** A retrospective cohort study was conducted at a large multicenter health system. Patients diagnosed with non-metastatic HPVOPC or unknown primary from 2012-2021 and treated with curative intent were included. Low-risk HPV types (6, 11, etc) and local recurrences were excluded. HPV molecular typing was prospectively performed according to institutional protocol. Cox regressions were used to measure the effect of HPV genotype (16 versus non-16) on overall survival (OS) and event-free survival (EFS). Gender, smoking status, alcohol use, ECOG performance status, T stage, N stage, and subsite (oropharynx versus known primary) were covariates. A secondary survival analysis according to high-risk HPV clade (A9 versus A7) was also performed. **Results:** The total cohort included 520 patients, the majority of whom were HPV16 (86.9%, $n = 452$), A9 clade (97.1%, $n = 505$), oropharynx primary (94.8%, $n = 493$), male (86.9%, $n = 452$), white (72.5%, $n = 377$), non-Hispanic (74.2%, $n = 386$), non-active smokers (88.3%, $n = 459$), ECOG 0 (75.6%, $n = 393$), and N2 stage (65.2%, $n = 339$). The most common non-16 HPV genotypes were 18 ($n = 7$), 33 ($n = 21$), and 35 ($n = 29$). HPV genotype was not associated with OS (HR = 1.64, 95% CI 0.85-3.16, $p = 0.14$) or EFS (HR = 1.15, 95% CI 0.64-2.07, $p = 0.65$). A7 clade was associated with a worse OS compared to A9 in the univariate analysis (HR = 3.43, 95% CI 1.07-10.97, $p = 0.04$), but not in the multivariate analysis (HR = 1.67, 95% CI 0.45-6.17, $p = 0.44$). Finally, HPV clade was not associated with EFS (HR = 1.38, 95% CI 0.34-5.60, $p = 0.66$). **Conclusions:** While HPV genotype was not associated with survival differences in patients with HPVOPC, HPV A7 clade only predicted worse OS in univariate analysis. Although the total cohort size was large, this analysis was limited by small numbers of subjects with non-16 HPV genotypes and non-A9 clade, which is reflective of the predominance of HPV16 in HPVOPC. Thus, a pooled multicenter collaboration is needed to further address this question. Moreover, future studies should investigate whether outcomes may be related to intratypic HPV16 variants that affect oncoprotein function and/or immunogenicity. Detection of a subgroup of HPVOPC with possible inferior outcomes has important implications for studying treatment de-escalation in HPVOPC. Research Sponsor: Philanthropy.

6057

Poster Session

Introduction of E-Score: A gene expression score to characterize immunogenic versus oncogenic HPV expression in HNSCC. *First Author: Bailey Fabiny Garb, University of Michigan, Ann Arbor, MI*

Background: Human Papillomavirus (HPV) integration in the human genome occurs in a majority of HPV(+) head and neck squamous cell carcinomas (HNSCC), with direct and indirect effects on host gene expression and tumorigenesis. Although previous studies showed that HPV integration in HNSCC is overrepresented in genes often somatically mutated in head and neck, lung, and urogenital cancers, reports are mixed for whether patients with HPV integration have worse clinical outcomes. These disparate results may be due to differences in how integration is defined. Integration can often lead to partial loss of the viral genome (e.g. HPV genes E1, E2, or E5) with retention of the oncogenes E6 and E7, which led to a low E2/E7 expression ratio being used as a biomarker for integration. Conversely, others have used the direct detection of DNA or RNA HPV-human breakpoints to identify tumors harboring integrated HPV. HPV integration and the retention or deletion of HPV genes can dramatically change the expression of HPV genes, and we hypothesize it also affects the host immune response. Hypothesis: Loss of non-oncogenic HPV genes relative to E6 and E7 levels reduces immunogenicity, leading to weakened immune cell infiltration and worse clinical outcomes. **Methods:** Bulk RNA sequencing data from HPV(+) HNSCC tumors ($n = 136$) was used to characterize the differences in retention or loss of HPV genes and calculate the E-Score as the sum of the logCPM of HPV genes E1, E2, E4, and E5 relative to E7. Cell type deconvolution was performed using ComBat to correct for batch effects, and CIBERSORTx to quantify cell type proportions within the tumor samples. Kaplan-Meier estimates of recurrence and overall survival (OS) were calculated, and Cox proportional hazards tests with covariates were used to test for association with recurrence and OS. To test the correlation between immune cell type inferred proportions and E-Score, T-Tests were performed between samples with high and low E-scores. **Results:** Low E-Score was significantly associated with recurrence ($p = 0.012$) but not with OS ($p = 0.39$) in the multivariate model accounting for age, tumor stage (AJCC8), smoking status, drinking status, BMI, marital status, and molecular tumor subtype (defined as IMU or KRT). For integration positive samples ($n = 66$), higher E-Score, suggesting lower rates of HPV gene loss, was correlated with higher percentages of dendritic cells ($p = 0.044$), macrophages ($p = 0.021$), and CD8⁺ T Cells ($p = 0.024$), but not CD4⁺ T cells ($p = 0.14$). This significance did not hold when looking at integration negative samples. **Conclusions:** These results suggest that HPV+ HNSCC patients with a loss of E1, E2, E4 and E5 tend to have less immune cell infiltration and are more likely to have recurrence. We conclude that E-Score is a potential prognostic biomarker of recurrence in HPV+ HNSCC and potential predictive biomarker for immunotherapy. Research Sponsor: U.S. National Institutes of Health.

6059

Poster Session

Spatial genomics to reveal an immunosuppressive tumor microenvironment after chemoradiation in head and neck cancer patients. *First Author: Jennifer Hsing Choe, Duke University Medical Center/Duke Cancer Institute, Durham, NC*

Background: Although chemoradiotherapy (CRT) remains the cornerstone of management for locoregionally advanced head and neck squamous cell carcinomas (HNSCC), recurrence occurs in ~50% of patients. We sought to characterize the impact of CRT on the tumor microenvironment (TME) and identify factors associated with progression. Emerging spatial biology technologies, such as NanoString GeoMx Digital Spatial Profiler (DSP), enable spatially defined whole-transcriptomic profiling of cells along the tumor-stromal interface in tumor biopsies to resolve immune cell identities, activation states and signaling pathways in adjacent tumor cells. We used a multimodal approach including immunohistochemistry (IHC), bulk tumor gene expression and spatial genomics to characterize paired pre- and post-CRT tumor samples from HNSCC patients. **Methods:** 20 patients with locoregionally advanced HNSCC who had undergone curative intent CRT and developed subsequent recurrence requiring salvage surgery from June 14, 2010 to June 14, 2020 were retrospectively identified at Duke University Medical Center. Matched formalin-fixed paraffin embedded tumor specimens collected prior to CRT and at salvage surgery were compared via IHC for markers of immune infiltration and PDL1 expression, bulk tumor whole transcriptomic profiling, and spatial transcriptomic analysis of tumor and stroma using DSP were further examined in "early" progressors (< 6 months after CRT) and "late" progressors (≥ 6 months after CRT). **Results:** IHC analyses demonstrated significant reductions in T-cell immune populations (total CD3⁺, CD8⁺, 4-1BB⁺ cell density [$p < 0.001$]) after CRT. PDL1⁺ expression was similar before and after CRT. Neither T-cell infiltrate nor tumor PDL1 levels at surgery were associated with progression. Bulk tumor gene expression analysis demonstrated that macrophage and fibroblast markers were increased post-CRT. In early progressors, molecular dissection of the tumor-stromal interface using DSP expression profiling revealed macrophage associated genes (*CD68*, *MRC1/CD206*, *CD163*, *F13A1*) at salvage surgery had a more pronounced increase in macrophage markers in stroma with enriched M2 genes compared to late progressors. **Conclusions:** Integrated spatial analysis with high resolution transcriptomics and IHC suggest CRT induces an immunosuppressive environment characterized by decreased T-cell infiltration and an influx of putative immunosuppressive macrophages. We hypothesize that tumor associated macrophages and/or fibroblasts may contribute to immunosuppression due to "reprogramming" of the TME after CRT. This exploratory study suggests that patients with progressive disease after chemoradiation may benefit from additional immunoregulatory therapies that ameliorate the immunosuppressive TME. These findings will be further validated in a larger cohort of patients. Research Sponsor: Genmab US.

6060

Poster Session

Clinical validity of TTMV-HPV DNA liquid biopsies for the diagnosis and surveillance of HPV-associated oropharyngeal carcinoma. *First Author: Scott A. Roof, Icahn School of Medicine at Mount Sinai, New York, NY*

Background: While there are several HPV biomarker assays, a commercially available assay evaluating tumor tissue modified viral DNA (TTMV-HPV DNA) (NavDx, Naveris Inc, Natick, MA) has shown impressive results in clinical trials and small cohort studies. Our aim was to establish the clinical efficacy of plasma TTMV-HPV DNA testing in the diagnosis and surveillance of HPV-associated OPSCC in a contemporary, real-world clinical setting. **Methods:** In this retrospective analysis, we evaluated the accuracy of the TTMV-HPV DNA assay in detecting HPVOPSCC in the diagnostic (pre-treatment) and surveillance phases of care between April 2020 and October 2022. For the diagnostic cohort, patients with OPSCC and at least one TTMV-HPV DNA measurement prior to initiation of primary therapy were included in the analysis. For the surveillance cohort, all TTMV-HPV DNA tests performed 3 months after completion of primary therapy for pathologically confirmed HPV-associated OPSCC were evaluated, regardless of pre-treatment TTMV-HPV DNA testing. Patients with suspected recurrence, but without pathologic confirmation, were excluded. HPV status was defined utilizing positive p16 staining on immunohistochemistry (93.2% diagnosis; 97.9% surveillance) or HPV polymerase chain reaction/in situ hybridization (79.6% diagnosis; 89.7% surveillance). **Results:** In the diagnostic cohort, 163 patients were included. The cohort included mostly men (87%) with median age 63, of which 93.3% had HPVOPSCC versus 6.7% had HPV negative OPSCC. The sensitivity in pre-treatment diagnosis was 91.5%; its specificity was 100%. In the surveillance cohort, 591 tests conducted in 290 patients were evaluated. 23 patients had pathologically confirmed recurrences. The assay demonstrated 79.2% sensitivity and 100% specificity in detecting the recurrences. Positive predictive value was 100% and negative predictive value was 98.2%. The median lead time from positive test to pathologic confirmation was 28 days, 6/18 (30%) had lead time >50 days (maximum 507 days). **Conclusions:** The commercially available NavDx TTMV-HPV DNA assay demonstrated 100% specificity, and therefore excellent positive predictive value, in both diagnosis and surveillance. However, the sensitivity was lower, 91.5% for the diagnosis cohort and 79.2% for the surveillance cohort, signifying that a negative value may require further work-up. Further studies will be required to determine the optimal timing of testing and how results should inform treatment decisions. Research Sponsor: None.

2x2 Tables for diagnosis (A) and surveillance (B) cohorts.

	A) Diagnosis Cohort (n = 163)		B) Surveillance Cohort (n = 591*)	
TTMV-HPV DNA	HPV+ OPSCC	HPV- OPSCC	Recurrence	Disease Free
Positive	139	0	38	0
Negative	13	11	10	543

#Surveillance cohort analysis performed at the test level; individual patients may have multiple tests.

6062

Poster Session

Peripheral blood epigenetic immune-profiling and survival outcomes with anti-programmed death (PD)-1 based therapy in recurrent/metastatic (R/M) squamous cell carcinoma of head and neck (SCCHN). *First Author: Kartik Sehgal, Center for Head and Neck Oncology, Dana-Farber Cancer Institute, Boston, MA*

Background: Most patients with R/M SCCHN do not derive durable benefit from standard-of-care anti-PD-1-based therapy. The currently utilized biomarker, PD-ligand-1 combined proportion score is limited by the availability and heterogeneity of tumor samples. There is an unmet need to develop easily accessible peripheral blood-based biomarkers for response to immunotherapy. **Methods:** We are conducting a prospective multi-center study to identify peripheral blood derived DNA-based methylation biomarkers measured in patients with R/M SCCHN on treatment with FDA-approved anti-PD-1 based therapy. DNA isolated from these samples undergo bisulfite conversion, methylation profiling using Illumina EPIC microarray, and cellular deconvolution to generate peripheral blood immune profiles (PMID 35140201), including granulocytic (g) and monocytic (m) myeloid derived suppressor cell (MDSC) scores. Associations between baseline peripheral blood immune profiles before the start of treatment with progression-free survival (PFS) and overall survival (OS) were evaluated using Kaplan Meier curves and Cox proportional hazards models adjusted for age and sex. Additionally, logistic regression models adjusted for age and sex were utilized to investigate the baseline immune profiles between subgroups of patients who received anti-PD-1 monotherapy with durable clinical benefit for at least 1 year (Group A) versus progression or death within 100 days (Group B) from start of therapy. **Results:** 61 patients with R/M SCCHN who received anti-PD-1 based therapy as of Oct 31, 2022, were eligible for this preliminary analysis. Mean (SD) age of the entire population was 66.4 (11.8) years, 82% were male. gMDSC score was the only immune parameter with a statistically significant association with PFS (HR 2.6 (1.40 – 4.87) independent of age and sex, with higher scores stratified by median value associated with shorter PFS (Median PFS: 75 days vs. 145 days). Memory CD4 T cells, total CD4 T cells, percentage of T regulatory /CD4 cells, and absolute memory B cells were significantly associated with OS in this population, independent of age and sex (Table). Among the subgroup treated with anti-PD-1 monotherapy, Group A with durable benefit (n = 7, 86% male, mean age: 64.7 years) had significantly higher proportion of CD4 naïve/total CD4 cells (p = 0.03), and significantly lower gMDSC (p = 0.015) & mMDSC (p = 0.000049) scores, compared with Group B (n = 27, 78% male, mean age: 66.4 years). **Conclusions:** Peripheral blood DNA-based epigenetic immune profiling can recognize clinically relevant methylation biomarkers of benefit from anti-PD-1 therapy before the start of treatment. Research Sponsor: U.S. National Institutes of Health.

	Hazards ratio (HR) for OS	p value
CD4 memory	0.19	0.006
CD4 total	0.19	0.006
Treg/total CD4	3.89	0.018
Absolute B memory	2.88	0.028
Neutrophils	2.54	0.086

6061

Poster Session

Spatial relationships and immune subsets in the tumor immune microenvironment of head and neck cancers. *First Author: Leanne E. Henry, University of Michigan, Ann Arbor, MI*

Background: The tumor microenvironment provides important insights into cancer behavior and its response to treatment. In particular, the cellular composition and spatial arrangement of tumor immune infiltrates are associated with patient prognosis and survival. We optimized and employed a novel method using readily available hematoxylin and eosin (H&E) slide images, termed the G-cross score, which reflects immune cell infiltration levels and their proximity to tumor cells. The G-cross score is calculated by estimating the probability distribution of immune cells, of any type, within a certain distance from a tumor cell, with higher scores indicating greater immune cell infiltration. However, because G-cross scores are calculated from H&E slides, the method is unable to distinguish among immune cell types. Using head and neck squamous cell carcinoma (HNSCC) patients having both G-cross scores and bulk RNA-seq data, we determined which subset of tumor-infiltrating immune cell types best correlate with G-cross scores, and its predictive and prognostic value. **Methods:** G-cross scores were calculated for 425 HNSCC samples from University of Michigan, of which 64 had paired bulk RNA-seq data. We applied the cell-type deconvolution tool, CIBERSORTx, to identify immune cell type proportions based on RNA-seq data. G-cross scores were correlated against cell-type deconvolution results, immune cell activation expression signatures, and validated gene expression-based radiosensitivity index scores. Pearson's correlation coefficient and p-value using HPV status as a covariate in a linear model was calculated for each comparison. For survival and recurrence analysis, Cox proportional hazards multivariate regression was performed using the entire 425 sample cohort. **Results:** G-cross scores were significantly correlated with total T cells (R = 0.52, p = 4.63×10⁻⁵), B cells (R = 0.33, p = 2.08×10⁻²), and dendritic cells (R = 0.46, p = 7.71×10⁻⁴), but not macrophages or mast cells. G-cross scores also had a positive correlation with T cell activation (R = 0.46, p = 2.17×10⁻⁴) and B cell activation (R = 0.53, p = 1.24×10⁻⁴) and were correlated with radiation sensitivity (R = -0.44, p = 6.67×10⁻⁴). Survival analysis showed higher G-cross scores were associated with a longer time to recurrence and improved overall survival (p = 3.0×10⁻⁴). **Conclusions:** G-cross scores are mainly driven by T cell and dendritic cell levels among tumor-infiltrating lymphocytes and are correlated with B and T cell activation. Importantly, G-cross scores also correlate with gene expression profiles associated with response to radiotherapy as well as time to recurrence and overall survival. G-cross scores may be an important biomarker of radiation response and indicative of protective immune subsets for HNSCC patients. Research Sponsor: U.S. National Institutes of Health.

6063

Poster Session

The impact of genetic predisposition to depression on quality of life in patients with head and neck cancer immediately post-treatment: A longitudinal study. *First Author: Melissa Henry, 3755 Cote Sainte-Catherine, Montreal, QC, Canada*

Background: The primary aim of this study was to investigate the contribution of genetic predisposition to depression, through polygenic risk scores (PRS), on quality of life levels in patients with head and neck cancer (HNC) immediately post-treatment period (i.e., 3 months post-diagnosis). **Methods:** Prospective longitudinal study of 223 consecutive adult patients with HNC (72% participation) newly diagnosed with a first occurrence of primary HNC, including saliva samples analyzed using the Illumina PsychChip, psychometric measures, Structured Clinical Interview, and medical chart reviews. **Results:** Level of quality of life at 3 months on the FACT-G+H&N was predicted by (r² = 0.51, r² adj. = 0.33, p = 0.001) the polygenic risk score for depression (standardized b = -0.28, p = 0.01) and a previous history of suicidal ideation (standardized b = -0.25, p = 0.04). Other variables were non-significant in the analyses: sociodemographic (i.e., age, sex, education, living alone), psychosocial (i.e., SCID current and past diagnoses (trend), past history of abuse), and medical variables (i.e., cancer stage and site, HPV status, functional status/ECOG, treatment). **Conclusions:** Our results outline the importance of attending to genetic predisposition and past history of suicidal ideation as markers for quality of life compromise immediately post-treatment in patients with head and neck cancers. Strategies are needed to address psychosocial vulnerability early-on as part of pre-habilitation in the treatment of patients with head and neck cancer. Research Sponsor: Quebec Health Research Fund (FRQS).

6064

Poster Session

Radiotherapy alone versus concurrent or adjuvant chemoradiotherapy for nasopharyngeal carcinoma patients with negative Epstein-Barr virus DNA post-induction chemotherapy. *First Author: Fang-Fang Kong, Department of Radiation Oncology, Fudan University Shanghai Cancer Center, Shanghai, Shanghai, China*

Background: Induction chemotherapy (IC) plus concurrent chemoradiotherapy has been recommended as the standard treatment for locoregionally advanced nasopharyngeal carcinoma (LA-NPC). However, concurrent chemotherapy was associated with increased toxicities, poor tolerance, and low completion rates. The aim of this study was to compare the efficacy and toxicity of IC+ radiotherapy (RT) and IC+ concurrent or adjuvant chemoradiotherapy (IC+CCRT/AC) in patients with negative post-IC EBV DNA. **Methods:** A total of 547 NPC patients with negative plasma EBV DNA post-IC were included. Patients were classified into the IC+RT group and the IC+ concurrent or adjuvant chemoradiotherapy (IC+CCRT/AC) group. Locoregional relapse-free survival (LRFS), distant metastasis-free survival (DMFS), overall survival (OS), and progression-free survival (PFS) were estimated and compared using the Kaplan-Meier method. Propensity-score matching (PSM) was performed to balance the variables. **Results:** The median follow-up time was 37 months. The 3-year LRFS, DMFS, OS, and PFS rates for the whole group were 92.2%, 92.4%, 96.4%, and 84.4%, respectively. There was no significant difference in LRFS, DMFS, OS, and PFS between the IC+RT and the IC+CCRT/AC group both before PSM (3-year rates of 91.1% vs. 92.6%, $p = 0.94$; 95.6% vs. 91.5%, $p = 0.08$; 95.2% vs. 96.8%, $p = 0.80$; 85.9% vs. 84.0%, $p = 0.38$) and after PSM (90.7% vs. 92.7%, $p = 0.77$; 96.8% vs. 93.7%, $p = 0.29$; 94.5% vs. 93.9%, $p = 0.57$; 84.7% vs. 85.6%, $p = 0.96$). Multivariate analysis demonstrated that treatment schedule was not an independent predictor for survival rates. Patients in the IC+RT group had fewer treatment-related acute toxicities and better tolerance. **Conclusions:** IC+RT displayed similar survival outcomes as IC+CCRT/AC for NPC patients with negative post-IC EBV DNA. Our current data seems not to support the routine use of concurrent or adjuvant chemotherapy after IC for unselected patients. Research Sponsor: None.

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Poster Session

One-year reductions in cisplatin-related chronic kidney disease (CKD) in patients with head and neck (HNC) cancer treated with avasopasem manganese: A prespecified analysis from the phase 3 ROMAN trial. *First Author: Bryan G. Allen, The University of Iowa Hospitals & Clinics, Iowa City, IA*

Background: Cisplatin-induced acute kidney injury (AKI), acute kidney disease (AKD), and chronic kidney disease (CKD) are associated with increased production of reactive oxygen species, notably superoxide, in conjunction with alterations in mitochondrial electron transport chain complex activities in tubular epithelial cells (Mapuskar et al. *Antioxidants* 2021;10:1329). These pathologies can be targeted and thereby inhibited by increasing superoxide dismutase activity, which converts superoxide to hydrogen peroxide. The investigational new drug avasopasem manganese (AVA), a selective dismutase mimetic, ameliorated cisplatin-induced kidney injury in mice (Mapuskar et al. *Redox Biol* 2019;20:98). Preclinical results also demonstrate that AVA does not interfere with cisplatin anticancer activity (Mohanty et al. *Cancer Res* 2018;78[13 suppl]:Abstract 2929). Consistent with this, a retrospective analysis of 1- and 2-year kidney function of a limited subset of patients treated in a randomized, placebo (PBO)-controlled phase 2b trial of AVA to reduce severe oral mucositis (SOM) from radiotherapy and cisplatin (CRT) suggested that AVA prevented or reduced cisplatin-related CKD compared to PBO (Steinbach et al. *J Clin Oncol* 2020;38[15 suppl]:Abstract 12071). **Methods:** The ROMAN phase 3 trial (NCT03689712; ITT $n = 407$) of CRT in combination with AVA or PBO demonstrated improved incidence, duration, and onset of SOM by AVA ($n = 241$) vs PBO ($n = 166$) (Anderson et al. *J Clin Oncol* 2022;40[16 suppl]:Abstract 6005). In ROMAN, prospectively defined follow-up of serum creatinine (sCr) and estimated glomerular filtration rates (eGFR) were assessed every 3 months for 1 year following 7 weeks of CRT. **Results:** At 1-year follow-up, AVA was associated with significant improvements in preservation of eGFR ($P = 0.0008$) and sCr ($P = 0.006$) levels vs PBO. Grade 3+ CKD (eGFR < 60 mL/min) results through 12 months show 10% AVA vs 20% PBO (relative risk 0.55, $P = 0.0043$). Regarding cisplatin schedule, patients receiving Q3W therapy show grade 3+ CKD of 12% AVA vs 22% PBO; patients receiving QW therapy show AVA 9% vs PBO 19%. During treatment, nominal reduction of the incidence of AKI adverse events (0.8% AVA vs 3.6% PBO) was also observed. **Conclusions:** At 1-year follow-up, AVA appears to reduce cisplatin-related CKD in the study population and may also reduce cisplatin-related AKI during treatment. These results carry significance beyond CRT for HNC, potentially impacting platinum-containing regimens in other cancers. Clinical trial information: NCT03689712. Research Sponsor: Galera Therapeutics, Inc.

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Poster Session

Multimodal detection in plasma of molecular residual disease (MRD) in locally advanced head and neck squamous cell carcinoma (LA-HNSCC). *First Author: Enrique Sanz Garcia, Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada*

Background: Despite intensive therapy, 30% of patients (pts) with LA-HNSCC relapse. Published data shows that MRD detection during follow up (FU) may predict relapse, e.g. human papillomavirus (HPV) DNA in p16+ pts post radiation (RT) or chemoradiation (CRT); or circulating tumor DNA (ctDNA) post surgery. MRD detection using multiple assays after definitive RT/CRT has not been reported. **Methods:** We enrolled pts with high risk LA-HNSCC (stage III HPV+, III-IVB HPV-) treated with curative intent: surgery $\pm$ adjuvant therapy, RT or CRT. Plasma was collected pre-treatment at baseline (B), at 4-6 weeks (FU1) and 8-12 weeks (FU2) post-treatment. RaDaR, a personalized liquid biopsy assay that targets patient specific somatic variants identified in whole exome sequencing (WES) from matched tumor tissue, was used to detect ctDNA, reported as estimated Variant Allele Fraction (eVAF). Cancer Personalized Profiling by deep sequencing (CAPP-seq) was used as a tumor naïve assay for ctDNA, reported as mean VAF. HPV sequencing (HPV-seq) in all and digital PCR (dPCR) in p16+ pts were used to detect HPV DNA. Relapse free survival (RFS) was estimated using Kaplan Meier and associations of ctDNA or HPV DNA with RFS using log-rank test. Assays were compared with Spearman correlation. **Results:** A total of 89 plasma samples from 35 pts were collected prospectively; 32 pts with at least a FU sample were evaluable; 26 had both. Median age was 63 years (34-71). Most pts were stage III HPV+ ($N = 16$, 50%) and received CRT ($N = 25$, 78%). No pts had clinical or radiological residual disease at FU2. Median FU was 18.3 months (5.1-25.9), there were 7 clinical relapses. RaDaR was applied in 17 pts with WES in matched tissue, including 6 with relapse. ctDNA at B was detected in 15/17 (88%). eVAF at B was not associated with RFS ($p = 0.98$). Two pts relapsed < 1 year after RT/CRT and had eVAF $> 0.001\%$ in FU2 sample; lead time to relapse was 100 and 245 days. FU1 sample of a pt who relapsed > 1 year post-CRT was close to the threshold for ctDNA+ with eVAF 0.0001%; lead time was 494 days. Three pts who received CRT relapsed > 500 days from FU2 sample (ctDNA-). CAPP-seq was applied to 29 pts; mean VAF correlated with eVAF at B ($r = 0.75$) but not at FU. ctDNA+ at FU using CAPP-seq was not associated with RFS ($p = 0.25$). HPV-seq was applied to 32 pts; specificity and sensitivity was 100% at B. Among p16+ pts with FU sample ($N = 15$), HPV DNA was detected in 4/4 with relapse and not in those without, predicting shorter RFS ($p < 0.01$). dPCR detected HPV DNA in 2/4 pts with relapse. HPV-seq and dPCR correlation was high at B ($r = 0.99$), lower at FU2 ($r = 0.66$). **Conclusions:** HPV DNA and ctDNA can be detected in LA-HNSCC before and after definitive therapy. RaDaR but not CAPP-seq may detect MRD in pts who relapse within 1 year after RT/CRT with a significant lead time. HPV-seq may be more sensitive than dPCR to detect HPV DNA in MRD. Validation in an interception study is planned (NCT04599309). Research Sponsor: Princess Margaret Cancer Centre; BMO Chair of Precision Medicine.

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Poster Session

Induction chemotherapy with nedaplatin, docetaxel and 5-fluorouracil followed by concurrent nedaplatin and radiotherapy in locoregionally advanced nasopharyngeal carcinoma: A single arm, open label, phase II clinical trial. *First Author: Chen Fangzheng, Affiliated Cancer Hospital & Institute of Guangzhou Medical University, Guangzhou, China*

Background: To evaluate the efficacy of induction chemotherapy with nedaplatin, docetaxel and 5-fluorouracil followed by concurrent nedaplatin combined with radical radiotherapy in locoregionally advanced nasopharyngeal carcinoma (LA-NPC). **Methods:** This is a prospective, single-arm, open-label, phase II trial. Patients with aged 18-65 years, newly diagnosed stage III-IVa (except T3-4N0) nasopharyngeal carcinoma were enrolled. Eligible patients received induction chemotherapy with docetaxel (60 mg/m² intravenously on days (D) 1, 22 and 43), Nedaplatin (60 mg/m² intravenously on D 1, 22 and 43) and fluorouracil (600 mg/m² per day as a continuous 120 hours (h) infusion on D 1-5, 22-26 and 43-47) every three weeks for three cycles, thereafter received intensity-modulated radiotherapy (IMRT) concurrently with nedaplatin (100mg/m² intravenously on D 1, 22 and (or) 43) every three weeks for two or three cycles. The primary end point was objective response rate (ORR). The secondary end points included overall survival (OS), progression-free survival (PFS), distant metastasis-free survival (DMFS) and local recurrence-free survival (LRFS). **Results:** Between March 2020 and June 2021, a total of 32 patients with LA-NPC were enrolled. With a median follow-up duration of 14.0 months (IQR 11.7-16.3), 32 patients (100%) achieved ORR at three months after treatment. The 12-month PFS was 95.7% (95% CI 87.3% to 100%) and the 12-month OS was 100%. The most common grade 3 or 4 adverse events during induction chemotherapy were neutropenia (3 [9.4%]), diarrhea (3 [9.4%]) and hepatotoxicity (3 [9.4%]), followed by leucopenia (2 [6.3%]) and fatigue (1 [3.1%]). The most common grade 3 or 4 adverse events during concurrent chemotherapy were mucositis (3 [9.4%]), leucopenia (1 [3.1%]), neutropenia (1 [3.1%]) and thrombocytopenia (1 [3.1%]). All of these adverse events were manageable. **Conclusions:** Induction chemotherapy with nedaplatin, docetaxel and 5-fluorouracil followed by concurrent nedaplatin combined with radical radiotherapy showed promising antitumor activity and manageable toxicities in patients with LA-NPC. Further phase III randomized controlled trials are warranted to validate our findings. Clinical trial information: NCT04834206. Research Sponsor: Affiliated Cancer Hospital & Institute of Guangzhou Medical University Clinical Research 5555 Program, Wu Jieping Medical Foundation (320.6750.2020-13-11).

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Poster Session

Induction chemotherapy and toripalimab for larynx preservation in resectable locally advanced laryngeal/hypopharyngeal carcinoma: Preliminary results of INSIGHT study. *First Author: Xiaomin Ou, Department of Radiation Oncology, Fudan University Shanghai Cancer Center, Shanghai, China*

Background: Previous studies have demonstrated excellent pathological response of induction PD-1 inhibitor with chemotherapy for locally advanced head and neck cancer. To our knowledge, there is scarce evidence on induction chemotherapy (ICT) and PD-1 inhibitor in organ preservation for patients (pts) with laryngeal/hypopharyngeal carcinoma. Hence, the aim of this study is to evaluate the efficacy and toxicities of ICT and PD-1 inhibitor (Toripalimab) followed by radiotherapy or surgery, for pts with resectable locally advanced laryngeal/hypopharyngeal carcinoma. **Methods:** This is a single-arm phase II study. Pts with histopathologic confirmed, resectable locally advanced laryngeal/hypopharyngeal squamous cell carcinoma and ECOG PS 0-1 were eligible. Three cycles of ICT (paclitaxel 175mg/m² d1, cisplatin 25mg/m² d1-3) combined with PD-1 inhibitor (Toripalimab 240mg d0) were given. Response assessment (RECIST 1.1) was performed post-ICT. Pts with complete response (CR)/partial response (PR) of primary tumor received concurrent chemoradiation, followed by maintenance therapy of Toripalimab for eight cycles. Otherwise, pts were referred to surgery, followed by adjuvant radiation (RT)/chemoradiation (CRT), and then maintenance therapy of Toripalimab. The primary endpoint is larynx-preservation (LP) rate at 3 months post-RT. Forty-two pts were planned. Based on a two-stage Fleming design (one-sided α :10%, power: 80%), if at least 22 pts attained LP of the first 27 pts in stage I or at least 32 pts attained LP of the 42 pts at the end of stage II, the null hypothesis would be rejected. The cohort would enroll 15 more pts in stage II if 19-21 pts in stage I observed LP, and the study would be terminated if the number of pts with LP were less than 18 in stage I. **Results:** A total of 27 pts were enrolled. By the cut-off date Feb 8th, 2023, all reached at least 3 months of follow-up post-RT. Median age was 63 (53-74) years with 92.6% male. Hypopharyngeal cancer accounted for 66.7%. 74.1% were T3 to T4, and 77.7% were N2 to N3. Six cases had primary invasion of esophagus and five pts underwent pretreatment tracheostomy. ORR of ICT was 85.2%. Afterwards, 21 pts were treated with concurrent CRT, while 6 pts received surgery of primary tumor. At 3 months post-RT, 23 pts attained organ preservation and the LP rate was 85.2%. With a median follow-up of 13.5 months, 1-year OS rate, PFS rate and LP survival rate was 83.1%, 79.5% and 79.4%, respectively. During ICT, 22.2% of pts experienced grade 3-4 treatment-related AEs (TRAEs). The most common grade 3-4 TRAEs were nausea and neutrophil count decreased. **Conclusions:** The primary endpoint LP rate was met. In this cohort of extensive locally advanced laryngeal/hypopharyngeal carcinoma, ICT and Toripalimab followed by radiotherapy or surgery resulted in satisfactory short-term LP rate and encouraging survival. Clinical trial information: NCT04995120. Research Sponsor: Shanghai Junshi Biosciences Co., Ltd.

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Poster Session

Induction therapy of toripalimab combined with docetaxel and cisplatin in locally advanced hypopharyngeal squamous cell carcinoma (HPSCC): A single-arm, phase II clinical trial. *First Author: Chunmei Bai, Peking Union Medical College Hospital, Beijing, China*

Background: PD-1 (programmed cell death protein-1) inhibitors combination with chemotherapy has a significant efficacy and approved indications in the first-line treatment of head and neck squamous cell carcinoma (HNSCC), but the efficacy of these combination therapies in locally advanced hypopharyngeal squamous cell carcinoma (HPSCC) remains unexplored. We conducted a single-arm, phase II trial to assess the efficacy and safety of toripalimab (a novel PD-1 inhibitor) combined with chemotherapy as induction treatment in locally advanced HPSCC. **Methods:** Patients with locally advanced HPSCC (cT1N+M0 or T2-4NanyM0, AJCC 8.0) were eligible. All patients received 2 cycles of intravenous docetaxel (75mg/m²), cisplatin (75mg/m²) and toripalimab (240mg) on day 1 every 21 days, followed by radical surgery or concurrent chemoradiotherapy (CCRT) with cisplatin (100mg/m², q21d). The primary endpoint was objective response rate (ORR) assessed by investigators per RECIST v1.1. Secondary endpoints were major pathologic response (MPR), 2 year disease-free survival (DFS) rate in patients received surgery, 2 year progression-free survival (PFS) rate in patients received CCRT and 2 year overall survival (OS) rate in all patients. **Results:** From July 2020 to January 2023, 34 patients (median age: 59, range: 46-72, male: 100%, stag IV: 100%) were enrolled. Patients with stage IVA an IVB disease were 19 (19/34, 55.9%) and 15 (15/34, 44.1%), respectively. 33 patients completed 2 cycles induction treatment and efficacy evaluation (1 patient dropped out). The evaluated ORR was 54.5%, including 3 pts achieving complete response and 15 achieving partial response. PD-L1 status (combined positive score, CPS) were known in 8 patients, ORR were 80% (4/5) and 66.7% (4/6) in patients with CPS $\geq$ 20 and CPS $\geq$ 1, respectively, 2 patients with CPS < 1 had stable disease. Treatment-related grade 3-4 adverse events occurred in 45.5% (15/33) of patients, leukopenia (42.4%) and neutropenia (3.1%). Immune-related AEs were acceptable, 1 patient (1/33, 3.0%) experienced grade 2 interstitial pneumonia and 2 patients (2/33, 6.1%) experienced grade 1 rash. In the following treatment, 27 patients (27/33, 81.8%) performed CCRT. 4 patients (4/33, 12.1%) underwent surgery followed by CCRT and 2 patients (2/33, 6.1%) refused further treatment. Among these 17 patients finished CCRT and radiological assessment, 9 patients (9/17, 52.9%) had complete response, 7 patients (7/17, 41.2%) had partial response and 1 patient (1/17, 5.9%) had progressive disease. Survival data not mature by cut-off date. **Conclusions:** Induction therapy of toripalimab combined with docetaxel and cisplatin was well tolerated and highly efficient for locally advanced HPSCC. Clinical trial information: NCT04296747. Research Sponsor: Shanghai Junshi Biosciences Co., Ltd.

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Poster Session

A pilot phase II trial of neoadjuvant camrelizumab plus nab-paclitaxel and cisplatin (NeoCPC) for locoregionally advanced, resectable squamous cell carcinoma of the head and neck. *First Author: Di Wu, Sun Yat-Sen University Cancer Centre, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangzhou, Guangdong, China, Guangzhou, Guangdong, China*

Background: For resectable squamous cell carcinoma of the head and neck (HNSCC), novel therapeutic approaches are still needed to improve outcomes. Neoadjuvant immunotherapy (NICT) is considered as a potentially effective strategy. We therefore conducted a pilot phase II trial to explore the efficacy and safety of neoadjuvant camrelizumab plus nab-paclitaxel and cisplatin (NeoCPC) in patients with locoregionally advanced, resectable HNSCC. **Methods:** In this open-label phase II trial, patients with untreated locoregionally advanced, resectable HNSCC (T2–T4, N0–N3b, M0; AJCC, 8th Edition) received NICT with camrelizumab (200 mg), nab-paclitaxel (260 mg/m²) and cisplatin (60 mg/m²) on day 1 of each 21-day cycle for three cycles, followed by radiotherapy or surgery. The primary endpoint was objective response rate (ORR) per RECIST version 1.1. Secondary endpoints included pathologic complete response (pCR), major pathologic response (MPR), safety, disease-free survival (DFS), and overall survival (OS). Genomic biomarkers (genetic mutations, tumour mutational burden [TMB] and immune microenvironment) in baseline tumor samples were explored. **Results:** Between April 2021 and January 2022, 48 patients were enrolled (median age, 59 years [range 27–73]; 42 men [87.5%]). After completion of neoadjuvant therapy, patients underwent surgery (27, 56.3%), chemoradiotherapy (15, 31.2%), radiotherapy (five, 10.4%) or continued immunotherapy as maintenance therapy (one, 2.1%). At a median follow-up time of 415 days, the ORR was 89.6% (43/45). Of the 27 patients who had surgery, 17 (63.0%) patients had an MPR, including 15 (55.6%) with a pCR. Patients with ORR were more likely to achieve pCR. One patient died of lung metastasis 6 months after completion of treatment. The 1-year OS and DFS rates were both 97.9%. Only 3 (6.3%) patients had grade 3 treatment-related adverse events (AEs): one with pneumonitis and two with neurotoxicity. No unexpected immune-related AEs were observed. For genetic analysis, the most frequently mutated genes were TP53 (77.1%), CDKN2A, FAT1, CND1 and NOTCH1. The lower radiographic tumor regression percentage was observed in TP53-altered ($p=0.01$) and TERT-altered ($p=0.002$) patients, whereas higher percentage was observed in HPV-positive patients. The median TMB was 3.15 mutations/MB. No significant difference was observed in TMB between patients with ORR and non-ORR (stable disease). There was a significant correlation between density of M1-like macrophage cells, CD8+ T cells in tumor area and radiographic tumor regression percentage ($p=0.009$, $p=0.0005$, respectively). **Conclusions:** NeoCPC showed promising efficacy with a high ORR and pathologic response rate for locoregionally advanced, resectable HNSCC, with an acceptable safety profile. Clinical trial information: NCT04826679. Research Sponsor: China Postdoctoral Science Foundation: 2022M713612.

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Poster Session

Nab-paclitaxel plus cisplatin versus docetaxel plus cisplatin and 5-FU induction chemotherapy followed by concurrent chemoradiotherapy in locally advanced nasopharyngeal carcinoma: A multicenter parallel controlled phase III trial. *First Author: Xing Lv, Sun Yat-sen University Cancer Center, Guangzhou, China*

Background: Although several large phase III clinical trials and meta-analysis have demonstrated significant clinical benefit of docetaxel combined with cisplatin and 5-FU (TPF) chemotherapy in head and neck cancer, serious adverse reactions are unsatisfactory. Therefore, this study was designed to evaluate the efficacy and safety of nab-paclitaxel plus cisplatin (TP) versus TPF induction chemotherapy (ICT) followed by concurrent chemoradiotherapy (CCRT) for locally advanced nasopharyngeal carcinoma (LA-NPC). **Methods:** In this open-label, phase 3 trial, patients were randomized 1:1 to received TP (260 mg/m² nab-paclitaxel and 80 mg/m² cisplatin on days 1 and 22) or TPF (60 mg/m² docetaxel and 60 mg/m² cisplatin on days 1 and 22; 3 g/m² 5-FU on days 1-5 and 22-26) every 3 weeks for 2 cycles, both groups of patients received CCRT (100mg/m² cisplatin and IMRT on days 43 and 64) every 21 days for 2 cycles. The primary endpoint was failure-free survival. Secondary endpoints included overall survival, objective response rate (ORR), quality of life and safety. **Results:** From January 2019 to July 2021, 281 patients were randomized to TP ($n=142$, TP arm) or TPF ($n=139$, TPF arm). The median age was 44 years (range, 20-63) in the TP arm and 45 years (range, 18-69) in the TPF arm. The pathological stages were 40.85% stage III and 59.15% stage IVA in the TP arm, while those of the TPF arm were 43.17% stage III and 56.83% stage IVA. There were 99.30% and 97.12% undifferentiated nonkeratinizing carcinoma in the two groups, respectively. All patients had Karnofsky performance status of 90. ICT was completed in 98.93% (100% in the TP arm and 97.84% in the TPF arm). The median relative dose intensity of nab-paclitaxel and cisplatin were 99.96% and 99.81% in the TP arm, 99.83%, 100% and 100% for docetaxel, cisplatin and 5-FU in the TPF arm, respectively. The ORR were 80.28% in the TP arm and 78.26% in the TPF arm after two cycles of ICT. 85.77% (83.10% in the TP arm and 88.49% in the TPF arm) completed the CCRT. After two cycles of CCRT, the ORR were 99.25% and 99.24%, respectively. 3 months after completion of all treatment, the ORR were 99.25% and 99.25%, respectively. During ICT, all treatment-related adverse events occurred in 40.14% of patients in the TP arm and 57.55% in the TPF arm. The most frequent grade 3 adverse events were neutropenia (0.70% vs 2.16%), leucopenia (0 vs 2.88%), diarrhea (0 vs 0.72%) in the TP arm and in the TPF arm. Over the entire course of treatment, the most common was 1 grade adverse events, and no patient developed grade 4 adverse events in the two groups. **Conclusions:** In this study, TP regimen showed similar trends in the ORR but excellent safety profile in patients with LA-NPC compared with TPF regimen, suggesting a potential therapeutic option for this population. Clinical trial information: ChiCTR1800019922. Research Sponsor: CSPC Ouyi Pharmaceutical Co., Ltd.

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Poster Session

Prospective study of integrating post-radiotherapy [¹⁸F] fluorodeoxyglucose-positron emission tomography/computed tomography scan and plasma Epstein-Barr virus DNA in surveillance of locoregionally advanced nasopharyngeal carcinoma. *First Author: Lin-Qun Tang, Department of Nasopharyngeal Carcinoma, Sun Yat-sen University Cancer Centre, State Key Laboratory of Oncology in South China, Collaborative Innovation Centre for Cancer Medicine, Guangdong Key Laboratory of Nasopharyngeal Carcinoma Diagnosis and Therapy, Guangzhou, China*

Background: To evaluate the role of [¹⁸F] fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) scan at 12-weeks after the end of Radiotherapy (RT) integrated with plasma EBV DNA in surveillance and standardized implementation of locoregionally advanced nasopharyngeal carcinoma (LA-NPC). **Methods:** This prospective study was conducted in patients with stage III-IVa LA-NPC. FDG-PET/CT examination and plasma Epstein-Barr virus (EBV) DNA measurements was performed pretreatment and at 12-weeks after the end RT. The primary study endpoint was the negative predictive value (NPV) and other supporting diagnostic test characteristics of 12-weeks FDG-PET/CT for the surveillance of residual locoregional disease and new distant metastasis. **Results:** From June 2018 to December 2019, 506 eligible patients were enrolled and entered follow-up (median, 45 months). At 12 weeks after the end of RT, there were 22 (4.3%) patients have residual locoregional disease, 30 (5.9%) patients developed distant metastasis and 6 (1.2%) patients presented both residual locoregional disease and distant metastasis. The NPV of 12-weeks FDG-PET/CT for overall residual diseases and distant metastasis was 96.3% (95% confidence interval [CI], 94.0%-97.8%) with sensitivity of 72.4% (95%CI, 58.9%-83.0%), specificity of 93.3% (95%CI, 90.5%-95.4%), positive predictive value (PPV) of 58.3% (95%CI, 46.1%-69.6%) and accuracy of 90.9% (95%CI, 88.4%-93.4%). In EBV DNA-based risk subgroups, the NPV of 12-weeks PDG-PET/CT was 96.8% (95%CI, 94.5%-98.2%) in patients with undetectable 12-weeks plasma EBV DNA and 87.0% (95%CI, 65.3%-96.5%) in patients with detectable 12-weeks plasma EBV DNA. **Conclusions:** 12-weeks PDG-PET/CT was reliable in the surveillance of LA-NPC and could help optimize the follow-up strategy and provide implications for timely and effective therapeutic regimen, especially for patients in different EBV DNA-based risk groups. Clinical trial information: NCT03601390. Research Sponsor: National Key Research and Development Program of China, National Natural Science Foundation of China, Guangdong Major Project of Basic and Applied Basic Research, Sci-Tech Project Foundation of Guangzhou City; the Sun Yat-sen University Clinical Research 5010 Program, Innovative Research Team of High-level Local Universities in Shanghai, Natural Science Foundation of Guangdong Province for Distinguished Young Scholar, Postdoctoral Innovative Talent Support Program, the Pearl River S&T Nova Program of Guangzhou, Planned Science and Technology Project of Guangdong Province, Key Youth Teacher Cultivating Program of Sun Yat-sen University, and Fundamental Research Funds for the Central Universities.

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Poster Session

Induction chemotherapy with nanosomal docetaxel lipid suspension (NDLS), cisplatin, and fluorouracil in patients with locally advanced head and neck squamous cell carcinoma. *First Author: Ghanashyam Biswas, Sparsh Hospital and Critical Care, Bhubaneswar, India*

Background: Nanosomal docetaxel lipid suspension (NDLS), a polysorbate-80 and ethanol free formulation, was developed to overcome the toxicity issues and to improve disease outcomes associated with conventional docetaxel. We evaluated the safety and efficacy of NDLS based TPF (NDLS, cisplatin and 5-fluorouracil [FU]) induction chemotherapy in patients with inoperable/unresectable Locally Advanced Head and Neck Squamous Cell Carcinoma (LA HNSCC). **Methods:** In this multicentric, single arm, open label, Phase IV clinical study, patients with inoperable/unresectable LA HNSCC received induction chemotherapy with NDLS (75 mg/m²; Day 1), cisplatin (75 mg/m²; Day 1) and 5-FU (750 mg/m²/day for 5 days) based TPF regimen every 3 weeks (q3w) for 4 cycles followed by radiotherapy. The study outcomes were overall response rate (ORR), disease control rate (DCR), progression-free survival (PFS) and overall survival (OS). **Results:** Fifty patients were enrolled in this study. Most of the patients belonged to the age group of 35-64 years (86%) and had a WHO performance status of 1 (66%). In the modified intent-to-treat (mITT) population (n = 40), the ORR after NDLS based TPF induction chemotherapy was 42.5%, which increased to 60.0% after loco-regional therapy. In the per-protocol (PP) population (n = 14), the ORR was 64.3%, which increased to 80.0% after loco-regional therapy (Table). At 2 years, the PFS and OS rates were 82.5% and 87.5%, respectively, in the mITT population and 85.7% and 100% respectively, in the PP population. The most common grade 3/4 adverse effects reported were neutropenia (10%), leukopenia (6%), febrile neutropenia (4%), asthenia (2%), diarrhea (2%), and thrombocytopenia (2%) respectively. Grade 3/4 infusion-related reactions, hyperglycemia or neuropathy were not reported. **Conclusions:** NDLS based induction chemotherapy was effective and well-tolerated in the treatment of inoperable LA HNSCC and showed high response rates. Clinical trial information: CTRI/2017/12/010938. Research Sponsor: Intas Pharmaceuticals Ltd.

Clinical response rate.				
Parameter	mITT		PP	
	Response to Chemotherapy (n = 40)	Response to chemotherapy and radiotherapy (n = 15)	Response to Chemotherapy (n = 14)	Response to chemotherapy and radiotherapy (n = 5)
PR, n (%)	17 (42.5)	9 (60.0)	9 (64.3)	4 (80.0)
SD, n (%)	14 (35.0)	3 (20.0)	2 (14.3)	0 (0.0)
ORR, n (%)	17 (42.5)	9 (60.0)	9 (64.3)	4 (80.0)
95% CI	[27.04-59.11]	[32.29-83.66]	[35.14-87.24]	[28.36-99.49]
2-year PFS, n (%)	33 (82.5%)		12 (85.7%)	
2-year OS, n (%)	39 (97.5%)		14 (100.0 %)	

CI, confidence interval; CR, complete response; DCR, disease control rate; mITT, modified intent-to-treat; ORR, overall response rate; OS, overall survival; PFS, progression free survival; PP, per-protocol; PR, partial response; SD, stable disease.

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Poster Session

CT radiomic signature to predict overall survival and chemotherapy benefit in stage I and II HPV-associated oropharyngeal carcinoma. *First Author: Bolin Song, Emory, Atlanta, GA*

Background: Chemoradiation is the standard of care for human papillomavirus (HPV)-associated oropharyngeal squamous cell carcinoma (OPSCC). However, not all patients would benefit from chemotherapy, especially patients with low-risk characteristics. We aim to develop and validate a prognostic and predictive radiomic image signature (pRis) to inform survival and chemotherapy benefit in stage I and stage II HPV-associated OPSCC. **Methods:** Radiographic scans for 491 patients with stage I and stage II HPV-associated OPSCC were acquired from 4 independent sources and divided into three cohorts D₁-D₃. D₁ comprised computed tomography (CT) scans from 60 radiotherapy treated patients and was used to identify prognostic features via a LASSO Cox model to predict overall and disease-free survival. The prognostic performance of pRis was evaluated on two test sets (D₂, n = 162; D₃, n = 269) using concordance index (C-index). An integrated nomogram was developed to demonstrate the incremental value of the pRis to the existing clinical factors for individualized survival estimation. Patients from D₂ and D₃ who received either radiotherapy alone or chemoradiation were used to validate pRis as predictive of added benefit of chemotherapy. **Results:** Seven radiomic features were selected to construct the image biomarker pRis, which was found to be prognostic of overall survival (OS) on univariate analysis in D₂ (hazard ratio [HR] = 2.14, 95% confidence interval [CI], 1.1-4.16, p = 0.02) and D₃ (HR = 2.74, 95% CI, 1.34-5.62, p = 0.006). Chemotherapy was associated with improved OS for high-pRis patients in both D₂ (radiation vs chemoradiation, HR = 4.47, 95% CI, 1.73-11.6, p = 0.002) and D₃ (radiation vs chemoradiation, HR = 2.99, 95% CI, 1.04-8.63, p = 0.04). In contrast, chemotherapy did not improve OS for low-pRis patients, which indicates these patients did not derive additional benefit from chemotherapy and could be considered for treatment de-escalation. **Conclusions:** The proposed radiomic signature was prognostic of patient survival and the binary pRis group informed chemotherapy benefit for stage I and II HPV-associated OPSCC patients. Research Sponsor: U.S. National Institutes of Health.

Hazard ratios and p values for patients receiving radiation alone vs chemoradiation according to pRis groups.		
	Hazard ratio (Confidence interval)	P value
D2, High-pRis	4.47 (1.73 – 11.6)	0.002
D2, Low-pRis	2.56 (0.745 – 8.77)	0.136
D3, High-pRis	2.99 (1.04 – 8.63)	0.04
D3, Low-pRis	0.28 (0.05 – 1.49)	0.135

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Poster Session

Neoadjuvant pembrolizumab, GX-188E, and GX-17 in patients with human papillomavirus-16- and/or 18-positive head and neck squamous cell carcinoma: Single-arm, phase 2 trial with single cell transcriptomic analysis and artificial intelligence-powered spatial analysis. *First Author: Hye Ryun Kim, Department of Internal Medicine, Division of Medical Oncology, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea*

Background: With the increasing prevalence of head and neck squamous cell carcinoma (HNSCC) associated with human papilloma virus (HPV) infection, effective treatment strategies for HPV-positive HNSCC are urgently needed. Here, we present the results of neoadjuvant checkpoint blockade of pembrolizumab, therapeutic HPV DNA vaccine of GX-188E, and long-acting interleukin-7 of GX-17 for patients with resectable HPV-16 and/or 18-positive HNSCC. **Methods:** In this single-arm, phase 2 trial, patients with resectable HPV-16 and/or 18-positive HNSCC were enrolled. Patients were given pembrolizumab 200mg on day 1 and day 22; GX-188E 2mg on day 1, 8, and 22; and GX-17 1200 ug/kg on day 8 before surgical resection. Major pathologic response (MPR; defined as residual viable tumor of less than or equal to 10%) was primary endpoint with null and alternative hypothesis of MPR rate ≤5% and ≥35%, respectively. Secondary objectives were safety, recurrence, and survival. **Results:** Of the 11 patients included, all underwent surgical resection after neoadjuvant treatment without delays in surgery or increased surgical complications. MPR was achieved in seven patients (63.6%) and pathologic complete response was achieved in four patients (36.3%), which met the primary endpoint. Single cell RNA sequencing of baseline and post-treatment paired specimens revealed that the proportion of follicular helper T cell cluster, featured with *CXCR5* and *BCL6* expression, was significantly increased among tumor-infiltrating immune cells, accompanied with the reinvigoration of CD8 T cell cluster toward less exhausted phenotypes, represented with the upregulation of *TCF7* and *CD28* expression. In addition, artificial intelligence-powered spatial analysis revealed that triple combination significantly increased the density of tumor-infiltrating lymphocytes, completely converting immunodesert and immune-excluded type of tumor to inflamed immune phenotype. **Conclusions:** Neoadjuvant pembrolizumab, GX-188E, and GX-17 showed promising activity and manageable safety profile in patients with resectable HPV-16 and/or 18-positive HNSCC. Therapeutic induction of brisk immune responses significantly reshaped the tumor microenvironment and associated with pathologic regression, warranting further investigation of pembrolizumab, GX-188E, and GX-17 for patients with HPV-positive HNSCC. Clinical trial information: NCT05286060. Research Sponsor: None.

Development of CT-based radiomic model to predict 5-year progression-free survival (PFS) in locally advanced head and neck squamous cell carcinoma (LAHNSCC) treated with definitive chemoradiation. *First Author: Gema Bruixola, Department of Medical Oncology- INCLIVA Biomedical Research Institute - Hospital Clinico Universitario- University of Valencia, Valencia, Spain*

Background: Definitive chemoradiation is the current standard treatment in LAHNSCC. Prognostic biomarkers that enable to reliably predict LAHNSCC disease progression are needed to stratify the risk of progression to tailor treatment intensity in future clinical trials. Imaging biomarkers have emerged as promising alternatives to non-invasively predict patient outcomes. Aim: to identify an imaging signature to predict progression-free survival (PFS) in LAHNSCC. **Methods:** A single-center, retrospective, observational study was designed. Clinical data and pre-treatment CT images from LAHNSCC patients treated with definitive chemoradiation from 2014 to 2022 were collected. Manual tumor segmentation was performed slice by slice by a qualified image technician and supervised by a radiologist with 20+ years in HNSCC using the DICOM viewer of Quibim platform. A total of 108 radiomic features (shape and textures) were extracted from each region of interest. Feature reduction techniques were applied to select the characteristics used in the classification model. The primary endpoint of this study was 5-year PFS. Random Forest, Support Vector Classifier (SVC), Logistic Regression, Gradient Boosting (GB) and Extreme Gradient Boosting classification models were used. A 5-fold cross validation strategy was followed to evaluate the performance of the models in terms of AUROC, sensitivity, specificity, and accuracy. The importance of each feature in the model was measured by applying the Shapley Additive exPlanations (SHAP) method. **Results:** Baseline CT exams from 102 LAHNSCC patients were included; 50% and 23% were stage IVA and IVB, respectively. The remaining 27% (stage II [3%] and stage III [24%]) were treated in an organ-preservation intention. 67% of patients presented locoregional or distant progression at 5 years. All radiomic features (108) and 6 clinical variables were used in the predictive model, for which a cross-validation was performed. GB as the feature selection technique and SVC as the classification model provided the best results. The final model was able to predict 5-year PFS with an average AUC of 0.82 (95% CI: [0.73, 0.91]), a sensitivity of 0.69 (95% CI: [0.57, 0.81]), a specificity of 0.82 (95% CI: [0.7, 0.94]) and an accuracy of 0.73 (95% CI: [0.62, 0.84]). From most to least important, features contributing to the predictive model were: TNM stage (SHAP: 0.038), glszm Small Area Emphasis (SHAP: 0.026), glcm Idmn (SHAP: 0.023), glszm Large Area High Gray Level Emphasis (SHAP: 0.018) and glrlm Run Entropy (SHAP: 0.015). **Conclusions:** Radiomic biomarkers from pre-treatment CT images in combination with TNM stage were predictive of 5-year PFS to chemoradiation in LAHNSCC patients and might be helpful for patient risk stratification. Further validation of these imaging biomarkers is ongoing. Research Sponsor: INCLIVA Biomedical Research Institute - University of Valencia.

Neoadjuvant low-dose radiotherapy, tislelizumab, combined with albumin-bound paclitaxel and cisplatin in resectable locally advanced head and neck squamous cell carcinoma (NeoRTPC02): The first-stage result from an open label, single-arm, two stage, phase II clinical trial. *First Author: Zhigang Liu, The Cancer Center of Affiliated Dongguan Hospital of Southern Medical University, Dongguan, Guangdong, China*

Background: Neoadjuvant immunotherapy and chemotherapy has been explored in phase I/II clinical studies in head and neck squamous cell carcinoma (HNSCC), confirming its safety and efficacy. However, the pathological complete response (pCR) / major pathological response (MPR) rate still needed for improvement. Recent studies revealed that low dose radiotherapy can overcome immunosuppressive tumors by reversing immune desertification when combining immunotherapy. Here, we conducted this clinical trial to explore the efficacy and safety of neoadjuvant low-dose radiotherapy, PD-1 inhibitor, combined with chemotherapy in resectable locally advanced head and neck squamous cell carcinoma. **Methods:** This was an open-label, single-arm, phase II clinical trial. Patients with untreated, histologically confirmed HNSCC staging III-IVB were included. The eligible patients were scheduled to be administered neoadjuvant low-dose radiotherapy (1GY/1F, D1, D2, D8, D15, Q3W), PD-1 inhibitor tislelizumab (200 mg D1, Q3W), combined with albumin-bound paclitaxel (100mg/m², D1, D8, D15, Q3W) and cisplatin (25mg/m², D1, D8, D15, Q3W) for two cycles. Radically surgical resection was planned to conduct 3-4 weeks after neoadjuvant therapy. The primary endpoint was pCR rate. The second endpoints consisted of MPR rate, objective response rate (ORR), RO resection rate, safety, non-surgery-delay rate and quality of life. 25 patients will finally be enrolled in this study. Simon's two-stage design was adopted, and 10 patients should be included in the first stage. If 2 or more of the first 10 patients reached pCR, the second stage would be successfully entered. **Results:** By Jan 10, 2023, 10 patients were enrolled. 7 out of 10 patients successfully received the study regimen and finished the operation on schedule. Our primary endpoint of first stage was met. 4/7 (57%) patients achieved pCR at the primary site, 3/7 (43%) patients achieved MPR. The pCR/MPR rate was 100%. RO resection rate was 100%. Totally 9 patients underwent MRI scan pre and post neoadjuvant therapy, and the assessment per RECIST criteria were as follow: 0/9 (0%) CR, 6/9 (66%) PR, 3/9 (33%) SD. The treatment-related adverse events (TRAES) were manageable. The most shared adverse events of grade 1/2 were anorexia (89%), anemia (89%) and nausea (66%). No surgical delay was observed. **Conclusions:** Neoadjuvant low-dose radiotherapy, tislelizumab, combined with albumin-bound paclitaxel and cisplatin contributed to an outstanding pCR/MPR rate of 100% (pCR rate of 57% and MPR rate of 43%) at present, and was generally tolerated in locally advanced HNSCC. The second stage is ongoing. Clinical trial information: NCT05343325. Research Sponsor: BeiGene Co., Ltd. and CSPC Co., Ltd.

Neoadjuvant chemoimmunotherapy for the treatment of locally advanced laryngeal and hypopharyngeal squamous cell carcinoma: A single-arm phase 2 clinical trial. *First Author: Yanfeng Chen, Sun Yat-sen University Cancer Center, Guangzhou, Guangdong, China*

Background: Standard treatment for patients with locally advanced laryngeal and hypopharyngeal squamous cell carcinoma (LHSCC) is total laryngectomy, which seriously affects the quality of life. Neoadjuvant treatment with Nab-paclitaxel plus cisplatin (TP) has favorable efficacy with acceptable toxicity for laryngeal preservation in LHSCC. Programmed death 1 (PD-1) blockade plus chemotherapy has shown a survival benefit and recommended as the first-line treatment in recurrent or metastatic head and neck cancer, but the safety and activity in the combination of TP and PD-1 blockade in locally advanced LHSCC need investigation. **Methods:** In this single-center, single-arm, phase 2 trial, newly diagnosed pts with stage T3-4N0-3M0 laryngeal SCC or T2-4N0-3M0 hypopharyngeal SCC were recruited. Eligible patients received chemotherapy [Nab-paclitaxel 240 mg/m² plus cisplatin 75 mg/m² and toripalimab[240 mg, d1]every 3 weeks for 3 cycles. After induction treatment, patients achieving clinical partial response (cPR) or complete response (cCR) received definitive radiotherapy, while those with stable diseases (SD) and progression disease (PD) received surgery plus adjuvant radiotherapy. Toripalimab was given intravenously once every 3 weeks for up to 10 cycles, including 3 cycles before. The primary endpoint was the objective response rate (ORR) according to RECIST 1.1 by investigator assessment to neoadjuvant chemoimmunotherapy. The secondary endpoints included laryngectomy-free survival (LFS), disease failure-free survival (DFS) and overall survival OS at 2 years, quality of life (QOL) and toxic effects. **Results:** From October 2020 to May 2022, 25 patients received neoadjuvant chemoimmunotherapy (median age 58 years; 23.9% men), 52% (13/25) and 48% (12/25) were hypopharyngeal and laryngeal squamous cell carcinoma. 80% (20/25) were clinical T3/4 and 64.0% (16/25) ≥N2. After neoadjuvant chemoimmunotherapy, 2 patients achieved CR, 21 achieved PR, with an ORR of 92% (23/25), 23 patients with CR/PR of the primary tumor received concurrent radiotherapy and immune maintenance therapy, 2 patients with SD/PD received laryngectomy. At a median follow-up of 17 months (range 8-27 months), 1-year DFS was 88.0%, 1-year OS was 96.0%, 1-year LPS was 92.0%. Respectively, only grade 1-2 adverse events occurred in 100% of patients, including loss of appetite (100%), anemia (92.0%), nausea (84.0%), vomiting (52.0%), hypothyroidism (16.0%), peripheral neuritis (20%), leukopenia (12.0%), rash (12.0%). **Conclusions:** Neoadjuvant treatment with TP plus toripalimab achieved impressive ORR and 1-year LPS rate with manageable toxicities in patients with LHSCC. Further follow-up is needed to confirm the long-term efficacy. Clinical trial information: ChiCTR2000033506. Research Sponsor: None.

Impact of acute kidney injury on overall survival in postoperative patients with head and neck cancer who received chemoradiotherapy with cisplatin: A supplementary analysis of a phase II/III trial of JCOG1008. *First Author: Yoshinori Imamura, Kobe University Hospital, Kobe, Hyogo, Japan*

Background: A randomized phase II/III trial of JCOG1008 demonstrated that chemo-radiotherapy (CRT) with weekly cisplatin at 40 mg/m² (Weekly arm) was noninferior to 3-weekly cisplatin at 100 mg/m² (3-weekly arm) in terms of overall survival (OS) for postoperative high-risk head and neck cancer (hazard ratio [HR], 0.69 [99.1% CI, 0.37 to 1.27 < 1.32]; *J Clin Oncol* 2022; 40: 1980-90). Acute kidney injury (AKI) is a major dose-limiting toxicity of cisplatin. Here, we investigated the impact of AKI on OS in patients treated with CRT in JCOG1008. **Methods:** A total of 251 patients who were treated with CRT in JCOG1008 were analyzed. AKI was defined as an increase in serum creatinine of ≥0.3 mg/dL or a 1.5-fold or more increase from baseline (≥stage I) within 30 days after completion of CRT, based on the AKI Network classification/staging system. OS in the two arms was compared by the development of AKI using the log-rank test. **Results:** The total incidence of AKI in the weekly arm was lower than that in the 3-weekly arm (38 of 122 [31.1%] vs. 56 of 129 [43.4%]). The incidence of stage II/III AKI was also lower in the weekly arm (8 of 122 [6.6%] vs. 19 of 129 [14.7%]). Total cisplatin dose was similar in patients who did and did not develop AKI in the weekly arm, but was lower in patients who developed AKI in the 3-weekly arm (Table). Moreover, no difference in OS was observed between patients who did and did not develop AKI in the weekly arm (HR, 1.06 [95% CI, 0.53 to 2.10]), whereas patients who developed AKI in the 3-weekly arm had poorer OS than those who did not (HR, 1.83 [95% CI, 1.04 to 3.21]). **Conclusions:** In this supplementary analysis of JCOG1008, development of AKI impacted OS in the 3-weekly arm, but not in the weekly arm. Consistent exposure to cisplatin through weekly fractionated administration appears of greater clinical significance than cumulative dose, providing maintenance of treatment intensity and better kidney safety, and likely also improving outcomes. Clinical trial information: JRCTS031180135. Research Sponsor: National Cancer Center Research and Development Funds (29-A-3, 25-B-2, and 2020-J-3); AMED under Grant Nos. JP16ck0106055, JP16ck0106093, and JP19ck0106321; and a Grant-in-Aid for Clinical Cancer Research (H23-009 and H26-052) from the Ministry of Health, Labor and Welfare of Japan.

Treatment delivery, compliance, and efficacy outcomes according to treatment arm.						
Parameter	3-weekly arm			Weekly arm		
	AKI (-) n=73	AKI (+) n=56	P-value	AKI (-) n=84	AKI (+) n=38	P-value
Total RT dose (Gy), median (IQR)	66 (66-66)	66 (66-66)	0.72	66 (66-66)	66 (66-66)	0.68
Duration of RT (days), median (IQR)	49 (47-50)	50 (47-52)	0.60	49 (46-50)	49 (47-50)	0.37
Total cisplatin dose (mg/m ² , IQR)	297.4 (258.9-299.1)	276.3 (219.7-298.0)	0.007	239.2 (199.5-276.7)	238.6 (197.3-277.2)	0.94
Proportion of actual to planned delivery of cisplatin (%), median (IQR)	99.2 (86.4-100.0)	92.4 (73.3-99.9)	0.009	85.7 (71.4-100.0)	85.7 (71.4-100.0)	0.83
3-year overall survival (%; 95% CI)	70.6 (58.6-79.8)	57.9 (43.6-69.7)	0.04	74.7 (63.9-82.7)	76.1 (59.1-86.8)	0.88
3-year relapse-free survival (%; 95% CI)	64.3 (52.2-74.1)	49.5 (35.8-61.9)	0.09	68.9 (57.8-77.7)	65.8 (48.5-78.5)	0.27

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Poster Session

Neoadjuvant tislelizumab combined with APF for patients with locally advanced head and neck squamous cell carcinoma: A prospective single-arm clinical trial. *First Author: Jing Yan, The Comprehensive Cancer Centre of Nanjing Drum Tower Hospital, Medical School of Nanjing University & Clinical Cancer Institute of Nanjing University, Nanjing, China*

Background: Seeking out a more effective and less-toxic regimen is necessary for patients with locally advanced head and neck squamous cell carcinoma (HNSCC). The aim of this study is to evaluate the efficacy and safety of neoadjuvant anti-programmed cell death-1 antibody tislelizumab combined with APF (albumin-bound paclitaxel, platinum and fluorouracil) followed by surgery or concurrent chemoradiotherapy. **Methods:** In this prospective, single-center, single-arm clinical study, previously untreated patients with locally advanced HNSCC, aged 18-75 years without severe comorbidities and contraindications to immunotherapy are enrolled. Eligible patients received A (200 mg/m² d1) P (60 mg/m² d1- d2) F (600 mg/m² CIV120h) induction chemotherapy along with tislelizumab (200 mg d1) every 3 weeks. The curative effect is evaluated (RECIST 1.1) after 3 cycles and a multidisciplinary team discuss whether to perform surgery. For patients undergoing surgery, treatment is completed if there is no residual and extra-capsular lymph node invasion; in case of positive surgical margin, or extracapsular lymph node invasion, or residual lymph nodes, patient will receive concurrent chemoradiotherapy (tumor bed and neck lymph drainage area 66 Gy~70 Gy, P 60 mg/m²). Those not suitable for surgery will receive radical concurrent chemoradiotherapy (GTV 66Gy~70Gy, PTV 50Gy, P 60 mg/m²) within 3 weeks after neoadjuvant treatment. The primary endpoint of efficacy evaluation is the pathological complete response (pCR) rate. Safety evaluation indicators include vital signs, laboratory indicators and adverse events (NCI CTC AE4.0). **Results:** From Apr 2022 to Jan 2023, 12 patients are screened and enrolled. For the 7 patients who complete 3 cycles of neoadjuvant therapy, 3 patients (42.8%) successfully undergo surgery, with 2 patients (28.5%) achieving pCR and 1 patient (14.3%) achieving major pathological response (MPR). For the other 4 patients, 1 patient (14.3%) achieve pCR by multipoint biopsy of the primary lesion and 2 patients (28.5%) obtain radiologic partial response (PR) by MRI. 1 patient' lymph nodes tend to increase during radiotherapy and that patient withdraw from clinical trial and undergo salvage surgery. The objective response rate (ORR) of neoadjuvant treatment is 85.7% and pCR rate is 42.9%. Grade 2 or higher AEs during neoadjuvant therapy include grade 2 liver function damage (n = 1, 8.3%), grade 3 myelosuppression (n = 1, 8.3%). 1 (8.3%) patient developed radiation-related oral mucositis (RTOG 2). No other obvious adverse reactions of radiotherapy, chemotherapy or immunotherapy are observed. **Conclusions:** Combining Tislelizumab with APF followed by surgery or radical concurrent chemoradiotherapy is feasible and effective in patients with locally advanced HNSCC, and further studies are needed to verify its effectiveness and safety. Research Sponsor: None.

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Poster Session

Safety and immunogenicity of TG4050: A personalized cancer vaccine in head and neck carcinoma. *First Author: Christian H.H. Ottensmeier, The Clatterbridge Cancer Centre NHS Foundation Trust, Liverpool, United Kingdom*

Background: Despite adjuvant therapy, over 50% of surgically treated head and neck squamous cell carcinoma (HNSCC) patients (pts) experience a recurrence of disease. Systemic stimulation of cellular immunity against tumor mutations using a viral vaccine may be an ideal modality to clear residual cancer cells. For this purpose, we developed a pipeline for the design of TG4050, a personalized cancer vaccine (PCV) using a Modified Vaccinia Ankara (MVA) viral vector. We report here preliminary safety and immunogenicity data from a phase I TG4050 study. **Methods:** Surgically resected stage III or IV, HPV negative HNSCC pts were enrolled in the study. pts must have achieved clinical remission after adjuvant chemoradiotherapy. A PCV for each pt was manufactured with up to 30 neoantigens identified using a state-of-the-art machine learning algorithm, from next generation sequencing (NGS) data. Pts randomized to arm A received the PCV after completion of primary treatment. Pts randomized to arm B received the PCV in the event of relapse, in conjunction with second line therapy. The PCV schedule consisted of an induction period of 6 weekly administrations, followed by booster doses once every 3 weeks for up to one year. Immune cells were collected by leukapheresis at baseline and at day 64. Primary endpoint was safety. Secondary endpoints included feasibility, disease free survival and immune response as assessed by ex-vivo IFN γ -ELISPOT. **Results:** At the time of data cut-off, a total of 31 pts were randomized, 15 in arm A and 16 in arm B. A vaccine was successfully designed for all randomized pts. Pts had no evidence of disease at baseline either at the clinical or molecular level, as assessed by ctDNA assessment. All adverse events (AEs) were mild to moderate and most were injection site reactions. Median follow-up was 9.2 months in arm A vs 7.6 months in arm B. None of the pts in arm A experienced relapse vs. 2 in the arm B. Immune monitoring demonstrated priming of a polypeptidic T cell response against the PCV in 100% of pts in arm A, among pts evaluated to date, with a mean of 9 responses per pt (6-19). Responses were observed regardless of HLA genotype, and without cross-reactivity to the wildtype antigen. Baseline tumor analyses revealed challenging genomic and immune profiles such as low TMB (avg of 3.06 $\pm$ 0.86 Mut/Mb), a majority of immune-desert tumors, and a low expression of important immune related factors including PD-L1 (16 pts out of 17 had a negative to moderate PD-L1 expression). **Conclusions:** Our preliminary data demonstrate that TG4050 is safe, well tolerated, and capable of inducing T cell responses in cold tumors. In summary viral based, PCVs designed to induce tumor-specific neoantigen may be associated with a safe tolerance and an improved outcome in HNSCC pts. Clinical trial information: NCT04183166. Research Sponsor: Transgene SA, NEC Corporation.

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Poster Session

Neoadjuvant durvalumab and tremelimumab in resectable locally advanced SCC of the oral cavity: DUTRELASCO study. *First Author: Michel Bila, University Hospitals Leuven - Catholic University Leuven, Leuven, Belgium*

Background: Promising rates of response to ICI have been observed in patients with OSCC. This is phase I/II study with focus on biological changes observed in sequential tissue acquisition. **Methods:** Eligibility criteria: Resectable OSCC stage IV Description of each treatment arm: Arm A: durvalumab (1500 mg) on day -14 and 6 cycles adjuvant Arm B: durvalumab (1500 mg) and tremelimumab (75 mg) combination on day -14 and 6 cycles adjuvant Primary endpoint: Biological response in tumor tissue by means of difference in CD8+ lymphocyte infiltration density (TIL) and % remaining viable tumor cells. Secondary endpoints: Recist v1.1 OS PBMC and plasma analysis scRNA-seq Statement of study design: open-label, prospective stratified, phase I/II study. **Results:** No ICI related toxicity interfered with surgery. 50 % of patients presented with at least 1 severe AE. There was no difference between both arms. 2 year OS is 64% in arm A and 80% in arm B. Both arms show a significant increase (p = 0.01) in TILs. We observed a significant decrease in viable tumor cells (p < 0.01). No objective pathological response with > 50% decrease of viable tumor cells was observed. T-cell expansion varied although a positive correlation between T-cell expansion and radiologic tumor shrinkage was demonstrated (p < 0.001). T-cell expansion was tumor-specific (p = 0.749). Differential gene expression analysis comparing expanding T-cells in tumors observed increased expression of effector/activation markers and immune cell homing in expanding T-cells, but reduced expression of naïve and immune regulatory markers. By also profiling tumor-draining lymph nodes, we observe that the addition of aCTLA4 affects the lymph nodes and primes CD4+ naïve T-cells, triggering their expansion. Systemically PD-1 expression in both CD4+ and CD8+ T cells is increased together with an upregulation of activation markers after ICI. 2 baseline plasma factors with predictive capacity for clonotype response were identified: baseline LAG-3 and B7.2(CD86). **Conclusions:** A 14-day window may be considered ethically sound, it might not provide sufficient time for evaluating pathological response. It is both safe and feasible to use neoadjuvant ICI treatment in OSCC. While the initial toxicity is low and does not interfere with standard of care surgical procedures, adjuvant treatment may result in higher toxicity. Response to ICI is not dichotomous but rather a continuous variable which we represent here as clonotype expansion. A positive correlation was demonstrated between T-cell expansion and radiologic tumor shrinkage after one cycle of ICB. T-cell expansion was tumor-specific and gene expression analysis observed increased expression of activation markers here further supporting this as a surrogate marker. Combination therapy facilitates expansion of both CD4+ and CD8+ T-cells versus just CD8+ T-cells with aPD-L1 alone. Clinical trial information: NCT03784066. Research Sponsor: AstraZeneca; VR 2016 2312 Doc.1521/4; EORTC IMMUCan.

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Poster Session

Combined pulsed radiotherapy (QUAD shot regimen) with immune checkpoint inhibition (ICI) to enhance immune response for LAHNSCC in patients considered ineligible for curative intent therapy. *First Author: Jennifer F. De Los Santos, Grandview Cancer Center, Birmingham, AL*

Background: Elderly patients with head and neck cancer (HNC) represent a growing population that would benefit from novel, less toxic approaches. Recent negative trial results adding ICI to chemo-RT for LAHNSCC (Javelin, Keynote 412) suggest that total nodal irradiation may create an immunosuppressive tumor microenvironment (TME), blunting the efficacy of ICI. This study was undertaken to use pulsed QUAD SHOT as an in-situ vaccine by stimulating the TME prior to delivery of ICI, excluding elective nodal sites, to enhance the immune response. **Methods:** 33 pts (20 males/13 females), with a median age of 81, seen at two community hospitals, ineligible for curative therapy, were treated with pulsed dose QUAD shot regimen to gross disease (44.4-59.2 Gy) spaced 3 weeks apart with addition of an approved ICI (Pembrolizumab or Cemiplimab). ERT was directed ONLY to GTV p+/n. ICI was administered in most pts after the 1st QUAD shot to enhance immune response. ICI was continued adjutantly until a > Grade 3 adverse event (AE) or progression of disease (POD). Pts with either advanced cutaneous or mucosal SCC were included (cSCC, mSCC). 39% presented with N1-2 adenopathy, and 24% presented with recurrent disease. PD-L1 status were not routinely obtained. **Results:** The median number of ICI cycles delivered was 5 (range 2-24). All pts completed at least 3 QUAD shots. Overall LRC for all 33 pts was 69.7%, with a mean follow-up of 11 months (1-39). LRC for 33 pts at 1 and 2 years after the end of radiation were 61.07% and 55.52%, respectively. The percentage of pts free from elective regional recurrences at 1 and 2 years was 87.13% for both cSCC and mSCC groups. Six pts (18%) experienced distant failure. Freedom from distant failure at 1 yr after QUAD shot completion by pathology was 100.00% for cSCC and 77.08% for mSCC. DFS for all 33 pts at 1 and 2 yrs were 59.39% and 37.12%, respectively. DFS at 1 year for cSCC was 100% and 53% for mSCC. Median DFS for the mSCC was 13.8 months. Overall survival for all 33 pts was 45.45% with a median OS time of 17.7 months. 1 and 2 year OS rates were 65% and 33%. Overall toxicity was low and manageable. Gr 3 mucositis occurred in 1 patient and 5 (15%) developed Gr 2 AE's. Gr 3/4 IMAR's were observed in 3 pts and included infusion reaction, colitis, and fatigue/FTT and were discontinued. 4 pts required post QUAD PEG's unrelated to radiation toxicity and due to POD. **Conclusions:** In elderly, frail, or comorbidly ill pts with LAHNC, the addition of ICI to involved field pulsed QUAD shot regimen tripled the median OS rate from prior publications with QUAD shot alone from 5.7 months to 17 months in our series. The low percentage of failure in the elective nodal beds was very encouraging based on our hypothesis. This approach represents the next step in an evolution away from conventional RT approaches that engender greater toxicity and warrants further study. Research Sponsor: Gregg and Stacy Bacchieri Philanthropic Fund.

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Poster Session

Are we ready for biomarker driven, radiation dose-adaptable de-escalation studies for HPV+ oropharyngeal cancer? *First Author: Krzysztof Misukiewicz, Hematology and Medical Oncology, Icahn School of Medicine at Mount Sinai, New York, NY*

Background: Plasma circulating tumor modified viral human papillomavirus (HPV) DNA (TTMV) is a sensitive and specific biomarker of HPV+ oropharyngeal squamous cell carcinoma (HPVOPC). Patients with unresectable locally advanced (LA) HPVOPC are currently treated with induction chemotherapy (IC) and standard (sd) or reduced dose (rd) of chemoradiation (CRT). Post IC TTMV can be used in the future to help assign patients to sdCRT or rdCRT. This approach may help to maintain high efficacy and minimize long-term side effects of CRT in HPVOPC. **Methods:** Patients with LA HPVOPC and High Risk (HR) features (radiographic ECE, T4 primary, >N2c, and isolated lung metastases) were treated with 3 cycles of TPF IC followed by rdCRT to 5600 cGy with weekly carboplatin in responders, sdCRT in clinical non-responders and in M1 patients who also received SBRT to isolated biopsy proven lung metastases. Patients with > 20 pack year smoking history were excluded. Patients were eligible for rdCRT if they had a significant clinical response to IC and were participating in the QB2 trial (NCT02945631). **Results:** Fourteen subjects had pre and post IC TTMV testing available for analysis. 9/14 subjects after IC received rdCRT to 5600 cGy with weekly Carboplatin. 2 subjects were removed from the QB study for clinically inadequate response, 1 withdrew consent and 2 were M1 and treated for cure. All 5 underwent sdCRT 7000 cGy. 13/14 patients had TTMV testing done prior IC, 1 subject had TTMV done after the start of cycle 1 of IC; all 14 of them had a pretherapy or (1 subject) immediate post infusion positive elevated TTMV test. 11/14 subjects developed negative TTMV after 1 or 2 cycles IC. 3/14 subjects after 1 cycle and additional 6/14 subjects after 2 cycles of IC developed negative TTMV. 3/14 subjects still had abnormal TTMV after 3 cycles of IC; 2/3 subjects underwent 7000 cGy. Remaining 1/3 had a negative repeat TTMV prior to CRT and underwent rdCRT with 5600 cGy. TTMV testing was done for all subjects after completion CRT and all were negative. All subjects in addition to standard surveillance had TTMV testing done during their surveillance visits. 2 subjects developed recurrent HPVOPC after CRT: 1 locoregional and 1 metastatic (elevated TTMV after IC; sdCRT). **Conclusions:** In contrast to NCCN guidelines, rdCRT in many academic institutions has become a standard for HPVOPC. We have demonstrated a prompt reduction of TTMV to 0 in a subset of patients receiving 1 cycle and in a majority after at least 2 cycles of IC. The small sample size of our study lacks the statistical power to demonstrate that the failing to attain negative TTMV after/during IC is associated with a poor prognosis and warrants more aggressive therapy. TTMV biomarker response may have important prognostic value in delivering primary therapy and warrants further larger and more structured studies. Research Sponsor: None.

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Poster Session

Use of machine learning derived features from CT and H&E whole-slide images to predict overall survival in head and neck squamous cell carcinoma. *First Author: Bolin Song, Emory, Atlanta, GA*

Background: Computed tomography (CT) and H&E whole-slide images (WSI) have been found to carry rich prognostic information for patients diagnosed with head and neck squamous cell carcinoma (HNSCC). However, most machine learning models aimed for outcome prediction only took advantage of single image modality. In this work, we developed and validated a prognostic machine learning method incorporating both CT and WSI to predict overall survival in HNSCC patients. **Methods:** Matched radiographic CT scans and digitized WSI were acquired from the Cleveland Clinic for 167 HNSCC patients, including 120 HPV-associated oropharyngeal cancer and 47 laryngeal cancer. Both primary tumor and the largest suspicious lymph node were annotated on CT scans and primary tumor was delineated on H&E WSI. We split the dataset into training and validation set using a 7:3 ratio, which resulted in 119 patients in the training set and 48 for hold-out validation. We applied a machine learning model (M_ML) using both CT and WSI as input to perform end-to-end predictions of overall survival. We used the harrell's concordance index (C-index) to evaluate the prognostic performance. Finally, we performed the multivariable cox proportional hazard analysis adjusting for clinicopathological variables (i.e. age, gender, smoking pack-year (PY), AJCC 7th edition overall stage, and treatment modality) to validate the independent prognostic significance of the model. **Results:** The combined machine learning model M_ML (C-index = 0.81) outperformed the model using CT images alone (C-index = 0.63) and WSI alone (C-index = 0.64) on the validation set. In multivariable analysis, M_ML is still statistically significant accounting for clinicopathologic factors (p = 0.0007). **Conclusions:** This pilot study shows that a multi-omic machine learning model utilizing both radiographic CT and digitized WSI can predict HNSCC overall survival and outperforms models using only a single modality. Research Sponsor: U.S. National Institutes of Health.

Variables	Hazard Ratio (Confidence interval)	p values
Age	1.05 (0.95 - 1.16)	0.36
Gender (Male vs Female)	8.72 (0 - 100)	0.99
Smoking PY	1 (0.97 - 1.03)	0.85
Clinical T stage (3, 4 vs 1, 2)	1.79 (0.32 - 9.98)	0.51
Clinical N stage (2, 3 vs 0, 1)	2.65 (0.32 - 21.76)	0.36
Treatment (CRT vs RT)	0.27 (0.02 - 3.17)	0.30
Cancer subtype (laryngeal vs oropharyngeal)	6 (0.23 - 158)	0.28
M_ML	129.7 (7.69 - 2188)	0.0007

Multivariable cox proportional hazard analysis accounting for clinicopathologic factors.

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Poster Session

10-year outcomes of technically unresectable oral cancers with neoadjuvant chemotherapy: Real-world data and implications for clinical practice. *First Author: Aditya Dhanawat, Tata Memorial Centre, Mumbai, India*

Background: Neo-adjuvant chemotherapy (NACT) followed by response assessment is the standard treatment algorithm for locally advanced oral cavity squamous cell carcinomas (OCSCC) in the Indian subcontinent. The 3-drug NACT regimen (Docetaxel-Cisplatin-5-FU) has shown improvement in progression free survival (PFS) and overall survival (OS) over 2-drug regimen (Docetaxel-Cisplatin) in a phase-3 randomised study. We have analysed the 10-year outcomes with this treatment algorithm. **Methods:** This was an institutional review board approved retrospective analysis of a prospectively collected dataset of borderline resectable OCSCC patients who received NACT. Adults with an eastern co-operative oncology group (ECOG) performance status (PS) 0-2 deemed technically unresectable in a multi-disciplinary clinic were included. All patients received 2-3 cycles of 3-weekly NACT. Patients with good general condition (GC) who became resectable underwent surgery followed by appropriate adjuvant therapy. Patients who were unresectable received definitive chemoradiation (CRT), palliative chemotherapy, radiotherapy or best supportive care based on GC. The OS was calculated from date of diagnosis to date of death. Kaplan-Meier method was used for estimation of 10-year OS and impact of different regimens on OS was calculated using the log-rank method. **Results:** A total of 3266 patients were analysed, of which 2857 (87.5%) were males. The median age was 46 years (IQR: 39 - 54). The most common subsites were buccal mucosa (54.7%), tongue (30.4%) and alveolus (7.9%). Patients presented with either stage IVA (51.3%) or IVB (48.7%). The major indications for NACT were edema up to zygoma (42.2%), involvement of hyoid (22.6%), and high infra-temporal fossa (11.5%). The most common NACT was Docetaxel-Cisplatin (50.2%) followed by Docetaxel-Cisplatin-5-Fluorouracil (29.0%) and Paclitaxel-Carboplatin (13.3%). Planned number of NACT cycles could not be completed by 361 (11.1%) patients. Of 3266 patients, 929 (28.4%) underwent surgery followed by adjuvant CRT (26.7%) or adjuvant RT (1.3%); 13.1% underwent definitive CRT, 35.8% received palliative chemotherapy, while 11.7% defaulted for definitive treatment. Pathological complete response was seen in 76 (8.2%) patients, while 871 (93.8%) achieved negative margins and 338 (36.4%) had extra-nodal extension. The median OS was 9 months (95% CI: 8.6 - 9.4). NACT with more than 2-drugs had an OS of 13.2 months (95% CI: 12 - 14.4) vs 7.5 months (95% CI: 7.1 - 7.97) for 2-drug regimens. The 10-years OS was also higher for more than 2-drugs regimen - 21% (95% CI - 17.4% - 24.9%) vs 5.14% (95% CI: 3.28% - 7.6%) (p = 0.000). 10-years OS of patients who underwent surgery vs those who did not was 22.28% vs 3.98% (p = 0.000). **Conclusions:** NACT with more than 2-drug regimens had survival benefit over 2-drug regimens in technically unresectable OCSCC. Research Sponsor: None.

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Poster Session

Tislelizumab plus chemotherapy as induction treatment followed by chemoradiotherapy or surgery in locally advanced hypopharyngeal squamous cell carcinoma: A single-arm, phase II trial. *First Author: Lin Gui, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing Key Laboratory of Clinical Study on Anticancer Molecular Targeted Drugs, Beijing, China*

Background: Induction chemotherapy (ICT) followed by chemoradiotherapy (CRT) is the standard of care for locally advanced hypopharyngeal squamous cell carcinoma (LA HPSCC). We aimed to assess whether add immunotherapy to ICT further improving patient outcomes. **Methods:** In this phase II, single-arm study, eligible pts aged 18-70 yrs diagnosed with stage III-IVB (AJCC 8th) HPSCC received induction therapy with tislelizumab (200 mg), cisplatin (75 mg/m²) and nab-paclitaxel (260 mg/m²) Q3W for 3 cycles. After assessment by multidisciplinary team, pts received surgery or CRT. The primary endpoint was objective response rate (ORR). Secondary endpoints include major pathologic response (MPR) in surgery group, disease control rate (DCR), 2-yr PFS rate in CRT group and 2-yr DFS rate. **Results:** 29 pts were enrolled (median age, 61 y; 97% male; stage III/IVA/IVB, 7%/90%/3%) from May to Nov 2022. Median follow-up was 22.3 months, no disease progression occurred in all patients. For all pts, the post-induction ORR and DCR were 82% and 100%. In surgery group (n = 10), all pts achieved R0 resection, and 5 (50%) pts reached pathological complete response (pCR). A patient with stable disease underwent a total laryngectomy achieved pCR by postoperative pathologic evaluation. Grade 3 and 4 treatment-related adverse event (TRAE) reached 82.8%, and mainly come from chemotherapy-related neutropenia. There was no TRAE leading to treatment discontinuation. **Conclusions:** These early data suggested that tislelizumab plus chemotherapy as induction treatment followed by chemoradiotherapy or surgery was safe and had the potential to provide clinical benefits for patients in LA HPSCC. The inconsistency between radiographic and pathological evaluation needs further exploration. Further follow-up is needed to confirm the long-term efficacy. Clinical trial information: ChiCTR2200060094. Research Sponsor: None.

ABSTRACT WITHDRAWN

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Poster Session

A multicenter, single-arm phase 2 study of surufatinib plus toripalimab for patients with locally advanced or metastatic radioactive iodine-refractory differentiated thyroid cancer. *First Author: Dongmei Ji, Fudan University Shanghai Cancer Center, Shanghai, China*

Background: For patients (pts) with radioactive iodine-refractory differentiated thyroid cancer (RAIR-DTC), there presents a considerable therapeutic challenge with poor long-term outcomes. The open-label, multi-cohort, single-arm phase 2 study was performed to evaluate surufatinib (a small-molecule inhibitor of VEGFR 1-3, FGFR1 and CSF-1R) in combination with toripalimab (an anti-PD-1 antibody) in pts with RAIR-DTC. **Methods:** Eligible pts were with locally advanced or metastatic RAIR-DTC who were not amenable for surgery or external beam radiotherapy, with a radiologically confirmed disease progression within 12 months before treatment, and with ≥ 6 months since last radioiodine treatment. Enrolled pts received surufatinib 250 mg orally, QD, plus toripalimab 240 mg IV, Q3W, until disease progression or reaching the maximum treatment duration with toripalimab of 24 months, or other protocol-specified criteria. The primary endpoint was objective response rate (ORR) per RECIST 1.1. **Results:** From March 2020 to November 2021, 15 pts were enrolled and received a median duration of 11.1 months of the combination treatment, with a median age of 61 years (range: 37-74). 9 (60%) pts were male, and 12 (80%) had papillary thyroid cancer. Of the 13 pts with PD-L1 immunochemical results, 6 pts had PD-L1 CPS $\geq 1\%$. As of 28 Dec 2022, the median follow-up duration was 22.11 months. Of the 15 pts with at least one post-baseline tumor assessment, the confirmed ORR was 33.3% (5 PRs) and DCR was 93.3%. mDoR was 8.34 months. mPFS (95%CI) was 10.91 months (4.01, NA). mOS was not reached, and 12-month OS rate was 100%. 14 (93.3%) pts had treatment-emergent adverse events (TEAEs), and 10 (66.7%) pts reported grade ≥ 3 TEAEs, most commonly ($\geq 10\%$ pts) with hypocalcemia (20%), diarrhea (20%) and hypertension (13%). There was no death due to TEAE in the study. **Conclusions:** Surufatinib plus toripalimab showed encouraging antitumor activity and tolerable safety profile in pts with locally advanced or metastatic RAIR-DTC. Clinical trial information: NCT04169672. Research Sponsor: HUTCHMED Limited.

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Poster Session

Phase II prospective trial of induction chemotherapy for advanced sinonasal squamous cell or poorly differentiated carcinoma. *First Author: Kevin J. Contrera, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: The standard treatment for resectable advanced sinonasal carcinoma is surgery followed by adjuvant therapy. Despite aggressive therapy, disease control and survival have historically remained poor. The role of induction chemotherapy (IC) has not been fully assessed. The objective of this study is to prospectively evaluate IC for local disease control, organ preservation, and response-based local treatment selection. **Methods:** This is a phase II, open-label, single-center trial of patients with previously untreated, resectable and nonresectable, locally advanced squamous cell or poorly differentiated carcinoma of the nasal cavity or paranasal sinuses. Eligible patients were > 16 years of age, had an ECOG Performance Status of 0-1, and stage II-IV, MO disease. Patients were treated with an IC regimen of docetaxel, cisplatin, and fluorouracil (TPF) for 2 cycles, then evaluated for response using clinical (symptoms and nasal endoscopy) and radiographic (RECIST 1.1 and PET) assessments. Those who achieved an objective response received a third cycle followed by chemoradiotherapy (CRT); non-responders underwent surgery with adjuvant radiotherapy. The primary endpoints were overall response rate (ORR) and 2-year local disease control. Secondary endpoints included disease-specific survival (DSS), overall survival (OS), disease-free survival (DFS), organ preservation, patterns of failure, and treatment toxicity. **Results:** 31 patients were enrolled between 2008 and 2020, of which 28 were evaluable for efficacy. Disease was T4a (57%) or T4b (21%), N+ (38%), and would have required maxillectomy (89%), craniotomy (54%), or orbital exenteration (29%). After IC, the ORR was 82.1% (7.1% complete response, 75.0% partial response), and the non-response rate was 17.9% (17.9% stable disease, 0% progressive disease). Patients then underwent CRT (79%) or surgery (21%). Following CRT, salvage surgery was performed for 41% of patients. Grade 3 or 4 adverse events occurred in 18% of patients. The 2-year local control rate was 53.6%. The 2-year DSS rate was 75% (median DSS not reached). For patients alive at 2 years, 63% had organ preservation (avoiding maxillectomy 38%, craniotomy 13%, orbital exenteration 38%). The median DFS and OS were 19.2 and 47.4 months, respectively. Factors associated with worse OS were nonwhite race ($P = .035$), T4 category ($P = .037$), overall stage IV ($P = .038$), and paranasal sinus subsite ($P = .002$). Surgery did not have significantly different OS than CRT ($P = .86$). **Conclusions:** This phase II study demonstrates the validity of induction chemotherapy as a guide for local treatment selection in patients with advanced sinonasal carcinoma. A majority of patients achieved disease control and organ preservation. The median survival was 4 years in a cohort with very advanced locoregional disease, with no survival difference between CRT and surgery. NCT03493425. Clinical trial information: NCT00707473. Research Sponsor: None.

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Poster Session

Larotrectinib (laro) long-term efficacy and safety in patients (pts) with tropomyosin receptor kinase (TRK) fusion thyroid carcinoma (TC). *First Author: Maria E. Cabanillas, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Neurotrophic tyrosine receptor kinase (*NTRK*) gene fusions are oncogenic drivers in a variety of tumor types, including TC. Laro is a first-in-class, highly selective, central nervous system (CNS)-active TRK inhibitor approved for tumor-agnostic use in pts with TRK fusion cancer based on a rapid, robust, and durable objective response rate (ORR) in both adult and pediatric pts with various cancers. Here, we report data on the subset of pts with TRK fusion TC treated with larotrectinib with long-term follow-up. **Methods:** Pts with TRK fusion TC enrolled in three laro clinical trials (NCT02576431, NCT02122913, NCT02637687) were included. Laro was administered at 100 mg twice daily to most pts; two pediatric pts received 100 mg/m². Responses were assessed per independent review committee (IRC) using RECIST v1.1. Data cut-off: July 20, 2022. **Results:** As of data cut-off, 30 pts were eligible for efficacy assessment by IRC. The median age was 61.5 years (range 6-80) and the median time since initial cancer diagnosis was 5.0 years (range 0-46). The gene fusions involved *NTRK1* ($n = 14$; 47%) or *NTRK3* ($n = 16$; 53%). Fifteen pts (50%) received no prior systemic therapies, and six (20%) received ≥ 2 ; 23 (77%) received prior radioiodine. ORR was 63% (95% confidence interval [CI] 44-80); three (10%) complete response, 16 (53%) partial response (PR), five (17%) stable disease, four (13%) progressive disease, and two (7%) not evaluable. For pts classified as differentiated TC (DTC; $n = 23$), the ORR was 78% (95% CI 56-93). For pts classified as anaplastic TC (ATC; $n = 7$), the ORR was 14% (95% CI 0-58). All four pts with CNS metastases at baseline had a PR. Median time to response was 1.9 months, and median duration of response (DoR) was 43.3 months (95% CI 21.6-not estimable [NE]) at a median follow-up of 32.3 months. Median progression-free survival was 35.5 months (95% CI 23.4-NE) at a median follow-up of 34.0 months. Median overall survival (OS) was not reached (NR; 95% CI 48.7-NE) at a median follow-up of 46.4 months; the 48-month OS rate was 71% (95% CI 54-88). Median OS was NR (95% CI 48.7-NE) in DTC and 8.8 months (95% CI 2.6-NE) in ATC. At data cut-off, five pts who had disease progression continued treatment for ≥ 4 weeks due to continued clinical benefit. Treatment-related adverse events (TRAEs) were predominantly Grade 1-2. Grade ≥ 3 TRAEs were reported in two (7%) pts (anemia and decreased lymphocyte count). There were no treatment discontinuations due to TRAEs. **Conclusions:** Laro continues to demonstrate a rapid and durable response, extended survival, and a favorable safety profile in pts with TRK fusion DTC. Limited single-agent activity was observed in ATC. These results support the wider adoption of next generation sequencing panels, which include *NTRK* gene fusions, in pts with advanced TC prior to the initiation of any systemic therapy. Clinical trial information: NCT02576431, NCT02122913, NCT02637687. Research Sponsor: Bayer HealthCare Pharmaceuticals, Inc.

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Poster Session

A phase II trial of nivolumab for patients with platinum-refractory recurrent or metastatic salivary gland cancer. *First Author: Yoshiaki Nagatani, Department of Medical Oncology and Hematology, Kobe University Hospital, Kobe-Shi Chuo-Ku, Japan*

Background: Salivary gland cancer is rare and has various pathological subtypes. With this rarity and heterogeneity, the therapeutic contribution of chemotherapy, including immune checkpoint inhibitors, for recurrent or metastatic salivary gland cancer (RM-SGC) has not been elucidated. The purpose of this trial was to investigate the efficacy and safety of nivolumab for patients with platinum-refractory RM-SGC. **Methods:** This open-label, single-arm, multicenter phase II trial was conducted at 9 centers in Japan. Eligible patients had platinum-refractory recurrent or metastatic salivary gland cancer with measurable lesions by RECIST v1.1 and an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0, 1, or 2. Nivolumab 240 mg/body was administered intravenously every 2 weeks until progression or unacceptable toxicity. The primary endpoint was objective response rate (ORR). We set the null hypothesis at 3% and the expected at 15% with a one-sided alpha of 0.1 and power of 80%. Secondary endpoints were disease control rate (DCR), progression-free survival (PFS), overall survival (OS), and safety. **Results:** Twenty-four patients (16 males; median age, 65.5 years [range, 34-78 years]) were enrolled between March 2018 and January 2022. Pathological types were salivary duct carcinoma (n = 10), adenoid cystic carcinoma (n = 6), adenocarcinoma not otherwise specified (n = 5), mucoepidermoid carcinoma (n = 2), and acinic cell carcinoma (n = 1). In the majority of cases the primary site was a major salivary gland (n = 21), namely the parotid gland in 16 patients and submandibular gland in 5. The primary endpoint of ORR was 8.3% (2/24, 80% CI, 2.2-20.6%), with 2 partial responses (PR) in patients with salivary duct carcinoma (2/10, ORR: 20.0%). DCR was 29.2% (7/24, 2 in PR and 5 in stable disease), and all of the other 17 patients (70.8%) showed progressive disease (PD) on first disease evaluation at 12 weeks. With a median follow up for survivors of 32.0 months, median PFS and OS were 3.0 months (95% CI, 2.8-3.2 months) and 25.0 months (95% CI, 10.9-39.1 months), respectively. There was no new safety concern with nivolumab monotherapy. **Conclusions:** This phase II trial of nivolumab monotherapy for patients with platinum-refractory RM-SGC did not meet its primary endpoint of ORR. Although nivolumab monotherapy may be worth further development in salivary duct carcinoma, these results may raise concerns over nivolumab monotherapy for RM-SGC. Translational research to elucidate the immune microenvironment of each pathological type is under investigation. Clinical trial information: UMIN000029636. Research Sponsor: None.

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Poster Session

Darolutamide for patients with androgen receptor positive salivary gland cancers (DISCOVERY): The results of phase 2 study of darolutamide monotherapy. *First Author: Susumu Okano, National Cancer Center Hospital East, Kashiwa, Chiba, Japan*

Background: There is no standard first-line treatment for recurrent/metastatic (R/M) or unresectable locally advanced (LA) salivary gland cancer (SGC). Androgen receptor (AR) overexpression is known to be particularly high (43-92%) in SDC, depending on histology, and has been identified as a potential molecular target for SGC treatment. However, the clinical utility of this approach has not been well investigated. Here, we evaluated the efficacy and safety of darolutamide for patients with AR-positive SGC. **Methods:** Eligibility included LA or R/M, SGC histologically confirmed positive for AR by the central laboratory; PS 0-1; adequate organ function; and no suitable local therapy. The study consists of two sequential components: a monotherapy part with darolutamide alone (monotherapy part) and a combination part with darolutamide and goserelin (combination part). Darolutamide was given orally at 1,200 mg daily until disease progression or unacceptable toxicity. Primary endpoint for the monotherapy part was overall response rate (ORR) as determined by the investigator. Secondary endpoints were ORR by independent central review (ICR), clinical benefit rate (CBR), disease control rate (DCR), progression-free survival (PFS), overall survival (OS), and safety. (ClinicalTrials.gov NCT05694819). **Results:** From Mar 2020 to Jan 2021, 24 patients were enrolled in the monotherapy component. Median age was 64.6 years and 23 were male. ECOG PS was 0/1 in 18/6 cases. Pathological diagnosis was salivary duct carcinoma, adenocarcinoma NOS, and carcinoma ex pleomorphic adenoma in 16, 4 and 4 patients, respectively. ORR by investigator was 8.3% (90% CI 1.5-24.0) and ORR by ICR was 20.8% (95% CI 7.1-42.2). CBR and DCR were 41.7% (95% CI 22.1-63.4) and 58.3% (95% CI 36.6-77.9), respectively. Median PFS and OS were 5.7 months (95% CI, 1.9-15.2) and not reached (95% CI, 15.5-not estimable [NE]), respectively, with a median follow-up period of 19.1 months. Nine patients (37.5%) had grade 3 or 4 treatment-related adverse events. There were no treatment-related fatal adverse events. **Conclusions:** This is the first prospective trial of darolutamide for AR-positive SGC. The response rate by ICR and other secondary endpoints confirmed clinically meaningful activity and a well-tolerated safety profile. Patient enrollment to the combination component is now ongoing to evaluate additional benefits. Clinical trial information: NCT05694819. Research Sponsor: Bayer pharmaceutical company.

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Poster Session

Clinical and genomic characterisation of adenoid cystic carcinoma of the head and neck, lung, and breast. *First Author: Emily Heathcote, The Christie Hospital NHS Foundation Trust, Manchester, United Kingdom*

Background: Adenoid cystic carcinoma (ACC) arises most commonly within the major salivary glands and other exocrine glands. ACC is typically a slow growing disease with high rates of recurrence many years after diagnosis. To inform post-operative surveillance and to provide comparator data for non-randomised studies, we sought to perform clinical and genomic characterisation of a cohort of 450 ACC patients, comparing outcomes between salivary ACC and other primary sites. **Methods:** 450 patients with ACC underwent clinical review at 4 UK NHS institutions. Electronic records were reviewed to extract clinical and demographic data. In 225 patients, DNA-based next-generation sequencing was performed to identify alterations in the most frequently altered genes in ACC (NOTCH1, ARID1A, KDM6A, SETD2, or TP53). Kaplan-Meier survival analyses calculated the time to first confirmed recurrence (TTFR) and overall survival from diagnosis (OS-diag) and from first confirmed recurrence (OS-rec). **Results:** Of 450 ACC patients, the primary site was most frequently the major salivary gland (44.7%; 201/450) comprising parotid (86), submandibular (96), sublingual (9) and salivary NOS (12). Other primary sites were sinonasal (99/450; 22.0%), upper aerodigestive (69/450; 15.3%), tracheobronchial (46/450; 10.2%), breast (16/450; 3.6%), skin (10/450; 2.2%), lacrimal (7/450; 1.6%), and other (2/450; 0.4%). Complete survival data were available in 440 patients. Recurrent/metastatic disease was confirmed in 69.8% (314/450). For these patients, the median TTFR was 4.5 yrs and for those with recurrence, the median OS from recurrence (OS-rec) was 4.8 yrs. The median TTFR in major salivary ACC was 5.8 yrs (95% CI 4.3 - 7.0). In comparison, the shortest median TTFR was seen in tracheobronchial (2.9 yrs, 95% CI 1.6 - 6.8; p = 0.019) and sinonasal ACC (3.8 yrs, 95% CI 2.9 - 5.0; p = 0.004). Breast ACC showed a differing survival pattern compared with major salivary ACC. Although the OS-diag in these two groups was not significantly different (9.75 yrs and 11.3 yrs respectively, p = ns), breast ACC showed a significantly increased TTFR (9.8 versus 4.4 yrs, p = 0.067), and a significantly reduced OS-rec (0.75 versus 4.8 yrs, p = < 0.001). KDM6A mutation was seen more frequently in primary sites outside the major salivary glands (p = 0.005). However, there was no relationship between primary tumour site and mutations in NOTCH1, ARID1A, SETD2 or TP53. **Conclusions:** In this real-world multi-centre UK study, tracheobronchial and sinonasal ACC have significantly shorter TTFR than major salivary ACC. This study suggests that breast ACC has a similar OS from diagnosis to major salivary ACC, but has an increased TTFR and shorter OS following recurrence. This may have implications for follow-up protocols after primary treatment of breast ACC, and initiation of systemic therapy following recurrence. Research Sponsor: The Christie Charity, Syncona Foundation, The Infrastructure Industry Foundation and Bayer.

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Poster Session

Safety and early efficacy results of phase 1 study of affinity tuned and trackable AIC100 CAR T cells in ICAM-1 positive relapsed and/or refractory advanced poorly differentiated and anaplastic thyroid cancers. *First Author: Samer Ali Srour, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: ICAM-1, a cell surface glycoprotein, is overexpressed in most ATC and PDTC. AIC100 is a 3rd-generation CAR T cell with micromolar affinity to ICAM-1, tuned lower than most CARs used to date in pre-clinical studies. Affinity tuned AIC100 are expected to selectively bind and kill tumor cells while safely sparing healthy cells. AIC100 also co-expresses somatostatin receptor 2 (SSTR2), which enables *in vivo* monitoring of AIC100 distribution and expansion by DOTATATE PET/CT scan. **Methods:** The objectives of this phase 1 dose escalation study are to assess the safety, preliminary efficacy and to determine RP2D of AIC100 in patients with ICAM-1⁺ relapsed/refractory PDTC or ATC. 3 dose levels (DL) are being explored-DL1 at 1x10⁶, DL2 at 1x10⁶ and DL3 at 5x10⁶ AIC100. AIC100 is received as a single infusion two days after completing lymphodepletion with Fludarabine/Cyclophosphamide. FDG and DOTATATE PET/CT scans are used to assess response and to track AIC100 *in vivo*, respectively. Response is assessed by RECIST1.1, starting at end of treatment (day 42 post AIC100). AIC100 is manufactured using Afflymune's Tune and Track CAR T cell platform. **Results:** As of Feb 14, 2023, 6 pts (4 ATC; 2 PDTC) with a median age of 59.5 yrs (48-70) were infused with AIC100, 3 each in DL 1 and 2. AIC100 was successfully manufactured for all patients and all infusion products met target transduction efficiency. No serious adverse events or DLTs were reported. Two patients had grade 1 CRS. No ICANs was reported. In 3 evaluable patients in DL1, 1 patient had stable disease with decreased FDG activity in PET that correlated with increased activity in the DOTATATE scan. From the 3 pts infused in the DL2, one is evaluable for efficacy at day 42. This is a patient with relapsed ATC who achieved PR with 42% reduction in target tumor lesion and remains in PR at 3 mths. The target lesion in this patient showed increased DOTATATE avidity at d14 post AIC100 infusion. This was followed by decreased FDG and DOTATATE avidity at d42 post AIC100 infusion, concomitant with decreased size, suggesting biological activity 42 days after CAR T infusion. Evaluation of CAR transgene demonstrated transient peripheral blood CAR T cell expansion. The second patient couldn't be assessed due to early withdrawal for disease-related toxicity. The 3rd patient in DL2 remains in the DLT period, pending efficacy evaluation. **Conclusions:** AIC100 demonstrated an excellent safety profile in DL1/DL2 treated patients with ATC and PDTC with no DLTs observed. The objective and relatively durable partial response in the first evaluable patient in the DL2, a patient with metastatic ATC who failed multiple lines of therapy, is unprecedented and very encouraging. Further investigations of AIC100 are ongoing at DL2 and DL3 to determine the RP2D. Clinical trial information: NCT04420754. Research Sponsor: Afflymune Therapeutics, Inc.

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Poster Session

Predictive biomarkers of benefit to axitinib plus avelumab in patients with recurrent/metastatic adenoid cystic carcinoma (R/M ACC). *First Author: Camilla Oliveira Hoff, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: ACC is a heterogeneous malignancy with no standard treatment for patients (pts) with R/M disease. Two distinct ACC subtypes have been identified proteogenomically, which contribute to ACC's biological variability. ACC-I is enriched with NOTCH activating mutations and MYC overexpression and has a poor prognosis (median survival [mOS] = 3.4 years). ACC-II has upregulation of TP63 and presents with an indolent disease course (mOS = 23.2 years). In a phase II trial of axitinib (VEGFR inhibitor) plus avelumab (PD-L1 inhibitor) in R/M ACC, clinical benefit was heterogeneous. We hypothesized that ACC subtype and gene expression profile are associated with benefit to axitinib plus avelumab. **Methods:** Cohort of 28 R/M ACC pts with radiological or clinical progression within 6 months (mos) of enrollment in the axitinib plus avelumab trial (NCT03990571). Target transcriptome profile including 19,616 probes was generated using HTG Transcriptome Panel [HTP]. Gene expression was used to identify ACC subtypes (ACC-I vs. ACC-II). Confirmed overall response rate (ORR), disease control rate (DCR), and progression-free survival (PFS) per RECIST v1.1 was assessed for each ACC subtype. An analysis of genes associated with benefit vs. no benefit from axitinib plus avelumab was conducted for the overall population and per ACC subtype. Benefit was defined as disease control (partial response [PR] or stable disease [SD]) and PFS longer than the median PFS. PFS > 6 mos was not used to define benefit due to the significant differences in PFS between ACC subtypes. **Results:** Out of 28 pts, 14 (50%) were classified as ACC-I and 14 (50%) were ACC-II. For ACC-I, ORR was 14.3% (2/14; 95%CI: 1.8-42.8%), DCR was 35.7% (2 PR + 3 SD; 95%CI: 12.8-64.9%) and median PFS was 1.86 mos (95%CI: 1.81-8.61 mos). For ACC-II, ORR was 21.4% (3/14; 95%CI: 4.7-50.8%), DCR was 100% (3 PR + 11 SD; 95%CI: 76.8-100%) and median PFS was 10.5 mos (95%CI: 7.40-NA). PFS was significantly longer for ACC-II vs. ACC-I (HR 0.19 [95%CI: 0.08 - 0.49], p = 0.0002). Through the previously defined benefit vs. no benefit cutoff, ACC-I had a 42.9% (6/14) and ACC-II had a 50.0% (7/14) benefit rate. Benefit in all ACC pts, ACC-I and ACC-II was associated with high expression of immune-related genes, especially B and T-lymphocyte function. Angiogenesis-related genes were not significantly upregulated in the benefit group as previously reported in renal cell carcinoma pts treated with the same combination. **Conclusions:** Clinical outcomes to axitinib plus avelumab were distinct between ACC-I and ACC-II subtypes, with ACC-II pts demonstrating an improved DCR and significantly longer PFS. Gene expression analysis revealed high expression of immune function-related genes in patients who benefited from axitinib plus avelumab in both ACC subtypes, indicating possible biomarkers predictive of benefit from the combination in ACC. Clinical trial information: NCT03990571. Research Sponsor: U.S. National Institutes of Health; Pfizer.

6098

Poster Session

Retrospective analysis of genetically matched therapies in salivary gland cancer entities using a real-world database in a tertiary salivary gland cancer expertise center. *First Author: Jetty A.M. Weijers, Department of Medical Oncology, Radboud University Medical Center, Nijmegen, Netherlands*

Background: Salivary gland cancer (SGC) is a rare cancer and includes twenty-two different entities. In the Radboudumc SGC expertise center, a real-world database was set up to uniformly collect data of SGC subtypes. More than 500 SGC patients have been enrolled and collection of data for 261 patients is currently completed. Here, we describe the retrospective analysis of genetic aberrations found in different SGC entities and the treatment of selected recurrent/metastatic (R/M) patients with genetically matched therapies (GMT). **Methods:** All SGC patients in the SGC registry of Radboudumc between 2017 and 2022 whose tumors underwent next generation sequencing (NGS) and/or gene fusion analysis within standard of care or clinical trial were included in this analysis. Both primary tumor specimen and metastatic tissue have been used for molecular analyses. GMT was given in basket trials or on basis of compassionate use for clinically relevant genetic aberrations that are considered actionable nowadays. **Results:** NGS and/or gene fusion analysis data was available for 162 out of 261 patients, and most frequently in salivary duct carcinoma (SDC) patients (82/162). The number of patients with genetic aberrations differed between SGC entities. In 112 patients at least one genetic aberration and/or gene fusion was detected regardless of whether the target was druggable. Ninety-three patients out of 112 patients had R/M disease. Both a gene fusion and one or more mutations were found in six patients (adenoid cystic carcinoma [AdCC], n = 3; SDC, n = 2; and secretory carcinoma [SC], n = 1). Depending on the SGC subtype, in 14.3 - 100% of the R/M cases with genetic aberrations and/or gene fusions a GMT was started (SDC, 14/60; AdCC, 3/21; SC, 2/2; mucoepidermoid carcinoma, 2/4). The most given GMT among patients were monoclonal antibodies and tyrosine kinase inhibitors (TKI), respectively in nine and eleven patients, moreover immunotherapy was started in one patient. For example, eight SDC patients were treated with ERBB2 targeting agents (4/8 mutations; 4/8 copy number variants in ERBB2), showing a complete response in three patients. Additionally, one partial response and two stable diseases were observed, two patients were lost of follow-up. Two SC patients treated with a TKI based on the presence of the *ETV6-NTRK* gene fusion showed radiologically a partial response. **Conclusions:** In 69% of the SGC patients at least one genetic aberration and/or gene fusion was found, and in 23% of the R/M cases GMT was administered. Response differs between entities and GMT; a complete response was achieved after initiation of GMT in several patients. These data justify the use of NGS and gene fusion analysis in all salivary gland cancer entities, notably in subtypes lacking standard systemic therapies as this could offer other therapeutic options. Research Sponsor: None.

6097

Poster Session

Monitoring epithelial, epithelial-mesenchymal, and mesenchymal circulating tumor cells on papillary thyroid cancer following thyroidectomy: A prospective cohort study. *First Author: Eunju Park, CytoDx Inc., Seongnam, South Korea*

Background: Monitoring the effectiveness of cancer-removal surgery is challenging in most cases. Therefore, robust and non-invasive techniques have been developed, and liquid biopsy is an apparent method for that purpose. In this prospective cohort study, we examined whether one type of liquid biopsy, an enumeration of circulating tumor cells (CTCs), can monitor the effectiveness of thyroidectomy in patients with papillary thyroid cancer (PTC). **Methods:** From January 2021 to January 2022, we recruited 62 PTC patients who had operated on isthmectomy, lobectomy, and total thyroidectomy for this study at Seoul National University Bundang Hospital. The blood samples from the recruited patients were collected before surgery and two weeks and three months after the surgery for CTC detection. We collected peripheral blood samples by venipuncture from each patient in EDTA tubes and stored them at 4°C until isolation and characterization of CTCs (within 6 hours). **Results:** We found the CTCs in 87% (54/62) of PTC patients, with an average number of 8.0. This number significantly decreased after thyroidectomy, with an average of 5.3 and 4.3 post-operation of two weeks and three months, respectively. In the peripheral blood of PTC patients, the CTCs with epithelial-mesenchymal and mesenchymal phenotypes were significantly more frequent than the epithelial phenotype of CTCs. Furthermore, PTC patients with lymphatic invasion, lymph node metastasis, or BRAF V600E mutation showed significantly decreased CTC count after surgery. **Conclusions:** PTC patients had a significantly higher number of CTCs undergoing epithelial-mesenchymal transition and showed a significant decrease in CTC count after surgery. This indicates that liquid biopsy using CTC enumeration can satisfy the purpose of monitoring the effectiveness of cancer-removal surgery. Clinical trial information: KCT0008179. Research Sponsor: CytoDx Inc.

6099

Poster Session

¹⁷⁷Lu-PSMA radioligand therapy for patients with recurrent/metastatic (R/M) salivary gland cancer (SGC): A phase II pilot study. *First Author: Carla M.L. Van Herpen, Department of Medical Oncology, Radboud University Medical Center, Nijmegen, Netherlands*

Background: New treatments are warranted due to limited systemic treatment options for SGC patients (pts). Gallium [68Ga]Ga prostate-specific membrane antigen (PSMA) PET imaging results in SGC pts have demonstrated PSMA expression of SGC and thus indicated that PSMA radionuclide therapy may be a useful option, especially in the case of adenoid cystic carcinoma (AdCC) and salivary duct carcinoma (SDC) subtypes. Therefore, this study (EudraCT number 2019-003857-27) evaluated the safety and efficacy of PSMA-targeted radionuclide therapy in AdCC and SDC pts. **Methods:** This was a single-center, single-arm, phase II pilot study. R/M AdCC (n = 10) and SDC (n = 5) pts with sufficient PSMA tracer uptake on [⁶⁸Ga]Ga-PSMA PET imaging, i.e., ≥ 1 lesion ≥ 1.5cm with PSMA expression above mean liver level, were treated with 2-4 cycles of 7.4 GBq [¹⁷⁷Lu]Lu-PSMA-I&T, with an interval of 6 ± 1 weeks. Baseline imaging was repeated for evaluation 4 weeks after cycle 2; in case of progressive disease (PD) per RECIST 1.1 the treatment was discontinued; otherwise, pts received the full treatment (4 cycles). All pts received whole body post-therapeutic imaging after 1, 24, 48, 72 h and 7d after each cycle. The primary endpoint was safety. Secondary endpoints include the objective response rate, progression-free survival (PFS), and overall survival (OS). **Results:** Between 6-2020 and 2-2023, 15 AdCC pts and 10 SDC pts were screened for eligibility. Five AdCC pts and 8 SDC pts were screen failures due to insufficient PSMA expression in 11 pts (AdCC n = 4; SDC n = 7) or due to brain metastases in 2 pts (AdCC n = 1; SDC n = 1). Ten AdCC and 2 SDC pts received at least one cycle of 7.4 GBq [¹⁷⁷Lu]Lu-PSMA-I&T. The most observed adverse events (grade 1-2) included: nausea (75%), dry mouth (75%), fatigue (67%), and anemia (58%). Two pts (17%) developed grade 3 toxicity: lymphocytopenia (n = 1) and hyponatremia (n = 1). No grade 4-5 toxicities were observed. Two pts (AdCC n = 1; SDC n = 1) received only 1 treatment cycle due to early PD. The interim-treatment evaluation resulted in the discontinuation of treatment after 2 cycles in an additional 3 AdCC and the second SDC pts due to PD. Six AdCC pts received the full treatment (4 cycles); no responses were observed; 3 pts (75%) showed stable disease of more than 3 months after treatment completion (5, 15 and 21 months); 3 pts showed PD at 3 months after treatment completion. Median PFS in 10 AdCC pts was 6.7 months (95%CI: 0.0-15.1); OS was not reached after a median follow-up of 11.9 months. **Conclusions:** [¹⁷⁷Lu]Lu-PSMA-I&T treatment in SGC pts is well-tolerated. The efficacy in AdCC was limited; only stable disease was achieved in 3 out of 10 pts. In most screened SDC pts, PSMA expression was insufficient to undergo [¹⁷⁷Lu]Lu-PSMA-I&T treatment; the 2 SDC pts included showed early PD. Dosimetry analyses will be performed to calculate the delivered radiation doses to organs at risk as well as tumor lesions. Clinical trial information: EUCTR2019-003857-27. Research Sponsor: Dutch Cancer Society; ACC-RF.

6100

Poster Session

Artificial intelligence (AI) analysis of tumor-infiltrating lymphocytes (TILs) in hematoxylin and eosin (H&E) slides to explore immune phenotypes in papillary thyroid cancer. *First Author: Myungwoo Nam, Lincoln Medical and Mental Health Center, Bronx, NY*

Background: Different biomarkers have been discovered to predict response to immunotherapy but the variability of response exists. TILs are a potential biomarker as infiltration of CD8+ T cells in the tumor microenvironment (TME) was related to treatment response to PD-1 blockade. Advanced well-differentiated papillary thyroid cancer (PTC) has limited standard-of-care treatment options and can exhibit a poor prognosis when exhausted. Our study aimed to classify the TME of PTC according to TILs. **Methods:** Using the TCGA PTC data, samples were classified into three immune phenotypes (immune-'desert', immune-'excluded', and 'inflamed') based on peri-tumor lymphocyte density from analysis of H&E slides using an AI model (Lunit SCOPE). Immune and stromal cell infiltration was inferred using xCell. Cytolytic scores (CYT) and thyroid differentiation scores (TDS) were calculated using mRNA expression. **Results:** Total of 383 samples were included. Immune phenotype analysis showed 183 (47.7%) 'desert', 133 (34.7%) 'excluded', and 67 (17.4%) 'inflamed'. Median age at diagnosis was the lowest in 'inflamed' (inflamed 41.5 vs excluded 47 vs desert 50, $p = 0.002$). TNM stages were as follows in the order of stages 1 to 4: inflamed 49/4/8/3, excluded 64/13/32/16, and desert 86/28/40/19. BRAF V600E mutation was most prevalent in 'excluded' (97/133, 72%), followed by 'inflamed' (32/67, 47.7%) and 'desert' (51/183, 27.8%). CYT was the highest in 'inflamed' (median: inflamed 186 vs excluded 53 vs desert 39, $p < 0.001$). TDS was the highest in 'desert' (median: inflamed -0.3 vs excluded -0.69 vs desert 0.73, $p < 0.001$). The 6 cell types with the most statistically significant difference in infiltration were activated dendritic cells (aDCs), DCs, B cells, epithelial cells (EpCs), CD8+ central memory T cells, and CD4+ memory T cells. The 'inflamed' showed the highest median value for all of these cells except EpCs. The cells with the highest median value in 'excluded' included EpCs, sebocytes, and immature DCs. The cells with the highest median value in 'desert' were lymphatic endothelial cells (ECs), ECs, and osteoblasts. Three immune phenotypes were associated with differential outcomes in disease-free survival (log-rank for trend, p -value = 0.01). There was no difference in overall survival. **Conclusions:** Our results suggest that 15% of PTC can have immune features which were related to a higher rate of response to immunotherapy across different tumor types. A previous study showed that PTC with a low TDS or BRAF V600E mutation is related to increased immune response indices. In our study, TDS or BRAF V600E mutation status could not distinguish the 'inflamed' from other phenotypes. This suggests that immune phenotype classification through TILs can provide distinct information about the TME of PTC. Research Sponsor: None.

TPS6102

Poster Session

A phase 2 study of magrolimab combination therapy in patients with recurrent or metastatic head and neck squamous cell carcinoma: ELEVATE HNSCC. *First Author: A. Dimitrios Dimitrios Colevas, Stanford Cancer Center, Stanford, CA*

Background: Novel combination therapies are needed to extend survival in patients (pts) with recurrent or metastatic head and neck squamous cell carcinoma (RM-HNSCC). Magrolimab is a monoclonal antibody that blocks CD47, a "don't eat me" signal often overexpressed on HNSCC cells. CD47 blockade by magrolimab induces macrophage-mediated phagocytosis of tumor cells and has shown preclinical activity and promising clinical efficacy in hematologic malignancies. Certain chemotherapies, including taxanes, enhance phagocytic signals on tumor cells, leading to potential synergistic antitumor activity when combined with magrolimab. This study is evaluating the safety, tolerability, and efficacy of magrolimab combination therapy in pts with RM-HNSCC. **Methods:** This open-label study includes 2 safety run-ins and 2 phase (ph) 2 cohorts. Safety run-in 1 includes pts with RM-HNSCC untreated in the RM setting to receive magrolimab + pembrolizumab (pembro) + platinum (cisplatin or carboplatin) + 5-fluorouracil (FU); safety run-in 2 enrolls pts with locally advanced or RM-HNSCC treated with 1-2 lines of prior systemic therapy in the locally advanced or RM setting who received magrolimab + docetaxel. Magrolimab is given intravenously as a 1-mg/kg priming dose on cycle 1 day 1 (C1 D1) to mitigate on-target anemia and 30 mg/kg on D8 and D15. Magrolimab 30 mg/kg is given on C2 D1, D8, and D15 and 60 mg/kg on D1 of C3+. Once the recommended ph 2 dose is determined, the ph 2 cohorts will follow the same dose schedules. In ph 2 cohort 1, pts receive magrolimab + pembro + platinum + 5-FU (arm A), pembro + platinum + 5-FU (arm B), or magrolimab + zimberelimab (anti-PD-1) + platinum + 5-FU (arm C). Pts enrolled in ph 2 cohort 3 receive magrolimab + docetaxel. An optional safety run-in and ph 2 cohort (cohort 2) of magrolimab + pembro in PD-L1+ RM-HNSCC may be opened at sponsor's discretion. Pembro, platinum, 5-FU, and docetaxel are given per standard of care. Reasons for treatment discontinuation may include unacceptable toxicity or disease progression. Safety is monitored throughout the study. Primary endpoints of the safety run-ins cohorts were incidence of adverse events and dose-limiting toxicities per CTCAE v5.0. Primary endpoints for the Ph 2 cohorts are progression-free survival (PFS) by independent central review (cohort 1 arm A vs B) and investigator-assessed objective response rate (ORR) by RECIST 1.1 (cohorts 2, 3). Secondary endpoints include magrolimab pharmacokinetics and antidrug antibodies (safety run-in, ph 2 all cohorts), ORR assessed by independent central review, investigator-assessed PFS by RECIST 1.1 (all cohorts) and overall survival (all cohorts), duration of response, and pt-reported outcomes. Planned enrollment is ~230 pts. Clinical trial information: NCT04854499. Research Sponsor: Gilead Sciences, Inc.

TPS6101

Poster Session

XRAY Vision: A phase 3 study of xevinapant plus radiotherapy (RT) for high-risk, cisplatin-ineligible patients with resected, locally advanced squamous cell carcinoma of the head and neck (LA SCCHN). *First Author: Robert L. Ferris, University of Pittsburgh Medical Center, Pittsburgh, PA*

Background: The current standard of care for patients with resected LA SCCHN who are at high-risk of disease recurrence and are cisplatin eligible is chemoradiotherapy (CRT; cisplatin + RT). For patients at high risk of disease recurrence who cannot receive cisplatin, treatment options are limited, and there is currently no treatment specifically recommended by international guidelines. Xevinapant is a first-in-class, small-molecule IAP (inhibitor of apoptosis protein) inhibitor that has been shown to restore cancer cell sensitivity to apoptosis, thereby enhancing the effects of chemotherapy and RT. In a randomized phase 2 study in patients with unresected LA SCCHN, treatment with xevinapant + CRT was associated with a 53% lower risk of death after 5 years of follow-up and reduced the risk of death or disease progression by 67% after 3 years of follow-up vs placebo + CRT. In preclinical SCCHN models, xevinapant + RT alone also demonstrated antitumor activity. These promising clinical and preclinical data provide a strong rationale for combining xevinapant and RT in cisplatin-ineligible patients with LA SCCHN. **Methods:** XRAY Vision (NCT05386550) is a randomized, double-blind, placebo-controlled, phase 3 study comparing xevinapant or placebo in combination with intensity-modulated RT (IMRT) in patients with resected LA SCCHN who are ineligible for cisplatin and have a high risk of relapse. Eligible patients must have histologically confirmed cancer of the oral cavity, oropharynx, hypopharynx, or larynx; undergone surgery with curative intent 4 to 8 weeks before the start of treatment; high risk of relapse; no residual disease by computed tomography scan; and ineligible for cisplatin (meeting ≥ 1 of the following criteria: estimated glomerular filtration rate < 60 mL/min/1.73 m²; hearing loss [grade ≥ 2 audiometric hearing loss or grade ≥ 2 tinnitus]; grade ≥ 2 peripheral neuropathy; and if aged ≥ 70 years old, unfit according to the G8 questionnaire [score ≤ 14]). Other eligibility criteria include ECOG performance status of 0 or 1 and adequate hematologic and hepatic function. Approximately 700 eligible patients will be randomized to oral xevinapant (200 mg/day on days 1-14 of a 3-week cycle) or placebo for 3 cycles + standard fractionation IMRT (66 Gy in 33 fractions, 2 Gy per fraction, 5 days per week) followed by 3 cycles of xevinapant or placebo. The primary endpoint is disease-free survival. Secondary endpoints include overall survival, time to subsequent cancer treatments, safety, and health-related quality of life. Patients will be followed up for a minimum of 60 months. Enrollment is planned in 27 countries, including the US, and countries in South America, Europe, and Asia. The study started in October 2022, and recruitment is ongoing. Clinical trial information: NCT05386550. Research Sponsor: The healthcare business of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945).

TPS6103

Poster Session

Palbociclib + cetuximab versus cetuximab in patients with CDKN2A-altered, anti-PD-1 resistant, HPV-negative head and neck squamous cell carcinoma (HNSCC): A phase 3 trial. *First Author: Jessica C. Ley, Washington University School of Medicine, St. Louis, MO*

Background: Cell cycle deregulation is ubiquitous in HNSCC. In HPV-negative HNSCC, the most common genomic cell-cycling alteration involves *CDKN2A*, which results in loss of p16 expression, hyper-activation of CDK4/6-cyclin D1, unrestrained cell cycling and tumor progression. The modest antitumor activity of cetuximab in HPV-negative HNSCC may be due to unregulated cell-cycling events downstream of EGFR. In cell-line, xenograft, and PDX models of HPV-negative HNSCC, selective CDK4/6 inhibition arrested cell cycling and inhibited tumor growth. *CDKN2A* alterations were predictive of efficacy. Palbociclib, a selective CDK4/6 inhibitor, in combination with an EGFR inhibitor synergistically reduced the viability of HPV-negative HNSCC cell lines. An exploratory analysis of a double-blind, randomized, phase 2 trial (PALATINUS) showed that overall survival (OS) was numerically superior in patients with *CDKN2A* altered, HPV-negative recurrent/metastatic (RM) HNSCC treated with palbociclib + cetuximab vs those treated with placebo + cetuximab (median 9.7 vs 4.6 months, HR 0.38); however, OS was similar between the two treatment arms in patients without *CDKN2A*-altered disease. Also, the TAPUR trial showed that palbociclib decreased target lesions in 25% of patients with *CDKN2A*-altered HN cancers. These data provide justification for a randomized trial of palbociclib + cetuximab vs cetuximab in patients with *CDKN2A*-altered, HPV-negative RM-HNSCC. Enrollment was limited to patients with anti-PD-1 resistant disease, since current treatments fail to improve OS in these patients. **Methods:** The primary aim of this open-label, phase 3 trial is to determine the OS of patients with *CDKN2A*-altered (mutation or deletion), anti-PD-1 resistant, HPV-negative HNSCC treated with palbociclib + cetuximab (Arm 1) vs cetuximab (Arm 2). Eligibility also requires 1-3 lines of prior therapy and no cetuximab for RM disease. Patients are randomized (2:1) to Arms 1 or 2, stratified by prior platinum or cetuximab (if given with curative-intent therapy). Patients receive 28-day cycles of palbociclib 125 mg/d orally on days 1-21 + cetuximab 400 mg/m² IV cycle 1 day 1, then 250 mg/m² weekly (Arm 1) or cetuximab (Arm 2). Tumor response is assessed using RECIST 1.1. A two-stage sequential design, including one interim and a final analysis, was planned. We hypothesized that the median OS of Arm 1 will be 9.7 months and of Arm 2 4.6 months. O'Brien-Fleming method was used to calculate the sample size at each stage and derive the boundaries of two-sided hypothesis with early stopping to reject or accept H_0 (HR = 1). Assuming 22 months enrollment and 12 months follow-up, 66 patients (Arm 1: 44; Arm 2: 22) will be enrolled in the first stage. If the study continues, an additional 15 patients will be enrolled (total Arm 1: 54; Arm 2: 27) which achieves 80% power at a two-sided α 0.05. Clinical trial information: NCT04966481. Research Sponsor: Pfizer; Joseph Sanchez Foundation.

TPS6104

Poster Session

Phase 2 trial of retifanlimab (anti-PD-1) in combination with INCAGN02385 (anti-LAG-3) and INCAGN02390 (anti-TIM-3) as first-line treatment in patients with PD-L1-positive recurrent/metastatic squamous cell carcinoma of the head and neck. *First Author: Ezra E.W. Cohen, Moores Cancer Center, University of California San Diego, La Jolla, CA*

Background: Anti-PD-(L)1 therapies have improved clinical outcomes in PD-L1+ squamous cell carcinoma of the head and neck (SCCHN). However, many patients either do not respond or develop resistance, partly due to additional immune checkpoint receptors including LAG-3 and TIM-3, which are frequently coexpressed with PD-1 on tumor-infiltrating lymphocytes. In preclinical studies, LAG-3 and TIM-3 blockade showed synergistic activity with PD-1 inhibition, and triple blockade improves T-cell reinvigoration and antitumor efficacy over single/double combinations. Emerging clinical evidence also supports blockade of PD-1, LAG-3, and TIM-3 as a promising combination approach in checkpoint inhibitor-naïve patients. This study aims to assess the efficacy and safety of the anti-PD-1 antibody, retifanlimab, in combination with INCAGN02385 (anti-LAG-3) and INCAGN02390 (anti-TIM-3) antibodies as first-line treatment in PD-L1+ recurrent or metastatic SCCHN. **Methods:** This randomized, double-blind, multicenter, phase 2 study (NCT05287113) includes patients with previously untreated, recurrent or metastatic, PD-L1+ (combined positive score [CPS] $\geq 1\%$) SCCHN and ECOG status of 0 or 1. Approximately 162 patients will be randomized 1:1:1 to receive (1) intravenous (IV) retifanlimab 500 mg every 4 weeks (Q4W) plus placebo controls, (2) retifanlimab plus IV INCAGN02385 350 mg Q2W plus placebo, or (3) retifanlimab plus INCAGN02385 plus IV INCAGN02390 400 mg Q2W. Patients will be stratified at randomization by LAG-3 expression (tumor proportion score $\geq 5\%$ vs $< 5\%$), PD-L1 CPS (1% - 19% vs $\geq 20\%$), and human papillomavirus p16 status (positive vs negative; oropharyngeal tumors only). Treatment will be administered in 4-week cycles for up to 2 years. The primary endpoint is progression-free survival (PFS; defined per Response Evaluation Criteria in Solid Tumors [RECIST] v1.1). Secondary endpoints are objective response rate per RECIST v1.1, duration of response, disease control, overall survival, and safety. Sample size calculation is based on a median PFS of 3 months, based on historical data for anti-PD-1 monotherapy in the first-line treatment setting for PD-(L)1+ advanced/metastatic SCCHN. PFS, overall survival, and duration of response data will be analyzed by the Kaplan-Meier method. Patient enrollment is ongoing. Clinical trial information: NCT05287113. Research Sponsor: Incyte Corporation.

TPS6106

Poster Session

A phase 2, open-label, multicenter study investigating efficacy and safety of RP3 oncolytic immunotherapy combined with other therapies in patients with locoregionally advanced or recurrent squamous cell carcinoma of the head and neck. *First Author: Kevin Joseph Harrington, The Institute of Cancer Research, The Royal Marsden Hospital, London, United Kingdom*

Background: Head and neck (HN) cancers were estimated to account for $> 50,000$ new cancer diagnoses and $> 11,000$ deaths in the US in 2022. Squamous cell carcinoma of the head and neck (SCCHN) comprises about 90% of HN cancers. For locally advanced (LA) SCCHN, standard initial therapy is concurrent chemoradiation therapy (CCRT) or definitive resection followed by adjuvant radiation $\pm$ chemotherapy; $> 50\%$ of patients (pts) relapse within 2 years. For recurrent/metastatic (R/M) SCCHN, standard first-line therapy includes immune checkpoint inhibitors (anti-PD-1) $\pm$ chemotherapy or cetuximab, chemotherapy $\pm$ cetuximab, or salvage surgery; prognoses are poor, and benefit of anti-PD-1 therapy is generally limited to pts with positive PD-L1 combined positive score (CPS). RP3 is an enhanced potency, modified version of herpes simplex virus type 1 expressing the fusogenic gibbon ape leukemia virus glycoprotein with the R sequence deleted (GALV-GP-R-), an anti-CTLA-4 antibody-like molecule, and costimulatory CD40- and 4-1BB-activating ligands. Intratumoral (IT) RP3 delivery may promote immunogenic tumor cell death and systemic antitumor response (abscopal effect), both of which may be further enhanced by standard therapies (eg, chemotherapy, anti-PD-1). This phase 2 study will evaluate the efficacy and safety of RP3 combined with other therapies in pts with advanced, inoperable LA or R/M SCCHN. **Methods:** Pts in the LA cohort (up to ~ 100 pts) must have inoperable, previously untreated, high-risk SCCHN eligible for curative intent CCRT and will be randomized 1:1 to receive RP3 + standard of care cisplatin-based CCRT, followed by nivolumab (nivo), vs CCRT alone. A formal safety assessment will be performed 3 weeks after the tenth patient randomized to RP3 + CCRT + nivo has completed CCRT. RP3 will be injected IT into primary tumor sites and/or superficial or deep nodal lesions. Pts in the RP3 group will receive up to 4 doses of RP3 every 3 weeks (Q3W; first dose at a concentration of 1×10^6 plaque-forming units [PFU]/mL; subsequent doses 1×10^7 PFU/mL). Nivo will be given at 240 mg Q2W or 480 mg Q4W (after CCRT completion, concurrent with fourth RP3 dose, for up to 1 year). The primary endpoint for the LA cohort is progression-free survival. Pts in the R/M cohort (up to ~ 30 pts) must have R/M SCCHN eligible for first-line systemic therapy for locoregional recurrence and/or distant metastases and PD-L1 CPS < 20 , and will receive RP3 + nivo + carboplatin/paclitaxel. RP3 will be injected IT as described above for up to 8 doses Q3W (first dose 1×10^6 PFU/mL; subsequent doses 1×10^7 PFU/mL; carboplatin/paclitaxel started at first RP3 dose). Nivo will be given as above, concurrent with third RP3 dose, for up to 2 years. The primary endpoint for the R/M cohort is overall response rate. Clinical trial information: NCT05743270. Research Sponsor: Replimune Inc.

TPS6105

Poster Session

A phase 2 study of neoadjuvant lenvatinib in locally advanced invasive thyroid cancer. *First Author: Amr Hesham Abdelhamid Ahmed, Division of Thyroid and Parathyroid Endocrine Surgery, Department of Otolaryngology-Head and Neck Surgery, Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston, MA*

Background: Lenvatinib is a multiple receptor tyrosine kinase (RTK) inhibitor that has demonstrated meaningful benefit in radioiodine (RAI)-refractory differentiated thyroid cancer (DTC). In SELECT, lenvatinib significantly prolonged progression-free survival (PFS) and was associated with an overall response rate (ORR) of 65% in patients with RAI-refractory DTC, with the greatest degree of tumor shrinkage occurring in the first 2 cycles. The robust activity of lenvatinib in DTC suggests that neoadjuvant treatment in patients presenting with bulky neck disease may make surgery more feasible, allows for optimal surgical outcomes and less aggressive surgical management. Neoadjuvant lenvatinib to improve surgical outcomes in locally advanced DTC has not been studied to date. This phase 2 study will examine the efficacy and safety of lenvatinib prior to thyroidectomy, with the goal of achieving more favorable surgical outcomes. **Methods:** This is a Simon two-stage Phase 2 open-label multicenter clinical trial for adult patients who meet the following criteria: have been diagnosed with locally advanced or persistent/recurrent thyroid and/or cervical nodal DTC, deemed at risk for R2 resection (surgical margins with macroscopic tumor) (as evident by vocal cord paralysis by laryngoscopic exam, imaging documenting extrathyroidal/extranodal extension, or major vessels involvement), have measurable disease per RECIST v1.1, have an ECOG performance status ≤ 1 , and no contraindication to surgery. A total of 28 patients will be enrolled from three centers (Massachusetts General Hospital/Massachusetts Eye & Ear Infirmary (MGH/MEEI), Memorial Sloan-Kettering Cancer Center (MSKCC), and MD Anderson Cancer Center (MDACC)). Participants will receive up to 6 cycles of lenvatinib prior to surgery depending on response. Participants will undergo restaging at the end of cycle 2, 4, and 6. Participants with sufficient response to treatment who projected to achieve an R0 or R1 resection will stop lenvatinib and proceed to surgery within 7-10 days from the last dose. Participants who do not have a sufficient response who are tolerating treatment, will receive an additional 2-4 cycles of lenvatinib, followed by surgery. The primary objective is the R0 (surgical margins free from tumor)/R1 (surgical margins free from macroscopic tumor) resection rate. Secondary outcome measures include R0/R1 resection rates in each of 5 pre-specified anatomic target interfaces (perithyroid muscles, cartilage, esophagus, recurrent laryngeal nerve, major vessels), evaluation of the change in surgical morbidity complexity MGH/MEEI-MSKCC-MDACC (MMM) score and the Invasive Thyroid Class, ORR prior to surgery per RECIST v1.1, and the safety of lenvatinib in this patient population. The study is currently accruing with 11 patients enrolled at time of submission. Clinical trial information: NCT04321954. Research Sponsor: Eisai.

TPS6107

Poster Session

A phase 2 open-label study of conditionally active biologic ozuriftamab vedotin (BA3021) in failed PD-1/L1 treatment of patients with recurrent or metastatic squamous cell carcinoma of the head and neck. *First Author: Alan Loh Ho, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Ozuriftamab vedotin (BA3021) is a conditionally active biologic (CAB) anti-receptor tyrosine kinase orphan receptor 2 (ROR2) humanized monoclonal antibody (IgG1) conjugated to monomethyl auristatin E (MMAE) using a cleavable linker (CAB ROR2 ADC) (Short, et al., 2014, Chang, et al. 2021). Conditional and reversible binding by CABs is designed to reduce off-tumor toxicity and immunogenicity, avoid tissue-mediated drug deposition, and improve pharmacokinetics (PK). ROR2 is a cell-surface transmembrane receptor protein tyrosine kinase highly expressed in several tumor types including head and neck squamous cell cancer (HNSCC). Increased ROR2 expression has been associated with tumor resistance to chemotherapy, programmed death-1 (PD-1) inhibitors, molecular targeted therapy, and radiation therapy. A pronounced unmet need exists as the majority of patients with recurrent or metastatic HNSCC experience disease progression with existing therapies (Chow 2020). **Methods:** BA3021-002 is a multi-center, open-label, single-arm Phase 2 study (n=40) designed to evaluate the efficacy and safety of BA3021 in patients previously treated with PD-(L)1 with ROR-2 expressing recurrent or metastatic HNSCC. Eligible patients include those with measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 criteria. Failure to prior treatment is defined as documented disease progression after no more than one PD-1/L1 inhibitor either administered as monotherapy or in combination therapy. Pharmacokinetic (PK), pharmacodynamic (PD), immunogenicity, and biomarker assessments will be performed. Enrollment is ongoing (NCT05271604) References: Chang, H.W., Frey, G., Liu, H., Steinman, L., Boyle, W.J. and Short, J.M. Proc. Natl. Acad. Sci. 2021 Mar. 2; 118(9). Chow LQ. Head and neck cancer. *N Engl J Med.* 2020 Jan 2;382(1):60-72. doi: 10.1056/NEJMr1715715. Short, J.M. Nature Biotechnology 2014 Nov 8, 13(20). Clinical trial information: NCT05271604. Research Sponsor: BioAtla.

TPS6108

Poster Session

Oral NRC-2694-A in combination with paclitaxel as therapy for recurrent and/or metastatic head and neck squamous cell carcinoma (R/M-HNSCC) that progressed on or after an immune checkpoint inhibitor (ICI): A multi-center, single-arm, phase 2 trial. *First Author: Douglas Adkins, Washington University School of Medicine, St. Louis, MO*

Background: HNSCC is the seventh most common cancer worldwide. Patients with R/M disease have limited treatment options and a poor prognosis. The USFDA has approved two ICI agents to treat R/M-HNSCC: pembrolizumab given as monotherapy or with platinum-based chemotherapy for first-line treatment of R/M disease and nivolumab (or pembrolizumab) monotherapy for treatment of disease that progressed on or after platinum-containing chemotherapy. In each setting, the ICI improved overall survival (OS); however, the absolute magnitude of the OS benefit was modest and most patients experienced disease progression within one year. There are no agents with regulatory agency-approval that are used to treat R/M-HNSCC that progressed on or after an ICI. Drugs commonly used in this setting have limited activity and include cetuximab (an epidermal growth factor receptor [EGFR] inhibitor), paclitaxel, docetaxel, a platinum, or 5-fluorouracil. Hence, there is an important unmet medical need to develop more effective treatments for R/M-HNSCC that progressed on or after an ICI. NRC-2694-A is an orally administered EGFR tyrosine kinase inhibitor, discovered and developed by NATCO Pharma Ltd., India. Based on the responses from Phase-I and Phase-II trials of NRC-2694-A in India, NAT2694US study is designed to evaluate the safety and efficacy of Oral NRC-2694-A in combination with paclitaxel in patients with R/M-HNSCC, who progressed on or after ICI therapy. **Methods:** NAT2694US is a multi-center, single-arm, Phase 2 study (NCI ClinicalTrials.gov Identifier: NCT05283226) with an estimated enrolment of 46 patients. Eligible patients are >18 years of age with an ECOG performance status of 0-2 and histologically confirmed unresectable, measurable R/M-HNSCC (of the oral cavity, oropharynx, hypopharynx, and larynx), radiological disease progression on or after ICI therapy, and no prior taxane for R/M disease. Patients receive 300 mg of oral NRC-2694-A once daily and 175 mg/m² of paclitaxel IV infusion once every 21-day cycle for 6 cycles or more. Tumor response assessment with CT/MRI scans is performed every 6 weeks. The primary endpoint is objective response rate (ORR) using RECIST v1.1 performed by the investigator. The study uses a Simon's 2-stage design with ORR H₀: 30% and H₁: 50% using a one-sided Type-1 error rate = 0.05. In Stage 1, fifteen patients are to be enrolled for tumor assessment. If objective response is observed in at least 6 of these 15 patients, then Stage 2 would be opened with the inclusion of 31 additional patients, leading to a total enrolment of 46 patients. The observation of objective response in at least 19 of 46 patients would reject the null hypothesis in favour of the alternative hypothesis. Enrolment to the NAT2694US trial is currently ongoing in USA. Clinical trial information: NCT05283226. Research Sponsor: NATCO Pharma Ltd.

TPS6110

Poster Session

A phase II trial of neoadjuvant nivolumab, docetaxel, and cisplatin therapy followed by surgery and radiation therapy for resectable high-grade salivary gland carcinoma. *First Author: Sehhoon Park, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea*

Background: Salivary gland carcinomas (SGCs) are rare entities that contribute to approximately 5% of head and neck malignancies. The current standard therapy for resectable SGC is complete surgical resection with adjuvant radiotherapy or chemoradiotherapy. However, the patients with high-grade histological subgroup tumors have the highest risk of regional and distant metastasis as the primary cause of treatment failure. The previous evidence demonstrates that neoadjuvant chemotherapy showed a statistically significant advantage in survival for patients with head and neck cancer. Based on the success of neoadjuvant immune checkpoint inhibitors (ICI) in preventing disease recurrence and achieving pathologic complete response (pCR) in different types of cancer, we designed this study by incorporating nivolumab combined with neoadjuvant cytotoxic chemotherapy in patients with potentially resectable high-grade SGCs. **Methods:** This study is the phase II, open-label, single-center study of nivolumab in combination with docetaxel, and cisplatin as a neoadjuvant therapy in high-grade resectable SGCs. All the patients must be confirmed with pre-defined high-grade histology and clinically node-positive. As the representative inclusion/exclusion criteria, all the patients must not receive prior cancer therapy in advance to study enrollment, including another kind of immunotherapy, cytotoxic chemotherapy, or radiotherapy. Three cycles of nivolumab (360mg), docetaxel (60mg per m²), and cisplatin (60mg per m²) are applied every three weeks. Three weeks after the last treatment, the patient is re-evaluated for the surgery and will undergo surgery within seven weeks after the last treatment. Based on the surgical pathologic outcome, additional radiotherapy will be initiated between 4 to 8 weeks after the surgery per the following guidance; R0: 59.4Gy/25fx; R1 or R2: 59.4Gy/25fx with optional boost 6.6Gy/3fx. The primary objective is the major pathologic response rate defined by ≤10% of tumors composed of viable tumors. Complete resection rate, response rate, downstaging at pathologic staging, two-year distant metastasis free-survival, disease-free survival, overall survival, safety results, surgical outcomes of facial nerve function, completeness of post-neoadjuvant surgery will be analyzed as the secondary objectives. The sample size was calculated using H₀ of mPR ≤25% and H₁ of mPR ≥50%, according to the one-arm binomial model (power of 90% and one-sided alpha of 0.05). A total of 50 patients will be recruited, include 40 evaluable patients. This study is currently recruiting patients at Samsung Medical Center, South Korea. The first subject received treatment in Nov. 2022 and three patients received the treatment. The time point for the primary analyses is Q3.2025. (ONO-4538-X78). Clinical trial information: NCT05727410. Research Sponsor: None.

TPS6109

Poster Session

Phase 2 trial of three schedules of CUE-101 administered before surgery or chemoradiotherapy in HLA-A*0201 positive patients with HPV16+ OPSCC. *First Author: Jesse Meir Zaretsky, Washington University School of Medicine, Department of Medicine, Division of Oncology, St. Louis, MO*

Background: Patients with locally advanced HPV+ OPSCC have a favorable prognosis; however, 10-40% will experience disease recurrence after curative-intent therapy (CIT). 80-90% of cases are caused by HPV genotype 16. HPV16 E7 is a promising HPV target as there is little variation among isolates and high epitope affinities for HLA-A*0201 have been identified. HLA-A*0201 is the most common class I allele in the USA, expressed in 40-50% of people of European descent. We aim to lower the recurrence rate in these patients by activating tumor antigen-specific CD8+ T cells. CUE-101 is a novel fusion protein comprised of HLA-A*0201, an HPV16 E7 epitope (aa residues 11-20), a reduced affinity human IL-2 variant, and an effector attenuated human IgG1 Fc domain. In pre-clinical models, CUE-101 demonstrated selective binding, activation, and expansion of HPV16 E7₁₁₋₂₀-specific CD8+ T cells. In the murine TC-1 tumor model, a murine surrogate of CUE-101 (mCUE-101) increased the frequency of tumor-infiltrating E7-specific CD8+ T cells and improved survival. Animals that remained tumor-free rejected TC-1 tumors upon re-challenge, demonstrating functional immunologic memory. In an ongoing phase 1 trial (NCT03978689) of HLA-A*0201+ patients with recurrent HPV16+ OPSCC, CUE-101 was well tolerated, resulted in expansion of target HPV16 E7₁₁₋₂₀-specific CD8+ T cells, and showed durable disease control in some patients. In this Phase 2 trial (NCT04852328), CUE-101 will be administered to HLA-A*0201+ patients with HPV16+ OPSCC before CIT. The aims of the trial are to evaluate the safety, tolerability, and pharmacodynamic and immunologic activity of CUE-101 in these patients. **Methods:** This is a non-randomized Phase 2 trial of three schedules of CUE-101 administered before CIT to HLA-A*0201+ patients with HPV16+ OPSCC. HPV16 status of tumor will be assessed by PCR. Safety assessments will be performed, and blood and tumor samples collected, at baseline and after CUE-101 administration. Following CUE-101, CIT will be administered. Each schedule will enroll 10 patients. CUE-101 (4 mg/kg IV) will be administered 14 days (Schedule A), 14 and 7 days (Schedule B), or 7 days (Schedule C) before day 1 of CIT. If Schedule A is safe and tolerable, Schedule B and then C will commence. A schedule will be deemed safe and tolerable if ≤2 patients experience grade 3-4 TRAEs and/or treatment-related delays of >7 days from the planned date of CIT. Immunologic activity is defined as measurable observation of or increases in HPV16-specific T cells in post-CUE-101 blood and/or tumor samples, relative to baseline, as assessed by either ELISpot or tetramer staining and flow cytometry. Exploratory measures of immune activity will be assessed by single-cell RNAseq and immunofluorescence in tumor samples. A schedule will be considered active if immunologic activity is observed in ≥3 patients. Clinical trial information: NCT04852328. Research Sponsor: Cue Biopharma, Inc.

TPS6111

Poster Session

A single-arm, multi-institutional, phase 2 study of a pembrolizumab-based organ preservation strategy for locally advanced larynx cancers: SMART-KEY (LACOG 0720) trial. *First Author: Thiago Bueno Oliveira, A.C. Camargo Cancer Center, São Paulo, Brazil*

Background: Standard treatments for locally advanced larynx cancers include concurrent cisplatin/radiation therapy, or induction chemotherapy followed by radiation therapy alone, with the goal of organ preservation. Both strategies have been shown to achieve similar laryngectomy-free survival (LFS), but failed to improve overall survival (OS) compared with radiation therapy alone or surgery followed by radiation therapy. Although cisplatin given concurrently with radiation therapy is commonly used for organ preservation, there are concerns regarding long-term outcomes, such as late toxicities. Pembrolizumab with chemotherapy has been shown to improve OS in recurrent/metastatic head and neck squamous cell carcinomas (HNSCCs). Additionally, pembrolizumab combined with radiation therapy has been shown to be safe in locally advanced HNSCC. LACOG 0720 is designed to evaluate a pembrolizumab-based, cisplatin-free, and concurrent chemoradiation therapy-free regimen for larynx preservation, in an attempt to improve outcomes and avoid late toxicities. **Methods:** LACOG 0720 is a phase 2, single-arm, multicentric trial assessing patients with newly diagnosed squamous cell carcinoma of the larynx (glottic or supraglottic) and clinical stages III, IVA, or IVB (AJCC 8th Ed.). Patients with large volume T4 disease (invasion through the cartilage or extension > 1 cm to the base of the tongue) or T1 disease are excluded. Patients receive 3 cycles of induction chemo-immunotherapy (carboplatin AUC6, paclitaxel 175 mg/m², and pembrolizumab 200 mg, IV every 21 days [q21D]), followed by concurrent radioimmunotherapy (Intensity-modulated radiation therapy with pembrolizumab 200 mg IV q21D for 3 cycles), followed by consolidation immunotherapy (pembrolizumab 200 mg IV q21D for 11 cycles). The primary endpoint is two-year LFS rate. Secondary endpoints include two-year larynx dysfunction-free survival, OS, overall response rate, short-term and long-term toxicities, causes of death, patterns of failure, and quality of life. Predictive biomarkers of response and survival will be evaluated as exploratory analysis. The sample size was calculated based on the primary endpoint. Using the Chi-square Test for One Proportion and considering a one-sided 10% significance level, 39 patients are needed to achieve 80% power to detect the difference between the null hypothesis; that the true laryngectomy-free survival at two years is 59%, and the alternative hypothesis that the laryngectomy-free survival at two years is 75%. From Feb 2022 to Feb 2023, 24 patients were enrolled in 10 Brazilian centers. Results are expected in July 2024. NCT04943445. Clinical trial information: NCT04943445. Research Sponsor: Merck & Co.; Merck Sharp & Dohme (MSD).

TPS6112

Poster Session

Response-adapted therapy for locally advanced nasopharyngeal carcinoma based on clinical response and circulating Epstein-Barr virus DNA level post induction chemotherapy. *First Author: Chaosu Hu, Department of Radiation Oncology, Fudan University Shanghai Cancer Center, Shanghai, China*

Background: For locally advanced nasopharyngeal carcinoma (NPC), the mainstay treatment is cisplatin-based concurrent chemoradiation (CCRT). Recent phase III clinical trials have demonstrated that induction chemotherapy (ICT) plus CCRT, compared with CCRT alone, further improved progression-free survival (PFS). However, not every patient has good response to ICT. Evidence has accumulated that those with poor response to ICT, or those with detectable Epstein-Barr Virus (EBV) DNA post ICT, correlated with poorer PFS. In addition, real-time monitoring of plasma EBV DNA response adds prognostic information, and has the potential utility for risk-adapted treatment intensification in NPC. The aim of this study is to clarify whether response-adapted strategy based on clinical efficacy and EBV DNA response confers survival benefit to patients with locally advanced NPC. **Methods:** This is an open-label, 3-arm, phase II study. Patients with pathologically confirmed, locally advanced NPC (III-IVA, excluding T3N0M0, 8th AJCC staging system), with pretreatment detectable plasma EBV DNA level and ECOS PS 0-1 were eligible. Patients will receive one cycle of GP-based ICT. After one cycle of ICT, plasma EBV DNA and head and neck MR are performed. Based on clinical efficacy (evaluated per RECIST 1.1 criteria) and changes of plasma EBV DNA after one cycle, patients will be divided into three arms. Patients with good response (Arm A: Early Responders, undetectable EBV DNA level and CR/PR) will directly receive CCRT. Patients with intermediate response (Arm B: Intermediate Responders, detectable EBV DNA and CR/PR/decreased SD; or undetectable EBV DNA yet without CR/PR) will be randomized to experiment subgroup (GP combined with Toripalimab for two additional cycles then CCRT and maintenance Toripalimab treatment) and standard subgroup (GP for two additional cycles then CCRT). Patients with poor response (Arm C: Treatment Resistant, increased EBV DNA level, or PD/enlarged SD) will be switched to TP regimen combined with Toripalimab, followed by CCRT and maintenance Toripalimab treatment. Sample size calculation is based on 2-year PFS rate for arm B as the primary endpoint (one-sided $\alpha = 0.10$, power = 0.80). Our target sample size is estimated to be 198-240, among them 168 for arm B. Secondary endpoints include adverse events determined by CTCAE v5.0, ORR at 3 months post-CRT, 2-year locoregional recurrence-free survival (LRFS) rate, 2-year distant metastasis-free survival (DMFS) rate, 2-year overall survival (OS) rate, as well as quality of Life for arm B. Exploratory endpoints include 2-year PFS rate, LRFS rate, DMFS rate, OS rate, ORR at 3 months post-CRT, adverse effects, and quality of life for arm A and arm C. This trial opened to accrual in July 2022 and the recruitment is ongoing. Clinical trial information: NCT05628922. Research Sponsor: Shanghai Junshi Biosciences Co., Ltd.

TPS6114

Poster Session

CCTG HN11: SPECT-CT guided elective contralateral neck treatment (SE-LECT) for patients with lateralized oropharyngeal cancer—A phase III randomized controlled trial. *First Author: John R. de Almeida, University Health Network, Toronto, ON, Canada*

Background: Lymphatic mapping identifies neck lymph nodes at risk for cancer spread in patients with lateralized oropharyngeal (OPC) squamous cell carcinoma. We hypothesize that a lymphatic mapping guided approach to radiotherapy (RT) treatment of the contralateral neck will enable safe de-escalation of therapy with acceptable disease control with potential benefits in RT related toxicity, QOL, swallowing function and economics. **Methods:** HN.11 is a Canadian Cancer Trials Group international multi-centre, non-inferiority randomized phase III trial comparing a lymphatic mapping-guided approach for management of the contralateral neck (experimental) vs. bilateral neck radiation therapy (RT) (control). The primary objective is to determine if a lymphatic mapping-guided approach for management of the contralateral neck has a non-inferior disease-free survival (DFS) compared to bilateral neck RT. Secondary objectives: To compare swallowing related QOL, xerostomia, isolated contralateral neck failure, overall survival, loco-regional failure, distant metastases, RT-related toxicities, patient reported adverse events (PRO CTCAE), gastrostomy tube usage, and economics indicators (resource utilization, lost productivity, financial toxicity, EQ5D). Exploratory objectives: Swallowing function using video fluoroscopic swallow studies, head and neck-cancer specific QOL, patterns of lymphatic drainage, radiomic prediction of contralateral lymphatic drainage, correlation of tumour somatic mutations and ctDNA with disease recurrence. **Statistical Design:** The target sample size is 510 patients. The experimental arm will be considered non-inferior if the upper limit of the one sided 95% confidence interval (CI) of the estimated hazard ratio (HR) does not exceed 1.46 (non-inferiority margin of 6.5% for 2-year DFS). In the primary intention-to-treat (ITT) analysis, the study has 81% power, with a one-sided type I error rate of 5%, assuming 5 years of accrual, 3-years of follow up to observe 178 DFS events, and a 5% loss to follow up. If non-inferiority is demonstrated in the ITT analysis, a secondary per-protocol analysis will be performed, analyzing those patients treated as per their allocation, with 80% power to detect non-inferiority of the experimental arm assuming a conservative 10% cross-over from the experimental to the control arm (i.e. failed lymphatic mapping). **Conduct to Date:** Study activation September 29, 2022. First enrollment was February 10, 2023. Supported by Canadian Cancer Society, Canadian Institutes of Health Research, National Cancer Trials Network (NCTN). Clinical trial information: NCT05451004. Research Sponsor: Canadian Cancer Society, Canadian Institutes of Health Research, National Cancer Trials Network (NCTN).

TPS6113

Poster Session

KEVLAR: A phase 2b, multi-institutional, randomized, blinded, controlled trial to assess the safety and efficacy of two schedules of RRx-001 vs. standard of care in attenuating severe oral mucositis (SOM) in patients receiving concomitant chemoradiation (CRT) for the treatment of locally advanced squamous cell carcinomas (SCC) of the oral cavity (OC) or oropharynx (OPC). *First Author: Tony R. Reid, EpicentRx, Inc., La Jolla, CA*

Background: The results of an open-labeled Phase 2a trial suggested that infusion of RRx-001 (bromonitroazidine), a nitrogen-containing NLRP3 inhibitor and Nrf2 activator, attenuated the course and severity of SOM associated CRT (cisplatin/IMRT) in cancers of the mouth or OPC without impeding tumor response. The primary efficacy objectives of KEVLAR are to replicate the findings of the earlier trial and to determine if a higher dose of RRx-001 (8 mg x 4 doses prior to CRT) will favorably impact overall SOM incidence. **Methods:** KEVLAR is a planned Phase 2b study to be conducted at about thirty sites in North America. Approximately 216 patients with pathologically confirmed SCCs of the OC or OPC will be randomized equally into one of 3 cohorts: Arm 1 will receive RRx-001, 8 mg/dose infusions twice weekly during the 2 weeks prior to CRT start; Arm 2 will receive RRx-001, 4 mg/dose in the same schedule; Arm 3 will receive best supportive care only. All patients will receive intensity modulated radiation therapy (IMRT) in 2.0-2.2 Gy fractions/weekday to a cumulative radiation dose of up to 72 Gy. CRT must include cisplatin administered either weekly (40 mg/m²) or tri-weekly (100 mg/m²). Radiation fields must include at least two oral sites at SOM risk planned to receive at least 55 Gy. Mucositis indicators will be assessed twice weekly by trained evaluators. OM will be scored centrally using WHO criteria from the first day of CRT until resolution of ulcerative OM (WHO grade ≤ 1). Adverse events will be evaluated using NCICTCv5 criteria. Patients will be followed for 24 months post the last day of radiation and tumor response will be recorded quarterly using RECIST criteria. Research Sponsor: None.

TPS6115

Poster Session

Randomized phase I/II trial of TheraT vectors expressing HPV16 specific antigens with neoadjuvant chemotherapy followed by transoral robotic surgery (TORS) or risk/response stratified chemoradiotherapy (CRT) for locoregional HPV16+ oropharyngeal cancer (OPC). *First Author: Ari Rosenberg, Department of Medicine, University of Chicago, Chicago, IL*

Background: HPV+ OPC is associated with excellent survival, yet standard therapy leads to substantial treatment-related toxicity. Among various de-escalation strategies, response adaptive de-escalation which selects pts based on neoadjuvant response is promising with excellent survival and reduced toxicity. Strategies to further deepen responses may allow more pts to be de-intensified which may improve survival and further reduce toxicity. As generation and maintenance of the HPV16+ malignant state of a cell requires the consistent expression of HPV-specific E7 and E6 oncoproteins, they represent a potential immunotherapy target, inspiring the development of HPV-specific immune activators, such as HB-200 platform. This platform contains two replicating live-attenuated vectors based on either lymphocytic choriomeningitis virus (HB-201) or Pichinde virus (HB-202), which express the same non-oncogenic (but highly antigenic) HPV16 E7E6 fusion protein and infect antigen presenting cells to induce and activate tumor-specific T cell responses. Data from in vivo models and early phase clinical studies indicate that HB-201 monotherapy and HB-201/HB-202 alternating two-vector therapy induces a robust antigen-specific circulating T cell response and anti-tumor activity, suggesting potential to provide therapeutic benefit to pts with HPV16+ OPC. Based on these studies we hypothesized that incorporation of the HB-200 platform with neoadjuvant chemotherapy followed by risk/response-stratified de-escalation in our ongoing randomized phase I/II study may deepen responses and facilitate de-escalation in a greater proportion of pts (NCT05108870). **Methods:** Eligible pts must have previously untreated HPV16+ OPC with T3-4 or N2-3 (AJCC-7th edition). Very low-risk disease with T1-2 and N0-1 are excluded. Pts receive neoadjuvant therapy with either HB-201 or HB-201/HB-202 alternating two-vector therapy for 3 doses in combination with carboplatin AUC 5 day 1 and paclitaxel 100mg/m² on days 1/8/15 of 21-day cycle for three cycles followed by risk/response adapted locoregional therapy with transoral robotic surgery (TORS) or RT to 50Gy (single-modality), CRT to 50Gy with cisplatin (intermediate de-escalation), or CRT to 70Gy with cisplatin (regular dose CRT). Eight pts have been enrolled in phase I portion with planned 74 pts (37 pts per arm) in phase II. The primary endpoint is deep response rate defined as proportion of patients with ≥ 50 shrinkage per RECIST v1.1. Secondary endpoints include OS, PFS, locoregional and distant control, and safety/tolerability. Exploratory analyses will include cell free HPV-DNA, and tissue/blood-based assessment of specific anti-tumor immunity. Clinical trial information: NCT05108870. Research Sponsor: Hookipa Pharma.

TPS6116

Poster Session

Phase 2 study of bintrafusp alfa in recurrent/metastatic olfactory neuroblastoma. *First Author: Dara Mark Bracken-Clarke, Center for Immuno-Oncology, CCR, NCI, NIH, Bethesda, MD*

Background: Olfactory neuroblastoma (ONB, esthesioneuroblastoma) is a rare malignant tumor of the nasal cavity, believed to arise from the basal cells of the olfactory neurosensory epithelium. ONB is often locally advanced at diagnosis with high rates of spread both locoregionally and systemically. Current therapy for locoregional disease is local resection with adjuvant (chemo-) radiotherapy. Actionable mutations are rare, and treatment options for recurrent or advanced, non-resectable, disease are limited and include off-label combination chemotherapy (most frequently platinum-containing) and somatostatin-directed therapies (ONB expresses somatostatin receptors). These are based on limited data, with response rates poorly characterized. Bintrafusp alfa is a first-in-class, bi-functional TGF- β "trap"/anti-PD-L1 fusion protein. Analysis of ONB has demonstrated both PD-1/PD-L1 (London et al, 2018) and TGF- β ligand expression (Romani et al, 2021). Pre-clinical and clinical data in advanced solid tumors demonstrate enhanced antitumor activity with combination PD-L1/TGF- β blockade, with responses observed independently of high PD-L1 levels (Strauss et al, 2020). Thus, combination PD-L1/TGF- β blockade in ONB is a rational approach in a setting of unmet clinical need. **Methods:** This study is a Phase 2 single-site, single-arm clinical trial of bintrafusp alfa (1200mg IV every 2 weeks for up to 26 doses) for patients with recurrent or metastatic ONB. Participants must co-enroll to the ONB Natural History study at the NCI (NCT4755205). Patients must not be candidates for local therapy, have received at least 1 line of systemic therapy (including a platinum salt), have RECIST 1.1 measurable disease and have adequate organ function. Prior checkpoint inhibitor therapy is permitted with patients cohorted according to checkpoint exposure; up to 21 checkpoint-naïve and 8 checkpoint-resistant patients will be enrolled. The primary objective is objective response rate by RECIST 1.1 with secondary endpoints including safety and tolerability, duration of response and overall survival; exploratory endpoints include pharmacokinetic analyses, PD-L1 and immune cell correlative analyses. The trial follows a Simon two-stage design, requiring ≥ 1 response in the first 12 patients. Tumor biopsy at enrollment is optional. Imaging for response assessment is planned for 8-week intervals and PET scan (preferably ^{68}Ga -DOTATATE) will be obtained for all patients at baseline and first restaging, then on an individualized basis per radiology advice. This study is presently open at the NCI with 5 patients enrolled as of January 2023. Clinical trial registry: NCT05012098. Clinical trial information: NCT05012098. Research Sponsor: U.S. National Institutes of Health.

TPS6117

Poster Session

IMRT followed by pembrolizumab in the adjuvant setting in anaplastic cancer of the thyroid (IMPAACT): Phase II trial adjuvant pembrolizumab after IMRT in ATC. *First Author: Maria E. Cabanillas, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Anaplastic thyroid carcinoma (ATC) has historically been an almost uniformly rapidly fatal disease. In patients with loco-regional disease with no distant metastasis (stage IVB), and without a targetable mutation, a combination of external beam radiation delivered via intensity modulated techniques (IMRT) +/- concurrent cytotoxic chemotherapy is the current standard of care. However, the relapse rate is very high within the first year of diagnosis. Our data show that 90% of ATCs express PD-L1, with 43% having expression levels greater than 50%. A clinical trial with an anti-PD1 drug in ATC patients with active disease showed that patients with ATC had a response rate of 19%. Additionally, as tumor PD-L1 expression has been linked to radioresistance and there is a need to target micrometastatic disease, using adjuvant checkpoint inhibitor is a rational strategy in these patients. **Methods:** This is an open label, single center, phase 2 trial of adjuvant pembrolizumab after external beam radiation to the primary tumor in patients with stage IVB ATC. The primary cohorts will include those with gross, locoregional disease who have completed treatment with IMRT +/- concurrent radiosensitizing chemotherapy. Patients will be treated with adjuvant pembrolizumab (400mg IV Q6 weeks for up to 9 cycles), 2-6 weeks after completion of radiation. Patients will be enrolled based on dose of radiation in cohort 1 (high dose group, > 51 Gy), cohort 2 (palliative dose group, < 50 Gy). Cohort 3, consisting of those who underwent surgery followed by IMRT plus concurrent chemotherapy will be an exploratory cohort. Restaging scans will be performed every 12 weeks after enrollment. MRI brain will be repeated every 6 months in the absence of evidence of progression. The primary endpoint is median PFS (from the start of adjuvant pembrolizumab) in cohorts 1 and 2. Secondary endpoint is median overall survival in cohorts 1 and 2. Cohort 3 (5 patients) will have an exploratory endpoint, to estimate the median disease-free survival (DFS). Statistics: Survival analyses will be performed using the Kaplan-Meier method. Based on historical data, the median PFS for unresected patients is 6.8 months. For an expected improvement of median PFS by 3.7 months, with a combined total of 30 evaluable patients in cohorts 1 and 2, we anticipate having 80.0% power using 1-sided 10% alpha for a one-sample log rank test. The trial began enrollment in July 2022. This trial is sponsored by philanthropic funds and Merck. ClinicalTrials.gov ID NCT05059470. Clinical trial information: NCT05059470. Research Sponsor: Merck; Philanthropic funds.

6500

Oral Abstract Session

Biologic indicators of donor socioeconomic disadvantage and recipient mortality following allogeneic hematopoietic cell transplantation. *First Author: Jennifer M. Knight, Medical College of Wisconsin, Milwaukee*

Background: Allogeneic hematopoietic cell transplantation (HCT) carries significant risks, with low socioeconomic status (SES) being predictive of increased mortality. Our team recently discovered that socioeconomic disadvantage among unrelated HCT donors results in decreased recipient overall survival (OS) and increased treatment-related mortality (TRM) within a cohort from the Center for International Blood and Marrow Transplant Research (CIBMTR). We also demonstrated that upregulation of the stress- and SES-related gene expression profile termed the ‘conserved transcriptional response to adversity’ (CTRA) is associated with low SES and worse outcomes among HCT recipients. Here, we hypothesize that donor immunologic characteristics associated with neighborhood socioeconomic disadvantage (CTRA) will confer prognostic risk to HCT recipients as indicated by inferior long-term recipient outcomes. **Methods:** Among a subset of the above cohort for which donor whole blood samples were available from the CIBMTR repository, we evaluated whether donor cell CTRA gene regulation was associated with inferior HCT outcomes at 3 years in recipients being treated for hematologic malignancy. Multivariable models adjusted for donor and recipient characteristics evaluated associations between donor CTRA and recipient OS, TRM, disease free survival (DFS), relapse, and acute and chronic graft versus host disease. Results were considered significant if $P < 0.05$. **Results:** We identified 263 donor-recipient pairs for study inclusion. Median recipient age at hematologic malignancy diagnosis was 53 years (range 19-77), 46% were female, and 54% had acute myeloid leukemia. Donors were 35% female and median age at donation was 31 years (range 18-60). In RNA sequencing data from HCT donors, greater CTRA expression was associated with reduced OS (covariate-adjusted $HR = 1.94/CTRA\ SD$, 95% CI [1.01, 3.71], $p = .046$) which was driven predominantly by increased TRM (adjusted $HR = 5.04$, [2.20, 11.50], $p = .0001$). These clinical outcomes are consistent with those observed to be associated with donor SES in our prior work. Donor cell effects on transplant outcomes derived predominantly from the pro-inflammatory component of the CTRA (OS: adjusted $HR = 1.67$, [1.20, 2.33], $p = .0026$; TRM: adjusted $HR = 2.21$, [1.21, 4.06], $p = .010$) and emerged above and beyond the effects of the recipients’ own SES, as well as multiple other recipient disease, treatment, and demographic factors. Donor CTRA was not associated with relapse, DFS, or other transplant outcomes. **Conclusions:** For the first time, we show that transcriptome patterning among HCT donors, consistent with neighborhood SES disadvantage, results in adverse recipient HCT outcomes. These findings suggest that SES has a biologic impact at either the stem or immune cell level that persists even when transplanted into a new host. Research Sponsor: U.S. National Institutes of Health; U.S. National Institutes of Health.

6502

Oral Abstract Session

Disparities in outcomes among hospitalized unhoused patients with cancer in the US. *First Author: Kanan Shah, NYU Grossman School of Medicine, New York, NY*

Background: Cancer is the 2nd leading cause of death among death among unhoused adults in the US. Use of aggressive medical interventions and costs during hospitalizations remains unstudied in the unhoused population. **Methods:** All hospitalized adults age ≥ 18 with a principal cancer diagnosis were identified in the 2016-2020 National Inpatient Sample (NIS). Logistic regression tested associations between unhoused status and: cost of care, mortality, and receipt of invasive procedures/systemic therapy. Adjusted analysis accounted for patient demographics, socioeconomic status, comorbidities, and effect modification of housing status by length of stay (LOS). **Results:** A total of 9,030 unhoused and 2,758,693 housed adults with cancer were included in the study. There were significant ($p < 0.01$) differences in age < 65 years (77% unhoused vs 41% housed), male sex (75% vs 53%), race (Black, 25% vs 13%; White, 58% vs 71%), and insurance type (Private, 6% vs 27%; Medicaid, 53% vs 11%). There were also differences by primary cancer diagnosis, with higher rates of lung (17% vs 14%) and liver (8% vs 3%) cancers. Unhoused persons received less chemotherapy inpatient (5% vs 7%) and fewer overall procedures (48% vs 58%), while experiencing longer LOS (median 6 vs 4 days). On adjusted analyses, unhoused adults were had lower odds of receiving invasive procedures (aOR [95%CI], 0.34 [0.27-0.42]) or systemic therapy (0.41 [0.20-0.85]); and were less likely to have a higher-than-median cost of stay 0.47 [0.39-0.57]). Additionally, unhoused adults were 35% and 20% less likely to have a higher-than-median cost of stay or die while hospitalized (95% CI 0.59 – 0.71 and 0.67 – 0.96, respectively). When accounting for the possibility of housing status being modified by LOS, unhoused persons remained significantly less likely than housed persons to receive inpatient procedures (aOR 0.38, 0.47, and 0.60 for short, medium, and long LOS, respectively; $p < 0.001$ for each) or have high cost of stay (adjusted OR 0.55, 0.71, 0.70, $p < .001$ for each), though the differences by housing status were attenuated with longer length of stay. **Conclusions:** In this first nationwide analysis of hospitalizations among unhoused adults with cancer, unhoused patients remained significantly less likely to receive invasive procedures or systemic therapy. These disparities in inpatient management despite the higher prevalence of more aggressive cancers and comorbidities among the unhoused highlight missed opportunities to improve cancer care. Research Sponsor: None.

6501

Oral Abstract Session

Evaluation of potential socioeconomic and racial/ethnic disparities in all-cause mortality in adolescent and young adult patients with cancer. *First Author: Scott Henderson, Kaiser Permanente Bernard J. Tyson School of Medicine, Pasadena, CA*

Background: Adolescent Young Adult (AYA) cancer patients, aged 15-39, have historically been understudied. For older adults, socioeconomic (SES) and racial/ethnic disparities in mortality have been demonstrated, but less is known about survival disparities for AYA patients. Most existing studies do not account for the influence of insurance status and access to care. To address this gap, we evaluated the association of SES and race/ethnicity with overall mortality for AYA cancer patients who were members of an integrated health delivery system with relatively equal access to care. **Methods:** Patients diagnosed with cancer at age 15-39 years old in Kaiser Permanente Southern California between 2010-2018 were included. The fourteen most common AYA cancer types within our cohort were included (excluding thyroid cancer due to low mortality rate). The Neighborhood Deprivation Index (NDI) was used as a marker of SES. Patients were placed into NDI quartiles (Q1: least deprived-Q4: most deprived). Mortality rate per 1,000 patient years was calculated for each racial/ethnic group and NDI quartile. Multivariable cox model was used to estimate hazard ratios (HRs) for all-cause mortality. Models included race/ethnicity and NDI subgroup simultaneously, adjusting for sex, age and stage at diagnosis, and cancer type. **Results:** A total of 6,380 patients (59% female, median age: 33) were followed for a maximum of ten years. Racial/ethnic distribution was 45% Hispanic, 36% non-Hispanic White, 10% non-Hispanic Asian/Pacific Islander, 7% non-Hispanic Black, 2% Other/Unknown. Overall mortality was 21.8 deaths per 1,000 person years. Crude mortality rates were higher among Non-White racial/ethnic groups (Asian/Pacific Islander: 26.7, Black: 26.2, Hispanic: 25.6, Other/Unknown: 30.3) compared to White patients (16.4). In the adjusted model, Hispanic ($HR = 1.32$, 95% confidence interval [CI] 1.03-1.50, $p = 0.004$) and Black ($HR = 1.35$, 95% CI 1.00-1.83, $p = 0.05$) patients experienced significantly higher risk of all-cause mortality compared to White patients. No mortality differences were observed between Asian/Pacific Islander and White patients. Patients from more deprived neighborhoods had higher mortality risk (Q1: 19.9, Q2: 19.8, Q3: 24.1, Q4: 27.4). In the adjusted model, there was no significant difference in all-cause mortality between Q1 and Q2-Q4 [Q2 ($HR = 0.88$, 95% CI 0.71-1.10), Q3 ($HR = 0.94$, 95% CI 0.75-1.17), Q4 ($HR = 0.96$, 95% CI 0.76-1.22)]. **Conclusions:** Our study suggests that for insured AYA cancer patients with similar access to care, Hispanic and Black patients have increased risk of all-cause mortality as compared to White patients, while no significant SES survival disparities were observed. These findings warrant further investigation, awareness, and intervention to address inequities in cancer care among vulnerable populations. Research Sponsor: None.

6503

Oral Abstract Session

Risk of early mortality in patients with cancer experiencing adverse financial events. *First Author: Hiba Khan, University of Washington/Fred Hutch Cancer Center, Seattle, WA*

Background: Patients with cancer are at higher risk for experiencing severe adverse financial events (AFE) compared to similar individuals without cancer. Among persons with cancer, those experiencing bankruptcy have poorer survival. In this study, we sought to determine whether AFEs less severe than bankruptcy have an increased risk of death among patients with cancer. **Methods:** Records for all patients diagnosed with a solid tumor between 2013 and 2018 were identified through the Western Washington State SEER cancer registry and were linked to quarterly credit reports from TransUnion. Patients who survived at least 2 years from date of diagnosis were included. Cancer patients experiencing any AFE, defined as third-party collections, charge-offs, delinquent mortgage payments, tax liens, foreclosures, and reposessions within 2 years of diagnosis were compared with cancer cases who did not experience these events. After adjusting for age, sex, race, area deprivation index, rural/urban status, marital status, AFE at diagnosis, cancer type, and stage of cancer, we fit a Cox proportional hazards model to examine the relationship between AFEs and overall survival, and also fit a separate model for each cancer type. **Results:** A total of 64,637 patients were diagnosed with cancer between 2013 and 2018, and survived 2 years post-diagnosis. The overall population was 84% white, 53% female, and had a median age of 64. 12,698 patients experienced any severe financial event. The adjusted hazard ratio for mortality among patients who did versus did not experience an AFE was 1.22 (95% CI, 1.145-1.299, $p < 0.001$), with age > 65 , Asian/Pacific Islander race, greater area deprivation index, and higher stage of cancer associated with increased risk for mortality. Among differing cancer types, patients with prostate cancer who experienced an AFE had the highest risk of death compared with patients with prostate cancer who did not experience an AFE ($HR\ 1.703$, 95% CI, 1.395 to 2.08, $p < 0.001$). **Conclusions:** Patients with cancer who experience severe AFEs within 2 years of diagnosis are at higher risk for mortality after adjusting for sociodemographic and clinical factors. When comparing within separate cancer groups, this association is strongest among patients with prostate cancer. Current analysis is limited by restricting population to those who survived at least 2 years after diagnosis; future work will expand population to include patients who died at any time point. Further research should investigate mechanisms for this increased mortality risk, to inform potential interventions and policy solutions, especially among the prostate cancer population. Research Sponsor: Kathryn Butler Foundation, Texas 4000 Foundation.

Cancer Type	HR	95% CI	p value
All	1.22	1.145 to 1.299	<0.0001
Prostate	1.703	1.395 to 2.08	<0.0001
Breast	1.18	0.993 to 1.403	0.0606
Colorectal	1.172	0.984 to 1.397	0.0759
Lung	1.169	0.998 to 1.37	0.0533
Other	1.149	1.049 to 1.259	0.0027

6504

Oral Abstract Session

Health insurance continuity and survival among children, adolescents, and young adults with blood cancer: An analysis based on SEER-Medicaid data.

First Author: Xu Ji, Emory University School of Medicine, Atlanta, GA

Background: Many previously uninsured patients do not receive Medicaid coverage until the point of, or after, cancer diagnosis, which may delay access to life-saving therapies. We examined whether continuous Medicaid coverage prior to diagnosis (vs. gaining Medicaid at, or after, diagnosis) provides a survival benefit in children and adolescents/young adults (AYAs) newly diagnosed with blood cancer. **Methods:** Using the linked SEER cancer registry-Medicaid enrollment data, we assessed coverage during the six months prior to, the month of, and the six months after cancer diagnosis (13-month window) in 29,873 children and AYAs (aged 0-39 years) diagnosed with blood cancer in 2006-2013. To measure insurance continuity, we categorized patients who had: (1) continuous Medicaid (enrolled for ≥ 6 months prior to through diagnosis), (2) newly gained Medicaid at/after diagnosis (enrollment only at or ≤ 6 months after diagnosis), (3) other patterns of non-continuous Medicaid, (4) private insurance, (5) other insurance, or (6) uninsured/unknown insurance. The last three groups contain patients in SEER not linked to Medicaid enrollment data; these patients' insurance at diagnosis was available in SEER. Kaplan-Meier (KM) survival curve of 5-year overall survival was stratified by insurance continuity category. Associations between insurance continuity and survival were examined using Cox proportional hazard models, for all blood cancers combined and by cancer type (leukemia, lymphoma, myeloma). Models also adjusted for age, sex, race/ethnicity, rurality, neighborhood socioeconomic status, and diagnosis year. **Results:** Of our sample, 44.1% had private insurance, followed by Medicaid (28.3%), other insurance (9.6%), and no insurance (3.9%) or unknown insurance (14.1%). Of Medicaid-insured patients, 44.9% had continuous Medicaid, 38.9% gained Medicaid at/after diagnosis, and 16.2% experienced other noncontinuous patterns. The KM-estimated 5-year survival probability was 89.3% for privately insured patients, followed by other insurance (88.1%), continuous Medicaid (78.2%), other patterns of noncontinuous Medicaid (74.3%), and newly gained Medicaid at/after diagnosis (70.6%; $p < 0.001$). In multivariable analysis, patients who newly gained Medicaid at/after diagnosis had a hazard ratio (HR) for death of 2.63 (95%CI=2.42-2.87), whereas patients with continuous Medicaid and those with other noncontinuous patterns had HRs of 2.08 (95%CI=1.90-2.28) and 2.31 (95%CI=2.04-2.60), respectively, compared to privately insured patients. This finding persisted across blood cancer types. **Conclusions:** Less than half of Medicaid-insured children and AYAs with blood cancer had continuous insurance coverage prior to and following cancer diagnosis. Lacking continuous Medicaid coverage was associated with inferior survival. Research Sponsor: The Leukemia & Lymphoma Society.

6505

Oral Abstract Session

Association of medical debt and cancer mortality in the US. First Author: Xin Hu, Emory University School of Public Health, Atlanta, GA

Background: Medical debt is associated with non-medical and medical financial hardship, such as food and housing insecurity, as well as delaying or forgoing recommended health care. This study examines county level associations between medical debt and cancer mortality in the US. **Methods:** We conducted a county level ecological study, using 2018 medical debt data from the Urban Institute linked with 2015-2019 mortality data from the National Centers for Health Statistics. All US counties with non-missing information on medical debt and other covariates were included. Primary outcomes were age-adjusted mortality rates per 100,000 person-years for all malignant cancers and by cancer type. Multivariable linear mixed models were used to estimate the association of percent of population with medical debt with cancer mortality, adjusting for county level sociodemographic characteristics. Additional analyses examined the association between median amount of medical debt per person and cancer mortality for the subset of counties with these data. Models were weighted by county level population size, with standard errors clustered at the state level. **Results:** Among 2,943 counties, an average of 19.8% of the population had medical debt, ranging from 0% to 53.6% across counties. Higher percentages of the population with medical debt were observed in non-metro areas, counties with higher percentages of non-Hispanic Black people, adults without high school education, living below poverty level, uninsured, or unemployed. One percentage point increase in the population with medical debt was associated with a 1.12 (95% CI=1.02-1.22) increase in age-adjusted mortality rate (per 100,000 person-years) for all malignant cancers, a 0.47 (95% CI=0.43-0.52) increase for lung cancer, a 0.09 (95% CI=0.07-0.11) increase for colorectal cancer, and a 0.06 (95% CI=0.04-0.07) increase for female breast cancer. Among 1,949 counties with the amount of medical debt available, each \$100 increase in median medical debt was associated with a 0.86 (95% CI=0.52-1.21) increase in age-adjusted mortality rate for all malignant cancers. Associations between increases in median medical debt and increased mortality rates were statistically significant for major cancer types. **Conclusions:** Medical debt is associated with significantly higher cancer mortality at the county level. Policies increasing access to affordable health care may improve cancer outcomes. Research Sponsor: None.

Association of medical debt and age-adjusted mortality rates.

Cause of Death	Any Medical Debt	Median Medical Debt, in hundreds
All malignant cancers	1.12 (1.02, 1.22)	0.86 (0.52, 1.21)
Lung and bronchus	0.47 (0.43, 0.52)	0.33 (0.18, 0.47)
Prostate	0.03 (0.02, 0.04)	0.03 (-0.002, 0.07)
Female breast	0.06 (0.04, 0.07)	0.05 (0.01, 0.09)
Colorectal	0.09 (0.07, 0.11)	0.06 (0.01, 0.11)

* Adjusted for county level education, racial/ethnic composition, metro status, uninsured and unemployment rates.

6506

Oral Abstract Session

The impact of single gene testing (SGT) on subsequent comprehensive genomic profiling (CGP) success in community oncology practice for advanced non-small cell lung cancer (NSCLC): Results from a prospective observational reference laboratory testing program. First Author: Mary K Nesline, Labcorp Oncology, Durham, NC

Background: CGP concurrently tests tumor tissue for guideline-recommended predictive biomarkers for optimal therapy selection and identification of clinical trials in NSCLC patients. A common practice in the community oncology setting is to first order SGT, then consider CGP when SGT results are negative or after treatment failure. Given the limited tissue available and the scope of alterations not tested by SGT, we sought to characterize the effects of prior SGT on subsequent CGP testing success, and therapeutic opportunities identified by CGP beyond SGT for NSCLC patients in the community setting. **Methods:** Reference laboratory information systems were used to prospectively contact clinicians across 80 community practices who ordered at least 1 SGT for guideline-recommended genomic variants in NSCLC. CGP was offered for their patients prior to SGT or upon receipt of negative SGT results. SGT included individual assays for *BRAF*, *EGFR*, *KRAS*, *MET* exon 14 skipping mutations; *ALK*, *RET*, and *ROS1* rearrangements; and PD-L1 IHC. CGP included DNA-seq for mutations, copy number variants in 523 genes including guideline-recommended genomic variants, MSI, and tumor mutational burden; RNA-seq for rearrangements/fusions/splice variants; and PD-L1 IHC. **Results:** Among a total of 580 NSCLC patients with CGP ordered (May 2021-December 2022), 168 (29%) had ≥ 1 SGT ordered prior to CGP (median=5). No patients had all SGT performed, with untested cases ranging from 10% for *ALK* to 90% for *MET* exon 14. The same FFPE tissue block was used for CGP in 150/168 (89%) of cases with prior negative SGT. Compared to CGP-only cases, CGP for cases with prior negative SGT was canceled twice as often at tissue review (16% vs 7%; $p=0.01$), had higher DNA extraction failures (13% vs 8%; $p=0.09$), and lower DNA sequencing success (70% vs 83%, $p<0.001$). CGP detected guideline-recommended variants in 51% of all cases. Among prior negative SGT cases, frequencies were higher in genes where SGT was performed less often and is less sensitive than CGP RNA-seq (*RET* fusions, *MET* exon 14 skipping). CGP also identified guideline-recommended variants in genes with no SGT offered during the study period (*ERBB2* mutations, *NTRK2/3* fusions), as well as variants with emerging evidence for FDA expedited program-designated clinical trial therapies in 28% of patients, including *NRG1* fusions and *BRAF* non-V600E, *KEAP1*, *KRAS* non-G12C, *NFE2L2*, *STK11*, and TP53 Y220C mutations. **Conclusions:** Prior negative SGT doubled subsequent CGP test cancellations for NSCLC due to tissue insufficiency and increased CGP DNA extraction failures. SGT practice in the community oncology setting does not meet practice guideline recommendations and negatively impacts the potential benefit of subsequent CGP for NSCLC patients. Research Sponsor: Eli Lilly and Company.

6507

Oral Abstract Session

Clinical value of timely targeted therapy (TT) for patients with advanced non-small cell lung cancer (aNSCLC) with actionable driver oncogenes (ADO). First Author: Thomas Stricker, Tennessee Oncology, Nashville, TN

Background: Recent real-world studies observed that some aNSCLC pts with ADO initiated non-targeted therapy (non-TT) before biomarker test results became available. This study assesses the clinical impact of the timing of first line (1L) TT in aNSCLC pts with ADO. **Methods:** In a retrospective analysis of the nationwide Flatiron Health electronic health record-derived de-identified database, pts aged ≥ 18 years, diagnosed (Dx) with aNSCLC between 1/1/2015-10/18/2022, had ADO (*ALK*, *BRAF*, *EGFR*, *RET*, *MET*, *ROS-1*, or *NTRK*) based on biomarker testing ≤ 90 days of advanced Dx, and received 1L treatment (tx) were included. Cohorts were defined by tx patterns after test result: Cohort 1 received 1L TT ≤ 42 days; Cohort 2 initiated 1L non-TT before or after testing but switched to TT ≤ 42 days; Cohort 3 initiated non-TT before or after testing and did not switch to TT ≤ 42 days. Pts were followed from test results + 42 days until 11/30/2022 or death, whichever earliest. Multivariate Cox regression evaluated real-world progression-free survival (rwPFS) and overall survival (OS) between cohorts. **Results:** A total of 5156 aNSCLC pts with ADO were included: 79% were treated in the community setting and 56% received NGS testing. Most common ADO were *EGFR* and *ALK* for both Cohort 1 (78% and 13%) and Cohort 2 (67% and 24%); *EGFR* (39%) and *BRAF* (35%) for Cohort 3. Cohort 3 included more rare mutations (*MET*, *NTRK*, *RET*). Statistically significant differences were observed in gender, race/ethnicity, practice type, and area-level socioeconomic status across all cohorts. There was no significant difference in outcomes observed between Cohort 2 and 1, but significantly inferior outcomes in Cohort 3 vs 1. **Conclusions:** Our findings demonstrated better outcomes with upfront 1L TT vs non-TT in aNSCLC pts with ADO. The comparable outcomes between pts who received 1L TT after test result and pts who switched to TT ≤ 42 days of test result available underscore the importance of timely tx decisions based on ADO detection in lieu of tx-switch at progression. Opportunities remain to improve utilization of NGS to identify all ADO upfront to inform the appropriate 1L TT when indicated. Research Sponsor: Genentech Inc./F. Hoffmann-La Roche.

Outcomes by tx pattern in aNSCLC pts with ADO.

	Median (95% CI) rwPFS, months	rwPFS adjusted Hazard Ratios (HRs)	Median (95% CI) OS, months	OS adjusted HRs
Cohort 1, n=3005 (reference group)	10 (10,11)	-	28 (27,29)	-
Cohort 2, n=162	13 (9,14)	0.92, $p=0.374$	26 (21,38)	0.96, $p=0.731$
Cohort 3, n=1989	6 (6,7)	1.18, $p<0.001$	21 (19,24)	1.12, $p=0.018$

6508

Oral Abstract Session

Practice- and provider-level inequities in next-generation sequencing (NGS) testing by race/ethnicity for patients (pts) with advanced non-small cell lung cancer (aNSCLC) treated in the community setting. *First Author: Gregory A. Vidal, The West Cancer Center, Germantown, TN*

Background: Inequities in NGS testing in pts with aNSCLC are well documented. Here, we examined elements of total inequity in NGS testing for pts with aNSCLC treated in the US community setting, in terms of within and between inequities at the practice and provider level. **Methods:** Using the nationwide, deidentified, electronic health record–derived Flatiron Health database, we studied pts with aNSCLC diagnosed in April 2018 or later and treated in the community setting. Testing quality was defined as an NGS result reported ≤60 days after advanced diagnosis. Total-practice inequity was the average percentage-point (pp) difference in the rate of testing quality for non-Latinx Black or Latinx pts compared with non-Latinx white pts. Within-practice inequity was the average pp difference in testing rates at a practice weighted by overall practice enrollment. Between-practice inequity was the covariance between a practice’s overall testing rate and the extent of practice-level racial/ethnic underrepresentation. We estimated these inequities at the practice and provider levels using a Bayesian approach. **Results:** Our study included a total of 12,045 pts (9,981 non-Latinx white, 1,528 non-Latinx Black, and 536 Latinx pts). Both within- and between-practice inequities contributed to total inequity in NGS testing for non-Latinx Black and Latinx pts compared with non-Latinx white pts (Table). For non-Latinx Black pts, between-practice inequities were estimated as 57% (3.77 pp/6.56 pp) of the total inequity in NGS testing; for Latinx pts, the contribution of between-practice inequity was 39% (3.13 pp/8.01 pp). At the provider level, between-provider inequities were the dominant contributor to total inequity in NGS testing for both non-Latinx Black and Latinx pts, accounting for 86% (5.88 pp/6.87 pp) of total provider-level inequity for non-Latinx Black pts and 64% (5.36 pp/8.43 pp) for Latinx pts. **Conclusions:** Inequities within and between practices, as well as between providers, are meaningful contributors to total inequity in NGS testing. Additional healthcare equity initiatives are needed to identify potential causes for lagging practices/providers to address inequities in NGS testing. Research Sponsor: Genentech Inc./F. Hoffmann-La Roche.

Average percentage-point difference in NGS testing inequity in Pts with aNSCLC.		
vs non-Latinx White pts (95% credible interval), %*	non-Latinx Black	Latinx
Practice level		
Total	6.56 (3.91, 9.17)	8.01 (3.81, 12.23)
Within	2.79 (–0.22, 5.72)	4.88 (–0.47, 10.18)
Between	3.77 (2.43, 5.13)	3.13 (–0.02, 6.24)
Provider level		
Total	6.87 (4.23, 9.46)	8.43 (4.17, 12.65)
Within	0.99 (–2.16, 4.11)	3.07 (–2.56, 8.56)
Between	5.88 (4.09, 7.65)	5.36 (1.73, 9.01)

* Negative values indicate higher NGS testing rate in non-Latinx Black or Latinx pts vs non-Latinx White pts.

6510

Poster Discussion Session

How patient-clinician education can strengthen partnerships and promote tangible actions to improve clinical trial diversity in breast and lung cancer trials. *First Author: Tariqa Ackbarali, PlatformQ Health Education, Needham, MA*

Background: Some of the greatest disparities in cancer care are related to clinical trial access for our patients. To address the racial/ethnic disparities in breast and lung cancer clinical trials, a tethered educational initiative was designed to empower patients, assess current clinician perceptions/practices, and improve awareness of real-world perspectives of clinical trials. **Methods:** Two, one-hour online, interactive, video-based programs were designed for patients, caregivers, and providers. This patient/caregiver program was hosted on CancerCoachLive and MedLive in November, 2022, while the provider program was hosted on ClinicalSeriesLive in December, 2022 and will remain on-demand until December 2023. This initiative was conducted in collaboration with TOUCH, the Black Breast Cancer Alliance, BlackDoctors.org, Moffitt Cancer Center, CancerCare, and the Lung Cancer Research Foundation. Herein, we report on an analysis from patients and providers regarding clinical trial diversity, behavioral impact, and qualitative insights. **Results:** As of data cut-off (02/10/23), 1,425 participants have engaged across both educational programs. Of participating patients, 46% were non-White (non-Hispanic), 36% were in remission, 36% were not on active treatment, and 29% were newly diagnosed. Following the program 81% were motivated to take one or more actions over the next two months: the most common actions being to research clinical trials (38%) or discuss clinical trials with a clinician (19%). Post-activity, 79% were confident to very confident discussing clinical trials with a clinician. Critical data related to clinician preferences was assessed and demonstrated a 23% increase in confidence from pre- to post-activity in improving diversity in clinical trial participation with preferences observed in both breast and lung cancers to offer clinical trials for newly diagnosed and second recurrence settings. Of those who are being offered clinical trials in the community setting, there was a higher likelihood for patients to be offered a clinical trial if their subtype was HER2+ breast cancer subtype or NSCLC with an actionable mutation. Data collection continues as this initiative is ongoing. Qualitative data including clinician write-in examples of behavioral impact and patient perspectives from the interviews will be shared. **Conclusions:** The outcomes discussed herein reveal a willingness from patients/caregivers to engage in clinical trial discussions and participate in clinical trials, if eligible. These educational programs positively impacted clinician motivation to address barriers to enrollment and clinical trial eligibility with their patients. Real-world accounts of patient experiences provide different perspectives that can help improve approaches to improve clinical trial diversity. Research Sponsor: Daiichi Sankyo Inc., Gilead Sciences, Inc., Merck & Co., Inc.; and Pfizer Inc.

6509

Poster Discussion Session

Strategies to increase accrual of underrepresented populations in Alliance NCTN trials. *First Author: Electra D. Paskett, The Ohio State University, Columbus, OH*

Background: Accrual of underrepresented populations (URPs-racial and ethnic minorities, women, rural populations, and younger and older populations) to clinical trials has been historically low, hampering progress in cancer treatment, symptom intervention and prevention for all. In 2018, the Alliance for Clinical Trials in Oncology (Alliance), as a part of the NCI’s National Clinical Trials Network (NCTN) and a Research Base for the NCI Community Oncology Research Program (NCORP) began a multi-pronged strategy to increase accrual of underrepresented minorities by race and ethnicity (URMs) to both treatment and cancer control trials conducted by the Alliance. **Methods:** Alliance leadership set a goal of 20% accrual for racial and ethnic minorities to all trials in 2018. The Health Disparities Committee (HDC) implemented several strategies over time including leadership promotion/expectation of goals; funding junior investigators and special projects focusing on URPs; working groups for specific populations in HDC; HDC co-chairs to selected protocols; translation services of patient facing materials; opening studies at NCORP Minority Underserved Sites; real time monitoring of accrual demographics, by Alliance and by site; protocols addressing aims for specific populations; closing protocol enrollment to majority populations; and increasing the study sample size to enroll additional minority participants to allow for analyzing intervention effects by subgroups. **Results:** Accrual data from 117 NCTN and NCORP trials led by Alliance was included from 2014-2022. Over time, accrual of racial and ethnic minorities increased from 13.6% to 25.3% for treatment and 13% to 21.5% for cancer control trials. This results in overall increase from 13.5 % to 23.6% of URMs for all trials, a 74.8% improvement. **Conclusions:** Intentional approaches to increase URMs has led to an increase in URM accruals to Alliance trials. Future strategies include implementation of the Alliance Patient Questionnaire to prospectively measure the prevalence of specific social determinants of health among patients enrolled to further expand the understanding and address the needs of unique population accrued to Alliance trials. In addition, accrual of women, rural populations, and younger and older adults (65+ years) are now being monitored over time to increase all URP accruals. Research Sponsor: U.S. National Institutes of Health.

6511

Poster Discussion Session

Mediators of racial/ethnic inequities in clinical trial participation among US patients with cancer, 2011-2022. *First Author: Jenny Guadamuz, Flatiron Health, New York, NY*

Background: In 2024, the US Food & Drug Administration will require drug sponsors to implement plans to improve racial/ethnic diversity in clinical trials. While minoritized populations are less likely to participate in cancer trials, it is unknown whether social determinants of health (SDOH) explain these inequities. Here we identified SDOH factors that contribute to racial/ethnic inequities in clinical trial participation among patients with 22 solid and blood cancers. **Methods:** This retrospective study used the nationwide Flatiron Health electronic health record-derived de-identified database of adult patients with cancer (2011-2022). Area-level SDOH (e.g., predominant race/ethnicity [proxy for segregation]) contextualizing where patients live were defined using the American Community Survey tract data. Patients were followed from cancer-specific diagnosis to clinical study drug receipt (proxy for trial participation), death, or last recorded activity. Associations of race/ethnicity and SDOH factors on trial participation were assessed using Cox proportional hazards models adjusted for clinical factors (diagnosis year, age, sex, performance status, stage, and cancer type). To elucidate which SDOH explain racial/ethnic inequities, mediation analysis was performed using nonlinear multiple additive regression trees models. **Results:** This study included 233,556 patients (median age: 68 years, 50.0% women; 65.6% non-Latinx [NL] White, 8.5% NL Black, 5.0% Latinx). Black and Latinx patients were more likely to live in marginalized areas (i.e., disproportionately minoritized, low socioeconomic status, limited English proficiency, and low vehicle ownership) than White patients. Overall, 4.9% of patients participated in trials. Fewer patients from community practices or in marginalized neighborhoods participated in trials. Black (3.4%; hazard ratio [HR] 0.55, 95% confidence interval [CI]: 0.51- 0.60) and Latinx patients (3.6%; HR 0.57, CI: 0.52-0.63) were less likely to participate in trials than White patients (5.8%). Black-White trial inequities were substantially mediated (58%, CI: 47%-68%) by practice type (e.g., community vs. academic center, 13%, CI: 10%-15%) and area-level SDOH (e.g., segregation [33%, CI: 25%-44%] and vehicle ownership [12%, CI: 8%-15%]). Mediators explained 55% (CI: 38%-71%) of the Latinx-White trial participation inequity; area-level SDOH—including segregation (29%, CI: 13%-37%), limited English proficiency (15%, CI: 9%-25%), and vehicle ownership (8%, CI: 5%-12%)—were the most important mediators. **Conclusions:** SDOH factors, especially manifestations of structural racism such as segregation, explained a substantial proportion of racial/ethnic inequities in trial participation among patients with cancer. These findings can inform targeted efforts to increase racial/ethnic diversity in cancer trials. Research Sponsor: Flatiron Health.

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Poster Discussion Session

Comparison of incident breast cancer cases in the largest national US tumor registries. *First Author: Jennifer Kay Plichta, Department of Surgery, Duke University Medical Center, Durham, NC*

Background: National tumor registries, such as the NCDB (National Cancer Database) and SEER (Surveillance, Epidemiology, and End Results Program), have been used to explore numerous research questions related to trends in disease incidence, treatment patterns, and outcomes. However, some have criticized that they may not fully represent the general population. As such, we sought to compare the incident breast cancer cases in the NCDB and SEER to a national population cancer registry. **Methods:** All patients diagnosed with malignant or in situ breast cancer 2010-2019 were selected from the NCDB (Fall 2022 release) and SEER-22 (November 2021 release) and compared to breast cancer patient counts from the US Cancer Statistics Public Use Database (USCS, 2021 submission). Patient frequencies were summarized by age, sex, race/ethnicity, and year of diagnosis. Percent case coverage was estimated as the number of patients in the NCDB or SEER divided by the number of patients in the USCS. Chi-square tests were used to compare patient counts across data sources. **Results:** In total, the USCS database reported 3,047,509 patients diagnosed with breast cancer between 2010-2019, of which, 77.5% (N=2,362,477) were included in the NCDB and 46.0% (N=1,403,272) in SEER. Over time, case coverage steadily improved for the NCDB (72.8% in 2010 to 81.5% in 2019), while only a minor increase was observed in SEER (46.0% in 2010 to 46.6% in 2019). When compared to the USCS, case ascertainment was notably lower for individuals age ≥ 50 in both the NCDB and SEER (both $p < 0.001$). The overwhelming majority of patients were captured by the NCDB (age < 50 : 81.7%; age ≥ 50 : 76.6%) while SEER identified approximately half (age < 50 : 49.4%; age ≥ 50 : 45.3%). Case ascertainment also varied significantly by patient sex across registries (both $p < 0.001$). For male breast cancers, 84.1% were captured in the NCDB, only 77.5% of female patients were included. In contrast, case coverage in SEER was better for females than males (46.1% vs 43.5%). Notably, registries varied significantly by race/ethnicity (both $p < 0.001$). Case coverage in the NCDB was highest for non-Hispanic White (78.2%), non-Hispanic Black (77.7%), and non-Hispanic Asian or Pacific Islander (72.5%) patients, and it was lowest for Hispanic (56.4%) and non-Hispanic American Indian/Alaska Native (41.1%). In SEER, case coverage was highest for non-Hispanic Asian or Pacific Islander (78.1%) and Hispanic (69.6%) patients, and it was considerably lower for all other subgroups (non-Hispanic Black 44.8%, non-Hispanic White 42.4%, and non-Hispanic American Indian/Alaska Native 36.6%). **Conclusions:** National US tumor registries provide data for a large sampling of breast cancer patients, and case coverage has improved over time. However, significant differences in case coverage were observed based on age, sex, and race/ethnicity, suggesting that analyses using these data sets should be interpreted with caution. Research Sponsor: U.S. National Institutes of Health.

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Poster Discussion Session

Enhancement in line of therapy (LoT) derivation from real-world data (RWD) from electronic health records (EHR) via integration of medical claims data. *First Author: Smrita Agrawal, ConcertAI, Bengaluru, Karnataka, India*

Background: Clinical RWD derived from EHRs is becoming increasingly important for clinical research, trial design, regulatory decisions etc. These applications require identification of lines of therapy (LoT) which are typically not captured in EHR and must be abstracted from other clinical and medication data. EHR data has significant missingness which can be complemented with other data sources such as medical claims data. In this study, we demonstrate how our proprietary line of therapy algorithms for solid cancers show significant improvements when built using integrated EHR and claims data when compared to EHR data alone. **Methods:** For this analysis, ConcertAI's RWD360 dataset integrated with a large administrative open-claims dataset ($> 90\%$ overlap) for 14 solid cancer indications (Breast, Bladder, Lung, Prostate, Pancreas, Melanoma, Liver, Head & Neck, Renal, Colorectal, Melanoma, Ovarian, Thyroid, Endometrial) was used. The date of advanced/metastatic diagnosis used as the index date for LoTs was derived from the EHR data and medications from both EHR and claims data were used. We ran our LoT algorithms on EHR data with and without claims data and evaluated the impact of integrating claims data on the quantity and quality of LoT output. **Results:** The inclusion of medication data from claims significantly increased (7-22%) the number of patients for which LoTs could be extracted from the EHR data. Furthermore, we observed increases in number of lines per patient, length of lines and medications per line across cohorts. The distance between index date and 1st line start date was shortened in a subset (2-12%) of patients as a result. In a small fraction of cases, we even observed removal of false lines as some of the lines moved to adjuvant/neoadjuvant setting by filling in missing medication from claims. Overall, 7-39% patients in the LoT cohorts were impacted by addition of claims. Results for a few cancer types are presented in Table 1. We also compared the top LoTs derived from the integrated dataset against the standard of care for that cancer and observed very good concordance. **Conclusions:** Deriving LoTs by integrating data from multiple data sources such as EHR and claims can significantly improve its accuracy. Research Sponsor: None.

Impact analysis of claims integration on LoTs for 5/14 solid cancer cohorts.

Cancer Indication	Breast	Lung	Prostate	Pancreas	Renal
# Pts with LoTs before claims integration	49826	53961	24309	12584	6639
# Pts with LoTs post claims integration	54557	57806	27191	13631	7478
# Pts added due to addition of claims	5034	3960	3019	1066	866
# False positive pts removed due to claims integration	303	115	137	19	27
# Pts with enhanced LoTs	18104	5421	9417	1461	1733
# Pts with decrease in days between index date and LoT start date	3680	1318	3018	308	442
# Total pts impacted	23441 (47.1%)	9381 (17.6%)	12436 (51.7%)	2527 (20.2%)	2626 (39.5%)

Pts, patients.

6513

Poster Discussion Session

Big data in oncology: Challenges and solutions. *First Author: Neil J. Shah, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Oncology care is complex and often multimodal. With recent technological advances, only a fraction of data is structured feasibly for research. Here we present a step-by-step method of building a novel comprehensive pan-cancer oncology data model using standard data definitions and industry-standard benchmarks. **Methods:** A team of 133 members was assembled including a project manager, bioinformatic engineers, business analysts, biostatisticians, data stewardship experts, clinical curators, and quality assurance (QA) managers. We first identified data domains that capture a comprehensive patient journey, leveraging existing oncology data models as a starting point, including NAACCR, PRISMM (Deb Schrag & Eva Lepisto), and mCODE (ASCO). A common data model was developed using standard terms plus 5-10 disease specific elements (DSE). REDCap was used as the database platform, as it is HIPAA compliant and allows customizations. The data was stored in AuroraDB using an architecture and products that provide scalability from both an integration and consumption perspective. **Results:** We identified 10 data domains, including 186 distinct elements: demographics (20), comorbidities (2); cancer diagnosis & staging (27), pathology (45), imaging (18), medications (11), oncology responses (11), radiation treatments (14), cancer surgeries (11), cancer genomic (19), tumor markers (8), and vitals (8). Standard ontologies were used, including ICD-O-3 histology codes, ICD-10 comorbidities codes, CPT cancer surgeries codes, and CTCAE 5.0 for toxicities. We identified a data steward for each tumor type across medical oncology, surgery, pathology, radiology, and radiation oncology domains who aided curator training and the identification of DSE. QA managers and analysts performed 20% source data verification. In addition, we built REDCap rules (applicable across a form), and complex queries (applicable across multiple forms). To support QA and clinical engagement, interactive Tableau dashboards were constructed. In addition, timing and quality errors were monitored via Tableau dashboards at the individual curator level to provide timely feedback, leading to improved data quality and curation efficiency in real time. The Medical oncology and radiology domains were the most time-consuming, whereas Cancer diagnosis was the most difficult to curate. **Conclusions:** We collected genomic and phenomic data for 15,579 patients across six tumor types to date. Collecting comprehensive oncology data across tumor types is possible but requires institutional support, collaboration between clinical & informatics teams, and a dedicated QA team. Research Sponsor: Memorial Sloan Kettering Cancer Center.

Tumor Type (15,579)	REDCap based rule (N)	Complex Queries (N)	Average time to complete a case (minutes)	Average number of forms per record
Lung (6,308)	224	66	196	50
Sarcoma (2,862)	228	50	269	56
Prostate (2,252)	134	50	346	72
Bladder (1,427)	198	54	235	60
Kidney (1,197)	227	61	193	58
Uterine (1,533)	224	48	123	42

6515

Poster Discussion Session

End-of-life spending analysis of randomized trial of machine learning nudges to prompt serious illness communication among patients with cancer. *First Author: Ravi Bharat Parikh, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA*

Background: Early serious illness conversations (SICs) between oncology clinicians and patients in the outpatient setting may improve mood and quality-of-life among patients with cancer. However, the impact of early SIC "nudges" on end-of-life spending is unknown. **Methods:** This was a secondary analysis of a stepped-wedge randomized trial (NCT03984773) that randomized 9 medical oncology practices and their high-risk patients at a large academic institution to a behavioral intervention to increase SICs (performance reports and peer comparisons; precommitments for high-risk patients; weekly opt-out text prompts before high-risk encounters) vs. standard of care, between June 2019 and April 2020. We identified high-risk patients using a machine learning (ML) algorithm predicting 180-day mortality. This secondary analysis included 1187 (957 intervention, 230 control) patients with complete data who died by December 2020. We abstracted spending (defined as inflation-adjusted reimbursements for acute care [inpatient + ED], office/outpatient care, intravenous chemotherapy, other therapy [e.g. radiation], long-term care, and hospice) from the institution's accounting system; we captured spending at University of Pennsylvania inpatient, outpatient, and pharmacy settings. To evaluate intervention impacts on spending, we used a two-part model: first, logistic regression to model zero versus nonzero spending, and second, generalized linear models with gamma distribution and log-link function to model daily mean spending in the last 180 days of life. Models were adjusted for clinic and wedge fixed effects and clustered at the oncologist level. **Results:** Median age at death was 68 years (IQR 15.5), 317 (27%) patients were non-White, and 448 (38%) patients had a SIC prior to death. The intervention was associated with lower mean spending in the last 180 days of life (mean daily spending \$377.96 [intervention] vs. \$449.92 [control]; adjusted mean difference -\$75.33, 95% CI -\$136.42, -\$14.23, $p = 0.016$) (Table), translating to \$13,559 total adjusted savings. Intervention patients incurred lower mean daily spending for chemotherapy (adjusted difference -\$51.35, $p < 0.001$), office/outpatient care (-\$14.59, $p < 0.001$), and other therapy (-\$10.35, $p = 0.043$). The intervention was not associated with differences in end-of-life spending for acute care utilization, long-term care, and hospice. Results were consistent for spending in the last 30 and 90 days of life and after adjusting for age, race, and ethnicity. **Conclusions:** A ML intervention to prompt SICs led to end-of-life savings, driven by decreased chemotherapy and outpatient spending. Clinical trial information: NCT03984773. Research Sponsor: U.S. National Institutes of Health.

Unadjusted spending in last 180 days of life.

	Intervention	Control
Total Spending	\$69,977	\$82,110
Mean Daily Spending	\$378	\$450
Acute Care	\$202	\$200
Outpatient	\$24	\$39
Chemotherapy	\$113	\$164
Other Therapy	\$29	\$40

6516

Poster Discussion Session

Biosimilar uptake and cost savings analysis before and after implementation of a pharmacist-driven substitution program within a National Community Oncology Network: One-year follow-up. *First Author: Melody Chang, American Oncology Network, Fort Myers, FL*

Background: As of December 2022, 22 of the 40 biosimilar approvals in the United States, are used for the treatment of cancer or for the supportive care of patients with cancer. Our organization is a network of community oncology practices, representing 107 oncologists at 76 locations across 17 states. Because our network faces formulary selection and reimbursement challenges related to a diverse payor mix across multiple states, we sought to see the impact of utilizing regional clinical pharmacists (RCPs) to assist with selection of the most cost-effective biosimilar products. **Methods:** In October 2021, our network initiated an RCP-driven biosimilar substitution program, whereby the RCP acts as a liaison between providers and financial teams to evaluate existing drug orders and their financial impact. We previously presented data on the financial impact to payors and providers before and after implementation of the program from 4/1/2021 to 4/1/2022. This study evaluates the one-year results following program implementation. Additionally, outcomes related to biosimilar utilization as well as financial impacts to payors, patients, and providers were assessed. Payor savings is defined as the difference of the calculated 80% Medicare ASP+6 for the administered biosimilar compared to the originator; patient savings is defined as the difference of the calculated 20% Medicare ASP+6 co-insurance for the administered biosimilar compared to the originator; provider savings is defined as the difference between the invoiced cost of the biosimilar compared to the originator. **Results:** By the end of 2022, preferred product utilization was achieved for >90% of bevacizumab, trastuzumab, and rituximab orders. Use of the preferred pegfilgrastim product increased from <20% in 4/2021 to >60% by 12/2022. Use of filgrastim biosimilar product increased from <75% in 4/2021 to >90% by 4/2022, then decreased to 55% by 12/2022 due to trending ASP. Payor preference prevented biosimilar switching in approximately 34% of cases. **Conclusions:** Use of institution-preferred biosimilar products increased across all agents in this study after implementation of the RCP-driven biosimilar substitution program, except for filgrastim. Significant cost savings were noted for payors, patients, and providers. Barriers to switching to institution-preferred products included non-medical switching requirements by payors, patient assistance and compassionate use programs, and patient and/or provider preferences. Research Sponsor: Part of this research was made possible through a competitive independent medical education grant supported by Pfizer, Inc. All data, analysis, and content are independent of industry influence.

Time Period	Payor Savings	Patient Savings	Provider Savings	Total Savings
4/1/2021-9/30/2021	\$8.0 million	\$2.0 million	\$11.3 million	\$21.3 million
10/1/2021-4/1/2022	\$10.8 million	\$2.7 million	\$10.6 million	\$24.1 million
1/1/2022-12/31/2022	\$26.4 million	\$6.6 million	\$23.5 million	\$56.5 million

6518

Poster Discussion Session

A multi-level system quality improvement project to reduce disparities in lung cancer screening: The Sylvester Lung Screening Project. *First Author: Nicole Ann Gay, UM/Sylvester Comprehensive Cancer Center, Miami*

Background: Racial disparities in lung cancer mortality and screening have been well documented in the USA. Annual screening with low dose Computed Tomography (CT) scans is completed in fewer than 6% of the eligible population. Research suggests that many factors contribute to low screening uptake, including barriers to care at patient, clinician, healthcare system, and community levels. In collaboration with the American Cancer Society, the University of Miami/ Sylvester Cancer Center underwent a multi-level system quality improvement (QI) project with the goal to decrease lung cancer screening disparities and improve guideline concordant lung cancer screening across the health care system. **Methods:** During the one-year multi-level QI project, interventions were put into place to increase lung cancer screening exams via improvements in EMR- identification of eligible patients, patient navigation and expanded provider education services in primary care clinics. Patient level interventions included a marketing campaign, patient navigation, and interpreters to address language barriers. The Patient-interface of the EMR 'Health Maintenance Gap' was optimized to alert eligible patients about screening. In addition, a full-time lung cancer screening navigator provided culturally competent, patient-centered counseling, while allowing for an increased capability to manage a higher volume of patients. Provider level interventions included teaching sessions about lung cancer screening and motivational communication skills, and BPA alerts. The primary outcome was the change in the number of screened patients. **Results:** With the implementation of these multi-level interventions, there was a twenty five percent improvement in the number of lung cancer screening exams completed during the project period January 2022- December 2022 compared to 2021 baseline, from 20 to 25%. The screening rate was highest among Hispanics (12%), followed by Blacks (8%), and Non- Hispanic Whites (NHW) (6%). The majority of LDCT results were Lung RADS Category 1 or 2 (93%). **Conclusions:** Multi-level interventions that target patients, clinicians, and the health care system can improve lung cancer screening rates in a short-term period. Developing patient-centered, culturally competent interventions is key to reducing disparities in lung cancer screening. This QI intervention was strengthened by tailoring intervention components to the educational primary care physicians and simplifying the referral process. Research Sponsor: American Cancer Society.

	Pre-Intervention (2021)	Post-Intervention (2022)
Eligible Screened (%)	996 202 (20.3%)	1323 334 (25.2%)
Race/Ethnicity		
NHW	32/345 (9.3%)	32/492 (6.5%)
Hispanics	72/474 (15.2%)	66/547(12.1%)
Black	14/101 (13.9 %)	11/137 (8%)
Asian	1/20 (5%)	1/20 (5%)
Missing Ethnicity Data	5.6%	16.9%
LUNG-RADS		
0	0	0
1	10	19
2	175	292
3	14	16
4	3	7

6517

Poster Discussion Session

The impact of adverse financial events on healthcare utilization and treatment costs at the end of life. *First Author: Chipo Natasha Kwendakwema, Fred Hutchinson Cancer Center, Seattle, WA*

Background: Patients with cancer are at higher risk of bankruptcy and other adverse financial events (AFE) compared to similar individuals without cancer. However, little is known about how AFEs affect cancer care, particularly at the end of life (EOL). We investigated the association between AFEs, healthcare utilization, and healthcare costs at the EOL among patients with cancer. **Methods:** Western Washington Surveillance Epidemiology and End Results (SEER) cancer registry cases were linked to credit records from TransUnion and to claims from commercial payers and Medicare. Patients with AJCC Stage I-IV solid tumors who died between January 2013 and December 2019 and who had continuous enrollment in commercial or Medicare insurance for the 6 months prior to death were included. Emergency department (ED) and inpatient (IP) visits in the last 3 months of life, place of death, and mean healthcare costs per patient (paid by insurer) were compared between patients with versus without AFEs (charge-offs, third-party collections, tax liens, delinquent mortgage payments, foreclosures, or repossessions). A multivariate logistic regression analysis was used to evaluate the association between AFEs, ED or IP visits (>1 of either), and inpatient death, adjusting for sociodemographic factors, comorbidities, payer type, and cancer stage. Two-sample t tests were used to compare mean per-patient costs in the last 6 and 3 months of life among patients with versus without an AFE. **Results:** A total of 13,545 patients (median age 75, 54% male) were included, of which 15.6% experienced an AFE. Patients with AFEs were more likely to have multiple ED or IP visits (OR 1.19, CI 1.07-1.34) and die in a hospital (OR 1.37, CI 1.22-1.55) (Table). Younger age, higher Carlson Comorbidity Index (CCI), and being partnered were also associated with greater EOL healthcare utilization while race, sex, payer type, and cancer stage were not. Mean total healthcare costs were higher in patients with AFEs than those without in the last 6 months (\$66,232, vs. \$55,831, p<0.0001) and 3 months (\$39,664 vs. \$33,638, p<0.0001) of life. **Conclusions:** We demonstrated an independent association between AFEs as measured in credit records, increased EOL healthcare utilization, and greater per-patient costs in the months before death. These findings suggest that addressing patient financial hardship could improve their EOL experience and decrease healthcare costs. Research Sponsor: Kathryn Butler Foundation, Texas4000 Foundation.

Predictors of EOL healthcare utilization.		
Predictors*	Multiple ED or IP visits	Inpatient death
AFE	1.19 (1.07-1.34), p<0.002	1.37 (1.22-1.55), p<0.0001
Age < 65	1.22 (1.06-1.40), p<0.005	1.19 (1.02-1.37), p<0.023
CCI > 1	1.27 (1.15-1.39), p<0.0001	1.31 (1.20-1.46), p<0.0001
Partnered	1.16 (1.06-1.26), p<0.001	1.17 (1.06-1.29), p<0.001

*Reference: no AFE, age 65+, CCI 0, no partner. Other predictors (not significant): race, payer type, cancer stage, and area deprivation index.

6519

Poster Discussion Session

Guideline-concordant use of olanzapine as part of a 4-drug antiemetic regimen for high emetic risk chemotherapy across the state of Michigan. *First Author: Ashley Bowen, Michigan Oncology Quality Consortium, Ann Arbor, MI*

Background: Chemotherapy-induced nausea and vomiting (CINV) is a feared side effect of cancer treatment. If not adequately controlled, CINV can negatively affect both quality of life and increase the costs of care. Clinical practice guidelines from both ASCO and NCCN recommend inclusion of olanzapine as part of a 4-drug antiemetic regimen in patients receiving high emetic risk chemotherapy (HEC). Uptake of olanzapine has been low, however, in part due to oncologists' lack of familiarity with the medication, lack of awareness or agreement with the guidelines, and lack of olanzapine inclusion on prepopulated order sets. Current labeling of olanzapine as an antipsychotic poses an additional barrier. The purpose of this project was to increase guideline-concordant prescribing of olanzapine as part of a 4-drug antiemetic regimen in patients receiving HEC in practices that are part of the Michigan Oncology Quality Consortium (MOQC), a physician-led consortium of nearly 90% of oncologists in Michigan. **Methods:** In 2019, MOQC began measuring guideline-concordant HEC prophylaxis with a 4-drug regimen of olanzapine added to corticosteroids, a 5HT3RA, and an NK1RA as part of its measure set. A quality improvement intervention was initiated that consisted of 1) dissemination of baseline measure performance and regular reporting of practice and state-level performance to MOQC practices, 2) information support through sharing of guidelines at biannual meetings (2019, 2022) and state-wide CINV education to improve prescriber knowledge and beliefs and support the practices in updating prepopulated antiemetic order sets, and 3) addition of value-based reimbursement in 2021 to encourage practice change. Measure performance was assessed using ASCO's Quality Oncology Practice Initiative (QOPI) program. **Results:** The patient sample included 5,703 patients. MOQC practices increased the guideline-concordant prescribing of olanzapine as part of a 4-drug antiemetic regimen in patients receiving HEC round over round from R1 2019 to R1 2022 (p<0.0001). **Conclusions:** MOQC has facilitated increased use of olanzapine as part of a 4-drug antiemetic regimen in patients receiving HEC through practice education, reporting, and value-based reimbursement. Ongoing work will focus on practices with low uptake and on demonstrating the impact of this important practice change on patient outcomes. Research Sponsor: None.

The percentage of patients receiving olanzapine as part of a 4-drug antiemetic regimen for HEC over time.

Round	min (%)	Q1 (%)	median (%)	Q3(%)	max (%)	overall (%)	p-value
R1 2019	0	0	0	0	22	7	3.12E-05 0.009
R2 2019	0	0	0	10	43	13	
R1 2020	0	0	0	9	75	17	
R2 2020	Data not available						
R1 2021	0	0	0	9	91	21	0.006
R2 2021	0	0	6	42	100	27	0.001
R1 2022	0	0	11	40	100	29	0.142

*Data is collected twice per year as designated by Round 1 (R1) and Round 2 (R2) in the table. P values show significance round-over-round.

6520

Poster Discussion Session

Impact of a web-based decision aid on socioeconomically disadvantaged patients' engagement in decision making (Alliance A231701CD). *First Author: Jessica R. Schumacher, Department of Surgery, University of Wisconsin, Madison, WI*

Background: Increased patient engagement in decision making may mitigate disparities in breast cancer surgical care. Socioeconomically disadvantaged patients disproportionately experience barriers to engagement. Decision aids (DA) increase engagement by providing information, establishing role expectations during the consult, and increasing confidence in surgeon interactions. The objective was to test the effectiveness of a surgical web-based DA in increasing engagement among breast cancer patients in clinics that care for a high proportion of socioeconomically disadvantaged patients. **Methods:** A stepped wedge trial was conducted with 10 NCI Community Oncology Research Program clinics (Alliance for Clinical Trials in Oncology Research Base, 6/19-12/21). Clinics were randomized to time of transition from usual care (UC) to delivery of a web-based DA. Patients with stage 0-3 breast cancer eligible for surgery provided consent prior to a surgical consult. Socio-economic disadvantage was assessed with the Area Deprivation Index measured at the zip+4 level and dichotomized. Patient engagement was measured by Patient's Self-Efficacy in Patient-Physician Interactions (PEPPI-5, follow-up survey) and count of Active Patient Behaviors (Street protocol, audio recorded consult). Intervention effects were tested with linear mixed-effects models, accounting for surgeon and clinic-level clustering, time, and enrollment post-COVID. Heterogeneity of treatment effect by socioeconomic disadvantage was assessed with an interaction term. **Results:** 573 patients enrolled. 44% (136/309) reviewed the DA. No significant difference in engagement was observed comparing DA and UC for PEPPI-5 (-0.80 [95% CI -2.13, 0.54], $p = 0.24$) or Active Patient Behaviors (2.52 [CI -4.11, 9.15], $p = 0.46$). Enrollment post-COVID was associated with increased Active Patient Behaviors (9.59 [CI 1.76, 17.43], $p = 0.02$) but no change in PEPPI-5 (-1.31 [CI -2.88, 0.26], $p = 0.10$). No heterogeneity of treatment effect was observed. **Conclusions:** In this trial conducted in clinics that serve diverse populations, no significant relationship was observed between a web-based DA and patient engagement. Conducting this stepped wedge trial during the pandemic was challenging. Future analyses will explore the impact of COVID on outcomes and effect of the decision aid for patients who reviewed it. UG1 CA189823; AHRQ R01HS025194; <https://acknowledgments.alliancefound.org>. Clinical trial information: NCT03766009. Research Sponsor: Agency for Healthcare Research and Quality; U.S. National Institutes of Health.

	Usual Care (n = 264)	Decision Aid (n = 309)
Age (years, median, range)	59 (30-87)	61 (27-90)
Race		
White	169 (64%)	207 (67%)
Black	60 (23%)	62 (20%)
Other	35 (13%)	40 (13%)
Socioeconomic Disadvantage	73 (28%)	59 (19%)
Enrollment Post-COVID	98 (37%)	281 (91%)
PEPPI-5 (n, median, range)*	239, 22.0 (7-25)	268, 22.0 (5-25)
Active Patient Behaviors (n, median, range)*	258, 17.5 (0-114)	301, 19.0 (0-112)

*Higher scores indicate higher engagement.

6522

Poster Session

The Man Van: Mobile targeted case finding for prostate cancer. *First Author: Masood Moghul, Royal Marsden Hospital NHS Trust, London, United Kingdom*

Background: Early intervention is potentially lifesaving in prostate cancer. The debate for screening continues with recent developments suggesting the arguments in favour are becoming stronger however, barriers to access remain. The Man Van project is designed to address these with a highly novel community-based targeting of high-risk groups on a mobile unit. **Methods:** A bespoke mobile health vehicle was moved to 8 community-based locations in areas of high deprivation indices in London, UK, inviting men for a health check consisting of: general health questionnaires, blood pressure, height/weight, HbA1c for diabetes and a PSA test. Telemedicine was used to inform patients of outcomes. Direct referrals to secondary care was performed. Community engagement was utilised to increase uptake using: primary healthcare centres, religious organisations and community centres. **Results:** Between December 2021 and December 2022, 618 men were seen at our Man Van clinics at a range of community settings (non-attendance rate 24%). The highest uptake was in locations where there was collaboration with primary care to recruit patients. The median age of attendees was 56 years, range 25-87. 43% of attendees were non-white (20% black). The median BMI was 27.7, range 16.2-50.5. 422 PSA tests were performed with 14 prostate cancers (3.3%) found till date. 9 (64%) of these cancers were grade group 2 (all > 5% pattern 4) or 3. Of patients diagnosed with prostate cancer the median age was 59 years, range 48-73, 10 were black (71%), median PSA 6.85 g/L, range 0.81-45, median IPSS score was 9.5, range 2-31, median IIEF-5 was 16, range 1-25. The IPSS score was significantly higher ($P < 0.05$) in men diagnosed with prostate cancer. 1 bladder (G3pT1) and 1 oesophageal cancer (T3N2M1) were also found. 3 patients had either HGPIN or ASAP, 3 patients had renal stones, 2 urethral strictures were found. 334 HbA1c tests were performed with 18 diabetics diagnosed (5.4%). 46 patients (7.4%) required input for benign urinary symptoms and 20 for erectile dysfunction (3.2%). Primary care referrals were as follows: 171 for hypertension (27.6%), 43 for an elevated BMI (7.0%), 37 for mental health issues (6.0%), 43 for excess alcohol intake (7.0%), 51 for smoking cessation assistance (8.3%). Significantly more patients 45 years were referred for primary care follow-up versus < 45 years ($P < 0.01$). Service evaluation questionnaires showed overwhelmingly positive support for the service. **Conclusions:** The Man Van initiative is a novel method of linking primary and secondary care for a range of health checks, including PSA. By improving community awareness and access in high-risk groups we demonstrate high uptakes for health checks including for prostate cancer and a willingness to engage with health improvement measures. As well as comparatively high levels of prostate cancers diagnosed at early stages, high levels of other health conditions were found; improving the economic value of the service. Research Sponsor: NHS England.

6521

Poster Session

Curating clinical trials: Helping patients find hope by exploring clinical trial opportunities. *First Author: Rhonda Abdel-Nabi, University of Windsor, Windsor, ON, Canada*

Background: Clinical trials are essential to the advancement of clinical therapies. However, only 5% of cancer patients enroll in clinical trials (CTs) due to limited accessibility. Given that greater participation in CTs is associated with better patient outcomes, patients from smaller centres are at a disadvantage. The Clinical Trials Navigators (CTN) program was established by Hamm (2022) to help patients in smaller communities navigate and enrol in CTs, resulting in clinical trial enrolment of 7% of patients. This study will provide updated results on the impact of the CTN program as it has expanded. **Methods:** Between March 2019 to September 2022, 241 patients were enrolled in the CTN program. Five Clinical Trials Navigators (CTNs) receive referrals from various sources: physicians, patients, and patient support groups. CTNs review medical information submitted and search five CT registries. Eligibility criteria is scrutinized. A second review of the CT list is conducted by two physicians to ensure accuracy. The number of potential trials is recorded at each step of review. Data collected includes: patient disease, stage, and number of prior therapies, time from referral to death, number of potential trials, number of trials that were phase I or phase II / III / IV, number of outgoing referrals, locations of the identified trials, and successful enrolment onto CTs. Patient information and results were inputted and analysed using REDCap. REB Category A approval has been granted on August 31, 2022. REB approval number is 22-439. **Results:** 41 Canadian cancer patients used the CTN program. The updated study found that 75.9% of patients were in stage IV of their disease, and 51% had at least two prior lines of therapy. 61.4% of patients deceased at last follow up, with a range of 0.3-37.5 months from CTN program referral to death, and a median of 5.9 months. CTNs identified a range of zero to 26 trials for each patient with a median of three trials: a range of zero to 10 phase I trials were found, and a range of one to eight phase II / III / IV trials were found. 25.5% of patients referred to a CT enrolled onto the recommended trial. The expanded CTN program resulted in CT enrolment of 8.5% of patients that follow-up information is available for. **Conclusions:** One quarter of patients referred to a CT by the CTN program were successfully enrolled, highlighting the CTN program as a successful tool to identify CTs for cancer patients and improve CT accrual. 8.5% of all patients with available follow-up information that participated in the CTN program were enrolled onto clinical trials. Further investigation into reasoning for early high mortality rates should be assessed. New initiatives to improve uptake of the CTN program are ongoing. Research Sponsor: Canadian Cancer Clinical Trials Network; Cancer Research Collaboration Fund.

6523

Poster Session

Association of social vulnerability with delays in starting guideline-adherent adjuvant therapy among patients with head and neck cancer. *First Author: Joshua Lee Cagle, Medical University of South Carolina, Charleston, SC*

Background: For patients with head and neck squamous cell carcinoma (HNSCC), initiation of postoperative radiation therapy (PORT) within 6 weeks of surgery is recommended by NCCN Guidelines and is the only Commission on Cancer Quality Metric for HNSCC due to the robust association of PORT delays with mortality and recurrence. Prior studies have identified that racial and ethnic minority and under-insured patients are at increased risk for PORT delay. However, no studies have examined the role of social vulnerability (i.e., social determinants of health such as education, housing, and transportation) in explaining disparities in PORT delay. To address this gap, this study seeks to evaluate the association of social vulnerability with delays in starting guideline-adherent PORT for patients with HNSCC. **Methods:** This is a multicenter retrospective cohort study of adult patients with HNSCC undergoing surgery at 3 urban academic centers followed by adjuvant therapy from 2018-2020. The primary outcome was delay in initiating guideline-adherent PORT (i.e., > 6 weeks [42 days] postoperatively). Time-to-PORT (TTP) was analyzed as a secondary outcome. Census-tract level Social Vulnerability Index (SVI) scores were calculated as a national percentile rank (0 to 1) with higher scores indicating greater social vulnerability. Multivariable logistic regression (MLR) was used to evaluate the association of SVI with PORT delay. Kaplan-Meier curves and a log-rank test were used to evaluate differences in TTP between patients in the highest social vulnerability quartile (SVI > 0.75) vs those in the lowest social vulnerability quartile (SVI ≤ 0.25). **Results:** The study included 505 patients undergoing surgery and adjuvant therapy. The mean age was 62.1 ± 11.9 years; 71% were male, 14% were Black and the most common tumor subsite was oral cavity (61%). The rate of PORT delay was 52% (95% CI 48-57%). Median TTP was 43 days (IQR 35-55 days). The mean overall SVI score was 0.48 ± 0.27. An increase in SVI of 0.25 was associated with a 33% increase in the odds of PORT delay (OR=1.33, 95% CI=1.08 to 1.63; $p=0.0067$) on MLR adjusted for facility, age, race, ethnicity, health insurance status, cancer subsite, rurality, and distance to the surgical facility. Patients in the highest SVI quartile had a significant increase in TTP relative to those in the lowest SVI quartile (log-rank $p=0.012$; median TTP = 47 and 42 days, respectively). **Conclusions:** In this multi-institution study, over half of patients with HNSCC experience delays in starting PORT. Increased census-tract level social vulnerability is associated with a greater risk of delayed initiation of guideline-adherent PORT. These data can be used to: 1) enhance existing risk prediction models and identify patients at-risk for PORT delay who might benefit from a targeted intervention and 2) improve institutional level risk-adjustment for case mix. Research Sponsor: U.S. National Institutes of Health; Triological Society/American College of Surgeons; Hollings Cancer Center.

6524

Poster Session

Analysis and optimization of equitable US cancer clinical trial center access by travel time. *First Author: Hassal Lee, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY*

Background: Racially minoritized and socioeconomically disadvantaged populations are underrepresented in cancer clinical trials. Data-driven, quantitative approaches are required to address this inequity. Here, we systematically analyze the geographical distribution of self-identified racial and socioeconomic demographics within commuting distance to cancer clinical trial centers and all hospitals U.S.-wide. **Methods:** We calculate self-identified racial and socioeconomic demographics of populations living within 30-, 60-, and 120-minute one-way driving commute times from U.S. cancer clinical trial centers and all U.S. hospitals. Data sources include the U.S. 2020 census (for race and socioeconomic data), OpenStreetMaps (for calculation of commuting times), NCT trial registry (for cancer clinical trial quantification), NCI Designated Cancer Centers List, Nature Index of Cancer Research Health Institutions and National Homeland Infrastructure Foundation-Level Data (for U.S.-wide hospital and cancer clinical trial center identification). Data analysis was conducted in R, and *Ggplot2* used for all data visualizations. **Results:** Analysis of clinical trial numbers between 2012–2022 identified 78 high-volume U.S. cancer trial centers. Compared to U.S. national averages, these centers are in areas with socioeconomically more affluent populations (+27.6K USD [95% CI +23.1 to 32.8K] median income unpaired mean difference; -0.073 [95% CI -0.063 to -0.084] deprivation index unpaired mean difference), with higher proportions of affluent self-identified White individuals (+10.1% unpaired mean difference [95% CI +6.8 to +13.7%]). The top 10th percentile of all U.S. hospitals (N=7,623) show a range of absolute sum difference from 2.4% to 35% from equal racial representation of White, Black/African American and Asian/Mixed/Other groups. For each U.S. city above 500,000 inhabitants, we compile map overlays that display all prospective hospitals within commutable distance to racially diverse and socioeconomically disadvantaged populations. These maps may inform the design of future clinical trials or investigations in enrollment and retention strategies for clinical trials. **Conclusions:** Our analysis identifies biases in the socio-demographics of populations living within commuting distance to U.S.-based cancer trial sites and enables the determination of more equitably commutable prospective satellite hospital sites that could be mobilized for enhanced racial and socioeconomic representation in clinical trials. Other recruitment barriers still need to be tackled to ensure racial and socioeconomic demographics within the geographical vicinity of a clinical site can translate to equitable trial participant representation. Research Sponsor: Cold Spring Harbor Laboratory.

6526

Poster Session

Evaluating social vulnerability impact on care and prognosis of head & neck-nervous system cancers in the US. *First Author: Salim Lutfallah, Louisiana State University Health and Sciences - School of Medicine, New Orleans, LA*

Background: In the current literature, the association between social determinants of health (SDH) and head & neck-nervous system cancer (HNNsC) is limited by the narrow scope of SDH assessed and the broad classifications of HNNsC. Our study utilizes the CDC-Social Vulnerability Index (SVI) to assess both the individual and collective impact of four social determinant themes on various HNNsC in US adults. **Methods:** This study utilized the SEER database to evaluate 116,373 adult patients from 1975-2017 who presented with HNNsC. Patients were assigned SVI scores based on county-of-residence at the time of diagnosis, encompassing total-SVI score and 4 sub-scores of socioeconomic status, minority-language status, household composition, and housing-transportation. Using these scores, univariate linear regressions were used to assess patient care (months of follow-up) and prognosis (months of survival). **Results:** As total-SVI score increased, decreases in months of follow-up (MOF) and months of survival (MOS) were observed for many HNNsC tumors (p less than 0.001) when comparing the lowest to highest vulnerability cohorts. There was a decrease ranging from 3.55-36.6% in the MOF, with the largest decreases occurring in embryonal, anaplastic oligodendroglioma, and anaplastic ependymoma tumor types, with the largest sub-score contribution coming from socioeconomic status for these three disease classes. Similarly, there was a decrease ranging from 6.90-45.81% in the MOS, with the largest decreases occurring in anaplastic ependymoma, anaplastic astrocytoma, and pilocytic astrocytoma tumor types with the largest sub-score contribution coming from socioeconomic status for these three disease classes. Increases in vulnerability within SDH themes contributed significantly to these total-SVI trends in MOF and MOS, with each social determinant impacting different disease classes to varying extents. Socioeconomic status was the most impactful sub-score for MOF in nine of fourteen disease classes, followed by housing-transportation and household composition, each leading the impact of two of fourteen disease classes, and minority-language status leading the impact of one of fourteen disease classes. Similarly, socioeconomic status was the most impactful sub-score for MOS in eight of fourteen disease classes, followed by housing-transportation leading the impact of three of fourteen disease classes, household composition leading the impact of two of fourteen disease classes, and minority-language status leading the impact of one of fourteen disease classes. **Conclusions:** The results of this study show that with increasing social vulnerability, there is a significant decrease in both the care (follow-up) and the prognosis (survival) of US adults with HNNsC and highlight which SDH contributes more to disparities. Research Sponsor: None.

6525

Poster Session

Are enrollment criteria for phase II and III clinical trials in acute myeloid leukemia arbitrarily restrictive? *First Author: Andrew Hantel, Division of Population Sciences, Dana-Farber Cancer Institute, Boston, MA*

Background: Ethical clinical research requires fair subject selection and a favorable risk-benefit ratio. Enrollment criteria can unfairly exclude patients if they are not based in safety. There are few data regarding variability within criteria, which can also represent unfair exclusion, or for acute myeloid leukemia (AML). **Methods:** We assessed enrollment criteria use and variability for frontline phase II and III therapeutic AML trials from 2010-2019 listed on Clinicaltrials.gov. Drug safety profiles were obtained from protocols, publications, and FDA labels. FDA publications guided a standardized abstraction and coding process. Associations between criteria and safety profiles were identified using χ^2 and t-tests. Regression modeling identified differences in infectious disease (ID) exclusion by sponsor adjusted for trial phase, year, size, and safety profiles. **Results:** 190 trials were eligible; 159 (84%) were phase II and 32 (17%) phase III. Trials were sponsored by the National Institutes of Health (NIH; 50; 26%), industry (109; 57%), and academic investigators (AI; 108; 57%). Exclusions and variability are shown in the table. ID exclusions were for HIV (96; 51%) and hepatitis B (60; 32%) and C (64; 34%). Older adults were considered as over 60 (42 trials; 39%), 65 (23; 21%), 70 (13; 12%), or 75 years (18; 17%). There was no association between QTc limits and the use of QTc prolonging drugs (criteria presence p=0.2; mean 450 vs 474 ms, p=0.3) or renal function limits and nephrotoxic drugs (presence p=0.2; mean 1.65 vs 1.67 ULN, p=0.8). Hepatitis B and C exclusions were associated with the use of drugs linked to viral reactivation (OR 2.1 [95% CI 1.1,3.9], 2.0 [95% CI 1.1,3.7]). This was not the case for HIV (OR 1.2 [95% CI 0.7,2.2]). Industry sponsorship was independently associated with hepatitis B and C exclusion (OR 3.0 [95% CI 1.2,7.3], 3.3 [95% CI 1.4,4.7]) and AI sponsorship with HIV exclusion (OR 2.5 [95% CI 1.4,5.5]). **Conclusions:** There is substantial variability in enrollment criteria for AML clinical trials. Many criteria are related to risks, but some exclusions and variability are not clearly based in safety. Avoiding arbitrary exclusions will likely enhance trial representativeness and enrollment rates. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology; U.S. National Institutes of Health.

Criterion	Limit	Trials with Criterion (%)	Median	Interquartile Range	Coefficient of Variation*	Range
ECOG Performance Status	Upper**	162 (85%)	2	1-3	26%	1-3
WBC Count	Upper	31 (16%)	25 10 ⁹ /L	25-50	57%	10-100
Renal Function	Upper	128 (67%)	1.5 ULN	1.3-2.0	27%	0.8-2.5
AST/ALT	Upper	118 (62%)	2.5 ULN	2.5-3.0	24%	1.5-5
Bilirubin	Upper	130 (68%)	1.6 ULN	1.5-2.0	32%	1.0-5.0
QTc	Upper	48 (25%)	470 ms	450-480	4%	450-500
Left Ventricular Ejection Fraction	Lower**	70 (37%)	45%	45-50	9%	35-50
Prior Anti-cancer Therapy Washout Period	Lower	95 (50%)	14 days	14-28	47%	1-90
Prior Malignancy Washout Period	Lower	68 (36%)	24 months	12-36	63%	6-60

*Standard Deviation/Mean. **Among studies of fit patients.

6527

Poster Session

Association of measures of socioeconomic deprivation with healthcare utilization in elderly patients enrolled in SWOG cancer clinical trials. *First Author: Dawn L. Hershman, Columbia University Medical Center, New York, NY*

Background: Reducing unplanned Emergency Room (ER) visits and hospitalizations is an important strategy for improving value. Patients enrolled in clinical trials are treated per protocol. While demographic factors have been associated with increased healthcare utilization, less is known about measures of socioeconomic deprivation (SD), which may be a proxy for structural barriers to access. We tested whether ER and hospital stays are more common among trial participants who live in areas of SD or have Medicaid insurance (MI). **Methods:** We examined ER visits and hospitalizations among cancer patients ≥ 65 years treated on SWOG clinical trials from 1999-2018 using trial data linked to Medicare claims. Neighborhood socioeconomic deprivation (NSD) was measured using patients' zip code linked to the Area Deprivation Index (ADI), measured on a 0-100 scale and categorized into tertiles (T1-T3). Higher ADI (T3) denotes areas of higher deprivation. Type of insurance was classified as Medicare alone or with Commercial, versus Medicare + MI. Outcomes were ER visits, hospital stays, and costs, all in the first year. Demographic, clinical, and prognostic factors were captured from trial records. Generalized estimating equations (GEE) were used, accounting for clustering by cancer type. Regression models were adjusted for age, race, and a study-specific prognostic risk score, and stratified by study and treatment. ADI and Insurance were considered separately to reflect neighborhood-level and individual-level measures of SD. **Results:** In total, N = 3,027 participants from 27 trials in bladder, breast, colorectal, lung, myeloma, and prostate cancers were analyzed. Median age was 71 years, 3% had Medicare + Medicaid and 22.3% were in the Highest ADI tertile. In all, 983 (32%) patients experienced hospitalization, and 1094 (36%) visited the ER. In multivariate GEE, patients living in more deprived areas were more likely to experience hospitalization (OR for ADI T3 compared to T1: 1.36, 95% CI, 0.95-1.94, p=.09) and to visit an ER (OR for ADI T3 compared to T1: 1.33, 95% CI, 1.08-1.63, p=.008). Overall, patients from the most deprived areas had a 61% increase in risk of either ER visit or hospitalization (OR for ADI T3 compared to T1: 1.61, 95% CI, 1.23-2.10, p<.001). Patients with MI were 86% more likely to visit an ER in the first year (OR 1.86, 95% CI, 1.49-2.33, p<.001). No increased risk of hospitalization was observed. **Conclusions:** Despite participation in cancer clinical trials, patients living in areas with higher deprivation or those with Medicare + MI had an increased risk of unplanned ER visits. These findings suggest that neighborhood deprivation and economic disadvantage may increase ER visits for socioeconomically vulnerable older patients with cancer. Efforts are needed to ensure adequate resources to prevent unplanned use of acute care in vulnerable populations. Research Sponsor: U.S. National Institutes of Health.

6528

Poster Session

Racial disparities in utilization of first line targeted therapies for metastatic breast cancer. *First Author: Yehoda M. Martei, University of Pennsylvania, Department of Medicine (Hematology - Oncology Division), Philadelphia, PA*

Background: This study evaluated whether there were racial disparities in utilization (decomposed as change in proportion of eligible patients initiating therapy over time and time to treatment initiation (TTI)) to CDK4/6 inhibitors and pertuzumab since FDA approval as first line (1L) treatment for ER+/HER2- and HER2+ metastatic breast cancer (MBC), respectively. **Methods:** This cohort study used the nationwide Flatiron Health electronic health record-derived de-identified database. Included women were ≥ 18 years old, diagnosed with de novo or recurrent MBC, who received 1L therapy, and documented as non-Hispanic White (NHW) or non-Hispanic Black/African American (NHB). Two cohorts were generated for patients with ER+/HER2- MBC diagnosed 3/2015-10/2021 and HER2+ MBC diagnosed 7/2012-9/2021. We estimated temporal trends in the proportion of NHW and NHB patients receiving respective therapy using logistic regression with natural cubic splines for time trends and tested for changes in uptake over time within each group as well as differences in trends between groups. A similar model was used for TTI among treatment initiators, using linear regression models. In addition to time and race, regression models included age, ECOG performance status, insurance, Medicaid expansion status, practice type, and proportion of black patients per practice among patients who met both cohort criteria. **Results:** 8318 patients (NHW=7006; NHB=1312) met ER+/HER2- cohort criteria and 2321 (NHW=1915; NHB=406) met HER2+ cohort criteria. There was a significant change over time in the proportion of NHW ($p<0.0001$) and NHB ($p<0.0001$) initiating 1L CDK4/6 inhibitors (Table). Temporal trends were also significantly different between NHW and NHB ($p<0.0001$). Higher ECOG performance status (OR=0.85 per unit increase, 95%CI 0.80-0.90; $p<0.001$) and an increasing proportion of black patients seen at practice (OR=0.45, 95%CI 0.29-0.71; $p<0.001$) were independent predictors of lower odds of initiating CDK4/6 inhibitors. Overall, 43% NHW vs 41% NHB received pertuzumab respectively. There was no significant difference in uptake trends for pertuzumab between NHW and NHB ($p=0.41$). There was no significant difference in the temporal trends of TTI for either CDK4/6 inhibitors ($p=0.74$) or pertuzumab ($p=0.84$). **Conclusions:** Utilization of CDK4/6 inhibitors steadily increased over time, however $> 25\%$ of eligible patients did not receive the drug, and less than half of individuals who met indication for pertuzumab were prescribed it. Racial disparities were significant for oral CDK4/6 inhibitors but not for intravenous pertuzumab. Research Sponsor: Flatiron Health, Inc.

Percentage initiating 1L CDK4/6 inhibitors.

Year	2015	2016	2017	2018	2019	2020
NHW	46	60	69	73	72	48
NHB	41	50	57	62	66	43

6529

Poster Session

Healthcare coverage, access, and affordability among adult immigrant cancer survivors in the United States. *First Author: Patricia Mae Garcia Santos, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Cancer is a leading cause of morbidity and mortality among US immigrants; however, barriers to care remain understudied. This study assessed disparities in health insurance, health care access, and affordability among immigrant cancer survivors in the United States. **Methods:** Adult cancer survivors aged ≥ 18 years who participated in the 2019-2022 National Health Interview Survey were classified as 1) natives 2) foreign-born (FB) citizens or 3) noncitizens. Logistic regression tested for associations between nativity/citizenship and insurance, access (i.e., urgent care, emergency room (ER), hospital admissions), and affordability (assessed by social determinants of health [SDoH]: financial hardship, food insecurity, housing assistance). Separate models adjusted for demographics, socioeconomic status, and comorbidities. **Results:** A total of 8,923 adults (90% natives, 7% FB citizens, 3% noncitizens) were included in the study. There were baseline differences in age < 65 (42% natives vs 61% FB citizens vs 76% noncitizens), female sex (57% vs 59% vs 73%), non-White race (15% vs 64% vs 77%), and Hispanic ethnicity (31% vs 62% vs 5%) between groups (all $p<0.05$). More noncitizens had household incomes $< 125\%$ of the federal poverty line (12% vs 18% vs 35%). On adjusted analysis, noncitizens were 3x as likely as natives to be uninsured (2.99 [1.36-6.53]; $p=0.006$) and FB citizens were 2x as likely to have Medicaid (2.10 [1.35-2.35]; $p=0.001$). Financial hardship was 1.5x more common among FB citizens (1.50 [1.18-1.91]; $p<0.001$) while receipt of housing assistance was $> 2x$ more common among FB citizens (2.98 [1.82-4.88]; $p<0.001$) and noncitizens (2.37 [1.08-5.22]; $p=0.03$). While more FB citizens (18%) and noncitizens (33%) were food insecure (vs. 11%), there were no associations with nativity/citizenship (Table). There were no significant differences in health care access across groups. **Conclusions:** In this nationwide analysis of adult cancer survivors, although there were no differences in health care access/utilization, immigrants and foreign-born citizens had higher rates of uninsurance and affordability concerns—suggestive of barriers to care. This may portend worse health outcomes in cancer survivorship. Research Sponsor: None.

		Natives N=8,235 Referent (%)	Foreign-Born Citizens N=559		Noncitizens N=129	
			%	aOR (95% CI)	%	aOR (95% CI)
Insurance	Private	55	44	0.86 (0.67-1.09)	35	0.49 (0.30-0.81)
	Medicaid	9	16	2.10 (1.35-2.35)*	31	1.87 (0.82-4.29)
	Uninsured	3	3	1.36 (0.67-2.77)	21	2.99 (1.36-6.53)*
Access (utilization) [†]	Urgent care	28	25	0.90 (0.68-1.20)	22	0.69 (0.39-1.20)
	ER	28	28	0.97 (0.73-1.27)	30	0.92 (0.56-1.51)
	Hospital	18	20	1.12 (0.83-1.51)	17	0.98 (0.52-1.84)
Affordability (SDoH)	Financial hardship	41	53	1.50 (1.18-1.91)*	64	1.31 (0.81-2.11)
	Food insecurity	11	18	1.30 (0.90-1.88)	33	1.41 (0.73-2.73)
	Housing assistance	3	9	2.98 (1.82-4.88)*	11	2.37 (1.08-5.22)*

* $p<0.05$; [†]within the last 12 months.

6530

Poster Session

Impact of free hospital-provided rideshare service on radiation therapy completion rates: A matched cohort analysis. *First Author: Eric Chen, University Hospitals Seidman Cancer Center, Department of Radiation Oncology, Cleveland, OH*

Background: Radiation therapy (RT) is generally given in consecutive daily sessions over multiple weeks. This poses challenges for patients who face barriers such as limited access to public or private transportation, limited financial resources, lack of social support, and long distances to healthcare facilities. Delayed or incomplete RT increases risk for worse clinical outcomes. The potential of rideshare service, which uses a private vehicle for hire arranged through a phone-based application or website, to facilitate timely RT is understudied. **Methods:** Retrospective data was collected on patients who received RT at a single institution from 2017-2022. Patient demographic and treatment characteristics were compared between those who did and did not utilize free hospital-provided rideshare service. RT completion rates were analyzed for a 1:1 matched non-rideshare cohort using optimal matching with the scaled Euclidean distance metric, to balance age, sex, race, performance status, number of fractions prescribed, Area Deprivation Index (ADI), distance to treatment center, year of diagnosis, treatment site, intent, and modality. ADI is a validated composite measure of community-level socioeconomic deprivation. **Results:** Of 2,906 patients who underwent RT, 58 utilized free hospital-provided rideshare service. Rideshare utilizers had a lower median age (60 vs 66, $p=.02$), and were more likely to identify as Black or African American (60 vs 22%, $p<.0001$) compared to non-rideshare utilizers. Rideshare utilizers also had higher ADI scores (median 9 vs 5, $p<.0001$), indicating higher socioeconomic disadvantage, and travelled shorter distances for treatment (median 5.0 vs 14.7 miles, $p<.0001$). More rideshare utilizers underwent RT for curative intent (79 vs 50%, $p<.0001$), concordant with a higher number of fractions prescribed (median 28 vs 5, $p<.0001$) as well as longer treatment course duration (median 39 vs 13 days, $p<.0001$). The most common treatment sites were head and neck (31%) and breast/chest wall (22%) for rideshare utilizers, and pelvis (27%) and brain (21%) for non-rideshare utilizers ($p<.0001$). Volumetric modulated arc therapy followed by 3D conformal were the most common treatment modalities in both groups. The matched cohort analysis revealed that RT completion rates were significantly higher for rideshare vs non-rideshare utilizers at 96 vs 81% ($p=.01$) overall, and 98 vs 78% ($p=.01$) for patients undergoing treatment with curative intent. **Conclusions:** Even after adjustment for socioeconomic, clinical, and treatment characteristics, utilization of free hospital-provided rideshare service was associated with improved RT completion rates. These findings are notable as the majority of rideshare utilizers come from socioeconomically marginalized communities, and would otherwise be expected to face significant barriers to RT completion. Research Sponsor: None.

6531

Poster Session

Associations of loneliness and mortality risk among cancer survivors in the United States. *First Author: Jingxuan Zhao, American Cancer Society, Atlanta, GA*

Background: Loneliness (i.e., the subjective feeling of being isolated from others), has been linked to multiple adverse health outcomes, including chronic conditions such as heart disease, mental health disorders, and higher risk for early mortality. However, associations between loneliness and worse health outcomes have not been thoroughly examined in cancer survivors. This study examined associations between loneliness and mortality risk among cancer survivors in the U.S. **Methods:** Cancer survivors were identified from the 2008-2018 Health and Retirement Study, a nationally representative longitudinal survey conducted biannually among individuals aged ≥ 50 years, with follow-up was through December 31, 2020. Loneliness was measured at every 4 years using an abbreviated 11-item version of the UCLA Loneliness Scale Version 3. Example items include feelings of lacking companionship and isolation from others. Items were summed to create total loneliness scores, which were categorized into four levels: 11-12 (low/no loneliness), 13-15 (mild loneliness), 16-19 (moderate loneliness), and 20-33 (high loneliness). Time-varying Cox proportional hazard models were used to examine the association of loneliness and mortality risk among cancer survivors, while accounting for measurements at multiple time points. Sex, marital status, educational attainment, number of health conditions other than cancer, and year since cancer diagnosis were included in multivariable models. **Results:** Among 5808 person-years, there were 724 deaths during the study period. Compared to the low/no loneliness group, survivors reporting greater loneliness had higher hazard ratios (HR), indicating higher mortality risks; the highest HR observed was among the high loneliness group (HR:1.90, 95%CI:1.58-2.29), following a dose-response association (Table). HRs were attenuated after adjusting for sociodemographic characteristics, but findings were largely unchanged, and HRs remained highest for the high loneliness group (HR:1.71, 95%CI:1.39-2.12). **Conclusions:** Any elevated loneliness was associated with higher mortality risks among cancer survivors. Programs to screen for loneliness among cancer survivors and to provide social support to those in need are warranted. Research Sponsor: None.

Association of loneliness and mortality risk among cancer survivors.

Loneliness Score	Unadjusted HR (95%CI)	Adjusted HR (95%CI)
11-12	1	1
13-15	1.28 (1.00-1.63)	1.21 (0.92-1.58)
16-19	1.62 (1.33-1.98)	1.47 (1.19-1.82)
20-33	1.90 (1.58-2.29)	1.71 (1.39-2.12)

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Poster Session

Outcomes of Black (B) versus White (W) patients (pts) with metastatic hormone-sensitive prostate cancer (mHSPC) treated with androgen deprivation therapy (ADT) with or without orteronel (Ort): Analysis of pt-level data from SWOG-1216 phase 3 trial. *First Author: Nicolas Sayegh, Huntsman Cancer Institute at the University of Utah, Salt Lake City, UT*

Background: Despite more aggressive prostate cancer (PCa) at presentation and higher mortality in real world, B pts with metastatic hormone resistant PCa did not have inferior outcomes than W pts when both were enrolled in clinical trials (PMID: 33951180). In the phase 3 S1216 trial, treatment with Ort, a novel CYP17 axis inhibitor, significantly improved progression-free survival (PFS) but not overall survival (OS) compared to bicalutamide (Bic) in pts with mHSPC receiving ADT. This trial enrolled the greatest number of B pts in a phase 3 trial in this setting to-date. We hypothesized that given comparable access to care as experienced in a clinical trial, outcomes in B pts would be similar to those of W pts in the mHSPC setting. **Methods:** Eligibility: Pts with mHSPC were enrolled. Only pts self-identifying as B or W were included in this analysis. PFS and OS for each group were estimated using Kaplan-Meier method. A multivariate analysis (MVA) adjusting for disease characteristics was conducted using a Cox proportional hazards model. **Results:** Among 1279 participants, 135 (10.6%) were B; 1077 (84.2%) were W. B and W were equally distributed between treatment arms, and had respectively similar proportion of pts with Gleason score ≥ 8 (61.3 vs 62.1%), Zubrod score ≥ 2 (5.1 vs 3.4%) and extensive disease (48.1 vs 48.7%). However, B pts, as compared to W, were younger (65.8 vs 68.4 yrs, $p=0.001$) and had a higher median baseline PSA (54.7 vs 26.7 ng/mL; $p<0.001$). PSA responses (≤ 0.2 ng/mL) at month 7 were similar in both groups ($p=0.296$). Overall, B vs W had similar median PFS (2.3 vs 2.9 yrs, $p=0.71$) and OS (5.5 vs 6.3 yrs, $p=0.65$). MVA confirmed similar PFS and OS after adjusting for known prognostic factors (Table). No interaction between race and treatment was observed (P-value interaction PFS= 0.77 and OS= 0.91). **Conclusions:** We demonstrate that even though B pts present with more aggressive disease in mHSPC setting, they did not have statistically significant worse OS and PFS than W pts and treatment effect was also similar for both racial groups. Equitable access to care may negate historical differences in outcomes among B vs W pts with advanced PCa. Funding: NIH/NCI/NCTN grant U10CA180888, U10CA180819; and Millennium Pharmaceuticals (Takeda Oncology). Univariate and MVA of PFS and OS. Research Sponsor: U.S. National Institutes of Health; Millennium Pharmaceuticals (Takeda Oncology).

Characteristic	PFS			OS		
	HR ¹	95% CI ¹	p-value	HR ¹	95% CI ¹	p-value
Race (Univariate; W vs B)	0.96	0.76-1.20	0.71	0.94	0.71-1.24	0.65
Race (W vs B)	1.12	0.88-1.42	0.4	1.01	0.75, 1.35	0.90
Treatment (Ort vs Bic)	0.58	0.50-0.68	<0.001	0.87	0.72, 1.04	0.14
Extensive disease (Yes vs No)	1.91	1.64-2.23	<0.001	2.06	1.69, 2.50	<0.001
Gleason (≥ 8 vs <8)	1.24	1.06-1.45	0.008	1.18	0.97, 1.43	0.10
Log PSA	1.21	1.16-1.26	<0.001	1.14	1.08, 1.20	<0.001

¹HR = Hazard Ratio, CI = Confidence Interval

6533

Poster Session

Selection biases in the systematic collection of breast biobank specimens. *First Author: Yael Bar, Massachusetts General Hospital, Boston, MA*

Background: A breast biopsy tissue biobank is a valuable resource for studying breast cancer biology and treatment response. However, underrepresentation of patient populations in biobanks limits the generalizability of findings. The aim of this study was to assess potential age and racial/ethnic disparities in the recruitment process for an institutional breast biopsy tissue bank. **Methods:** Ultrasound-guided (USG) research biopsy cores were collected immediately after routine clinical biopsy from January 2019 to October 2022 at a large academic center. Study eligibility included patients (pts) aged > 18 years undergoing USG clinical breast biopsy with a radiographically evident mass ≥ 0.6 cm in the longest dimension. Eligible pts, identified by a research associate on the day of the biopsy, were invited to participate at the discretion of the radiologist performing the biopsy. Those approached either consented or declined a research biopsy. Demographic and clinical data of eligible pts were extracted from the EMR. **Results:** 2449 pts underwent USG breast biopsy and 1309 were deemed eligible for a research biopsy. Of the eligible population, 564 (43%) consented to the study, 322 (25%) declined, and 423 (32%) were not approached. Consented pts were younger compared to those who declined or to those not approached (median age 49, 51, and 51 years, respectively; $p = .01$). Comparison of study groups by age and race categories are shown in the table. Pts > 70 were less likely to be approached compared to pts < 70 ($p = .01$). However, The likelihood of pts being approached to consent did not differ significantly with age ($p = .09$). Of the eligible pts, 951 (73%) were White, 327 (25%) were non-White (10% Asian, 8% Black, 1% Hispanic, and 7% other race), and race was unknown for 31 (2%) pts. White and non-White pts were equally likely to be approached ($p = .3$). However, approached non-White pts were significantly less likely to consent compared to White pts ($p = .01$). Within the non-White population, Black pts were more likely to decline a research biopsy, with only 50% of approached Black pts consenting compared to 66% of White pts, 61% of Asian pts and 55% of pts of other race. **Conclusions:** We found disparities based on age and race/ethnicity in participation in a breast biopsy tissue biobank. Older pts were less likely to be offered participation but equally likely to consent when invited, while Black pts were equally likely to be offered participation, but less likely to consent when invited, compared to other racial subgroups. Our findings support targeted interventions to increase participation across diverse subgroups of pts. Research Sponsor: None.

	Age, n (%)		p	Race, n (%)			p
	< 70	> 70		White	Non-White*	Unknown	
n	1090	219		951	327	31	
Approached	753 (69)	133 (61)	.01	653 (69)	215 (66)	18 (58)	.3
Not approached	337 (31)	86 (39)		298 (31)	112 (34)	13(42)	
n	753	133		653	215	18	
Consented	488 (65)	76 (57)	.09	433 (66)	119 (55)	12 (67)	.01
Declined	265 (35)	57 (43)		220 (34)	96 (45)	6 (33)	

* Asian, Black, Hispanic, Other.

6534

Poster Session

Beyond transportation: Financial hardship, food insecurity, and care access barriers among US cancer survivors with transportation barriers to care. *First Author: Changchuan Jiang, Roswell Park Comprehensive Cancer Center, Buffalo, NY*

Background: Health care payers and providers increasingly focus on addressing social determinants of health (SDoH) in order to reduce disparities in care and patient outcomes in the US. Transportation barriers to health care, a key SDoH, are associated with increased emergency department use and mortality risk among cancer survivors. Transportation barriers may also be associated with other potentially addressable aspects of SDoH and access barriers. To inform future interventions, we examined financial hardship and barriers to timely care among cancer survivors with transportation challenges in a nationally representative sample. **Methods:** We identified 18,140 adults with a history of cancer from the 2011-2018 National Health Interview Survey. Transportation barriers were defined as delay in care due to lack of transportation over the past 12 months. Primary outcomes included 1) medical financial hardship (FH) in any of the three following domains: material (problems paying medical bills), psychological (worrying about medical bills), and behavioral hardship (delaying/forgoing care due to cost); 2) food insecurity (worrying food would run out); and 3) delayed care due to other factors (long wait times, inability to get an appointment quickly). We estimated the proportion of survivors who report any financial hardship, food insecurity, or other factors that lead to care delays than survivors without transportation barriers (86.0% vs 45.3%, $p<0.001$). Additionally, survivors with transportation barriers were more likely to experience medical financial hardship (73.2% vs 38.3%, $p<0.001$), including material (50.3% vs 27.1%, $p<0.001$), behavior (57.5% vs 20.4%, $p<0.001$), and psychological (33.5% vs 15.4%, $p<0.001$) hardship than survivors without transportation barriers. Additionally, survivors with transportation barriers were more likely to experience food insecurity (43.9% vs 12.0%, $p<0.001$) and care delays due to other factors (45.6% vs. 11.6%, $p<0.001$). **Conclusions:** Most cancer survivors with transportation barriers to care also report struggling financially and experiencing additional barriers to timely care. Findings highlight the importance of screening and addressing social needs and comprehensive interventions to address barriers to care access in this vulnerable population. Research Sponsor: None.

6535

Poster Session

County-level jail incarceration and cancer mortality in the US. *First Author: Jingxuan Zhao, American Cancer Society, Atlanta, GA*

Background: Incarceration has been linked to poor community health outcomes, such as worse preterm births and mortality in the US, although little research has examined cancer outcomes. This study examined associations of county-level jail incarceration and cancer mortality. **Methods:** Annual county-level local jail incarceration rates (1990-2018) were obtained from the Vera Institute of Justice. We calculated annual county-level mortality rates (2000 -2019) with invasive cancer as the underlying cause of death (ICD-10 codes: C00-C97) using National Vital Statistics System. Associations of county-level jail incarceration and cancer mortality overall, and by sex, race, and common cancer sites were examined with generalized estimating equations with Poisson distribution and standard errors clustered at county level. To assess the short-, medium-, and long-term associations, we used lagged county-level incarceration rates by 1, 5, and 10 years prior to mortality rates in separate analyses. **Results:** Over the 20-year study period, each 1 per 1000 increase in county jail incarceration rate was associated with a 1.2% increase in cancer mortality rate in the short-term (model with 1-year lags, rate ratio (RR): 1.012, 95% CI: 1.009–1.015) and 1.1% increase in medium-term (5-year lags (RR: 1.011, 95% CI: 1.008–1.014) and 0.8% increase long-term (10-year lags (RR: 1.008, 95% CI: 1.004–1.012). After adjusting for county-level sociodemographic characteristics, the RRs were attenuated but remained statistically significant. Jail incarceration was associated with higher cancer mortality for all common cancers included in the study (Table) and for White people, but not for Black people. The magnitude of associations was similar for medium- and long-term effects (5- and 10-year lags, respectively). **Conclusions:** Higher county-level jail incarceration rates were associated with higher county-level cancer mortality rates, underscoring the collateral health consequences of mass incarceration. Efforts to identify interventions to decrease the cancer mortality burden in these communities are warranted. Research Sponsor: None.

Association of county-level incarceration and cancer mortality.		
	Adjusted RR	95%CI
All cancers	1.007	1.004-1.009
Sex		
Male	1.007	1.004-1.009
Female	1.006	1.004-1.008
Race		
White	1.007	1.007-1.007
Black	1.000	0.997-1.003
Cancer Site		
Female breast	1.004	1.003-1.006
Colorectal	1.007	1.005-1.009
Prostate	1.004	1.002-1.007
Lung	1.009	1.006-1.012

*Model with 1-year lag of prior county-level incarceration rates.

6536

Poster Session

An intersectional approach to cervical cancer screening disparities by race/ethnicity and immigrant status. *First Author: Jane J. Chen, Warren Alpert Medical School of Brown University, Providence, RI*

Background: Racial/ethnic minority and immigrant groups individually experience lower rates of cervical cancer (CC) screening. Although immigrants represent large proportions of racial/ethnic minorities, few studies have explored the interacting health consequences of these social categories. Intersectionality is a theoretical framework which recognizes that studying social categories independently cannot capture their cumulative effects on health. In the context of CC screening, only one study took this approach but did not analyze several important barriers to care. This study aims to analyze the joint influence of race/ethnicity and immigrant status on screening and identify barriers unique to each intersectional group. **Methods:** Data from the National Health Interview Survey years 2005, 2010 and 2015 were drawn from IPUMS. Analyses were restricted to those eligible for CC screening (n=17,941). Multivariable logistic regression was used to model the interactional effect of race/ethnicity and immigrant status on screening up to date (UTD) status adjusting for confounders. Variables reflecting socioeconomic status (SES), access to care, acculturation and language were separately included to see whether they explained identified disparities. Finally, amongst women not UTD on screening, reasons for this were analyzed. All analyses were adjusted for complex survey design. **Results:** US born Non-Hispanic Black women had higher odds of being UTD on screening (OR 1.63, 95% CI [1.23, 2.18]) while immigrant Non-Hispanic White (OR 0.45 [0.29, 0.71]), immigrant Asian (OR 0.29 [0.2, 0.42]) and immigrant Hispanic/Latinx women (OR 0.51 [0.39, 0.67]) had lower odds compared to US born Non-Hispanic White women. Adjusting for SES (OR 0.87 [0.65, 1.16]) and access (OR 1 [0.74, 1.36]) attenuated the ORs for immigrant Hispanic/Latinx women but not immigrant Asian and White women. Adjusting for acculturation attenuated the ORs for immigrant Hispanic/Latinx (OR 0.84 [0.58, 1.22]) and White women (OR 0.68 [0.42, 1.12]) only. Adjusting for language increased but did not attenuate the ORs for all immigrant groups. Analyses of reasons for not screening showed immigrant Non-Hispanic White, Black and Asian women had greater proportions selecting "Didn't need or know needed this test" versus other groups (10-12% vs. 5.4-8.4%). **Conclusions:** Immigrant status continues to explain much of the CC screening disparities previously attributed to race/ethnicity. SES and access to care remain important barriers for immigrant Hispanic/Latinx women but less so for other immigrant groups. This study reveals that acculturation is an important barrier for immigrant Non-Hispanic White and Hispanic/Latinx women, possibly representing disparities in knowledge. Language barriers may also contribute in all immigrant women. Further intersectional studies are needed to identify remaining barriers. Research Sponsor: None.

6538

Poster Session

The association between continuity of Medicaid enrollment and cancer survival in young adults diagnosed with cancer. *First Author: Kimberly J. Johnson, Washington University in St. Louis, St. Louis, MO*

Background: Disparities in young adult cancer survival between individuals with Medicaid and private insurance have been reported. To further understand the association between insurance-related access to healthcare and young adult cancer survival, we used Surveillance, Epidemiology, and End Results (SEER)-Medicaid linked data to test two hypotheses: 1) Those linked to Medicaid have lower cancer survival than those not linked, and 2) those with discontinuous enrollment in Medicaid around the time of diagnosis have lower survival than those with continuous enrollment. **Methods:** SEER-Medicaid linked data from 2006 to 2013 were obtained. Follow-up for vital status was through 2018. We included individuals diagnosed with a first malignant primary cancer diagnosed between 20 to 39 years. We excluded individuals who were linked to Medicaid enrollment records in multiple states during the same year. Individuals were defined as Medicaid-linked if they were linked to Medicaid in any U.S. state or the District of Columbia from 2006 to 2013. Medicaid enrollment was classified as continuous (enrolled within both the three months before and after diagnosis) and discontinuous (enrolled only within the 3 months before or after diagnosis or only at diagnosis). We used survival analysis methods including Kaplan-Meier (KM) curves and Cox Proportional Hazards (PH) regression models to evaluate survival differences in association with Medicaid linkage and enrollment timing after adjusting for race and a measure of census tract poverty. **Results:** Our analytic dataset included 137,259 young adults, among which there were 22,955 cancer deaths. KM curves showed consistently lower survival probabilities over time in young adults who linked vs. those not linked to Medicaid and in those with discontinuous vs. continuous enrollment (p < .0001). Adjusted Cox PH regression models indicated that those who linked to Medicaid had a 2.19 (95% CI 2.14-2.25) times higher hazard of death vs. those who did not link. Those with continuous and discontinuous Medicaid enrollment had a 1.91 (95% CI 1.84 to 1.99) and 3.32 (95% CI 3.19 to 3.45) times higher hazard of death, respectively, vs. those not linked to Medicaid. Similar patterns were consistently observed for specific cancer types. **Conclusions:** These results confirm an insurance-associated disparity in a national sample of young adult cancer patients and provide additional information on risks in association with Medicaid enrollment continuity. These results further support the critical need for consistent health insurance coverage in young adults and for additional research to understand social, economic, and access-related factors leading to lower survival in the Medicaid population. Lowering administrative burdens for Medicaid enrollment, eligibility, and renewal are potentially important strategies for improving cancer outcomes. Research Sponsor: None.

6537

Poster Session

Associations of cancer history, food insecurity, and nonmedical financial worry and mortality risk in the US. *First Author: Zhiyuan Zheng, American Cancer Society, Atlanta, GA*

Background: Cancer survivors often face substantial out-of-pocket medical costs, which can adversely affect their financial well-being. Cutting expenses on food and housing to save money are common coping strategies. However, little is known about the extent to which food insecurities and non-medical financial worries affect mortality risk after consideration of medical financial hardship. **Methods:** The 2013-2018 National Health Interview Survey (NHIS) and the NHIS linked mortality files with vital status through December 31, 2019 were used to identify cancer survivors (ages 18-64: n=5,110; ages 65-79: n=4,949) and individuals without a cancer history (ages 18-64: n=115,643; ages 65-79: n=24,785). Medical financial hardship included 3 domains: material, psychological, and behavioral. Food insecurity (e.g., worry about food running out) and non-medical financial worries (e.g., paying for monthly bills and housing) were separately summarized and categorized as severe, moderate, and minor/none levels. Using age as the time scale, associations of cancer history, food insecurity and non-medical financial worry and mortality risk were examined with weighted Cox proportional hazards models. Adjusted models included medical financial hardship, sex, educational attainment, marital status, health insurance, comorbid conditions, and survey year. All estimates accounted for complex survey design. **Results:** In our sample, about 13.8% (ages 18-64) and 7.9% (ages 65-79) reported moderate to severe levels of food insecurity, respectively; 32.1% (ages 18-64) and 19.2% (ages 65-79) reported moderate to severe levels of non-medical financial worries, respectively. In adjusted analyses, cancer survivors had increased mortality risk. After controlling for medical financial hardship, food insecurity was associated with higher mortality risk in both age groups, following a dose-response relationship (Table); Non-medical financial worry was associated with higher mortality risk in the 65-79 age group (Table). **Conclusions:** Standardized and comprehensive assessment of financial hardship and other social needs, such food insecurity, is essential to identify and mitigate adverse economic impacts of cancer. Research Sponsor: None.

Adjusted associations of cancer history, food insecurity and non-medical financial worries and mortality risk.

		Ages 18-64			Ages 65-79		
		HR	95CI	P	HR	95CI	P
Cancer history	Yes	1.95	1.74-2.19	<.001	1.18	1.09-1.27	<.001
	No		ref			ref	
Medical financial hardship	3 domains	1.32	1.12-1.57	0.001	2.15	1.75-2.64	<.001
	1-2 domains	1.30	1.18-1.43	<.001	1.59	1.48-1.71	<.001
	0 domains		ref			ref	
Food insecurity	Severe	1.69	1.48-1.92	<.001	1.57	1.33-1.87	<.001
	Moderate	1.53	1.35-1.72	<.001	1.42	1.26-1.62	<.001
	Minor/none		ref			ref	
Non-medical financial worries	Severe	1.08	0.91-1.29	0.381	1.37	1.11-1.69	0.003
	Moderate	1.02	0.90-1.17	0.748	1.16	1.02-1.32	0.027
	Minor/none		ref			ref	

6539

Poster Session

Association of Medicaid expansion with timely receipt of treatment and survival among patients with HER2-enriched breast cancer. *First Author: Kewei Sylvia Shi, American Cancer Society, Atlanta, GA*

Background: HER2-enriched breast cancer (estrogen and progesterone receptors negative and HER2-positive) has no worse prognosis than other breast cancers if it is treated with HER2-targeted therapy. Medicaid expansion under the Affordable Care Act (ACA) has been shown to be associated with improved access to care and outcomes for many cancers, but its impact on care for HER2-enriched breast cancer is unknown. To fill this gap, we examined the association of Medicaid expansion with receipt of guideline-concordant treatment, time to treatment, and survival among newly diagnosed nonelderly women with HER2-enriched breast cancer. **Methods:** Women aged 18-62 years newly diagnosed with HER2-enriched breast cancer between 2010 and 2018 were identified from the National Cancer Database. Our primary outcomes included receipt of stage-based guideline-concordant treatment, initiation of treatment <60 days, and stage-specific 2-year overall survival. A difference-in-differences (DD) approach compared outcome changes following the expansion in Medicaid expansion vs. non-expansion states. A linear probability model estimated treatment outcome, and a flexible parametric survival model evaluated survival. All models were clustered at the state level and adjusted for age group, race/ethnicity, rurality of residence, zip code-level income, comorbidity, and diagnosis year. **Results:** A total of 31,354 patients with HER2-enriched breast cancer were included, including 19,255 in expansion states and 12,099 in non-expansion states. Compared to patients in expansion states, patients in non-expansion states were more likely to be racial/ethnic minorities, uninsured, and diagnosed at late-stage. Medicaid expansion was not significantly associated with changes in receipt of surgery for stage I-III disease but was associated with an increase of 4.42 percentage points (ppt, 95% CI: 0.09, 8.74) in receipt of chemotherapy/targeted therapy for stage IV disease, with an increase from 90.4% pre-expansion to 92.8% post-expansion in expansion states and a decrease from 93.7% to 91.9% in non-expansion states. Medicaid expansion was also significantly associated with a 2.41 ppt increase in initiating guideline-concordant treatment within 60 days (95% CI: 0.66, 4.17; 83.5% to 82.5% in expansion states vs. 86.6% to 83.7% in non-expansion states), and a 1.18 ppt increase in two-year survival rate (95% CI: 0.03, 2.33; 94.0% to 94.9% in expansion states vs. 94.3% to 94.1% in non-expansion states). The increase in two-year survival associated with Medicaid expansion was most prominent for stage III patients (DD=3.63 ppt; 95% CI: 0.64, 6.62). **Conclusions:** Medicaid expansion was associated with increased receipt of timely treatment and improved 2-year survival among nonelderly women newly diagnosed with HER2-enriched breast cancer. Research Sponsor: None.

6540

Poster Session

Disparities in uptake of novel therapies for acute myeloid leukemia. *First Author: Andrew Hantel, Division of Population Sciences, Dana-Farber Cancer Institute, Boston, MA*

Background: Multiple novel therapies have recently been approved to treat acute myeloid leukemia (AML). Inequities in the uptake of novel treatments have been seen in other cancers but are not known for this population. **Methods:** We performed a retrospective analysis of the nationwide Flatiron Health electronic health record (EHR)-derived de-identified database. We assessed sociodemographic associations with novel AML therapies use within two-years of Food and Drug Administration (FDA) approval from 1/2014-8/2022. Therapies were: glasdegib, venetoclax, ivosidenib, midostaurin, CPX-351, gilteritinib, enasidenib, and gemtuzumab ozogamicin (GO). Univariable associations were assessed using χ^2 testing. Logistic regression modeling of community practices assessed associations between novel therapy receipt and sociodemographics adjusted by treatment year. Variable categories are shown. **Results:** Of 8081 patients in 280 clinics, 3102 (38%) received at least one novel therapy. The cohort was predominantly older (69; interquartile range [57, 77]), male (56%), non-Hispanic (NH)-White (88%), and treated at a community practice (75%). There were 4808 patients treated within 24-months of a novel therapy approval, of which 1937 (40%) received a novel therapy. Venetoclax represented 59% of novel treatments prescribed. Bivariate associations were seen between novel therapy receipt within 24-months of approval and high SES and non-Hispanic (NH)-White race-ethnicity; similar associations were seen when assessed at the treatment regimen level. In a logistic regression model of community practices (N=2,459), older patients (OR 1.01; 95%CI 1.00, 1.02), females (OR 1.2; 95%CI 1.0, 1.4), and those from high (vs low) SES (OR 1.4; 95%CI 1.1, 1.6) were more likely to receive novel therapy; there were no associations with sex or race-ethnicity. **Conclusions:** In this large national database of adults with AML, almost half received novel therapy within 24-months of FDA approval. Though there was no dichotomous difference in uptake by race-ethnicity in community practices, younger and more affluent patients were more likely to receive novel therapy, concerning for disparities in uptake. Research Sponsor: American Cancer Society; Conquer Cancer Foundation of the American Society of Clinical Oncology; U.S. National Institutes of Health.

	Overall Pts Receiving Novel Therapy, N = 3,102		χ^2 p-value		Pts Treated Within 24 Months FDA Approval, N = 4,808			Pts Receiving Novel Therapy Within 24 Months FDA Approval, N = 1,937		χ^2 p-value
	N			N						
Practice Academic	8081	1978 (24%)	788 (25%)	0.006	4808	1273 (26%)		510 (26%)		0.001
Community		5945 (74%)	2,237 (72%)			3443 (72%)		1373 (71%)		
Both		158 (2.0%)	77 (2.5%)			92 (1.9%)		54 (2.8%)		
SES (Yost Index Tertile)	5508			<0.001	3169					0.002
High		2234 (41%)	916 (44%)			1286 (41%)		564 (44%)		
Low		1987 (36%)	683 (33%)			1136 (36%)		418 (33%)		
Medium		1287 (23%)	502 (24%)			747 (24%)		296 (23%)		
Race-Ethnicity	6127			0.2	3657					0.078
Persons of Color		759 (12%)	264 (12%)			448 (12%)		158 (11%)		
NH-White		5368 (88%)	1993 (88%)			3209 (88%)		1271 (89%)		

Pts, patients.

6543

Poster Session

Racial and ethnic disparities in employment of patients and caregivers following breast cancer diagnosis. *First Author: Marisa C. Weiss, Breastcancer.org, Ardmore, PA*

Background: Breast cancer (BC) can negatively impact employment, risking healthcare benefits, financial security and quality of life, especially for underserved minority populations. To better understand the impact of BC diagnosis and treatment on employment, Breastcancer.org conducted an online survey. **Methods:** Between 6/7-7/12/2022, Breastcancer.org community members were recruited to participate in an anonymous survey in English or Spanish via email, social media, or website ads. Eligible participants were US residents, age ≥ 18 , and diagnosed with BC within the past 10 years. Consented participants answered questions on socio-demographics, financial toxicity, and employment status. **Results:** Of 2,420 screened, 1,710 met eligibility, and 1,437 participated (84% participation rate). Mean age and time since diagnosis was 46 and 2 years, respectively; 75% were in active treatment for non-metastatic (89%) or metastatic (11%) BC. Patients identified as 60% White (n=868), 26.7% Hispanic (n=384), 8% Black (n=121), or 4% Other (n=64). 94% were women. BC negatively impacted employment for 92% of patients. Full-time employment went from 62% at diagnosis to 40% by the time of the survey. This was more pronounced in metastatic (56% to 25%) vs non-metastatic (63% to 42%) patients (p=0.015). 64% attributed employment changes to their diagnosis, noting reduced hours/income (40%), job change (26%), disability (13%), permanent job loss (13%), and/or early retirement (12%). 36% noted changes in their caregiver's employment status as well with 30% of caregivers having reduced hours/income, 30% taking time off work, and 27% changing jobs; 9% of caregivers had permanent job loss and 10% retired early. Hispanic patients were younger (p<0.001) and more likely to have young children (p<0.001) and take unpaid leave (p=0.02). (Table). BC diagnosis was also more likely to impact their caregiver's employment (58%, vs White 25% or Black 41% patients, p<0.001). **Conclusions:** Breast cancer can cause significant, lasting negative effects on employment status for patients and caregivers that can decrease financial security of the entire family unit. Hispanic patients and individuals with metastatic disease appear to be at highest risk. Legislative protections and financial support may be required to mitigate the significant financial toxicity of a cancer diagnosis, especially for the most vulnerable. Research Sponsor: Gilead Sciences Inc., Pfizer Inc., Lilly.

	Total (n=1,437)	Hispanic (n=384)	Non-Hispanic White (n=1,282)	Non-Hispanic Black (n=121)	Other (n=64)
Age (mean, yrs)	46	38*	50	46	49
Time since Dx (mean, yrs)	2	2	3	2	3
Children <18	55%	83%*	43%	57%	53%
Employment after Dx (% Change)					
Full-time	40% (-22%)	36% (-25%)	41% (-22%)	46% (-17%)	42% (-19%)
Part-time	19% (+6%)	23% (+10%)	17% (+5%)	18% (+7%)	13% (+2%)
Retired	13% (+4%)	2% (+1%)*	19% (+5%)	10% (+3%)	14% (+3%)
Unpaid leave	8% (+5%)	13% (+10%)*	6% (+4%)	6% (+3%)	3% (+3%)
Unemployed	6% (+4%)	7% (+4%)	5% (+4%)	6% (+3%)	8% (+2%)

* p $\leq$ 0.05.

6541

Poster Session

Talk, test, and take one click to curb prostate cancer mortality. *First Author: Sandhya Cautha, Bronxcare Health System, Bronx, NY*

Background: Prostate cancer remains the most commonly diagnosed cancer and the second leading cause of cancer-related death in men in the United States. BronxCare Health System (BCHS) serves the Bronx neighborhoods of Morris Heights, Fordham South, and Mount Hope, notable for the highest prostate cancer incidence rate in New York City as per the American Cancer Society Cancer Action Network report 2019, highlighting the need for prostate cancer screening among the patient population we serve. An anonymous voluntary paper survey was performed in 2019 at BCHS to determine primary care physician understanding and implementation of current PSA testing guidelines. The study showed that primary care providers at BCHS approach PSA testing in a wide variety of ways and screen a wide age range of patients suggesting a need for intervention. An electronic medical record (EMR) decision support tool activated during primary care visits for men aged 55-69 years was implemented beginning January 1, 2021 which facilitates the provider and patient engagement in a shared decision-making discussion. This a follow-up study to determine the effect of this EMR application on PSA order rates and prostate cancer diagnosis rates at BCHS. **Methods:** The total number of patients who had PSA and lipid panel (LP) screening were extracted from the EMR of BCHS for potentially eligible men (aged 55-69) seen during primary care visits during the years 2016-2022. LP is done annually as a part of routine screening for adults aged 55-69 and is taken as an equivalent of primary care visits. PSA screening rates were compared to LP screening rates to control for unforeseen variables. Similarly, the number of newly-diagnosed prostate cancers among the same population of men was extracted for the years 2016-2021. Data for 2022 is still not available. 2016-2020 are pre-EMR and 2021 and 2022 are post-EMR flag years. The pre and post-EMR flag PSA and prostate cancer diagnosis numbers were compared by calculating Z scores and p-values. **Results:** The year-wise PSA, LP, and newly-diagnosed prostate cancers (PC) are tabulated below. The proportion of men who had PSA testing among all men aged 55-69 who had LP testing in each pre-EMR flag year was compared to each post-EMR flag year. A significant increase (p < 0.00001) was noted in the proportion of men who had PSA screening after implementation of the EMR application. Similarly, the proportion of men with newly-diagnosed prostate cancer among all men aged 55-69 who had PSA screening significantly increased after EMR application (p < 0.00001). **Conclusions:** A decision support tool embedded in the EMR has been an effective approach in increasing prostate cancer screening rates and may help curb prostate cancer mortality in our patient population as early detection in right men at the right age has the potential to reduce prostate cancer mortality. Research Sponsor: None.

Year	LP	PSA	PC
2016	2531	728	91
2017	2561	651	82
2018	2834	686	80
2019	2972	792	79
2020	2917	877	73
2021	3359	2428	126
2022	3365	2246	NA

6544

Poster Session

Depression, systemic inflammation, and exposure to discrimination among sexual and gender minority (SGM) cancer survivors. *First Author: Charles Stewart Kamen, University of Rochester Medical Center, Rochester, NY*

Background: Our prior research shows that SGM cancer survivors experience high rates of depression, due in part to exposure to discrimination. Depression among cancer survivors in general has been linked to markers of systemic inflammation including peripheral blood interleukin (IL)-6, tumor necrosis factor alpha (TNF α), and C-reactive protein (CRP). To date, no studies have examined the association of these markers with depression among SGM cancer survivors in the context of discrimination. **Methods:** Cross-sectional patient-reported data and serum samples were collected from 66 SGM cancer survivors (see Table). Depression was assessed by the Patient Health Questionnaire (PHQ)-9, discrimination by the Harassment, Rejection, and Discrimination Scale (HHRDS), IL6 and TNF α by multiplex assay, and CRP by ELISA. We used a clinical cut-point for depression of 10 on the PHQ-9, indicating moderate depressive symptoms, and assessed associations between continuous variables using bivariate correlations and multivariate linear regressions. **Results:** More SGM cancer survivors exceeded the clinical cut-point for depression (15.9%) than cancer survivors in prior general population samples (11.3%). Higher depression among SGM cancer survivors was associated with higher levels of exposure to discrimination (r=0.28, p=0.03), TNF α (r=0.30, p=0.02), and CRP (r=0.39, p=0.002); exposure to workplace discrimination, specifically, was associated with higher levels of CRP (r=0.32, p=0.02). In multivariate models controlling for demographic and clinical characteristics, CRP remained a significant predictor of depression (β =0.34, p=0.01). **Conclusions:** This study replicates prior findings of high levels of depression among SGM cancer survivors. It provides preliminary evidence that markers of inflammation, specifically CRP, are uniquely predictive of depression among SGM cancer survivors in the context of exposure to discrimination. These findings need to be replicated in larger samples and evaluated for potential use in providing supportive cancer care to SGM survivors. Research Sponsor: U.S. National Institutes of Health.

Sample characteristics (N=66).	
Sexual orientation	
Bisexual	3 (4.5%)
Lesbian/Gay	62 (94%)
Another orientation	1 (1.5%)
Gender identity	
Cisgender man	21 (31.8%)
Cisgender woman	44 (66.7%)
Transgender man	1 (1.5%)
Race/Ethnicity	
Black	2 (3.0%)
Latino	2 (3.0%)
Non-Latino White	62 (94.0%)
Age, mean (range)	56 (28-78)
Employment Status	
Employed	44 (66.7%)
Retired/disabled/unemployed	22 (33.3%)
Cancer type	
Breast	27 (40.9%)
Prostate	8 (12.1%)
Endometrial	6 (9.1%)
Lymphoma	6 (9.1%)
Other	19 (28.8%)
Months since treatment, median (range)	6 (0-170)
Depression, mean (s.d.)	5.24 (4.63)
Discrimination, mean (s.d.)	22.22 (9.40)
IL6, mean (s.d.)	8.65 pg/mL (16.79)
TNF α , mean (s.d.)	4.25 pg/mL (1.46)
CRP, mean (s.d.)	0.20 mg/mL (0.34)

6545

Poster Session

Association of major adverse financial events and later stage cancer diagnosis in the US. *First Author: Robin Yabroff, American Cancer Society, Atlanta, GA*

Background: Studies have documented an increased risk of bankruptcy and other financial hardships for individuals following a cancer diagnosis in the US. Few studies, however, have examined how patients' financial situation prior to cancer diagnosis is associated with cancer stage at diagnosis. This study assessed the prevalence of the specific major adverse financial events (AFEs) of bankruptcies, liens, and evictions prior to cancer diagnosis and their association with later stage diagnosis. **Methods:** Individuals aged 21 to 69 years diagnosed with cancer during 2014-2015 were identified from the SEER population-based registries for Seattle, Louisiana and Georgia. Registry data were linked with LexisNexis consumer data to identify patients with a history of court-documented AFEs. All AFEs occurring at any time prior to cancer diagnosis were identified. The association of AFEs and later stage cancer diagnoses (Stages III/IV) was assessed with sex-specific multivariable logistic regression. **Results:** Among 101,649 individuals diagnosed with cancer linked to LexisNexis data, 36,791 (36.2%) had a major AFE reported prior to diagnosis. The most recent event occurred a mean of 7.8 years prior to diagnosis. For individuals with an AFE, one-third experienced multiple events. Within each registry, AFEs were most common among non-Hispanic Black, unmarried, and low-income individuals. However, even in the highest income group, 27% had a prior AFE. Individuals with prior AFEs were more likely to be diagnosed with later stage cancer than individuals with no prior AFE (males-odds ratio (OR) 1.09; 95% CI, 1.03 to 1.14; $P < .001$ and females-OR 1.11; 95% CI, 1.06 to 1.17; $P < .0001$), after adjusting for age, race and ethnicity, marital status, income prior to diagnosis, registry, and type of cancer. The association between a major AFE and later stage diagnosis was observed regardless of when the event occurred relative to cancer diagnosis. **Conclusions:** In this novel cancer registry, LexisNexis consumer data linkage, we found that one-third of individuals newly diagnosed with cancer had a pre-diagnosis bankruptcy, lien, or eviction. Individuals with these AFEs were more likely to have later stage diagnosis, even after accounting for traditional measures of socioeconomic status, such as income. The prevalence of pre-diagnosis AFEs underscores patient financial vulnerability at the time of their cancer diagnosis, even before experiencing any subsequent financial burden associated with cancer treatment. Our findings are especially timely, with growing efforts by health care providers to screen and address patient social needs as part of oncology care. Research Sponsor: None.

6546

Poster Session

Racial disparities in cancer mortality in patients with gastrointestinal malignancies following Medicaid expansion. *First Author: Naveen Manisundaram, Department of Surgery, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Racial minorities experience disparities in receipt of cancer treatment and survival. The optional Medicaid expansion provision of the Affordable Care Act provided federal funding to participating states to improve healthcare access for disadvantaged populations by expanding Medicaid eligibility criteria. This study aimed to investigate the effect of Medicaid expansion on racial disparities in mortality among patients with gastrointestinal malignancies. **Methods:** A cross-sectional cohort study of patients with pancreatic ductal adenocarcinoma (PDAC), colorectal cancer (CRC), and gastric adenocarcinoma (GC) of any stage was conducted using the National Cancer Database (2009-2019). Difference-in-difference analysis (DID) was performed to compare adjusted 2-year mortality separately among Black and White patients residing in Medicaid expansion states (MES) and non-expansion states (non-MES) before (2009-2013) and after (2014-2019) expansion. Differences in receipt of surgery and chemotherapy were also evaluated. **Results:** A total of 86,052 patients were included for analysis, including 19,188 patients with PDAC, 60,404 with CRC, and 6,460 with GC. Two-year mortality decreased among Black patients with PDAC residing in MES compared to non-MES following expansion (DID -9.4%, $p < 0.001$) (Table). Mortality also decreased among Black and White patients with CRC in MES compared to non-MES following expansion (DID -4.2%, $p < 0.001$ and -2.9%, $p = 0.047$). Among patients with GC, Black patients in MES experienced a marked reduction in mortality compared to non-MES (DID -7.7%, $p = 0.07$). Both Black and White stage 3-4 PDAC patients had an increase in receipt of chemotherapy in MES following expansion (DID 3.7%, $p = 0.28$ and DID 2.7%, $p = 0.20$). Rates of surgery, but not chemotherapy receipt, increased among Black patients with stage 4 CRC in MES following expansion (DID 5.7%, $p = 0.03$ and 1.0%, $p = 0.66$, respectively). A greater increase in receipt of chemotherapy was observed among Black patients with stage 4 GC in MES than in non-MES (DID 11%, $p = 0.06$). **Conclusions:** Medicaid expansion was associated with a greater reduction in 2-year mortality rates for Black patients residing in MES than for those in non-MES. Existing racial disparities in mortality remained the same or worsened in non-MES but in almost all cases were mitigated in MES following Medicaid expansion. Research Sponsor: U.S. National Institutes of Health.

Difference in adjusted 2-year mortality in black compared to white patients in expansion (MES) and non-expansion states (non-MES) following Medicaid expansion.

		2009-2013		2014-2019		DID*	P-Value
		Non-MES	MES	Non-MES	MES		
Pancreas (%)	White	81.4	78.2	69.9	67.5	0.7	0.65
	Black	77.0	77.8	74.6	66.0	-9.4	< 0.001
CRC* (%)	White	29.0	28.3	27.2	22.3	-4.2	< 0.001
	Black	32.4	29.5	30.4	24.6	-2.9	0.047
Gastric (%)	White	69.8	61.9	61.3	57.1	3.7	0.23
	Black	67.9	62.2	62.7	49.2	-7.7	0.07

*Difference in difference (DID); colorectal cancer (CRC).

6547

Poster Session

What is your preferred language? Evaluating equal access to oncology clinical studies for non-English-speaking participants. *First Author: Dame Idossa, University of Minnesota, Minneapolis, MN*

Background: Oncology clinical research studies (CRS) are essential for developing new therapies and improving patient outcomes, yet the lack of diversity among research participants remains an issue. The logistical complexity of participating in CRS, lack of funding, limited location of study sites, socioeconomic barriers, and the exclusion of non-English speakers (NES) likely contribute to this lack of diversity. In this study, we sought to evaluate what proportion of oncology CRS exclude NES. **Methods:** We searched ClinicalTrials.gov on December 28, 2022, to identify registered oncology CRS in the most prevalent cancer types: breast, lung, colorectal, and prostate cancers. Only US based studies were included. We reviewed the inclusion and exclusion criteria of each study and identified those that excluded NES. Trials with available informed consent forms (ICFs) were examined to evaluate length, available languages, and readability. Descriptive analysis and chi-squared tests were used to explore associations between study characteristics and the exclusion of NES. **Results:** We identified 12,393 CRS, of which 2527 were excluded due to duplicates listed under more than one cancer type. Of 9866 evaluable studies, 1195 (12%) explicitly excluded NES individuals from participating. Of these, 161 (13%) allowed Spanish-speaking participants. Breast cancer trials had the highest proportion of CRS which excluded NES (17%), followed by trials in colorectal (13%), prostate (9%), and lung (7%) cancer. When analyzed by funding sources, studies funded by academic institutions had the highest proportion of CRS that excluded NES individuals (24%) compared to 15% of NIH funded, 19% of other government-funded, and 2% of industry-funded studies ($p < 0.001$). Compared to interventional studies, observational research studies were more likely to exclude NES (11% vs 20%; $p < 0.001$). Notably, most CRS did not have ICFs available online. Of the 242 (2%) studies that had ICFs available for review, only 3 (1%) had ICFs available in another language – all of which were in Spanish. Furthermore, many ICFs were lengthy, with a median of 11 pages (range 1-54), and complex, with a median readability of 12th grade Flesch Kincaid level (range 6-26). **Conclusions:** Many oncology CRS, especially those funded by academic institutions, exclude NES, impacting 1 in 10 individuals in the US. This exclusion is not always explicit, making it likely that our findings underestimate the issue. Requiring English proficiency for research study participation will continue to contribute to the underrepresentation of historically excluded populations and NES patients with cancer from clinical trials and other research studies. Eliminating exclusionary criteria based on language and providing adaptive resources for NES participants is crucial for ensuring that oncology research is inclusive and grounded in equity. Research Sponsor: None.

6548

Poster Session

Sexual orientation and gender identity data collection among NCI community oncology research program (NCORP) practices: A 5-year landscape update. *First Author: Elizabeth Jane Cathcart-Rake, Department of Medical Oncology, Mayo Clinic, Rochester, MN*

Background: National organizations (ASCO, ACS, ACCR) have advocated for routine collection of sexual orientation and gender identity (SOGI) in cancer clinics to advance cancer health equity. In 2017, only 24% of NCI Community Oncology Research Program (NCORP) practices collected sexual orientation (SO) data, while 10% collected gender identity (GI) data; recent progress in collection is unknown. **Methods:** In 2022, NCORP practices again completed a Landscape Assessment to assess research capacity (funding support from 2UG1CA189824) and were asked whether they routinely collect SOGI data in the electronic health record (EHR). The proportions of practices reporting collection of SO and/or GI data and population level differences over time were calculated using Fisher's exact tests. Univariate associations between SOGI data collection and site-related variables were evaluated using logistic regression; significant associations were then tested in separate multivariate logistic regression models. **Results:** 271 practices responded to the Landscape Assessment; 42% (114) reported that they routinely collect SO data, 58% (157) reported that they collect GI data; both were significantly higher than 2017 ($p < 0.001$). Compared to other regions, practices in Northeastern states were significantly more likely to report collecting GI, but not SO. Practices with higher proportions of White patients were also more likely to collect GI ($p < 0.001$). Practices with community outreach staff were more likely to collect SO (Table 1). There were no significant differences in SOGI collection by Medicaid/Medicare patients, new cancer cases per year, or practice ownership. In both 2017 and 2022, sites in Southern states were less likely to collect GI than sites in other regions. **Conclusions:** Progress was made in SOGI collection between 2017 and 2022, but fewer than half of NCORP sites routinely collect SOGI data; in spite of national guidelines. Further examination of the cultural context of SOGI collection could inform efforts to improve data collection in the South and other regions. The lack of data on sexual and gender minority patients in the EHR contributes to health inequity and deficiencies in patient-centric care. Research Sponsor: U.S. National Institutes of Health.

Variable	Comparison Group	Univariate		P	Multivariate	
		Collection Reported to Occur N (%)	Collection Reported to Not Occur N (%)		Odds Ratio (95% Confidence Interval)	P
Gender Identity Practice Group Region		N=157	N=114	0.023		0.045
	Midwestern	70 (45%)	44 (39%)		REF	
	Western	32 (20%)	18 (16%)		1.39 (0.63, 3.13)	
	Northeastern	19 (12%)	7 (6%)		2.08 (0.73, 5.91)	
Percent New White Patients Sexual Orientation Staff Dedicated to Community Outreach		N=112	N=159	0.02		<0.001
		29 (25%)	23 (14%)		2.07 (1.12, 3.81)	

6549

Poster Session

Patient-level interventions to increase guideline concordant treatment among Black breast cancer patients: Can they close the racial gap in survival after diagnosis? *First Author: Juan Yanguela, University of North Carolina at Chapel Hill, Chapel Hill, NC*

Background: While we have seen impressive improvements in breast cancer (BC) survival over the last few decades, substantial racial disparities persist. Inequities in the receipt of guideline-concordant treatment contribute to worse survival in Black BC patients. Previous studies have shown that patient-level disparity reduction interventions (e.g., patient navigation) can significantly increase guideline-concordant treatment receipt among Black patients, with positive spillover effects in nonBlack patients. The aim of this study was to estimate the potential impact of disparity reduction interventions on racial inequities in survival after BC diagnosis in North Carolina. **Methods:** We used data from the Cancer Information and Population Health Resource, which links multipayer claims to North Carolina's cancer registry for biological women diagnosed with BC in 2004-2017. We calculated Black/nonBlack disparities in the receipt of chemotherapy (CTx) within 4 months of diagnosis for patients ages <70 with hormone-receptor negative stage I-II BC (CTx cohort; N=2223) and the receipt of endocrine therapy (ET) within 12 months of diagnosis for stage I-III hormone receptor-positive BC (ET cohort=16220). We then simulated the potential increase in the proportion of patients receiving CTx and ET if proven patient-level disparity-reduction interventions were implemented across the state. Based on the literature, we assumed that the effects of these interventions in increasing treatment receipt would be same in the CTx and ET cohorts. We estimated the effect of this potential increase in CTx and ET receipt on 10-year overall survival using cohort-, race-, and treatment receipt-stratified Markov models. We report confidence bounds representing 95% of simulation results. **Results:** Over the 2004-2017 period, 72.9% and 70.8% of Black patients in our cohorts received CTx and ET, respectively. This was significantly lower than among nonBlack patients ($p<.05$). State-wide implementation of disparity reduction interventions could increase CTx and ET receipt among Black patients to 86.7% (80.9-92.5%) and 84.2% (78.5-89.9%), respectively. As a result, the racial 10-year survival gap would decrease from 9.4 to 8.1 (5.7-10.5) percentage points in the CTx cohort, and from 6.2 to 5.4 (4.0-6.7) percentage points in the ET cohort. **Conclusions:** Patient-level interventions can reduce disparities in guideline-concordant-treatment receipt. However, increases in treatment receipt alone would not be enough to close the racial survival gap, suggesting that, in isolation, patient-level interventions are unable to eliminate disparities. Action on the structural factors that disadvantage Black BC patients is needed. Our team is conducting community-engaged work to share and interpret these findings. Research Sponsor: American Cancer Society; Pfizer.

6551

Poster Session

The intersection of neighborhood-level disadvantage and overall lung cancer survival. *First Author: Kathleen Kennedy, Department of Hematology Oncology University of Illinois of Chicago College of Medicine, Chicago, IL*

Background: Despite recent advances in lung cancer therapeutics leading to considerable improvement in survival, disparities continue to persist among socially disadvantaged populations. Although the reasons underlying this phenomenon are uncertain, we posit that neighborhood-level factors could play a role. Furthermore, neighborhood disadvantage may lead to epigenetic changes which promote malignant progression. This study aimed to determine the effects of neighborhood-deprivation index (NDI), a validated 13-factor-based measure, that combines income, education, employment, and housing in a neighborhood, on lung cancer mortality. **Methods:** A retrospective cohort study assessed the relationship of NDI with survival weighted by age, stage, and DNA methylation among biopsy-proven lung cancer from two U.S. medical centers, Johns Hopkins University and the University of Illinois Chicago, between 2008-2020. In our analysis, U.S.-standardized NDI values for each year of sample collection were computed at the U.S. census tract level and categorized into quartiles. Participants' residential addresses were geocoded to U.S. census tracts and linked to NDI quartiles. DNA extraction from liquid biopsy samples was performed for quantification of DNA methylation. **Results:** The study included 184 lung cancer patients, with 89 in the low-deprivation group and 95 in the high-deprivation group. The high-deprivation group had a higher percentage of females (57% vs. 48%), a higher percentage of African Americans (AA) (50% vs. 36%), a lower pack-year smoking history (30 vs. 39 median pack-years), and a higher percentage with stage IV disease (28% vs. 20%) than the low-deprivation group. Overall, NDI was significantly higher among AA when compared with Whites ($p=0.003$) and associated with lung cancer stage at diagnosis with an odds ratio of 1.17 ($p=0.02$). There was a significant correlation between DNA methylation and stage for HOXA7, SOX17, ZPF42, TAC1 and HOXA9. Only HOXA7 DNA methylation correlated with NDI ($p=0.003$). The high-deprivation group had a significantly shorter survival duration compared to the low-deprivation group, with a 1-year survival rate of 79% vs. 90%, a 2-year survival rate of 70% vs. 84%, and a 5-year-survival rate of 51% vs. 73% ($p=0.02$). After adjusting for age at diagnosis, stage, and DNA methylation status, belonging to the high-deprivation group was associated with a higher mortality risk with a hazard ratio of 2.02 ($p=0.04$). **Conclusions:** Neighborhood-level socioeconomic status and DNA methylation may be associated with late stage lung cancer at diagnosis; whereas NDI shows a potential association with shorter survival and increased mortality risk. Higher neighborhood deprivation among AA suggests that changes in health care policy that account for neighborhood-level indices of socioeconomic deprivation may enable more equitable improvement of lung cancer mortality. Research Sponsor: The University of Illinois at Chicago - Department of Surgery Start-up Funds.

6550

Poster Session

Disparities in clinical trial enrolment at a Canadian comprehensive cancer centre: A 15-year retrospective study. *First Author: Gilla Shapiro, Princess Margaret Cancer Centre, Toronto, ON, Canada*

Background: Disparities in clinical trials limit the generalizability of study findings and perpetuate disparities in treatment access and outcomes, but there is a paucity of data in the Canadian context. The objective of this study was to examine disparities in cancer clinical trial enrollment at a large, comprehensive Canadian cancer center. **Methods:** We conducted a retrospective cohort study of clinical trial enrollment among all newly diagnosed cancer patients (N=154,880) at the Princess Margaret Cancer Centre in Toronto, Canada (2006-2021). Multivariable Bayesian hierarchical logistic regression with random effect for most responsible physician was used to examine the correlates of clinical trial enrollment, comparing the population of enrolled and non-enrolled patients. Odds ratios were adjusted for patient variables (sex, age at diagnosis, language, geography, primary care provider), and census tract-level marginalization (residential instability, material deprivation, dependency, ethnic concentration), disease variables (cancer site and disease stage at diagnosis), and provider variables (most responsible physician (MRP), and MRP's sex, language, medical training, and department). **Results:** Overall, 11.2% of patients enrolled (n=17,400) in a clinical trial, with 5-, 10-, and 15-year cumulative incidences of 12%, 15%, and 18%, respectively. Small, but significant differences were observed between enrollees and the overall patient population. Lower odds of enrollment were observed in patients who were female (adjusted odds ratio [AOR], 0.82; 95% confidence interval [CI], 0.78-0.86; $p<.001$), ≥ 65 years (AOR vs <40, 0.61; 95% CI, 0.56-0.65; $p<.001$), non-English language speakers (AOR vs English, 0.72; 95% CI, 0.67-0.77; $p<.001$), lived ≥ 250 km away from the cancer center (AOR vs <15km, 0.71; 95% CI, 0.62-0.80; $p<.001$), or lived in areas with greater material deprivation (AOR, 0.94; 95% CI, 0.93-0.96; $p<.001$) or higher ethnic concentration (AOR, 0.96; 95% CI, 0.94-0.98; $p<.001$). Greater odds of enrollment were found in patients with metastatic disease (AOR, 1.19; 95% CI, 1.13-1.25; $p<.001$) and in those with a primary care provider (AOR, 1.69; 95% CI, 1.55-1.85; $p<.001$). **Conclusions:** Disparities were observed in clinical trial enrollment, despite a publicly funded health care system. While broader prospective data collection efforts are critical to better understand the influence of patient, provider and system factors on clinical trial enrollment, these findings suggest the need for targeted strategies to increase diversity in clinical trial access. Research Sponsor: Princess Margaret Cancer Centre.

6552

Poster Session

Impact of the COVID-19 pandemic on insurance transitions among commercially insured cancer patients in Washington state. *First Author: Scott David Ramsey, Fred Hutchinson Cancer Center, Seattle, WA*

Background: Insurance transitions following cancer diagnosis can disrupt care and impact outcomes. The COVID-19 pandemic impacted employment for millions of Americans, threatening their ability to maintain insurance. Using a large database linking commercial insurance to cancer registry records, we evaluated insurance transitions among newly diagnosed cancer patients in the pre- and post-COVID periods. **Methods:** We linked Western Washington SEER cancer registry records and enrollment records from two commercial insurers covering 3 million persons and Medicaid in Washington State. Eligible persons were ages 18-63 and commercially insured in the 12 months prior to their first cancer diagnosis. Post-diagnosis follow-up periods were stratified into pre-COVID (January 2017 – February 2020) and post-COVID (March 2020 – December 2020). We created logistic regression models to look at factors associated with (1) disenrollment for any reason and (2) transition to Medicaid, accounting for age, sex, race, year of diagnosis, cancer site, AJCC stage, comorbidities, and Area Deprivation Index (ADI), and diagnosis during the pandemic. **Results:** Among 5,458 newly diagnosed solid tumor patients enrolled in commercial plans pre-COVID, 16.9% disenrolled for any reason over 12 months following diagnosis. Among disenrollees, 10.0% transitioned to Medicaid. Patients with Lung, Oral, and Myeloma cancers had the highest disenrollments (21.2%, 21.0%, and 19.3% respectively). Among the 1,224 diagnosed post-COVID, 9.7% disenrolled for any reason. Among those who disenrolled, 21.0% enrolled in Medicaid. Patients with Leukemia, Melanoma, Oral, and Gynecologic cancers had the highest disenrollments (23.3%, 14.5%, 13.6%, and 13.6% respectively). In logistic regression, persons diagnosed after the pandemic were less likely to disenroll compared to the pre-pandemic period (Table). Transitions to Medicaid was not greater post-Pandemic. Advanced stage, comorbidity, and living in high ADI regions were significantly associated with transitioning to Medicaid. **Conclusions:** Newly diagnosed cancer patients with commercial insurance during the COVID-19 pandemic were substantially less likely to disenroll than those diagnosed before the pandemic. The findings may reflect pandemic-related preferences for job stability during a time of personal and societal crisis. Research Sponsor: Andy Hill Care Fund.

Factors [Only significant associations shown]	Any Disenrollment Estimate (95% CI)	Transition to Medicaid Estimate (95% CI)
AJCC stage (ref = in situ)		
4	1.13 (0.82, 1.56)	3.21 (1.38, 7.46)
Post-COVID period (ref = Pre-COVID)	0.52 (0.42, 0.64)	1.20 (0.75, 1.89)
Comorbidity Score (ref = 0)		
2+	1.10 (0.81, 1.50)	2.30 (1.25, 4.24)
ADI (ref = 1)		
8	1.42 (1.02, 1.96)	4.14 (1.80, 9.55)
9	1.01 (0.65, 1.56)	7.05 (3.03, 16.40)
10	1.26 (0.80, 1.98)	4.57 (1.68, 12.46)

6553

Poster Session

Translated consent documents (CDs) and use in non-industry sponsored studies (NISS). *First Author: Maria A Velez, Department of Medicine, Division of Hematology/Oncology, UCLA, Los Angeles, CA*

Background: Patients (pts) from historically underrepresented groups often have limited English proficiency (LEP). One challenge specific to obtaining consent from these pts to participate in clinical trials is the need for translated CDs. CD translation leads to enrollment delays and increases costs to study sponsors. We hypothesized that NISS, for which the principal investigator pays translation costs, would consent proportionately fewer pts with a primary language other than English and pts with LEP compared to industry sponsored studies (ISS). **Methods:** Pts' primary language and English proficiency were assessed for all 12,082 consent events with appropriate available data at the Jonsson Comprehensive Cancer Center from 2013 to 2018. Pts with LEP were pts (or parent/guardian for pediatric pts) who had a primary language other than English, and the electronic health record indicated that the pt required a translator within 6 months of the consent date. CD language was documented per chart review when available, and when not, languages of available IRB-approved CDs were evaluated. The proportion of consent events for pts with a primary language other than English and with LEP were compared between NISS and ISS using generalized estimating equations, and the odds of signing CDs in the pts primary language were evaluated by multivariable analyses. Discrepant CD language data was evaluated by McNemar's test. All analyses were performed using SAS 9 (SAS Institute, Cary, NC, USA). **Results:** Pts with a primary language other than English represented 8.1% of consent events in ISS vs 4.4% in NISS ($p<0.001$) and 5.5% vs 2.8% ($p<0.001$) for pts with LEP. Pts with a primary language other than English represented 4.5% vs 1.2% of consent events utilizing CDs in the pts' primary language in ISS vs NISS ($p<0.001$) and 3.7% vs 0.9% ($p<0.001$) for pts with LEP. On multivariable analyses, the odds for pts with a primary language other than English of signing CDs to a NISS was 0.74 (CI, 0.63-0.94, $p=0.005$), and of signing CDs in their primary language was 0.38 (CI, 0.27-0.52, $p<0.001$) compared to pts whose primary language was English. The odds for pts with LEP of signing CD to a NISS was 0.74 (CI, 0.58-0.95, $p=0.02$), and signing CDs in their primary language was 0.35 (CI, 0.25-0.50, $p<0.001$) compared to pts whose primary language was English. Of 52 pts who signed CDs for both ≥ 1 NISS and ≥ 1 ISS, 18 signed in discrepant languages, with 16 of those 18 signing translated CDs for the ISS but not the NISS ($p=0.002$). **Conclusions:** Although the role of cost as an effect driver cannot be proven in a retrospective analysis, consistent with our hypothesis, the proportion of consent events utilizing appropriately translated CDs for pts with a primary language other than English and pts LEP was lower in NISS vs ISS, driven by lower odds of signing CDs and lower frequency of signing translated CDs. Approaches that reduce translation costs for investigators should be investigated. Research Sponsor: Jonsson Comprehensive Cancer Center Seed Grant.

6555

Poster Session

Disparities in lung cancer screening in a diverse urban population and the impact of a community-based navigational program. *First Author: Hina Khan, The Warren Alpert Medical School of Brown University, Providence, RI*

Background: Lung cancer (LC) is the leading cause of cancer death in the US in both men and women; causing 25% of all cancer deaths. Annual lung cancer screening (LCS) with a low-dose CT (LDCT) in high-risk individuals (aged 50-80 with a >20 pack-year smoking history) decreases LC deaths by 20% and is recommended by USPSTF. Despite the efficacy, uptake of LDCT remains low at 6% nationally, and 13% in Rhode Island. Patient (pt) and provider perceived barriers, along with racial, ethnic and socioeconomic disparities widen the gap. We evaluated the implementation of a LCS navigation program at an urban community health center (CHC) with a multiethnic, socioeconomically underserved population. **Methods:** A bilingual (English and Spanish speaking) pt navigator was integrated into routine clinic practice at a large primary care CHC group, across 4 sites, starting in January 2022. The navigator's role was to assess pt and provider awareness of the LCS process, assess for systemic barriers, and provide navigational support for the LDCT process. Pts eligible for LCS at the CHC from 1/2022 to 12/2022 were retrospective examined; 50 to 80 years and a >20 pack-year smoking history. The navigator administered a questionnaire to assess barriers to LDCT and demographic variables. **Results:** A total of 360 eligible pts were seen across the CHC practice in 2022, of which 149 (41.4%) agreed to undergo LDCT after counseling and shared decision making and 28% of these (n 101) completed LDCTs. 153 of the eligible pts completed the survey questionnaire. Of these, 50% were females; 40% were Hispanic/Latinx, 40% were non-Hispanic/Latinx and 22% declined to answer. Majority, 61% were white, 10% African American/Black and 28% declined to answer. A sizeable proportion were non-English speaking (34%) and resided in cities with Rhode Island's lowest per-capita incomes (Pawtucket 48%), Central Falls (32%) and North Providence/Providence (10%). In assessing barriers to LCS, 46% of pts were not aware of the LCS process and 44% were unaware that LCS was covered by health insurance; 58% of eligible pts did not recall their PCP discussing LCS. Of the LDCTs resulted available at the time of analysis, 84% were Lung RADS-1 and 16% Lung RADS-4 category. **Conclusions:** Our study highlights the unique barriers to LCS in an urban multiethnic community. While access to LCS remains an issue, pt awareness of the lung cancer screening process was the major barrier. A patient navigation program is critical to the success of LCS in a community, by providing education to patients and providers and the necessary logistical support needed in the LDCT process. With a community based navigational program, we demonstrate a significant increase in lung cancer screening rates in our population to 28% as compared to the state LCS rate of 13%. (Supported by the Robert A. Winn Diversity in Clinical Trials Career Development Award). Research Sponsor: Win CDA Diversity in Clinical Trials Career Development Award.

6554

Poster Session

Examining clinical trial eligibility for oncology patients with human immunodeficiency virus (HIV): A global cross-sectional analysis. *First Author: Umar Abdullahi, The Christie NHS Foundation Trust, Manchester, United Kingdom*

Background: People Living with HIV (PLWH) are at higher risk of developing cancer, and malignancy is the most common cause of death in PLWH in the USA. In 2017 a joint research statement by the American Society of Clinical Oncology and Friends of Cancer Research (ASCO-FCR) examined trial inclusivity, stating PLWH should not be excluded from clinical trials due to HIV positivity alone without justification. It also provided guidance for designing trial inclusion criteria using CD4 count, use of antiretroviral therapy (ART), ART-related drug interactions and HIV-associated complications. To review incorporation of ASCO-FCR recommended wording and current compliance, we examined global eligibility for PLWH in clinical trials. **Methods:** Clinicaltrials.gov was searched on 15 Nov 2022 for open and recruiting trials worldwide, using terms 'advanced cancer' and 'interventional'. Trials lacking systemic treatment were deemed non-evaluable. Evaluable studies' eligibility criteria were manually reviewed for specific criterion excluding PLWH or diagnosis/history of immunodeficiency (outright exclusion). Therapy type and study phase were captured and their relationships to outright exclusion were significance tested using odds ratios (OR) with 95% confidence intervals (CI). **Results:** The search rendered 2388 evaluable clinical trials. Eligibility criteria outrightly excluded PLWH in 1194 (50%) , of which 1113 (93%) were early phase trials (Phase 0-2). 206 evaluable trials (8.6%) permitted inclusion of PLWH aligned with ASCO-FCR guidance, including 3 (0.1%) with a cohort for PLWH. AIDS-defining illness was an exclusion criterion in 27 trials (1%), and specific interactions to ART in 10 (0.4%). Early phase trials had a significantly higher likelihood of outright exclusion of PLWH when compared with late phase trials (OR 2.98; 95% CI 2.16-4.11, $p<0.0001$). Trials investigating immunomodulatory agents were more likely to outrightly exclude PLWH than those investigating other drug classes (OR 1.60; 95% CI 1.36-1.88, $p<0.0001$). Criteria which may implicitly exclude PLWH were identified, including 204 (8.5%) citing active/chronic/severe infection, 189 (7.9%) listing CYP and P-gp interaction criteria and 3 (0.1%) "immunodeficiency". **Conclusions:** Despite adequate time to incorporate, most currently recruiting oncology clinical trials do not use ASCO-FCR guidance for including PLWH. Half of evaluated trials excluded PLWH without reason. Early phase and immunotherapy trials were significantly more likely to exclude PLWH without exception, despite data to support immunotherapy use for PLWH. Covert inclusionary barriers exist in criteria that lack HIV-specific guidance, and this may further exclude PLWH. Consideration of recommendations and guidance in eligibility criteria for oncology trials is critical to address current inequities in care for PLWH and cancer. Research Sponsor: None.

6556

Poster Session

Racial disparity in dose intensity of early-stage breast cancer chemotherapy. *First Author: Margaret Q. Rosenzweig, School of Nursing, University of Pittsburgh, Pittsburgh, PA*

Background: There are persistent, entrenched racial disparities noted in breast cancer outcomes. A basis for these disparities can be racial inequality for stage matched Black vs. White women in receiving early-stage breast cancer (ESBC) chemotherapy dose intensity of, at minimum, 85% or more of chemotherapy (historic gold standard) within prescribed timeframe. Our study measured dose reductions, early terminations, and overall dose intensity of ESBC chemotherapy in urban breast cancer centers and compared by race. **Methods:** Using a longitudinal, comparative descriptive design, treatment characteristics were measured in women receiving ESBC cancer chemotherapy in seven cancer centers in Western PA and Eastern Ohio. Dosing scheduled was calculated per patient chemotherapy prescription. Actual dose was measured as percentage of chemotherapy received / prescribed in "prescribed time," meaning exact, ideal time to complete chemotherapy calculated from dose initiated without delay, dose reduction or early stoppage. The second measurement, "in any time," measured chemotherapy completed over any course of time, incorporating delays and reductions. Results were dichotomized according to 85% of prescribed dose for both outcomes and compared by patient self-reported race (Black or White). **Results:** This study was conducted from August 2017 through June 2022. N=260 patients, race self-reported as 100 Black (38.5%) and 160 White (61.5%). Overall, n=36 (13.8%) had early termination of therapy. Early termination was more common for Black patients, 21%, vs 10% for White patients ($p=.04$). N=100 (38.3%) of all patients had some dose reduction, racially divided by 46.4% of Black patients vs. 34.3% of White patients, NS. By projected endpoint, Black patients received 77% (SD 24.1) of prescribed chemotherapy; White patients 86.7% (SD 16.6), $p=.001$. By "in any time" endpoint, Black patients received 86.5%, (SD 22.8) of prescribed therapy, White patients received 93.5% (SD 13.2), $p=.002$. By "in any time" measurement, 15% of White patients and 25% of Black patients did not receive the gold standard of 85% of prescribed chemotherapy. N= 7 of delays or terminations were due to disease progression, or poor response, and rarely, (n=4) to patient nonadherence. Largely, delays and early cessation were due to chemotherapy toxicity. **Conclusions:** Racial disparities in dose intensity and alterations of prescribed ESBC chemotherapy must be eliminated. Further examining the racial differences around dose delays and early chemotherapy termination, including racial barriers to patient-clinician communication around chemotherapy related toxicity, is essential to ensure equitable ESBC care and outcomes. Research Sponsor: U.S. National Institutes of Health.

6557

Poster Session

A quantitative synthesis of disparities in the inclusion of racial/ethnic minorities and older women in breast cancer trials. *First Author: Mahnoor Islam, Medical University of South Carolina, Charleston, SC*

Background: Trials that inadequately include underrepresented minority (URM) populations widen inequities in cancer care. We assessed reporting patterns, representation, and trends of URM representation in breast cancer (BC) trials. **Methods:** We analyzed all phase 2/3 trials for age disparity and trials recruiting from the US for racial/ethnic disparity amongst BC RCTs (1990-2021). Enrollment-incidence ratios (EIR), which compare trial proportions (TP) from age subgroups against global estimates of incidence in the corresponding age group (from Global Burden of Disease) and racial/ethnic subgroups against US-population-based incidence in the corresponding racial/ethnic group (from SEER 22), were calculated. Individual-trial EIRs were pooled using random-effects meta-analyses. EIRs of <0.80 indicated meaningful underrepresentation, while EIRs >1.20 indicated meaningful overrepresentation. Meta-regression was used to explore associations between key trial characteristics and EIR, and trends in EIR over the last three decades. **Results:** Of 842 global trials with 490,657 participants, 232 (27.6%) reported the number of participants in specific age strata and 144 (17.1%) reported outcomes by age. Only 60 trials recruited exclusively from the US. Of these, 41 (68.3%) reported race and 24 (40.0%) reported ethnicity, and 2 (3.3%) analyzed outcomes by race. Older adults aged ≥65 years (TP: 24.3%; EIR: 0.53 [95% CI: 0.47-0.60]) and Hispanic women (TP: 5.3%; 0.54; 0.40-0.75) were underrepresented across global trials and US-only trials respectively. Black women were significantly underrepresented in trials that led to FDA approval (0.38; 0.25-0.58) but not in US-only trials. Stratified analysis by BC subtype (with subtype-specific population incidence) showed underrepresentation of Black women in US-only trials for HER2+ BC (0.66; 0.47-0.93), Hispanic women in ER+ BC (0.42; 0.20-0.90), Asians in triple-negative BC (0.24; 0.11-0.53), and older women in HER2+ BC (0.35; 0.31-0.40) and triple-negative BC (0.36; 0.29-0.45). From 1990-2021, the representation of older women declined significantly (meta-regression coefficient for EIR: -0.4 per 10 years), while Black and Hispanic representation showed no significant change. Black (p = 0.02) and Hispanic representation (p = 0.05) worsened significantly in larger trials. **Conclusions:** Published reports of BC trials do not consistently report the inclusion of URM. Older and Hispanic women were consistently underrepresented, whereas Black women were underrepresented in large, practice-changing trials. Research Sponsor: None.

Representation of each subgroup given as an EIR with a 95% confidence interval.		
	US-only	Trials that led to FDA approval
White	0.97 (0.95-1.00)	0.85 (0.74-0.96)
Black	1.02 (0.75-1.39)	0.38 (0.25-0.58)
Asian	1.27 (0.63-2.56)	2.59 (1.85-3.63)
Hispanic	0.54 (0.40-0.75)	0.67 (0.42-1.07)

6559

Poster Session

Source of funding and enrollment disparity in cancer clinical trials. *First Author: Irbaz Bin Riaz, Mayo Clinic, Phoenix, AZ*

Background: Recent findings that Black and Hispanic patients were significantly underrepresented in industry-sponsored prostate cancer trials warrant a detailed investigation across cancer types to assess the association between funding source and enrollment disparities. **Methods:** Phase II/III clinical trials in prostate, breast, colorectal, and lung cancers reporting age, gender, race/ethnicity, and reporting NIH or industry as the funding source were considered eligible for inclusion. For age, and gender analysis, all trials were considered eligible. For race/ethnicity analysis, trials recruiting from the United States (US) were considered eligible. Enrollment-incidence ratios (EIR) comparing trial proportion from age/gender or racial/ethnic subgroups against global cancer incidence in the corresponding group (from Global Burden of Disease) or US-population-based incidence in the corresponding racial/ethnic subgroup (from SEER 22), were computed. Trial-level EIRs were pooled using a random-effects model and subsequently stratified by funding source. A univariate meta-regression was conducted to assess the temporal changes in EIR by each funding category. **Results:** Of 42,390 studies initially identified, 2234 trials (1989-2021) met the eligibility criteria. Regarding age, 361 (16%) trials reported age categories by 65 years threshold. Of 698 trials recruiting from the US, 498 (71%) reported race, and 198 (28%) reported ethnicity. Regarding representation, older adults were under-represented (EIR: 0.66; 95% CI: 0.62-0.70) in the industry but not in NIH-sponsored clinical trials (0.79; 0.62-1.00). Regarding gender, no significant disparity was observed regarding the enrollment of men and women in colorectal and lung cancer clinical trials. In terms of race, there was a greater under-representation of Black patients in industry sponsored trials (0.29; 0.26-0.32) as compared to NIH-sponsored clinical trials (0.65; 0.57-0.74) [P_{int} <0.01]. Asian patients were significantly overrepresented in industry sponsored trials (3.17; 2.69-3.74) but not in NIH sponsored clinical trials (1.43; 0.85-2.41) [P_{int} <0.01]. Hispanic patients were significantly under-represented in both, industry (0.27; 0.22-0.34) and NIH-sponsored clinical trials (0.35; 0.22-0.55) [P_{int} 0.32]. Secondary analyses including trials recruiting exclusively from the US, and analyses by specific cancer types showed consistent results. Recruitment of older adults, men, and Black patients is decreasing over time. **Conclusions:** There is a consistent under-representation of older adults in industry-sponsored, and of Black and Hispanic patients in both industry-sponsored and NIH-sponsored clinical trials. The under-representation of Black patients is likely to be greater in industry-sponsored trials, which has worsened over the last three decades. Research Sponsor: None.

6558

Poster Session

Disparities in intensity of care at the end-of-life for patients with gastrointestinal cancer. *First Author: Gladys M. Rodriguez, Division of Oncology, Stanford University School of Medicine, Stanford, CA*

Background: Racial/ethnic minority patients experience disparities along the cancer continuum. Studies show that racial/ethnic minorities with cancer have higher rates of intensity of care at the end-of-life (EOL) compared to non-Hispanic Whites (NHW). Less is known whether disparities in intensity of care at EOL exist among racial/ethnic minority patients with a gastrointestinal (GI) cancer. **Methods:** Using the California Cancer Registry linked to hospital discharge data, we conducted a retrospective study of patients ≥18yrs with upper GI, pancreatic, or colorectal cancer who died from 2005-2018. We evaluated if race/ethnicity was associated with EOL intensity of care defined as hospital/ED visit or death, ICU, intubation, CPR & dialysis within 14-days of death. We used logistic regressions to calculate odds ratios adjusting for age, socioeconomic status (SES), insurance, geography, stage, comorbidities, and NCI-designated centers. **Results:** 189,837 patients with GI cancer died: 41,389 (21.8%) with upper GI, 46,554 (24.5%) with pancreatic & 101,894 (53.7%) with colorectal cancer. 118,995 (62.7%) were NHW, 14,146 (7.5%) Black, 33,802 (17.8%) Hispanic & 22,894 (12.1%) Asian/Pacific Islander (API). Median age was 74.6 yrs, 54.1% male, 85.9% lived in urban areas, 48.9% had Medicare, 16.1% had low SES & 35.7% had Stage 4. Black, Hispanic, and API patients compared to NHW had higher odds of intensity of care at EOL (Table). **Conclusions:** This study shows disparities in intensity of care at the EOL among racial/ethnic minorities with GI cancers. Solutions are urgently needed to reduce such disparities in care. Research Sponsor: National Institute on Minority Health and Health Disparities of the National Institutes of Health under Award Number K23MD013474; Conquer Cancer Foundation of the American Society of Clinical Oncology.

Cancer	Race/ Ethnicity	Hospital Admission	ED visit	Hospital/ ED Death	ICU admission	Intubation	CPR	Dialysis
Upper GI	Black	1.95 (1.56-2.42)	1.59 (1.36-1.86)	1.36 (1.11-1.66)	1.38 (1.21-1.58)	1.48 (1.30-1.69)	1.71 (1.39-2.11)	1.58 (1.22-2.03)
		1.37 (1.22-1.55)	1.30 (1.18-1.43)	0.99 (0.89-1.12)	1.00 (0.91-1.11)	1.02 (0.93-1.12)	1.21 (1.03-1.41)	1.49 (1.24-1.79)
		1.31 (1.15-1.48)	0.74 (0.67-0.83)	1.41 (1.26-1.58)	1.09 (0.98-1.21)	1.13 (1.02-1.24)	1.18 (1.00-1.41)	1.47 (1.24-1.79)
	Hispanic	1.53 (1.28-1.82)	1.66 (1.43-1.93)	1.40 (1.18-1.66)	1.60 (1.38-1.85)	1.61 (1.39-1.85)	2.04 (1.63-2.56)	1.55 (1.2-2.0)
		1.20 (1.07-1.35)	1.10 (0.98-1.23)	0.98 (0.87-1.10)	1.03 (0.90-1.17)	1.03 (0.91-1.16)	0.97 (0.78-1.20)	1.30 (1.06-1.60)
		1.17 (1.03-1.33)	0.82 (0.72-0.94)	1.51 (1.34-1.70)	1.30 (1.14-1.49)	1.35 (1.19-1.54)	1.07 (0.83-1.36)	1.13 (0.89-1.44)
Pancreatic	Black	1.25 (1.11-1.41)	1.47 (1.32-1.62)	1.30 (1.15-1.46)	1.44 (1.33-1.56)	1.47 (1.36-1.59)	1.86 (1.66-2.10)	1.84 (1.63-2.09)
		1.43 (1.30-1.58)	1.14 (1.05-1.23)	1.11 (1.02-1.21)	1.04 (0.97-1.11)	1.09 (1.02-1.16)	1.17 (1.06-1.30)	1.54 (1.38-1.71)
		1.33 (1.21-1.47)	0.74 (0.68-0.82)	1.41 (1.29-1.54)	1.19 (1.10-1.27)	1.19 (1.14-1.31)	1.22 (1.03-1.30)	1.51 (1.34-1.70)
	Hispanic	1.25 (1.11-1.41)	1.47 (1.32-1.62)	1.30 (1.15-1.46)	1.44 (1.33-1.56)	1.47 (1.36-1.59)	1.86 (1.66-2.10)	1.84 (1.63-2.09)
		1.43 (1.30-1.58)	1.14 (1.05-1.23)	1.11 (1.02-1.21)	1.04 (0.97-1.11)	1.09 (1.02-1.16)	1.17 (1.06-1.30)	1.54 (1.38-1.71)
		1.33 (1.21-1.47)	0.74 (0.68-0.82)	1.41 (1.29-1.54)	1.19 (1.10-1.27)	1.19 (1.14-1.31)	1.22 (1.03-1.30)	1.51 (1.34-1.70)

NHW=Reference.

6560

Poster Session

CONSENT: Randomized controlled trial of enhanced informed consent compared to standard informed consent to improve patient understanding of early phase oncology clinical trials. *First Author: Abhijit Pal, The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust, London, United Kingdom*

Background: Early phase oncology clinical trials have become increasingly complicated in terms of patient selection and trial procedures. Informed consent has been contentious due to potential ethical issues associated with performing experimental research on patients with advanced cancer who lack standard treatment options. Prior research has shown significant gaps in patient understanding regarding the nature and intent of these trials. CONSENT aimed to test whether enhanced informed consent can improve clinical trial comprehension. **Methods:** We randomized patients eligible to participate in one of four investigator-initiated early phase oncology clinical trials at the Royal Marsden Drug Development Unit to either a control arm or an experimental arm, stratified by age and educational level. The control arm received the full-length trial PIS, followed by electronic or paper administration of the Quality of Informed Consent Questionnaire Parts A (QuIC-A). The experimental arm received the full-length trial PIS, exposure to a two-page study specific aid and 10 online educational videos (both co-designed with patients and clinicians), followed by administration of the QuIC-A. The primary endpoint was the difference in the QuIC-A score between the control and experimental arm. The accrual target was at least 17 evaluable patients per arm to detect an 8-point difference (80% power, alpha 0.05). **Results:** 23 patients were accrued to the control arm (17 evaluable) and 22 patients (18 evaluable) were accrued to the experimental arm. Patients were evaluable if they had completed the QuIC-A. 38% of the participants were over the age of 65, 91% identified as White, 56% had completed a university degree and 97% spoke English at home. We did not observe a significant improvement in the primary endpoint in evaluable patients – control (QuIC-A - 76.5/100) vs experimental arm (QuIC-A - 77.4/100), p value = 0.39 (one sided, two sample t-test). 20 participants provided feedback on the enhanced consent materials via a study questionnaire –75% found both the 2-page study aid and the videos not at all distressing or uncomfortable and 85% found them either quite useful or very useful. **Conclusions:** This is the first prospective randomized trial evaluating the impact of communication interventions on informed consent in advanced cancer patients considering early phase oncology clinical trials. The co-designed interventions were deliverable online and were acceptable and useful for patients. We did not demonstrate an improvement in the primary endpoint with a high QuIC-A score observed in the control arm- this could be explained by the study population which was highly educated, White and spoke English at home. Future studies should focus on groups with lower literacy and from culturally and linguistically diverse backgrounds. Clinical trial information: NCT04407676. Research Sponsor: Royal Marsden Hospital and Institute for Cancer Research.

6561

Poster Session

The patient experience of prior authorization for cancer care: Anxiety, delays, and the erosion of trust. *First Author: Fumiko Chino, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Prior authorization (PA) requires healthcare providers to obtain pre-approval from insurance for medical care. While PA is intended to promote evidence-based standards and reduce unnecessary care, it requires clinicians and patients to navigate an often-complex approval process. Delays or denied care can be particularly problematic for patients with cancer and their experience with PA remains unexplored. **Methods:** Social media recruitment enrolled adult cancer patients with a self-reported personal experience with PA to an anonymous online survey of investigator-designed questions on their experience. Descriptive statistics and univariate tests characterized survey responses, and multivariable analysis, controlling for age, diagnosis, race/ethnicity, and education, assessed associations with healthcare and insurance trust and delays in care. **Results:** 178 patients completed the survey; they were mostly women (90%), non-Hispanic white (84%), college graduates (81%), young [18-39 (42%), 40-54 years old (34%)] with private insurance (86%). PA was most frequently required for imaging (71%), IV chemotherapy (48%), surgery (47%), radiation (34%). Most care was ultimately given as recommended (58%); however, 20% of respondents didn't receive recommended care due to delays or denials, and 9% received recommended care but paid out-of-pocket. PA delayed 69% of care, with 51% of patients noting a delay ≥ 2 weeks. Delays did not vary by demographic, clinical, insurance, or treatment factors (all $p > .05$). 67% of patients had to personally get involved in the PA process by either calling their insurance (53%) or filing an appeal (25%); 20% of patients and/or their caregivers spent ≥ 11 hours dealing with PA issues. Overall PA experience was rated as "bad" (40%) or "horrible" (32%) for most respondents. Self-reported PA-related anxiety was significantly higher than self-reported baseline anxiety (mean = 74 vs mean = 37, 0-100 scale, $t = 16.6$, $p < .001$) and was significantly correlated with time spent on PA ($\rho = .16$, $p = .04$) and overall PA experience ($\rho = .34$, $p < .001$). While 18% felt PA made them trust their cancer team less, 89% said it made them trust their insurance company less, and 83% said it made them trust the healthcare system less. Patient involvement in the PA process (vs. healthcare team handling) was associated with higher-than-expected trust in their cancer team ($\chi^2 = 19.6$, $p < .001$), and increased odds of distrusting their insurance company ($\beta = 5.7$, 95% CI: 1.8, 17.6) and distrusting the healthcare system ($\beta = 3.2$, 95% CI: 1.3, 7.9). Having to file appeal was associated with 2.9 increased odds (95% CI: 1.2, 7.2) of experiencing a delay in care. **Conclusions:** PA practices may substantially delay care for patients with cancer increasing anxiety and eroding trust in healthcare. Streamlining the PA process could both allow optimal quality of care and improve the patient experience with cancer care. Research Sponsor: Memorial Sloan Kettering Cancer Center; U.S. National Institutes of Health.

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Poster Session

Survival analysis of patients treated at oncology practices with more aggressive end-of-life practice patterns. *First Author: Maureen Canavan, Yale School of Medicine, New Haven, CT*

Background: Despite national focus on measuring and reducing end-of-life (EOL) systemic treatment among cancer patients, recent studies show a consistently high use of systemic anticancer therapy (SACT) at the EOL, as well as a shift to more targeted therapies. A criticism of measures that focus on deceased populations is that they do not account for patients who received treatment at the same time in their disease trajectory and had a positive response to therapy. We sought to explore whether being treated at an oncologically aggressive (OA) practice (defined as higher practice-level EOL SACT treatment rates), was associated with a survival benefit among patients in six common cancer types. **Methods:** This survival analysis used the nationwide Flatiron Health electronic health record (EHR)-derived de-identified database. We included all adult patients with a confirmed diagnosis of metastatic disease in breast (mBC), colorectal (mCRC), renal cell carcinoma (mRCC) or pancreatic cancer (mPanc), or advanced disease in non-small cell lung (aNSCLC), or bladder cancer (aUC), between 2015 and 2019. The primary exposures were the practice-level risk-standardized 30-day EOL SACT rates calculated among decedents. The primary outcome was real-world overall survival (rwOS) among all patients. Adjusted hazard ratios (aHR) for each quintile of increasing OA EOL SACT rates (Q2-Q5) were estimated using disease-specific Cox proportional hazard models (reference: Q1), adjusting for patient and practice-level factors. Bonferroni correction was applied to account for multiple comparisons. **Results:** A total of 78,446 patients from 144 practices were included in the analysis with most patients seen at less OA practices (Q1-Q2). Patients seen at most OA practices (Q5) were less likely to be < 65 (32.5% vs 38.9% in Q1), Black (6.3% vs 12.2%), have Medicare (5.9% vs 10.7%) or Medicaid (1.5% vs 4.1%). After adjusting for covariates, there was no statistically significant difference in rwOS between patients treated at the most (Q5) and the least OA practices (Q1; table). However, there was variation among the moderately OA practices. Patients with mPanc seen at moderately OA (Q2-Q4) had 12% to 19% lower hazards of deaths (aHR range 0.81-0.88), compared to those at the least OA practices (Q1), but these associations were not statistically significant (Bonferroni corrected p -values > 0.05). **Conclusions:** When using rates of SACT at EOL to define OA practices, patients treated at these practices do not have improved survival. Research Sponsor: This study was sponsored by Flatiron Health Inc, which is an independent subsidiary of the Roche group.

aHRs for most OA practice quintile (Q5) compared with least OA practice quintile (Q1) by disease.		
Disease	aHR (95% confidence interval)	p-value
mBC (N = 11,627)	0.93 (0.76 - 1.15)	0.501
mCRC (N = 15,786)	0.89 (0.72 - 1.09)	0.257
mRCC (N = 4,617)	0.97 (0.70 - 1.34)	0.845
mPanc (N = 7,349)	0.86 (0.71 - 1.05)	0.135
aNSCLC (N = 34,163)	0.94 (0.87 - 1.02)	0.119
aUC (N = 4,792)	0.94 (0.69 - 1.28)	0.703

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Poster Session

Use of direct oral anticoagulants (DOACs) in oncology: A phase IV study on impact of edoxaban treatment in Italian patients with cancer with venous thromboembolism during antineoplastic therapy (EDO1 trial, GOIRC 05-2018). *First Author: Filippo Giovanardi, IRCCS AUSL Reggio Emilia, Reggio Emilia, Italy*

Background: The EDO1 Study (EUDRACT 2018-003833-14) was designed to evaluate venous thromboembolism (VTE), a common complication of cancer and cancer therapy. VTE contributes to mortality and morbidity, and may interfere with therapy. When drafting the protocol, the standard treatment for VTE consisted of low-molecular weight heparin followed by vitamin K antagonists. DOACs are as effective as vitamin K antagonists in the treatment of VTE. Edoxaban has been confirmed to be effective and safe in the treatment of VTE. Adverse events (AEs) associated with DOACs can delay or interfere with chemotherapy; to date, data regarding the impact of Edoxaban treatment on cancer treatment AEs are scanty. **Methods:** In this multicentric, phase IV study, patients receiving an antineoplastic treatment (and candidates for at least 3 additional months of treatment) and diagnosed with VTE, received Edoxaban as per clinical practice. Patients received between 6 and 12 months of Edoxaban and were evaluated at baseline and after 1, 3 and 6 months. Primary endpoint was the impact of Edoxaban-related AEs on antineoplastic therapy, defined as delays/interruptions/reductions due to adverse drug reactions (ADR) related to Edoxaban (bleeding, hepatobiliary toxicity, renal toxicity, anemia, hypersensitivity reactions). As secondary endpoint, we assessed patient-reported outcomes (PROs) during treatment with Edoxaban (health-related quality of life: FACT-G, expectations and satisfaction with anticoagulant treatment: PACT-Q2 and ACTS). For each tool, mean scores at each time point were calculated. **Results:** One hundred and fifty patients were enrolled, 147 patients were evaluable. The Incidence density rate of antineoplastic therapy delay/interruption/reduction due to ADR related to Edoxaban was 0.8% per person-month (90% CI: [0.4; 1.5%] and 95% CI: [0.4; 1.6%]). For all the patient-reported outcomes, mean scores were maintained at different time points. **Conclusions:** The results of the study clearly show that the edoxaban treatment is well tolerated and has no relevant impact on the delivery of cancer treatments. Results in terms of quality of life and patients' satisfaction with anticoagulant treatment are reassuring. Clinical trial information: EUDRACT 2018-003833-14. Research Sponsor: GOIRC.

PROs results: Compliance and mean scores at different time-points.				
	Baseline	1 month	3 months	6 months
Expected questionnaires	147	129	103	73
Completed questionnaires (FACT-G)*	138 (93.9%)	109 (84.5%)	90 (87.4%)	59 (80.8%)
FACT-G total score	66.44	69.59	69.06	69.92
PACT-Q2 convenience score	79.44	85.48	85.60	84.70
PACT-Q2 satisfaction score	60.05	64.00	66.95	65.64
ACTS Burdens scale	52.36	54.71	55.15	54.62
ACTS Benefits scale	10.05	9.99	9.82	10.16

*Compliance was slightly different among questionnaires.

ABSTRACT
WITHDRAWN

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Poster Session

The IMPACT of an interdisciplinary goals-of-care program on readmission rates at a comprehensive care center. *First Author: Cerena Leung, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Unplanned readmissions are associated with substantial distress for patients and their families. We hypothesized that goals-of-care (GOC) discussions, by improving goal-concordant care, may reduce unplanned readmissions. However, only a handful of studies have specifically examined this question. We assessed the implementation of a system-wide multicomponent interdisciplinary GOC (myGOC) program on the 30-day unplanned readmission rate and other hospital outcomes for medical patients at our comprehensive cancer center. **Methods:** In this retrospective cohort study, we compared the 30-day unplanned readmission rates in consecutive medical patients during the pre-implementation period from May 1, 2019 to December 31, 2019 and the post-implementation period from May 1, 2020 to December 31, 2020. The primary outcome was the 30-day unplanned readmission rate as defined by Vizient. Secondary outcomes included 7-day unplanned readmission rates, inpatient do-not-resuscitate (DNR) orders and supportive care consults. A multi-variate analysis model was used to examine the association between 30-day unplanned readmission rates and the implementation of the myGOC program adjusting for age, sex, race, index hospitalization type, and Sequential Organ Failure Assessment (SOFA) score. **Results:** This study included 7028 and 5982 unique medical patients during the pre- and post-implementation period, respectively. The 30-day unplanned readmission rates decreased from 13.7% before to 12.0% after implementation of the myGOC program. After adjusting for covariates, the myGOC implementation remained significantly associated with a reduction in 30-day unplanned readmission rates (OR [95% CI] 0.85 [0.77, 0.95], $p=0.003$). Other factors significantly associated with a decreased likelihood of a 30-day unplanned readmission were hematologic malignancies (vs. solid: 0.71 [0.64, 0.79]), White race (vs. Hispanic: 0.86 [0.75, 0.98]), an inpatient DNR order (0.30 [0.25, 0.37]), an ICU admission (0.58 [0.48, 0.71]), and an emergent admission (vs. elective: 0.86 [0.76, 0.99]). We also observed a significant decrease in 7-day unplanned readmission rates (0.75 [0.64, 0.89], $p=0.0009$), an increase in inpatient DNR orders (1.48 [1.35, 1.63], $p<0.0001$) and an increase in supportive care consults (1.22 [1.13, 1.31], $p<0.0001$) post-implementation. **Conclusions:** Implementation of a system-wide multicomponent GOC intervention was associated with a significant reduction in 30-day unplanned readmission rates after accounting for other key clinical factors. Research Sponsor: U.S. National Institutes of Health.

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Poster Session

Reducing infusion center wait times in a resource-limited setting. *First Author: Amy Little Jones, University of Texas Southwestern Medical Center, Dallas, TX*

Background: Time toxicity is increasingly recognized as an important factor in quality of life in cancer patients, and this effect may be amplified in under-resourced oncology settings. In the safety-net oncology center at Parkland Health (PH), wait time from infusion appointment check-in to treatment start was 147 minutes in June 2022, which led to significant patient frustration, delays in care, and staff dissatisfaction. We aimed to decrease wait time by 20% by December 2022. **Methods:** Baseline wait time data for patients getting infusions in the oncology infusion center was collected daily from the electronic medical record (EMR) time stamps of check in and infusion start (first IV medication given), and the average time was calculated. A value stream map detailing the steps required to start infusion with time stamps was produced. Stakeholders were queried to identify causes of delay, an Ishikawa diagram was constructed, and a priority matrix was developed to determine the most impactful interventions. The first PDSA cycle (July-Oct 2023) intervention consisted of working group formation and implementation of separate infusion pathway for patients getting injections ("fast track"). The second PDSA cycle (Nov-Dec 2023) intervention was rescheduling infusion-only patients to the least congested times of the day to relieve the bottleneck that occurred in the late mornings for patients with labs or provider visit prior to infusion. Patients and infusion center providers were surveyed about their perception of wait times. **Results:** Average wait times decreased from 147 minutes to 131 minutes during first PDSA cycle, a 10.8% improvement from baseline. From Nov-Dec 2023 during second PDSA cycle, wait time improved to 127 minutes, a 15.7% improvement from baseline. The average daily number of infusions and injections increased from 106/day baseline to 115/day by Dec 2023; an increase of 8.5%. Qualitative surveys of patients and infusion providers endorsed increased satisfaction with infusion process. **Conclusions:** Using established quality improvement methods, we improved average wait times for Parkland Health oncology infusion patients by 15.7% over a 6 month period. While we did not meet our goal, we increased daily capacity to treat patients by 8.5% while improving overall infusion wait time. We also improved perceptions of quality of care. Research Sponsor: Niarchos Foundation.

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Poster Session

Trends of using immune checkpoint inhibitors near end of life in limited resources setting: Experience of single cancer center in the MENA region. *First Author: Kamal Hosni Al-Rabi, Department of Internal Medicine, King Hussein Cancer Center, Amman, Jordan*

Background: Immune checkpoint inhibitors (ICIs) are standard of care nowadays in the treatment of many solid tumors as single agent or in combination. Recent literature suggested increased use of ICI near end of life; our aim was to find the characteristics of the patients who received ICI 30 days or less before their death. **Methods:** Data of patients with advanced solid tumors who have (ICI) therapy and died with disease were retrospectively retrieved. Patients were categorized into those dying within 30 days of the last dose of ICI and those receiving the last dose of ICI more than 30 days before death. Variables of potential interest were compared between the two groups by the Chi-square and independent sample t -tests as appropriate. **Results:** A total of 411 patients were included in this analysis; 135 (33%) received the last dose of ICI within 30 days of death and 276 (67%) received their last dose more than 30 days before death. Major cancer types included: lung ($n=214$; 52%), kidney ($n=61$; 15%), melanoma ($n=44$; 11%), head and neck ($n=41$; 10%), and others ($n=154$; 37%). Patients' characteristics: median age = 58, majority were males (310; 75%), 105 (26%) had ECOG PS ≥ 3 , and 147 (36%) had brain metastasis. Patients who received the last dose of ICI within 30 days of death had more frequent ICU admissions (50 (37%) vs. 60 (22%), $p=0.001$), and were less likely to die under the care of the hospice care service (22 patients (16%) vs. 84 (31%), $p=0.001$). In addition, patients who received the last dose of ICI within 30 days of death were more likely to have a full code status (89 (66%) vs. 147 (53%), $p=0.015$), and have received a lower number of doses of ICI treatments (mean number of doses: 4.2 vs. 6.5 doses, $p=0.001$). We did not observe any significant difference between the two groups regarding type of cancer, age, gender, ECOG PS, presence of brain metastasis, number of hospital admissions, dying inside hospital, and number of emergency room visits. **Conclusions:** Immune checkpoint inhibitors may be overused near end of life which leads to minimal clinical benefits, less likelihood of dying under hospice care, and utilization of ICU resources. Research Sponsor: None.

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Poster Session

The effects of social determinants of health on colorectal cancer screening. *First Author: Isabelle Franklin, Kaiser Permanente Bernard J. Tyson School of Medicine, Pasadena, CA*

Background: Colorectal cancer is the 3rd leading cause of cancer death in the United States yet has consistently lagged in screening rates compared to other cancers. While patient-reported barriers have been previously described, few studies have analyzed how patients' social needs affect screening rates. **Methods:** This cross-sectional study includes 3974 Kaiser Permanente (KP) patients ages 50-75 years who completed the 2020 KP National Social Needs Survey. Survey respondents were from the seven KP regions of Southern California, Northern California, Colorado, Washington, Northwest, Georgia, and Hawaii. Five Social Needs categories were assessed: Financial Strain, Housing Instability, Transportation Issues, Social Isolation, and Food Insecurity. Being up to date on CRC screening was determined from patients' KP electronic health records, defined as meeting HEDIS criteria for screening. Multivariate analyses compared the level of social need to the respondents' completion of colorectal screening between the years of 2019-2021, adjusting for age, sex, race/ethnicity, diagnostic category group (DxCG), neighborhood deprivation index (NDI), and insurance type. **Results:** Among the 3974 survey respondents, 92.2% were up to date on their colorectal cancer screening. Not being up to date on CRC screening was significantly associated with having any social need and having severe needs in four of the five social need domains adjusted for sociodemographic and health status (Table). Patients were less likely to be screened if they had severe financial strain (OR 0.54, 95% CI 0.40-0.73), severe social isolation (OR 0.52, 95%CI 0.38-0.71), severe transportation issues (OR 0.33, 95% CI 0.18-0.61), and severe food insecurity (OR 0.41, 95% CI 0.27-0.62). No significant association between screening status and the domain of severe housing instability were found (OR 0.74, 95% CI 0.52-1.06). **Conclusions:** Respondents with financial strain, social isolation, food insecurity, and transportation issues had lower odds of being up to date with colorectal cancer screening. Future efforts aimed to improve colorectal cancer screening rates should assess patients' social needs and target ways to address these potential barriers to screening. Research Sponsor: Kaiser Permanente Bernard J. Tyson School of Medicine.

Odds of colorectal cancer screening by social needs.

Parameter	Adjusted Odds Ratio ¹	95% CI
Severe Financial Strain (Yes vs No)	0.54	0.40 0.73
Severe Social Isolation (Yes vs No)	0.52	0.38 0.71
Severe Food Insecurity (Yes vs No)	0.41	0.27 0.62
Severe Housing Instability (Yes vs No)	0.74	0.52 1.06
Severe Transportation Issue (Yes vs No)	0.33	0.18 0.61
Any Severe Social Need (Yes vs No)	0.54	0.42 0.70

¹ Receipt of colon cancer screening adjusted for age, neighborhood deprivation index, sex, DxCG risk score, race/ethnicity, primary spoken language, insurance type.

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Poster Session

Profile of toxicities and quality of life in long-term survivors treated with immunotherapy: A prospective cross sectional trial. *First Author: Paolo Bossi, Medical Oncology Unit, Department of Medical & Surgical Specialties, Radiological Sciences & Public Health, University of Brescia, ASST Spedali Civili, Brescia, Italy*

Background: Long-term cancer survivors (LTS) patients (pts) treated with immunotherapy (IT) represent a relatively new population whose characteristics, such as long-term toxicities, quality of life (QoL), and financial toxicities, need to be elucidated in a real-world setting. The aim of this study is to evaluate long-term toxicities in patients free of disease progression and treated with IT. **Methods:** This is a cross-sectional, multicentric study, involving ten Italian centres. Pts should have started IT (as monotherapy or combination, either in curative or adjuvant setting) more than 2 years before accrual and they needed to be progression free at last follow up (fup). Subjects who discontinued IT for disease progression or who started any subsequent line of systemic treatment were excluded. We retrieved baseline demographic and clinical characteristics of the pts, as well as haematological and biochemical exams at the start of IT (baseline) and at the last fup. We also assessed the patient's toxicities (according to CTCAE v5.0) at last fup and we submitted to each patient three questionnaires: PRO-CTCAE (selection of questions), EORTC QLQ C30, and FITALY (for financial toxicities), which were analysed according to subdomains. **Results:** We enrolled 141 LTS pts treated with IT from 2013 to 2022. Median age was 69 years (35-88), most were male (72%), and still receiving IT at time of last fup (72%). Primary tumour was in lung (43%), genito-urinary tract (26%), or melanoma (14%). IT included pembrolizumab and nivolumab in 40% and 32% of cases, respectively. The median global health status of QoL was 83 (IQR 25). Any toxicities > G2 negatively impacted on individual functional scales (physical, p=0.02; role, p= 0.06; and social p=0.08). A higher baseline Charlson Comorbidity Index was associated with worse global health status (p=0.02) at last fup. Most frequent low grade adverse events were fatigue, dyspnoea, and insomnia; younger age (< 65 years) was associated with higher pain (p=0.04). PRO-CTCAE questionnaires showed that the prevalent complained symptoms were rheumatological and cutaneous, regardless of tumor site. The most affected domain of financial toxicities was financial stress, including costs for out of pocket medications and transports. Pts with melanoma (p=0.01), with skin toxicities (p=0.04), and younger than 65 years (p=0.01) were at higher risk of financial toxicities (global score). **Conclusions:** Overall QoL is well preserved in LTS treated with IT. At long term fup, the pts complained mostly about rheumatological and skin adverse events. Financial stress due to out of pocket costs was the most affected financial toxicity domain. Baseline comorbidities predicted a worse long-term global health status, while young age, skin toxicities and melanoma predicted higher financial toxicities. Research Sponsor: ASCAPE Grant.

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Poster Session

Just ASK: A quality improvement project to enhance smoking assessment and treatment. *First Author: Graham W. Warren, Medical University of South Carolina, Charleston, SC*

Background: Persistent smoking after cancer diagnosis causes adverse clinical outcomes. ASCO and other organizations view smoking assessment and treatment as indicators of high-quality cancer care. Yet, adoption of clinical practice guidelines like the 3As (Ask, Advise and Assist) for smoking assessment and treatment has been slow and inconsistent in cancer care settings. **Methods:** Led by the American College of Surgeons Cancer Programs' Commission on Cancer (CoC) and National Accreditation Program for Breast Centers (NAPBC), the "Just ASK" national quality improvement project focuses on enhancing smoking assessment and treatment in cancer care settings. All CoC/NAPBC programs (~2000) were invited to participate, which consisted of educational webinars, online resources, and 3 online surveys (baseline, 6- and 12-month) collecting information on smoking assessment and treatment practices, plus other variables (e.g., organizational priority, implementation barriers). Program participation was incentivized by fulfillment of accreditation standards. **Results:** In total, 776 programs (731 CoC, 45 NAPBC), participated. At baseline, most programs strongly endorsed the importance of addressing smoking within cancer care and the majority of programs reported routinely assessing smoking (90%) and advising all patients reporting current smoking to quit (71%). However, routine delivery of evidence-based smoking cessation assistance (e.g., quitline referral, cessation medications, counseling services) was low (all < 30%). Program retention was excellent (91%). As shown in the table, the 12-month follow-up revealed marked improvements in evidence-based Ask, Advise and Assist, practices. **Conclusions:** At enrollment, the importance of addressing smoking was evident and high rates of smoking assessment were reported. At 12-month follow-up, marked improvement was reported in all quality indicators of the 3As. These findings guided the sharing of strategies for improving patient assessment, clinical workflow and documentation. Suboptimal delivery of smoking cessation assistance persisted despite overall improvements, which highlight persistent challenges and opportunities for implementing smoking assessment and treatment in cancer care settings. Research Sponsor: U.S. National Institutes of Health.

Assessment and Treatment Practices	Baseline (n=776) Always or Usually	12-month follow up (n=703) Always or Usually
Ask patients about smoking	696 (90%)	690 (98%)
Advise patients to quit smoking	553 (71%)	588 (84%)
Assist patients in quitting	323 (42%)	424 (60%)
Provide self-help information	209 (27%)	395 (56%)
Refer patients to Quitline	219 (28%)	367 (52%)
Refer patients to tobacco treatment specialist in cancer program	204 (26%)	289 (41%)
Provide individual counseling in person	141 (18%)	190 (27%)
Prescribe FDA approved cessation medications	136 (18%)	179 (25%)

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Poster Session

Multimodal interventions targeting identified barriers to improve lung cancer screening in northeast Georgia. *First Author: Swathi Kanakamedala, Northeast Georgia Medical Center, Gainesville, GA*

Background: Lung cancer is the leading cause of cancer deaths with over 50% of patients diagnosed at an advanced stage. Lung cancer screening (LCS) guidelines were recently updated in 2021, which expanded the age group and reduced the pack years, and thereby increased eligibility. However, the underutilization of low dose computed tomography (LDCT) scans is seen nationwide. In 2015, the National Health Interview Survey found that only 3.9% of eligible adults underwent LCS. The barriers for LCS identified in national literature included failure of electronic medical records (EMR) to notify providers of eligible patients, lack of insurance coverage, patient refusal, and lack of patient and provider awareness. This quality improvement project was performed to improve LCS in primary care clinics (graduate medical education [GME] and non-GME) at a tertiary medical center in northeast Georgia by addressing these barriers. **Methods:** In GME clinics, the goal was to double LDCT scans from 14 to 28 monthly. In non-GME clinics, the goal was to increase LDCT scans by at least 50% from 28 to 42 weekly. LDCT scans performed between January 1st to May 31st 2022 was used as baseline data. The interventions spanned over six months, from June 1st to November 30th 2022. Multimodal interventions were used to target various barriers. Accurate tobacco history in the EMR was improved by participating in the nationwide Just Ask Campaign. Flyers posted in clinics provided information on current guidelines and a QR code for patients to determine their LCS eligibility. Provider reference guides highlighted LCS guidelines and billing codes. Community events and social media were used to spread LCS awareness. **Results:** During the implementation phase, the average monthly LDCT scans increased to 23 scans in GME clinics and 40 scans weekly in non-GME clinics. In GME clinics, the goal of 28 scans monthly was achieved in one out of six months. In non-GME clinics, the goal of 42 scans weekly was surpassed in four out of six months. The Long-Range Acoustic Device (L-RAD) scoring system helped diagnose three cancers in the GME clinics and about one cancer for every 10 L-RAD4 in non-GME clinics. The baseline period LDCT scans of 78 (GME) and 656 (non-GME) increased to 177 (GME) and 1109 (non-GME) during the intervention period. **Conclusions:** This multimodal approach in addressing known barriers to increase LCS across primary care clinics in a single healthcare system is feasible and was associated with short-term improvements. Although the targets were not met every month, there was a notable improvement during the intervention period. A major limitation was the inability to determine which intervention had the greatest impact. A newly identified barrier was the lack of follow up scans being ordered by providers. This project demonstrates the potential to increase LCS using a multimodal approach, which can be implemented in similar healthcare systems. Research Sponsor: None.

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Poster Session

Use of germline testing in patients with prostate, pancreatic, or ovarian cancer in Washington (WA) state. *First Author: Qin Sun, Fred Hutchinson Cancer Center, Seattle, WA*

Background: Germline genetic mutations are seen in approximately 10-15% of patients with prostate, pancreatic, and ovarian cancer. While universal germline testing is recommended for patients with these cancers to inform both familial risk and therapeutic approach, underutilization of germline testing has been reported. We investigated the rates of and factors associated with germline testing in a population-based sample of patients with prostate, pancreatic, and ovarian cancer in WA state. **Methods:** We linked Washington state cancer registry records from 2017-2019 with claims records for two large commercial insurers, Medicare, and Medicaid. Patients with prostate (metastatic, regional node-positive, or high-risk localized), pancreatic, and ovarian (including fallopian tube and peritoneum) cancer who were diagnosed in 2017-2019 were identified. Using claims from this database, we identified patients who received germline testing in the first two years of diagnosis. We excluded those who were not continuously enrolled in a health plan during the testing period of interest or died within 3 months of diagnosis. We used a multivariate logistic regression model to investigate factors associated with germline testing. **Results:** Among 2,077 patients, 429 (20.7%) received germline testing. Testing rates were 6.3% (53 of 842 patients) in prostate cancer, 15.4% (118 of 765 patients) in pancreas cancer, and to 54.9% (258 of 470 patients) in ovarian cancer; median time to testing for prostate, pancreas, and ovarian cancer was 162, 133, and 64 days respectively. Testing rates were higher in later years, in patients with more advanced stage cancers and lower in Asian patients and patients with more comorbid conditions. **Conclusions:** Despite guideline recommendations, germline testing rates are low among cancer patients in WA state, with the lowest rates in prostate cancer patients and in Asian and higher comorbidity populations. Underutilization of germline testing may not only adversely affect treatment, but also represents a missed opportunity for testing of high-risk families. Further studies should identify and address barriers to germline testing in high-risk populations. Research Sponsor: Fred Hutchinson Cancer Center.

Factor [Only significant factors shown]	Odds Ratio	95% CI Lower	95% CI Upper	p-value
Asian (ref = White)	0.50	0.28	0.90	0.02
Dx year 2019 (ref = 2017)	1.77	1.29	2.44	0.00
Pancreas (ref = Ovary)	0.15	0.11	0.20	<.0001
Prostate (ref = Ovary)	0.04	0.02	0.05	<.0001
AJCC Stage 2 (ref = 0 and 1)	2.53	1.36	4.71	0.00
AJCC Stage 3 (ref = 0 and 1)	2.63	1.61	4.30	0.00
AJCC Stage 4 (ref = 0 and 1)	3.35	2.04	5.52	<.0001
Comorbidity Score 2+ (ref = 0)	0.56	0.40	0.78	0.00

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Poster Session

Reporting of patient reported outcomes in randomized clinical trials (RCTs) in non-small cell lung cancer (NSCLC) patients (pts). *First Author: Laura Palmeri, Syneos Health, Farnborough, United Kingdom*

Background: A patient-centric approach to clinical trials has become necessary, with regulators emphasizing the importance of pts' experience. PRO is of utmost relevance for pts with cancers such as NSCLC, that are likely to be highly symptomatic and/or with an unfavorable prognosis. **Methods:** To evaluate the rate at which PRO included in clinical trials are made publicly available when trial results are published, we searched Citeline Trialtrove, a registry of clinical trials, for NSCLC phase 3 RCTs, recruiting during 2017-2022, with PRO listed - regardless of publication type. We excluded supportive care, radiotherapy, and unpublished trials. We identified publications associated with the trial, and extracted various parameters, including if PRO outcome was published. **Results:** Of 122 NSCLC RCTs identified, 66 listed at least 1 PRO. Trials were reported as full-text (43), abstract (9), 1 only in a trials registry; 13 not published. Fifty-three trials were included, all had PRO as a secondary endpoint. The sponsor was industry in the majority of the trials. Most enrolled stage III/IV NSCLC pts, and 1st/2nd line or maintenance. 24 PRO tools were used, mainly EORTC QLQ LC13 (35 trials), EORTC QLQ C30 (34), EQ-5D-5L (14), LCSS (8), EQ-5D-3L (6). Seven trials listed 1 tool, 26 listed 2, 18 listed >3. PRO was reported in 36 (68%) of the published trials. In the subgroup of trials with disease control (DC) benefit and no overall survival (OS) benefit, PRO was reported in 15/21 (71%) trials. PRO benefit was shown in 9 of them. Of 43/53 trials published as full-text, 31 (72%) had PRO reported. A benefit in at least 1 PRO tool was reported in 21 studies, 9 did not show a PRO benefit; in 5 trials, only descriptive and no comparative analysis of PRO was reported. Of the 21 trials with PRO benefit, 19 had a DC benefit and 10 had also OS benefit. PRO was reported together with the first reporting of other outcomes in 18 (50%) trials, and after 7-32 months after the initial one in 18 trials. **Conclusions:** Of 122 RCTs only 66 had at least 1 planned PRO, and only 35 had it published. Even where full-text was available or no OS benefit shown, about 1/3 of the trials did not report PRO. Characteristics as disease stage, therapy line, sponsor, and primary endpoint did not differ between all included trials and those reporting PRO. The reporting rate increased compared to our previous report yet it is not satisfactory. The importance of quality of life and pts centric outcomes, and the great efforts needed from pts and operators to collect the data, should translate into routine, timely and appropriate reporting of PRO to allow a thorough assessment of treatment effect. Research Sponsor: None.

	All N (%)	PRO reported N (%)
Stage III/IV	53	36
1 st /2 nd line or maintenance	47 (89)	32 (89)
Sponsor	37 (70)	26 (72)
Industry	45 (85)	30 (84)
Industry-academic	3 (6)	3 (8)
Academic	5 (9)	3 (8)
Primary endpoint	28 (53)	19 (53)
OS	12 (23)	7 (19)
DC - OS	36 (68)	24 (67)
DC		

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Poster Session

Machine learning and postoperative complications: Determining risk before surgery in patients with cancer. *First Author: Matthew C Hernandez, City of Hope National Medical Center, Duarte, CA*

Background: In patients with advanced cancer who need unplanned surgery, shared decision making is complex. Surgical risk assessment with high accuracy and in real time may help improve prediction of postoperative outcomes. We previously trained and tested an explainable machine learning model (MLM) to estimate postoperative Clavien-Dindo grade 3 or higher (CD 3+) complication risk in cancer inpatients undergoing unplanned surgery. In this prospective validation study, we report the performance of the MLM Surgical Risk Score (SRS) in the prediction of postoperative outcomes as well as determine association of the risk score with hospital length of stay and mortality. **Methods:** A MLM SRS for cancer inpatients requiring an unplanned, same-hospitalization major surgery was generated using real-time patient specific EHR data. The SRS was integrated into surgeon preoperative workflow. Postoperative outcomes including complications, length of hospital stay, and 30-day mortality were reported. The SRS was dichotomized as high or low based on prior validation threshold for postoperative CD3+ complication development. Model performance was assessed with area under receiver operating characteristic (AUROC) and area under precision-recall curves (AUPRC). Differences in outcomes between high and low-risk SRS groups were studied using Mann-Whitney U test and Fisher's exact test. **Results:** During the study period, 135 cancer inpatients were assessed by surgeons for 166 major unplanned operations. Of the 166 operations, 126 were completed and 40 were cancelled. The SRS was high in 81 (49%) and low in 85 (51%). The most common cancer diagnosis was colorectal (n=39, 28.8%). Operations performed with the highest frequencies were for enteral access (e.g.gastrostomy) followed by exploratory laparotomy and enterectomy. CD 3+ complications were identified in 31% of the completed operations (n=39/126) and included death (n = 10); abscess (n=4); postoperative hemorrhage (n=3); and anastomotic leak (n=2). The SRS predicted CD 3+ complications with a precision of 47% and recall of 73%, resulting in an AUROC of 0.75 and AUPRC of 0.58. When comparing patients with high-risk to low-risk SRS, median overall LOS was 10 vs 7 days (p=0.013), median LOS after operation was 9 vs 6 days (p=0.003), 30-day mortality was 19.0% vs 5.3% (p=0.015), and 30-day postoperative mortality was 13.2% vs 3.3% (p=0.04). **Conclusions:** In this prospective study, preoperative SRS generated from a trained MLM on real-time EHR data demonstrated an excellent ability to predict individual risk of postoperative complications. In addition, patients with high SRS have longer postoperative LOS and increased mortality. By improving discrimination of risk of postoperative complications and informing on treatment outcomes, integration of the MLM SRS into the consenting process may enable better informed decision making in cancer inpatients. Research Sponsor: None.

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Poster Session

Incidence of infusion related reactions of daratumumab-hyaluronidase-fihj: Pre-post intervention study of premedication omission. *First Author: Kashyap Padmaraju, University of Chicago Medical Center, Chicago, IL*

Background: Daratumumab-hyaluronidase-fihj subcutaneous (Dara-SQ) is utilized frequently in the treatment of newly diagnosed and relapsed/refractory multiple myeloma (MM). Initially approved as an intravenous formulation, daratumumab (Dara-IV) showed significant infusion related reactions (IRRs), requiring premedication (acetaminophen, diphenhydramine, dexamethasone, and some add montelukast) prior to each dose. Dara-SQ was shown to be noninferior to Dara-IV with significantly fewer IRRs. Despite the reduced IRR risk, indefinite premedication is also recommended in the package insert for Dara-SQ. Given that IRRs are rare after the first dose of Dara-SQ and premedication extends the time for patients in an infusion center, we investigated whether premedication may be safely omitted after the first cycle. **Methods:** This pre-post interventional quality improvement study included all patients aged 18 years or older diagnosed with MM or amyloidosis that received at least one dose of Dara-SQ between July 1st, 2020 – December 31st, 2022. Omission of premedication (excluding dexamethasone) after four doses of Dara-SQ was introduced June 1st, 2022. The pre-interventional arm followed standard of care with premedication continued (Arm 1) and post-interventional arm included patients with premedication omitted after fourth dose (Arm 2). Patient demographics, prior therapy, Dara-IV exposure, and premedication usage were collected to evaluate the primary endpoint: incidence of IRR after premedication omission. Secondary analysis included any IRR prior to intervention, timing of reaction, reaction management, and post-reaction management. **Results:** A total of 102 patients (63 in Arm 1 and 39 in Arm 2) were included in the study, with a median age of 69 (38-86) years old; 52% African American and 54% male. IRR prior to fourth dose occurred in 1.6% (1/63) for Arm 1 vs. 5.1% (2/39) for Arm 2 [p= 0.6], Dara-IV exposure was 52.4% (33/63) in Arm 1 vs. 10.2% (4/39) in Arm 2 [p= 0.02], and indication was newly diagnosed MM in 21% (13/63) of Arm 1 vs. 41% (16/39) of Arm 2 [p= 0.03]. For the primary objective, there were zero reactions in both arms. All three reactions prior to fourth dose occurred after the first dose of Dara-SQ, with a median time to reaction of 4.8 hours. These were all grade 2 per CTCAE v5.0, with all patients discharged home after reaction, and all patients received subsequent Dara-SQ without issues. For the two reactions prior to fourth dose in Arm 2, premedication was omitted after 6 doses in one patient and 8 doses in the other with no further issues on subsequent doses. Estimated therapy time saved was 194 hours, with an estimated savings of \$145,500 thus far. **Conclusions:** IRRs to Dara-SQ occur early, are rare, and mild in course. Omitting premedication after a minimum of four Dara-SQ doses is safe and carries substantial time savings for patients and infusion centers. Research Sponsor: None.

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Poster Session

Data driven insights from multiple OCM practices to optimize care for managing high-risk cancer patients across multiple cancer types. *First Author: Srisairam Achuthan, Integra Connect, West Palm Beach, FL*

Background: Medicare's Oncology Care Model (OCM) aims to improve the quality and coordination of care for cancer patients. Previously, Integra Connect (IC) developed machine learning (ML) based risk prediction models called Integra Predict (IP) for In-Patient Admissions, Emergency Department Visits and End-of-Life in active chemotherapy patients within the next six months. The patients were risk-stratified with the purpose of optimizing clinical resources utilization. Our objective is to demonstrate the insights derived from an updated IP version applied to OCM patients from three IC network practices: P₁ (a multi-state network of community oncology practices), P₂ (a single site community oncology practice) and P₃ (a regional network of oncology practices connected to academic medical institution). **Methods:** For training the ML models, 90,417 OCM reconciliation episodes from PP4-PP8 (Jan. 2018-June 2020) from 10 distinct IC practices were used. The models comprise 37 features: 12 adverse events (within last 6 month of episode start date), 7 comorbidities (in the past irrespective of lookback period), 7 latest vital sign measurements recorded within 30 days of date of prediction, 11 demographic and other clinical attributes. Based on LogLoss, 54 ML experiments were performed leading to three best algorithms to predict the risk for In-Patient Admissions, Emergency Department Visits and End of Life. To generalize our ML approach, we leveraged an additional holdout dataset in periods PP9 and PP10 (July 2020 - June 2021) pertaining to practices P₁, P₂ and P₃ with 6378, 973 and 5921 episodes, respectively. Matthew Correlation Coefficient (MCC) was chosen as the metric to test the generalizability of the models. For each model, the variance of MCC was then computed. To uncover secondary factors influencing clinical care, top-3 frequently reported adverse events and top-5 comorbidities were determined. **Results:** For each ML model, the variance of MCC applied to the holdout dataset was low (order of 10⁻⁴). Types of cancers reported differed within P₁, P₂ and P₃. However, across these practices, irrespective of the cancer type, the most frequently reported adverse events (pain, anemia, and cachexia) and comorbidities (cardiovascular disease, chronic pulmonary disease, dyspnea at rest, dorsopathies and renal disease or failure) observed were the same. **Conclusions:** Low variance in MCC implies ML models are applicable to different types of community oncology practices. A care coordination program for high-risk cancer patients involving the monitoring of pain, cachexia and anemia can lead to optimal utilization of clinical resources within these practices. Program expansion involving optimal management of comorbidities such as cardiovascular disease, chronic pulmonary disease, diabetes, dyspnea at rest and renal disease or failure may yield additional benefits. Research Sponsor: Employer (Integra Connect) sponsored.

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Poster Session

Palliative care consultation and end-of-life outcomes in a retrospective cohort of patients treated with immune checkpoint inhibitors. *First Author: Chance H. Bloomer, Wake Forest Baptist Medical Center, Winston-Salem, NC*

Background: Immune checkpoint inhibitors (ICI) can prolong survival for various cancers and are generally available as treatment options for most patients because of their favorable adverse effect profile. Although ICIs provide treatment for many patients who would otherwise be out of options, their variable and often delayed efficacy may postpone the de-escalation of care at the end of life. Palliative Care consultation (PCC) is well-established among patients receiving cytotoxic chemotherapy, but its effectiveness is less certain among patients receiving newer treatment modalities. We aimed to test the association of PCC with end-of-life (EOL) outcomes among patients treated with an ICI for any type of cancer. **Methods:** We created a retrospective registry of all patients who received at least one dose of ICI for any indication between 2/1/2011 and 4/7/2022 at a comprehensive cancer center and its outreach clinics. The investigators created a secure, cloud-based registry (REDCap), validated it with data quality rules, and resolved all discrepancies; clinical research specialists at Vasta Global captured most of the data. We used the chi-square test to compare categorical variables, defined statistical significance as $p < 0.05$, and used SAS version 9.4 for analyses. The study had institutional IRB approval. **Results:** The cohort consisted of 3,142 patients with lung cancer (45%) as the most common cancer type, followed by melanoma (14%) and head and neck squamous cell carcinoma (9%). ICI was most often given in the first line setting (46%) with good baseline performance status (ECOG 0-1, 50%). 915 (29%) patients had PCC, which was associated with a higher rate of code status de-escalation from "Full Code" at any point before death (92% vs. 87%, $p = 0.007$). There was no association between PCC and either the initiation of ICI within 30 days of death (7% vs. 5%, $p = .0172$) or any dose of ICI within 14 days of death (5% vs. 6%, $p = 0.33$). Among patients with a confirmed location of death (1013, 32%), PCC was associated with a similar rate of death in the hospital at any level of care (30% vs. 28%, $p = 0.51$). **Conclusions:** PCC was associated with code status de-escalation before death but similar risks of late ICI dosing or inpatient status at the time of death. Further studies are needed to risk-stratify patients starting ICI to identify the subgroups that would benefit the most from PCC. Research Sponsor: U.S. National Institutes of Health.

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Poster Session

Use of statistical process control charts to identify impactful implementation strategies for an ePRO-based symptom management program across the SIMPRO Consortium. *First Author: Jim W Doolin, Dana-Farber Cancer Institute, Boston, MA*

Background: Collecting electronic patient reported outcomes (ePROs) reduces the burden of cancer and prevents acute care hospitalizations. However, broad implementation in the routine care setting remains challenging, partly because the optimal implementation strategies – actions that are most likely to encourage adoption and use – are not known. Since 2019, the SIMPRO Consortium has deployed an ePRO-based symptom management program (eSyM) across 6 community-based cancer centers. **Methods:** We used statistical process control (SPC) charts to identify variation due to special versus common causes (random variation) for one key performance indicator (KPI) – the weekly ePROs response rate. All 6 SIMPRO sites contributed data for this analysis: 3 for chemotherapy patients and 3 for surgery patients. Sites had to have at least 18 months of KPI data; information from the first 4 months after eSyM rollout were excluded to account for program ramp-up. The KPI was calculated as the number of patients who submitted an ePRO questionnaire divided by the number eligible to submit a questionnaire each week. The upper and lower confidence limits were set at ± 2 sigma to allow for 95% of observations to fall within the limits. Three rules were applied to identify special cause variation: 1) astronomical points (outside sigma limits), 2) shifts (8 or more points above or below a center line), and 3) trends (6 or more points consecutively ascending or descending). Implementation strategies that mapped to special cause variations were selected as those most likely to impact the KPI. **Results:** Across the 6 sites that deployed eSyM, the mean KPI performance ranged from 19.7%-35.7%. SPC charts detected multiple special cause variations in the KPI at all 6 sites, though the patterns varied by site. All sites demonstrated positive and negative astronomical variations as well as positive and negative shifts. Three sites demonstrated negative trends; no sites demonstrated positive trends. Direct patient outreach was the implementation strategy most frequently associated with special cause variation, followed by changes in promoting the ePRO program to clinical staff. Positive changes were associated with strategy initiation; negative changes were associated with strategy discontinuation. **Conclusions:** Applying SPC charts to a KPI from the eSyM deployment highlighted the effect of personal communication with patients and providers, suggesting that these implementation strategies could offer value to other sites deploying eSyM. The absence of positive trends early in eSyM program deployment underscores the need to identify better implementation strategies and allocate more resources to foster program adoption and sustainability. Applying SPCs to other KPIs, such as symptom severity and healthcare utilization, could improve eSyM deployment and impact. Research Sponsor: U.S. National Institutes of Health.

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Poster Session

Mortality among oncology patients with multiple unplanned hospital admissions. *First Author: Thomas J Roberts, Massachusetts General Hospital Cancer Center, Boston, MA*

Background: Previous work has shown that patients with solid tumors with an unplanned hospital admission have a median overall survival of approximately six months, and readmission rates are high within this patient population, especially near the end of life. However, the relationship between multiple unplanned hospital admissions and survival and whether patient characteristics are associated with differences in survival have not been studied in this patient population. **Methods:** We recorded all hospital admissions to an inpatient oncology unit for patients with solid tumors from October 1, 2021, through September 30, 2022 and categorized admissions as planned (chemotherapy administration or desensitization) or unplanned. For all unplanned admissions we reviewed the electronic health record for unplanned admissions in the previous six months. For patients with one or more prior unplanned admission, we captured demographics, admitting diagnosis, discharge disposition, and vital status including date of death. We examined median overall survival for patients with two unplanned hospital admissions within six months, median survival for patients with three or more unplanned hospital admissions within six months and 90-day survival in patients with two or more unplanned admission. We also used multivariate Cox proportional hazards models to evaluate whether patient demographics, cancer type, and hospital length of stay were associated with differences in survival. **Results:** There were 1,561 unplanned admissions during the period of analysis. Of these admissions, 692 (44%) were preceded by at least one unplanned admission within the prior six months. A total of 400 patients had two or more admissions. Forty-five percent of readmitted patients had a diagnosis of gastrointestinal malignancy. Median overall survival for patients after a second unplanned admission was 76 days (95% CI 60 - 110), and median overall survival after a third unplanned admission was 50 days (95% CI 35 - 99). Median overall survival was 49 days (95% CI 39 - 67) for readmitted patients with a length of stay of at least seven days. Ninety-day survival was 45% (95% CI 39 - 51) among patients with two admissions and 34% (95% CI 26 - 43) among patients with three or more admissions. In multivariable models, longer length of stay was associated with decreased survival (HR 1.03, 95% CI 1.01-1.05). Age and sex were not associated with differences in survival, and overall survival was similar across all disease groups except head and neck, which was associated with improved survival (HR 0.42, 95% CI 0.21-0.85). **Conclusions:** Patients with solid tumors with multiple unplanned hospital admissions in less than six months represent a distinct population with exceptionally poor outcomes, regardless of the primary tumor site and patient demographics. This easily identifiable population may benefit from targeted interventions to improve the quality of end-of-life care. Research Sponsor: U.S. National Institutes of Health.

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Poster Session

The association between systemic anticancer therapy (SACT) at the end of life (EOL) and acute care use among patients treated at oncology practices participating in the Oncology Care Model (OCM). *First Author: Maureen Canavan, Yale School of Medicine, New Haven, CT*

Background: Receipt of chemotherapy near EOL has been shown to harm patient and caregiver experience, increase hospitalizations, intensive care unit (ICU) and emergency department (ED) use and drive-up costs. As rates of chemotherapy at EOL have declined, we have seen increases in the rates of immunotherapy at EOL. It is unknown whether use of EOL immunotherapy is associated with the same pattern of higher downstream acute care use and cost. Using data from OCM, a Centers for Medicare and Medicaid Services (CMS) alternative payment model, we evaluated the relationship between SACT type and acute care utilization within 30 days of death. **Methods:** Using anonymized Integra Connect data for OCM episode claims attributed to 8 multi-site OCM practices between July 2016 and December 2021, we stratified patients by SACT type received within 30 days of death (immunotherapy (IO), chemotherapy (CT), or none) and used chi-square tests to compare the proportion of decedents who had inpatient admission, ICU stay, ED visits without inpatient admission, and hospice use within 30 days of death. **Results:** Among 14,169 OCM decedents, 2,227 (15.7%) received IO within 30 days of death, 6,627 (46.8%) received CT and 5,315 (37.5%) received no SACT (table). Patients who received no SACT at EOL were significantly more likely to start hospice within 30 days of death (76%) and to be in hospice for ≥ 3 days prior to death (61%) compared with IO (65% and 40%) and CT patients (59% and 37%) respectively (all p -values < 0.05). Patients who received IO or CT were significantly more likely to have an inpatient stay within 30 days of death (66% and 68% respectively) compared with patients who received no SACT at EOL (58%, p -values < 0.001). No difference in ED visits within 30 days of death between IO (18%), CT (20%), and no SACT (19%) $p < 0.270$. **Conclusions:** Patients who received chemotherapy or IO therapy within 30 days of death had higher proportion of inpatient admissions, ICU stay and lower rates of hospice than patients who received no SACT at the EOL. Patients who did not have any SACT at EOL were more likely to utilize hospice services and for a longer time. Further research should explore whether these findings are generalizable to patients outside of OCM and the magnitude of costs associated with these acute care metrics. Research Sponsor: None.

Acute care and hospice utilization within 30 days of death by SACT treatment within 30 days.

	IO 2,227		CHEMO 6,627		NO SACT 5,315		p-value
	N	%	N	%	N	%	
ICU	869	39.0	2700	40.7	1667	31.4	< 0.01
Inpatient	1475	66.2	4538	68.5	3065	57.7	< 0.01
ED	408	18.3	1310	19.7	1009	19.0	0.270
Hospice started	1444	64.8	3895	58.8	4033	75.9	< 0.01
Hospice for ≥ 3 days	898	40.3	2487	37.4	3228	60.7	< 0.01

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Poster Session

Real-world program-based lung cancer care. *First Author: Wei Liao, Baptist Cancer Center, Memphis, TN*

Background: Low dose CT screening (LDCT) and lung nodule programs (LNP) promote early lung cancer detection, improve survival; Multidisciplinary Care Programs (MDC) promote guideline-concordance. The impact of such program-based care on 'real-world' population-level lung cancer survival and mortality is uncertain. We evaluated program-based lung cancer care versus care outside structured programs in a large community healthcare system. **Methods:** We linked prospective observational databases for LDCT, LNP and MDC with the Tumor Registry of Baptist Cancer Center facilities across Mississippi, Arkansas and Tennessee, categorizing all lung cancer patients between 2011 and 2021, according to program- (LDCT, LNP, MDC) versus non-program-based care. We compared stage distribution, care patterns, survival and mortality by standard statistical methods. **Results:** Of 12,089 patients, 250 (2%), 1236 (10%), 1045 (7%) and 9558 (79%) were diagnosed through the LDCT, LNP, MDC or no program, respectively; non-program-based care sequentially diminished from 96% in 2011 to 67% in 2021, diagnosis through LDCT increased from 0.3% to 7%, LNP from 0.9% to 21%; and MDC alone decreased from a high of 13% in 2015 to 5% in 2021. Black persons, 28% of the whole cohort, were 13% of LDCT, 25% of LNP, 31% of MDC, and 28% of non-program-based care recipients (p = 0.0005). Median (IQR) tumor size was 20mm (13 – 34), 25mm (17 – 44), 35mm (20 – 55) and 35mm (20 – 55), respectively (p < 0.0001); 40-46% of patients across programs had adenocarcinoma; clinical stage was I or II in 58%, 48%, 38% and 29% and IV in 16%, 27%, 31% and 42% in the respective programs (p < 0.0001). 2609 patients (21.6%) had surgery, including 49.2%, 37.7%, 36.1% and 17.2% in LDCT, LNP, MDC and non-program-based care respectively, among whom aggregate pathologic stage was I in 76%, 71%, 54% and 60% (p = 0.0005). Surgery was the sole treatment modality in 27.6%, 21.5%, 12.9% and 10.6%, respectively (p < 0.0001). Despite higher proportions with more advanced pathologic stage, 30.8% of recipients of non-program-based care received adjuvant therapy, compared to 42% among recipients of program-based care, including 39.0%, 37.1% and 49.3% in LDCT, LNP and MDC, respectively (p < 0.0001); 8.7% of patients in programs received no treatment, compared to 20.1% of non-program-based care. Aggregate 5-year overall survival rates were 60% (95% CI: 52% - 69%), 45% (95% CI: 42% - 49%), 30% (95% CI: 27% - 33%), and 18% (95% CI: 17% - 19%), respectively (p < 0.0001). Adjusting for age, sex, race, patient-level rurality and histology, with non-program-based care as reference, the aHR were 0.3 (95% CI: 0.234 – 0.373), 0.51 (95% CI: 0.464 – 0.556, and 0.66(95% CI: 0.607 – 0.712). Results were consistent even without patients who received no treatment. **Conclusions:** Program-based care was associated with more favorable lung cancer characteristics, better quality of care and survival. Disseminating program-based care should be explored as a matter of urgent public policy. Research Sponsor: Baptist Memorial Health Care Foundation for initial funding support: Grant # 15BD03.

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Poster Session

The association of HIV and other risk factors with triple-negative breast cancer in South African women. *First Author: Jacob Dubner, Columbia University Medical Center, New York, NY*

Background: Breast cancer (BC) mortality in South Africa (SA) is double that of the United States. The aggressive triple-negative breast cancer (TNBC) subtype comprises 20.9% of BC cases among Black women in Southern Africa. SA has the second highest HIV prevalence worldwide, but if and how HIV affects the risk of developing TNBC is not well understood. **Methods:** Using the South African Breast Cancer and HIV Outcomes (SABCHO) prospective cohort of newly diagnosed BC patients from six public hospitals in SA, we evaluated the association of HIV with risk of TNBC relative to other BC subtypes. We developed multivariable logistic regression models to test for this association while adjusting for key demographic and reproductive risk factors. **Results:** Of 3,883 women with BC, 16.4% had TNBC and 23.0% were HIV-positive. The overall median age of BC diagnosis was 55 years. Among HIV positive patients, the median age of BC diagnosis was 45 years, without a difference between TNBC and non-TNBC cases (p = 0.244). Only 7.2% of women were nulliparous (4.6% in TNBC and 7.6% in non-TNBC subgroups). Of women who had at least 1 full-term pregnancy, 11.2% did not breastfeed, without a difference between TNBC and non-TNBC cases (p = 0.292). In our final multivariable logistic regression model, HIV-positive status was associated with increased risk of TNBC relative to non-TNBC (OR: 1.40; 95% CI: 1.12-1.74, compared to HIV-negative with BC). Parity without breastfeeding was also associated with increased risk of TNBC relative to non-TNBC (OR: 1.72; 95% CI: 1.07-2.84, compared to nulliparous with BC). HIV status and the combined parity/breastfeeding variable had no statistically significant interaction. In exploratory analyses, measures of HIV control at time of BC diagnosis were not associated with BC subtype. **Conclusions:** In this large prospective case-only study conducted in SA, we found that women living with HIV were more likely than HIV-negative women to have TNBC (relative to other BC subtypes), regardless of the extent of HIV control. Whether this relationship is mediated by immune mechanisms or other factors should be the focus of future research. Our findings highlight the importance of rigorous BC screening and early detection among HIV-positive women given their increased relative risk of developing TNBC. Research Sponsor: U.S. National Institutes of Health; Conquer Cancer Foundation of the American Society of Clinical Oncology.

Multivariable logistic regression model for SABCHO cohort adjusting for demographic and reproductive factors (TNBC vs non-TNBC).

Factor	Exposed Category	Multivariable Model ¹ Odds Ratios (95% CIs)
Ethnicity	Black	1.21 (0.93-1.60)
Wealth Index		0.99 (0.93-1.07)
HIV Status	Positive	1.40 (1.12-1.74)
Age of Menarche	≥15 years	1.06 (0.88-1.29)
Parity and Breastfeeding	Parous, no breastfeeding	1.72 (1.07-2.84)
	Parous, breastfeeding	1.51 (1.00-2.35)
Ever on Contraceptive	Yes	1.14 (0.92-1.41)

¹Bolded odds ratio indicates p-value < 0.05; ²Model adjusted for age.

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Poster Session

Proportion of patients in phase I solid tumor oncology trials receiving treatments that are clinically efficacious. *First Author: Carlos Umberto Muzlera, Princess Margaret Cancer Center, University Health Network, Toronto, ON, Canada*

Background: Phase I trials are frequently regarded as possessing therapeutic intent by patients, oncologists, and governing medical bodies alike. While obtaining initial observations of clinical activity of investigational agents is an aim of phase I trials, such estimates utilize surrogate measures, such as objective response rate, which are difficult to conceptualize and less meaningful to a vulnerable patient population compared to clinical endpoints. Furthermore, phase I studies lack a comparator arm. To date, there are no published estimates of the probability a phase I solid tumor participant receives a treatment at a dose that has greater clinical efficacy than the standard of care for their disease setting. Such data is required to enable fully informed decisions around consent. **Methods:** A random sample of 1000 phase I solid tumor oncology trials conducted world-wide, initiated between 2007 and 2012, and enrolling 29,953 patients was obtained from 2223 eligible trials on ClinicalTrials.gov. ClinicalTrials.gov, PubMed, Embase, Medline, and ASCO reports were queried between December 1, 2022 and February 1, 2023 for randomized, controlled phase III trials testing the same regimen and indication as that used in each phase I trial. Phase III trials were considered positive if they demonstrated statistically significant superiority over an acceptable standard of care at the time of enrolment of the corresponding phase I trial with respect to overall survival, health related quality of life, or a validated surrogate for these clinical endpoints. All statistical tests were 2-sided. **Results:** A total of 0.82% (245) phase I trial patients received a treatment at a dose that was subsequently demonstrated in a randomized, controlled phase III trial to have statistically superior clinical efficacy over an acceptable standard of care at the time of phase I trial enrolment for the same disease setting. The mean objective response rate for both published and unpublished sampled phase I trials in the advanced or metastatic setting was 4.2%. Meta-regression showed a statistically significantly greater proportion of patients receiving a clinically efficacious therapy in biomarker trials (rate ratio = 3.78., 95% CI = 1.15 – 10.24, P = 0.02) and trials with an expansion cohort (rate ratio = 3.12, 95% CI = 1.05 – 8.89, P = 0.03). Proportions were statistically significantly lower for first in class treatments (rate ratio = 0.21, 95% CI = 0.03 – 0.76, P = 0.03). **Conclusions:** One in 122 patients in phase I solid tumor trials received a treatment that subsequently demonstrated superior clinical efficacy over the standard of care at the time of phase I trial enrolment. Considering published estimates of serious adverse events rates of 10-19%, this reveals low therapeutic value for phase I trial participation. Research Sponsor: None.

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Poster Session

Breast cancer staging for patients with “low risk” disease: Are they all the same? *First Author: Jennifer Kay Plichta, Department of Surgery, Duke University Medical Center, Durham, NC*

Background: Studies have shown that a low (<11) Oncotype DX recurrence score (RS) is associated with better survival outcomes. RS is currently included in the AJCC prognostic staging criteria. Not all patients with a low RS are downstaged. It has been suggested that a low RS should further downstage patients regardless of other disease factors. We explored survival outcomes for patients with a low RS to assess if additional patients should be downstaged. **Methods:** Using the National Cancer Database, female patients ages 18-75 with invasive unilateral pT1-3, pN0-1, MO hormone receptor positive (ER+ and/or PR+), HER2- breast cancer and a RS <11, diagnosed 2010-2018 were identified. Patients who received neoadjuvant treatment were excluded. Patients were grouped based on the AJCC 8th edition prognostic stage (IA, IB, IIA, IIB, IIIA). Variables were summarized, and unadjusted overall survival (OS) was estimated using the Kaplan-Meier method. Cox proportional hazards models were used to estimate the association of stage with OS after adjustment for available covariates. **Results:** Of the 54,961 patients with a RS <11, median follow-up was 57.7 months (95% CI 57.3-58.1), and median age was 61yo (IQR 52-67). Most tumors were grade 1 (37.6%) or 2 (56.9%) with ductal histology (75.3%). The median tumor size was 1.5 cm (IQR 1-2), and most were pN0 (83.3%). Although most patients with a RS <11 were stage IA (94.2%), some had a higher stage assignment (5.1% stage IB, 0.6% IIA, 0.1% IIB, <0.01% IIIA). Most patients (93.4%) received endocrine therapy (ET), and few (3%) received chemotherapy. Patients treated with chemotherapy more often had younger age, lobular histology, higher grade, larger tumor size, and/or pN+ disease (all p<0.001). Unadjusted OS was reduced with higher stage (log-rank p<0.001), and this remained true when limited to only those who received ET without chemotherapy (log-rank p<0.001). After adjustment for relevant covariates including treatment, higher stage remained associated with worse OS [stage IA: ref; IB: HR 1.66 (95% CI 1.34-2.05); IIA: HR 2.29 (95% CI 1.44-3.65); IIB: HR 2.48 (95% CI 1.03-5.95); overall p<0.001]. **Conclusions:** For patients with a low RS, survival outcomes vary with current AJCC prognostic disease stage, suggesting that not all patients with a RS <11 should be downstaged based on RS alone. Anatomic and other non-genomic factors remain relevant when assessing prognosis. Research Sponsor: Duke University Medical Center; U.S. National Institutes of Health.

OS rates (95% CI) by AJCC prognostic stage among those with RS <11, treated with surgery and endocrine therapy without chemotherapy (RS <11).

AJCC Prognostic Stage	N	1yr OS	3yr OS	5yr OS
IA	47092	0.998 (0.998-0.999)	0.990 (0.989-0.991)	0.975 (0.974-0.977)
IB	2218	0.998 (0.995-0.999)	0.980 (0.973-0.985)	0.949 (0.937-0.960)
IIA	246	0.992 (0.967-0.998)	0.963 (0.926-0.981)	0.907 (0.851-0.943)
IIB	38	1.000 (1.000-1.000)	0.939 (0.777-0.985)	0.895 (0.700-0.966)
IIIA	5	1.000 (1.000-1.000)	1.000 (1.000-1.000)	1.000 (1.000-1.000)

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Poster Session

Trends in the use of maintenance therapy in ovarian cancer. *First Author: Naomi N. Adjei, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Emerging maintenance therapies in advanced ovarian cancer (OC) remain of high interest since 70% of patients (pts) will relapse and ultimately succumb to OC. This study analyzes nonclinical factors associated with maintenance therapy (MT) in OC. We define MT in OC as the use of polyADP-ribose polymerase inhibitors (PARPi) and/or bevacizumab (bev) following platinum-based chemotherapy. **Methods:** We used data from Optum's de-identified Clinformatics Data Mart Database F to conduct an analysis of OC pts with Medicare or commercial health insurance. Pts were included if they had 1 inpatient or 2 outpatient diagnosis codes for OC from 01/2017 to 12/2020 and received platinum-based chemotherapy after diagnosis. Pts were excluded if they did not have continuous coverage from diagnosis until 6 months after completion of platinum-based chemotherapy or death. MT was identified by insurance claims for PARPi or bev received within 6 months after completion of platinum-based chemotherapy. Descriptive statistics were used to summarize patient characteristics. Multivariable logistic regression was used to evaluate associations between pts' nonclinical characteristics and MT use. Trends in MT use were reviewed by year. Subgroup analysis comparing trends in PARPi use to bev use was also performed. The median time from last chemotherapy until initiation of MT was 22 days. **Results:** 5,652 pts were included in the study with a median age of 70 years. The majority were white (70.7%), Medicare-insured (71.8%), and treated in the South (42.8%). 33.6% of pts received MT and 66.4% of pts received neither PARPi nor bev. More pts received bev alone (19.6%) compared to PARPi alone (10.3%) or combination MT (3.7%). Olaparib was the most commonly prescribed PARPi. After adjusting for insurance type, both PARPi and bev use increased significantly over time from 2017 to 2021. Pts with more comorbidity burdens (i.e. higher Elixhauser comorbidity index) were more likely to receive MT compared to pts with less comorbidity [OR (95% CI): 1.44 (1.26-1.65)]. MT use was significantly associated with treatment in the South compared to the Northeast [1.22(1.01-1.46)] and younger age, pts > 76 years were less likely to use MT compared to pts < 56 years old [0.78 (0.62-0.98)]. In the subgroup analysis, PARPi use was significantly associated with age, race and region compared with no MT use, while bev use was not associated with these factors. **Conclusions:** Age, comorbidity status, and geographic location of treatment were associated with MT use. The increasing use of MT over time is consistent with published data since both agents have demonstrated a progression free survival advantage and have tolerable toxicity profiles. With increasing focus on MT in OC, a better understanding of nonclinical factors associated with MT use is imperative to eliminating potential disparities in OC outcomes. Research Sponsor: This work was supported by the T32 Training Grant CA101642.

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Poster Session

Real-world analysis of cardiac, gastrointestinal, and hematologic toxicities between commonly used antiemetics in everyday oncology clinical practice. *First Author: Kavitha Beedupalli, Louisiana State University (Shreveport) Program at Feist-Weiller Cancer Center, Shreveport, LA*

Background: Antiemetics are highly effective in chemotherapy-induced nausea and vomiting. We utilized Food and Drug Administration Adverse Event Reporting System (FAERS) database to evaluate adverse events (AEs) caused by selected antiemetics commonly used in outpatient oncology practice. **Methods:** We analyzed the FAERS database to assess the cardiac, gastrointestinal (GI), and hematologic AEs for metoclopramide, olanzapine, ondansetron, and promethazine from 2013 through 2022. The disproportionality signal was analyzed by calculating Reporting Odds Ratio (ROR) with a 95% confidence interval (CI)—considered significant when the lower limit of 95% CI was > 1. **Results:** A total of 20,302 AEs were identified, out of which 8,135 (40.1%) were cardiac—arrhythmia and QTc prolongation; 8,656 (42.5%) were GI—nausea/vomiting, constipation/diarrhea, abdominal pain/discomfort, and dyspepsia; and 3,511 (17.3%) were hematologic—leukopenia, thrombocytopenia, anemia, and pancytopenia. Compared to other antiemetics, promethazine and olanzapine had higher cardiac and hematologic AEs, respectively, whereas metoclopramide, followed by ondansetron had higher GI AEs (Table). **Conclusions:** Antiemetics are readily available and effective, yet the preference for a particular drug or drug combination varies. Our study highlights selected antiemetics AEs in order to help individualize treatment for this often challenging and frequently encountered entity. Research Sponsor: None.

	Metoclopramide	Olanzapine	Ondansetron	Promethazine
Cardiac				
-Arrhythmia	554 (5.7%)	2,593 (6.5%)	1,672 (13.8%)	883 (26.6%)
-QTc Prolongation	307 (3.2%)	1,179 (2.9%)	778 (6.4%)	169 (5.1%)
Total Cardiac AEs, no. (%)	861 (8.9%)	3,772 (9.4%)	2,450 (20.2%)	1,052 (31.7%)
ROR (95% CI)	0.27 (0.25-0.30)	0.43 (0.41-0.46)	0.32 (0.30-0.34)	1.65 (1.49-1.84)*
GI				
-Nausea, and Vomiting	977 (10.1%)	1,383 (3.5%)	1,446 (11.9%)	216 (6.5%)
-Constipation, and Diarrhea	546 (5.7%)	1,091 (2.7%)	1,001 (8.3%)	108 (3.2%)
-Abdominal Pain, Discomfort, and Dyspepsia	274 (2.8%)	549 (1.4%)	926 (7.6%)	139 (4.2%)
Total GI AEs, no. (%)	1,797 (18.6%)	3,023 (7.6%)	3,373 (27.8%)	463 (13.9%)
ROR (95% CI)	2.22 (2.05-2.40)*	0.65 (0.53-0.59)	1.56 (1.47-1.65)*	0.52 (0.47-0.59)
Hematologic				
-Leukopenia	74 (0.8%)	893 (2.2%)	210 (1.7%)	10 (0.3%)
-Thrombocytopenia	124 (1.3%)	482 (1.2%)	387 (3.2%)	30 (0.9%)
-Anemia	118 (1.2%)	401 (1.0%)	403 (3.3%)	29 (0.9%)
-Pancytopenia	52 (0.5%)	151 (0.4%)	134 (1.1%)	13 (0.4%)
Total Hematologic AEs, no. (%)	368 (3.8%)	1,927 (4.8%)	1,134 (9.3%)	82 (2.5%)
ROR (95% CI)	0.62 (0.55-0.70)	1.75 (1.66-1.93)*	0.95 (0.88-1.02)	0.24 (0.19-0.03)
Overall Reported AEs	9,625	39,939	12,110	3,319

* Asterisk in the table denotes a positive signal.

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Poster Session

Survival of patients with solid tumors and sepsis admitted to intensive care in a tertiary oncology center: A retrospective analysis. *First Author: Sam Smith, Imperial College London, London, United Kingdom*

Background: Sepsis is a life threatening organ dysfunction caused by a dysregulated host response to infection. Patients with cancer are at high risk of developing sepsis and requiring admission to the intensive care unit (ICU). Patients with cancer and sepsis have been found to have worse survival than non-cancer patients, with 90 day survival for cancer patients ranging from 28% to 72%. Survival differs between studies due to multiple factors including variably mixed haemato-oncology and solid tumor cohorts and varying definitions of sepsis. Our objectives were to accurately assess short, medium and long term survival of patients admitted to ICU with a solid tumor and sepsis and to identify the best predictors of 90 day survival at admission. **Methods:** We conducted a retrospective cohort survival analysis. We identified adults (aged 18 years and over) admitted to ICU with sepsis and a solid tumor between 1st January 2011 and 31st December 2020 at a tertiary oncology center with hospitals at two sites (London and Surrey, United Kingdom). We defined sepsis using the Sepsis-3 definition. The primary outcome was 90 day survival, but we also calculated 30 day, 180 day, 1 year and 5 year survival. Survival was calculated excluding patients lost to follow up. Univariate and multivariate analyses were undertaken to identify factors that differed between survivors and non-survivors at day 90. We used the parametric accelerated failure time model for multivariate analysis to generate time ratios (TR). **Results:** 625 patients were identified, with 131 patients lost to follow up by 5 years. The median age was 64 years (Interquartile Range 54-71) and 56% were male. 84.8% (530/625) survived to ICU discharge. The 30, 90 and 180 day survival rates were 72% (439/610), 59.5% (353/593) and 51.7% (300/580) respectively. 1 year survival was 38.7% (221/571) and 5 year survival 8.1% (40/494). Multivariate analysis identified the presence of localized (TR 7.85, 95% CI 4.00 -15.41) or regionalized disease (TR 4.71, 95% CI 2.74-8.08) compared to distant metastatic disease, surgery on the day of admission (TR 6.78, 95% CI 3.24-14.19), lactate (TR 0.80, 95% CI 0.74-0.87), SOFA score (TR 0.84, 95% CI 0.79-0.89), previous radiotherapy (TR 0.53, 95% CI 0.32-0.88), previous medical cancer treatment (TR 0.67, 95% CI 0.42-1.07), bacteremia (TR 2.14, 95% CI 1.25-3.64) and albumin (TR 1.06, 95% CI 1.02-1.10) as independent predictors of 90 day survival. **Conclusions:** This study of solid tumor patients admitted to ICU is one of the largest to date with the longest follow up period, providing up to date survival data to inform clinicians and patients. Patients with solid tumors and sepsis admitted to ICU have short and medium term survival rates comparable to non-cancer populations and therefore the presence of cancer should not prevent ICU admission. Prior oncological therapies may affect survival in patients admitted to ICU with sepsis. Research Sponsor: None.

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Poster Session

Multicenter, retrospective population-based study on the incidence of medication-related osteonecrosis of the jaw in patients with breast cancer with bone metastases. *First Author: Christine Brunner, Department of Gynecology and Obstetrics, Medical University of Innsbruck, Innsbruck, Austria*

Background: Antiresorptive therapy with bisphosphonates or denosumab is standard care for patients with primary or secondary osseous metastasized breast cancer. The most important toxicity of this class of drugs is medication-related osteonecrosis of the jaw (MRONJ). MRONJ represents a major medical burden and impairs quality of life. Based on recent studies, the risk of MRONJ occurrence ranges from 1% to 3%. The objective of this study was to assess the population-based incidence of MRONJ in breast cancer patients with bone metastases in Tyrol, Austria. **Methods:** This retrospective multicenter study was conducted between 2000 and 2020 at nine centers across Tyrol, Austria, including 8,860 patients with breast cancer. Depending on whether patients with bone metastases received denosumab, bisphosphonates or denosumab following bisphosphonates they were allocated to one of three groups. Data was collected using an electronic case report form (e-CRF) and managed via the web-based database AskiMed. MRONJ incidences with 95% confidence intervals and the differences between the median of cumulative incidences were calculated in patients treated with bisphosphonates and/or denosumab. **Results:** A total of 639 patients had bone metastasis and received antiresorptive therapy. MRONJ was diagnosed in 56 (8.8%) patients. Regarding the 292 (45.7%) patients treated with denosumab alone, the MRONJ incidence was 11.6% (95%CI 8.2%-15.9%). The group of patients treated with only bisphosphonates included 255 (39.9%) patients; their MRONJ incidence was 2.7% (95%CI 1.1%-5.6%). Of the 92 (14.4%) patients receiving both antiresorptive therapies consecutively, the MRONJ incidence was 16.3% (95%CI 9.4%-25.5%). Thus, a total of 49 (12.8%) MRONJ cases were detected in patients using denosumab alone as well as using the combination of denosumab following bisphosphonates. Patients treated with denosumab developed a MRONJ in median 60 months earlier than with bisphosphonates alone or followed by denosumab. The hazard ratio for MRONJ from start of therapy of denosumab compared to bisphosphonates alone or followed by denosumab was 7.9 (3.8-16.2; p-value < 0.0001). **Conclusions:** This study showed a substantially higher MRONJ incidence for denosumab alone or bisphosphonates followed by denosumab in the tyrolean cohort when compared to other recent studies. Future comparative real-world-evidence research provide explicit benefit-harm tradeoffs to inform treatment decision making. Research Sponsor: None.

Real-world evidence to inform clinical insights on tissue-agnostic approvals of therapies. *First Author: George W. Sledge, Caris Life Sciences, Phoenix, AZ*

Background: Many tissue-agnostic (TA) approvals were based on clinical trials with limited patient numbers without covering all tissue types (TT), raising the question of whether these indications were truly tissue agnostic. Real world evidence (RWE) offers an opportunity to investigate TTs not included in clinical trials/studies to answer this question. Herein we investigate the seven TA approvals to date in a large real world database and report clinical outcomes. **Methods:** A total of 186,581 tumors from over 35 TTs tested with comprehensive molecular profiling including NextGen sequencing of DNA and RNA were investigated for TA alterations (TMB-High (≥ 10 mutations/MB), MSI-H/MMRd, BRAF V600E mutations and NTRK1/2/3/RET fusions) at Caris Life Sciences (Phoenix, AZ). Time-on-treatment (TOT) from RWE was obtained from insurance claims and calculated from treatment start to finish. Kaplan-Meier estimates were calculated for molecularly defined patient cohorts. Significance was determined as p values of <0.05 . **Results:** Among all tumors, 21.2% carried at least one TA alteration, 17.2%, 3.4% and 0.6% had 1, 2 or 3 alterations, respectively. TMB-H in 18.7%, MSI-H/dMMR was seen in 3.9%, BRAF V600E in 2.8% of tumors, NTRK1/2/3 and RET fusion seen in 0.16% and 0.23%. TA alterations were most prevalent in BCC (86%) & SCC (82%) of skin, MEL (71%), THCA (51%) and NSCLC (44%) and least in liposarcoma (0), meningioma (0.7%) and GIST (1.4%). Among tumors treated based on TA indications, substantial variability of TOT among TTs was observed (see table). Looking at TTs included (INC) and not included (nINC) in KEYNOTE-158 and other studies for TMB-H and pembro, median TOT for nINC was similar to INC (N=242 vs 2322, 6.1 m vs 6.3 m, p = 0.55). Nevertheless, statistically significant differences in median TOTs were seen across nINC when comparing TMB-H vs. TMB-L (6.1m vs. 2.9m, HR: 0.58 [95% CI: 0.50-0.67], p<0.001) and in a subset of 838 MSS tumors (4.9m vs. 2.8m, p<0.001). **Conclusions:** RWE data adds substantially to our understanding of the demographics of TA indications and suggests that some TA treatment benefits may be tissue-specific. Recent TA indications will require further accumulation of cases to draw meaningful conclusions regarding whether TA indications are, in fact, tissue agnostic. Research Sponsor: None.

RWE of TA-positive pembro-treated tumors from 11 selected TTs (TMB-H TT group 1 had significantly longer TOT (months) than group 2; MSI-H TT group A had longer TOT than B; b longer than C all p<0.05).

	TMB-H N	TOT (CI%)	MSI-H/MMRd N	TOT (CI%)
NSCLC	1556	6.4 (5.8-7) ¹	30	7.5 (2.8-15.1)
UCEC	363	7 (6.1-8.2) ¹	30	6.9 (5.9-8) ^B
MEL	245	6.5 (5.4-7.2)	99	
CLC	237	7.3 (5.6-8.9) ¹	218	7.7 (5.6-9.1)
BLAC	210	5.5 (0.9-6.1) ²	15	9.8 (3.5-22.4)
CUP	111	5.4 (3.9-7.7)	23	2.5 (0.7-6.4) ^C
CESC	80	5.4 (3.2-8.8)	15	8.8 (2.1-18.4)
STAD	54	8.4 (4.2-10.5)	51	8.6 (3.5-14.9)
SBA	21	12.9 (3.5-17.5)	18	14.3 (8.6-24.5) ^A
NEC	17	3.7 (0.9-5.5) ²	8	3.7 (0.6-5.6) ^C
SCLC	12	2.4 (0.7-5.8) ²	0	

Malnutrition risk at diagnosis and influence on survival in patients with solid tumors at a large academic cancer center. *First Author: Kunal C. Kadakia, Levine Cancer Institute, Charlotte, NC*

Background: Malnutrition is common in cancer patients and negatively impacts quality of life, tolerance to anti-cancer therapies and is associated with poor prognosis. It is, however, unclear if patient-reported malnutrition risk at initial diagnosis is related to overall survival (OS) in solid tumor oncology outpatients in the United States. **Methods:** A cohort of 3,562 patients who completed the malnutrition screening tool (MST), a validated assessment of malnutrition risk, at initial diagnosis of any stage solid tumor and had available survival data were analyzed. The primary objective was to evaluate the relationship of high malnutrition risk (≥ 2 of 5 = high risk for malnutrition, H-MST) to OS and was assessed using Kaplan Meier techniques and Cox proportional hazards models. Unadjusted analyses were performed, and adjusted multivariable analyses evaluated the impact of H-MST on OS controlling for key clinical baseline confounders. **Results:** The median age was 63 years (IQR: 54-71), with 62% females and 81% White. Most common cancer sites were breast (28%), gastrointestinal (GI, 21%), and thoracic (13%) and 80% were non-metastatic. Median follow up was 48.3 months. H-MST was associated with lower OS in the unadjusted model, median OS in months was 32.5 [H-MST] vs not reached in low MST [L-MST] (HR 3.3, 95% CI 2.9-3.7, p = < 0.001). Multivariable analysis confirmed that H-MST remained independently associated with OS when controlling for age, sex, cancer site, stage, BMI, and symptom scores. Landmark OS rates at 50 months were 60% [H-MST] vs. 69% [L-MST] (HR 1.51 95% CI 1.3-1.7, p = < 0.001). Adjusted subgroup analyses by cancer site showed the independent impact of H-MST was relatively similar across groups (Table). **Conclusions:** High malnutrition risk at initial diagnosis was independently associated with shorter survival across a large representative cohort of solid tumor oncology outpatients. The screening occurred before any anti-cancer therapy and it is noteworthy most had non-metastatic disease. These data highlight the need for systematic screening to identify patients at malnutrition risk who need additional assessment early during cancer. Further research on how to optimize allocation of limited nutrition resources for those with high malnutrition risk is needed. Research Sponsor: None.

	Sample Size/Number of Events	50-month survival rate (High-MST, %)	50-month survival rate (Low-MST, %)	HR (95% CI) High MST vs Low MST	P-Value
Entire Cohort	3562/1145	60	69	1.51 (1.33-1.72)	< 0.001
Subgroup					
Non-Upper GI	337/124	54	63	1.56 (1.07, 2.28)	0.021
Upper GI	382/271	20	32	1.61 (1.22, 2.13)	< 0.001
Head & Neck	133/44	63	66	1.15 (0.61, 2.15)	0.665
Thoracic	453/289	24	36	1.45 (1.13, 1.87)	0.004
Gynecologic	334/89	61	77	2.03 (1.30, 3.16)	0.002
Genitourinary	430/119	67	73	1.33 (0.88, 1.99)	0.175
Breast	1011/104	87	90	1.14 (0.64, 2.06)	0.657
Other	482/105	70	79	1.62 (1.04, 2.52)	0.034

Site of metastasis (SoM) and its impact on clinical outcomes in 8 cancer cohorts. *First Author: Rohini George, ConcertAI, Bengaluru, Karnataka, India*

Background: The prognosis of metastatic cancer is in general poor. This can be affected by several factors including age, histology, treatment choices & SoM etc. **Methods:** This retrospective study leverages ConcertAI's deeply curated Patient360 datasets for 8 solid cancers to assess the impact of SoM on the outcomes of patients. For the purpose of this analysis, we focused on the most common SoM (bone, brain, lung & liver). Patients had either a Single SoM (SSM) or Multiple SoM (MSM) and we focused this analysis on patients with SSM. The overall survival (OS) & progression free survival (PFS) from the date of metastasis as well as the time to metastasis (TTM) from initial diagnosis were determined for each cohort. We also computed a consolidated OS & PFS for all patients with MSM. **Results:** 140K patients were included in this study of which 60K patients had a SoM. The distribution of SoM is dependent on the primary cancer type. For example, in breast & prostate cancer, bone metastasis accounts for 50-80 % of the metastatic cohort whereas it is only 8-21% in lung & melanoma. As expected, the overall values of OS/PFS were primarily governed by the primary cancer type (Table), but this analysis provides further interesting insights: 1. Within a cohort, there were significant differences in the prognosis of patients based on the SoM. Brain & liver had a poorer prognosis compared to the other SoM across most cohorts. 2. The relative prognosis for some SoM were dependant on the primary cancer type. For example, there was a very significant difference between the OS/PFS values in the breast cancer cohort when comparing brain vs bone as SoM. However, in the lung cancer cohort, this difference was less pronounced, and the trend was flipped. 3. For some cohorts the SSM for certain sites had a worse prognosis than the MSM. In breast cancer the OS of the brain & liver SoM was worse than the MSM. 4. The TTM is also dependent on the primary cancer and there is a correlation between the average TTM and the OS of the cohort. **Conclusions:** The patterns of cancer metastasis and the absolute and relative prognosis for a particular SoM is dependent on the primary cancer type. Such insights from a large real-world data study can impact clinical decisions regarding the aggressiveness of treatment based on the primary cancer type as well as the metastatic site. Research Sponsor: None.

Metastatic patient counts and outcomes (OS/PFS in years) for 4/8 cancer cohorts.						
	SSM	Bone	Lung	Liver	Brain	MSM
Primary Cancer Type (Mets/overall counts)	Count / OS / PFS					
Breast (12346 / 49361)	7110 / 5.17 / 1.5	3695 / 5.33 / 1.65	1372 / 5.84 / 1.6	613 / 3.05 / 0.91	361 / 0.71 / 0.23	5236 / 3.23 / 0.83
NSCLC (26667 / 52814)	15666 / 1.6 / 0.68	3285 / 1.19 / 0.54	5412 / 1.93 / 0.77	938 / 0.99 / 0.49	3797 / 1.54 / 0.68	11001 / 1.1 / 0.46
Melanoma (3220 / 10479)	1702 / 4.61 / 0.76	130 / 0.42 / 0.26	453 / 1.26 / 0.48	739 / 1.67 / 0.38	301 / 0.41 / 0.22	1518 / 2.01 / 0.38
Prostate (7087 / 10679)	5555 / 4.38 / 1.48	4470 / 4.25 / 1.44	137 / 2.46 / 0.48	335 / 1.19 / 0.19	14 / 0.22 / 0.19	1532 / 3.46 / 1.11

Real-world behavioral restriction practices of cancer patients (pts). *First Author: Eliya Shachar, Sourasky Medical Center, Oncology Division, Tel Aviv-Yafo, Israel*

Background: Quality of life (QoL) assessments do not measure pts' ability to maintain normal daily activities during cancer therapy. Misbeliefs might promote avoidance of activities perceived as dangerous, compromising pts QoL. We examined the daily practices of actively treated pts with cancer. **Methods:** A locally validated questionnaire at the Tel-Aviv Sourasky Oncology Division was distributed internationally using the Belong.life social and professional digital health platform. We examined real-world pts reported practices, provided voluntarily and anonymously. The survey consisted of 15 questions, including demographic, clinical, behavioral parameters and sources guiding and supporting pts practices. Independent clinical and demographic variables were analyzed. Statistical analysis was performed, and a multivariate logistic regression was conducted to identify factors predicting restrictive behaviors. **Results:** The study population comprised 1,395 pts receiving active cancer therapy, reporting their outcomes from the Belong digital platform. Most respondents were from the United States (1082, 77.70%) and Israel (223, 16%), over the age of 40 (1309, 93.8%), and female (987, 70.75%). Most common tumor types were breast (394, 28.24%) and gastrointestinal cancers (199, 14.26%). The majority of pts (1,005, 72.88%) reported on at least 1 adopted limitation in daily activities, and 305 (21.86%) maintained more than half of these constraints. Daily life restrictions included avoiding sun exposure (779, 57.83%), international travel (417, 33.33%), indoor public places (malls, etc) (431, 33.13%), hair dyeing (271, 22.72%), domestic tourism (284, 21.93%), contact with friends and family (231, 17.69%), children and grandchildren (202, 16.33%), outdoor public spaces (190, 14.62%), and contact with pets (135, 10.41%). Multiple sources were implicated by the pts as guiding their behavior, with the most common being health-care professionals (951, 65.95%), followed by both non-medical authorities and health-care team (320, 22.19%), and non-medical advisors, including internet, pts forums, partners, friends, and family (171, 11.86%). Pts who maintained strict ($\geq 50\%$ of the limitations) and less strict restrictions, demonstrated no significant association between country of origin (p = 0.118), and education level (p = 0.3591). A significant association was noted between younger age (p = 0.0014), female sex (p = 0.0141) and primary cancer site (p < 0.0001), and the adoption of strict restrictions. **Conclusions:** The majority of pts reported compromised daily activities, which are likely attributed to misconceptions about therapy and disease, deleteriously impacting QoL, therefore, impeding their ability to continue to conduct a complete and meaningful life. These findings require development of tools examining patients' real-daily life activity as an additional endpoint in clinical trials. Research Sponsor: None.

Measuring variation in the quality of systemic anti-cancer therapy delivery across hospitals: A national population-based evaluation. *First Author: Jemma Megan Boyle, London School of Hygiene and Tropical Medicine, London, United Kingdom*

Background: To date, there has been little systematic assessment of the quality of care associated with systemic anti-cancer therapy (SACT) delivery across national healthcare systems. We evaluated hospital-level toxicity rates during SACT treatment as a means of identifying variation in care quality. **Methods:** All colorectal cancer patients receiving SACT within 106 English National Health Service hospitals between 2016 and 2019 were included. Severe acute toxicity rates were derived from hospital administrative data using a validated coding framework. Variation in hospital-level toxicity rates was assessed separately in the adjuvant and metastatic settings. Toxicity rates were adjusted for age, sex, comorbidity, performance status, tumour site, and TNM staging. **Results:** Of the 8,173 patients receiving SACT in the adjuvant setting, 2,074 (25%) had a toxicity with adjusted hospital-level rates varying from 11% to 49%. Of the 7,683 patients receiving SACT in the metastatic setting, 3,625 (47%) had a toxicity with adjusted hospital-level rates varying from 25% to 67%. Compared to the national mean toxicity rate in the adjuvant cohort, six hospitals were more than 2 standard deviations (2SD) above, and four hospitals were more than 2SD below. Similarly, in the metastatic cohort, six hospitals were more than 2SD above, and seven hospitals were more than 2SD below the national mean toxicity rate. **Conclusions:** There is substantial variation in hospital-level severe acute toxicity rates in both the adjuvant and metastatic settings, despite comprehensive risk-adjustment. Ongoing reporting of this performance indicator can be used to focus further investigation of toxicity rates and stimulate quality improvement initiatives to enhance care. Research Sponsor: None.

Real-world response endpoints in patients with mNSCLC treated with chemotherapy across real-world datasets. *First Author: Brittany Avin McKelvey, Friends of Cancer Research, Washington, DC*

Background: Response Evaluation Criteria in Solid Tumors (RECIST) based response rate (RR) is used for efficacy evaluation in clinical trials and relies on imaging data collected at specified timepoints for uniform assessment. In routine clinical practice, the method and timing of response assessment can vary, and imaging data from electronic health records (EHR) and other real world (rw) sources may not be available, making RECIST-based assessment of rw-response rate (rwRR) using rw data (RWD) challenging. Friends of Cancer Research formed a multi-stakeholder partnership to assess available data attributes to measure response across RWD sources to inform development of a consistent method for measurement. **Methods:** The study included seven EHR data partners who identified and analyzed a cohort of 1,380 patients (pts) with metastatic non-small cell lung cancer (mNSCLC) treated with first-line platinum doublet chemotherapy, following a common protocol and statistical analysis plan. The availability and frequency of data components to assess response including raw images, radiology imaging reports, and clinician response assessments from provider notes were assessed. Response endpoints measured included rwRR, rw-duration of response (rwDOR), and the association of rwR with rw-overall survival (rwOS), rw-time to treatment discontinuation (rwTTD), and rw-time to next treatment (rwTTNT). **Results:** The availability of data components varied across RWD sources (Table). Images were not widely accessible, thus response was analyzed using clinician response assessments (median proportion of pts evaluable, 77.5%). Of these assessments, the majority relied on imaging interpretation. The median rwRR was 46% with a median rwDOR of 119 days. The table provides median rwTTD, rwTTNT, and rwOS across data sources. **Conclusions:** The rwRR among pts with mNSCLC calculated using the clinician assessment was relatively consistent across all RWD sources, with consistent trends in time to event endpoints. While variability in the availability of data components to assess response was observed, the demonstrated feasibility of response endpoints based on clinician assessment suggests further exploration may inform drug effectiveness evaluation with RWD. Research Sponsor: Friends of Cancer Research (Non-profit).

Group*	Pts Evaluable for rwR (pts by Images)	Pts Ev by Radiology Reports	Pts Ev by Clinician Response Assessment	Median rwRR (95% CI)	Median rwDOR, days: Responders /Non-Responders (RNR)	Median rwTTD, days: RNR	Median rwTTNT, days: RNR	Median rwOS, days: RNR
A	3.5%	73%	79.5%	42% 115 (86, 199)	142/69	200/100	375/245	
B	0.5%	55%	80.5%	53% 133 (108, 182)	128/84	209/98	464/314	
C	40.5%	77%	77.5%	46% 146 (102, 210)	147/63	234/93	832/213	
D	0%	0%	74%	40% 100 (74, -)	105/70	140/115	614/414	
E	79.5%	79.5%	76%	38% 119 (98, 231)	132/48	235/93	474/184	
F	0%	66.5%	69%	52% 182 (147, 287)	99/43	219/109	436/353	
G	0%	85.5%	88.3%	49% 105 (77, 672)	112/21	198/61	392/86	

*n=200 pts except G: n=180.

Tumor lysis syndrome in solid tumors: A retrospective cohort study of the National Inpatient Sample from 2016 to 2019. *First Author: Akshit Chitkara, University of California Riverside, Riverside, CA*

Background: Tumor lysis syndrome (TLS) is a life-threatening oncologic emergency. Patients with a rapidly proliferating tumor or high tumor burden after cytotoxic chemotherapy, predominantly in hematologic malignancies, are at increased risk of TLS. The advancement in therapeutic strategies of oncology in the past few decades has expanded the spectrum of malignancies associated with TLS. A dearth of literature on the incidence of TLS in various solid malignancies exists. Using the National Inpatient Sample (NIS) data, this study aims to highlight the solid malignancies at risk of TLS, highlight the demographic factors, and draw a comparison with that in hematological malignancies. **Methods:** The NIS 2016-2019 dataset was analyzed utilizing univariate and multivariate logistic regression analysis for the predictors of TLS (P<0.05). StataCorp. 2021. Release 17. College Station, TX: StataCorp LLC, BE version with Stata's svy command, and appropriate weights, were used to perform the analysis. The overall fit was analyzed using Receiver Operative Curves (ROC), and sensitivity analysis was analyzed using the e-value package. **Results:** From 2016-2019, a total of 51,385 (48,917-53,853) hospitalizations had an incidence of TLS. We included 16,249 cases of TLS in patients treated for the ten most common malignancies in the US. We found that older age, male sex, and black race were associated with higher odds of TLS. It was reported highest in large hospitals and urban non-teaching hospitals. The regional distribution of the TLS suggests the highest odds in the Western region. The odds of getting TLS were highest among Leukemias and Lymphomas, respectively. Among solid tumors, the odds of getting TLS were highest in uterine cancer patients, followed by lung, breast, pancreatic, and liver cancer among the top five. (Table). **Conclusions:** In this study, we conclude that solid tumors, mainly uterine, followed by lung and breast, have significantly higher odds of TLS, more so in larger or non-teaching hospitals. There is a need to establish specific management guidelines to prevent these TLS cases that will improve the morbidity and mortality associated with TLS and help build more cost-effective treatment regimens. Research Sponsor: None.

Demographic Characteristics	OR of TLS	95% CI	Hematologic Malignancies	OR of TLS	95% CI
Age	1.01	1.006 to 1.009	Leukemias	56	52.59 to 59.84
Female vs. Male Sex	0.61	0.58 to 0.64	Lymphomas	34.16	31.62 to 36.90
Black Race vs. White	1.31	1.22 to 1.41	Solid Malignancies	OR of TLS	95% CI
Asian or pacific Islanders vs. White	1.31	1.15 to 1.48	Uterine cancer	6.82	5.22 to 8.91
Large vs. Small sized hospitals	2.05	1.82 to 2.31	Lung cancer	4.74	4.27 to 5.26
Medium vs. Small sized hospitals	1.39	1.23 to 1.57	Breast cancer	3.39	2.77 to 4.16
Urban non-teaching vs. Rural hospitals	1.66	1.38 to 1.99	Pancreatic cancer	3.21	2.56 to 4.02
Western vs. Northeast region	1.18	1.05 to 1.33	Liver cancer	3.19	2.50 to 4.08

Molecular testing utilization in patients with advanced non-small cell lung cancer (NSCLC) in Washington (WA) state. *First Author: Lauren Shih, Fred Hutchinson Cancer Center, Seattle, WA*

Background: Therapies targeted at driver mutations (e.g. EGFR, ALK) in NSCLC have contributed to improved patient survival. While current guidelines recommend that all patients diagnosed with stage IV NSCLC undergo molecular testing to determine eligibility for targeted therapies, real-world testing patterns have not been well described. In a retrospective study using cancer registry and insurance claims, we evaluated rates of molecular testing in a population-based sample of NSCLC patients in WA. **Methods:** We linked WA state cancer registry records from 2017-2019 with claims records for Medicare, Medicaid, and two large commercial insurers. Patients diagnosed with stage IV NSCLC who had continuous insurance enrollment for 2 months prior to and 12 months following diagnosis were identified. Using insurance claims data, we identified patients who received any molecular testing (either testing for specific markers or comprehensive molecular profiling). We compared proportions of patients who received and did not receive molecular testing by insurance type, race, ethnicity, gender, and diagnosis (Dx) year. We performed a multivariate regression analysis to determine factors associated with completion of molecular testing. **Results:** 1048 eligible patients were identified. The median age was 70. Patients were predominately insured by Medicare (62.6%) and non-Hispanic white. 90.3% of all patients underwent molecular testing. Molecular testing rates were similar between white and non-white patients (90.4% vs 89.2%, p=0.647). Testing rates were significantly lower among Hispanic patients vs non-Hispanic patients (77.8% vs 90.7%, p=0.018). Testing rates were lowest among Medicaid enrollees (86.4%) compared to Medicare (88.4%), commercial (97.2%) or multiple insurances (94.9%) (p=0.0018). A multivariate analysis demonstrated that patients age ≥65 and Medicaid patients were less likely to receive molecular testing while females were more likely to receive testing; year of Dx did not impact testing rates (Table). **Conclusions:** While the rate of adherence to recommended molecular testing was high in the overall cohort, testing rates were lower in Hispanic patients, older patients, males, and those with Medicaid insurance. Given the therapeutic implications of testing, drivers of these observed disparities warrant further study to ensure equitable access to efficacious treatment. Research Sponsor: Fred Hutchinson Cancer Center.

Multivariate analysis for patients undergoing molecular testing.	Odds Ratio	95% Confidence Interval
Age ≥ 65 (ref=Age <65)	0.39	(0.18, 0.85)
Female (ref=Male)	1.76	(1.15, 2.69)
Non-White (ref=White)	0.89	(0.49, 1.62)
Hispanic (ref=non-Hispanic)	0.38	(0.16, 0.91)
Medicaid (ref=Commercial)	0.16	(0.04, 0.59)
Medicare (ref=Commercial)	0.34	(0.10, 1.15)
Multiple Insurance (ref=Commercial)	0.74	(0.19, 2.91)
Dx 2018 (ref=2017)	1.20	(0.72, 2.01)
Dx 2019 (ref=2017)	0.96	(0.59, 1.58)

6597

Poster Session

Disparities in PI3K/mTOR inhibitor use, toxicities, and outcomes among patients with metastatic breast cancer. *First Author: Claire Sathe, New York Presbyterian Hospital/Columbia University Irving Medical Center, New York, NY*

Background: Advances in breast cancer treatment have led to improvements in survival among patients with metastatic breast cancer (MBC). Nevertheless, Black patients and patients with lower socioeconomic status (SES) continue to bear a disproportionate mortality burden. Furthermore, because landmark trials for novel anticancer agents lacked racial diversity, their toxicity profile for minority patients remains uncertain. Our study examines the impact of race and other sociodemographic characteristics in the use and toxicity outcomes of PI3K and mTOR inhibitors (PI3K/mTORi). **Methods:** We conducted a retrospective analysis of EHR-derived data from the Flatiron Health Database (FHD). A dataset was constructed to include patients with hormone receptor-positive, HER2-negative MBC diagnosed between 1/1/2011 and 1/31/2022. Outcomes included PI3K/mTORi use, rates of hyperglycemia and dose reduction, and time on treatment. Multivariable logistic regression was used to evaluate factors associated with use and outcomes. **Results:** A total of 13,388 patients with MBC were included in our analysis, of which 2,620 (19.6%) received PI3K/mTORi (78.3% everolimus, 14.7% alpelisib, 6.9% both agents). Overall, 67.5% of all patients were categorized as White, 9.8% as Black/African-American (Black/AA); 18.9% were >75 years old; 10.1% were treated at an academic site; 4.0% had Medicaid insurance. Insurance through Medicaid was associated with lower use of PI3K/mTORi compared to commercial insurance (15.6% vs 18.8%; OR: 0.76, 95% CI: 0.59-0.99, p=0.04), as was advanced age (10.9% for >75 years old vs 22.9% for <60 years old; OR: 0.68, 95% CI: 0.58-0.80, p<0.001) and poorer performance status at diagnosis (15.1% for ECOG $\geq$ 2+ vs 22.9% for ECOG 0; OR: 0.84, CI: 0.72-0.98, p=0.03). Odds of PI3K/mTORi use were almost 50% higher for patients treated at an academic center (OR: 1.46, CI: 1.06-2.05, p=0.02). While Black/AA patient had lower rates of use than White patients (17.4% vs 20.1%), they had similar odds of receiving PI3K/mTORi on multivariable analysis (OR: 1.00, CI: 0.85-1.17, p>0.9). Black/AA patients experienced higher rates of hyperglycemia on PI3K/mTORi than White patients (67.6% vs 52.5%). On multivariable analysis, odds of hyperglycemia were twice as high for Black/AA patients (OR: 2.1, CI: 1.33-3.35, p<0.01). However, rates of dose reductions and time on PI3K/mTORi therapy did not differ significantly among White vs Black/AA patients. **Conclusions:** This analysis of real-world data suggests that lower SES is associated with decreased PI3K/mTORi use. Efforts to improve access to these life-prolonging agents are warranted. Of concern, we also found racial disparities in toxicity outcomes, with Black patients having twice the risk of hyperglycemia. Greater attention to the tolerability of novel agents in diverse populations is warranted. Research Sponsor: American Cancer Society; Breast Cancer Research Foundation.

6598

Poster Session

Decomposing racial differences in financial hardship among older cancer survivors. *First Author: Elizabeth Davis, Boston University, Boston, MA*

Background: Despite Medicare coverage, financial hardship is a prevalent issue among older cancer survivors, particularly among those belonging to a racial/ethnic minority. Sociodemographic, clinical, and area-level factors may mediate this relationship; however, no studies have assessed the extent to which these factors contribute to disparities. **Methods:** Surveys assessing financial hardship after cancer were completed by 721 patients age 65+ of Black or white race completing primary cancer treatment for breast, prostate, colorectal, prostate cancer or lymphoma at University of Alabama at Birmingham between 2000 and 2019. Financial hardship included material, psychological, and behavioral domains. Material hardship included ever 1) borrowing money/going into debt, 2) filed for bankruptcy, 3) worried about paying large medical bills, and 4) made any other financial sacrifices due to cancer. Psychological hardship was measured by asking if participants were ever worried about paying large medical bills related to cancer, its treatment or effects of treatment. Behavioral hardship was measured by asking if participants were unable or delayed in obtaining medical care, tests, treatments or prescriptions in the last 6 months. Non-linear Blinder-Oaxaca effect decomposition methods evaluated the extent to which individual-level sociodemographic, clinical, and area-level factors contributed to racial disparities in financial hardship. **Results:** Median age at survey was 78 (IQR = 73-82), majority were female (53%) and non-Hispanic White (84%). The most common cancers were breast (34%) and prostate (27%), followed by lung (17%), lymphoma (9%) and colorectal (14%). Ninety percent were diagnosed at an early stage and median time from diagnosis to survey was 8y (IQR = 5-12). There were no significant clinical differences between Black and white patients. Overall, 22% reported any financial hardship; 14% material, 3% behavioral, and 14% psychological. Black, compared to White participants reported significantly (p < 0.001) higher rates of overall (39% v 18%), material (29% v 11%), and psychological (27% v 11%) financial hardship. Notably, Black patients had higher rates of being unable to cover cancer-related costs (23% v 7%), worrying about paying large medical bills (27% v 11%), and having to borrow money or go into debt (9% v 3%). Overall, the observed characteristics explained 81% of racial differences in financial hardship among cancer survivors, primarily by differences in income (24%), cancer diagnosis and stage (22%), and area deprivation (15%). **Conclusions:** These results identify primary contributors to racial disparities in financial hardship among older cancer survivors, which can be used to develop interventions aimed at eliminating inferior healthcare outcomes experienced by certain racial groups, inform policy, and allocate resources to those at greatest risk for financial hardship. Research Sponsor: American Cancer Society.

6599

Poster Session

Commercial vs. Medicaid insurance and use of high-priced anticancer treatments. *First Author: Aaron Philip Mitchell, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Financial incentives presented by the larger markups on cancer drugs among commercial payors may result in increased use of high-priced drugs among commercially insured vs. Medicaid insured patients. We evaluated the association between patient insurance type and the likelihood of receiving higher-priced treatments. **Methods:** We linked cancer registry, administrative claims, and demographic data for individuals diagnosed with cancer in North Carolina from 2004-2011, who had either commercial or Medicaid insurance. We selected cancer types with multiple FDA-approved, guideline-recommended chemotherapy options, and large differences in price between the higher-priced and lower-priced options during the study period: advanced colorectal, lung, and head-and-neck cancer (HNC). The primary outcome was receipt of the higher-priced treatment option, and the primary exposure was insurance type: commercial vs. Medicaid. We estimated risk ratios (RR) for the association between insurance type and higher-priced treatment using log binomial models with inverse probability of exposure weights to control confounding by age, county-level poverty prevalence, and selected comorbidities. We assessed for potential modification of the RR by setting (hospital outpatient vs. physician office) and academic designation (NCI-designated comprehensive cancer center vs. other); these were exploratory analyses due to sparse data and subsequently limited confounding control. **Results:** Of 812 patients: 209 (26%) had Medicaid insurance; 311 (38%) had NHC, 263 (32%) colon or rectal cancer, and 238 (29%) lung cancer. The crude risk of higher-priced treatment was 36% (215/603) for commercially insured and 27% (57/209) for Medicaid insured (RR:1.31, 95%CI 1.02-1.67). After weighting the association was attenuated (RR:1.15, 95%CI 0.81-1.65). While limited by imprecision and the potential for uncontrolled confounding, exploratory subgroup analysis suggested that, compared to Medicaid insurance, commercial insurance was associated with numerically higher risk of higher-priced treatment among patients treated by non-NCI designated providers (RR:1.53, 95%CI 1.14-2.04), and within both the physician office (RR:1.36, 95%CI 0.95-1.95) and hospital outpatient (RR:1.08, 95%CI 0.58-2.02) settings, but lower risk of high-priced treatment within NCI cancer centers (RR:0.39, 95%CI 0.22-0.71). **Conclusions:** Individuals with Medicaid vs. commercial insurance access high-priced treatments at a similar proportion after accounting for differences in case mix, morbidity, and SES. However, modification of the association by and academic setting, observed in exploratory subgroup analysis, suggests the possibility that insurance type may affect treatment for some patient groups. This study was limited by focus on a single state and the potential for residual confounding. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology; U.S. National Institutes of Health.

6600

Poster Session

The evolving landscape of chemotherapy for the treatment of early-stage breast cancer from 2006-2019: Results of a retrospective cohort study. *First Author: Jenna Bhimani, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Chemotherapy has been a part of the evolving landscape of treatment for women with early-stage breast cancer (EBC). Over the last 20 years, standard treatment has included over 20 different drug combinations recommended by the National Comprehensive Cancer Network (NCCN), with nearly 45 variations on dosing and schedule across drug combinations. Little is known about the real-world landscape of chemotherapy used in EBC and how treatment patterns have changed with the advent of new standards of care. We evaluated chemotherapy patterns for women with EBC in the Optimal Breast Cancer Dosing (OBDC) Study, which uses electronic health record (EHR) data from KPNC (Kaiser Permanente Northern California) and Kaiser Permanente Washington (KPWA). **Methods:** In a cohort of 34,322 women diagnosed and treated for primary stage I-IIIa breast cancer aged 18+ at KPNC and KPWA, we explored patterns of chemotherapy use over time, from 2006 to 2019. We conducted stratified analyses based on receipt of pertuzumab and/or trastuzumab, due to their longer treatment duration. **Results:** Overall, 13,383 (39.0%) women received intravenous chemotherapy, with a decline observed in receipt of chemotherapy over time (40.5% in 2006 vs 35.9% in 2019) (p-trend<0.001). Of the women who received chemotherapy, 8.5% received neoadjuvant treatment, increasing from 4.1% in 2006 to 14.5% in 2019 (p-trend<0.0001). The average duration of chemotherapy was 5.4 months in 2006, increasing to 6.3 months in 2019 (p-trend<0.0001), and the number of chemotherapy infusion visits increased from an average of 10.7 visits in 2006 to an average of 12.5 in 2019 (p-trend<0.0001). Of those who received chemotherapy, 26.8% received trastuzumab or pertuzumab, with receipt of trastuzumab/pertuzumab increasing over time (p-trend<0.0001). For those receiving trastuzumab/pertuzumab, there was a decrease in treatment duration and average number of chemotherapy administration visits (p-trend<0.0001 for both). Conversely, for those not receiving trastuzumab/pertuzumab, there was an increase in the treatment duration and average number of visits (p-trend<0.0001 for both). **Conclusions:** While the prevalence of women receiving chemotherapy in our cohort has decreased since 2006, there has been a marked increase in neoadjuvant chemotherapy among those women receiving chemotherapy, as well as an increase in both the duration of chemotherapy treatment and number of associated chemotherapy administration visits, a pattern specifically observed in non-trastuzumab/pertuzumab containing regimens. The change in average duration and number of visits represents a shift in treatment patterns for patients and providers. Understanding trends in breast cancer chemotherapy is useful to inform clinical care and administrative planning for sites delivering chemotherapy for early-stage breast cancer. Research Sponsor: U.S. National Institutes of Health.

6601

Poster Session

Integrating the 31-gene expression profile test into clinical decision-making to guide risk-aligned care decisions for patients with stage I-III cutaneous melanoma: NCI-SEER Analysis. *First Author: David Hyams, Desert Surgical Oncology, Rancho Mirage, CA*

Background: Cutaneous melanoma (CM) management depends on an estimate of recurrence risk or death. Because of recognized disease risk and drug efficacy, pembrolizumab immunotherapy has been approved for stage IIB-C patients. However, it is a treatment with potential financial and biological toxicities with 16% of patients experiencing severe treatment related adverse events. Improved risk stratification could identify individuals for whom more selective management would be appropriate. In collaboration with the NCI Surveillance, Epidemiology, and End Results (SEER) program, which includes information on patients tested with a 31-gene expression profile (31-GEP) test in an unbiased and unselected manner, we confirm the 31-GEP adds independent prognostic value in patients with stage I-III CM, and investigated whether the 31-GEP could identify stage IIB-C patients who might reasonably avoid adjuvant therapy while also identifying patients with stage I disease who might benefit from more aggressive diagnostic and/or therapeutic intervention. **Methods:** SEER registries linked CM cases diagnosed 2013-2018 to 31-GEP test results provided by Castle Biosciences (9,207 matched) using a registry trusted third party (honest broker), including subsets of stage IIB-IIC (n=775) and stage I (n=5,651) melanoma. The primary endpoint was melanoma-specific survival (MSS). The 31-GEP risk-groups included Class 1A (low), Classes 1B/2A (intermediate), and Class 2B (high). Each was compared using Kaplan-Meier analysis and the log-rank test. **Results:** In the overall cohort, patients with a Class 1A result had a significantly higher 5-year MSS than a Class 1B/2A or Class 2B result (97.4% vs. 93.5% vs. 83.3%, $p < 0.001$). In multivariable analysis, a Class 2B result (HR=3.26, $p < 0.001$) and positive lymph node status (HR=3.41, $p < 0.001$) were the strongest predictors of diminished MSS. In stage IIB-C, 18.8% (146/775) of patients received a Class 1A result with an associated 5-year MSS of 89.1% (vs. Class 2B: 76.6%, $p = 0.001$), despite the absence of pembrolizumab approval for the evaluated SEER population. Alternatively, 4.6% (260/5,651) of patients with stage I disease had a Class 2B result, with an associated 5-year MSS of 92.3% (vs. Class 1A: 98.0%, $p < 0.001$). **Conclusions:** The SEER database allowed a non-biased analysis of a large cohort of patients with stage I-III CM who were tested with the 31-GEP. The 31-GEP identifies patients, including those with stage IIB-C disease, with favorable outcomes and could help physicians and patients decide whether to pursue adjuvant therapy. Moreover, the 31-GEP identifies high-risk patients, including those with stage I disease, for whom more aggressive follow-up and early intervention should be considered. Research Sponsor: Castle Biosciences, Inc.

6602

Poster Session

Evaluating depth of disparities in relation to relative survival rates: Analysis of SEER data. *First Author: Alma Habib, Ohio State University Wexner Medical Center, Columbus, OH*

Background: Prior studies have identified widening survival disparities between Black vs White patients (pts) in solid tumors with higher 5-year relative survival rates (RSR), a surrogate for higher amenability to treatment (Tehranifar et al., 2009). Given major advancements in treatment for hematologic malignancies leading to higher RSR, we sought to evaluate whether disparities worsened with higher RSR, especially among Black pts compared to White pts, in the modern era of therapy. We hypothesized that racial disparities would be larger in malignancies with higher amenability, as measured by 5-year RSR. **Methods:** We identified first hematologic malignancies among pts ages ≥ 18 years diagnosed between 2009-2019 in a collection of 17 Surveillance, Epidemiology and End Results (SEER) Program registries. We treated RSR as a continuous variable. Cox proportional-hazards model was used to correlate RSR and race with overall survival (OS) controlling for other pt characteristics. The interaction between RSR and race was included in the model to test if the racial effect on OS differed at various RSR levels. **Results:** We identified 363,340 pts who met inclusion criteria. Median age was 66 years and 55% were male. 82% were White and 10% Black. With a median follow-up of 48 months (mos), median RSR was 68.2% and median OS was 101 mos (95% CI 100-102 mos). Black pts had a lower median RSR than White pts, 63.8% vs 68.9%, and lower median OS, 90 mos (95% CI 87-93 mos) vs 99 mos (95% CI 98-100 mos). On univariable analysis, all variables were statistically significant given the large sample size. On multivariable analysis (MVA), Black pts had a higher risk of death than White pts. The interaction between 5-year RSR and race was highly significant ($p < 0.01$, not shown in Table), as indicated by slightly increasing hazard ratios (HRs) reflecting Black-White survival differences with increasing RSR level (i.e., as RSR increased, Black pts had slightly worse OS than White pts) (Table). **Conclusions:** We hypothesized that with increasing RSR, Black-White disparities might increase, as all effective therapies which contribute to improved RSR might not be equitably available to all populations. We observed that statistically significant disparities were present across RSR levels and increased only minimally for those with hematologic malignancies with higher RSR. In conclusion, disparities are prevalent in hematologic malignancies despite the degree of amenability to treatment. Research Sponsor: None.

MVA*	HR (95% CI)	p-value
Age, 5-year older	1.268 (1.265-1.271)	<.01
Male vs Female	1.177 (1.165-1.190)	
Year of Diagnosis, 1-year later	0.978 (0.976-0.980)	
Race, Black vs White at RSR level**		
30	1.247 (1.209-1.285)	
50	1.262 (1.237-1.286)	
70	1.277 (1.251-1.303)	
90	1.292 (1.251-1.334)	
5-year RSR, 10% higher		
White	0.785 (0.781-0.789)	
Black	0.790 (0.783-0.797)	

*Controlled for other pt variables. **Cutpoints used for ease of visualization for the purpose of this chart.

6603

Poster Session

Demographic disparities in lung cancer mortality and trends in the United States between 1999 and 2020: A population-based CDC database analysis. *First Author: Alexander Didier, The University of Toledo College Of Medicine and Life Sciences, Toledo, OH*

Background: Lung cancer is the leading cause of cancer-related mortality in the US and is projected to account for 127,070 deaths in 2023. While the lung cancer mortality rate has been decreasing over the last decade, demographic disparities in mortality still exist. We sought to determine the impact of demographic factors on lung cancer mortality and trends in the US. **Methods:** We queried the Centers for Disease Control database for mortality statistics with an underlying cause of death of lung and bronchus cancer (ICD-10 code C34.0.x) between the years 1999 – 2020. Age-adjusted mortality rates (AAMR) were calculated per 100,000 deaths. We assessed the AAMR by demographic variables, including race (Hispanic, Non-Hispanic White, Non-Hispanic Black, Non-Hispanic Asian or Pacific Islander, Non-Hispanic American Indian/Native American), geographic density (Urban, Suburban, Rural), sex, age (25-44, 45-64, 65+ years), and US Census Region. Temporal trends were evaluated using Joinpoint regression software. Average annual percent change (AAPC) was considered statistically significant if $p < 0.05$. **Results:** Between 1999 and 2020, lung cancer led to 3,380,830 deaths. The AAMR decreased by 42% from 55.1 to 31.8 with an associated AAPC of -2.6% ($p < 0.001$). In 1999, men had an AAMR of 76.8, almost twice as high as women, who had an AAMR of 40.2. These differences became less pronounced over time, and in 2020 men had an AAMR of 38.1, while women had an AAMR of 26.9. Between 1999 and 2020, rural populations experienced the highest AAMR at 52.3, and the slowest rate of decrease at -1.7% annually ($p < 0.001$), compared with urban populations who experienced the lowest AAMR of 40.6 and fastest AAPC decrease of -3.1% ($p < 0.001$). Non-Hispanic Black individuals experienced the highest AAMR at 49.8, with an annual decrease of -3.0% ($p < 0.001$), followed by Non-Hispanic White individuals who had an AAMR of 48.5 with an annual decrease of -2.5% ($p < 0.001$). Subgroup analysis demonstrated that Non-Hispanic Black men who resided in rural counties experienced the highest mortality at 60.2, with an associated decrease of -2.9% annually ($p < 0.001$). States in the 90th percentile of mortality included Arkansas and Kentucky; states in the 10th percentile of mortality included Hawaii and Utah. The West experienced the fastest decrease at -3.1% annually ($p < 0.001$), while the Midwest experienced the slowest decrease at -2.0% annually ($p < 0.001$). **Conclusions:** While lung cancer mortality has been decreasing since 1999, not all demographic groups have experienced the same rates of decline, and disparities in outcomes remain prevalent. Vulnerable subgroups may benefit from targeted interventions, such as tailored smoking cessation education and efforts to increase participation in clinical trials. Expansion of screening CT scans and telehealth platforms may also improve access to care for these populations. Research Sponsor: None.

6604

Poster Session

Association between severe adverse event management and overall survival in patients treated with immune checkpoint inhibitor with advanced non-small-cell lung cancer. *First Author: Jarushka Naidoo, Beaumont RCSI Cancer Center, Dublin, Ireland*

Background: The impact of severe adverse event (sAE) management (mgmt) on clinical outcomes in cancer patients (pts) receiving immune checkpoint inhibitor (ICI) therapy has not been fully examined. We aimed to evaluate the association between mgmt of sAEs and overall survival (OS) in pts receiving ICIs for advanced non-small cell lung cancer (aNSCLC). **Methods:** Data were drawn from the ConcertAI Patient360 dataset, a curated EMR-based US oncology database representing 19,000+ NSCLC patients. aNSCLC pts who initiated ICI in the first 3 lines of anti-cancer therapy from 1/15 - 8/31/21 with no record of clinical trial enrollment or diagnosis of a second primary cancer were included. sAEs (dermatologic, gastrointestinal, endocrine, hepatic, respiratory, rheumatic, renal, and cardiac) and mgmt actions were curated from unstructured data from ICI initiation through the earliest of: 100 days after ICI discontinuation, start of a non-ICI regimen, end of study period, or death. Cox regression was used to evaluate the association between sAE mgmt actions (as time-varying covariate) and OS adjusting for baseline characteristics including line of therapy. The earliest sAE and mgmt action per patient were examined in OS analysis. **Results:** 3,211 pts were identified (median [IQR] age 67 [13] years, 55.1% male). Median [Q1-Q3] duration of follow-up from ICI initiation was 8.2 [3.3-17.5] months. Most pts had advanced disease at initial diagnosis (82.0%) and started ICI in first line (61.6%). The most common ICI regimens in the first 3 lines were nivolumab (29.5%) and pembrolizumab + carboplatin + pemetrexed (29.1%). 8.6% of pts had at least one sAE, most often diarrhea (3.5%). Median [Q1-Q3] time from ICI initiation to first sAE was 84 [34-211] days. Mgmt actions any time after first sAE included anti-cancer treatment interruptions [dose reduction (4.0%), hold (20.6%), discontinuation (2.2%)], sAE treatment [corticosteroids (71.8%), immunosuppressive drugs (2.5%)], hospital admission [hospitalization (57.4%), emergency department visit (24.6%)], and other/unknown (4.3%). Overall, median [95% CI] OS was 13.6 [12.6-14.6] months. Compared with pts with no sAEs, pts with sAEs whose earliest mgmt action was hospital admission (N=155) or sAE treatment (N=71) had a higher risk of all-cause mortality (adjusted HR [95% CI] 1.61 [1.38-1.88] and 1.53 [1.22-1.91], respectively). Pts with sAEs first managed with anti-cancer treatment interruptions (N=39) had similar risk of all-cause mortality (0.91 [0.66-1.25]) compared with pts with no sAEs. **Conclusions:** Pts with sAEs first managed with hospital admission or sAE treatment had shorter OS than those with no sAEs. No difference was observed for sAEs first managed with anti-cancer treatment interruptions. Findings suggest early treatment interruption for sAEs does not impact OS. Research Sponsor: Bristol-Myers Squibb.

6605

Poster Session

Intrathecal drug delivery systems for cancer pain control: Insights on current contemporary practices in the US. *First Author: Vasudha Goel, University of Minnesota, Minneapolis, MN*

Background: About a third of cancer survivors report moderate to severe pain. Intrathecal drug delivery system (IDDS) is an implantable pain control option for treating intractable chronic pain not responsive to systemic opioid therapy. Studies on the current practices in the US around the utilization of IDDS for cancer pain are lacking. **Methods:** The Nationwide inpatient sample (NIS) dataset is funded by the Agency for healthcare research and quality (AHRQ) for multistate healthcare research & decision-making. Adult patients admitted to hospitals with a primary or secondary cancer diagnosis between 2016-19 were included. Patients undergoing IDDS implantation were identified using the validated International Classification of Diseases, 10th Revision, Procedure Coding System codes (00HU33Z Insertion of infusion device into spinal canal, percutaneous approach and 0JH80VZ Insertion of infusion pump into abdomen subcutaneous tissue and fascia, open). Baseline demographics, hospital characteristics, and type of cancer associated with IDDS implantation were evaluated in the study. **Results:** 22,895 patients underwent IDDS surgery amongst 7.06 million hospitalizations from 2016-19. The IDDS cohort consisted of patients in the 65-79 years age group (40.49%), female sex (50.42%), and Caucasian ethnicity (75.82%). Most IDDS surgeries were performed in large, urban teaching hospitals. **Conclusions:** Despite recommendations supporting IDDS use, a small minority received the treatment with significant racial & socioeconomic disparities in IDDS use. Research Sponsor: None.

	No IDDS 7,042,953	IDDS surgery 22,895	Total population 7,065,848	p-value
Age (Years)				<.0001
18-34	154240 (2.19%)	820 (3.58%)	155060 (2.19%)	
35-49	544645 (7.73%)	2815 (12.3%)	547460 (7.74%)	
50-64	2186090 (31.04%)	8365 (36.54%)	2194455 (31.05%)	
65-79	2959744 (42.02%)	9270 (40.49%)	2969014 (42.02%)	
≥ 80	1198235 (17.01%)	1625 (7.1%)	1199860 (16.98%)	
Gender				<.0001
Male	3636884 (51.64%)	11345 (49.6%)	3648229 (51.63%)	
Female	3403269 (48.32%)	11525 (50.4%)	3414794 (48.33%)	
Race				<.0001
White	4883598 (69.34%)	17360 (75.82%)	4900958 (69.34%)	
Black	931800 (13.23%)	1480(6.46%)	933280 (13.23%)	
Hispanics	576785 (8.19%)	1460 (6.38%)	578245 (8.18%)	
Asian or Pacific Islander	221740 (3.15%)	1205 (5.26%)	222945 (3.16%)	
Native American	31230 (0.44%)	90 (0.39%)	31320 (0.44%)	
Location of Hospital				<.0001
Rural	483944 (6.87%)	1115 (4.87%)	485059 (6.86%)	
Urban	6559009 (93.13%)	21780 (93.13%)	6580789 (93.14%)	
Hospital bed size				<.0001
Small	1190979 (16.91%)	1510 (6.6%)	1192489 (16.88%)	
Medium	1905423 (27.05%)	2535 (11.07%)	1907958 (27.0%)	
Large	3946552 (56.12%)	18850 (82.33%)	3965402 (56.12%)	
Teaching Status				<.0001
Non-Teaching	1759899 (24.99%)	2535 (24.94%)	1762434 (24.94%)	
Teaching	5283054 (75.01%)	20360 (88.93%)	5303414 (75.06%)	

6607

Poster Session

Development of natural language processing (NLP) models for extracting key features from unstructured notes to create real-world data (RWD) assets for clinical research at scale. *First Author: Smity Agrawal, ConcertAI, Bengaluru, Karnataka, India*

Background: RWD derived from Electronic Health Records (EHR) has detailed clinical information about patient journeys that can assist in clinical research, trial design, safety assessments etc. However, much of the vital information is locked away in unstructured clinical texts and needs to be converted to structured format to be useful for downstream applications. We demonstrate how this can be achieved at scale with a high degree of accuracy through NLP. **Methods:** NLP models were developed to extract data for 11 clinical variables from unstructured notes of ~98k lung cancer patients and merged with the structured data into a common data model (Table). These models were a combination of domain knowledge, rule-based models, machine learning models, and deep learning models. The increase in fill rate per variable over structured data only was used to quantify the improvement by NLP. The accuracy of the models was assessed against a manually curated dataset comprising of 752 patients. **Results:** The NLP models significantly improved the fill rate of key clinical variables and were able to extract the information from clinical notes with high accuracy (Table). For some variables such as NSCLC/SCLC status, surgery, tumor grade and histology, all or most of the data was extracted via NLP. Metastatic status via NLP included distant metastasis, locally advanced disease and no metastasis whereas in the structured data, only data for distant metastasis was present. In the case of Performance Status (PS), even though a significant number of patients had at least 1 PS recorded in the structured data, NLP significantly increased longitudinal capture, thus increasing the density of this variable per patient. **Conclusions:** NLP models can be developed and used to enrich structured RWD data by extracting information from unstructured documents thus significantly improving the utility of this data for downstream applications. Given the high accuracy of these models and the scale at which they can be run, this can be a good alternative to human curation or can augment human curation enabling the creation of very large-scale datasets for clinical research. Research Sponsor: None.

Performance of NLP models and their contribution to enriching structured RWD.												
NLP Field (# of patients = 98676)	Stage at Dx	T Stage at Dx	N Stage at Dx	M Stage at Dx	NSCLC / SCLC	Tumor Histology	Tumor Grade	Metastatic Status	Metastatic Site	Lung Cancer Surgery	PS	
# of unique patients in RWD	57065	50139	51897	55035	0	10534	2771	34067	31510	0	70773	
# of unique patients in RWD- NLP	83864	66138	66724	66593	88795	94677	56662	92627	47004	22844	82679	
% contribution from NLP	32	20.9	22.2	17.4	100	88.9	95	63.2	33	100	58*	
Precision/Recall	0.92/ 0.87	0.92/ 0.83	0.89/ 0.85	0.9/ 0.81	0.98/ 0.91	0.87/ 0.88	0.91/ 0.90	0.88/0.87	0.94/0.97	0.87/0.67	0.97**	

* Calculated based on patients where at least 1 PS value was added by NLP. ** Accuracy.

6606

Poster Session

The safety of seasonal influenza vaccination among patients prescribed immune checkpoint inhibitors: A self-controlled case series study using administrative data. *First Author: Alicia Ann Grima, Dalla Lana School of Public Health, University of Toronto, Toronto, ON, Canada*

Background: Immune checkpoint inhibitor (ICI) therapy for cancer patients carries a risk of severe immune-related adverse events (IRAEs). Since vaccines are immunomodulatory, administering seasonal influenza vaccinations to individuals on ICI therapy may exacerbate this risk. However, these vaccines provide substantial benefit to this at-risk population. As severe IRAEs are rare, previous vaccine safety studies in this population have been underpowered and have shown conflicting results. **Methods:** We used health administration data on adult Ontarians who initiated ICI therapy and received an influenza vaccine between January 1, 2012, and December 31, 2019. We conducted a self-controlled case series study, with a pre-vaccine control period (12-weeks post-ICI initiation to 14 days before vaccine), risk period (42 days post-vaccine), and a post-vaccine control period (until observation end). Each individual contributed a maximum of 2 years of person-time. Emergency department (ED) visit(s) and/or hospitalization for any cause was used as a surrogate measure of severe IRAE frequency. We fitted a fixed effect Poisson regression model incorporating seasonality and time to estimate incidence. **Results:** We identified 1133 patients who received an influenza vaccine on ICI therapy. The majority were aged ≥66 years (72.7%), male (62.8%), and had lung cancer (53.9%). A quarter (25.9%) experienced an ED visit and/or hospitalization during the observation period. The rate of ED visits and/or hospitalization per person-days in the risk and control periods were similar, with an incidence rate ratio of 1.04 (95% CI: 0.75, 1.45). Subgroup and sensitivity analyses revealed similar findings. **Conclusions:** Receipt of a seasonal influenza vaccine was not associated with an increased incidence of ED visit or hospitalization among adults on ICI therapy. The results from this analysis suggest no significant safety concern with administering influenza vaccines to this patient population. Research Sponsor: Canadian Immunization Research Network (CIRN).

6608

Poster Session

A pragmatic, single-arm clinical trial of a dose-adjustment algorithm for preventing cytopenia-related delays during FOLFOX chemotherapy. *First Author: Gabriel A. Brooks, Dartmouth Cancer Center, Lebanon, NH*

Background: Unplanned delays are common during FOLFOX chemotherapy, and cytopenias (neutropenia and/or thrombocytopenia) are the most common cause of delays. We evaluated a novel, provider-driven FOLFOX dose-adjustment algorithm designed to reduce unplanned delays while maintaining chemotherapy dose intensity. **Methods:** We conducted a pragmatic, single-arm clinical trial to evaluate the FOLFOX dose adjustment algorithm (NCT04526886). The algorithm prescribed graded chemotherapy dose reductions without delay on day 1 of cycles 2-6 for patients with an absolute neutrophil count (ANC) of 750 to 1499/microL and/or a platelet count of 50 to 99 K/microL. The algorithm prescribed a delay when ANC was less than 750 or platelet count was less than 50 on day 1 of cycles 2-6. Chemotherapy dose adjustments and delays for reasons other than cytopenias were at the discretion of the treating provider. Patients receiving initial treatment with FOLFOX chemotherapy (with or without concomitant monoclonal antibodies) were eligible. Subjects received standard chemotherapy doses in cycle 1 (bolus 5-FU 400 mg/m2, oxaliplatin 85 mg/m2, and infusional 5-FU 2400 mg/m2/46 hours). Use of granulocyte colony stimulating factor (G-CSF) was not permitted, except for patients who had already experienced an unplanned delay. The primary outcome was any unplanned delay prior to completion of day 1 of cycle 6 of chemotherapy (with an interval of >18 days between cycles.) We tested whether the incidence of any unplanned delay was less than the historical rate of 43%, using a one-sample test of proportions. Chemotherapy relative dose intensity (RDI) over cycles 1-6 was a key secondary outcome. **Results:** 48 of 54 enrolled subjects were evaluable. The median age was 66, and 50% were female. The most common primary cancer sites were colorectal (n = 31) and gastroesophageal (n = 12). Metastatic cancer was present in 67%, and 35% received a concurrent monoclonal antibody. Sixteen of 48 subjects had any unplanned delay before completing cycle 6 (33%, 95% CI 0.22-0.47, p = 0.08 for comparison with historical proportion of 43%), and 7 subjects had any cytopenia-related delay (15%, CI 0.07-0.27). Twenty-one subjects (44%) had one or more algorithm-driven chemotherapy dose reductions without a delay, and 8 cycles were delivered without delay with an ANC of 750-999 (without G-CSF). The mean (median) chemotherapy RDIs were: bolus 5-FU, 65% (67%); oxaliplatin, 85% (90%); and infusional 5-FU, 92% (97%). **Conclusions:** The 33% observed incidence of any unplanned chemotherapy delay was nominally but not significantly lower than the historical rate of 43%. The incidence of any cytopenia-related delay was 15%, lower than the historical rate of >30%. Further refinement and evaluation of the FOLFOX dose adjustment algorithm may help to reduce unplanned delays and their attendant disruptions and costs for patients and providers. Clinical trial information: NCT04526886. Research Sponsor: Dartmouth Cancer Center.

6609

Poster Session

Assessment of patient reported outcomes (PROs) completion patterns in patients with cancer: Examining real-world data. *First Author: Nada Al-Antary, Henry Ford Health System, Detroit, MI*

Background: Use of Patient Reported Outcomes (PROs) in clinical practice plays a major role in improving care, quality of life, hospitalization, emergency room visits and consequently improving overall survival. However, robust information on real-time assessment of PROs in cancer patients is insufficient, as most available data are limited to specific populations enrolled in clinical trials. This thereby increases disparities among minorities of race, age, and socioeconomic status, creating a barrier between the benefits of PROs and these underserved populations. This study examines the response rates, patterns and characteristics of patients completing PROs in a tertiary cancer center. **Methods:** Patients with a cancer diagnosis and an oncologic provider visit at a tertiary cancer center were offered an opportunity to complete Patient Reported Outcome Measures (PROMs) between August 2020 and July 2022. We used the National Institute of Health's computer adaptive tests Patient-Reported Outcomes Measurement Information System (PROMIS) instruments in pain interference, physical function, fatigue, and depression. Seven days prior to their clinical appointment, patients were assigned the PROMIS instruments in MyChart, then offered in-clinic completion with a tablet at check-in, if not completed online. A decision tree model was employed to assess the factors that may influence patients' PROMs completion (age, gender, race, marital status, insurance, stage, comorbidity score, and provider specialty and location). **Results:** A total of 8,535 patients were offered the PROMIS CAT version 2.0 instrument during the study period. The two most important factors that determine whether a patient completed PROMs in order of importance were provider specialty and patient race. Patients were more likely to complete PROMs if they had a visit with a provider in Radiation Oncology (RC) or Surgery specialty compared with Medicine or Supportive Oncology specialty (40.86% versus 29.68%). Among patients who had a visit with a provider in RC or Surgery specialty, there was a better chance of PROMs completion with White race compared to Black or Other races (45.83% versus 33.69%). Of those who had a visit with a provider in Medicine or Supportive Oncology specialty, there was a better chance of PROMs completion with Other or White races compared to Black race (32.40% versus 22.19%). **Conclusions:** We found that provider specialty and patient race were the most important factors influencing patients' PROMs completion. In order to realize the full benefit of PROs in patient care, multilevel interventions can be employed to increase patient-provider utilization of PROs. Moreover, efforts should focus on a patient-centered design to address patient and provider barriers impeding PROs accessibility and completion. Research Sponsor: None.

6611

Poster Session

Using real-world evidence (RWE) in regulatory decision making: A study of 6 oncology approvals with RWE included in the product label. *First Author: Jihong Zong, Bayer HealthCare Pharmaceuticals Inc., Whippany, NJ*

Background: The 21st Century Cures Act in 2016 enhanced the FDA's ability to include the use of real-world data (RWD) and consideration of RWE in the development and approval of new medical products. Currently, limited assessments of the use of RWE in FDA approved oncology product reviews exist in the literature. This study was conducted to determine how RWE was used in FDA decisions for oncology drug approvals between 2015 and 2022. **Methods:** A systematic review of FDA submission documents and product labels available on the FDA website from 2020 to 2022, in addition to an exhaustive manual search of grey literature and the results of a targeted literature search from 2015 to 2019 were used to identify RWE that were included in FDA submission documents and in approved product labels. **Results:** In total, 124 oncology product evaluations were reviewed in the 2020 to 2022 literature search. Twenty-nine oncology product NDAs and BLAs included RWE to support efficacy, safety, or indication, of which the majority (n=26) ultimately had RWE accepted as evidence by the FDA for the submission. In these cases, RWE was used to add context (n=16), to support the indication or safety (n=7), to provide substantial basis for indication or safety (n=2), as a statistical comparison (n=2), or for informational purposes only (n=1). Feedback from the FDA reviewers for reasons RWE studies were not considered during product approval reviews included methodology issues, sample size concerns, and omission of patient level data. Ultimately, across the 2015 to 2019 targeted literature review and the 2020 to 2022 FDA submission document review, 6 oncology product labels incorporated RWE: pembiciclib, uridine triacetate, lutetium Lu 177 DOTATATE, bevacizumab-adv, naxitamab-gqgk, and decitabine/cedazuridine. RWE was used to support the initial indication for the majority of products (n=5) and also supported label expansion (n=1). RWE was incorporated in the product label postmarketing experience section (n=3), the clinical studies section (n=2), and the warnings/precautions section (n=1). **Conclusions:** These results suggest that RWE has become an important part of regulatory decision-making for oncology drug approval. Twenty-six of 29 RWE studies were accepted as evidence for the submission. For the 6 oncology products that include RWE in the product label, RWE was most frequently used to support the initial indication and was included in the post-marketing experience section. These examples show consistent use of RWE since the approval of the 21st Century Cures Act and provide evidence of a promising new direction with the creation of the FDA guideline/program for RWE. Research Sponsor: Bayer.

6610

Poster Session

Molecular diagnostic classification for cancers of unknown primary (CUP): Post-testing diagnosis and treatment impact analysis from real-world claims data. *First Author: Zachary Rivers, Tempus Labs, Inc., Chicago, IL*

Background: Next-generation sequencing-based molecular diagnostic classifiers can help identify the tissue of origin for CUP, and enable the selection of site-specific therapies (as opposed to empiric chemotherapy) for this vulnerable population with high unmet need. NCCN guidelines do not endorse the use of tissue of origin classifiers as standard of care for CUP patients due to limited clinical evidence. Here, we linked results of a commercial molecular diagnostic classifier with claims data to understand how this test impacted patient care. **Methods:** We assessed de-identified claims data from the Komodo Healthcare Map (a database including provider visits, laboratory tests, procedures, imaging, and prescriptions) linked to the Tempus Tumor Origin (TO) test—a machine learning classifier that uses RNA-seq data to classify tumors into one of 68 histological subtypes. Eligible patients had pathologist-confirmed CUP and were classified as one of 9 subtypes (each having n>10). Impact was determined by identifying either one or more new diagnostic codes or new subtype-related medication claims following TO testing. **Results:** We analyzed data from 490 patients: 483 for the diagnosis analysis and 213 for the medication analysis (206 patients appear in both, due to differences in timing of diagnosis vs. medication claims). We found that post-TO testing, 49.9% (n=241) of patients had a diagnostic code change, 63.8% (n=136) had a treatment change, and 41% (n=85) had both. In total, 59.6% (n=292) of patients were impacted by the use of this classifier, with variation according to predicted subtype (Table). Cancer types with specific treatment options were more likely to have changes in diagnostic code or treatment. For CUP predicted as lung adenocarcinomas, 85% of the cases had a new subtype-aligned medication, and 78% were specifically placed on immunotherapy (IO) compared with 24% of overall patients. **Conclusions:** Using real-world claims data, we show that molecular diagnostic testing utilizing Tempus TO impacted care for a majority of CUP patients. This cohort will be followed to identify how TO testing decisions impact outcomes. Research Sponsor: Tempus Labs.

Cancer Type	Diagnosis Impact	Medication Impact	IO Impact	Total
Breast	15/24 (63%)	10/16 (63%)	3/16 (19%)	16/25 (64%)
Colorectal	57/107 (53%)	26/52 (50%)	4/52 (8%)	69/108 (64%)
Female Reproductive Tract	16/50 (32%)	17/26 (65%)	0/26 (0%)	25/54 (46%)
Gastroesophageal	25/47 (53%)	19/27 (70%)	4/27 (15%)	32/48 (67%)
Lung Adenocarcinoma	13/37 (35%)	9/13 (69%)	3/13 (23%)	19/37 (51%)
Lung Squamous Cell	61/96 (64%)	23/27 (85%)	21/27 (78%)	67/96 (70%)
Pancreatic	19/34 (56%)	7/13 (54%)	6/13 (46%)	21/34 (62%)
Urothelial	19/55 (35%)	15/25 (60%)	3/25 (12%)	25/55 (45%)
	16/33 (48%)	10/14 (71%)	8/14 (57%)	18/33 (55%)

6612

Poster Session

Patient reported outcomes (PROs) collection modalities among patients diagnosed with cancer: Online vs in-person. *First Author: Eric Adjei Boaky, Henry Ford Health System, Detroit, MI*

Background: Patient reported outcomes (PRO) can be valuable clinical tools to embed the voice of patients into the clinical assessment. PROs provide important metrics to guide treatment decision making, improve quality of life, reduce acute care, and extend survival in cancer patients. Different modalities for collecting patient reported outcome measures (PROMs) exist (e.g., electronic, paper, telephone); yet little is known about factors associated with PROMs completion modality. More information on PROMs completion modality may determine addressable barriers. We sought to determine whether patients' sociodemographic and clinical factors differed by completion modality. **Methods:** Beginning in 2021 all patients diagnosed with cancer who had a visit with an oncologic provider at a tertiary cancer center were assigned the National Institute of Health's computer adaptive tests Patient-Reported Outcomes Measurement Information System (PROMIS) instruments in pain interference, physical function, fatigue, and depression through the MyChart patient portal 7 days prior to the visit. If this was not completed at the time of the visit, it was available for completion on a tablet during check-in. The outcome variable was completion modality defined as the method a patient used to complete their PROMs (MyChart vs. In-Person). Multivariable logistic regression model was used to estimate the association between patients' sociodemographic and clinical factors (age, sex, race/ethnicity, marital status, insurance type, stage, provider specialty) and completion modality. **Results:** A total of 2915 patients completed PROMs, of which 54% completed using MyChart and 46% completed in-person. The average age of patients was 59.6 (SD=12.4) years, most were females (63.1%), White (69.4%) and married (59.2%). Compared to male patients, females were less likely to complete PROMs in-person (aOR=0.80, 0.67–0.95). However, patients were more likely to complete PROMs in-person if they were of Black race (aOR=1.85, 1.52–2.24) or Other race (aOR=1.48, 1.12–1.96) vs. White; single (aOR=1.30, 1.05–1.62) vs. married; or have Medicaid/other insurance (aOR=1.52, 1.15–2.01) vs. private insurance. Patients who had visits with a radiation oncology provider (aOR=1.50, 1.20–1.86) or surgical oncology provider (aOR=1.32, 1.07–1.62) were more likely to complete PROMs in-person compared to those who had visits with a medical oncology provider. **Conclusions:** Almost half of the patients completed PROMs in-person during check-in, which was unexpected in the context of trends toward mobile-based patient engagement. Patients in underserved populations were the most likely to complete PROMs in-person. Although offering PROMs remotely may be more efficient and allow monitoring between visits, offering an in-person option helps to capture PROs from underserved populations. Research Sponsor: None.

6613

Poster Session

An assessment of the provider financial risk impacts of adoption of biosimilars in the Medicare Oncology Care Model. *First Author: Joshua A. Roth, Pfizer, Inc., New York, NY*

Background: In 2016, Medicare launched the Oncology Care Model (OCM)—a Value-Based Payment (VBP) initiative providing per-beneficiary prospective payment to providers, and performance-based financial incentives/risks based on cost of care in 6-month ‘episodes’ vs. risk-adjusted benchmarks for cancer patients receiving chemotherapy. Oncology biosimilars may play an important role in managing financial risk in the OCM and other VBP models, but the real-world impact remains uncertain. The objective of this study was to quantify the impact of biosimilar adoption on oncology provider financial risk under the OCM using real-world data. **Methods:** We estimated the impact of biosimilar adoption on provider financial risk from 2019 to 2021 by modeling the methods (episode framing, pricing, & risk adjustment) of the OCM. Cancer episodes were identified from the 5% Medicare Limited Data Set (LDS). The study sample consisted of cancer treatment episodes with use of any of the following agents or their biosimilars: bevacizumab, rituximab, trastuzumab, epoetin alfa, filgrastim, and pegfilgrastim. Financial risk was defined as the difference in observed total cost of care vs. OCM target episode cost. The primary outcome was the difference in financial risk (expressed in nominal \$USD) under observed use of reference and/or biosimilars vs. hypothetical use of 100% reference agent. **Results:** The study sample included 8851 6-month episodes initiating between 1/2019 and 6/2021. Biosimilar adoption resulted in a mean cost reduction of \$1,020 per episode vs. hypothetical 100% use of reference agents. Biosimilar use increased markedly over the study horizon—with 24% of episodes with a biosimilar in Half (H1) 2019, increasing to 65% by H1 2021, and driven by increased use of antineoplastic (1% to 36%) vs. supportive care biosimilar agents (23% to 34%). Mean financial risk reduction grew with the rapid adoption of biosimilars over this period. The average risk reduction in episodes initiating in H1 2021 was about 10 times larger than that seen in episodes initiating in the H1 2019 (\$2060 vs \$201, See Table). Observed mean cost was below the OCM target cost (\$48808) in H1 2021 but exceeded the target cost in all other periods (range: +\$1451 to +\$4966). **Conclusions:** From 2019 to 2021, rapid adoption of biosimilars in Medicare fee-for-service beneficiaries included in the LDS led to substantial cost savings and reduction in risk for cancer episodes evaluated under the OCM methods. Broad adoption of biosimilars is a key strategy that providers in oncology VBP models will need to consider to manage financial risk. Research Sponsor: Pfizer.

Time Period	Observed Episodes	Observed Cost Per Episode	Cost Per Episode with 100% Reference Agent	Reduction in Financial Risk with Biosimilar Use
H1 2019	1985	\$53241	\$53443	-\$201
H2 2019	1779	\$53278	\$53661	-\$383
H1 2020	1760	\$49118	\$50084	-\$966
H2 2020	1606	\$49727	\$51423	-\$1696
H1 2021	1721	\$48587	\$50648	-\$2060

6615

Poster Session

Racial disparities in survival and stage at diagnosis among adolescent and young adult patients with cancer. *First Author: Kekoa A. Tappara, Stanford Cancer Institute, Palo Alto, CA*

Background: Adolescent and young adult (AYA) patients (15-39 years) are an under-recognized population with high risk of select malignancies. Compared to pediatric and adult patients, AYA patients have not achieved improvements in cancer survival. No studies have evaluated overall survival (OS) and stage at diagnosis among all 5 federally recognized races in the US. Here we aim to investigate OS and stage at diagnosis among AYA patients by race. **Methods:** A retrospective cohort study of AYA patients diagnosed between 2004-2017 was conducted with the National Cancer Database. Patients with the 10 deadliest AYA cancers with at least 6 months of follow-up were included. Primary endpoints were OS (time from diagnosis to death) and late stage at diagnosis (stage III/IV or Grade III/IV for central nervous system (CNS) cancer). Kaplan-Meier estimates and log-rank tests assessed OS. OS and late stage were evaluated by race using multivariable Cox proportional hazard (adjusted hazard ratio [aHR]) and logistic (adjusted odds ratio [aOR]) regressions, respectively, with 95% confidence intervals (95%CI). All regressions were adjusted for sociodemographic and cancer characteristics. **Results:** 291,899 AYA patients were included: 64% female, 65% stage I/II, and 62 month median follow-up. Cancer sites included 27% breast, 16% lymphoma, 13% melanoma, 11% testis, 9% CNS, 7% colorectal, 7% cervix, 5% sarcoma, 3% ovary, and 2% lung. Race included 82.3% Non-Hispanic White (NHW), 14.0% Black, 2.9% Asian, 0.5% American Indian and Alaska Native (AIAN), and 0.3% Native Hawaiian and other Pacific Islander (NHPI). OS differed for all cancers by race ($p < .0001$), except for lung ($p = .008$), CNS ($p = .32$), and ovary ($p = .28$). OS was significantly inferior for NHPI, Black, and AIAN but superior for Asian, versus NHW (Table). NHPI had inferior OS (aHR, 95%CI) for melanoma (4.5, 2.0-10.0), colorectal (1.8, 1.3-2.4), lymphoma (1.7, 1.1-2.1), and cervix (1.6, 1.1-2.4) cancers. Black patients had inferior OS for melanoma (1.6, 1.2-2.2), lymphoma (1.5, 1.4-1.6), and breast (1.4, 1.3-1.4) cancers. Asian patients had superior OS for breast (0.7, 0.7-0.8) and lung (0.7, 0.6-0.9) but inferior survival for testis (1.9, 1.3-2.9) cancers. Asian patients had inferior OS for colorectal (1.4, 1.0-1.9). Late stage at diagnosis was higher for NHPI, Black, and Asian patients, compared to NHW patients (Table). **Conclusions:** Both NHPI and Black AYA patients with cancer have higher risk of death and late stage disease at diagnosis, compared to NHW patients. Our data reveal racial disparities among Indigenous AYA patients masked by prior data omission. Research Sponsor: Stanford Cancer Institute – Women Cancer Center’s Innovation Award; Stanford Cancer Institute – SCI Fellowship Award; Stanford Cancer Institute – Cancer Innovation Award.

Race	aHR	95%CI	P	aOR	95%CI	P
White	1.00	Ref		1.00	Ref	
AIAN	1.15	(1.02-1.30)	0.021	1.09	(0.96-1.22)	
Asian	0.90	(0.85-0.95)	<0.001	1.20	(1.14-1.26)	<0.001
Black	1.22	(1.19-1.26)	<0.001	1.40	(1.36-1.43)	<0.001
NHPI	1.25	(1.09-1.44)	0.002	1.34	(1.16-1.55)	<0.001

6614

Poster Session

An application of extrapolating clinical data from single-arm trials to assess comparative effectiveness. *First Author: Kangho Suh, University of Pittsburgh, Pittsburgh, PA*

Background: Single arm studies pose some challenges to determining comparative effectiveness of treatments. Such is the case with the tumor agnostic tropomyosin receptor kinase (TRK) inhibitors, larotrectinib and entrectinib. Larotrectinib and entrectinib are indicated for treatment of advanced cancer in patients (pts) with *NTRK* gene fusions. Lacking head-to-head trials, modeling methods are useful to estimate relative benefit. A direct naïve comparison, where single arms from separate trials are compared, can be used. Here, we estimate and compare long term benefit for pts receiving larotrectinib or entrectinib for *NTRK* gene fusion-positive non-small cell lung cancer (NSCLC) and colorectal cancer (CRC) by extrapolating survival curves to generate expected life-years (LYs) and quality-adjusted life-years (QALYs). **Methods:** We used partitioned survival methods to forecast comparative effectiveness. Larotrectinib survival data were derived from an updated July 2021 analysis of 21 adults (≥ 18 years of age) with NSCLC and 15 pts with CRC (NCT02122913, NCT02637687, and NCT02576431). Survival data for entrectinib were derived from published literature. Extrapolation of results were necessary to estimate long-term outcomes since the mean follow-up was less than three years. Progression free survival and overall survival for both treatments were estimated using several parametric survival distributions (Exponential, Weibull, Log-logistic, and Log-normal), then selecting based on AIC and clinical plausibility. QALYs were estimated by adjusting the time spent in the pre progression and post progression health states by utility values from the literature. A discount rate of 3% was applied to LYs and QALYs. Model uncertainty was evaluated using one-way and probabilistic sensitivity analyses. **Results:** In the larotrectinib trials, response rates were 86% and 33% in NSCLC and CRC, respectively. Exponential curves were fit for both treatments. In the entrectinib trials, response rates were 70% in NSCLC and 29% in CRC. The larotrectinib model estimated 7.3 LYs (95% Credible Interval [CrI]: 3.3, 11.4) and 4.3 QALYs (95% CrI: 2.2, 6.5) in NSCLC and 1.7 LYs (95% CrI: 0.8, 3.2) and 1.3 QALYs (95% CrI: 0.7, 2.3) in CRC. The entrectinib model estimated 2.7 LYs (95% CrI: 1.7, 4.2) and 1.6 QALYs (95% CrI: 1.1, 2.3) in NSCLC and 0.5 LYs (95% CrI: 0.2, 1.6) and 0.4 QALYs (95% CrI: 0.1, 1.1). Compared to entrectinib, larotrectinib produced additional gains of 4.7 LYs and 2.7 QALYs in NSCLC and 1.1 LYs and 0.9 QALYs in CRC. Limitations include non-matched baseline differences in the trial populations. **Conclusions:** In the absence of head-to-head trials, comparative effectiveness can be assessed by extrapolating from single armed studies indicated for the same patient population. Larotrectinib improved survival and quality adjusted survival vs entrectinib. Additional studies are needed to confirm these findings. Research Sponsor: Bayer US LLC.

6616

Poster Session

Real world utilization and disparities in outcome in the use of novel anti-androgen agents for metastatic prostate cancer. *First Author: Samina Hirani, Virginia Commonwealth University Health, Richmond, VA*

Background: Despite advances in treatment, disparities exist in prostate cancer treatment and utilization of treatment resources based on several factors including race and socioeconomic status. As evidence-based guidelines increasingly define novel androgen receptor inhibitors (ARIs) as the standard of care, it is important to understand how the utilization of ARIs impacts the outcome. In this study, we investigated the relationship between the utilization of the two most commonly used ARIs, Abiraterone and Enzalutamide, and survival among patients with metastatic prostate cancer. **Methods:** We conducted a retrospective analysis of patients in the Surveillance, Epidemiology, and End Results (SEER)-Medicare database from January 1st, 2013 to December 31, 2017. All patients aged 18 years and above with metastatic prostate cancer were included. The objective of these study was to determine the utilization of ARIs in different groups (age, race, location, income status and marital status) and investigate the impact of these variables on the survival. Kaplan-Meier survival curves were used for the survival analysis. Patients were stratified by: who received an ARI alone or in combination vs. who did not. Log-rank tests were used to compare the stratified survival probability curves by groups. A multivariate proportional hazards model was used to compare the instantaneous risk of death in metastatic prostate cancer between patients based on selected covariates. All hypothesis tests were two-tailed with a p -value < 0.05 considered statistically significant. **Results:** A total of 5889 patients with metastatic prostate cancer were included in the analysis. The median age was 73 years; 39% of patients received an ARI alone or in combination with other agents. Among the patients who received ARIs, 77%, 15% and 8% were white, black and of other races, respectively. Use of ARIs were more in urban locations (98.1% vs. 1.9% at rural locations) and in patients with higher and mid-level incomes (73.0% vs. 22.7% in low-income group). While survivals were inferior in all subgroups of patients who did not receive ARIs, survivals was better in white race (vs. black and others) as well as in younger age group who received ARIs. However, in the latter group, there was no statistical difference in survival in rural vs. urban locations and low income vs. high and mid-income groups. **Conclusions:** Our study shows that 39% of patients with metastatic prostate cancer in the SEER Medicare population utilized an ARI. There was a significant underutilization of ARIs in non-white, rural locations and low-income subgroup. White race and younger age populations were associated with better survival irrespective of use of ARIs. Among patients who did not receive ARIs, survivals were inferior in rural (vs. urban) and low-income (vs. high and mid-income) patients, but survivals were equivalent in these subgroups who received ARIs. Research Sponsor: External research grant to Dr. Asit Paul by Hyde Family.

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Poster Session

Effects of concomitant gut-microbiome altering medications on immune checkpoint inhibitors therapy: A retrospective study. *First Author: Rohit Singh, University of Vermont Medical Center; Division of Hematology-Oncology, Burlington, VT*

Background: In cancer patients, gut microbiota influences the antitumor immune response, efficacy, and safety of immune checkpoint inhibitors (ICIs). Antibiotics (ATBs), proton pump inhibitors (PPIs), and corticosteroids can alter the distribution of gut microbiota, resulting in dysbiosis, which can potentially reduce the efficacy of ICIs and may contribute to increased incidence of immune-related adverse effects (irAEs). **Methods:** We conducted a retrospective observational study to investigate the influence of concurrent medicines on patients receiving ICIs at the University of Vermont Cancer Center. We examined the medical records of people who received ICIs alone or in combination with chemotherapy or targeted therapy as a first-line therapy between January 2017 and June 2022. Patients who got ATBs, PPIs, and corticosteroids (>10 mg prednisone) one month before commencing ICIs and during the first six months of treatment were compared to those who did not. We looked at the relative risk for overall survival and the occurrence of irAEs in both cohorts. **Results:** We identified 266 patients, of which 99 (37%) have died. The mean age was 64 years, 55% were male, and 97% of the patients were White. Lung cancer was the most commonly identified malignancy at 36%, and 55% of the cancers were stage IV. The median ECOG was 1, and the median Charlson morbidity index was 6. Of the total cohort, 62% received antibiotics, 67% received steroids, 45% received PPIs, 31% received two of the three, and 27% received all three. The relative risk (RR) of death in the cohort which received antibiotics was 1.53 ($p = 0.02$), the cohort which received steroids was 1.73 ($p = 0.006$), and the cohort that received PPIs was 1.61 ($p = 0.006$). For the group that received two or all three medications, the RR was 2.18 ($p = 0.003$). Regarding irAEs, the group that received steroids had a RR of 2.13 ($p = 0.07$); however, most of these patients likely received steroids for an irAE. Antibiotics and PPIs were not associated with a higher risk of irAEs. One of the significant limitations of our study is the small sample size and the retrospective data collection. Data is also confounded because it includes patients who have received ICIs in combination with chemotherapy or other agents. **Conclusions:** Our study suggests that patients who received any of the gut microbiome-modifying medications before starting and within the early phase of ICIs treatments are at higher risk of mortality, likely owing to the poor efficacy of ICIs or possibly because these patients are sicker at baseline. However, we must be judicious with using such medications when patients undergo treatment with ICIs. Large prospective studies looking at this association are needed to understand the risk and potential outcomes. Research Sponsor: None.

Medications	RR for death	P-value
Antibiotics	1.53	0.02
Steroids	1.73	0.006
PPIs	1.61	0.006
Two or more	2.18	0.003

6618

Poster Session

An indirect comparison of elranatamab's (ELRA) objective response rate (ORR) from MagnetisMM-3 (MM-3) vs real-world external control arms in triple-class refractory (TCR) multiple myeloma (MM). *First Author: Luciano J. Costa, University of Alabama at Birmingham, Birmingham, AL*

Background: ELRA is a BCMAxCD3 bispecific antibody being investigated for the treatment of R/R MM. The phase 2 MM-3 trial was single-armed; the aim of this study (NCT05565391) was to contextualize the efficacy data from MM-3 with two real-world (RW) external control arms. **Methods:** A retrospective cohort study was conducted to indirectly compare the efficacy observed in MM-3 Cohort A (BCMA-naïve; N=123) from the 9-month data cut with two US-based oncology electronic health record databases, Flatiron Health (FH) and COTA, as external controls. MM-3 inclusion (eg, prior MM diagnosis, ECOG ≤ 2, refractory to ≥ 1 PI, ≥ 1 IMiD, and ≥ 1 anti-CD38) and exclusion (I/E) criteria (eg, plasma cell leukemia, smoldering MM) were applied to each RW database to obtain comparable patient populations across sources. After imposing MM-3 I/E criteria, comparisons between data sources on ORR were conducted by estimating rate ratios (RRs) using log-binomial regression models (unweighted analysis). RRs were also estimated using both inverse probability treatment weighting (IPTW) and augmented IPTW (doubly robust) analyses to account for key covariates (eg, age, comorbidities, ECOG, ISS, prior lines/refractoriness, cytogenetic risk, extramedullary disease, lab values). **Results:** The 123 patients from MM-3 Cohort A were compared with the 152 and 233 patients identified from the FH and COTA databases, respectively. Treatment regimens in the RW sources included various combinations of PIs, IMiDs, and mAbs, among other agents (eg, selinexor). Across unweighted, IPTW, and doubly robust analyses, the ORR for ELRA was significantly higher than treatments used for TCR MM patients from RW sources (Table; all $p < .05$). **Conclusions:** Among TCR MM patients who resemble those of the MM-3 trial, ELRA showed improved ORR compared with treatments currently used in clinical practice. Research Sponsor: Pfizer.

ORR comparison between elranatamab in MM-3 cohort A and RWD external control arms.						
	MM-3 Cohort A	FH	P	MM-3 Cohort A	COTA	p
N	123	152		123	233	
Unweighted analysis						
ORR % (95% CI)	61.0 (51.8-69.6)	30.3 (23.1-38.2)	-	61.0 (51.8-69.6)	31.3 (25.4-37.7)	-
RR (95% CI)			<.0001		1.95 (1.54-2.47)	<.0001
N	MM-3 Cohort A 122*	FH 149*		MM-3 Cohort A 123	COTA 213*	
IPTW analysis						
ORR % (95% CI)	56.0 (41.1-76.2)	31.3 (19.4-50.4)	-	75.7 (65.6-87.4)	34.2 (27.2-43.0)	-
RR (95% CI)		1.79 (1.01-3.15)	.0447		2.22 (1.69-2.90)	<.0001
Doubly robust analysis						
ORR % (95% CI)	61.7 (54.5-68.9)	27.6 (20.0-35.2)	-	63.5 (55.2-71.9)	33.7 (27.5-39.8)	-
RR (95% CI)		2.24 (1.68-2.97)	<.0001		1.89 (1.53-2.35)	<.0001

FH, Flatiron Health; CI, confidence interval; ORR, objective response rate; RR, rate ratio. *Some patients were excluded from the IPTW and doubly robust analyses due to missing values for variables used in the propensity score model.

6619

Poster Session

Real-world outcomes of patients (pts) with malignant solid tumors treated with immune checkpoint inhibitors (ICI) in relation to smoking status: The SAKK 80/19 SMOKER study. *First Author: Tämer El Saadany, Division of Oncology/Hematology, Kantonsspital Graubünden, Chur, Switzerland*

Background: ICIs are the standard of care for the treatment of different advanced solid organ tumors. Especially in advanced non-small-cell lung cancer, never-smokers were shown to have an inferior outcome when compared to ex-smokers/smokers, suggesting that the smoking status could be a predictive marker for survival benefits under ICI treatment. **Methods:** Pts within the Swiss Alpine Tumor Immunology Registry (AlpineTIR) treated with an ICI were differentiated by their smoking status (ex-smokers/smokers versus never-smokers). Overall survival (OS) and progression-free survival (PFS) from the start of the first ICI treatment were analyzed by smoking status. Further, subgroup analyses for OS and PFS were done for the most common disease entities. **Results:** A total of 702 pts were included, from which 455 pts (65%) were ex-smokers/smokers, 213 pts (30%) were never smokers, and 34 pts (5%) had an unknown smoking status. The median follow-up time from the administration of the first ICI to the statistical analysis was 2.7 years (95% CI: 2.3 to 3.2 years). The most frequent tumors were lung cancer (50%), melanoma (13%), renal cell cancer (7%), bladder cancer (6%), and others (24%). Across all indications, the median OS was 1.7 years (95% CI: 1.4 to 2.6 years) for never-smokers ($n = 213$) and 1.5 years (95% CI: 1.2 to 1.8 years) for smokers ($n = 455$) (HR: 1.10, 95% CI: 0.89 - 1.37). The median PFS was 6.3 months (95% CI: 4.4 to 8.3 months) for non-smokers and 6.2 months (95% CI: 5.2 to 7.0 months) for smokers (HR: 1.05, 95% CI: 0.87 - 1.27). In lung cancer pts, the median OS was 1.4 years (95% CI: 0.8 to 2.8 years) for never-smokers ($n = 43$) and 1.4 years (95% CI: 1.2 to 1.7 years) for smokers ($n = 302$) (HR: 1.02, 95% CI: 0.68 - 1.51). In melanoma pts, the median OS was 3.4 years (95% CI: 1.8 to not reached (NR) years) for never-smokers ($n = 54$) and 1.7 years (95% CI: 0.8 to NR years) for smokers ($n = 34$) (HR: 1.35, 95% CI: 0.72 - 2.53). In renal cell cancer pts, the median OS was 1.5 years (95% CI: 1.0 to 3.6 years) for never-smokers ($n = 28$) and 3.5 years (95% CI: 0.6 to NR years) for smokers ($n = 17$) (HR: 0.74, 95% CI: 0.31 - 1.78). In bladder cancer pts, the median OS was 1.8 years (95% CI: 0.6 to NR years) for never-smokers ($n = 17$) and 1.4 years (95% CI: 0.5 to NR years) for smokers ($n = 26$) (HR: 0.88, 95% CI: 0.39 - 1.99). **Conclusions:** No survival difference between smokers and non-smokers with metastatic solid organ tumors treated with ICIs could be detected. Interestingly, even in the subgroup of lung cancer pts, no difference was seen. Based on these data, the smoking status should not guide ICI treatment decisions. Research Sponsor: Swiss Cancer Foundation.

6620

Poster Session

The impact of using Elsevier ClinicalPath oncology treatment pathways on survival and cost of care. *First Author: Monica Schmidt, Cone Health, Greensboro, NC*

Background: Cone Health is a 921 bed hospital system in North Carolina with a comprehensive cancer center. Our aim was to determine the value of using Elsevier's ClinicalPath oncology pathways on short-term survival and cost of care from the patient and health system perspectives. Cancer treatment has become more complex as it progresses more toward precision medicine modalities. As such, clinical decision support tools, such as ClinicalPath, have gained traction. Health systems struggle to survive after the COVID pandemic, with residual financial impacts lingering into 2023. It is more important than ever before that health systems focus on value where the patient benefits and financial sustainability are improved. **Methods:** We used a retrospective cohort study design with matching. Exposure was the use of the ClinicalPath decision support tool in Epic (exposed) versus no use of the tool (not exposed). We matched on cancer body site, AJCC clinical stage, the goal of treatment, Elixhauser comorbidity score, and year of a cancer diagnosis. We were able to match 509 exposed to 509 unexposed. Our primary outcomes were 12-month survival from the time of the first treatment and contribution margin. We used a log-rank calculation based on our hazard ratios (Freedman method) to determine the sample size required for each group, assuming a power of 80%. We used a Weibull parametric model to assess 12-month survival with additional covariates. An OLS model was used to evaluate the contribution margin. **Results:** Results demonstrate that when ClinicalPath is used to guide treatment, patients are half as likely to die within 12 months from treatment compared to the unexposed (HR 0.50; 95% CI 0.37-0.68). The OLS contribution model found, on average, that margin has an associated 74.0% (0.74; 95% CI 0.58-0.90) increase when ClinicalPath is used to guide treatment compared to the unexposed. This equates to a crude increase in contribution margin for cancer treatment of \$58,362, on average per case, when ClinicalPath is used. Variable direct costs are higher when using ClinicalPath. This means, on average, it costs more to treat patients on pathway using best available evidence. Still, they have better short-term survival and payers are covering the additional costs given the increase in contribution margin for our system. **Conclusions:** Short-term recurrence free survival is significantly improved when providers utilize ClinicalPath compared to not using the tool consistent with the primary aim of the CDS solution. Newer, more efficacious treatments may have higher initial costs, as expected. Still, the effectiveness of these treatments on survival in the real-world setting is born out in the current study. The higher initial direct costs are counterbalanced by a higher contribution margin per patient providing evidence that improved outcomes in cancer therapy can also provide a positive ROI for provider organizations. Research Sponsor: None.

6621

Poster Session

Rates of emergency department visits and acute-care hospital admissions after starting chemotherapy or having surgery across six community-based cancer centers. *First Author: Michael J. Hassett, Dana-Farber Cancer Institute, Boston, MA*

Background: Cancer patients who start chemotherapy or have surgery are at risk for serious adverse events, which can include emergency department visits (EDV) and acute-care hospital admissions (ADM). These events are relevant to patients, clinicians, health systems, and policy makers. Few studies have described the frequency and predictors of EDVs and ADMs in the routine care setting. We sought to address this knowledge gap, and to describe the impact of the COVID pandemic on these events, using data from the SIMPRO consortium of six US-based health systems. **Methods:** In 2019, SIMPRO started a phased deployment of an electronic health record-integrated symptom management program (eSyM) as part of the routine care provided to patients with a suspected or confirmed gastrointestinal, thoracic, and gynecologic malignancy. eSyM prompts patients to complete symptom questionnaires and provides symptom management resources for 180 days after starting chemotherapy and 60 days following surgery. This analysis includes all patients, whether they used eSyM resources or not. Outcomes, which were measured using EHR-based encounter data, included the rates of EDVs and ADMs at 30 and 90-days after starting chemotherapy or following discharge from surgery. To account for potential confounding, we used multivariable logistic regression for the 30-day outcomes and Cox regression for the 90-day outcomes. **Results:** From September 2019–December 2022, 8664 patients started chemotherapy and 11,578 had surgery, with 3075 and 2587 patients, respectively, experiencing at least one outcome event (Table). 90-day outcomes varied significantly across health systems for chemotherapy (EDV 2-21%, ADM 5-28%) and surgery (EDV 7-14%, ADM 9-18%) patients. In multivariable analyses, patients who reported an employment status of disabled were more likely to report an EDV (OR 1.73-1.96) and an ADM (ORs 1.52-1.96). Widowed status was associated with greater odds of having an ADM (ORs 1.29-1.30), but not an EDV. Cox regression found chemotherapy recipients experienced lower hazards of an EDV, but not an ADM, during 2020 (coinciding with the start of the COVID pandemic). For surgery patients, there was no significant association between calendar year and EDVs or ADMs. [p<0.001 for all reported values]. **Conclusions:** A meaningful proportion of patients who started chemotherapy or had surgery for a suspected or confirmed malignancy in the routine-care setting had an EDV or ADM within 90 days. Most events occurred within 30 days. Further work is required to ascertain how many of these encounters are avoidable and what structural or procedural interventions could improve outcomes. Clinical trial information: NCT03850912. Research Sponsor: U.S. National Institutes of Health.

Chemotherapy Patients (N=8664)		Surgery Patients (N=11,578)	
	Percent	Percent	
Age	(median)	(67)	(63)
Sex	Female	54	69
Race	Non-white	21	10
EDVs	30 days	7.3	5.4
	90 days	13.9	9.5
ADMs	30 days	10.6	8.0
	90 days	21.6	12.9

6623

Poster Session

Financial toxicity, quality of life, symptom burden, and access to resources in early-phase clinical trial (EP-CT) participants. *First Author: Sienna Durbin, Massachusetts General Hospital, Boston, MA*

Background: EP-CTs are an important therapeutic option for patients, and financial toxicity represents an increasing concern in oncology. Little is known about the financial toxicity of EP-CT participants. We sought to describe financial toxicity in EP-CT participants and assess associations of this factor with patient characteristics, quality of life (QOL), symptom burden, and access to resources. **Methods:** We prospectively enrolled consecutive adults participating in EP-CTs at Massachusetts General Hospital from 04/2021 – 01/2023. Participants completed surveys prior to treatment initiation that assessed financial toxicity (Comprehensive Score for Financial Toxicity [COST tool], higher scores indicate greater financial wellbeing). We adapted a financial toxicity grading scale proposed by the creators of the COST tool to define levels: low (COST $\geq$ 26) and high (COST 0–25). We surveyed QOL (Functional Assessment of Cancer Therapy-General) and symptom burden (psychological: Patient Health Questionnaire-4 [PHQ4]; physical: Edmonton Symptom Assessment System [ESAS]). Patients were asked their concerns regarding access to resources. We explored associations of financial toxicity with patient characteristics, QOL, symptom burden, and access to resources. **Results:** Of 221 eligible patients, we enrolled 196 (median age = 62.3 years [range 31.8-88.6], 57.1% female). Most common tumors were gastrointestinal (33.2%) and breast (20.4%); most (93.7%) had metastatic disease. Patients had an average COST score of 28.4 (SD 9.0), with 33.7% reporting high financial toxicity. Patients with high financial toxicity were more likely to be <65 years (70.0% vs 47.7%, p=0.003), unemployed (44.6% vs 17.7%, p<0.001), lack a college degree (52.3% vs 25.6%, p<0.001), and have income $\leq$ \$60,000 (60.6% vs 25.4%, p<0.001) compared to those with low financial toxicity. Compared to those with low toxicity, patients with high financial toxicity also had lower QOL scores (69.9 vs 77.3, p<0.001) and increased psychological (1.3 vs 0.9, p=0.02) and physical (19.3 vs 15.9, p=0.091) symptom burden, although increased physical symptoms did not reach statistical significance. Those with high financial toxicity were more likely to report concerns regarding access to several resources (housing [10.6% vs 2.3%, p=0.033], bill paying [31.8% vs 3.8% 3.8%, p<0.001], food [9.0% vs 0.7%, p<0.006], employment [21.2% vs 1.5%, p<0.001]; there was no significant difference in transportation [22.7% vs 16.1%, p=0.261]). **Conclusions:** We found that one third of EP-CT participants report high financial toxicity and identified factors associated with higher toxicity. We demonstrated novel associations between high financial toxicity and lower QOL, greater depression, and increased concerns regarding access to resources. Findings highlight the need to address financial toxicity among this population. Research Sponsor: None.

6622

Poster Session

Improved outcomes from reflex comprehensive genomic profiling-guided precision therapeutic selection across a major US healthcare system. *First Author: Brian Piening, Earle A. Chiles Research Institute at Robert W. Franz Cancer Center, Providence Cancer Institute, Portland, OR*

Background: An ever-increasing number of biomarker-guided therapies, some with pan-cancer indications have expanded the oncologist's toolbox for fighting advanced cancer. Despite this, not all advanced cancer patients receive tumor genomic testing, or are tested for a limited number of targets. Still others are tested too late in their care journey to benefit from precision therapy. To assess the impact of removing testing barriers, we developed a reflex testing protocol where comprehensive genomic profiling (CGP) was routinely ordered by pathologists at time of diagnosis for advanced cancer patients. **Methods:** Reflex CGP testing was primarily initiated by the pathologist at the time of advanced cancer diagnosis. Testing was performed between 2019 and 2021 via CGP using the ProvSeq 523 lab-developed test, and testing was performed at no cost to the patient. Post-CGP, stage 4 patients were followed for $\geq$ 12 months. We assessed time to therapy, therapy selection, and overall survival (OS). Therapies were stratified by presence of biomarkers associated with approved targeted therapies (TT), presence of biomarkers for immunotherapies (IO), and/or therapies that were guideline based (GB) and not associated with a specific biomarker. As much key patient information is only consistently available in free-text medical charts, we implemented a novel natural-language processing (NLP) approach based on deep learning and large language models to accelerate abstraction. **Results:** A cohort of 1,423 advanced cancer patients met the study criteria. The median age was 66 years, 53% were female, and 82% white. The 3 most tested tumor types were 22% non-small cell lung cancer, 16% colorectal cancer, and 12% breast. Overall, 49% (N=704) of patients had a biomarker result considered actionable for an approved TT or IO. Median (IQR) time-to-treatment initiation post-CGP was 19 (2-70) days. In patients with no actionable TT or IO biomarkers (N=719), 63% were treated with chemotherapy-based regimens, 11% with GB, 17% with unmatched TT, and 8% with unmatched IO. Of patients who had only an actionable TT biomarker (N=287), 18% received matched TT and 13% received GB. 36% of patients with only an actionable IO biomarker (N=317) received matched IO monotherapy. 48% of patients with both actionable TT and IO biomarkers (N=100) received matched TT or IO monotherapy, and 5% received GB. Across all tumor types, patients receiving a TT had better OS compared to patients receiving chemotherapy with 12 months OS (%) of 70.1 (95% CI=64.4 - 76.3) for TT-treated patients, compared to 62.9 (95% CI=58.8 - 67.3) for chemotherapy only. **Conclusions:** CGP-guided precision therapy use is associated with significantly higher survival in a reflex testing population. A reflex protocol can overcome key barriers to the use and timing of genomic testing to improve access to these life-extending treatment modalities. Research Sponsor: Illumina; Providence Foundation of Oregon.

6624

Poster Session

Evaluation of cachexia and outcomes in patients with aggressive B-cell non-Hodgkin lymphoma. *First Author: Nicholas Demetriou, Feinberg School of Medicine, Northwestern University, Chicago, IL*

Background: Cancer cachexia is a muscle wasting syndrome characterized by anorexia, asthenia, and weight loss. Cachexia rates are as high as 35% for aggressive B-cell Non-Hodgkin Lymphomas (B-NHL), and is considered an independent factor in cancer outcomes compared to other disease burden markers. However, there remains no set protocol to identify hematologic cancer patients at risk for cachexia, and current imaging-based measures for muscle wasting can be costly and burdensome. Weight loss grading scale (WLGS) is a newly validated method to assess cachexia in solid tumor cancers but not hematologic malignancies. This study evaluates the relationship between WLGS and cancer treatment outcomes in B-NHL patients. **Methods:** This was a retrospective cohort study of adult patients with aggressive B-NHL treated between 2005-2020. WLGS grade was used as a cachexia marker to analyze its effect on outcomes. WLGS combines weight loss (since diagnosis) with a patient's BMI at that same time. A grade of 0 indicates no cachexia, and a grade of 4 indicates severe cachexia. Data for WLGS grade was captured for patients at 3- and 12-months post-treatment induction. Survival curve analyses assessed disability-free survival (DFS) (time from induction therapy to a patient requiring rehabilitative, home health, or skilled nursing services), progression-free survival (PFS), and overall survival (OS) outcomes. **Results:** Our cohort included 258 B-NHL patients. Within our study population, 45% were female, with an average age of 57 at diagnosis. B-NHL patients with higher WLGS, defined as a grade $\geq$ 2, composed 22% and 18% of patients at 3- and 12-months post-induction therapy, respectively. Patients with elevated WLGS were found to have significantly higher progression rates compared to lower WLGS grade individuals at 3 months (HR=1.8, p=0.049) and 12 months (HR=2.4, p=0.014) post-induction therapy. Furthermore, higher WLGS patients had significantly greater rates of disability compared with lower WLGS patients at 3 months (HR=1.7, p=0.013) and 12 months (HR=1.7 p=0.025) post-induction therapy. Finally, patients with a WLGS of 4 at 12 months post-induction therapy demonstrated significantly lower OS (HR=323, P<0.0001) than all other patients. **Conclusions:** In conclusion, WLGS, a new marker for cachexia, is highly correlated with morbidity and mortality outcomes in B-NHL patients. Specifically, PFS and DFS were significantly lower in groups with higher WLGS grades, and OS was significantly lower for individuals with a WLGS of 4. Weight and BMI, the two metrics used to calculate the WLGS score, require minimal time and resources to assess. Thus, regularly tracking weight can be an adjuvant screening to imaging and biomarker testing to identify patients at increased risk for disease progression or disability. The accessibility of WLGS tracking would further benefit disease tracking in resource-scarce areas and simplify disease assessment. Research Sponsor: None.

6625

Poster Session

Efficacy-effectiveness gap with immune checkpoint inhibitors in solid cancers: A population based cohort study. *First Author: Saroj Niraula, University of Manitoba/CancerCare Manitoba, Winnipeg, MB, Canada*

Background: Immune checkpoint inhibitors (ICIs) have been central in oncology drug development in the last decade often demonstrating large improvements in overall survival (OS) in pivotal randomized controlled trials (RCTs). Patient selection and/or care may be less stringent in the real world but ascertaining that benefits are translated satisfactorily from pivotal RCTs into the real world is crucial, as patients often base their treatment decisions on outcomes quoted to them from pivotal RCTs. **Methods:** After necessary ethics approvals, we collected relevant data on all consecutive patients with advanced solid cancers treated with ICIs in the province of Manitoba, Canada from inception to June 30, 2022 using pharmacy database and cancer registry. Eight most frequent ICI indications are included here. Survival probabilities were plotted using Kaplan-Meier Method, and descriptive statistics used to report relationship between variables. To put outcomes into perspective, we report real world data alongside that of pivotal RCTs used to support approvals of respective ICIs by Health Canada and the US FDA. **Results:** Eight ICI indications included 992 patients followed for a median of 40 months (range: 21-86 months). Patients required to meet precise provincial formulary criteria to receive ICIs, adopted mostly from the inclusion criteria of the corresponding pivotal RCTs. Median OS was shorter in the real world population not only compared to the experimental arms of the respective pivotal RCTs [by a median of 16 months (range: 3 - 38 months)] but also compared to their control arms [by a median of 3 months (range 3 to 32 months)]. This translated into an average of 51.1% (standard deviation: 20.1) compromise in median OS with ICIs in the real world compared to that observed in respective pivotal RCTs. **Conclusions:** Treatment with ICIs within high standards of practice in a Canadian province overall offered less than half the median OS observed in pivotal RCTs supporting their approvals. Current ICI treatment decisions by patients (and physicians) may therefore be based on highly inaccurate expectations. Our results should inspire rigorous phase IV clinical studies to identify pertinent real-world variables affecting outcomes including treatment related morbidity and mortality, with an ultimate aim to narrow the alarming efficacy-effectiveness gap. Research Sponsor: None.

ICI	Indication	Pivotal RCT Outcomes (months)		Real World Outcomes		
		Median F/U	Median OS (Experimental Arm)	Median OS (Control Arm)	Number of Patients	Median F/U (months)
Pembrolizumab	Melanoma	57.7	32.7	15.9	89	53
Pembrolizumab	NSCLC	25.3	30	14.2	327	32.2
Pembrolizumab	RCC	42.8	45.7	40	96	21
Nivolumab	NSCLC	40.3	12.9	9.8	153	49.1
Nivolumab	RCC	72	25.8	19.7	87	47
Ipilimumab	Melanoma	60	15	6.6	81	86.3
Ipilimumab + Nivolumab	RCC	67.7	55.7	38.4	54	32.2
Durvalumab	NSCLC	34.2	47.5	29.1	105	28.1

6626

Poster Session

Electronic health record (EHR)-based machine learning (ML) to predict disease recurrence after surgical resection of early-stage non-small cell lung cancer (eNSCLC). *First Author: Steven Pisano, ConcertAI, Cambridge, MA*

Background: Surgical resection (SR) is a guideline-recommended definitive therapy for patients (pts) with eNSCLC. However, 30–50% pts develop disease recurrence (DR) within the first 5 years (yrs) after surgery. ML applied to routinely collected EHR data could facilitate timely identification of pts at risk of DR who would benefit from enhanced surveillance or initial treatment (Tx) intensification. **Methods:** eNSCLC pts with stage IB–IIIA at the time of SR between Jan 2010 – February 2022 were identified from ConcertAI Patient360 oncology database comprising structured and curated records from US-based EHR. DR was defined as the human-curated earliest advanced/metastatic diagnosis date from SR. Gradient boosting (GB), random forest (RF), and logistic regression (LR) algorithms with 6-fold nested cross-validation were trained and compared to predict the risk of DR or death at 2 yrs from SR. Pts who did not experience DR and were lost to follow-up within 2 yrs from SR were removed. Feature importance was defined using Shapley Additive Explanation (SHAP)-derived odds ratios (OR). Due to low prevalence of DR at 2 yrs, AUPRC was used as performance metric. Pts in the 1st and 4th quartiles of predicted probabilities from XGB model were defined as low-risk vs. high-risk groups. **Results:** Among 3597 pts, median age was 68.3 yrs (IQR 12.5), 51.8% were female, and 8.6% were Black. 24.4% developed DR within 2 yrs. GB, RF, and LR models had similar ability to predict DR at 2 yrs with mean hold-out set AUPRC of 0.33. In GB model, DR prevalence at 2 yrs was 34% in the high-risk vs. 18% in the low-risk group in hold-out set. NO stage, T stage < 3, receipt of adjuvant immune checkpoint inhibitor (ICI), and presence of EGFR mutations were protective against DR at 2 yrs, while history of anemia and congestive heart failure (CHF) were risk factors (Table). SHAP revealed a N stage-by-adjuvant therapy and a N stage-by-CHF interaction: benefit from adjuvant chemotherapy (CT) was limited to higher N stages, while adjuvant ICI was beneficial for all N stages. CHF was a risk factor for lower N stages but not for higher N stages. **Conclusions:** ML applied to structured and unstructured EHRs identified predictors of risk of DR at 2 yrs after surgery in eNSCLC and may identify high-risk pts who would benefit from enhanced surveillance plans and Tx intensification in the eNSCLC setting. The model indicated favorable outcome from adjuvant targeted therapies in EGFR mutated pts. Research Sponsor: ConcertAI.

Feature importance (Mean OR, 95% CI).

Adjuvant ICI	0.78 (0.66, 0.92)
N-stage (0 vs >0)	0.80 (0.74, 0.92)
T-stage (< 3 vs ≥ 3)	0.84 (0.79, 0.88)
History of anemia	1.30 (1.18, 1.56)
History of CHF	1.16 (1.06, 1.28)
EGFR exon 19 deletions or L858R	0.94 (0.89, 0.97)
Interactions	% DR at 2 yrs
N-stage-by-CHF	N=0: (CHF = 33.7, no CHF = 20.4); N>0: (32.6, 31.1)
N-stage-by-adjuvant CT	N=0: (CT = 20.1, no CT = 21.4); N>0: (27.8, 33.9)

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Poster Session

Endoscopist volume and the quality of colonoscopy of the Korean National Cancer Screening Program. *First Author: Dong Jun Kim, College of Medicine, The Catholic University of Korea, Seoul, Seocho-gu, South Korea*

Background: The Korean government established the National Cancer Screening Program (KNCSPP). The KNCSPP has provided annual faecal immunochemical test (FIT) for adults aged 50 years or older, and colonoscopy or a double-contrast barium enema test to those with positive results from the FIT. High-quality screening colonoscopy is mandatory to achieve maximum possible CRC prevention. The case volume has been shown to correlate with outcomes in surgical specialties. In contrast, relevant data on colonoscopy is limited. This study aimed to assess the quality indicators of organized CRC screening according to annual colonoscopy volume using KNCSPP data. **Methods:** We used the KNCSPP data from 2018 to 2020, which accounted for 378,354 colonoscopy examinations. We used cancer registration data of an extended health insurance program using ICD-11 codes (C18-20). A total of 12,109 CRC patients were registered within 1 year of the date of colonoscopy. We calculated the annual number of colonoscopy examinations by an individual endoscopist. We excluded endoscopists who had a very low or high number of examinations with the highest 1% or lowest 1% as outliers. The final number of endoscopists was 16,552 and colonoscopy examinations were 331,231 during 2018–2020. The annual colonoscopy volume by individual endoscopists was divided into four groups (2–12, 13–24, 25–36, and 37 or more examinations). Multiple linear regression analysis was performed to confirm the association between test accuracy indicators and colonoscopy frequency using a generalized linear model (GLM). We calculated the estimates of the rates for each indicator by adjusting the year. **Results:** The positive and false positive rates, sensitivity, specificity, and positive predictive value were 4.09%, 1.07%, 83.53%, 98.93%, and 74.68%, respectively. The cancer detection and interval cancer rates were 30.53% and 6.29%, respectively. Quality indicators were related to the annual colonoscopy volume of the endoscopist. Endoscopists with a higher annual colonoscopy volume were more likely to have higher sensitivity, specificity, and positive predictive value than those with a lower annual colonoscopy volume. Endoscopists with higher annual colonoscopy volumes were more likely to have lower positive rates, cancer detection rates, false positive rates, and interval cancers rate than those with lower annual colonoscopy volumes. **Conclusions:** This study found that the annual volume of colonoscopy examinations was associated with better colonoscopy quality in an organized CRC screening program. A high colonoscopy load could be a sign of substantial experience and lead to better outcomes, as has been shown for surgery. The relationship between quality indicators and case volume is logical and plausible; therefore, more research is required to determine the number of cases that need to be performed in a year to adequately maintain high colonoscopy quality. Research Sponsor: National Cancer Center Korea.

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Poster Session

An ehealth intervention during radical radiotherapy: Patient-Reported Outcome Side effects (PROSE) study—An emerging approach from sub-Saharan Africa. *First Author: Omolola Salako, Coll of Med, Univ of Lagos, Lagos, Lagos, Nigeria*

Background: PROSE is an electronic patient-reported outcome tool for real-time, remote monitoring of treatment related side-effects. It enables a two way communication between the patient and clinicians. Remote monitoring of treatment related toxicities can eliminate underreporting of side effects (SE), facilitate timely symptom assessment, and improve management of SE. These will thereby reduce morbidity and hospitalization and improve treatment outcomes and quality of life of affected patients. The overarching goal of the study is to enhance the efficiency of the conventional weekly SE clinic using an emerging technology and thereby create evidence for a personalized digital health interventions for cancer patients in Africa. **Methods:** A prospective study among adult cancer patients receiving radical radiotherapy for head and neck, pelvic, and breast cancers at NSIA-LUTH Cancer Centre in Nigeria between March and October 2022. Eligible (≥18 years, KPS≥75%) and consenting participants were trained on to report their SE daily and receive remote clinical advice on proscare.com. The PROSE tool was built as an adapted version of the Patient Reported Outcome version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). The study participants were monitored throughout their radiotherapy sessions and two weeks thereafter. The cancer care team can review the Patients Reported Outcome (PRO) data through a dedicated log-in portal during the SE clinic. Participants scored their SE daily and EORTC QLQ-30 quality of life surveys were administered thrice during the study and 2 weeks thereafter. SE reports were chosen according to the site of disease; 12 items for head and neck tumors, 9 items for breast tumors, 14 items for female pelvic and 18 items for male pelvic tumors. Patient's PROSE tool application utilization was defined as >50% daily reporting during study period. **Results:** A total of 137 participants were screened, of which 120 met the eligibility criteria. Of the 120 patients eligible, 23 had technical issues with the use of the PROSE tool application and 1 died during the study; thus, 96 participants data were analyzed. More than 40,000 SE reports were generated during the study. SE with highest symptom burden include urinary frequency in male pelvic cancers (n=17), radiation dermatitis in breast cancer (n=40), diarrhea in female pelvic cancer (n=19) and xerostomia in head/neck cancers (n=20). The app utilization rate was 58%. **Conclusions:** There was a moderate utilization (58%) of the PROSE tool application. The PROSE pilot study demonstrated the potential utility of the PROSE application as a promising tool and data resource that offers a great opportunity to improve cancer care and the development of predictive clinical algorithms by engaging patients in their own care and increased SE reporting of acute radiation toxicities. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology.

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Poster Session

Real-world study of treatment patterns and clinical outcomes in patients with metastatic non-small cell lung cancer (mNSCLC) post-approval of immunotherapy in the community oncology setting. *First Author: Alexander I. Spira, Virginia Cancer Specialists, US Oncology Network, Fairfax, VA*

Background: Clinical outcomes in patients with mNSCLC have improved post-approval of immunotherapy (IO). However, limited real-world data exists describing the evolution of treatment patterns and impact on outcomes in later lines of therapy (LOT). Here we describe the treatment landscape and outcomes of patients with mNSCLC without driver mutations within community oncology settings. **Methods:** This retrospective observational study included adult patients with mNSCLC who initiated first LOT (LOT1) for mNSCLC in the US Oncology Network from 1/1/2015 to 12/31/2020 (followed through 3/31/2022), using structured electronic health records. Patients who initiated LOT1 with a targeted therapy or EGFR/ALK/ROS1 inhibitor during any LOT were excluded. Second, third, and fourth LOT (LOT2, LOT3, LOT4) were assigned using start and stop dates. Treatment patterns up to LOT4 were summarized descriptively by period of treatment initiation (early-IO period: 2015–2017; post-IO period: 2018–2020). Overall survival (OS) and time to next treatment (TTNT) were assessed by LOT using Kaplan-Meier analysis. **Results:** Overall, 11,035 patients met study criteria, of which 3,835 (35%) patients initiated LOT2, 1,264 (11%) patients initiated LOT3, and 393 (4%) patients initiated LOT4 between 2015 and 2020, respectively. From 2015–2017 to 2018–2020, pembrolizumab plus platinum chemotherapy with pemetrexed or paclitaxel as LOT1 increased from 3% (n = 176) to 42% (n = 2,448), and pembrolizumab monotherapy increased from 9% (n = 465) to 26% (n = 1,518). In patients who initiated LOT2, IO followed by docetaxel ± ramucicrumab increased from 1% (n = 15) to 15% (n = 295), whereas this sequence from LOT2 to LOT3 was used in 23% (n = 111) from 2015–2017 and 20% (n = 159) from 2018–2020. Median (95% CI) OS was 13.3 (12.6, 14.0) months vs. 14.7 (13.8, 15.3) months from initiation of LOT1 in 2015–2017 vs. 2018–2020, respectively (P = 0.187). Clinical outcomes by LOT and period of treatment initiation are presented as median (95% CI) in the table below. **Conclusions:** Understanding evolving treatment patterns in the community oncology setting is important for uncovering opportunities for mNSCLC treatment optimization. This descriptive study reveals the increasing use of mono- and combination IO followed by docetaxel ± ramucicrumab in the community setting. Additionally, longer OS was noted in the post-IO period, suggesting possible extended benefits from earlier LOT. Research Sponsor: Mirati Therapeutics.

		2015-2017	2018-2020	Log rank p-value
LOT2	N (%)	1,828 (48%)	2,007 (52%)	-
	OS	10.6 (9.7, 11.4)	12.4 (11.5, 13.6)	0.015
	TTNT	5.3 (4.9, 5.7)	6.2 (5.9, 6.7)	0.006
LOT3	N (%)	477 (38%)	787 (62%)	-
	OS	7.9 (6.9, 9.0)	11.1 (9.3, 13.0)	0.033
	TTNT	4.8 (4.3, 5.3)	5.4 (5.0, 6.0)	0.096
LOT4	N (%)	106 (27%)	287 (73%)	-
	OS	6.0 (4.7, 8.1)	10.1 (8.3, 15.3)	0.016
	TTNT	4.3 (3.0, 5.1)	5.0 (4.4, 5.7)	0.013

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Poster Session

Racial disparities in hospitalization outcomes among patients with cholangiocarcinoma. *First Author: Inimfon Jackson, Albert Einstein Medical Center, Philadelphia, PA*

Background: Studies have reported on the rising incidence and mortality outcomes among patients diagnosed with cholangiocarcinoma (CCA) but racial disparities in outcomes among inpatients have not been explored in this population. We examined the racial disparities in outcomes among adult hospitalized patients with a diagnosis of CCA. **Methods:** Retrospective cohort analyses were conducted using data from the National Inpatient Sample (NIS), 2016-2020. Multivariate logistic and linear regression models were used to examine the association between race/ethnicity and patient disposition, length of stay, elective admissions, and total hospital charges. **Results:** In the adjusted analyses, while Black patients had 14% higher odds (95% Confidence Interval (CI): 1.04–1.25) of being discharged to a facility/home with home health care versus routine discharge when compared to their White counterparts, Hispanics had 14% lower odds (95% CI: 0.79–0.95). Black patients had 39% higher risk (95% CI: 1.19–1.63) of death versus routine discharge relative to the White patients. Compared to White patients, Blacks (AOR: 1.23; 95% CI: 1.13–1.34), Hispanics (AOR: 1.15; 1.06–1.25) and other race/ethnicities (AOR: 1.20; 1.10–1.31) were more likely to have a length of hospital stay greater than 5 days relative to 5 days or less. Hispanics (β: \$16,789; 95% CI: \$11,480–\$22,099) were found to have higher total hospital charges when compared to the White CCA patients. Additionally, Black (AOR: 0.68; 95% CI: 0.60–0.78) and Hispanic patients (AOR: 0.87; 95% CI: 0.77–0.99) were less likely to be admitted electively to the hospital. **Conclusions:** Despite advances made in treatment of patients with CCA, the prognosis remains poor. We report disparities in various hospitalization outcomes among adult patients with a diagnosis of CCA. Health care providers need to be aware that these disparities exist and health policies should be implemented to narrow the gap in existing disparities. Research Sponsor: None.

		Race/Ethnicity			
		Whites	Blacks	Hispanics	Others
Facility/Home Health Vs Routine [AOR (95% CI)]	Ref	1.14 (1.04–1.25)	0.86 (0.79–0.95)	0.89 (0.80–0.99)	
Died Vs Routine [AOR (95% CI)]	Ref	1.39 (1.19–1.63)	0.89 (0.75–1.05)	1.06 (0.90–1.26)	
Elective admission [AOR (95% CI)]	Ref	0.68 (0.60–0.78)	0.87 (0.77–0.99)	0.88 (0.78–1.00)	
Length of stay >5 days [AOR (95% CI)]	Ref	1.23 (1.13–1.34)	1.15 (1.06–1.25)	1.20 (1.10–1.31)	
Total charges [β (95% CI)]	Ref	3914.47 (-35.82–7864.75)	16789.48 (11480.02–22098.95)	14293.19 (9138.74–19447.64)	

NIS = National Inpatient Sample; AOR= Adjusted odds ratio; β=point estimate; Ref=Reference; CI=confidence intervals; models adjusted for age, gender, hospital region, hospital location, Charlson comorbidity index and type of insurance, boldface signifies statistical significance.

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Poster Session

Evaluation of studies with commonly used real world data sources submitted to ASCO journals: Initial steps toward furthering transparent reporting. *First Author: Benjamin Bates, Department of Medicine, Rutgers-Robert Wood Johnson Medical School, New Brunswick, NJ*

Background: Real world data (RWD) are used to understand treatment, care, and outcomes of patients with cancer. Reporting guidelines for observational studies, such as RECORD (health), RECORD-PE (treatment) and TRIPOD (prediction), were developed to increase the transparency of studies using RWD. These guidelines are not required for publication in ASCO Journals (JCO- Journal of Clinical Oncology, PO- Precision Oncology, OP- Oncology Practice, CCI- Clinical Cancer Informatics, GO- Global Oncology). Our objective was to describe the use of RWD among studies submitted to ASCO Journals and evaluate the applicability of guidelines and adherence to guidelines. **Methods:** ASCO submission system was used to identify all studies submitted to ASCO Journals between 2018–2022. Based on the abstract, the studies were categorized on whether selected RWD were used: SEER, Medicare, National Cancer Database [NCDB], Flatiron, CancerLinQ, IQVIA, Optum, MarketScan. Through manual review of the published manuscripts, we calculated positive predictive value (PPV) of our algorithm to identify the RWD. We estimated acceptance rate. For each study we evaluated the following: (1) linkages with other RWD; (2) applicability of reporting guidelines RECORD, RECORD-PE, TRIPOD; (3) use of flow diagram (RECORD) or study design figure for treatment and outcome assessment (RECORD-PE). **Results:** The PPV of our search algorithm was 79% (95%CI 73–84) but varied by journal (PPV 73–100; p=0.02). Based on our algorithm, among the 16,133 original reports submitted, 1,156 (7.2%) used one of the RWD sources. Overall acceptance rate among RWD sources was 18%. There was variability in submissions and acceptance rate of RWD by journal. OP and GO most and least frequently received a manuscript with the selected RWD 13% and 1%, respectively. GO accepted 77% of manuscripts that used selected RWD (88% of which were SEER). JCO accepted 3.5% of RWD manuscripts. Medicare, SEER, and NCDB were frequently identified data sources (61%, 31%, and 11%, respectively). SEER was linked to Medicare claims, surveys, or other sources in 77% of studies. The other data sources accounted for <5% each, although submission of EHR-linked to claims/registry increased over time (OR 1.26: 95%CI 1.07–1.49). RECORD, RECORD-PE and TRIPOD were applicable to 100%, 10% and 8% of the studies. RECORD-PE and TRIPOD were most applicable to PO/OP/CCI and CCI, respectively. A flow diagram demonstrating selection of participants was present in 31% of the studies. A figure to visualize study design was used in <5% of RECORD-PE relevant studies. **Conclusions:** RWD are commonly submitted and published within ASCO Journals. Reporting guidelines are applicable and particularly important when linkages occur. Studies using oncology RWD may benefit from reporting guidelines tailored to the unique qualities of these data sources and populations. Research Sponsor: None.

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Poster Session

Cancer survival (SURVCANCER BRAZIL): Analysis of 132,621 cases from 19 hospital-based registries in southernmost Brazilian state comparing public and private insurance. *First Author: Juliana Giacomazzi, Hayde Health; Instituto Tacchini de Pesquisa em Saude (ITPS); Latin American Cooperative Oncology Group (LACOG); Post Graduate Program in Epidemiology, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil*

Background: Brazilian data for cancer survival are scarce. Therefore, we aimed to describe the 5-year overall survival (OS) of individuals with public and private insurance from Rio Grande do Sul/RS (Brazil) diagnosed with the 17 most incident tumors in the country. **Methods:** Data from 19 of the 27 hospital-based cancer registries from RS were integrated with the Brazilian Information System data. Individuals with confirmed cancer diagnoses between 2005–2017 were included. Passive follow-up time was calculated as the difference between diagnosis and death (from any cause) or censure date. Survival was estimated by Kaplan-Meier method. Comparison between the survival of individuals assisted by public or private insurance was evaluated using hazard ratios (HR) estimated by multivariate frailty and Cox regression models with adjustments for age, sex, and economic status. **Results:** 5-year OS was higher for patients with private health insurance for 13 of the 17 cancers studied. **Conclusions:** The survival trends among cancer patients assisted by public and private health insurance systems reveal vast differences that may be likely attributable to differences in access to early diagnosis and optimum treatment. We hope our results will help government officials understand that ongoing cancer survival surveillance is an indispensable source of information and a key policy tool for public health decisions. Research Sponsor: In part by Roche; fapergs and researchers.

Cancer	Coverage	5-year Overall Survival	HR adjusted	p-value
Bladder	Private	57.2 (52.5-62.3)	1.08 (0.89-1.31)	0.410
	Public	56.0 (53.7-58.4)		
Brain	Private	35.5 (30.6-41.1)	1.20 (1.01-1.40)	0.034
	Public	30.6 (27.7-33.8)		
Breast	Private	87.2 (86.1-88.3)	1.40 (1.25-1.57)	<0.001
	Public	79.7 (79.1-80.4)		
Colorectal	Private	64.1 (62.0-66.3)	1.43 (1.30-1.57)	<0.001
	Public	52.1 (50.9-53.2)		
Cervix	Private	68.8 (64.0-73.9)	1.24 (1.00-1.53)	0.043
	Public	58.3 (56.6-59.9)		
Larynx	Private	60.7 (55.1-66.9)	1.53 (1.22-1.91)	<0.001
	Public	42.0 (39.6-44.6)		
Leukemia	Private	49.5 (43.0-56.9)	1.20 (0.97-1.48)	0.089
	Public	43.4 (41.0-46.0)		
Lung	Private	30.5 (28.3-32.9)	1.26 (1.17- 1.37)	<0.001
	Public	19.2 (18.2-20.2)		
Lymphoid	Private	73.0 (69.9-76.3)	1.48 (1.24-1.77)	<0.001
	Public	58.2 (56.4-60.0)		
Melanoma	Private	75.7 (72.2-79.3)	1.37 (1.10-1.71)	0.004
	Public	68.5 (66.3-70.7)		
Esophagus	Private	31.9 (26.9-38.0)	1.41 (1.19- 1.67)	<0.001
	Public	21.5 (20.1-23.1)		
Oral Cavity	Private	64.3 (58.1-71.2)	1.66 (1.27- 2.16)	<0.001
	Public	45.5 (42.7-48.5)		
Ovary	Private	56.9 (50.6-64.0)	1.13 (0.86-1.47)	0.360
	Public	54.7 (51.8-57.6)		
Prostate	Private	86.3 (84.9-87.6)	1.42 (1.24-1.61)	<0.001
	Public	77.0 (76.2-77.9)		
Stomach	Private	43.6 (39.5-48.2)	1.60 (1.38-1.84)	<0.001
	Public	27.4 (25.7-29.2)		
Thyroid	Private	97.3 (96.3-98.4)	3.26 (1.84-5.74)	<0.001
	Public	91.2 (89.4-93.1)		
Uterus	Private	69.7 (64.4-75.6)	1.00 (0.77-1.30)	0.990
	Public			

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Poster Session

Real-world analysis of commercially insured and Medicare Advantage patients with advanced cancer and rates of molecular testing. *First Author: Stacey DaCosta Byfield, Optum Labs, Eden Prairie, MN*

Background: Guideline-recommended molecular testing has become essential for biomarker-guided clinical decision making, particularly for patients with advanced (adv) disease. Several biomarkers have indications that are tumor type-agnostic (starting with MSI in 2017, NTRK in 2018, TMB in 2020, and RET and BRAF in 2022). Biomarker testing is covered by insurers, both Medicare (covers comprehensive genomic profiling [CGP] and non-CGP panels) and commercial (at least non-CGP). This study aimed to understand utilization of biomarker testing across tumor types. **Methods:** This retrospective analysis used de-identified administrative claims from Optum Labs Data Warehouse. Adult Commercial (COM) and Medicare Advantage (MA) enrollees diagnosed with any 1 of 6 adv cancer types from 1/2018 to 8/2021 were identified; the date of the first claim indicating adv cancer was the index date. Continuous enrollment for 12 months prior to (baseline), and ≥ 6 months post-index date, unless they died (follow-up) was required. Biomarker testing was captured using Current Procedural Terminology (CPT) codes indicating CGP (> 50 gene panels), non-CGP (at most 5-50 gene panels), or CPT code 81479 (unlisted molecular pathology procedure) during the study period. The primary analysis evaluates testing in the follow-up only, with secondary analyses evaluating testing including the baseline (to account for testing prior to the index date). **Results:** We identified 16,931 breast (BC), 16,838 non-small cell lung (NSCLC), 8,755 colorectal (CRC), 4,244 pancreatic (PC), 2,610 ovarian (OC), and 1,231 gastric (GC) adv cancer patients meeting study criteria. Overall biomarker testing rates in the follow-up period were: 37% NSCLC, 19% BC, 41% CRC, 35% PC, 51% OC, 35% GC. The Table shows testing rates by cancer, insurance type, and panel size during follow-up. Testing rates were lower among MA patients compared to COM patients. Even considering baseline and follow-up periods, overall biomarker testing rates were low, and lower among MA compared to COM: 48% NSCLC (53% COM, 47% MA), 27% BC (34% COM, 22% BC), 56% OC (61% COM, 53% MA), 42% PC (53% COM, 38% MA), 47% CRC (56% COM, 42% MA), 41% GC (54% COM, 35% MA). **Conclusions:** Considering guideline recommendations, rates of biomarker testing across tumor types are far from optimal despite insurance coverage for testing. Identification of barriers to biomarker testing and interventions to overcome these are needed to improve adherence to biomarker testing guidelines. Research Sponsor: Illumina.

Biomarker testing in follow-up.

Commercial	NSCLC N=2,800	BC N=6,717	OC N=862	PC N=1,020	CRC N=2,972	GC N=362
Any biomarker test, %	44	22	57	45	49	48
CGP, %	14	5	19	18	15	19
Non-CGP, %	32	11	29	24	29	26
81479, %	15	12	30	18	23	18
Medicare Advantage	NSCLC N=14,038	BC N=10,214	OC N=1,748	PC N=3,224	CRC N=5,783	GC N=869
Any biomarker test, %	36	17	49	32	36	30
CGP, %	12	5	22	13	11	13
Non-CGP, %	23	8	24	16	21	13
81479, %	11	9	22	12	13	10

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Poster Session

A comparison of the Optum Clinicogenomics Solid Tumor Database and the SEER Population-Based Cancer Registry. *First Author: Alexa Woodward, Optum Life Sciences, Eden Prairie, MN*

Background: Real-world data (RWD) and real-world evidence (RWE) are increasingly utilized across a range of research and regulatory applications, including biomarker discovery, risk stratification, external control arms, and post-market surveillance. Two-thirds of FDA approvals in 2021 utilized genomic data and the growing interest in targeted therapies will likely continue this trend. While genomics or any one type of RWD alone yields an incomplete view of the patient journey, Optum's clinicogenomic data links de-identified longitudinal clinical and claims data to next-generation sequencing (NGS) results. Ensuring the value of this data requires identifying and limiting biases and maximizing diversity. **Methods:** To evaluate the robustness and representativeness of Optum's Clinicogenomic Solid Tumor Database, we compared demographic and clinical characteristics to the Surveillance, Epidemiology and End Results (SEER) database across 16 solid tumor types. Variables of interest included age at diagnosis, sex, self-identified race, year of diagnosis, and metastatic status. The Optum data was derived from clinical data that includes 156 million lives and claims data that covers 95 million lives. The solid tumor sub-cohort used for this analysis included 157,164 patients diagnosed between January 1, 2011, and December 31, 2021 with linked broad-panel NGS results. SEER Incidence Data included patients diagnosed between January 1, 2011, and December 31, 2018. Using the Optum data, we also report average continuous enrollment and sequential testing frequency across all solid tumor types. **Results:** The overall distributions of age at diagnosis, sex and race were similar across all cancer types, with a few exceptions. On average, SEER had a larger proportions of patients 80 years and older (15% vs 7.2%, all solid tumors) and of Asian race (7.1% vs 3.2%, all solid tumors). Cancer diagnoses in the Optum data increased year over year corresponding with the increasing availability and uptake of genetic testing in oncology, while the SEER data was equally distributed across all years. The average continuous enrollment for solid tumor patients was 8.1 years in the Optum data, and 13% of patients had sequential testing results from > 1 time point. **Conclusions:** Given the increased reliance on RWD and RWE as part of the drug development and regulatory approval processes, ensuring the representativeness of clinicogenomic databases is paramount. This analysis of general patient characteristics across the Optum Clinicogenomics and SEER solid tumor databases found largely similar distributions of key variables. Observed differences between these two representative databases reflect the genetic testing landscape in oncology and provide the opportunity to investigate disparities related to accessing genetic services, corresponding targeted treatment options, and health outcomes. Research Sponsor: Optum.

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Poster Session

Prognosis and risk of suicide after cancer diagnosis. *First Author: Connor J Kinslow, Columbia University Medical Center, New York, NY*

Background: Suicide rates are elevated acutely after cancer diagnosis. We sought to create a unifying theory that explains variations in suicide risk across cancer sites, stages, and demographics. Based on the stress-diathesis model, we hypothesized that suicide risk correlates with cancer prognosis and that the impact of prognosis on suicide risk is greatest for populations with higher baseline risks of suicide. **Methods:** We identified all patients with newly diagnosed cancers from 2000-2019 in the Surveillance, Epidemiology, and End Results (SEER) 17 database, representing 27% of U.S. cancers diagnosed over the past 20 years. Multiple primary-standardized mortality ratios (SMR) were used to determine the relative risk of suicide within the first 6 months compared to the general U.S. population, adjusted for age, sex, race, and year of follow-up. We correlated suicide and 2-year overall survival rates for 20 cancer sites using a weighted linear regression model. **Results:** We identified 9,046 suicides among 6,811,940 persons diagnosed with cancer, 1,610 of which occurred within 6 months of diagnosis. There were 5.3 suicides per 10,000 person-years, compared with an expected rate of 1.7 (SMR 3.1 [95% CI 3.0-3.3]). Suicide risk correlated strongly with prognosis (increased risk of 9.5% per percent survival deficit at 2 years, $R^2 = 0.88$, $P < .0001$). The impact of prognosis on suicide risk was greater for demographic groups with higher baseline risks of suicide. For men, the risk of suicide increased by 3 suicides per 10,000 person-years ($R^2 = 0.84$, $P < .0001$) versus 0.3 in women ($R^2 = 0.54$, $P < .0001$). The impact of prognosis on suicide risk was also greater for persons age 60+ and for white (versus black) race. **Conclusions:** Poorer prognosis correlates with suicide risk in patients with cancer and has a greater effect on populations with higher baseline rates of suicide. Our model should provide a useful framework for triaging patients that need increased surveillance or urgent psychiatric referral. Research Sponsor: None.

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Poster Session

Disparity in regional recruitment across global cancer trials: A meta-analysis. *First Author: Noureen Asghar, Creighton University, Papillion, NE*

Background: Equitable regional enrollment in clinical trials is critical to addressing global inequities in health care outcomes. Therefore, we quantified disparities in regional recruitment in global cancer trials. **Methods:** Phase II/III clinical trials in prostate (PC), breast (BC), colorectal (CRC) and lung cancer (LC), and reporting regional recruitment were identified from Medline. Global regions were defined as North-America (NA) and South-America (SA), Europe (EU), Africa (AF), Asia (AS), and Australia (AU). For multi-regional trials, enrollment incidence ratios (EIR) which compare region-wise trial enrollment against global estimates of region-wise specific cancer incidence obtained from Global Burden of Disease 2019 database. Trial-level EIRs were pooled using random-effects meta-analysis. A pooled EIR of < 1.0 indicates underrepresentation of a particular region in clinical trial enrollment compared to the actual burden of the specific cancer in that region. Statistical analyses were conducted in R v4.1.2. **Results:** Of the total 2125 trials identified, 1681 (79.1%) trials with 691,800 participants reported information regarding regional recruitment. Among those, only 1400 (65.9%) trials reported proportions of patients from pre-defined regions. A total of 1231 (57.9%) trials were single-regional recruiting patients from EU (589; 47.8%), NA (329; 26.7%), AS (295; 23.9%), AU (10; 0.8%), AF (4; 0.3%), and SA (4; 0.3%). There was significant underrepresentation of patients from AS (EIR: 0.47; 95% CI: 0.41-0.54) in cancer clinical trials. This was consistent across different cancers: PC (0.49; 0.35-0.71), BC (0.63; 0.43-0.94), CRC (0.63; 0.43-0.94), LC (0.39; 0.30-0.50). Similarly, there is a trend of under-representation of patients from AF (0.67; 0.43-1.04). Consistently, patients from were under-represented in PC (0.43; 0.24-0.77) and LC (0.26; 0.09-0.79) trials. Patients from NA (1.27; 1.08-1.51), EU (1.64; 1.57-1.72), and AU (5.41; 3.90-7.51) were significantly over-represented in multi-regional cancer clinical trials. The results are provided in table. **Conclusions:** There is suboptimal reporting of region-wise enrollment in cancer clinical trials. Representation of Africa and Asia in cancer clinical trials appears to be less than their expected share based on their burden of cancer incidence. Research Sponsor: None.

Region	EIR (95% CI)				
	Overall	PC	BC	CRC	LC
AF	0.67 (0.43-1.04)	0.43 (0.24-0.77)	0.73 (0.36-1.49)	1.70 (1.16-2.50)	0.26 (0.09-0.79)
AS	0.47 (0.41-0.54)	0.49 (0.35-0.71)	0.63 (0.43-0.94)	0.63 (0.43-0.94)	0.39 (0.30-0.50)
AU	5.41 (3.90-7.51)	5.27 (2.76-10.07)	8.33 (5.36-12.93)	8.33 (5.36-12.93)	5.58 (2.43-12.84)
EU	1.64 (1.57-1.72)	1.26 (1.14-1.39)	1.79 (1.65-1.94)	1.79 (1.65-1.94)	2.00 (1.80-2.22)
SA	1.37 (1.11-1.69)	0.76 (0.56-1.03)	0.99 (0.55-1.77)	0.99 (0.55-1.77)	1.89 (1.32-2.71)
NA	1.27 (1.08-1.51)	1.12 (0.94-1.33)	8.49 (6.09-11.84)	8.49 (6.09-11.84)	0.90 (0.68-1.18)

6637

Poster Session

Real world data for venous thromboembolisms (VTEs) in patients with active cancer: Thromboprophylaxis pooled analysis from GMat and ACT4CAT studies. *First Author: Nikolaos Tsoukalas, On behalf of the Hellenic Society of Medical Oncology, Athens, Greece*

Background: Venous Thromboembolisms (VTEs) lead to many negative consequences for patients with active cancer and are reported up to 20%. They affect anticancer treatment plan, increase morbidity, mortality, economic burden, and escalate psychological drain. Current guidelines recommend pharmacologic prophylaxis for thrombosis in ambulatory cancer patients with Khorana score ≥ 2 . **Methods:** GMat and ACT4CAT are prospective observational phase IV studies conducted by HeSMO in Greece. The aim was to record the clinical practice for ambulatory patients with active cancer who received thromboprophylaxis and enrolled after signing informed consent. Studies were approved by the bioethics committee. **Results:** 1157 patients from 26 oncology clinics enrolled who received thromboprophylaxis. Tumor types: gastrointestinal 38.5%, lung 24.8%, urological 12.2%, gynecological 6.9%, breast 6.1% and others 11.5%. Treatment lines: 1st 62.5%, 2nd 15.1%, 3rd 4%, adjuvant 9.7% and neoadjuvant 5.9%. Age ≥ 65 in 55.2%, BMI ≥ 30 in 17.8% and males 59.9%. High-Risk for Thrombosis Agents (HRTAs) received 82.3%: platinum agents (52.9%), antimetabolites (49.0%) and immunotherapy (10.2%). Notably, 52.7% of anticancer agents had potential drug-drug interactions (DDIs) with Direct Oral Anticoagulants (DOACs). High thrombotic risk factors presented in table. Thromboprophylaxis duration was 5.1 ± 3.3 months with: tinzaparin 91.2%, fondaparinux 4.6%, bemiparin 2.3%, enoxaparin 1.2%, rivaroxaban 0.4% and apixaban 0.3%. Intermediate thromboprophylaxis doses of Low Molecular Weight Heparins (LMWHs) received 62% of patients; 50% in adjuvant setting & 72.6% in metastatic. 32 thrombotic events reported (efficacy: 97.2%, 95%CI: 96.3-98.2%) and 26 grade 1 or minor bleedings (2.2%, 95%CI: 1.4-3.1%). Patients receiving intermediate doses of LMWHs had less risk for thrombosis ($p=0.0308$). **Conclusions:** VTEs prophylaxis in ambulatory patients with active cancer was found safe and effective. Apart from Khorana score, metastasis, HRTAs and DDIs seem to affect clinical decision for thromboprophylaxis mainly with LMWHs and often using intermediate doses irrelevant of clinical setting. Cancer Associated Thrombosis (CAT) is not negligible risk for patients and oncologists appeared to be aware about this. Clinical trial information: NCT03292107, NCT03909399. Research Sponsor: None.

Neoplasm type	Incidence	Female	Age ≥ 65	BMI ≥ 30	Smoking	Metastasis	HRTAs	DDIs	Radiotherapy	Comorbidities
Lung	24.8	21.4	56.5	18.5	88.5	82.5	82.9	58.9	34.3	46.1
Pancreatic	21.5	41.6	54.6	11.2	50.2	75.7	96.4	63.1	3.3	35.8
Urological	12.2	10.3	58.9	19.2	71.6	70.1	72.1	44	19.3	53.2
Colorectal	9.5	39.8	58.2	15.5	50.9	81.3	89.1	27.3	15.6	52.3
Stomach	7.4	29.1	60.5	11.6	62.8	74.1	91.8	40.7	10.5	47.6
Gynecological	6.9	100	55	35	30	71.1	87.3	71.3	5.1	46
Breast	6.1	98.5	37.1	20	31.4	67.7	52.9	61.4	45.5	60.6
Head & neck	1.3	30	33.3	33.3	80	63.6	80	60	73.3	53.3
Others	10.3	47.3	56.3	20.2	57.1	59.6	64.4	40.3	27.4	47.9

6639

Poster Session

Oncologists' receipt of pharmaceutical industry payments and use of non-recommended and low-value cancer care services. *First Author: Aaron Philip Mitchell, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Personal payments from the pharmaceutical industry to US physicians are common and influence physician practice. Prior studies have found that industry payments sway physicians' selection among effective, medically appropriate treatments. However, whether industry payments may be associated with non-recommended and low-value care has not been assessed. The objective of this study was to estimate the association between oncologists' receipt of industry payments and use of non-recommended and/or low-value (NR/LV) interventions. **Methods:** Population-based cohort study using fee-for-service Medicare claims and Open Payments records of industry payments. We identified four NR/LV cancer interventions: 1) denosumab for castrate-sensitive prostate cancer; 2) GCSF for patients at low risk for neutropenic fever; 3) nab-paclitaxel instead of paclitaxel for breast and lung cancer 4) branded drug instead of a generic or biosimilar. Study sample: Medicare beneficiaries with an incident cancer diagnosis (identified by new occurrence of a cancer diagnosis code in proximity to claims for cancer treatment) from 2014-2019. We applied additional requirements as appropriate to identify four sub-cohorts, corresponding to patients at risk for each of the NR/LV treatments, and identified the treating oncologist using claims. The primary exposure was receipt, by a patient's oncologist, of any industry payments for the corresponding NR/LV treatment of interest, within 365 days before the patient's index cancer date. The primary outcome was receipt of the corresponding NR/LV treatment. We fit general linear models controlling for patient characteristics and calendar year. To assess robustness, we also accounted for physician-level fixed effects in separate models. **Results:** Cohort sizes were: denosumab N = 9,799; GCSF N = 271,485; nab-paclitaxel N = 86,394; branded drug N = 13,386. Controlling for patient characteristics and calendar year, industry payment was associated with an increase in the absolute prevalence of denosumab (+17.5% [95%CI: 15.3 to 19.7%]), GCSF (+5.8% [95%CI: 5.4 to 6.1%]), and nab-paclitaxel (+7.6% [95%CI: 7.1 to 8.1%]) use, but lower branded drug use (-4.6 [95%CI: -5.8 to -3.3]). In physician-level fixed effects models, industry payment was associated with increased denosumab (+7.4% [95%CI: 2.5 to 12.2%]) and nab-paclitaxel (+1.7% [95%CI: 0.9 to 2.5%]) use, but not with GCSF (+0.4% [95%CI: -0.3 to 1.1%]) or branded drugs (+1.2% [95%CI: -5.8 to 8.3%]). **Conclusions:** Recent receipt of industry payments by physicians was associated with increased use of several forms of NR/LV cancer treatment. These findings raise quality-of-care concerns regarding physician-industry financial relationships. Additional work is needed to further explore the causal relationship between payments and non-recommended treatments, and between payments and patient outcomes. Research Sponsor: U.S. National Institutes of Health; NIHCM.

6638

Poster Session

Cost of genetic testing, delayed care, and suboptimal treatment associated with polymerase chain reaction (PCR) versus next-generation sequencing (NGS) testing strategies in metastatic non-small cell lung cancer (mNSCLC). *First Author: Christine M. Bestvina, University of Chicago, Chicago, IL*

Background: NGS testing for genomic alterations has been found to expedite time to appropriate targeted therapy initiation compared to PCR testing in mNSCLC. This study assessed US payers' costs of testing, delayed care, and suboptimal treatment initiation for PCR versus NGS testing in patients with mNSCLC. **Methods:** A decision tree model evaluated testing for guideline-recommended alterations (EGFR, ALK, ROS1, BRAF, KRAS, MET, HER2, RET, NTRK1/2/3) in patients with newly-diagnosed mNSCLC from first test until appropriate therapy initiation using 1) liquid or tissue NGS (60% [90% tissue, 10% liquid] of patients), 2) exclusionary KRAS test followed by sequential PCR tests (5%), 3) sequential PCR tests (5%), or 4) hotspot panel (30%) PCR tests. The proportion of patients testing positive for a targetable alteration and time to appropriate therapy initiation were evaluated. Cost components included genetic testing, testing-related medical services, delayed care (i.e., costs for medical services while waiting for test results), immunotherapy (IO)/chemotherapy (CTX) initiation prior to test results, and suboptimal treatment initiation after test results (i.e., costs of first-line IO/CTX in patients falsely testing negative for an actionable mutation). **Results:** In a modeled cohort of 1 million members (75% commercial, 25% Medicare), an estimated 1,119 patients had mNSCLC and were tested. The proportion of patients testing positive for a targetable alteration was 45.9% for NGS and 39.4% for PCR testing (Table). Total mean per patient costs were lower for NGS (\$8,866) than for PCR (\$18,252), driven by more rapid treatment with appropriate therapy (2.1 versus 5.2 weeks), resulting in lower delayed care costs and IO/CTX costs prior to test results. **Conclusions:** Results suggest that NGS testing may lead to better patient care and reduced costs to the health system relative to PCR testing. Costs of inappropriate IO/CTX initiation are an important component of increased costs of PCR-based approaches. Research Sponsor: Janssen Scientific Affairs, LLC.

	NGS Number tested (N)=671	Sequential N=56	Exclusionary N=56	Hotspot Panel N=336	PCR Approaches Combined* N=447
Results					
Proportion testing positive for a targetable alteration	45.9%	37.9%	33.1%	40.7%	39.4%
Proportion initiating suboptimal treatment	0.0%	8.0%	12.8%	5.2%	6.5%
Time to appropriate therapy initiation, weeks	2.1	10.5	10.1	3.5	5.2
Total testing-related costs, per patient	\$8,866	\$27,939	\$28,032	\$15,009	\$18,252
Gene testing	\$4,022	\$4,669	\$4,051	\$6,091	\$5,659
Medical	\$1,245	\$1,919	\$1,806	\$1,250	\$1,403
Delayed care	\$1,301	\$6,445	\$6,220	\$2,155	\$3,199
Treatment initiation prior to test results	\$2,298	\$12,374	\$11,901	\$3,862	\$5,930
Suboptimal treatment initiation after test results	\$0	\$2,532	\$4,053	\$1,651	\$2,061

*Sum of components differs slightly due to rounding.

6640

Poster Session

Palliative care as a component of high-value and cost-saving care during hospitalization for metastatic cancer. *First Author: Sifan Lu, SUNY Downstate Health Sciences University, Brooklyn, NY*

Background: Randomized controlled trials have demonstrated that palliative care can improve both quality of life and survival for outpatients with advanced cancer, but there is limited population-based data on the value of inpatient palliative care. We assessed palliative care as a component of high-value care among a nationally representative sample of inpatients with metastatic cancer. We further identified care, patient, and hospital characteristics significantly associated with high costs. **Methods:** This study analyzed hospitalizations of patients ≥ 18 years with a primary diagnosis of metastatic cancer from the National Inpatient Sample (covering 97% of the U.S. population) from 2010-2019. We utilized multivariable mixed-effects logistic regression to assess medical services (receipt of palliative care, invasive medical ventilation (IMV), systemic therapy), patient demographics, and hospital characteristics that were associated with higher charges billed to insurance and hospital costs. We utilized generalized linear mixed-effects models to determine cost savings associated with provision of palliative care. **Results:** Among 397,691 hospitalizations from 2010 to 2019, the median charge per admission increased by 24.9%, from \$44,904 in 2010 to \$56,098 in 2019, while the median hospital cost remained stable at \$14,300. Receipt of inpatient palliative care was associated with significantly lower charges (Odds Ratio [OR], 0.62; 95% CI, 0.61-0.64; $P < .001$) and costs (OR, 0.59; 95%CI, 0.58-0.61; $P < .001$). Factors associated with high charges were receipt of invasive medical ventilation ($P < .001$) or systemic therapy ($P < .001$), Hispanic patients ($P < .001$), and young age (18-49 years, $P < .001$). For-profit hospitals were more likely to bill higher charges (OR, 5.05; 95%CI, 4.78-5.33, $P < .001$) but less likely to incur high hospital costs (OR, 0.51; 95%CI, 0.48-0.54, $P < .001$) than public hospitals. In adjusted generalized linear mixed effects regression, palliative care provision was associated with a \$1,293 (-13.4%, $P < .001$) reduction in costs per hospitalization compared to no palliative care, independent of receipt of invasive care and age. Significant interactions were observed between receipt of palliative care and patient age group (-9.6% for 18-49 years; -14.7% for ≥ 70 years), receipt of IMV (-6.4% for IMV receipt; -14.0% for no IMV), hospital ownership (-19.6% for for-profit; -10.5% for public), and year of hospitalization (-15.4% for 2010; -8.9% for 2019). **Conclusions:** Inpatient palliative care is associated with reduced hospital costs for patients with metastatic cancer, irrespective of age and receipt of aggressive interventions. Assuming inpatient palliative care receipt increases by 50%, we estimate \$4,045,000 in annual national savings. Integration of inpatient palliative care may de-escalate costs incurred through low-value inpatient interventions. Research Sponsor: None.

6641

Poster Session

The role of private insurance characteristics in the out-of-pocket costs of patients with multiple myeloma. *First Author: Hamlet Gasoyan, Cleveland Clinic, Cleveland, OH*

Background: Over the past two decades, the major advances in the treatment of multiple myeloma have improved overall survival considerably. High costs of novel medications and patient out-of-pocket costs were suggested to have a role in treatment disparities but available data on total- and patient-out-of-pocket costs are dated. We examined the costs in privately insured patients with newly diagnosed multiple myeloma in the first year after the diagnosis, based on insurance plan characteristics.

Methods: This retrospective study used the IBM MarketScan Commercial Database for the years 2011–2019, which consists of medical and prescription medications data from 120+ large employers and 40+ health plans in the US. The primary outcome variables were total- and patient out-of-pocket costs during 1 year after the index diagnosis. **Results:** 5,487 privately insured adults with an index multiple myeloma diagnosis during 2012–2018 were identified. Approximately 41% (n=2,240) of the study population received bortezomib, 38.6% (n=2,117) received lenalidomide, and 5.7% (n=314) received carfilzomib during 1 year after the index diagnosis. The median total cost of care in the first year after multiple myeloma diagnosis increased from \$133,938 (interquartile range, \$19,770 – \$292,501, expressed in 2018 USD) in patients diagnosed in 2012 to \$252,559 (\$33,089 – \$380,662) in patients diagnosed in 2018. The median patient out-of-pocket costs were \$3,147 (interquartile range \$1,562 – \$5,441, 2018 USD) in patients diagnosed in 2012 and \$3,711 (\$1,756 – \$6,466) in patients diagnosed in 2018. Among patients diagnosed in 2018, the median patient out-of-pocket cost was \$1,706 (\$902 – \$2,873) for patients with low out-of-pocket cost plans, \$3,428 (\$1,794 – \$6,371) for those with average out-of-pocket cost plans, and \$5,623 (\$3,517 – \$7,810) for patients with high out-of-pocket cost plans. **Conclusions:** While the total cost of care in the first year after multiple myeloma almost doubled during the study period, the patient out-of-pocket costs remained relatively stable. The protections imposed by the Affordable Care Act are likely key in preventing surges in patient out-of-pocket costs. Additional legislative action could help curb the price increases for multiple myeloma medications. Research Sponsor: Dr. Hamlet Gasoyan received support from the Cancer Intervention and Surveillance Modeling Network's Junior Investigator Career Enhancement Research Award.

Year	2012	2013	2014	2015	2016	2017	2018
Median Out-Of-Pocket Cost (Interquartile Range)	3,147 (1,562 - 5,441)	3,505 (1,708 - 5,565)	2,915 (1,464 - 5,099)	2,884 (1,531 - 5,181)	3,363 (1,576 - 5,618)	3,132 (1,483 - 5,299)	3,711 (1,756 - 6,466)
Median Total Cost (Interquartile Range)	133,938 (19,770 - 292,501)	151,713 (27,392 - 297,279)	126,898 (20,134 - 291,692)	161,508 (19,420 - 333,108)	201,603 (27,291 - 350,144)	175,070 (19,831 - 340,040)	252,559 (33,089 - 380,662)

Costs pooled from different years were expressed in 2018 US dollars, using the Consumer Price Index.

6643

Poster Session

Unnecessary thrombophilia testing reduction: Quality improvement project. *First Author: Konstantin Golubykh, UPMC Harrisburg, Harrisburg, PA*

Background: The American Society of Hematology (ASH) recommends reducing inpatient thrombophilia testing but adherence to these recommendations remains suboptimal. We report the results of a quality improvement (QI) project which aimed to minimize unnecessary testing. **Methods:** We performed retrospective review of records of patients with a new diagnosis of venous thromboembolism (VTE) across 3 hospitals in Central PA from September 2021 to December 2021 to see how many patients underwent thrombophilia workup. Our QI project consisted of education for physicians based on ASH recommendations with lectures, bi-weekly emails, and educational posters. We then performed a second retrospective review of patients admitted under the same conditions between June 1, 2022, and August 31, 2022, to reevaluate thrombophilia testing rates. The cost of testing was extrapolated from institutional hospital cost reports. Descriptive statistics included reporting the categorical variables as number and percent. The categorical variables were compared between groups with Fisher's exact test or the chi-square test. **Results:** During the first study period, 310 patients had new VTE. Provoking factors were found in 269 patients (86.7%) and 41 patients (13.2%) had unprovoked VTE. Overall, 33 out of 310 patients (10%) underwent thrombophilia workup, with a total of 175 tests performed. Thrombophilia testing rate was significantly higher in the unprovoked group (29.3% vs 7.8%, $p = 0.0003$). Both groups have equally received inpatient hematology consult (33.83% vs 47.50%, $p = 0.0920$). Only 16% of thrombophilia tests were recommended by hematology consult while the rest was ordered by the primary team. The cost of all tests ordered outside of hematology recommendation was \$34,083 (\$344 per person). Of the group that got tested regardless of provoking factors, there was no difference between hospital length of stay (2–12 days vs 3–12 days, $p = 0.0665$) or anticoagulation choice. During the second study period, 191 patients had new VTE. Provoking factors were found in 157 patients (82.1%) while 34 patients (17.9%) had unprovoked VTE. Overall, 21 out of 191 patients (10.9%) underwent thrombophilia workup, with a total of 78 tests performed. More testing was ordered in the unprovoked group (26.47% vs 7.64%, $p = 0.0040$). More inpatient hematology consults were performed in the unprovoked group (64.71% vs 40.76%, $p = 0.0110$). Of the hematology consults, 12 out of 21 patients (57%) had thrombophilia testing recommended by hematologist. The rate of thrombophilia testing ordered outside of hematology consultation has decreased from 84% to 43% after our intervention, resulting in a \$16,635 savings for that quarter. **Conclusions:** Our experience confirmed that thrombophilia work up was costly and did not impact quality of care. Despite the relatively low frequency of inpatient workup, eliminating unnecessary testing saved our health system \$16,635 in a 3-months period. Research Sponsor: None.

6642

Poster Session

Estimated life-years gained and resultant cost savings from follow-up colonoscopy after a positive multi-target stool DNA (mt-sDNA) test for colorectal cancer screening in commercially insured and Medicare populations. *First Author: A. Mark Fendrick, University of Michigan, Ann Arbor, MI*

Background: Although follow up colonoscopy (COL) after a positive stool-based colorectal cancer (CRC) screening test is necessary to complete the CRC screening process, follow-up COL rates remain suboptimal, especially among underserved populations. As of January 2023, federal policies require commercial insurers and Medicare to eliminate out of pocket costs for follow-up COL. To estimate the implications of this policy change, we compared the clinical and fiscal outcomes for a simulated cohort receiving a follow-up COL after a non-invasive CRC test (\$0 cost sharing), compared to the same cohort not completing follow-up COL (status quo). **Methods:** Using the validated CRC-AIM model, we simulated a cohort of 6 million average-risk individuals who received mt-sDNA (commercial patients at age 45 and Medicare patients at age 65) and further analyzed only the population with positive mt-sDNA. Life-years gained, CRC incidence, CRC-related mortality and total costs of care (inclusive of CRC screening and treatment) were calculated for a cohort that underwent follow-up COL and compared these outcomes to that same cohort that did not complete follow-up COL. The cost of follow-up COL was assumed to be \$1,576 for Medicare and \$3,086 for commercially insured patients (\$0 out of pocket costs for all). **Results:** Patients undergoing follow-up COL after a positive mt-sDNA experienced more life-years (83 per 1,000 commercially insured patients and 80 per 1,000 Medicare beneficiaries) compared to those who did not undergo follow-up COL. The follow-up COL resulted in reductions in CRC incidence and CRC mortality by 14% and 16% for commercial and 19% and 23% for Medicare beneficiaries, respectively. Compared to those patients with a mt-sDNA positive test result and did not complete follow-up COL, the total cost per patient for those receiving follow-up COL was \$3,339 less for commercially insured (\$15,690 – no follow up vs. \$12,351 – follow up) and \$4,382 less for Medicare beneficiaries (\$19,337 – no follow up vs. \$14,955 – follow up). Total spending for patients receiving follow-up COL was cost-saving when compared to no follow-up as long as the COL costs were less than \$6,269 for commercial plans and \$5,753 for Medicare. **Conclusions:** Completing a follow-up COL after a positive mt-sDNA screening saves lives, enhances equity, and lowers total expenditures. Thus, health care stakeholders should invest in efforts to identify and reduce barriers that ultimately lead to an increase uptake of this potentially lifesaving and cost-reducing intervention. Research Sponsor: Exact Sciences Corporation.

6644

Poster Session

Association between targeted cancer drug net health benefit and uptake, patient out-of-pocket spending, and total spending. *First Author: Kelsey S. Lau-Min, Massachusetts General Hospital, Boston, MA*

Background: Targeted cancer drugs (TCDs) have revolutionized oncology, but they are widely variable in their clinical benefit and are often accompanied by high patient-out-of-pocket (OOP) costs. The ASCO Value Framework uses published clinical trial data on survival, toxicity, and potential for symptom palliation to quantify the net health benefit (NHB) of any given cancer drug. We aimed to evaluate the association between NHB and uptake, patient OOP spending, and total spending for eight oral TCDs approved for the first line treatment of an advanced solid tumor based on one or more clinical trials comparing to a non-TCD control arm. **Methods:** We conducted a retrospective cohort study of incident pharmacy claims for oral TCDs prescribed to patients aged 18–64 years between 2012–2020 in the nationwide Health Care Cost Institute de-identified commercial claims dataset. NHB scores were calculated for each TCD of interest using the ASCO Value Framework and categorized as high (>60), medium (40–60), and low (<40) net health benefit. Distributions of incident 28-day TCD supplies were plotted over time by NHB category. The primary outcome was patient OOP spending (patient copay + coinsurance + deductible), whereas the secondary outcome was total spending (patient OOP spending + pharmacy reimbursement). Generalized linear models were used to evaluate the association between each outcome of interest and TCD NHB, adjusted for cancer indication. **Results:** We included 8,524 incident pharmacy claims for eight TCDs with nine indications in breast cancer, non-small cell lung cancer (NSCLC), melanoma, and pancreatic cancer. NHB scores ranged from 7 (erlotinib for pancreatic cancer) to 81 (crizotinib for ALK-rearranged NSCLC), with 1,145 (13%), 6,608 (78%), and 771 (9%) of pharmacy claims falling into low-, medium-, and high-NHB categories, respectively. Medium- and high-NHB TCDs accounted for the majority of incident TCD prescriptions throughout the study period. Median patient OOP spending was \$18.78 for the first 28-day TCD supply (IQR \$0.00–\$87.57), with 45% of patients paying \$0 and 8% paying >\$1,000 OOP. Patient OOP spending was not significantly associated with TCD NHB category (difference \$0.94, 95% CI -\$49.99–\$51.87 for medium vs low NHB; difference \$58.86, 95% CI -\$28.04–\$145.75 for high vs low NHB). Median total spending was \$10,118.79 (IQR \$6,365.95–\$10,600.37) for an incident 28-day TCD supply. There was a \$1,083.56 increase in total spending for each 10-point increase in NHB score (95% CI \$1,050.27–\$1,116.84, $p < 0.01$ for $H_0 = \$0$). **Conclusions:** Although TCDs are widely variable in their NHB, low-NHB TCDs are not prescribed as frequently as medium- and high-NHB TCDs. Total spending on TCDs is high and positively associated with NHB. Commercially insured patients are largely shielded from high OOP spending on TCDs. Research Sponsor: Robert Wood Johnson Foundation.

6645

Poster Session

Association of early completion of portable medical orders with inpatient costs at end-of-life for patients with acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS). *First Author: Marissa LoCastro, University of Rochester School of Medicine & Dentistry, Rochester, NY*

Background: Patients with hematologic malignancies receive more aggressive care at end-of-life (EOL) compared to patients with solid tumors. Costs of care in patients with hematologic malignancies at EOL are high, particularly in the inpatient setting. We previously found that early completion of portable medical orders [termed medical orders for life sustaining treatment (MOLST) in New York state] is associated with less intense care at EOL for patients with AML and MDS. Thus, we hypothesized that early MOLST completion would also be associated with lower inpatient costs at EOL among patients with AML and MDS. **Methods:** We previously conducted a retrospective study of 358 adults patients with AML or MDS treated at Wilmot Cancer Institute and its affiliated sites who died between January 1, 2014, and December 31, 2019. Of these, 271 patients were eligible for cost analysis. Cost of inpatient care received at the University of Rochester Medical Center (URMC) within the last 30 days of life was obtained from our Finance Decision Support Department. Patients were excluded if inpatient costs at EOL were unavailable. **Results:** Mean age of patients was 69 years (N=271, range 20-95); 84% (n=227) of patients were hospitalized within 30 days of death. One-third (34%, n=93) of patients completed a MOLST early (>30 days prior to death) whereas 66% (n=178) either did not complete a MOLST or completed a MOLST late (less than or equal to 30 days prior to death). Mean and median inpatient cost of care for all patients at EOL was \$39,284 and \$19,703, respectively. The rate of hospitalization was lower for patients who completed a MOLST early vs late/never (73.1% vs 90.5%, respectively; $p=0.0003$), although there was no difference in the number of inpatient visits between the two groups (median=1 visit in both groups; $p=0.23$). In addition, median cost of inpatient care was lower for patients who completed a MOLST early vs late/never (\$10,673 vs \$23,177, respectively; $p<0.0001$). After adjusting for age, sex, and diagnosis, there was a trend toward lower EOL costs in patients completing a MOLST early ($p=0.07$). **Conclusions:** In patients with AML or MDS, early MOLST completion may be associated with lower inpatient costs at EOL. Viewing MOLST completion as a surrogate for a goals-of-care discussion, it follows that interventions aimed to increase the frequency of early goals-of-care discussions, advanced care planning, and MOLST completion are likely to improve quality of care and decrease costs at EOL in these patient populations. Research Sponsor: University of Rochester CTSA award number TL1 TR002000 from the National Center for Advancing Translational Sciences of the National Institutes of Health; Conquer Cancer Foundation of the American Society of Clinical Oncology; U.S. National Institutes of Health; Wilmot Research Fellowship Award.

6646

Poster Session

Maxed out: Reaching the annual maximum out-of-pocket limit among insured patients diagnosed with cancer. *First Author: Matthew P. Banegas, University of California San Diego, La Jolla, CA*

Background: Patients with cancer face potentially high out-of-pocket costs associated with their medical care, which may lead to adverse medical and financial outcomes. Depending on their health insurance plan, patients may have to pay several thousands for medical care costs until they reach the annual maximum out-of-pocket (MOOP) spending limit; after which care costs are covered by insurance. The purpose of this study was to measure the proportion of adult patients who reach their health plan MOOP limit in the year of cancer diagnosis. **Methods:** Electronic health record data from 13,057 patients aged ≥ 18 years, diagnosed with cancer between Jan. 1, 2016–March 31, 2021 [index cancer], with ≥ 12 months of continuous health insurance coverage pre-cancer diagnosis were included. The primary outcome was defined as reaching the MOOP limit in the health plan benefit year of index cancer diagnosis (binary, yes/no). We additionally created a secondary outcome using 3 categories: (i) did not reach MOOP; (ii) reached MOOP prior to cancer diagnosis; (iii) reached MOOP after cancer diagnosis. Descriptive statistics were used to assess the distribution of outcomes across patient characteristics including health insurance type (e.g., commercial), high-deductible health plan (HDHP), cancer type, age at diagnosis, and Census-level household income was included. Multivariable logistic regression estimated the association between patient characteristics and the primary outcome. Complete case analyses were performed using Stata 16.1. **Results:** Patients' mean age was 66 years (standard deviation [sd]: 13) and mean Census-level household income was \$73,100 (sd: \$24,000). Approximately 40% of patients had commercial health insurance and 62% had Medicare; 2% (n=283) had a HDHP. Breast (18%), lung (11%) and prostate (11%) cancers were most common. The mean annual MOOP limit was \$3,040 for commercial plans and \$2,688 for Medicare plans. Among patients with a commercial plan insurance, 46% reached their MOOP limit including 8% before and 37% after cancer diagnosis. For Medicare patients, 20% reached their MOOP limit, including 3% before and 17% after cancer diagnosis. Patients with a HDHP (adjusted Odds Ratio [aOR]: 2.61, 95% CI: 1.96-3.47), breast cancer (aOR: 2.29, 95% CI: 1.84-2.84), and lung cancer (aOR: 2.71, 95% CI: 2.04-3.61) had significantly greater odds of reaching the MOOP than those with a non-HDHP and other cancers. Household income was also significantly associated (aOR: 0.97, 95% CI: 0.95-0.99) with reaching the MOOP. **Conclusions:** A substantial proportion of patients reach the annual MOOP limit during the year of cancer diagnosis, representing a population at high-risk for medical financial hardship. Future longitudinal studies are needed to assess the trajectory of OOP spending and implications on care utilization and health outcomes. Research Sponsor: U.S. National Institutes of Health.

6647

Poster Session

National survey of financial burdens and experience among patients with cancer receiving charitable co-pay assistance. *First Author: Jeffrey M. Peppercorn, Massachusetts General Hospital, Boston, MA*

Background: High healthcare costs can pose a barrier to access and contribute to financial hardship among patients with cancer. Charitable co-pay assistance (CPA) foundations provide financial support to patients facing high out-of-pocket costs, but little is known about the sociodemographic characteristics, financial burdens, views and experience of those receiving assistance. **Methods:** We conducted a national, cross-sectional survey of CPA grant recipients receiving financial assistance from the HealthWell Foundation (charitable CPA foundation) to cover cancer drug costs. The primary outcome of interest was self-reported financial distress (FACIT-COST). Secondary outcomes included measures of out-of-pocket spending, patient perspectives on CPA support, healthcare access and costs, and the impact of financial burden on healthcare utilization. **Results:** Among 1,108 CPA grant recipients, over 20 cancer types were represented, including 30% with solid tumors and 70% hematologic malignancy. Average age of CPA recipients was 72 (range: 41-92), 60% were male, 88% white, 55% college educated, and 67% had annual income < \$60,000. 96% had Medicare (53% Traditional, 43% Advantage, 58% with supplemental insurance), and 66% believed insurance would prevent them from paying high drug costs. However, 54% reported spending > \$500 per month on healthcare, with 39% spending > 10% of household income. Among 17% reporting delays in starting therapy due to cost, 28% reported delay > 4 weeks. Overall, 18% reported skipping medical services due to cost, and 24% believed they would not have received their treatment without CPA. On the COST scale, 56% reported mild financial toxicity (COST 14-25) and 27% moderate/severe (COST < 14) despite CPA. In bivariate analysis, younger age, solid tumor, lower income, female gender, higher anxiety and depression (PHQ4), greater comorbidity, and traditional Medicare were all significantly associated with greater financial distress (lower COST scores, $P < 0.05$ for all). Most (76%) CPA recipients believed that doctors should be aware of costs when making decisions, and 91% supported Medicare negotiating drug prices with manufacturers. With regard to why they required CPA, only 6% attributed it to failure to discuss costs with their doctor, 14% to the healthcare system, 51% to poor insurance coverage, 61% to their financial status, and 82% to high drug costs. Notably, 73% reported a decrease in financial concerns as a result of CPA. **Conclusions:** In this large national sample of CPA grant recipients with cancer, most had Medicare and believed insurance would shield them from high drug costs, yet many reported delays in starting therapy prior to CPA and ongoing financial distress. CPA may play an important role in securing access to therapy but these findings highlight an ongoing need to address financial toxicity and understand potential disparities in access to CPA. Research Sponsor: HealthWell Foundation.

6648

Poster Session

A health economic model to assess the impact of prehabilitation on hospital cost savings in gastrointestinal cancer, modelled on English National Health Service tariff. *First Author: Bernarda Zamora Zamora Talaya, Imperial College, London, London, United Kingdom*

Background: Prehabilitation is increasingly being recognised as a high-priority intervention to improve physical and psychological health in cancer patients, prevent treatment-related functional decline and to reduce the incidence and severity of post-surgical complications. The aim of this study is to develop a health economic (HE) model to evaluate the impact of prehabilitation in patients undergoing gastrointestinal cancer surgery. **Methods:** The objective of the HE model is to estimate the impact of prehabilitation on reducing treatment costs. Data was extracted from systematic reviews and meta-analysis on the effects of prehabilitation in gastrointestinal cancer surgery to identify: i) treatment pathway, ii) prehabilitation components (nutrition/exercise/psychological intervention), and iii) effects on three study outcomes (length of hospital stay, reduction of post-operative complications, and reduced Intensive Care Unit (ICU) stay). The modelling study accounts for the number of hospital admissions and unit costs from NHS hospitals, including cost per bed-day from NHS Reference costs 2017-18 and complication costs and ICU cost from NHS Reference National Cost Schedule 2019-20. Double counting has been corrected to account for the compounded effects on length of stay and complications. The HE model considers the average effect of each study outcome and their confidence intervals. This provides a range of potential impact of prehabilitation in terms of cost reduction based on NHS tariff. **Results:** Patient weighted average cost savings from prehabilitation was £785, excluding ICU costs. Breakdown of cost savings include £178.6 from reduced length of hospital stay, £214.8 and £434.5 cost savings originating from reductions in minor and major complications, respectively (excluding ICU complication costs). ICU cost savings from prehabilitation were £1,620. For the NHS, based on 237,000 annual surgical procedures, this amounts up to £186,082,321 in cost savings, from a reduction in complications and 421,840 hospital days, and £52,761,227 from ICU stay. **Conclusions:** In addition to the impact on post-operative complications and hospital stay, this study has demonstrated that prehabilitation results in significant costs savings to healthcare systems. The cost savings are largely from a reduction in the incidence and severity of post-operative complications. The latter contributing to reduced ICU costs. Research Sponsor: None.

6649

Poster Session

Value-driven colorectal cancer survivorship through partnership with primary care. *First Author: Gloria Hui Jia Chan, Department of Haematology-Oncology, National University Cancer Institute, Singapore, Singapore*

Background: The risk of recurrence for colorectal cancer (CRC) is low after 5 years (<1.5% per year) hence, surveillance visits, CEA blood tests and annual CT scans are not recommended beyond this period (NCCN guidelines). Importantly, right-siting survivorship care to the community allows primary care providers (PCP) to focus on preventive health beyond cancer. The National University Cancer Institute, Singapore, a tertiary, academic cancer center developed a program to transition CRC survivorship care to the community after 5-years of active surveillance. Patients (Pts) are discharged to the community with a survivorship care plan and followed-up via phone calls. We hypothesize that by transitioning CRC survivors to the community, we can optimize healthcare resources by reducing specialist visits and tests at the cancer center without compromising outcomes. **Methods:** From July 2018, CRC pts beyond 5-years from diagnosis with no evidence of cancer recurrence were eligible for transition. Pts were followed prospectively to determine date of cancer recurrence, issues preventing transition to the community and a phone survey on pt satisfaction was conducted for those who transitioned to primary care. Data on healthcare utilization amongst pts who transitioned vs. pts who remained in tertiary care was collected. Data cutoff was June 2022. Statistical analysis was performed with IBM SPSS Statistics (v28.0). **Results:** Between July 2018 - June 2022, there were 791 CRC pts who were eligible for transition, of which 534 pts (67.5%) had no clinical issues preventing transition and included in this analysis. 54.3% (N=290) were males and stage distribution of cancers were 14.2%, 34.0%, 47.1% and 4.7% for stages I, II, III and IV, respectively. The mean number of years since diagnosis was 6.88 (range: 5-16 years; SD 2.25). 380 pts (71.2%) were transitioned to the community. There was consistently higher utilization of healthcare resources in the group not transitioned vs. transitioned: mean number of consults (2.86 vs 1.02; $p<0.001$); CEA (1.23 vs 0.31; $p<0.001$); CT scans (0.08 vs 0.05; $p=0.221$) and colonoscopies (0.25 vs 0.16; $p=0.031$). Mean healthcare expenditure (mean gross bill per year) was consistently higher in pts across all categories for the group not transitioned vs. transitioned: consults (\$158 vs \$56; $p<0.001$); CT scans (\$60 vs \$39; $p=0.273$); CEA (\$26 vs \$7; $p<0.001$) and colonoscopies (\$208 vs \$126; $p=0.018$). Importantly, recurrence rates were low with no difference in both groups (0.8% vs 1.3%; $p=0.629$). 82% of CRC pts were satisfied or very satisfied with follow-up care provided by their PCPs on a subsequent survey. **Conclusions:** We have demonstrated value-driven survivorship care by right-siting CRC survivors into the community. Healthcare resources were optimized with reduction in specialist visits and tests which lead to lower costs while recurrence rates remain low. Pt satisfaction in the community was also high. Research Sponsor: None.

6651

Poster Session

The impact of a cancer-specific novel therapy adjustment (NTA) in Medicare value-based care programs: A simulation exercise. *First Author: Erica Feinberg, US Oncology Network, Dallas, TX*

Background: The Oncology Care Model (OCM) was a value-based care program implemented by the Centers for Medicare & Medicaid Innovation (CMMI) between July 1, 2016, and June 30, 2022, that aimed to provide high-quality care while reducing total cost of care (TCOC). In 2023 CMS plans to implement the Enhancing Oncology Model (EOM), which builds on lessons learned from the OCM. Over 200 novel therapies were approved by the FDA between 2016 and 2022. Novel therapies come with increased cost, leading to concerns that the model could discourage use of novel therapies. CMMI implemented a novel therapy adjustment (NTA) to offset the increased cost of these expensive therapies, when a practice has a higher proportion of novel therapy expenditures. A key change in the EOM is the calculation for NTA at the individual cancer type level compared to full population of episodes in the OCM. We studied the impact of moving from a population-based NTA to a cancer type-based NTA calculation. **Methods:** Claims and performance data from 10 performance periods (PP) in the OCM (PP1 to PP10) for 14 practices in The US Oncology Network were reviewed. Descriptive statistics for the simulation were evaluated to determine changes from population-based NTA to cancer-based NTA. The OCM NTA methodology was deconstructed to apply the NTA at a cancer type level. We performed a simulation exercise by applying cancer specific NTA methodology systematically to the claims and performance data. We then evaluated the impact of NTA on the EOM cancer types. **Results:** 20.95% of the TCOC was attributed to novel therapy expenditures in the OCM for all cancer types (range 0.0% - 49.4%) vs 24.2% (range - 3.5% - 43.7%) of TCOC for the EOM cancer types (high-risk breast, colon, lung, high-risk prostate, myeloma, lymphoma and chronic leukemia) in the same time-frame. 75.5% of the novel therapy expenditures in the OCM came from the 7 EOM cancers. In the OCM only 31.8% of eligible performance periods received a NTA. Had the NTA been applied at the cancer type level, 49.5% of eligible episodes would have received an adjustment. The top cancers with the most novel therapy use as a percentage of TCOC were lung, myeloma and high-risk/ castrate-resistant prostate. The NTA for these practices adjusted the benchmark by an average of 0.56% (range -0.21% to 1.1%) over 10 periods. When applied at a cancer type level, NTA increased the adjustment by 3 times to an average of 1.73% (range -1.16% to 2.11%). **Conclusions:** The NTA applied at a cancer type level would have resulted in more instances where practices would have qualified for a benchmark adjustment. We believe that the EOM approach to NTA applied at a cancer type level is more favorable for participating practices and provides valuable financial protection when incorporating clinically appropriate novel therapy for cancer treatment. We commend CMMI for making improvements to the NTA risk adjustment methodology within the EOM. Research Sponsor: None.

6650

Poster Session

Impact on costs and outcomes of multi-gene panel testing for advanced solid malignancies: A cost consequence analysis using linked administrative data. *First Author: Alberto Hernando-Calvo, Princess Margaret Cancer Centre, Toronto, ON, Canada*

Background: To date, economic analyses of tissue-based next generation sequencing genomic profiling (NGS) have required models with multiple assumptions, with little real-world evidence on overall survival (OS), clinical trial enrollment or end-of-life (EOL) quality of care. The OCTANE clinical trial (NCT02906943) is a prospective study evaluating the role of NGS for advanced solid tumors in Ontario, Canada. We performed a cost consequence analysis of OCTANE. **Methods:** We undertook a longitudinal, propensity score-matched retrospective cohort study using linked administrative data. OCTANE patients (pts) at Princess Margaret Cancer Centre from August 2016 until March 2019 undergoing NGS panel testing (555 or 163-gene panels) were matched with contemporary controls from across Ontario not enrolled in OCTANE. Patients were matched according to 19 variables including age, sex, place of residence, tumor site, symptom burden, income quintile, comorbidities and prior lines of systemic therapy. Primary outcomes were mean per capita health care costs (2019 Canadian dollars [CAD]) from the public payer's perspective, OS, clinical trial enrollment and EOL quality metrics. Full 2-year follow-up data was available. Sensitivity analyses considered alternative matched cohort specifications. **Results:** There were 782 OCTANE pts with 782 matched controls. Variables were balanced after matching (standardized difference [std. diff.] <0.10). Most common tumor sites were: Ovary (30.4%), endometrium (15.0%) breast (12.3%) and colon (8.6%). OCTANE pts had higher mean healthcare costs than controls (\$79,702 vs. \$59,550), mainly due to costs of oncology visits (\$33,165 vs. \$26,197), outpatient clinic visits (\$8,696 vs. \$5,114) and emergency visits (\$1,723 vs. \$1,373) (all $p<0.05$). Publicly funded drug costs were less for OCTANE pts (\$20,015 vs. \$24,465). Overall, OCTANE enrollment was not associated with improved OS (restricted mean survival time (RMST) [standard error]: 1.50 (± 0.03) vs. 1.44 (± 0.03) years, log-rank $p=0.153$), but OCTANE was associated with longer OS in ovarian cancer (RMST: 1.69 (± 0.05) vs. 1.45 (± 0.06) years, $p=0.011$) and biliary tract tumors (RMST: 1.16 (± 0.13) vs. 0.80 (± 0.11) years, $p=0.02$). Importantly, OCTANE correlated with increased clinical trial enrollment (25.5% vs. 9.5%, $p<0.001$) and better EOL quality due to fewer deaths in hospital (10.2% vs 16.4%, $p=0.003$). Results were robust in sensitivity analysis. **Conclusions:** There was an increase in healthcare costs associated with NGS testing for advanced cancers. The impact on OS was not significant in the overall population, but varied across tumor types. OCTANE was associated with greater trial enrollment, lower publicly funded drug costs and fewer in hospital deaths suggesting important considerations in determining the value of NGS for advanced cancers. Clinical trial information: NCT02906943. Research Sponsor: Ontario Institute for Cancer Research through funding provided by the Government of Ontario (#IA-035 and P.HSR.158) and Canadian Network for Learning Healthcare Systems and Cost-Effective Omics Innovation (CLEO) via Genome Canada (G05CHS).

6652

Poster Session

Assessment of price variation in colorectal cancer screening procedures at US hospitals. *First Author: Ishan Paranjpe, Stanford, Stanford, CA*

Background: Following the 2021 Hospital Price Transparency Final Rule, US hospitals were mandated to publish their insurer-negotiated prices. We identified factors contributing to price variability of colorectal cancer (CRC) screening procedures across the US. **Methods:** We compared prices of colonoscopy, flexible sigmoidoscopy, CT colonography, fecal occult blood test, fecal immunochemical test, and Cologuard across U.S. hospitals using the Turquoise dataset (N = 6,378). Psychiatric, rehabilitation, and pediatric hospitals were excluded. Prices in the top and bottom 1% were also excluded to minimize the effect of outliers. Prices were adjusted by the Medicare Geographic Price Index to account for regional variability. We then compared prices across several subgroups, including National Cancer Institute (NCI) designated hospitals, teaching hospitals, and investor owned hospitals. Significance was assessed using the Kruskal-Wallis test. To quantify price variability across insurance plans within a hospital, we defined the within-center ratio as the 90th percentile rate at a hospital divided by the 10th percentile rate. To quantify variability across hospitals, the across-center ratio was defined as the 90th percentile median rate across all hospitals divided by the 10th percentile median rate. **Results:** 1,460 hospitals reported commercial prices for colonoscopy with a median commercial price of \$1,867 (IQR: \$1,208 - \$2,689). For colonoscopy, the within center ratio was 2.5 (IQR: 1.5 - 3.8) and the across-center ratio was 6.2. Prices for other procedures are provided in the table. Compared to non-investor owned hospitals, prices of colonoscopy (\$2,082 vs \$1,787, $P<0.001$) and flexible sigmoidoscopy (\$2,022 vs \$1,289, $P<0.001$) were significantly higher at investor owned hospitals. Furthermore, across investor classes, hospitals with >5% ownership from private equity firms had the highest median price for both colonoscopy (\$2,898), and flexible sigmoidoscopy (\$2,697). We did not find significant differences in price by NCI designation, academic teaching center affiliation, overall hospital mortality, overall hospital readmission rate, or urban/rural location. **Conclusions:** CRC screening procedure prices vary significantly both within and across hospitals. Private equity and other investor owned hospitals had significantly higher prices compared to non-investor owned hospitals. Research Sponsor: None.

Code type	Code description	Number of centers	Median commercial price, \$ (IQR)	Within center ratio (IQR)	Across center ratio
45378	Colonoscopy	1,460	1,867 (1208 - 2689)	2.5 (1.5 - 3.8)	6.2
45330	Flexible Sigmoidoscopy	1,332	1,473 (823 - 2251)	2.3 (1.4 - 3.9)	15.9
82270	Fecal occult blood test (guaiac)	1,300	16 (7 - 32)	3.2 (1.7 - 6.7)	13.1
82274	Fecal Immunochemical test	1,185	41 (25 - 65)	2.5 (1.6 - 4.3)	5.5
74263	CT colonography	644	1,060 (675 - 1621)	1.8 (1.1 - 3.3)	5.8
81528	Cologuard	199	560 (509 - 1074)	1.7 (1 - 2.6)	3.4

TPS6653

Poster Session

The FOR ME (Fostering Opportunities in Research through Messaging and Education) study: Developing a culturally sensitive narrative intervention to promote equity in clinical trials. *First Author: Neha Hippalgaonkar, University of Illinois Chicago, Chicago, IL*

Background: Black women are more likely to die from breast cancer than women of any other race/ethnicity. Contributing factors to this inequity include structural and socioeconomic determinants of health, differential access to novel therapies, tumor biology and comorbidities. In 2020, only 7.2% of enrollees in clinical trials that led to approval of 3 novel drugs for breast cancer were Black. Underrepresentation of patients from racial/ethnic minority groups in clinical trials is a contributing factor to health disparities. The first aim of this study is to conduct multiple qualitative methods with multi-level stakeholders to identify barriers, facilitators, and intervention priorities that would assist Black breast cancer patients to make informed decisions about participating in clinical trials. Secondly, we aim to create a culturally sensitive, narrative intervention designed to support decision making and motivate Black breast cancer patients to participate in clinical trials. Aim 3 will pilot a study to determine acceptability of the intervention among patients and assess whether it increases clinical trial participation in a safety net oncology practice.

Methods: Community-based participatory research approaches are guiding our research methodologies. First, we are conducting interviews and story circles with Black women with breast cancer, community partners and advocates, and oncologists and clinical trials office staff. These interviews will identify themes to inform intervention content. Next, interviews and focus groups will invite feedback on the educational/motivational content of the intervention and will be used to develop a culturally sensitive script and storyboards. A video production company will produce the narrative intervention. Finally, focus groups and interviews with participant cohorts will provide feedback on the completed intervention. Black women diagnosed with breast cancer will view the intervention in an oncology clinic. Using a pretest/posttest design, we will analyze the acceptability of the intervention and its effect on intention to participate in clinical trials. We will then conduct a quasi-experimental study in a safety net oncology practice to determine whether the rate of clinical trial participation among Black breast cancer patients increases following implementation of the intervention as a standard component of new patient education. Recruitment started in July 2022, and currently, 14 of 30 interviews with patients are completed. Aim 1 interviews with patients, oncologists, clinical trial staff, and advocates are expected to finish by April 2023, and results will be presented. Research Sponsor: American Cancer Society.

TPS6654

Poster Session

Understanding patient acceptance and compliance of a blood-based colorectal cancer screening test. *First Author: Karen Kim, The University of Chicago, Chicago, IL*

Background: The Covid-19 pandemic has caused a significant disruption in healthcare utilization. The halt and delay of CRC screening have led to a substantial decline in CRC screening rates. The backlog and the slow resuming of CRC screening will have significant consequences. Although COVID-19 created challenges in CRC screening, it also presents an opportunity for potential innovative approaches that may improve patient compliance and screening rates, such as a blood-based CRC screening test which can be done at the point of care without preparation. Adherence to CRC screening is poor among vulnerable populations even before COVID-19, and these populations disproportionately receive health care in safety-net settings, such as federally qualified health centers (FQHCs). Thus, FQHCs play a significant role in improving CRC-related outcomes and ensuring health equity. This study will examine patient compliance with CRC screening by offering another option, a blood-based screening test, after failing to complete a stool-based screening test or colonoscopy in six months at three FQHCs.

Methods: The study will use a stepped wedge cluster trial design and include an initial period of no exposure. Each FQHC will have a cluster of 10 to 17 primary care clinics. After the initial no-exposure period, two FQHCs will implement a blood-based CRC screening test at their primary care clinics. Another FQHC will follow nine months later. Each FQHC will contribute to exposed and unexposed observations and function as its own control. This study will collect quarterly data to capture the impact, feasibility, and acceptability over time. The primary endpoint will be assessed by calculating the number of participants who, otherwise, will not have participated in the CRC screening. In addition, the effectiveness of the implementation strategies will be assessed since transferring innovations into real-world settings is complex, and practical strategies are critical to accelerating future implementation and assisting decision-making. The study will recruit patients who fail to complete a CRC screening after six months and meet the inclusion criteria: between 45-75 years of age, average risk for CRC, capable of and willing to give informed consent, and willing to provide a blood sample. For eligible patients, a blood-based CRC screening test developed by a CLIA-certified laboratory and made commercially available (Guardant Health, CA) will be offered at no cost. An order will be obtained from the participant's primary care provider before the blood sample is collected. This study plans to enroll up to 2,400 patients over a 3-year period. Patient compliance is a significant barrier to improving CRC screening, and the key to increasing screening participation is patient acceptance of the screening method. A blood-based screening test may offer an alternative for patients who fail to comply with other CRC screening modalities. Clinical trial information: NCT0536713. Research Sponsor: Guardant Health.

7000

Oral Abstract Session

Safety and efficacy of obecabtagene autoleucel (obe-cel, AUTO1), a fast-off rate CD19 CAR, in relapsed/refractory adult B-cell acute lymphoblastic leukemia (r/r B-ALL): Top line results of the pivotal FELIX study. *First Author: Claire Roddie, University College London, London, United Kingdom*

Background: Obe-cel is an autologous CD19CAR with a fast off-rate CD19 binding domain designed to reduce CAR-T immunotoxicity and improve persistence. Its clinical activity has been tested in r/r paediatric and adult B-ALL trials (CARPALL, Ghorashian S et al., Nat Med 2019; ALLCAR19, Roddie C et al., JCO 2021) and more recently in adults with r/r B-cell malignancies (NCT02935257). Here, we present data from adult r/r B-ALL patients treated with obe-cel in the pivotal FELIX study (NCT04404660). **Methods:** FELIX is an open-label, multi-centre, global, single-arm Phase Ib/II study enrolling r/r B-ALL patients with morphological disease ($\geq 5\%$ BM blasts), measurable residual disease (MRD) ($\geq 0.1\%$ to $< 5\%$ BM blasts), or isolated extramedullary disease (Cohorts A, B and C). CAR-T products were generated using an automated closed process from fresh leukapheresate. Patients underwent bridging therapy as necessary and lymphodepletion with fludarabine (4x30mg/m²) and cyclophosphamide (2x500mg/m²). Patients received a target dose of 410E+6 CAR T cells as a split dose on Day 1 and Day 10. The dosing schedule is based on the % BM blasts performed locally prior to the pre-conditioning. Primary endpoint was overall remission rate (ORR) defined as proportion of patients achieving CR/CRi by central assessment. **Results:** As of 9th September 2022, a pre-specified interim analysis was conducted based on the first 50 patients infused in Cohort A who have been followed for 3 months or discontinued before month 3. The median age was 50 years (range 20-81), 22% had Ph+ B-ALL. The median number of prior lines of treatment was 2 (range 1-5), 42% underwent prior transplant. At screening, patients had a median of 55% BM blasts (range 6-96%) and 26% had EMD. The geometric mean of peak CAR expansion was 126147.6 copies/ug genomic DNA. Persistence was ongoing in majority of responders at last follow-up. Based on central assessment, the CR/CRi was 70% [95% CI: 55%, 82%] (p-value < 0.0001). As of 9th September 2022, a total of 92 patients received obe-cel and were evaluable for safety. 63% developed any grade CRS (3% Grade ≥ 3) at a median of 9 days post-infusion and a median duration of 5 days. Any grade ICANS was observed in 23% (8% Grade ≥ 3) at a median of 15 days post-infusion and of median duration 8 days. Other common Grade ≥ 3 adverse events regardless of causality were febrile neutropenia (25%) and anaemia (20%). **Conclusions:** The pre-specified interim analysis of the FELIX study demonstrated that obe-cel for adult r/r B-ALL is safe with low rates of Grade > 3 CRS and/or ICANS, even in patients with high burden disease. Obe-cel is effective with high CR/CRi rates and ongoing CAR T persistence in the majority of responders. The trial has completed dosing of all patients in Cohort A. Additional data and longer follow up will be reported at the conference. Clinical trial information: NCT04404660. Research Sponsor: Autolus Therapeutics plc.

7002

Oral Abstract Session

Enhanced anti-tumor activity of CD5 CAR T cells manufactured with tyrosine kinase inhibitors in patients with relapsed/refractory T-ALL. *First Author: LaQuisa C Hill, Center for Cell and Gene Therapy, Baylor College of Medicine, Houston Methodist Hospital, Houston, TX*

Background: An effective CAR T cell platform for the therapy of T-ALL requires minimizing CAR-driven fratricide of normal T cells. CD5 is a pan-T-cell surface protein present in ~85% of T-ALL. We developed a 2nd generation CD5 CAR that produces minimal T cell fratricide without additional engineering. Tonic CAR signaling accelerated terminal differentiation of CD5 CAR T cells potentially reducing their potency. In this study, we evaluated whether blocking tonic signaling with tyrosine kinase inhibitors (TKI) ibrutinib and dasatinib improves anti-leukemic activity of CD5 CAR T cells in patients with r/r T-ALL (NCT03081910). **Methods:** In the initial cohort of patients (CH1, n = 8), we generated CD5 CAR T cells from autologous PBMCs followed by expansion in the presence of IL-7 and IL-15 without TKI. In the subsequent cohort (CH2, n = 7) we manufactured cells from autologous (Arm A; n = 4) or HSC donor-derived (Arm B; n = 3) PBMCs in the presence of TKI. A total of 14 pts were treated (9 adult and 5 pediatric; age 11-70 years [median 36 yrs]); one pediatric pt was treated on both cohorts. **Results:** In CH1, all pts received autologous CAR T cells: 1 pt on DL1 (1x10⁷ CAR T cells/m²), 5 on DL2 (5x10⁷ CAR T cells/m²), and 2 on DL3 (1x10⁸ CAR T cells/m²). In CH2, we treated 4 pts on Arm A (one on DL2; 3 on DL3) and 3 pts on Arm B (all on DL1). The overall expansion of CAR T cells was comparable between cohorts, but we observed more sustained persistence of CD5 CAR T cells in pts on CH2. In CH1, one pt experienced a morphologic CR. Of 7 pts treated on CH2, we observed 4 MRD-negative CRs (2 on Arm A and 2 on Arm B). The CAR T cells produced minimal early toxicity with most grade ≥ 3 AEs related to cytopenias, febrile neutropenia and transient abnormal laboratory values. CRS occurred in 3 pts on CH1 and 4 on CH2 (Arm A: n = 1; Arm B: n = 3); all $\leq$ grade 2. No pts developed ICANS. Two pts in CH2 (one on Arm A and Arm B) developed EBV viremia and post-transplant/immunodeficient lymphoproliferative disease (LPD) at wks 5 and 7 post-infusion, respectively. Both were treated with intensive multiagent chemotherapy, and one pt also received EBV specific T cells (EBVSTs) with significant reduction in viral load. Unfortunately, both passed away from complications of treatment for PTLD (unrelated to EBVSTs) with no evidence of residual T-ALL. No other significant infections occurred. **Conclusions:** These results demonstrate CD5 CAR T cells can induce clinical responses in heavily treated patients with r/r T-ALL. Manufacturing CD5 CAR T cells with TKI improved their potency and anti-tumor activity but also possibly suppressed CD5+ virus-specific T-cells thus leading to 2 cases of EBV associated LPD. We have subsequently modified our clinical protocol to administer prophylactic rituximab to EBV seropositive pts and identify a partially matched EBVST line prior to CAR T cell infusion as a strategy to prevent additional cases of LPD in future subjects. Clinical trial information: NCT03081910. Research Sponsor: U.S. National Institutes of Health.

7001

Oral Abstract Session

Outcomes following brexucabtagene autoleucel administered as an FDA-approved therapy for adults with relapsed/refractory B-ALL. *First Author: Gregory Roloff, University of Chicago, Chicago, IL*

Background: In October 2021, brexucabtagene autoleucel (brexu-cel) became the first CAR-T cell therapy to receive FDA approval for adults (≥ 18 yrs) with relapsed/refractory (r/r) B-ALL. Approval was based on Phase II results of ZUMA-3, a single-arm, open-label, multicenter trial which reported on 55 treated patients with CR/CRi achieved in 71%; cytokine release syndrome (CRS) and neurologic toxicities occurred in 89% (grade 3-4, 24%) and 60% (grade 3-4, 25%), respectively. Here, we report outcomes of 76 adults with r/r B-ALL treated with post-approval brexu-cel at 13 U.S. centers. **Methods:** Retrospective data were collected across centers participating in a real-world outcomes collaborative of CAR-T in ALL (ROCCA). Descriptive statistics, Kaplan-Meier methodologies and cumulative incidence functions were used to summarize outcomes. **Results:** Among 76 patients infused, median age was 44 yrs (range, 18-81); 54% were male, 57% were non-Hispanic White (25% Hispanic), and 71% had Ph-neg disease. Median number of previous lines of therapy was 3.5 (range, 1-9) including blinatumomab in 53% and inotuzumab in 37%; 46% had relapsed post-transplant. Prior to apheresis, 69% of patients had active disease ($> 5\%$ marrow blasts or presence of extramedullary disease), including 8 patients with CNS3 disease, 19% had detectable measurable residual disease (MRD) only, and 12% were MRD-neg. Median time from apheresis to infusion was 31 days. Lymphodepletion was predominantly with flu/cy (88%); 5 received cy/cladribine, and one patient each received single agent cy, single agent cladribine, and single agent bendamustine. Among 65 patients at least 28 days post-CAR-T with response assessed, 90.8% achieved CR/CRi, of whom 83% were MRD-neg, including CNS disease clearance in 7/8 CNS3 patients. CRS and ICANS (ASTCT criteria) occurred in 81.6% (grade 3-4, 6.6%) and 59% (grade 3-4, 38.6%), respectively. Median follow-up for survivors was 196.5 days (IQR 135.5-284.5). At last follow-up, 21 patients progressed/relapsed and 13 had died (7 of B-ALL; 6 of neurotoxicity/infection). Cumulative incidence of relapse and death in remission at 180 days were 31.5% (95% CI: 19.7%-44.1%) and 8.9% (95% CI: 3.5%-17.5%), respectively, while six-month PFS and OS were 58.8% (95% CI: 44.6%-70.5%) and 86.7% (95% CI: 75.8%-92.9%), respectively. Eleven patients underwent allogeneic transplant in CR/CRi after brexu-cel; all of whom remain in remission at last follow-up. **Conclusions:** These data are the first to demonstrate post-approval efficacy and toxicity rates of brexu-cel in adults with r/r B-ALL. Unlike the ZUMA-3 population, 31% of patients infused in this real-world cohort lacked morphologically detectable disease and 8 had CNS3 prior to apheresis. Our data confirm high response rates associated with brexu-cel in adult ALL, but also highlight the need for interventions to reduce associated toxicities. Research Sponsor: None.

7003

Oral Abstract Session

Efficacy and safety results from the COMMANDS trial: A phase 3 study evaluating luspatercept vs epoetin alfa in erythropoiesis-stimulating agent (ESA)-naïve transfusion-dependent (TD) patients (pts) with lower-risk myelodysplastic syndromes (LR-MDS). *First Author: Guillermo Garcia-Manero, Department of Leukemia, University of Texas M.D. Anderson Cancer Center, Houston, TX*

Background: Most pts with LR-MDS have limited responses to ESAs, thus there is an unmet need to treat anemia and reduce TD. Here we report interim results from the open-label, randomized phase 3 COMMANDS trial (NCT03682536) comparing the efficacy and safety of luspatercept vs epoetin alfa in ESA-naïve pts with LR-MDS. **Methods:** Eligible pts were ≥ 18 years old with IPSS-R-defined LR-MDS with or without RS, $< 5\%$ bone marrow blasts, sEPO levels < 500 U/L, required RBC transfusions (defined as 2-6 RBC units/8 weeks [wk]) for ≥ 8 wk immediately prior to randomization, and were ESA naïve. Pts were randomized 1:1 to receive subcutaneous luspatercept (starting dose 1.0 mg/kg, titration up to 1.75 mg/kg) once every 3 wk or epoetin alfa (starting dose 450 IU/kg, titration up to 1050 IU/kg) weekly for ≥ 24 wk. Primary endpoint was achievement of RBC transfusion independence (TI) ≥ 12 wk within the first 24 wk, with a mean hemoglobin increase ≥ 1.5 g/dL. Secondary endpoints included achievement of hematologic improvement-erythroid (HI-E) response ≥ 8 wk per IWG 2006 criteria, RBC-TI 24 wk and ≥ 12 wk, and safety. **Results:** As of Aug 31, 2022, 178 pts received luspatercept and 176 epoetin alfa, with median treatment durations of 41.6 and 27.0 wk, respectively. Baseline pt characteristics were balanced across treatment arms. Of 301 pts included in the efficacy analysis, 86 (58.5%) pts receiving luspatercept vs 48 (31.2%) epoetin alfa achieved the primary endpoint of RBC-TI ≥ 12 wk with concurrent mean Hb increase ≥ 1.5 g/dL within the first 24 wk ($P < 0.0001$). HI-E ≥ 8 wk was achieved by 109 (74.1%) luspatercept and 79 (51.3%) epoetin alfa pts ($P < 0.0001$). Within the first 24 wk of treatment, RBC-TI 24 wk and ≥ 12 wk was achieved by 70 (47.6%) and 98 (66.7%) luspatercept pts, respectively, vs 45 (29.2%) and 71 (46.1%) epoetin alfa pts ($P = 0.0006$ and 0.0002). Treatment-emergent adverse events (TEAEs; any grade) were reported by 164 (92.1%) luspatercept and 150 (85.2%) epoetin alfa pts; 8 (4.5%) and 4 (2.3%) pts discontinued due to TEAEs. Treatment-related AEs were reported by 54 (30.3%) luspatercept and 31 (17.6%) epoetin alfa pts. AML progression was reported in 4 (2.2%) luspatercept and 5 (2.8%) epoetin alfa pts. Overall rates of death were comparable between arms during treatment and post-treatment (32 [18.0%] luspatercept, 32 [18.2%] epoetin alfa pts). **Conclusions:** Compared with epoetin alfa, luspatercept led to clinically meaningful and statistically significant improvements in RBC-TI and erythroid response, as well as duration of response. Luspatercept safety results were consistent with previous findings. These data show, for the first time, superiority of an innovative therapy over ESAs in ESA-naïve pts with TD LR-MDS. Luspatercept could represent a new standard of care for pts with TD LR-MDS. Clinical trial information: NCT03682536. Research Sponsor: Bristol Myers Squibb.

7004 Oral Abstract Session

IMerge: Results from a phase 3, randomized, double-blind, placebo-controlled study of imetelstat in patients (pts) with heavily transfusion dependent (TD) non-del(5q) lower-risk myelodysplastic syndromes (LR-MDS) relapsed/refractory (R/R) to erythropoiesis stimulating agents (ESA). *First Author: Amer Methqal Zeidan, Department of Internal Medicine, Yale School of Medicine and Yale Cancer Center, Yale University, New Haven, CT*

Background: Unmet needs remain for red blood cell (RBC) TD pts with LR-MDS R/R or ineligible for ESA. In P2 of the IMerge study (NCT02598661), heavily RBC TD ESA R/R non-del(5q) LR-MDS pts naive to lenalidomide and hypomethylating agents (len/HMA) treated with imetelstat, a telomerase inhibitor, achieved durable and continuous transfusion independence (TI). We report primary data from the P3 study of imetelstat in such pts. **Methods:** Heavily RBC TD ESA R/R non-del(5q) LR-MDS pts naive to len/HMA were randomized 2:1 to receive imetelstat 7.5 mg/kg or placebo every 4 wks. Primary endpoint was 8-wk TI; subgroup analyses included IPSS risk, prior transfusion burden and ring sideroblast (RS) status. Secondary endpoints included 24-wk TI, TI duration and hematologic improvement-erythroid (HI-E). Variant allele frequency (VAF) changes were explored. **Results:** As of Oct 2022, 178 pts were randomized. The primary endpoint was met (Table); 39.8% vs 15.0% of pts receiving imetelstat vs placebo, respectively, achieved 8-wk TI. The rate of 8-wk TI was significantly higher with imetelstat vs placebo across subgroups, including RS negative pts. Median TI duration was significantly longer for imetelstat vs placebo, 51.6 vs 13.3 wks, $P < 0.001$. Pts receiving imetelstat had significantly higher mean hemoglobin ($P < 0.001$) and fewer transfusions ($P = 0.042$) over time than those on placebo. In 3 of 4 genes frequently mutated in MDS, VAF reduction was significantly greater in pts treated with imetelstat than placebo: SF3B1 ($P < 0.001$), TET2 ($P = 0.032$), DNMT3A ($P = 0.019$) and ASXL1 ($P = NS$). SF3B1 VAF reduction correlated with longer TI duration, $P < 0.001$. No new safety signals were identified. The most common Grade 3/4 AEs were thrombocytopenia and neutropenia, with similar rates of Grade ≥ 3 bleeding and infections on imetelstat and placebo. In pts treated with imetelstat, cytopenias were manageable, of short duration, and $>80\%$ were reversible to Grade ≤ 2 within 4 wks. **Conclusions:** For this LR-MDS pt population, imetelstat demonstrated statistically significant and clinically meaningful efficacy with high 8- and 24-wk TI rates, prolonged TI duration and increased hemoglobin. VAF reduction and its correlation to clinical endpoints support imetelstat's disease-modifying potential. Safety results were consistent with prior reported experience. Clinical trial information: NCT02598661. Research Sponsor: Geron Corporation.

IMerge P3 clinical endpoints.			
Measure, n (%)	Imetelstat N=118	Placebo N=60	P ^a
8-wk TI	47 (39.8)	9 (15.0)	<0.001
TI duration, median wks (95% CI) ^b	51.6 (26.9-83.9)	13.3 (8.0-24.9)	<0.001 ^d
24-wk TI	33 (28.0)	2 (3.3)	<0.001
HI-E ^c	50 (42.4)	8 (13.3)	<0.001

^aCochran Mantel Haenszel test stratified by prior transfusion burden and IPSS; ^b8-wk TI, Kaplan-Meier estimate; ^c2018 IWG; ^dStratified log-rank test.

7006 Oral Abstract Session

Chemotherapy-free treatment with inotuzumab ozogamicin and blinatumomab for older adults with newly diagnosed, Ph-negative, CD22-positive, B-cell acute lymphoblastic leukemia: Alliance A041703. *First Author: Matthew Joseph Wieduwilt, Atrium Health Wake Forest Baptist Comprehensive Cancer Center, Winston-Salem, NC*

Background: Older adult patients (pts) with Philadelphia-chromosome-negative (Ph-) acute lymphoblastic leukemia (ALL) have poor survival with chemotherapy. The α -CD22 Ab-drug conjugate inotuzumab ozogamicin (InO) and α -CD19/CD3 T-cell engager blinatumomab (blina) were each superior to chemotherapy in Phase III studies in relapsed/refractory B-ALL. Because InO induces high CR rates and blina can induce durable remissions in low burden disease, we conducted a Phase II trial of induction InO then blina for older adults with newly-diagnosed (ND), Ph-, B-ALL. **Methods:** Eligible were pts ≥ 60 years old with ND, Ph-, CD22+ ($\geq 20\%$ of blasts) B-ALL without plan for allogeneic HCT (alloHCT). Pts with CNS leukemia or liver disease were excluded. Induction IA was InO 0.8 mg/m² day (d) 1, 0.5 mg/m² d8, d15 IV on a 21d cycle. Pts with adequate cytoproduction (marrow blasts by $\geq 50\%$ or cellularity $\leq 20\%$) after IA went to IB if in CR/CRi (InO 0.5 mg/m² d1, d8, d15 IV; 28d cycle) or IC if no CR/CRi (InO 0.8 mg/m² d1, d8, d15 IV; 28d cycle). Those without cytoproduction to IA started course II blina. Pts without events in IA/B/C received course II blina CIV (9 mcg/d x 7d then 28 mcg/d x 21d; 14d break; 28 mcg/d x 28d). Pts with CR/CRi to InO received 2 more 28d cycles of blina, others received 3 more. CNS prophylaxis was methotrexate 15 mg intrathecal x 8. The primary endpoint was 1-yr event-free survival (EFS) with a lower limit of a 90% CI for 1-yr EFS $>10\%$ defined as success. EFS was the time from therapy start to failure to achieve CR/CRh/CRi by end Course II, progression, relapse, or death, whichever occurred first. **Results:** Thirty-three eligible pts were treated (1 ineligible, 2nd malignancy). The median age was 71 years (range 60-84). Median WBC count was 3,200/mcl (range 6-38,000). Median CD22 expression was 92% (range 21-100%). Eight pts had therapy-related ALL. The cumulative CR rates through Course IA/B/C and Course II were 85% and 97%, respectively (Table). With median follow up of 22 mo, the 1-yr EFS was 75% (95% CI 61-92%). The 2-sided 90% CI was 63-89% for 1-yr EFS with lower bound above 10% indicating regimen success. Twelve pts had events: 9 relapses, 2 deaths in remission (1 after alloHCT), and 1 death without remission from respiratory failure with sinusoidal occlusion syndrome of liver. The 1-yr OS was 84% (95% CI 72-98%). Nine pts have died, 6 after relapse. **Conclusions:** InO induction then blina consolidation is highly active for ND, Ph-, CD22+ B-ALL. The regimen is an option for older adults and a comparator regimen for future studies. Support: U10CA180821, U10CA180882, U10CA180820 <https://acknowledgments.alliancefound.org>. Clinical trial information: NCT03739814. Research Sponsor: U.S. National Institutes of Health; Pfizer/Amgen (drugs, correlatives).

N=33	I A/B/C	II
Composite CR*	28 (85%)	32 (97%)
CR	15 (45%)	19 (58%)
CRh	11 (33%)	12 (36%)
CRi	2 (6%)	1 (3%)
Refractory	3 (9%) [†]	-
1-yr EFS	75% (95% CI 61-92%)	
1-yr OS	84% (95% CI 72-92%)	

*CR+CRh+CRi
[†]1 completed IA only

7005 Oral Abstract Session

A first-in-human study of CD123 NK cell engager SAR443579 in relapsed or refractory acute myeloid leukemia, B-cell acute lymphoblastic leukemia, or high-risk myelodysplasia. *First Author: Anthony Selwyn Stein, City of Hope National Medical Center, Duarte, CA*

Background: SAR'579 is a trifunctional natural killer (NK) cell engager targeting CD123 antigen and co-engaging Nkp46 and CD16a on NK-cells. SAR'579 facilitates the formation of a cytolytic synapse between NK-cells and CD123-positive tumor cells leading to NK-cell activation and tumor cell killing. We herein report preliminary safety and efficacy data of SAR'579 from a phase 1/2 trial in patients with relapsed or refractory acute myeloid leukemia (R/R AML), B-cell acute lymphoblastic leukemia or high risk-myelodysplasia (NCT05086315). **Methods:** SAR'579 was administered intravenously twice weekly or once weekly (QW), depending on the dose level (DL) for the first 2 weeks of cycle 1 and then weekly for rest of induction cycles. A patient receives approximately three 28-day induction cycles with patients achieving a complete remission (CR) or incomplete hematologic recovery (CRi) per International Working Group criteria transitioning to a 56-day maintenance period with dosing approximately every 29 days. The primary objectives were to establish safety/tolerability and anti-leukemic activity (composite complete remission [CRc] = CR+CRi). **Results:** With a cutoff date of January 27, 2023, total 23 patients with R/R AML across 6 DLs (3 patients DL1 and 4 each in DL2 - DL6) were included in the safety population. The median age was 70 years (range: 21 - 80) with 9 patients (39.1%) reporting prior hematopoietic stem cell transplantation (HSCT) and 16 (69.6%) had prior exposure to venetoclax. Patients received a median of 2 cycles (range: 1 - 7) for median duration of 7 weeks (range: 1 - 25) and escalating doses of SAR'579 between 10 - 3000 μ g/kg/dose in cycle 1 and 100 - 3000 μ g/kg QW for the rest of induction cycles. No dose limiting toxicities (DLTs) were observed among the 21 DLT-evaluable patients, until highest dose of 3000 μ g/kg QW. The most common treatment emergent adverse events (TEAEs) included infusion-related reactions (n = 10 [43.5%]) and nausea (n = 7 [30.4%]). TEAEs were reported in 22 patients (95.7%) with grade 3/4 adverse events (AEs) in 18 (78.3%) and treatment-related AEs in 16 patients (69.6%), respectively. There were 2 cases of cytokine release syndrome (n = 1 grade 1 and n = 1 grade 2) and no case of immune effector cell-associated neurotoxicity syndrome. No patient reported TEAE leading to permanent discontinuation of SAR'579. The CRc rate was 13.0% (3/23 patients evaluable for response). In DLs with a highest dose of 1000 μ g/kg QW, 3/8 (37.5%) patients achieved a CR (2 CR/1 CRi). The median time to first CR/CRi was 16.1 weeks 95% confidence interval (8.1 - Not Estimable [NE]), and the median duration of CR/CRi is NE due to limited follow-up time. **Conclusions:** SAR'579 was well tolerated up to doses of 3000 μ g/kg QW with observed clinical benefit in patients with R/R AML. The trial continues to accrue patients. Clinical trial information: NCT05086315. Research Sponsor: Sanofi.

7007 Oral Abstract Session

A phase I trial of dose-adjusted EPOCH plus inotuzumab ozogamicin (InO) in adults with relapsed/refractory (R/R) B lymphoblastic leukemia/lymphoma (B-ALL). *First Author: Noam Edward Kopmar, University of Washington/Fred Hutchinson Cancer Center, Seattle, WA*

Background: Outcomes for adults with R/R B-ALL remain poor, with existing options limited by efficacy and safety. InO has been combined with low-intensity chemotherapy, the benefit of which is unclear. DA-EPOCH is safe and active as frontline therapy in adults with ALL, so we combined this with InO in adults with R/R B-ALL (NCT03991884). Aims: The primary objective was to estimate the maximum tolerated dose (MTD) of InO when added to DA-EPOCH. **Methods:** Eligible patients (pts) were adults with R/R CD22+ B-ALL with $\geq 5\%$ blood or marrow (BM) blasts or ≥ 1 site of measurable extramedullary disease (EMD); other eligibility criteria included ECOG ≤ 2 and no history of sinusoidal obstructive syndrome (SOS) or chronic liver disease. DA-EPOCH was given on days (d) 1-5 with GCSF. After cycle 1, dose adjustments to EPOCH were made based on hematologic nadirs from the prior cycle. Three dose levels (DL) of InO were studied, with InO given on d 8 + 15 as follows (respectively): 0.3 + 0.3 mg/m² (DL1); 0.6 + 0.3 mg/m² (DL2); and 0.6 + 0.6 mg/m² (DL3). Up to 4 28-d cycles were given. The MTD was the highest DL of InO that yielded $\leq 33\%$ rate of dose limiting toxicity (DLT), defined as grade 4+ non-heme treatment-related adverse events (TRAEs), any SOS regardless of timing, unable to complete 1 cycle due to TRAE, and treatment delays > 3 weeks. After the first 5 pts received DL1, a Bayesian Optimal Interval Design was used. Target accrual was 24 pts. BM and EMD response was assessed by NCCN criteria, with measurable residual disease (MRD) evaluated by multiparameter flow cytometry (MFC) and clonoSEQ. **Results:** 24 pts were screened: all were enrolled and evaluable for DLT and response. Median age was 46 (range: 28-76) years; median prior lines of therapy was 3 (range: 1-16); 13 pts (54%) had previously received allograft (HCT). 5 pts were enrolled at DL1, 8 pts at DL2, and 11 pts at DL3. There were 4 total DLTs: 1 at DL1 (grade 4 sepsis) and 3 at DL3 (grade 4 hyponatremia; delay for pancytopenia; grade 5 SOS after post-study HCT). DL3 was thus determined to be the MTD. No deaths occurred on study. Three pts (12%) had Grade 3 AST/ALT elevation; the SOS rate was 4%. Other grade 3+ non-heme TRAEs seen in >1 pt included infections (6 pts; 9 events), neutropenic fever (7; 8), and oral mucositis (3; 4). In the pts with $\geq 5\%$ blood/BM blasts (n=20), the CR/CRi rate was 85%. By MFC, 70% achieved MRD- (45% after 1 cycle); using clonoSEQ, 33% were MRD-. Of the 6 pts with EMD, 83% responded (4 CR; 1 PR). The per-protocol and intent-to-treat (ITT) overall response rate was 83%. With median follow-up of 12 months (m), the median overall and relapse-free survival were 19 m and 12 m. Nine (38%) pts received post-study HCT. **Conclusions:** The addition of InO to DA-EPOCH in adults with heavily-pre-treated R/R B-ALL is safe, with ITT response rates among the highest reported to date. Many pts proceeded to HCT. Further investigation of this combination is warranted. Clinical trial information: NCT03991884. Research Sponsor: Pfizer; U.S. National Institutes of Health.

7008

Oral Abstract Session

Specialty cancer care and survival in AYA ALL: A U.S. multi-state analysis.

First Author: Lori S. Muffy, Division of Blood and Marrow Transplantation and Cellular Therapy, Stanford University School of Medicine, Stanford, CA

Background: Unlike children with acute lymphoblastic leukemia (ALL) who receive cancer care almost exclusively from pediatric oncologists at specialized cancer centers (SCC; defined here as National Cancer Institute and/or Children's Oncology Group designated cancer centers), adolescents and young adults (AYAs; 15-39 years) in the United States receive care in a variety of settings. Using state-wide population-based data, we sought to describe the health care delivery settings in which AYAs with ALL receive treatment and determine associations between front-line treatment at an SCC and leukemia-specific and overall survival (LSS/OS). **Methods:** We used data from the 2004-2018 California (CA), New York (NY), and Texas (TX) state cancer registries to identify front-line treatment setting of AYAs newly diagnosed with ALL. Multivariable logistic regression models evaluated characteristics associated with receiving treatment at an SCC. Cox proportional hazards regression models evaluated the associations with LSS/OS. All models were adjusted for gender, age, sex, race/ethnicity, socioeconomic status, insurance, and diagnosis year. **Results:** The cohort was comprised of 2283 (CA), 795 (NY), and 955 (TX) AYAs with ALL. Across all states, approximately 70% were ≤ 18 years and 65% were male. Race/ethnicity varied by state: a majority in CA (63%) and TX (64%) were Hispanic, while most in NY were non-Hispanic White (NHW) (50%). Health insurance coverage also varied: most in CA were publicly insured (48%), while most in NY were privately insured (54%); TX had the highest rate of uninsured (18%). Treatment at an SCC occurred in 48.2% (CA), 44.4% (NY), and 19.5% (TX) of AYAs, increasing in CA and NY over time, but remaining unchanged in TX. Among all states, older age and uninsured status were significantly associated with lower odds of treatment at an SCC. In both CA (OR 0.58, 95% CI 0.45-0.74) and TX (OR 0.55, 95% CI 0.35-0.86), Hispanic patients had significantly lower odds of treatment at an SCC than NHW. In NY (OR 0.45, 95% CI 0.31-0.67) and TX (OR 0.49, 95% CI 0.3-0.88), publicly insured AYAs had significantly lower odds of receiving treatment at an SCC than those with private insurance. Front-line treatment at an SCC was significantly associated with both superior LSS (HR 0.73, 95% CI 0.63-0.85) and OS (HR 0.73, 95% CI 0.63-0.85) in CA and superior LSS (HR 0.70, 95% CI 0.51-0.94) and OS (HR 0.61, 95% CI 0.45-0.83) in TX; a non-significant association was seen in NY (LSS: HR 0.86, 95% CI 0.65-1.12; OS: HR 0.83, 95% CI .64-1.08). **Conclusions:** Only 20-50% of newly diagnosed AYA ALL patients receive front-line treatment at SCCs, with age, race/ethnicity, and insurance type independently influencing AYA ALL care setting. We show that the treatment of ALL at an SCC is associated with superior survival, highlighting the importance of statewide and national policy efforts to improve access and reduce inequities in AYA ALL. Research Sponsor: Leukemia and Lymphoma Society.

7010

Poster Discussion Session

Identification and management of clonal hematopoiesis of indeterminate potential (CHIP) in cancer survivors: The Cleveland Clinic experience. *First Author: Teodora Kuzmanovic, Cleveland Clinic, Cleveland, OH*

Background: Clonal hematopoiesis (CH) of indeterminate potential (CHIP) is found in healthy populations as well as cancer patients (pts) and is associated with (w/) cardiovascular disease (CVD), risk of hematologic neoplasms (HN), and all-cause mortality. Germline variants (var) predispose to CHIP. However, described var are nonspecific to solid tumor pts. Identifying CHIP risk factors and mitigation strategies is paramount for improving outcomes. **Methods:** Pts in breast (BC) and head & neck cancer (HNC) survivorship (2020-2023) following curative treatment (tx) were eligible for our 10 year (yr) prospective study of annual next generation sequencing (NGS) and complete blood count (CBC) to identify CHIP. Mutations (mt) were classified as clinically significant (CS) or var of unknown significance (VUS), and as CH (med. VAF 4.7%) or potentially germline (PG; med. VAF 50%). Pts w/ CHIP were managed in both CHIP Clinic (CC) and Preventive Cardiology (PC) for monitoring and CVD reduction. Fisher's exact and ANOVA tests were used for analyses. **Results:** Of 168 pts enrolled (117 BC, 51 HNC), 158 had NGS: 73 yr 1, 85 through yr 2 or 3; 22 pts received chemotherapy (CT), 49 radiation therapy (RT), 72 CT & RT (CRT). Sixty-eight pts (43%) had a mt; 21 (13%) had CHIP (6 w/ PG VUS). CHIP was found to be associated w/ older age (69 vs. 58, $p=0.0002$). The most common CHIP mt were *DNMT3A* ($n=11$), *PPM1D* (6), *TET2* (6), *JAK2* and *TP53* (2). Two pts without yr 1 mt developed CHIP in yr 2. For *PPM1D*, 2 PG VUS were point mt from DNA transitions while 6 CHIP were truncating from transversions and deletions. All pts w/ *PPM1D* had RT (7/8 CRT), suggesting a molecular signature which varies from transition-driven aging. Six pts had thrombocytopenia (TP), 3 w/ *PPM1D* CHIP. TP was more common in CHIP (OR 11, $p=0.0356$) and *PPM1D* (OR 29, $p=0.0016$). In this cohort, anemia was not seen in pts w/ CHIP ($p=0.048$). Normal CBC was 6x less common in pts w/ CRT ($p=2.3 \times 10^{-7}$). Seven CHIP pts were seen by PC; 4 had yr 2 NGS following PC visit. All pts had addition of new/dose escalation of current CVD medication. Two CHIP pts had stable NGS; 2 CHIP & PG VUS pts had clonal changes including mt disappearance and acquisition. Of note, the PG VUS's were assessed for institutional incidence in 3,918 HN pts w/ NGS data and in Mastermind (MM) for frequency of occurrence in published literature. Sixteen PG VUS (40%) occurred at our institution (13 found in MM, 7 classified as rare (avg gnomAD MAF 6×10^{-4}) and associated w/ HN, notably *TET2* ($n=3$). **Conclusions:** This ongoing prospective study is one of the largest to report characteristics and outcomes of CHIP pts in CC/PC and is expected to accrue more in expansion. We anticipate highlighting risk factors for CHIP progression and report novel PG VUS, which may portend health risks based on their prevalence in HN. Furthermore, it appears that a strategy for CVD prevention may promote clonal stability in survivorship pts. Research Sponsor: Velosano.

7009

Poster Discussion Session

Adherence and satisfaction with remote cognitive training in blood or marrow transplant (BMT) survivors: The cognitive training and attitudes towards genetics (cTAG) study. *First Author: Noha Sharafeldin, Department of Hematology & Oncology, School of Medicine, University of Alabama at Birmingham, Birmingham, AL*

Background: Cognitive impairment is prevalent in hematologic cancer survivors treated with BMT. There is a need for remote, accessible, and engaging interventions in order to mitigate adverse cognitive outcomes following treatment. We report on feasibility, satisfaction and preliminary efficacy of a remote cognitive training intervention in BMT survivors. **Methods:** Participants enrolled in the cTAG study were randomized to either using the online brain games Lumosity program daily for 12 weeks, or the waitlist arm. Cognitive function was assessed using a comprehensive battery covering executive function, processing speed, attention, memory and learning domains, and PROMIS Short Form4a for cognitive complaints. Participants' satisfaction was measured using an exit survey. Standardized T-scores (mean: 50; standard deviation: 10), were used for domain-specific outcomes. An intention-to-treat analysis was used to model the change in cognition at 12 weeks compared to baseline, between study arms, controlling for baseline cognitive reserve, age, sex and race/ethnicity to enhance estimate precision. **Results:** Feasibility: 150 eligible patients were approached, 88 (58.7%) consented and 71 (80.7%) were randomized. Fifty-five patients completed the study (28 on active and 27 on waitlist arm). Post-randomization attrition rate was 19.7%. Median age at time of test was 58y (range: 27-74); 60% males, 83.6% Non-Hispanic White and 16.4% non-Hispanic Black, and 49% with low cognitive reserve. There were no significant differences between study arms. Adherence on active arm: Median of 87.5% for 4.9 days/week and 10/12 weeks. Preliminary Efficacy: Compared to the waitlist arm, scores improved for the active arm in attention (2.14 points, SE=1.01, p -value=0.039) and memory domains (5.63, SE=2.40, p -value=0.02). There was no significant change on cognitive complaints between the two arms. Satisfaction: Overall 78.2% of patients had no prior experience with cognitive training, 58.7% felt it helped their recovery, 82.6% found time commitment reasonable, 87% found it easy to follow, fun, engaging and appropriately challenging. The intervention had a 91.3% satisfaction rate; 73.9% indicating they would continue training and 87% would recommend it to others. Participants' perceived benefit from training was highest for attention (89.1%), memory (73.9%), and visual tasks (69.6%). Only 11% of participants perceived benefits for real word tasks. **Conclusions:** The intervention was feasible, favorably rated, and associated with both perceived and objective improvements in attention and memory domains. Remote cognitive training carries several advantages for BMT patients including early and convenient at home administration supporting its clinical utility and potential long-term adoption following treatment. Clinical trial information: NCT03094026. Research Sponsor: Leukemia and Lymphoma Society; Be The Match Foundation.

7011

Poster Discussion Session

Association of Agent Orange and myeloproliferative neoplasms, thrombosis, and bleeding among veterans. *First Author: Andrew Chua Tiu, Georgetown Lombardi Comprehensive Cancer Center, Washington, DC*

Background: The Myeloproliferative Neoplasms (MPNs) which include Polycythemia Vera (PV), Essential Thrombocythemia (ET), and Primary Myelofibrosis (MF) are acquired stem cell disorders with constitutively activated pathways from shared mutations leading to thrombotic and bleeding complications. Agent Orange (AO) is a chemical herbicide that was utilized during the Vietnam War and was associated with sarcomas and B-cell lymphomas. There is inadequate evidence of the association between AO exposure and development of MPNs, increased risk of bleeding, arterial thrombosis (AT), and venous thrombosis (VT). **Methods:** Utilizing the Veterans Affairs Informatics and Computing Infrastructure (VINCI) database, we performed a case control study from January 1, 2006 - January 26, 2023. We utilized ICD-9 and I0 codes to identify MPN patients, any AT, VT, and bleeding events. Age-matched controls (1:1) were selected from VINCI database. Qualitative data was compared by chi-square test. **Results:** We included all 95,768 MPN patients (0.7% MPN crude prevalence rate), 43,263 ET, 48,854 PV, and 3,651 MF patients. Among all MPNs, 6.4% were female, 93.6% were male, 76% were White, 13.8% Black, 0.8% American Indian, 0.9% Pacific Islander, and 8.5% unknown race. 86.8% of patients with MPN were aged 60 years or older. When comparing MPNs vs. controls, there was increased AT (29.5% vs. 24.5%, $p < 0.0001$), VT (6.7% vs. 3.8%, $p < 0.0001$), and both AT & VT (8.1% vs. 4.2%, $p < 0.0001$). Among female MPN patients, there were 16.2% AT, 6.1% VT, 45.5% bleeding events vs. 30.4% AT, 6.7% VT, and 39% bleeding events among male MPN patients, respectively, $p < 0.0001$. Among MPN patients who are greater than 60 years old, 95.4% had AT, 88% had VT, 94.4% had both AT & VT, and 89.4% had bleeding events. Bleeding events were higher in ET (44%), PMF (41.5%), PV (35%) vs. the control group (24.6%), $p < 0.0001$, and gastrointestinal bleeding was the most common site for both controls and MPNs followed by genitourinary or pulmonary. Among the different races, there is higher AT (range 22.6-31.5%) compared to VT (range 5.3-7.8%). There is a significant association between AO exposure and development of MPNs (odds ratio 1.61, 95% CI 1.57 to 1.65, $p < 0.0001$). There is a higher AT (36%) among MPNs with AO exposure compared to 28.2% in MPNs without AO exposure, $p < 0.0001$. There is a higher AT (28.7%) among controls with AO exposure compared to 24% in controls without AO exposure, $p < 0.0001$. There was 41.2% bleeding event with MPN with AO exposure compared to 39% in MPN without AO exposure, $p < 0.0001$. **Conclusions:** This is the largest database evaluating MPNs, thrombosis, and bleeding in veterans exposed to AO. There is an association of increased risk of development of MPNs, increased AT, and increased bleeding with AO exposure. Further studies including JAK2 mutation, CHIPs, and cardiovascular risk factors will be needed to evaluate contribution to thrombosis and bleeding risk. Research Sponsor: None.

7012 Poster Discussion Session

Updated efficacy and safety data from the AGILE study in patients with newly diagnosed acute myeloid leukemia treated with ivosidenib + azacitidine compared to placebo + azacitidine. *First Author: Stéphane De Botton, Institut Gustave Roussy, Paris, France*

Background: Ivosidenib (IVO) is a potent oral targeted inhibitor of mutant *IDH1*. In the AGILE study in patients (pts) with newly diagnosed *IDH1*-mutated acute myeloid leukemia, IVO plus azacitidine (AZA) significantly improved event-free survival (EFS), overall survival (OS), complete remission (CR), and CR or CR with partial hematologic recovery (CR+CRh) rates v placebo (PBO) plus AZA. As of March 2021, median OS (mOS) was 24 months (IVO+AZA) v 7.9 months (PBO+AZA; HR: 0.44; p=0.0005). Long-term follow-up data are presented. **Methods:** In the double-blind AGILE study, pts were randomized 1:1 to IVO 500 mg QD + AZA 75 mg/m² SC or IV for 7 days in 28-day cycles, or PBO+AZA. Long-term follow-up data (June 2022) for OS, blood count recovery, transfusion independence and safety are described here. **Results:** 148 pts were randomized: 73 to IVO+AZA; 75 to PBO+AZA. Median treatment duration was 10.8 months (IVO+AZA) v 3.2 months (PBO+AZA). Five PBO+AZA pts crossed over to IVO+AZA after March 2021 (Table), and no adjustment was made for crossover in the updated OS analysis. At a median follow-up of 28.6 months, mOS was 29.3 months (95% CI 13.2, not reached) for IVO+AZA v 7.9 months (95% CI 4.1, 11.3) for PBO+AZA (HR 0.42 [0.27, 0.65]; p<0.0001). OS rates were 62.9% and 38.3% at 12 months and 53.1% and 17.4% at 24 months, with IVO+AZA and PBO+AZA, respectively. In the IVO+AZA arm, hemoglobin levels steadily increased from baseline (BL; 88.8 g/L) to cycle 8, and then stabilized; mean platelet count recovered from BL values (72.7 x 10⁹/L) as early as week 8 (171.9 x 10⁹/L) and remained stable; and mean neutrophil counts rapidly increased from BL (0.98 x 10⁹/L) to week 3 (3.99 x 10⁹/L) and week 4 (4.36 x 10⁹/L), and then stabilized to within the normal range. Conversion from BL transfusion dependence (red blood cell and/or platelet transfusion dependence) to post-BL transfusion independence was significantly higher with IVO+AZA than PBO+AZA (53.8% v 17.1%, respectively; p=0.0004). There were fewer neutropenic fever events (27.8% v 33.8%) and infections (34.7% v 51.4%) with IVO+AZA than with PBO+AZA. TEAEs led to discontinuation of IVO+AZA or PBO+AZA in 26.4% and 25.7% of pts, respectively. **Conclusions:** Updated data on OS (>5 months longer mOS and a greater risk reduction in deaths compared to the initial analysis), transfusion independence, blood count recovery and safety confirms the clinically and statistically robust benefit in favor of IVO+AZA at long-term follow up. Patient disposition. Clinical trial information: NCT03173248. Research Sponsor: This study was supported by Agios Pharmaceuticals, Inc. Servier Pharmaceuticals LLC has completed the acquisition of Agios' oncology business.

	Patients, n (%)	
	IVO+AZA (n=73)	PBO+AZA (n=75)
Randomized but not treated	1 (1.4)	1 (1.3)
On-treatment with IVO/PBO	21 (28.8)	0
On-treatment with AZA	19 (26.0)	3 (4.0)
Crossed over to IVO+AZA	-	5 (6.7)
Discontinued IVO	-	2 (2.7)
Ongoing with IVO	51 (69.9)	3 (4.0)
Discontinued IVO/PBO	-	74 (98.7)
Discontinued AZA	53 (72.6)	71 (94.7)

7014 Poster Discussion Session

Outcomes of 3- versus 5-day administration schedule of consolidation cytarabine in adults with acute myeloid leukemia (AML). *First Author: Kendall Diebold, University of Alabama at Birmingham, Birmingham, AL*

Background: Consolidation therapy with intermediate to high-dose cytarabine is critical to prevent relapse in AML. Cytarabine is typically administered every 12 hours on days 1, 3, 5. Two large studies have examined a condensed 3-day administration schedule in patients <60 years and demonstrated a shorter time to absolute neutrophil count (ANC) recovery without compromising long term outcomes. However, use of this regimen in patients ≥60 years has not been evaluated. Here we report our experience with the condensed administration schedule compared with the standard schedule in patients over and under 60 years. **Methods:** All patients with AML in first complete remission (CR) following intensive induction chemotherapy receiving consolidation at our institution between 1/1/2020 to 12/31/2021 were included in the study. Patients received cytarabine every 12 hours on days 1, 3, 5 (AC135) from 1/1/2020 – 12/31/2020 and cytarabine every 12 hours on days 1, 2, 3 (AC123) from 1/1/2021 – 12/31/2021. All patients received peg-filgrastim support. Data was collected to determine time to ANC recovery >1,000/μL, hemoglobin (Hb) >8g/dL, and platelets >75,000/μL. Comparison of continuous variables between two groups was done using multiple t-tests. **Results:** Between 1/1/2020 - 12/31/2021, 91 patients received at least one cycle of consolidation with 212 individual encounters. 38 patients received all cycles with AC135, 45 received AC123, and 8 received at least one cycle each of AC123 and AC135. Median age of the AC123 cohort was 50.2 years (range 19-72 years) and 54.3 years for the AC135 cohort (range 22-72 years). For patients ≥60 years of age, 33% (71/213) of the encounters were in the AC123 cohort and the rest in AC135 cohort. Median dose of cytarabine was 5,100 mg/dose in AC123 and 4,600 mg/dose in AC135 (p=0.02). Median time to ANC recovery, hemoglobin, and platelets as well as hospital-related outcomes are described in the table. In patients ≥60 years, median time to ANC recovery was 16.5 vs. 18.6 days (p=0.03) and platelet recovery was 17.4 vs. 19.7 (p=0.0008) in AC123 vs AC135 respectively. No neurotoxicity events were noted. Complication rates were similar in both arms. **Conclusions:** Our study demonstrates that AC123, as compared to AC135, is safe and leads to earlier hematopoietic recovery in adults under and over 60 years. AC123 should be considered the preferred schedule of consolidation therapy administration. Research Sponsor: None.

	AC123 N=115	AC135 N=97	P-Value
Median time to ANC >1000/ μL (days)	15.75	18.59	0.000002
Median time to Hemoglobin >8g/dL (days)	18.15	19.97	0.012
Median time to Platelets >75,000/ μL (days)	16.23	20.25	0.00000013
Median Time to Next Cycle (days)	34.55	33.22	0.6
Hospitalization rate (%)	13.48	28.86	0.1
N = 45			
Neutropenic Fever rate (%)	8.69	14.43	0.3
N = 24			
Documented Infection (%)	9.56	18.55	0.2
N = 29			
Bacteremia (%)	1.74	6.19	0.4
N = 8			
Bleeding Requiring Intervention (%)	3.47	6.19	0.4
N = 10			

7013 Poster Discussion Session

Addition of venetoclax to FLAI induction chemotherapy (VFLAI) improves survival in patients with intermediate and high-risk AML vs FLAI and 3+7: A GIMEMA Italian cooperative analysis. *First Author: Giovanni Martinelli, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori IRST (IRCCS), Meldola, Italy*

Background: Venetoclax combined with intensive chemotherapy proved to be safe with promising activity. The GIMEMA AML1718 trial (NCT03455504) was based on the administration of venetoclax-FLAI (fludarabine, idarubicin, cytarabine) to intermediate/high-risk ELN2017 AML. **Methods:** To investigate the potential advantage of the addition of venetoclax, patient-level data from GIMEMA AML1718 (V-FLAI group, n=57) were compared to “3+7”-like induction (AML1310, Venditti et al. 2019, 3+7 group, n=445), and to FLAI real-life experience (Guolo et al. 2016, FLAI group, n=155) using a propensity score matching. In the model, we included the following variables: age at diagnosis, gender, ELN2017 risk classification and allogeneic transplant rate. For determining adequate balance, the diagnostic method employed was the standardized mean difference, visualized through a Love plot; a standardized bias score less than 0.2 was used as a criterion. The final weighted sample sizes are 183 (3+7), 54 (V-FLAI) and 155 (FLAI). Weights were calculated with a multinomial logistic regression model. The Odds Ratio (OR) were estimated using logit models. Survival curves were compared by standard and pairwise Log-rank test. **Results:** FLAI, V-FLAI and 3+7 cohorts differed in terms of age (median: 52 vs 54 vs 49 years, respectively, p<0.001), in terms of risk category (p<.001) - since the low risk was not represented both in V-FLAI and FLAI trials -, in terms of transplant rate (45% vs 49% vs 27%, p<0.001) and female sex (43% vs 35% vs 48%, p=0.15). Being more recent, AML1718 had a shorter median follow-up (10.5 vs 75.8 vs 104.8 months). The matching weights produced the best balance, with SMDs <0.18 for all variables. After weighting, the CR rate observed in the V-FLAI group was higher than FLAI and 3+7, as well as MRD-negativity rate. In terms of Odds Ratio (OR) the probability of achieving CR in V-FLAI and FLAI patients was significantly higher compared to 3+7 patients (p=0.01 and p=0.03, respectively). Conversely, V-FLAI and FLAI did not differ in their probability to achieve CR (p=0.34). Concerning MRD, the OR associated to V-FLAI group was significantly higher (namely, a higher probability of MRD-negativity) of that associated to both FLAI and 3+7 treatments (p=0.005 vs FLAI; p=0.001 vs 3+7). Looking at survival outcomes at 12 months, upon weighting, DFS estimate of the V-FLAI group was higher than “3+7” and FLAI (p=0.048). **Conclusions:** VFLAI resulted in a deeper disease response as compared to other regimens. These results highlight the potential benefit of venetoclax added to intensive induction chemotherapy and suggest the role of fludarabine-based regimens as a backbone for high-risk disease. Research Sponsor: None.

	CR (OR)		MRD-negativity (OR)	
	Estimate	p	Estimate	p
FLAI vs 3+7	0.55	0.03	0.22	0.48
V-FLAI vs 3+7	0.91	0.01	1.40	0.001
V-FLAI vs FLAI	0.36	0.34	1.18	0.005

7015 Poster Discussion Session

A randomized, double-blind, phase 3 study of jaktinib versus hydroxyurea (HU) in patients (pts) with intermediate-2 or high-risk myelofibrosis (MF). *First Author: Yi Zhang, The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, China*

Background: Ruxolitinib and HU are recommended by Chinese MF guideline for splenomegaly. There is an unmet need for new treatments. Jaktinib, a novel JAK and AVCR1 inhibitor, showed promising activity on splenomegaly, anemia, and MF symptoms in a phase 2 study (NCT03886415). Here we present the interim results of a phase 3 study, which assessed the efficacy and safety of jaktinib compared to HU. **Methods:** Pts aged ≥ 18 with primary or post-ET/PV MF, DIPSS Int-2 or high risk, and no prior or ≤10 days' treatment with a JAK inhibitor were enrolled and randomly assigned (2:1) to receive jaktinib 100 mg bid plus HU placebo or HU 0.5g bid plus jaktinib placebo, stratified by DIPSS risk status (Int-2 or high risk). One interim analysis was pre-specified to be conducted when 70 pts completed the week (wk) 24 visit or met the criteria for treatment termination before wk 24. The primary endpoint was the proportion of pts with a spleen volume reduction of ≥ 35% from baseline (SVR35) at wk 24, measured by MRI/CT images and assessed centrally. Secondary endpoints included the best spleen response rate (defined as achieving SVR35 at any time), the proportion of pts with a ≥ 50% reduction in Total Symptom Score (TSS50), improvement of anemia, safety, etc. **Results:** This interim analysis (cut-off: April 8, 2022) included 47 pts receiving jaktinib and 23 receiving HU. 66.0% (jaktinib) and 69.6% (HU) had a baseline hemoglobin (Hb) < 100 g/L. 59.6% (jaktinib) and 69.6% (HU) were JAK2V617F positive. The SVR35 rates at wk 24 were 72.3% for jaktinib vs. 17.4% for HU (p≤0.0001). The best spleen response rates were 80.9% of jaktinib-treat pts vs. 26.1% of HU-treated pts (p=0.0001). The median maximum percentage change from baseline in spleen volume were -46.59% vs. -18.50%. The TSS50 rates at wk 24 were 63.8% for jaktinib vs. 43.5% for HU (p = 0.1163). 5 of 7 jaktinib-treated and two of 5 HU-treated pts who required RBC transfusion at baseline achieved a ≥50% decrease in RBC transfusion by wk 24. In transfusion-independent pts with baseline Hb ≤100 g/L, 39.3% for jaktinib and 15.4% for HU had a ≥20 g/L Hb increase. The most common grade ≥3 hematological treatment emergent adverse events (TEAEs) (jaktinib vs. HU) were anemia (25.5% vs. 43.5%), thrombocytopenia (17.0% vs. 39.1%), leukopenia (2.1% vs. 21.7%), neutropenia (2.1% vs. 21.7%) and decreased lymphocyte count (2.1% vs. 13.0%). Most common non-hematological TEAEs were upper respiratory tract infection (21.3% vs. 21.7%), elevated bilirubin (12.8% vs. 26.1%), fever (12.8% vs. 21.7%) and diarrhea (10.6% vs. 21.7%), predominantly of grade 1 or 2. TEAEs leading to treatment discontinuation occurred in 8.5% of jaktinib and 17.4% of HU. **Conclusions:** Jaktinib demonstrated significant clinical benefits over HU in MF pts for spleen response with improved symptom response and less cytopenias. Jaktinib may be a new treatment option for MF pts, especially for those with anemia. Clinical trial information: NCT04617028. Research Sponsor: Suzhou Zelgen Biopharmaceuticals Co, Ltd.

7016

Poster Discussion Session

Safety and efficacy of luspatercept for the treatment of anemia in patients with myelofibrosis: Results from the ACE-536-MF-001 study. *First Author: Aaron Thomas Gerds, Cleveland Clinic, Cleveland, OH*

Background: Many patients (pts) with myelofibrosis (MF) experience anemia resulting from disease or JAK inhibitor therapy. The open-label, phase 2 ACE-536-MF-001 study (NCT03194542) evaluated the safety and efficacy of luspatercept (LUSPA) for the treatment of MF-related anemia. **Methods:** Eligible pts comprised 4 cohorts based on transfusion dependence (TD, defined as receiving 4–12 red blood cell [RBC] units/84 days [d] immediately up to cycle 1 d 1) and stable ruxolitinib (RUX) treatment; cohort 1: no TD, no RUX; cohort 2: TD, no RUX; cohort 3A: no TD, RUX; cohort 3B: TD, RUX. Pts received subcutaneous LUSPA 1.0 mg/kg (1.33 mg/kg for pts in cohort 3B expansion) with titration up to 1.75 mg/kg in 21-d cycles. Disease response was assessed at d 169 and treatment extended for pts showing clinical benefit; pts were followed for ≥ 3 years (y) post last dose. The primary endpoint was anemia response (defined as 84 consecutive d: ≥ 1.5 g/dL hemoglobin [Hgb] from baseline without transfusion [cohorts 1 and 3A] or RBC transfusion-free [cohorts 2 and 3B]); secondary endpoints included duration of response (DOR), transfusion frequency, change in Hgb level, and symptom response. **Results:** Of 95 pts in the ITT group, the most common reason for treatment discontinuation was lack of clinical benefit at d 169 (n = 28). Median (range) age was 71.0 (50–89) y. Most (54.7%) pts had primary MF, intermediate-risk 2 disease (75.8%), and > 2 y since initial diagnosis (74.7%). Median prior RUX therapy was 18.1 months (cohorts 3A/3B) and 84.7% of pts had baseline transfusion burden 6–12 units/84 d (cohorts 2/3B). Mean treatment duration was 42.8 weeks. Cohort 3B had the highest anemia response rate with 26.3% (95% CI, 13.4–43.1) of pts transfusion independent during the primary treatment period and 31.6% (95% CI, 17.5–48.7) transfusion independent during the entire treatment period; median (range) DOR was 448 d (85–1582). In cohort 3B: 19 (50.0%) pts had reduced transfusion burden by $\geq 50\%$ during the primary treatment period; 8 (21.1%) pts achieved mean Hgb increase ≥ 1.5 g/dL from baseline throughout the entire treatment period and 6 (15.8%) achieved a mean $\geq 50\%$ reduction in symptom score from baseline. Overall, 47.4% of pts had ≥ 1 treatment-related adverse event (TRAE), most frequently hypertension (17.9%, 5.3% grade ≥ 3); 3.2% of pts had a serious TRAE. One TRAE led to LUSPA discontinuation. Two (2.1%) pts had transformation to acute myeloid leukemia. Nine pts died on treatment from: post-procedural hemorrhage, pneumonia, intracranial hemorrhage, septic shock, ischemic stroke, multiple organ dysfunction syndrome, renal failure, pneumonitis, and myelofibrosis (n = 1 each); no deaths were considered related to the study drug. **Conclusions:** In pts with MF, the safety profile of LUSPA was consistent with previous studies and efficacy results showed promising improvements in anemia and transfusion burden in all cohorts. Clinical trial information: NCT03194542. Research Sponsor: Bristol Myers Squibb.

7018

Poster Discussion Session

Spleen volume reduction (SVR) predicts overall survival (OS) in myelofibrosis (MF) patients on pacritinib (PAC) but not best available therapy (BAT): PERSIST-2 landmark OS analysis. *First Author: Helen Ajufu, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: MF is a life-limiting malignancy characterized by marrow fibrosis, splenomegaly, and progressive cytopenias. JAK2 inhibitors can reduce spleen volume, which is considered a surrogate for disease response. For example, $\geq 10\%$ SVR on ruxolitinib (RUX) is associated with improved OS among patients with platelet (PLT) counts $\geq 100 \times 10^9/L$. RUX cannot be administered at full dose in patients with lower PLTs, and it is not known whether the association between SVR and OS persists in such patients. PAC is a JAK1-sparing inhibitor of JAK2/IRAK1/ACVR1 that demonstrated SVR benefit vs BAT (including RUX) in PERSIST-2, which enrolled MF patients with PLTs $\leq 100 \times 10^9/L$. Here we present a retrospective landmark OS analysis of the relationship between SVR and OS on PERSIST-2. **Methods:** This analysis includes PERSIST-2 patients who were alive and on study at the start of the 12-week SVR window (study week 10) on PAC 200 mg BID or BAT. Spleen volume was assessed radiographically (MRI or CT). OS was evaluated among SVR responders vs non-responders within each treatment arm using different SVR thresholds ($\geq 35\%$, $\geq 20\%$, $\geq 10\%$, $> 0\%$) and a landmark analysis methodology. OS was compared using the log-rank test. **Results:** Among patients on PAC (n = 89), any SVR ($> 0\%$) at 12 weeks was significantly associated with improved survival (HR = 0.08 [95% CI: 0.01, 0.51], P = 0.0007). Among all SVR response thresholds, SVR $\geq 10\%$ demonstrated the greatest separation in OS curves between responders vs. non-responders on PAC, with no deaths on study among 65 responders compared to 5 deaths among 24 non-responders (HR = 0.0 [95% CI: 0.0, 0.14], P < 0.0001). By contrast, SVR did not predict OS benefit on BAT (n = 84), including RUX (n = 39). For example, 11% (3/28) of patients on BAT who achieved SVR $\geq 10\%$ died compared to a similar number (14%, 8/56) of non-responders (HR = 0.63 [95% CI: 0.17, 2.37], P = 0.49). Of the 28 patients on BAT who achieved SVR $\geq 10\%$, 23 (82%) were treated with RUX. Among these 23 patients, most patients were receiving low-dose RUX at the time of the landmark: 78% were on ≤ 10 mg BID and 43% were on ≤ 5 mg BID. By contrast, the median relative dose intensity on PAC was 100% (200 mg BID) through week 12 among both SVR $\geq 10\%$ responders and non-responders. **Conclusions:** In MF patients with PLTs $\leq 100 \times 10^9/L$, achieving SVR on full-dose PAC was associated with significant OS benefit. By contrast, this association was not found with BAT, even though most responders were on RUX, albeit at low doses. As PAC can be given at full dose regardless of PLT count, it is possible that PAC may offer a unique survival advantage for MF patients with moderate or severe thrombocytopenia who achieve spleen reduction. Clinical trial information: NCT02055781. Research Sponsor: CTI BioPharma Corp.

7017

Poster Discussion Session

Phase 1/2 study of the activin receptor-like kinase (ALK)-2 inhibitor zilugisertib (INCB00928, LIMBER-104) as monotherapy or with ruxolitinib (RUX) in patients (pts) with anemia due to myelofibrosis (MF). *First Author: Prithviraj Bose, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Elevated levels of the iron regulator hepcidin can cause functional iron deficiency anemia; hepcidin dysregulation is central to anemia of chronic inflammation observed in several malignancies such as MF. ALK2 (ie, ACVR1) contributes to MF-associated anemia via hepcidin upregulation. We evaluated the safety and activity of zilugisertib, a selective, oral ALK2 inhibitor, in pts with anemia due to MF. **Methods:** The ongoing open-label, multicenter, phase 1/2 dose-escalation/expansion INCB 00928-104 study (NCT04455841) is evaluating zilugisertib alone (treatment group A [TGA]) or with RUX (treatment group B [TGB]). Eligible pts are ≥ 18 years old with primary/secondary MF of intermediate (Int)-1 (TGB only) or Int-2/high-risk (TGA and TGB) per the Dynamic International Prognostic Scoring System (DIPSS) and are transfusion-dependent or have symptomatic anemia. The primary endpoint is safety and tolerability. Secondary endpoints include efficacy (per anemia response parameters), pharmacokinetics, and pharmacodynamics (eg, hepcidin and iron metabolism parameters). **Results:** 31 pts were enrolled by data cutoff (30Nov2022), with 20 in TGA (50 mg once daily [qd], n = 4; 100 mg qd, n = 4; 200 mg qd, n = 6; 400 mg qd, n = 6) and 11 in TGB (100 mg qd, n = 4; 200 mg qd, n = 5; 400 mg qd, n = 2). Median (range) age was 73 (53–84) y for TGA and 77 (64–85) y for TGB. 65% of TGA pts had received prior RUX therapy. Overall, 90% of pts had Int-2 risk DIPSS, and the remainder had high-risk DIPSS (1 pt in TGA, 2 in TGB). 60% of pts in TGA and 27% in TGB were transfusion-dependent at the time of enrollment. Median baseline (BL) hemoglobin (Hb) was 7.7 (range, 7.10) g/dL in TGA and 8.5 (range, 8.9) g/dL in TGB. BL hepcidin was high in both cohorts (median [range]: TGA, 171 [185–35] ng/mL; TGB, 123 [72–50] ng/mL; normal range, 0–50 ng/mL). At the time of analysis, dose escalation was ongoing in both treatment groups. No dose-limiting toxicities (DLTs) or study drug-related serious adverse events (AEs) occurred in either treatment group. Maximum tolerated dose had not been reached at the time of analysis. Treatment-emergent AEs (TEAEs) were mainly low grade. Grade ≥ 3 TEAEs occurred in 7 pts, with thrombocytopenia the most common (n = 4). Reduction in hepcidin following zilugisertib dosing was observed in TGA and TGB, with maximal hepcidin reduction at 6 h postdose. Hb increase of > 1.5 g/dL from BL occurred in 3 pts (27%) in TGB and 1 pt (5%) in TGA. **Conclusions:** Treatment with zilugisertib monotherapy or in combination with RUX in this patient population was generally well tolerated, with predominantly grade 1/2 TEAEs and no DLTs. Reduced hepcidin levels were observed with both monotherapy and in combination with RUX, and preliminary improvements in anemia were observed, which suggest potential for therapeutic activity. Clinical trial information: NCT04455841. Research Sponsor: Incyte Corporation.

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Poster Discussion Session

Pelabresib (CPI-0610) monotherapy in high-risk essential thrombocythemia refractory or intolerant to hydroxyurea: Preliminary results from MANIFEST study. *First Author: Francesco Passamonti, University of Insubria, Varese, Italy*

Background: High-risk essential thrombocythemia (HR ET) is characterized by thrombocytosis, thrombohemorrhagic events and systemic symptoms. Pts can experience intolerance, inadequate response or loss of response to first-line cytoreductive therapies (hydroxyurea [HU] or interferon alfa-2a). BET protein inhibition is a novel therapeutic strategy that downregulates inflammatory cytokines and may inhibit differentiation and proliferation of abnormal megakaryocytes involved in ET pathogenesis. Results from the Phase 2 MANIFEST study (NCT02158858) suggested potentially encouraging clinical efficacy in pts with myelofibrosis treated with Pelabresib (PELA), an oral, small-molecule, investigational BET inhibitor. Here we present preliminary results from MANIFEST Arm 4 investigating PELA monotherapy in HR ET refractory or intolerant to HU. **Methods:** Eligible pts had platelets $> 600 \times 10^9/L$ and ≥ 2 symptoms (average score ≥ 3 /TSS ≥ 15). Pts received PELA monotherapy 225 mg QD. The primary endpoint was complete hematologic response (CHR; normalization of platelet count ($\leq 400 \times 10^9/L$), WBC count ($\leq 10 \times 10^9/L$) confirmed after one cycle [after 3 weeks]) and normal spleen size. Secondary endpoints included partial HR (PHR; platelets 400–600 $\times 10^9/L$ and WBC $\leq 10 \times 10^9/L$), symptom improvement ($\geq 50\%$ TSS reduction) and safety. **Results:** As of July 2022, 20 pts with HR ET were treated: median age 64 yrs (42–83), median Hgb 13 (10–16) g/dL, median platelet count 772 (418–1255) $\times 10^9/L$ and median TSS 32.7 (6.9–123). The majority of pts had a hematologic response (90% [18/20] unconfirmed CHR or PHR); confirmed CHR was observed in 40% (8/20) (Table). Median platelet and WBC count at Wk 12 was 446 $\times 10^9/L$ and 8.2 $\times 10^9/L$, respectively. TSS reduction was reported in 86% (12/14 pts); median TSS reduction at Wk 12 was $\sim 31\%$. Hgb levels remained stable through Wk 24. The most common nonhematologic AEs were nausea (60%; 10% Gr 3), diarrhea (35%; 5% Gr 3) and dysgeusia (35%; no Gr 3). Hemorrhagic or thromboembolic events were reported in 30% pts (15% Gr 3). No events of thrombocytopenia and no Gr 4 events or higher were reported. **Conclusions:** Preliminary results from Arm 4 of the MANIFEST study suggest potential clinical benefit with PELA monotherapy in pts with HR ET refractory or intolerant to HU as supported by hematologic responses and symptom improvement. Safety results are consistent with the known safety profile of PELA and as expected in the underlying study population. Clinical trial information: NCT02158858. Research Sponsor: Constellation Pharmaceuticals, Inc., a MorphoSys Company.

Best Response (N=20)	CHR, n (%) (Primary endpoint)	
	Confirmed*	Unconfirmed†
- WBC Count $\leq 10 \times 10^9/L$	8 (40)	12 (60)
- Platelet Count $\leq 400 \times 10^9/L$	19 (95)	12 (60)
PHR, n (%)	4 (20)	6 (30)
Confirmed*	4 (20)	6 (30)
Unconfirmed†	6 (30)	6 (30)
Symptom Improvement (N=14)	TSS50	7 (50)
	Median TSS reduction, Wk 12, %	$\sim 31\%$

*Confirmed CHR/PHR: conditions met in two consecutive cycles. †Unconfirmed CHR/PHR: conditions met in one cycle but not the next.

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Poster Discussion Session

Refining risk stratification in CMML: A comprehensive assessment of the IPSS-M and other molecularly informed models. *First Author: Luis E. Aguirre, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL*

Background: Multiple molecularly-informed models have been designed in hopes of improving prognostication in CMML. More recently the IPSS-M was introduced for MDS and showed improved prognostic accuracy over the IPSS-R. Here we aimed to analyze whether the applicability of the IPSS-M extends to CMML and provide a definitive comparison between all major molecularly-informed models. **Methods:** A total of 367 pts with CMML treated at Moffitt Cancer Center with annotated clinical and molecular data were analyzed. The mean IPSS-M score was used as reference. Correlative analysis between CPSS-Mol, Mayo Molecular (MMM), GFM and IPSS-M was performed. Time-to-event analyses were estimated using Kaplan–Meier. We used Cox regression for survival endpoints. Model discrimination was evaluated using Harrell’s C concordance index. **Results:** We identified 987 driver point mutations involving 21 genes across 367 pts. We identified at least 1 mutation in 96% of pts (n = 352). Median follow-up was 4.4 yrs (3.8-5.0). The most prevalent mts were *TEF2*, *SRSF2*, *ASXL1*, *RUNX1* and *NRAS*. Using the IPSS-M schema, pts were classified as very low (7%, n = 26), low (29%, n = 108), moderate low (21%, n = 76), moderate high (16%, n = 58), high (18%, n = 65) and very high-risk (9%, n = 34). The IPSS-M identified 6 risk categories with mOS of 5.0, 5.1, 3.9, 2.6, 1.7 and 1.1 yrs, ranging from VL to VH (p < .05) and a 4-yr cumulative incidence of AML evolution of 2%, 14%, 17%, 18%, 25% and 14% respectively (p < .05). CPSS-Mol and IPSS-M equally showed improved OS discrimination over the MMM and GFM as demonstrated by an 11% and 6% increase in c-index respectively (0.71 vs 0.60 and 0.65). Similarly, CPSS-Mol outperformed CPSS by 3% (0.71 vs 0.68), as did IPSS-M relative to IPSS-R (6%, 0.71 vs 0.65). A 4-to-4 mapping between CPSS-Mol and IPSS-M risk groups (by merging VL/L and H/VH into LR and HR), resulted in the re-stratification of 57% of pts (n = 202). 22% (n = 15) of LR CPSS-Mol pts were upstaged. 30% (n = 23) of HR pts were downstaged 87 pts (23.7%) developed AML: 34 by 1 (9.2%), 60 by 2 (16.3%) and 79 by 4 yrs (21.5%). There was significant segregation between IPSS-M and CPSS-Mol groups and AML risk (p < .05), but not MMM (p = .191). CPSS-Mol showed the highest accuracy, followed by IPSS-M, MMM and GFM (0.66 vs 0.63 vs 0.57 vs 0.52). We then analyzed the predictive value of the models in pts receiving frontline HMA (n = 146). IPSS-M retained its prognostic accuracy with significant segregation between strata (p < .01), as did CPSS-Mol (p < .01) and MMM (p = .01). **Conclusions:** The IPSS-M can be used reliably in pts with CMML and shows comparable prognostic accuracy to the CPSS-Mol. Both outperformed MMM and GFM. All models retained its predictive value in pts receiving frontline HMA. This carries particular importance in community settings where CMML tends to be misdiagnosed as MDS. In such instances use of the IPSS-M is unlikely to adversely impact outcomes when used to guide treatment decisions. Research Sponsor: None.

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Poster Session

Outcomes of 10-day decitabine with venetoclax for AML. *First Author: Alexander Coltoff, Medical University of South Carolina, Charleston, SC*

Background: Venetoclax (VEN) + a hypomethylating agent (HMA) has improved outcomes for patients with acute myeloid leukemia (AML). VIALE-A showed improved overall response rate (ORR) and overall survival (OS) with VEN + HMA in newly diagnosed AML (ND AML); the complete remission (CR) rate was 36.7% and the median OS was 14.7 months. Later, DiNardo et al. reported a trial of 10-day decitabine (DEC10) + VEN with a CR rate of 65.7% and a median OS of 18 months in a ND AML cohort. We report real world outcomes of VEN + DEC10 for AML induction. **Methods:** We reviewed 82 adult patients treated with VEN + DEC10 at our institution. Patients received 1 or 2 cycles of VEN + DEC10 followed by additional cycles of VEN + 5-day decitabine (DEC5) per physician discretion. **Results:** Twenty-four patients had ND AML, 28 had secondary AML (sAML) and 30 had relapsed/refractory (R/R AML) with a median age (years) of 72, 70, and 59 in each group, respectively. Cytogenetics were poor-risk in 13 ND patients (54.2%), 14 sAML patients (50%), and 17 R/R patients (56.7%). Twenty-two patients (26.8%) had *TP53* mutations. Six patients (7.3%) received rasburicase. Neutropenic fever was seen in 46 patients (56.1%), and 34 (41.5%) had documented infections. Thirty-eight patients (46.3%) were re-hospitalized during cycle 1 (C1), at a median of 22 days after starting. The median time from the start of C1 to C2 was 41 days. Thirty-day mortality was 7.3%. In ND AML, ORR was 91.7% and composite CR rate (CRc; CR + CR with incomplete hematologic recovery(CRi)) was 75%. Nine of 15 patients (60%) in CR were negative for measurable residual disease (MRD-). In sAML, ORR was 53.6% and CRc rate was 50% (35.7% MRD- CR). CRc was achieved by eight of 16 (50%) untreated sAML patients vs six of 12 (50%) who were previously treated. In R/R AML, ORR was 56.7% and CRc rate was 43.3% (53.8% MRD- CR). *TP53*-mutated AML had an ORR of 59% and a CRc of 50%. Median OS was 5.5 months in *TP53*-mutant AML, 7.4 months in R/R AML, and was not reached in ND AML or sAML. Fifteen patients (18.3%) received an allogeneic transplant (3 ND, 3 sAML and 9 R/R) in MRD- CR (n = 11), MRD+ CR (n = 2) and CRi (n = 2). At a median of 263 days post-transplant, there were 3 relapses and the median OS was not reached. **Conclusions:** VEN + DEC10 compared favorably with published data, yielding high ORR, CR, and MRD- CR rates in ND AML. CR rate for R/R AML with VEN + DAC10 was similar to that for ND AML in the VIALE-A trial. These results warrant a prospective, randomized trial of VEN + DEC10 vs VEN + DEC5 in AML. Research Sponsor: None.

	ND AML (n=24)	sAML (n=28)	R/R AML (n=30)
ORR	22 (91.7%)	15 (53.6%)	17 (56.7%)
CR	15 (62.5%)	8 (28.6%)	10 (33.3%)
CRi	3 (12.5%)	6 (17.9%)	3 (10%)
MRD- CR	9 (37.5%)	5 (17.9%)	7 (23.3%)
Not evaluated/refractory	2 (8.3%)	13 (46.4%)	13 (43.3%)
Median time to best response, months	2.1 (0.7-5.5)	1.6 (0.7-7.0)	2.1 (0.7-6.2)
Number of cycles to best response, median	2 (1-5)	2 (1-3)	2 (1-5)
Number of cycles, median	2 (1-15)	2 (1-7)	2 (1-8)
Second cycle of VEN + DEC10	7 (29.1%)	6 (21.4%)	8 (26.7%)

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Poster Session

Implications for acute myeloid leukemia (AML) treatment and care during the COVID-19 pandemic: A Connect Myeloid Registry study. *First Author: Bart L. Scott, Fred Hutchinson Cancer Research Center, Seattle, WA*

Background: For patients (pts) with AML, timely treatment is critical. The COVID-19 pandemic broadly disrupted healthcare (eg, decreased blood donations), possibly causing delays in AML treatment and care. To determine the extent of the COVID-19 impact on AML, this analysis examines the effect of the pandemic on managing pts with AML in the Connect Myeloid Registry (NCT01688011). **Methods:** The Registry is a large, US, multicenter, prospective, observational cohort study that includes newly diagnosed pts with AML aged ≥55 y. Pt characteristics (including assessment for transplant) were analyzed from December 2013 to March 2020 (from Registry opening to the start of the pandemic; Period 1), from March 2020 to May 2021 (during major healthcare disruptions; Period 2), and from May 2021 to January 2022 (resource stabilization and increased vaccine availability; Period 3). Monthly COVID-19 incidence was calculated per weekly US government data (CDC COVID Data Tracker; 2023). Rates of visits (office, remote) and transfusions were calculated by monthly events/person-year. Overall survival (OS) was estimated using the Kaplan–Meier method. **Results:** In this analysis, 650 pts were included in Period 1, 87 pts in Period 2, and 36 pts in Period 3; demographics and baseline characteristics were balanced across periods. Prior to the COVID-19 pandemic (Period 1), 25.1% of pts were not assessed for transplant; however, after the onset of the pandemic, this increased (45.5% and 44.4% in Periods 2 and 3, respectively). When monthly US COVID-19 cases increased, in-person visits and transfusion rates generally decreased in the Registry (Table). The proportion of pts receiving oral-containing induction regimens was 49.4% (40/81) in Period 1 (starting in January 2019, due to FDA approval of venetoclax in November 2018) and 50.6% (44/87) in Period 2, with a slight increase to 63.9% (23/36) in Period 3. No significant differences in OS by period were observed. **Conclusions:** In this analysis of pts with AML in the real-world setting, a pattern of increased COVID-19 cases in the US was accompanied by fewer transfusions, fewer in-person visits, and fewer assessments for stem cell transplantation, without a significant impact on OS. Clinical trial information: NCT01688011. Research Sponsor: Bristol Myers Squibb.

Month in 2020	US COVID-19 cases, n (per 100,000 CDC COVID Data Tracker)	Rate of office vs remote; Overall visits in registry, events/person-year	RBC and platelet transfusion rate in the Registry, events/person-year	Direction of change in COVID-19 cases since previous month	Direction of change (≥5%) in office visits since previous month	Direction of change (≥5%) in transfusion rate since previous month
Feb	55	2.04 vs 0.70; 2.74	13.0			
Mar	68,767	2.12 vs 1.12; 3.24	12.4	↑	—	↓
Apr	835,148	1.82 vs 1.46; 3.28	8.97	↑	↓	↓
May	752,762	1.92 vs 1.00; 2.92	9.69	↑	↓	↓
Jun	708,151	3.40 vs 0.94; 4.34	7.95	↓	↑	↓
Jul	1,779,634	2.22 vs 0.76; 2.98	6.73	↓	↓	↓
Aug	1,620,559	1.98 vs 0.89; 2.87	10.5	↓	↓	↓

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Poster Session

Impact of age, prior therapies, and subsequent transplant on long-term outcomes of adults with relapsed or refractory B-cell acute lymphoblastic leukemia (R/R B-ALL) treated with brexucabtagene autoleucel (brexu-cel) in ZUMA-3. *First Author: Bijal D. Shah, Moffitt Cancer Center, Tampa, FL*

Background: Brexu-cel is an autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy approved in the US for adults with R/R B-ALL and in the EU for adults ≥26 y with R/R B-ALL based on positive results of ZUMA-3. After 3-y follow-up in ZUMA-3, brexu-cel demonstrated an overall complete remission (CR)/CR with incomplete hematologic recovery (CRI) rate of 71% and a median overall survival (OS) of 26.0 mo in all treated pts (N = 55) and 38.9 mo in pts with CR (n = 31; Shah et al. EU CAR T 2023. Abstract 34). Here we report 3-y outcomes by age, prior therapies, and subsequent allogeneic stem cell transplant (alloSCT). **Methods:** Pts (≥18 y) had R/R B-ALL and received 1 brexu-cel infusion (1×10⁶ CAR T cells/kg) following leukapheresis and conditioning chemotherapy. The primary endpoint was overall CR/CRI rate per independent review. Post hoc subgroup analyses were exploratory, with descriptive statistics reported. **Results:** As of July 23, 2022, the median follow-up in Phase 2 (N = 55) was 38.8 mo (range, 32.7-44.6). The CR/CRI rate (95% CI) was 67% (35-90) for pts < 26 y (n = 12) and 72% (56-85) for pts ≥26 y (n = 43). The median (95% CI) OS was 28.6 mo (0.6-not estimable [NE]) for pts < 26 y and 34.1 mo (15.9-NE) for pts ≥26 y. Grade ≥3 treatment-related adverse events (TRAEs) occurred in 92% of pts < 26 y and in 88% of pts ≥26 y. For pts with 1 prior therapy (n = 10), the CR/CRI rate was 90% (95% CI, 55-100) and for pts with ≥2 prior therapies (n = 45), the CR/CRI rate was 67% (95% CI, 51-80); medians (95% CI) for OS were not reached (NR; 2.1-NE) and 25.6 mo (14.2-38.9), respectively. The incidence of Grade ≥3 TRAEs was 90% for pts with 1 prior therapy and 89% for pts with ≥2 prior therapies. The CR/CRI rates (95% CI) for pts with (n = 25) and without (n = 30) prior blinatumomab (blina) were 60% (39-79) and 80% (61-92). The median (95% CI) OS was 14.2 mo (3.2-26.0) for pts with prior blina and NR (18.6-NE) for pts without prior blina; Grade ≥3 TRAEs occurred in 80% and 97% of pts, respectively. For responders (CR/CRI) who did (n = 10) or did not (n = 29) proceed to subsequent alloSCT, the median (95% CI) OS was NR (7.6-NE) and 38.9 mo (18.6-NE), respectively. Similar efficacy results were observed in a pooled subgroup analysis of Phase 1 and 2 pts treated at the pivotal dose (N = 78), with a median follow-up of 41.6 mo (range, 32.7-70.3). **Conclusions:** Adults with R/R B-ALL benefitted from brexu-cel, regardless of age, number of prior therapies, prior blina exposure, or subsequent alloSCT status. Survival appeared longer in pts with fewer prior therapies and in blina-naïve pts; however, small pt numbers and unmatched baseline characteristics limit interpretation of these results. Additional studies are needed to determine the impact of prior therapies and/or subsequent alloSCT on outcomes of pts who receive brexu-cel. Clinical trial information: NCT02614066. Research Sponsor: Kite, a Gilead Company.

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Poster Session

UCHMC 1812: A phase 1b trial of CPX-351 plus gemtuzumab ozogamicin for relapsed/refractory acute myeloid leukemia. *First Author: Daria Louise Gaut, University of California Los Angeles, Los Angeles, CA*

Background: Gemtuzumab ozogamicin (GO) is effective in favorable-risk acute myelogenous leukemia (AML), while its activity is limited in higher-risk AML in part due to multi-drug resistance (MDR) mechanisms, particularly P-glycoprotein efflux pumps. CPX-351 provides a survival benefit in secondary AML, a disease characterized by high MDR activity. The objective of this trial is to utilize CPX-351 as a bulk cytoreduction agent, to first reduce the high MDR leukemia clones, followed by sequential treatment with GO in a more favorable leukemia environment. **Methods:** This was a multicenter phase Ib trial of CPX-351 plus GO in relapsed/refractory (R/R) AML patients with standard 3+3 dose escalation design (NCT03904251). Cohort A was treated with CPX-351 100 u/m² on days 1, 3, and 5 plus GO 3 mg/m² (max 4.5 mg) on day 7. Cohort B was treated with the same regimen plus an additional dose of GO 3 mg/m² on day 4. The primary endpoint was the maximum tolerated dose (MTD), defined as < 2 dose limiting toxicities (DLTs) in the highest dose cohort. Secondary endpoints were IWG complete remission (CR) rate at day 28-42, liver veno-occlusive disease (VOD) rate diagnosed by the Baltimore criteria, and time of hematologic recovery (defined as ANC > 1000/uL and platelet count > 100,000/uL). Patients were enrolled at 4 University of California Hematologic Malignancies Consortium (UCHMC) centers: UC Los Angeles, UC San Francisco, UC Davis, and UC Irvine. **Results:** Thirteen participants were enrolled. The median age was 63 years (range 29-75). Eleven had relapsed disease, and two had refractory disease. Most received one prior line of therapy (n=9). Seven had ELN 2022 adverse-risk disease at initial diagnosis, and two had intermediate-risk disease. The MTD was not reached. DLTs were observed in 1/6 participants in cohort A (grade 3 rash), and 1/6 participants in cohort B (grade 5 intracranial hemorrhage in the setting of severe thrombocytopenia). There were no cases of liver VOD. Of 12 evaluable participants, 4 achieved CR (33%), of whom 3 were negative for measurable residual disease by multiparametric flow cytometry, and 1 one achieved partial remission. The median age of responders was 30 years (range 28-65). The median time to return of normal hematopoiesis in those who achieved remission was 37 days (range 36-43). Three participants received allogeneic hematopoietic cell transplant (alloHCT) following investigational therapy: one remains in remission 34 months post-transplant, one died of infectious complications shortly after alloHCT, and one relapsed at day +60. **Conclusions:** CPX-351 plus two doses of GO 3 mg/m² is a feasible treatment with acceptable toxicity and reasonable marrow recovery kinetics. However, only three participants went on to curative alloHCT. Further evaluation for efficacy in a larger patient population is needed to determine the utility of this regimen in R/R AML. Clinical trial information: NCT03904251. Research Sponsor: Pfizer and Jazz.

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Poster Session

Examining safety and durable disease remission in R/R B-ALL after autologous CD19-directed CAR T cells produced by novel PRIMCAR manufacture platform. *First Author: Zhi Yang, Chongqing Precision Biotech Co., Ltd., Chongqing, China*

Background: CD19 chimeric antigen receptor (CAR) T cell therapy has shown promising efficacy in the r/r B-ALL. However, the life-threatening side effect and disease relapse limited its wide application. To overcome these limitations, we established a novel PrimeCAR platform (PRIMCAR) and reported the preliminary safety and effectiveness data of MC-1-50 CAR-T cells before (Shi Qi, et al. J Clin Oncol 2022; 40 [suppl 16]. Abstract 7008). Here, we present updated data. **Methods:** In this Phase I /II study (NCT04271410), MC-1-50 CAR T cells were manufactured by the PRIMCAR platform, which reduces manufacture periods to about 2 days. Patients (pts) received single-dose of MC-1-50 at dose ranged 1-5×10⁵ CAR+/kg (Level 1, 1×10⁵ CAR+/kg; Level 2, 2×10⁵ CAR+/kg; Level 3, 3×10⁵ CAR+/kg; Level 4, 5×10⁵ CAR+/kg). Pts were pre-conditioned with fludarabine (25-30 mg/m²) and cyclophosphamide (200-300 mg/m²) daily for 3 days. Toxicity was graded by CTCAE, CRS and ICANS were graded by ASTCT criteria. **Results:** 19 pts with r/r B-ALL were infused. Disease characteristics and outcomes are shown in the table. No DLTs were reported. 18 pts (94.7%) experienced CRS, including 10 (52.6%) at grade 1, 7 (36.8%) at grade 2, 1 (5.3%) at grade 3, and no ≥ 4 CRS were observed. Three pts (15.8%) experienced ICANS, including 2 (10.5%) at grade 1, 1 (5.3%) at grade 2, and no ≥ 3 ICANS occurred. All patients achieved CR/CRi (BM MRD-) in the first month. All patients received no other anti-tumor therapy until relapse was confirmed. The median DOR was not reached. 6 patients confirmed relapse, including 4 were CD19 negative and 2 were CD19 positive but with CD19 gene mutation at the time of relapse. All patients in 4 dose levels had good CAR-T expansion and exhibited long persistence features. Only 3 patients experienced the loss of CAR-T. **Conclusions:** Treatment of r/r B-ALL at a very low dose resulted in excellent safety profiles while exhibiting a high and durable efficacy. That makes this PRIMCAR platform potential for outpatient administration in the future. Clinical trial information: NCT04271410. Research Sponsor: ChongQing Precision Biotech Co., Ltd.

Disease characteristics and safety outcomes.							
ID	Age	Gender	Prior HSCT	Tumor burden (%)	Dose (×10 ⁵ /kg)	CRS	ICANS
ALL01-01	17	M	N	71.1	1	2	/
ALL01-02	39	M	N	82.8	1	1	/
ALL01-03	26	M	N	51.7	1	1	/
ALL01-04	38	F	N	30.2	1	1	/
ALL01-05	8	M	Y	25.4	1	2	1
ALL01-06	71	M	N	83.0	1	/	/
ALL02-01	34	M	N	68.8	2	2	/
ALL02-02	52	F	N	58.4	2	1	/
ALL02-03	22	F	N	34.6	2	1	/
ALL02-04	70	F	N	44.5	2	2	1
ALL02-05	25	F	N	77.3	2	1	/
ALL02-06	24	M	Y	83.0	2	3	/
ALL02-07	36	F	N	33.6	2	2	1
ALL03-01	39	F	N	79.3	3	2	/
ALL03-02	21	M	N	79.0	3	1	/
ALL03-03	23	F	N	83.0	3	1	/
ALL03-04	48	M	N	3.3	3	1	/
ALL04-01	29	F	Y	0 ^a	5	2	2
ALL04-02	6	M	N	28.0	5	2	/

^aThe patient has only extramedullary lesions.

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Poster Session

Efficacy and safety of venetoclax in combination with cytarabine and azacitidine (VAA) in relapsed/refractory acute myeloid leukemia: An open-label, single-arm, phase II study. *First Author: Liangshun You, The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, China*

Background: While the understanding of AML has been improved over decades, the outcome of relapsed/refractory AML remains dismal. Venetoclax-based regimen has not yet been systematically assessed in R/R AML. Clinical trials of VEN-based regimen designed for R/R AML are urgently needed to further evaluate its efficacy and safety among these patients. We innovatively combined VEN with azacytidine and cytarabine (termed as VAA). **Methods:** a) Patients: Eligible patients aged 18-70 years and had a confirmed diagnosis of relapsed/refractory AML. b) Trial design and regimens: Phase 2, open-label, single-arm, multicenter study of VAA regimen in R/R AML patients. A stepwise ramp-up of VEN dosing was adopted to achieve the target dose (400 mg), beginning with 100mg on day 1, and escalated to 200mg on day 2, and 400 mg on day 3-day 9. Cytarabine (10mg/m²) was administered by subcutaneous injection twice daily from day 1 to 10, and AZA (75mg/m²) was administered by intravenous injection once daily from day 1 to 7. c) End points and assessments: Primary efficacy endpoints were CRc including CR and CRi, PR and MLFS per IWG for AML. Secondary endpoints were OS and DOR. The safety endpoints were adverse events graded per CTCAE. d) Statistics analysis: As of the date of submission, 29 patients have completed efficacy evaluation and 1 patient is still in the trial. This study was designed to detect a target CRc rate of 65% (historical rate 40%), with 80% power and type 1 error rate at 0.05, and the planned sample size was 31 patients. All P values were two sided. **Results:** a) Patients: 30 R/R AML patients were enrolled.b) Efficacy: The CRc rate among all patients was achieved in 62.1% (18/29), including CR in 34.5% and CRi in 27.6% patients, following with 13.8% patients obtaining PR. CRc rates were preserved across subgroups with 59.1% (13/22) in ELN intermediate/adverse group, 62.5% (5/8) in those who ≥65 years and 50.0% (7/14) in those whose baseline bone marrow count ≥30%. Noticeably, CRc rate in patients diagnosed with M4/5 reached 72.7% (8/11). With a median follow-up of 6.95 months, median OS and median DOR are not yet reached. Estimated 12-month OS was 86%, and Estimated 12-month DOR was 62.6%. In ELN intermediate/adverse risk patients, the median DOR was 7.5 months. Estimated 12-month OS rate and DOR rate were 84.3% and 63.8%, respectively. Patients with prior bone marrow count less than 30% and with no prior HMA-based therapy were associated with favorable estimated 12-months DOR rate. The regimen had similar efficacy in patients younger than 65 years compared with those >65 years. c) Safety: No TLS events were observed. No treatment-related deaths occurred. **Conclusions:** VAA regimen represents a feasible and safe new choice for R/R AML patients, especially with satisfactory effect in ELN intermediate/adverse group and in those with advanced ages. Clinical trial information: chict2100051119. Research Sponsor: None.

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Poster Session

Survival outcomes with CPX-351 vs 7+3 by baseline bone marrow blast percentage in older adults with newly diagnosed high-risk or secondary acute myeloid leukemia: A 5-year follow-up study. *First Author: Ellen K. Ritchie, Weill Cornell Medicine, The New York Presbyterian Hospital, New York, NY*

Background: CPX-351, a dual-drug liposomal encapsulation of daunorubicin and cytarabine in a synergistic 1:5 molar ratio, is approved for newly diagnosed therapy-related acute myeloid leukemia (AML) or AML with myelodysplasia-related changes in the US and Europe following positive efficacy and safety data from the pivotal phase 3 clinical trial (NCT01696084). A previous exploratory analysis of the trial data (median follow-up 20.7 months) showed improved survival outcomes with CPX-351 vs conventional 7+3 chemotherapy in adults with newly diagnosed high-risk or secondary AML (sAML) irrespective of baseline bone marrow (BM) blast percentage. Here we report 5-year follow-up data (median follow-up 60.9 months) to provide insights into the longer-term efficacy and safety of CPX-351 in these patient subgroups. **Methods:** Patients (60–75 years) with a pathologic diagnosis of AML (high-risk/sAML) per the WHO 2008 criteria (≥20% blasts in peripheral blood or BM) and an ECOG PS of 0–2 were randomized to receive CPX-351 or 7+3 chemotherapy. In these post hoc subgroup analyses at 5 years follow-up, overall survival (OS), event-free survival (EFS) and complete remission (CR) were assessed by baseline BM blast percentage. The analysis included patients with low (< 20%) BM blasts to account for changes in blast count thresholds in the updated WHO AML classification. **Results:** Overall, median OS and EFS were longer with CPX-351 vs 7+3 in each subgroup; median OS was greatest in low blast subgroups for both treatments (Table). Higher CR rates were observed with CPX-351 vs 7+3 irrespective of baseline BM blasts. Median Kaplan-Meier (KM)-estimated survival rates increased with CPX-351 vs 7+3 across BM blast subgroups. The CPX-351 safety profile was comparable across BM blast subgroups and consistent with the known safety profile of 7+3. **Conclusions:** These 5-year follow-up data suggest that CPX-351 results in improved outcomes irrespective of baseline BM blast percentage vs conventional 7+3 chemotherapy in older adults with AML. Clinical trial information: NCT01696084. Research Sponsor: Celator Pharmaceuticals, Inc., now a subsidiary of Jazz Pharmaceuticals.

Baseline BM blasts		< 20% ^a		20%–40%		> 40%–60%		> 60%	
Treatment		CPX-351	7+3	CPX-351	7+3	CPX-351	7+3	CPX-351	7+3
n		21	22	62	65	34	34	32	29
Median OS, mo		12.6	7.3	11.6	6.0	8.1	4.9	4.7	2.9
HR (95% CI)		0.38 (0.19, 0.75)		0.62 (0.42, 0.91)		0.72 (0.43, 1.21)		0.67 (0.40, 1.14)	
Median EFS, mo		3.0	1.1	2.5	2.2	5.0	1.0	2.0	1.2
HR (95% CI)		0.60 (0.32, 1.14)		0.81 (0.55, 1.18)		0.45 (0.27, 0.77)		0.54 (0.31, 0.95)	
CR, n (%)		7 (33) (23)		25 (40)		21 (32)		16 (47)	
OR (95% CI)		3.78 (0.68, 21.05)		1.22 (0.56, 2.66)		2.89 (0.99, 8.44)		1.72 (0.41, 7.21)	
Median KM-estimated 5-year survival rate, % (95% CI)		26.0 (9.6, 46.1)		0 (12.9, 33.4)		22.4 (9.2, 34.4)		19.4 (8.1, 21.1)	
								8.8 (2.3, 18.1)	
								6.3 (1.1, 14.9)	

^aAML diagnosis confirmed by an independent pathologist; patients may have had baseline BM blasts < 20% with AML diagnosis based on other factors.

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Poster Session

First-in-human trial of tocilizumab in combination with a standard induction chemotherapy in newly diagnosed acute myeloid leukemia patients: The phase 1 T0CILAM study. *First Author: Pierre Peterlin, CHU de Nantes, Service d'hématologie Clinique, Nantes, France*

Background: Numerous studies have pointed out the pathological role of deregulated expression of Interleukin-6 (IL-6) in cancers. In acute myeloid leukemia (AML), IL-6 promotes chemo-resistance and correlates with poor prognosis. One explanation is that AML cells express IL-6 receptor (R) and self-produce IL-6 at once, favouring blast proliferation and survival. Therefore, IL-6 blockade may represent a new promising therapeutic strategy for AML. Here, we have tested Tocilizumab (Toci), an anti-IL-6R antibody, in combination with a standard AML induction chemotherapy. **Methods:** This was a monocentric Phase 1 study testing three escalating doses of Toci (4, 6 and 8 mg/kg) administered at day (d) 8 of a standard AML induction chemotherapy (Idarubicin 8 mg/m² d1 to d5 + cytarabine 100 mg/m² d1 to d7). All adults (> 18 yo) with a newly diagnosed (excluding patients (pts) with a favorable risk according to ELN-2017 classification if < 60 yo) or a relapsed/refractory AML were eligible. The main objective was to determine the maximum tolerated dose of Toci for further phase 2/3 studies. Patients had to be included 2 by 2, according to a continual reassessment method while targeting a related-experimental drug toxicity level < 30%. A maximum of 12 pts had to be included. Toxicity was evaluated using NCI version5 criteria. Responses were evaluated according to ELN-2017 criteria between d30/d45 of induction. Also, IL-6 and Toci plasma levels were assessed. All pts gave informed consent and the trial was registered at Clinical trials under NCT04547062. **Results:** Between Dec/2020 and Dec/2022, 12 pts were treated, including 2 pts at 4 mg/kg, 2 at 6 mg/kg and 8 at 8 mg/kg of Toci. The median age was 66 yo (range: 56-73), all pts had a newly diagnosed AML, ELN risk was intermediate: 25%; unfavorable: 75%. No dose limiting toxicity related to Toci was documented. Two pts died during induction, 1 of infection and 1 of cerebral haemorrhage. Complete remission (CR) rate for evaluable pts was 90% (n = 9/10). After induction, 7 received a consolidation and 7 were allo-transplanted. With a median follow-up of 600d, 4 patients have relapsed and 7 have died, 1-y OS and LFS were estimated at 43% (21-88%) and 39% (19-82%), respectively. Dosages of IL-6 (pg/mL) showed a significant increase after Toci injection (median 23,2 (2.6-53.5) vs 202,9 (21.1-6189.2) after 8d and 481,5 (53.8-7327.4) after 15d), suggesting a good saturation of the targets (IL6-R) on AML cells and a potential anti-leukemic effect. Median dosages of Toci (µg/ml) were higher 8d and 15d after injection at L2 (34.8; 17.2) and L3 (38.5; 12.9) compared to L 1 (10.9; 1.4). **Conclusions:** The combination of Toci to a standard AML intensive induction appears to be very safe providing both high CR rate and the expected biological effect. We now recommend a dose of 8 mg/kg of Toci given at d8 of induction for further phase 2/3 studies. Clinical trial information: NCT04547062. Research Sponsor: donation from the association la Commission LEAF - TOUS AVEC FABIEN.

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Poster Session

BOS-371, a monoclonal antibody against IL1RAP: Characterization in pre-clinical models of AML. *First Author: Kip A West, Boston Pharmaceuticals, Cambridge, MA*

Background: IL1 receptor accessory protein (IL1RAP) is a cell surface protein overexpressed on leukemia stem cells (LSC) and progenitors in AML, CML and high-risk MDS. It is an indispensable co-receptor for the IL1 superfamily, but its role reaches beyond anti-apoptotic pathways. IL1RAP directly interacts with and potentiates signaling of FLT3 and c-KIT which have significant roles in AML pathogenesis. High IL1RAP is correlated with poor prognosis and IL1 blockade attenuates expansion of LSCs. Thus, targeting IL1RAP has emerged as a promising immunotherapeutic approach for myeloid malignancies. BOS-371 is a humanized monoclonal antibody targeting IL1RAP that has been Fc-engineered to enhance its capacity to induce antibody directed cell cytotoxicity (ADCC) and deplete IL1RAP-expressing AML cells. **Methods:** The preclinical activity of BOS-371 was characterized using multiple assays. In vitro analysis included: binding affinity in IL1RAP-expressing cell lines; inhibition of IL1-dependent signaling as measured by IL1 α -stimulated secretion of IL6 from MRC5 lung cancer cells; measurement of ADCC in co-cultures of human NK cells with either IL1RAP-expressing cell lines or primary AML cells; and cell growth by monitoring metabolic activity of primary AML cells. In vivo efficacy of BOS-371 was determined in AML models: MV4-11 and ML2 cells (CDX) implanted in NOG and NOD-SCID mice, respectively, and patient-derived (PDX) leukemia cells implanted in NOG mice. **Results:** BOS-371 binds with high affinity to IL1RAP-expressing cells (average EC50 337pM) leading to potent inhibition of IL1 signaling (IC50 600pM). Co-culture assays in the presence of BOS-371 showed potent induction of ADCC with an EC50 of 60-70pM (cell lines) or 4-11pM (primary cells) and 80-100% cell lysis (both cell lines and primary cells). The ability of BOS-371 to impact AML cell growth exclusively through inhibition of IL1 signaling was measured in a panel of 15 primary AML samples. Incubation with BOS-371 led to IC50s ranging from 20-700nM in responsive samples. Evaluation of BOS-371 activity in vivo showed that administration of BOS-371 resulted in significant anti-leukemic activity. In CDX studies, BOS-371 treatment led to > 50% decrease in systemic disease and engraftment in bones and organs. The results observed in CDX AML models were reproduced in PDX mouse models of AML, where decreases in both peripheral (> 70%) and bone marrow (> 50%) disease burden in response to BOS-371 were observed. **Conclusions:** These findings demonstrate that BOS-371 binds with high affinity to IL1RAP, potently inhibits IL1 signaling and induces ADCC, leading to anti-leukemic activity in vitro and in vivo. The preclinical results support the clinical investigation of BOS-371 for the treatment of myeloid malignancies. A Phase 1 trial is currently in development. Research Sponsor: Boston Pharmaceuticals.

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Poster Session

Cardiotoxicity of CPX-351 vs 7+3 in patients with untreated high-risk acute myeloid leukemia. *First Author: Joshua Mitchell, Cardio-Oncology Center of Excellence, Washington University School of Medicine, St. Louis, MO*

Background: CPX-351, a dual-drug liposomal encapsulation of daunorubicin and cytarabine in a synergistic 1:5 molar ratio, is approved for newly diagnosed, therapy-related acute myeloid leukemia (AML) or AML with myelodysplasia-related changes in the United States and Europe. While CPX-351 demonstrated improved overall survival and a similar safety profile vs 7+3 in the phase 3 clinical trial (NCT01696084), the safety of CPX-351 related to cardiac function has not been fully described, an important consideration, due to the known cardiotoxicity risk from anthracyclines. This post hoc analysis assessed the impact of CPX-351 vs 7+3 chemotherapy on cardiac impairment in a subset of adults with newly diagnosed high-risk or secondary AML (sAML) from the phase 3 trial. **Methods:** In the phase 3 trial, 309 patients (60-75 years old; AML according to WHO 2008 criteria) were randomized 1:1 to receive CPX-351 (100 units/m² on days 1, 3 and 5; days 1 and 3 for second induction) or 7+3 (cytarabine 100 mg/m²/day for 7 days [5 days for second induction] and daunorubicin 60 mg/m² on days 1-3 [days 1-2 for second induction]). Cardiac impairment was determined by cardiac adverse events (AEs) as well as echocardiogram (ECHO) measures including left ventricular ejection fraction (LVEF) and global longitudinal strain (GLS), which were assessed at baseline and two follow-up visits. **Results:** The study population included 102 patients (CPX-351, n = 57; 7+3, n = 45) with normal baseline LVEF (LVEF > 53%) and at least one post-baseline ECHO measure (LVEF or GLS). Median (min, max) age was 68 (60, 75) years for CPX-351 vs 66 (60, 75) years for 7+3. The mean cumulative dose of daunorubicin while on study was lower for patients receiving CPX-351 vs 7+3 (378 vs 570 mg, respectively). Lower proportions of CPX-351 vs 7+3-treated patients had LVEF < 53% (12% vs 31%) or GLS $\leq$ 18% (25% vs 38%) at follow-up 1 or 2. A clinically significant change in LVEF (> 10% decrease from baseline and LVEF < 53%) or GLS (> 12% relative decrease from baseline and GLS < 18%) was less common in patients treated with CPX-351 vs 7+3 (9% vs 20% and 21% vs 44%, respectively) at follow-up 1 or 2. The frequency of any cardiac AE by treatment group was similar for both CPX-351 and 7+3 (40% vs 42%). Tachycardia was the most common cardiac AE in CPX-351-treated patients (21% vs 9% in 7+3-treated patients), while atrial fibrillation was the most common cardiac AE in 7+3-treated patients (11% vs 4% in CPX-351-treated patients). **Conclusions:** The results of this post hoc analysis of data from the phase 3 trial show that CPX-351 is associated with less cardiotoxicity in adults with newly diagnosed high-risk or sAML, when compared with 7+3. The lower mean cumulative doses of daunorubicin while on study with CPX-351 appear to result in better cardiac outcomes with CPX-351 vs 7+3 chemotherapy. Characteristics of CPX-351, such as liposomal delivery, may also contribute to this effect but require further study to confirm this. Clinical trial information: NCT01696084. Research Sponsor: Jazz Pharmaceuticals.

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Poster Session

Identification of factors to predict low risk febrile neutropenia admissions in patients with acute myeloid leukemia (AML) following intensive chemotherapy. *First Author: Khushboo Pal, University of Washington, Seattle, WA*

Background: Febrile neutropenia (FN) is the most common reason for hospital readmission following chemotherapy for AML. Standard practice for FN in AML is hospitalization for rapid administration of IV antibiotics, thus FN is a major driver of healthcare resource utilization and cost. Whether this approach is justified in all situations is unknown. While FN risk models have been developed focusing on solid tumors, factors predicting uncomplicated courses of FN in AML, which may allow identification of patients suitable for outpatient management, have not been studied. We therefore examined whether baseline clinical characteristics could predict which AML patients with FN have a lower risk of progression to severe illness. **Methods:** We retrospectively reviewed medical records from 7/29/2014-12/24/2022 to identify adults with FN (fever >38.3C and white blood count <1000/ μ L). Included were patients with high-grade myeloid neoplasm (>10% blasts in blood/marrow) who received intensive chemotherapy (cytarabine dose $\geq$ 100 ² /day) within 8 weeks. We collected baseline clinical and disease variables. Outcomes were: infections identified, hospital length of stay (LOS), intensive care unit (ICU) admission, and survival. A "low-risk [LR]" outcome was defined as a LOS <72hrs without ICU admission or inpatient death. Univariate and multivariable (MV) logistic regression models were used to assess covariate associations with outcomes. **Results:** We identified 350 FN admissions in 198 patients with a median age 62 (range: 21-87) yrs. 63% were newly diagnosed and 37% relapsed/refractory. 12% had prior transplant. Median duration of neutropenia prior to fever was 12 (1-287) days. 46% had transfusion <24 hours prior to fever. The median LOS was 5 (1-56) days. 9% of patients went to ICU and 6% died inpatient. Overall, 15% of admissions were classified as LR. 57% had an infection identified. The table shows factors in MV analysis that predicted an infection identified or high-risk (HR) admission. **Conclusions:** Only 15% of AML admissions for FN were LR. Factors that predict HR outcomes in standard FN models such as the MASCC score—e.g. age, prior fungal infection—were not predictive of HR outcomes in AML. As a next step, we will compare our model to other published models used to predict poor outcomes after FN, which have not been developed or validated in AML. Research Sponsor: None.

MV model for infection identification and high-risk admission following FN in AML.			
Factor	Odds ratio	95% CI	P-value
Identification of infection, AUC =0.71			
Newly diagnosed disease	0.53	0.32-0.86	0.011
Absolute lymphocyte count	0.2	0.05-0.85	0.029
Initial heart rate	1.02	1.01-1.04	<0.01
Highest fever/24 hrs	1.59	1.14-2.21	0.01
HR admission, AUC = 0.76			
Age	0.97	0.95-1.00	0.04
Prior fungal infection	0.53	0.24-1.19	0.12
Prior transplant	0.62	0.25-1.56	0.31
Higher fever/24 hours	2.91	1.78-4.76	<0.01

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Poster Session

Shattering myths regarding Hispanic ethnicity and survival in acute myeloid leukemia: Insights from the National Cancer Database. *First Author: Naveen Premnath, University of Texas Southwestern Medical Center, Dallas, TX*

Background: Previous smaller studies suggest that despite younger age at presentation, Hispanic patients (HP) with acute myeloid leukemia (AML) have worse prognosis than non-Hispanics patients (NHP). **Methods:** We queried the National Cancer Database (NCDB) between 2004 to 2017 for adults aged ≥ 18 years for a diagnosis of AML using the ICD-O-3 diagnosis code. Baseline characteristics and outcomes were compared. **Results:** A total of 144,146 patients with AML were identified during the study period of which 9173 were Hispanic (6.4%). The median age at diagnosis was 66 years overall. Hispanics were younger at presentation with median age 55 compared to 67 in non-Hispanics ($p < 0.001$). A higher proportion of HP were uninsured and in the lowest income quartile compared to NHP across all AML subtypes. HP had statistically significant longer survival across AML subtypes except for tAML. When adjusted for age, sex, Charlson Deyo Comorbidity Index, insurance, chemotherapy, transplant, and income status using a multivariate Cox regression analysis, HP had non-inferior survival to NHP. **Conclusions:** We present the largest study to date in Hispanics with AML. Hispanics presented at younger ages and had worse socioeconomic factors compared to NHP and when adjusted for multiple variables, did not have worse outcomes as reported in prior data. We believe previous studies in HP demonstrating worse prognosis may reflect bias and confounding given smaller patient numbers and are suggestive of disparities in access to health care and present opportunities for improvement. Research Sponsor: None.

Multivariable cox survival analysis.

	APML (n = 11657)		AEL (n = 2583)		AML with MDS changes (n = 10739)		tAML (n = 4789)		Myeloid Sarcoma (n = 1351)		AML-NOS (n = 113027)	
	HR	p	HR	p	HR	p	HR	p	HR	p	HR	p
Age												
< 21 (Reference)	1		1		1		1		1		1	
21-40	1.16	0.37	8.19	0.04	1.23	0.49	0.99	0.95	0.71	0.25	1.11	0.03
41-60	1.71	< 0.001	13.56	0.01	1.9	0.03	1.41	0.11	1.1	0.72	1.69	< 0.001
61-70	2.97	< 0.001	17.66	0.004	2.59	0.001	1.87	0.004	1.73	0.06	2.69	< 0.001
71-80	4.4	< 0.001	23.82	0.001	3.40	< 0.001	2.2	< 0.001	1.99	0.01	3.94	< 0.001
> 80	5.4	< 0.001	26.69	0.001	3.87	< 0.001	2.59	< 0.001	2.44	0.002	5.01	< 0.001
Sex												
Male (Reference)	1		1		1		1		1		1	
Female	0.88	< 0.001	NA		NA		NA		NA		0.96	< 0.001
Charlson Deyo Score												
0 (Reference)	1		1		1		1		1		1	
1	1.60	< 0.001	1.35	< 0.001	1.32	< 0.001	1.39	< 0.001	1.14	0.14	1.3	< 0.001
2	1.94	< 0.001	1.53	< 0.001	1.51	< 0.001	1.51	< 0.001	1.11	0.46	1.5	< 0.001
3	2.41	< 0.001	1.72	< 0.001	1.81	< 0.001	1.64	< 0.001	1.65	0.007	1.69	< 0.001
Transplant												
Yes	NA		0.94	0.56	0.97	0.66	0.90	0.09	NA		1.22	< 0.001
No (Reference)	NA		1		1		1		1		1	
Income status lowest quartile												
Yes	1.16	< 0.001	NA		1.09	0.001	1.18	< 0.001	0.94	0.56	1.13	< 0.001
No (Reference)	1		1		1		1		1		1	
Chemotherapy received												
Yes	0.20	< 0.001	0.46	< 0.001	0.46	< 0.001	0.93	0.07	0.7	< 0.001	0.42	< 0.001
No (Reference)	1		1		1		1		1		1	
Ethnicity												
Hispanic	0.89	0.07	0.92	0.41	1.01	0.90	0.93	0.40	0.81	0.13	0.86	< 0.001
Non-Hispanic (Reference)	1		1		1		1		1		1	

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Poster Session

Results from a phase (Ph) 1 clinical study of the all-oral regimen of CC-486 and venetoclax for acute myeloid leukemia (AML). *First Author: Maria Amaya, University of Colorado, Aurora, CO*

Background: Venetoclax (Ven) with azacitidine (Aza) is the standard of care for newly diagnosed AML patients who are unfit for intensive induction chemotherapy. It is well known that this treatment also has activity in the relapsed and refractory (R/R) setting. However, this regimen requires seven consecutive daily SQ or IV doses of Aza each month. The relative inconvenience of this, and its negative impact on quality of life, may lead to its early discontinuation, possibly decreasing the overall efficacy of this regimen. An all-oral regimen may decrease infusion center visits, and potentially increase the efficacy of the regimen due to improved compliance. CC-486 is the oral formulation of Aza that is currently approved for post-induction chemotherapy maintenance in AML. **Methods:** This is a single center open label, Ph 1 study investigating CC-486 and Ven in R/R AML patients. In the dose escalation phase, subjects received CC-486 at one of two cohorts (200 mg PO days 1-14 and 300 mg PO days 1-14). Ven was given at the 400 mg/day PO regimen, for 28 days, after an initial in-patient dose escalation per the standard of care. Using a 3+3 study design for the two cohorts, we aimed to determine the maximum tolerated dose (MTD) of CC-486 in combination with Ven. An expansion cohort is planned for 10 patients treated at the MTD. **Results:** As of February 1, 2023, 8 patients have been accrued. The average age at the time of enrollment was 64, and median prior treatment regimens was 1 (range 1-3). Four patients had received Ven in prior treatments. In cohort 1, there were no DLT events. There have been no DLT events in 5/6 patients enrolled in cohort 2. The most common hematologic toxicities were Gr 3-4 neutropenia (n = 7, 88%), Gr 3-4 anemia (n = 6, 75%), and Gr 3-4 thrombocytopenia (n = 4, 50%). The most common non-hematologic toxicities were Gr 1-2 nausea (n = 4, 50%), Gr 1-2 fatigue (n = 2, 25%), and Gr 1-2 diarrhea (n = 2, 25%). Best responses were complete remission (CR) (n = 2, 25%), partial remission (PR) (n = 1, 13%), and stable disease (SD) (n = 2, 25%). Three patients proceeded to an allogeneic stem cell transplant. **Conclusions:** CC-486 and Ven is an all-oral regimen being investigated for the treatment of R/R AML. Our Ph 1 dose escalation thus far has demonstrated a favorable safety profile for this regimen. Full Ph 1 findings and the MTD will be presented at the meeting. Responses have been seen in both dose cohorts, and patients have been bridged to hematopoietic stem cell transplant. Clinical trial information: NCT05287568. Research Sponsor: Bristol Myers Squibb.

Patient characteristics and responses.

Cohort	Age	ENL Risk	Prior Lines of Therapy, Prior Ven (Y/N)	Best Response	Cycles Received	Reason For Discontinuation
1	80	Adverse	3 - Y	N	SD	3
1	81	Adverse	1 - Y	N	SD	1
1	53	Favorable	1 - N	N	CR	1
2	92	Adverse	2 - Y	N	PD	1
2	70	Adverse	1 - Y	N	PD	2
2	62	Intermediate	1 - N	N	CR	2
2	40	Adverse	1 - N	N	PR	1
2	36	Favorable	1 - N	N	PD	1

* PD = Progressive disease.

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Poster Session

Comparison of next-generation sequencing and flow cytometry in detecting minimal residual disease in adult acute lymphoid leukemia: Evaluating clinical outcomes in a single-center study. *First Author: Vinay Nittur, University of Southern California, Norris Comprehensive Cancer Center, Los Angeles, CA*

Background: Detection of measurable residual disease (MRD) is an important biomarker to direct treatment for adult patients with acute lymphoblastic leukemia (ALL). Currently, multiparameter flow cytometry (MFC) is standard of care and can detect residual leukemia cells in 1 out of 100,000 cells (1×10^{-5}). Routine use of next-generation sequencing (NGS) assays with higher levels of sensitivity may improve disease-free survival and overall survival in adult ALL patients. The clonoSEQ MRD assay (Adaptive Biotechnologies Corporation, USA) can detect MRD at a sensitivity of 1×10^{-6} . In this study, we compare the detection of MRD by clonoSEQ assay and MFC in adult ALL patients at a single institution. **Methods:** We performed a retrospective study evaluating 92 adult patients with B- or T-ALL admitted to Norris Comprehensive Cancer Center between 2014 and 2022. Patients were excluded if they did not achieve complete remission (N=9) or if they presented with prior relapse (N=27). Median time to first complete remission (CR1) was 2.38 months. Among our cohort (N=56 patients), all patients underwent pre-treatment bone marrow sampling which was used for Clonoseq assay. 52 patients had contemporaneous MFC which was used for comparative analysis. MRD on MFC was defined as residual leukemia cells at a sensitivity of 1×10^{-5} . MRD on Clonoseq assay was evaluated at 1×10^{-6} ; residual cells under this limit were considered MRD-. **Results:** Demographics are summarized in the table. Median time to follow-up from MRD assessment was 18.0 months. 10 patients relapsed (17.9%), 3 patients died (5.4%), and 20 patients (35.7%) underwent allogeneic transplant during first remission. Among 52 patients analyzed by both MFC and NGS at CR, 26 (50%) were concordantly MRD- by NGS and NGF, 13 (25%) were discordantly MRD- by NGF but MRD+ by NGS, and 13 (25%) concordantly MRD+ by NGS and NGF. Residual cell levels between NGS and NGF were strongly correlated (R-Squared = 0.6744, $p < 0.001$), however, MRD status was significantly different between NGS and NGF ($p < 0.001$ using Fisher's Exact Test). This difference was likely driven by disparities in the limits of detection between both methods. **Conclusions:** Assessment of MRD using the clonoSEQ assay over a standard MFC-based approach adds crucial prognostic information among adult ALL patients who achieved CR. Research Sponsor: None.

Demographics of CR1 patients by clonoseq MRD.

	Negative (<10 ⁻⁶) (N=30)	Positive (≥10 ⁻⁶) (N=26)	Total (N=56)	p value
Age, Years	46.3 (29.9, 61.2)	40.9 (27.6, 52.4)	44.5 (27.8, 54.9)	0.384 ¹
ALL Type				0.263 ²
T-Cell	6 (20.0%)	2 (7.7%)	8 (14.3%)	
B-Cell	24 (80.0%)	23 (88.5%)	47 (83.9%)	
Mixed	0 (0.0%)	1 (3.8%)	1 (1.8%)	
Ph Chromosome Status				1.000 ²
Ph negative	16 (53.3%)	14 (53.8%)	30 (53.6%)	
Ph positive	5 (16.7%)	4 (15.4%)	9 (16.1%)	
Ph like	9 (30.0%)	8 (30.8%)	17 (30.4%)	

¹Kruskal-Wallis rank sum test. ²Fisher's Exact Test for Count Data.

7035

Poster Session

Clinical outcomes of patients with newly diagnosed acute myeloid leukemia receiving treatment in a safety-net hospital system. *First Author: Jason Lu, Baylor College of Medicine, Houston, TX*

Background: Standard induction therapy for acute myeloid leukemia (AML) results in 5-year overall survival (OS) rates of 30-45%. Further risk stratification and novel therapeutic options have improved 5-year OS rates to 75-80% in certain subgroups. Despite these advances, many patients lack proper socioeconomic resources, leading to limited access to new therapies, clinical trials, and hematopoietic cell transplantation (HCT), which remains the only curative therapy for AML. Many of these patients receive care within publicly funded 'safety net' institutions designed to serve all individuals, regardless of ability to pay, insurance status, or immigration status. Outcomes of historically underserved patients with AML treated within a large county hospital system remain unknown. **Methods:** This retrospective cohort analysis evaluated clinical outcomes of patients aged ≥ 18 years with newly diagnosed AML (ND-AML) treated in the Harris County Health System, Houston, TX, from January 2005 to July 2019. **Results:** One hundred ninety-two patients with ND-AML were included (de novo AML [n = 140], secondary AML [n = 45], and therapy-related AML [n = 7]). Median age was 52 years (range: 19-89) at diagnosis, and 102 (52.3%) were male. Most patients identified as Hispanic (n = 110). Sixty-two percent of patients were uninsured or indigent, receiving care under the county's financial assistance programs. The majority had adverse risk 84 (44.3%), while 78 were intermediate (40.6%), and 26 favorable risk (13.5%). Standard induction therapy was administered in 172 (88%) of patients. Cytarabine and Anthracycline (7+3) based regimens were most commonly used (72.8%). 192 patients were evaluable for response. 139 (72.4%) achieved composite complete remission (CR/CRi) and 41 (21.4%) had primary refractory disease. For those who achieved CR after first or second induction, the median duration of CR was 16.7 months. with 25 (13.7%) ultimately receiving HCT. Common reasons for not receiving HCT included lack of insurance (19.2%) or non-citizen status (23.1%) (n = 77). 82 of the 139 patients who achieved CR relapsed. After a median follow up of 16 months, five-year OS rates were 20.7% from our entire cohort of patients. **Conclusions:** In this cohort of patients treated in a safety-net system, median OS and EFS were lower than reported outcomes in the past decade. In addition, only 13.7% received HCT, one of the only curative treatments for AML. Some barriers included inability to refer to transplant center due to lack of financial support or immigration status. Addressing socioeconomic and institutional barriers to AML therapy and HCT will advance care for disadvantaged patients, thereby improving outcomes of patients AML. Research Sponsor: None.

7036

Poster Session

Clinical and molecular characteristics of patients with AML with an exceptional response to ivosidenib. *First Author: Justin M. Watts, University of Miami, Sylvester Comprehensive Cancer Center, Miami, FL*

Background: Ivosidenib (IVO) was approved based on a CR/CRh rate of 31.8% in IDH1 mutant (IDH1m) R/R AML; median duration of CR/CRh (DOR) was 8.2 months (mo). The purpose of this study is to elucidate the clinical and molecular characteristics of exceptional responders to single agent IVO. **Methods:** We analyzed all patients (pts) with IDH1m R/R AML who received IVO 500mg QD on the phase 1 dose escalation/expansion study and had a DOR of ≥ 12 mo. **Results:** Of 179 pts who received IVO 500 mg QD, 57 (31.8%) achieved a CR/CRh. Of these, 20 (35.1%) had a DOR ≥ 12 mo. After excluding 7 pts who went to HSCT, 13 (22.8% of responders, 7.3% of cohort) had DOR ≥ 12 mo (exceptional response) and 8 (14% of responders, 4.5% of cohort) had DOR > 24 mo. The 13 exceptional responders all achieved CR as best response, and median DOR was 42.6 mo. Median OS was not reached; estimated OS at 48 mo was 67.1%. Median EFS was 44.4 mo. Reasons for discontinuing treatment included relapse (n=4), adverse event unrelated to IVO (n=3), and patient (pt) decision (n=3). Three pts remain on treatment. All pts who relapsed had DOR between 1-2 years; none of the 8 pts with DOR > 2 years relapsed. Baseline characteristics are in the table. The most common co-mutations were DNMT3A, ASXL1, SRSF2, and JAK2 (3 each, 23%). Five pts (39%) had a splicing factor mutation. No pts had FLT3 or RTK pathway mutations other than JAK2. Only 1 pt with NPM1 had an exceptional response, and 1 pt had TP53 (VAF 3.6%). Six pts (46%) had an abnormal karyotype, 6 normal (46%), and 1 missing (8%). Most pts had intermediate-risk cytogenetics (10 pts, 77%), 2 poor-risk, and 1 missing. The median IDH1 VAF was 25% (range 10-50%). The median number of co-mutations was 1 (range 0-6). Having 0-1 co-mutations was associated with a longer response. Eleven pts (85%) had an IDH1 R132C mutation; 1 each (7.7%) had R132H and R132L mutations. Mutation clearance of IDH1 was noted in 8 pts (61.5%). **Conclusions:** A subset of pts with IDH1m R/R AML have prolonged CR on single agent IVO without HSCT (22.8% of CR/CRh responders) and no pts in CR for > 2 years (14% of CR/CRh responders) relapsed. A low mutational burden, lack of RTK pathway mutations and canonical AML drivers, and co-occurrence of mutations associated with clonal hematopoiesis appear to be associated with exceptional response. Clinical trial information: NCT02074839. Research Sponsor: Agios Pharmaceuticals, Inc; Institut de Recherches Internationales Servier.

Characteristic	
Age, n (%)	
<60	1 (7.7%)
60 – <75	9 (69.2%)
75 – >85	3 (23.1%)
Sex, n (%)	
M	7 (53.9%)
F	6 (46.2%)
ECOG at baseline, n (%)	
0	3 (23.1%)
1	7 (53.8%)
2	3 (23.1%)
Type of AML, n (%)	
De novo	9 (69.2%)
Secondary	4 (30.8%)
Prior intensive chemotherapy	
Y	7 (53.8%)
N	6 (46.2%)
Number of prior therapies, n (%)	
1	9 (69.2%)
2	2 (15.4%)
3	2 (15.4%)
Relapse type, n (%)	
Primary refractory	5 (38.5%)
Refractory relapse	0 (0.0%)
Untreated relapse	8 (61.5%)
Baseline bone marrow blasts, n (%)	
<20%	5 (38.5%)
20% – <50%	4 (30.8%)
>50% – <75%	4 (30.8%)
>75%	3 (23.1%)
Prior Transplant	10 (79.0%)
Y	
N	
Treatment duration	
12 – <24 months	4 (30.8%)
24 – <36 months	3 (23.1%)
36 – <48 months	1 (7.7%)
48 – <60 months	1 (7.7%)
≥ 60 months	4 (30.8%)

7038

Poster Session

Evaluation of cardiac failure and recovery in acute myelogenous leukemia. *First Author: Matthew Wu, University of Washington/Fred Hutchinson Cancer Center, Seattle, WA*

Background: Cardiac failure causes significant comorbidity and death in acute myeloid leukemia (AML) patients, with incidence estimated at 10-15% (Neuendorf N Blood Adv. 2020). We sought to describe the post-treatment cardiac experience in AML survivors including factors associated with onset, persistence, and outcome of cardiac dysfunction during and following treatment. **Methods:** 86 patients with AML or other high-grade myeloid neoplasms treated with induction chemotherapy with or without allogeneic hematopoietic cell transplant were identified at the University of Washington/Fred Hutchinson Cancer Center from 1/2000-1/2022. All patients sustained cardiac dysfunction, defined as left ventricular ejection function (LVEF) decline of 10% with absolute LVEF below 50% during chemotherapy. A multivariable analysis was performed to compare those who recovered (LVEF recovery) and those who did not (LVEF non-recovery), examining baseline health factors, disease risk (ELN 2017), time to dysfunction and recovery, most probable cause of cardiac dysfunction based on cardiologist evaluation, and goal-directed medical therapy (GDMT) use and dosage. **Results:** 48% (41 out of 86) failed to recover following LVEF decline. This cohort tended to be older, male, and had more ASCVD risk factors ($p < 0.05$). Neither the choice of chemotherapy regimen ($p = 0.43$) nor the cumulative anthracycline dose ($p = 0.44$) was significantly different between the LVEF recovery and non-recovery groups. Onset of cardiac dysfunction tended to occur later in the LVEF recovery cohort (median 72 vs. 48.5 days, $p = 0.660$). In subjects who recovered, the median time to recovery was 87 days (range 2-268 days). When chemotherapy was identified as the probable cause, it was associated with greater likelihood of eventual recovery ($p = 0.014$), whereas ischemic coronary etiology was associated with non-recovery ($p = 0.005$). Failing to recover from cardiac dysfunction correlated with shorter survival (median 229 vs 650 days, $p = 0.005$). Multivariable analysis is shown in the Table below. Importantly, the use of GDMT with higher doses of renin-angiotensin inhibitor medications (RAASi) were associated with higher probability of recovery (not shown, $p < 0.05$). **Conclusions:** The present study demonstrates cardiac recovery occurring in over half of AML patients who experienced cardiac dysfunction during their chemotherapy. Recovery was more common in patients whose cardiac dysfunction is precipitated by chemotherapy and in patients who received GDMT with aggressive use of RAASi. Since cardiac recovery was associated with improved survival, next steps include establishing a cardiac monitoring algorithm to initiate early and aggressive GDMT. Research Sponsor: None.

	Correlation value (B)	p-value
Age	-0.68	0.002*
ASCVD Risk	-0.25	0.023*
Cumulative AC dose	0.002	0.444
Heart Failure Etiology		
Chemotherapy	1.15	0.014*
Sepsis	0.268	0.467
Iatrogenic	0.223	0.739
Ischemia	-2.890	0.005*
ELN 2017 Risk	-1.384	< 0.001

7037

Poster Session

A step toward genomic equity: Mutational profiling of patients with myeloid neoplasm in the largest minority-serving hospital in metropolitan Chicago. *First Author: Maha AT Elsebaie, John H. Stroger, Jr. Hospital of Cook County, Chicago, IL*

Background: Information on genomic landscape of myeloid neoplasms comes from large studies of patients with predominantly European ancestry. Minority-serving hospitals offer unique opportunities to study ethnically diverse populations. **Methods:** In this retrospective study at the Stroger Hospital of Cook County, we included patients ≥ 18 years old with myeloid neoplasms or premalignant conditions who underwent mutational profiling via next generation sequencing (NGS). We utilized two commercially available myeloid panels: “FoundationOneHeme” (406 gene panel) and “Tempus” (648 gene panel). Patient demographics were collected, including self-reported race/ethnicity. We compared data distribution using Kruskal-Wallis, Pearson’s χ^2 , or Fisher’s exact tests. Overall survival (OS) probabilities were compared using the log-rank test. **Results:** Ninety-four patients underwent NGS between 04/01/2020 and 12/31/2022, including 45 females (47.9%). 38 patients (40.4%) identified as Black, 28 (29.8%) as White, and 28 (29.8%) as Other (10.6% Asian, 9.6% Mexican/South American, and 9.6% undetermined). 30 patients (32%) identified as Hispanic and 64 (68%) as Non-Hispanic. Diagnoses included Acute myeloid leukemia (AML, 32%), Myelodysplastic syndromes (MDS, 13%), MDS/MPN overlap syndrome (7%), and Clonal Hematopoiesis of Indeterminate Potential (7%). Eighty-eight patients had at least one pathogenic variant and harbored 259 mutations in 74 genes. Commonly mutated genes were ASXL1 (23%), JAK2 (17%), DNMT3A (14%), and TET2 (13%). Non-White patients were more likely to have IDH2 mutations (5% Black vs. 0% White vs. 14% Other races, $p = 0.011$). Mutation count didn’t differ between racial $p = 0.525$ or ethnic groups $p = 0.345$. AML & MDS patients were more likely to have TET2, RUNX1, TP53, and IDH2 mutations. In addition, 24% of AML & MDS patients had mutated ASXL1. TET2, SRSF2, and RUNX1 mutations were common among MDS/MPN patients (Table). AML & MDS patients had poor OS, but OS didn’t differ between racial/ethnic groups. **Conclusions:** Premalignant mutations (e.g., ASXL1, TET2) predominated in our patients and tended to co-occur, increasing the overall mutational burden. Non-White patients were more likely to have IDH2 mutations. Adverse markers were common among AML & MDS patients, likely contributing to their dismal survival. Studies inclusive of ethnically diverse patients are needed to accurately translate genetic findings into clinical practice. This report from a large, minority-serving hospital represents a step toward promoting genomic and healthcare equity. Research Sponsor: None.

Distribution of mutations by diagnosis.				
	AML & MDS	MDS/MPN	MPN	p-value
ASXL1 ^{Mut}	10	3	8	0.483
TET2 ^{Mut}	5	3	3	0.040
SRSF2 ^{Mut}	5	5	1	0.001
RUNX1 ^{Mut}	6	2	0	0.009
TP53 ^{Mut}	8	0	0	0.011
IDH2 ^{Mut}	6	0	0	0.035
FLT3 ^{Mut}	5	0	0	0.131

7039

Poster Session

Analysis of short-term efficacy and safety of mitoxantrone hydrochloride liposome regimen therapy in adult acute myeloid leukemia. *First Author: Jun Ma, Department of Hematology & Oncology, Harbin Institute of Hematology & Oncology, Harbin, China*

Background: Acute myeloid leukemia (AML) is highly heterogeneous, and more than half of patients (pts) will experience refractory or relapse, with poor prognosis. Currently, chemotherapy and hematopoietic stem cell transplantation (HSCT) are the main treatments for AML. Mitoxantrone is a synthetic anthracenedione anti-cancer drug that is effective in lymphoma, leukemia, and other solid tumors. Mitoxantrone hydrochloride liposome (PLM60) is the first approved mitoxantrone nano-drug, which has shown favorable pharmacokinetic characteristics and significantly prolong the survival time of animals compared with the same dose of mitoxantrone (Li 2008). However, there is still a lack of systematic reports about the real-world application of PLM60 in AML. **Methods:** We performed a multicenter retrospective analysis of 82 pts with newly diagnosed AML and relapsed/refractory (R/R) AML, who received at least one cycle of PLM60 regimen between January 2022 and November 2022. Pts aged 18 years and above with confirmed diagnosis of AML according to the 2016-revised WHO criteria were eligible for inclusion, except acute promyelocytic leukemia (APL). The median dose of PLM60 in the regimen was 20.0 (range 10.3–31.6) mg/m². Efficacy was assessed by composite complete remission (CRc) rate and overall response rate (ORR), and logistic regression analysis was performed to analyze factors affecting the curative effect. Adverse events were assessed by Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. **Results:** 82 pts were enrolled with a median age of 50.5 (range 20-83) years. There were 71 cases of de novo AML and 11 cases of secondary AML. Targeted sequencing was performed on 86.6% of pts (71/82). FLT3 was the most commonly mutated gene found in 22.5% (16/71), followed by ASXL1 mutated in 12.7%, NPM1 in 11.3%, and TP53 in 11.3%. 4.9% (4/82) of pts underwent HSCT. Among the 25 newly diagnosed pts, CRc rate was 72.0% (18/25) and ORR was 92.0% (23/25). Among the 57 R/R pts, CRc rate was 24.6% (14/57) and ORR was 40.4% (23/57). The courses of induction failure (OR= 16.617, P= 0.026), and the duration of the first complete remission (CR1) (OR= 20.647, P= 0.007) were independent influencing factors of the efficacy. Common grade 3/4 AEs included decreased neutrophil count (84.1%), thrombocytopenia (76.8%), anemia (73.2%), febrile neutropenia (47.6%), pulmonary infection (11.0%) and upper respiratory tract infection (2.4%). The overall safety was acceptable and controllable. **Conclusions:** The PLM60 regimen had an encouraging efficacy and showed a manageable safety profile with the most adverse events being hematologic toxicities. Research Sponsor: CSPC Ouyi Pharmaceutical Co., Ltd.

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Poster Session

Association of intensive chemotherapy with the rate of pathogenic driver mutation clearance in acute myeloid leukemia. *First Author: Ruby Maini, Ochsner Clinic Foundation, New Orleans, LA*

Background: Identification of pathogenic molecular mutations (PMM) as drivers in the development of acute myeloid leukemia (AML) and in initial prognostic assessment has become clinical practice. Persistence of PMM in a morphologic leukemia free state is correlated with high risk of relapse and poor prognosis. Therapy for induction of remission and elimination of all markers of residual disease remains controversial, especially with the addition of venetoclax to hypomethylating agents (HMA). Here we compare the rates of PMM clearance between intensive chemotherapy (IC) and less intensive chemotherapy (LIC) regimens. Secondary, we assessed differences in ethnicity between white and black patients (pts). **Methods:** Retrospective study from a leukemia treatment center in Louisiana. De-identified pt records from 2018-2022 assessed for demographics: race, age, sex and diagnosis: AML, ELN 2017 staging, and mortality by IC vs. LIC regimen. IC included anthracycline and cytarabine containing regimens. LIC included HMA, with or without venetoclax. Chi-Squared analysis preformed, threshold for significance at $p < 0.05$. **Results:** 408 pts with non-M3 AML who underwent treatment, 180(44.1%) were female, 91(22.3%) were black, 303(74.3%) were white, 273(66.9%) received IC while 135(33.1%) received LIC. NGS found a total of 280 pre-treatment PMM. Among 217 pts who received treatment, the rate of mutation clearance with IC was 55.2%, compared with 50.8% LIC ($p = 0.55$). Stratifying by race, black pts had a twofold mutation clearance compared to white pts OR = 1.76, 95% CI (0.91 – 3.44). Similar proportions of pts received LIC vs IC among both white (74.1% vs 74.4%) and black (22.2% vs 22.3%). There was no statistically significant difference for overall survival on chemotherapy regimen intensity ($p = 0.1991$), race ($p = 0.2736$), or gender ($p = 0.6912$). **Conclusions:** In our study, PMM clearance was similar between IC and LIC inductions. Although these findings are from a single center, the ability to clear driver mutations at a similar rate to IC may offer a significant advantage of LIC with venetoclax. Mutation clearance is often used as a surrogate marker for residual disease, it may be reasonably inferred that these regimens serve as suitable induction regimens for pts who may be considered for allogeneic stem cell transplantation. Blacks make up a greater proportion of the population in Louisiana (~33%) as compared to the national average (~13%). Often underrepresented in prospective clinical trials, blacks made up 22.7% of subjects providing increased insight to clinical responses. No difference in mortality based on race and a trend toward greater mutational clearance in blacks. Emphasizing the importance of standardizing care in treatment centers and the need for greater representation in prospective clinical trials to understand better how differences in race may impact treatment outcomes. Research Sponsor: None.

7042

Poster Session

Comparison of characteristics and prognostic impact of *FUS-ERG* and *AML1-MTG16* fusion genes in adult AML patients: A retrospective study from 1988 to 2022 with a medical database. *First Author: Ziyue Zhou, Zhejiang University, Hangzhou, Zhejiang, China*

Background: *AML1-MTG16* and *FUS-ERG* are two rare fusion genes in acute myeloid leukemia (AML). Their clinical characteristics and factors influencing prognosis have been summarized in a cohort of pediatric patients, but no systematic review is approached in adult. **Methods:** We retrospectively analyzed the clinical data of adult AML patients with *AML1-MTG16* or *FUS-ERG* fusion genes, who were reported on Mitelman Database, PubMed and China national knowledge infrastructure (CNKI) from 1988 to 2022 or have received treatment in the First Affiliated Hospital, Zhejiang University School of Medical, and compared them with patients with *RUNX1-RUNX1T1*, exploring their clinical features and prognosis. **Results:** 314 patients were totally included for analysis. In comparison of *RUNX1-RUNX1T1* group ($n = 209$), *FUS-ERG*-positive patients ($n = 108$) significantly exhibited a younger onset age (34.5y vs. 41y), higher WBC count ($16.7 \times 10^9/L$ vs. $10.4 \times 10^9/L$), higher recurrence rate (61.8% vs. 30.4%), and a worse response to chemotherapy (complete remission rate: 71.6% vs. 91.8%), while patients with *AML1-MTG16* ($n = 24$) presented primarily as the secondary AML (83.3%) with a significantly elder age (56y vs. 41y). The *FUS-ERG* patients had a worse median overall survival (OS) of 13 months (95%CI: 11.6-14.4, $P < 0.01$) and a worse median disease free survival (DFS) of 7.5 months (95%CI: 6.5-8.5, $P < 0.05$) than control group, which also occurred in those had *AML1-MTG16* gene with a median OS of 18.5 months (95%CI: 12.4-24.6, $P < 0.01$) and a median DFS of 14 months (95%CI: 3.7-24.3, $P = 0.10$). As shown in the table below, CR after induction chemotherapy, hematopoietic stem cell transplantation (HSCT), trisomy, monosomy and age of patients were associated with the prognosis of *FUS-ERG* group. Unlike pediatric patients, the adult *AML1-MTG16* patients did not perform a better outcome (OS: HR = 0.90, $P = 0.83$; DFS: HR = 0.54, $P = 0.34$) in contrast with *FUS-ERG* patients. **Conclusions:** The retrospective study summarized the clinical characteristics of *AML1-MTG16* and *FUS-ERG*, identifying their distinctions on multiple aspects such as prior disease, recurrence rate, response to chemotherapy and cytogenetics. *AML1-MTG16* exhibited extremely bad prognosis like *FUS-ERG* in adult population, which varied from the results in pediatric cohort. Several factors including age, CR after induction chemotherapy, HSCT, trisomy and monosomy were relevant to the prognosis of *FUS-ERG*. Research Sponsor: Natural Science Foundation of Zhejiang Province, China (Y23H080018); Special fund for international cooperation of Zhejiang University (2-2050205-22-688(10)); Key research and development program of Zhejiang Province, China (No. 2022C03005).

Multivariate analysis of survival parameters in *FUS-ERG* group.

Prognostic variable	OS		DFS	
	HR [95%CI]	P	HR [95%CI]	P
Age > 60	3.67 [1.42-9.46]	0.01	3.77 [0.78-18.28]	0.10
CR attain	0.28 [0.14-0.59]	< 0.01	0.87 [0.33-2.28]	0.78
HSCT	0.18 [0.09-0.36]	< 0.01	0.32 [0.14-0.75]	0.01
Monosomy	2.26 [1.04-4.90]	0.04	3.15 [0.87-11.42]	0.08
Trisomy	2.18 [1.04-4.60]	0.04	1.05 [0.50-2.23]	0.89

7041

Poster Session

Predictors of early port infection in adult patients with acute myeloid leukemia. *First Author: Hyndavi Kandala, University of Alabama at Birmingham, Birmingham, AL*

Background: The most concerning complications following port placement are infection and thrombosis. Early infections in patients with hematological malignancies are reported at 2-5% post-placement. However, data specific to patients with Acute Myeloid Leukemia (AML) is sparse. Here, we report infection rates within 30 days of placement and factors associated with increased risk of infection in patients with AML. **Methods:** We retrospectively reviewed charts of patients ≥ 18 years with AML who had ports placed between January 2019 to September 2022 at our institution. Baseline and peri-placement characteristics were collected. Port infection was defined as at least one of the following: 1) site infection, 2) gram-positive bacteremia, or 3) bacteremia that was documented by Infectious Disease consultants as a port source. Infections were classified as very early (< 7 days) and early (7-30 days). Variables were compared in each group by using Pearson's chi-square test. **Results:** A total of 101 ports were placed in 98 patients with AML. The median age at placement was 64 years and 58% of patients were female. A total of 14 (13.9%) port infections were identified; 5 (35.7%) were very early and 9 (64.2%) were early infections. The median time to infection was 15 days (range 1-25 days). 5 (35.7%) patients had site-only infections, 6 (42.8%) had isolated bacteremia, and 3 (21.4%) had both. 13 (93%) patients were hospitalized, and 1 patient died from infectious complications. 8 (57%) of infected ports were removed. 57 patients were on regimen-specific prophylactic antibiotics at the time of placement, of whom 12 developed an infection (21%). The infection rate was 10% vs 23% ($p = 0.1$) in patients with ANC $\geq 500/\mu L$ and ANC $< 500/\mu L$ respectively at 1 week after port placement, with no difference based on ANC at the time of placement. The infection rate was 21.9% vs. 6.5% in patients with platelets $< 100 \times 10^3/\mu L$ and $\geq 100 \times 10^3/\mu L$ ($p = 0.01$) at the time of placement; 28% vs. 8.6% in patients with albumin < 3.5 g/L and ≥ 3.5 g/L ($p = 0.02$). The infection rate was numerically higher in Venetoclax-based regimens (19%) compared with cytarabine-based regimens (8%) ($p = 0.06$). Rates of infection were similar among inpatient and outpatient placements (14%). 5/53 patients (9.4%) were in complete remission (CR), 3/29 (10.3%) of newly diagnosed, and 6/19 (31.5%) relapsed/refractory (R/R) AML patients developed an infection ($p = 0.02$). **Conclusions:** In our single-institution study, a higher-than-expected port infection rate of 14% was seen in patients with AML. Platelets $\leq 100 \times 10^3/\mu L$ and albumin < 3.5 g/L at the time of placement, Venetoclax-based regimens, and R/R state were associated with significantly higher rates of infection. Interestingly ANC at the time of placement was not associated with an increased infection rate. Strategies to prevent early infections in these high-risk patients are much needed. Research Sponsor: None.

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Poster Session

An analysis of a first-in-human study of NEXI-001 donor-derived antigen-specific CD8+ T-cell treatment of relapsed AML after allogeneic hematopoietic cell transplantation (HCT). *First Author: Monzr M. Al Malki, City of Hope, Duarte, CA*

Background: NEXI-001 is a non-genetically engineered donor-derived cellular therapy product consisting of $> 90\%$ CD3+/CD4- T cells that includes significant numbers of CD8+ T cells that are of early memory subtypes and target 5 specific HLA A2.01-restricted peptides from the WT1, PRAME, and Cyclin A1 antigens that are commonly expressed on AML blasts and leukemic stem cells. **Methods:** AML patients who relapse after allogeneic HCT have a high unmet medical need. These patients have a poor prognosis (2-year survival rate $< 10\%$) and few treatment options. Currently 11 patients have completed the 4-week dose-limiting toxicity (DLT) period in the 3+3 design of the dose-escalation stage of this NEXI-001 phase I trial. The following doses of NEXI-001 T cells were administered during the DLT period: Cohort 1, 4 patients received an infusion of 50M (million) to 100M T cells; Cohort 2, 4 patients received an infusion of 200M T cells; and Cohort 3, 3 patients received infusions of 200M T cells on Days 1, 8, and 15. **Results:** The NEXI-001 antigen-specific T cells were found to persist and expand in peripheral blood, traffic to bone marrow, and maintain a less differentiated immunophenotype in blood and bone marrow for ≥ 3 months. No DLTs have occurred. NEXI-001-related adverse events have included grade 2 cytokine release syndrome (2), grade 1 diarrhea (2), grade 2 orthostatic hypotension (1), and a grade 3 GVHD of the gut in week 3 of the first NEXI-001 cycle that resolved within 72 hours with corticosteroid treatment. Clinical activity consisting of the following have occurred in patients within each cohort; neutrophil and platelet count recovery resulting in decreased transfusions and decreases in blasts in peripheral blood and bone marrow. A patient who achieved an MRD- remission following bridging therapy and then was administered a single infusion of 200M NEXI-001 T cells has continued to remain in CR at 6 months of follow-up. A patient in Cohort 3 who relapsed after alloHCT with extramedullary disease manifested by a pleural effusion has achieved a 45% decrease of the symptomatic moderate effusion at baseline to an asymptomatic small effusion after the administration of three 200M NEXI-001 T cells on Days 1, 8, and 15 of the first 4-week cycle. The patient remains asymptomatic at 3 months of follow-up with no detectable AML blasts in peripheral blood or bone marrow and a stable small effusion. A PET scan of the chest showed no areas of increased uptake. **Conclusions:** Early results indicate that the antigen-specific NEXI-001 T cells have the potential to enhance GvL effects and is tolerated with easily manageable side effects. Greater clinical activity has been observed with increased doses of the NEXI-001 T cells. The trial remains ongoing, and the data support an Expansion Cohort of the study that will allow for a more complete assessment of clinical activity. Clinical trial information: NCT04284228. Research Sponsor: NexImmune, Inc.

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Poster Session

Real-world (RW) use of venetoclax (VEN) in patients (pts) with acute myeloid leukemia (AML) in a US RWE database (COTA). *First Author: Amer Methqal Zeidan, Department of Internal Medicine, Yale School of Medicine and Yale Cancer Center, Yale University, New Haven, CT*

Background: VEN + hypomethylating agents (HMAs)/low-dose cytarabine was approved for the treatment (tx) of pts with AML who are ≥ 75 y or ineligible for intensive chemotherapy (CT) in 11/2018. To understand the use, safety, and efficacy of VEN in clinical practice, the COTA AML database, using pt-level curated electronic health record data from centers across the US, was analyzed. **Methods:** This is a retrospective, descriptive analysis of deidentified secondary data from the COTA AML database in the US. Data was abstracted for adults diagnosed with AML who initiated first-line (1L) tx on or after 01/01/2018 and received ≥ 1 VEN tx at any point. Pts with no diagnosis date or with concurrent primary malignancies were excluded. Follow-up was until the last recorded event (last visit or death). The study period for this analysis was 01/2018 to 09/2022. **Results:** Of 3836 pts with AML in the database, 1163 pts initiated 1L tx in or after 2018; of these, 636 received ≥ 1 VEN tx at any point. See Table for baseline demographic data. Most VEN-treated pts were seen by community healthcare providers (407/636, 64%). Genetic/molecular data were limited. Of the most frequently tested mutations, the most common were *TP53* (129/461, 28%), *RUNX1* (109/444, 25%), *TET2* (101/414, 24%), *ASXL1* (92/417, 22%), and *DNMT3A* (91/424, 22%). Of pts who received VEN, 47% (299/636) received 1L VEN, and the majority (269/636, 42%) received VEN + HMAs. For pts with tx prior to VEN (pretreated), 262/337 (78%) were previously treated with CT. 1L pts were more often treated in community centers than pretreated pts (73% vs 56%), had more comorbidities (56% vs 40%), and *TP53* positivity (19% vs 10%) at baseline. Of 284 VEN-treated pts with available response data, 180 (63%) had a complete response (CR). Median OS (mOS) of VEN-treated pts was 14.4 mo from 1L tx initiation (de novo AML, 17 mo; secondary AML, 14 mo). mOS from diagnosis was 14 mo for newly diagnosed and 18 mo for pretreated pts. Toxicity was the main cause of dose reduction and discontinuation. Median duration of VEN tx was 78 d. Dose reduction was reported in ~30% of VEN-treated pts. Of VEN-treated pts, 53% (338/636) discontinued at least 1 VEN regimen, with a median time to discontinuation of 49.5 d. **Conclusions:** This study provides an overview of the RW use of VEN in pts with AML in the US since its approval in 11/2018. Despite the study period starting earlier than VEN approval, almost half of pts with AML who initiated tx after 2018 received 1L VEN. The RW CR rate in VEN-treated pts with available data was 63%, but over half of VEN-treated pts had VEN tx discontinuation. Research Sponsor: Novartis Pharmaceuticals Corporation.

Characteristic	All pts N=3836	VEN-treated N=636
Male, n (%)	2045 (53)	347 (55)
Age at diagnosis, y, median (range)	65 (52-74)	71 (62-78)
Comorbidity, n (%)	1439 (38)	303 (48)
Initiated 1L tx on or after 2018, n (%)	1163 (30)	636 (100)
AML type, n (%)		
De novo	1459 (38)	209 (33)
Secondary	1176 (31)	234 (37)
Not specified	1201 (31)	193 (30)

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Poster Session

Capped F10, a novel DNA directed fluoropyrimidine, in TP53 mutated acute myeloid leukemia (AML). *First Author: Timothy S. Pardee, Comprehensive Cancer Center of Atrium Health Wake Forest Baptist, Winston Salem, NC*

Background: Acute myeloid leukemia (AML) is an aggressive malignancy characterized by resistance to treatment and poor outcomes. One of the most devastating mutations in AML involves loss of the tumor suppressor TP53. AML harboring this loss carries a dismal prognosis and there is a clear need for new approaches. **Methods:** To identify new therapeutics, a TP53 null and WT isogenic cell line pair was generated using CRISPR/CAS9 using a murine AML cell line. Clonal isolates were obtained and loss of detectable TP53 was confirmed by Western Blotting. A high throughput screen of currently FDA approved anticancer agents was performed. **Results:** When agents were ranked by equal cytotoxicity against TP53 null and WT AML cells 20% (6/30) of the top 30 agents targeted the folate/thymidylate synthase axis. This suggests that thymidylate synthase (TS) is a vulnerability in TP53 null AML cells. To confirm TS as a target in TP53 null AML an additional murine AML TP53 null/WT cell line pair was generated using CRISPR/CAS9. When these cell lines were treated with doxorubicin the TP53 null cells were significantly more resistant ($p \leq 0.001$ at 10nM). Capped F10 (CF10) is a second generation fluoropyrimidine oligonucleotide that has been shown to be a highly potent inhibitor of TS. In contrast to doxorubicin, CF10 treatment resulted in significant cell death when dosed in the low picomolar range with minimal differences between the null and WT cell lines ($p = 0.31$ at 50pM). To extend this result TP53 WT or null cells were injected into syngeneic recipients and upon engraftment mice were treated with CF10 at 300mg/kg twice weekly. CF10 provided a significant survival benefit in the TP53 null but not WT injected mice consistent with CF10 having activity against TP53 null AML ($p = 0.035$ vs 0.13). To confirm a TP53 independent mechanism, competition assays were performed with CAS9 expressing AML cells partially infected with a vector expressing an sgRNA targeting TP53 and a GFP reporter. When the mixed population was treated with the IC₉₀ concentration of 5-fluorouracil there was a highly significant increase in GFP+ cells indicating a TP53 mediated cell death ($p < 0.001$). In contrast when cells were treated with the IC₉₀ concentration of CF10 there was a non-significant increase in GFP+ population ($p = 0.074$) consistent with a mainly TP53 independent mechanism. Fluoropyrimidine based therapy can be myelo-suppressive especially in patients with low dihydropyrimidine dehydrogenase (DPD) activity. To assess the tolerability of CF10, healthy WAG/RAJ rats were treated with the DPD inhibitor ethynyl uracil at 2mg/kg alone or in combination with either 141 mg/kg CF10 or the molar equivalent of 50 mg/kg 5-fluorouracil (5-FU) and weight determined. In contrast to 5-FU, CF10 treated animals did not have a significant change in weight compared to controls. **Conclusions:** Taken together these data suggest that CF10 is a promising new agent for TP53 null AML. Research Sponsor: Comprehensive Cancer Center of Atrium Health Wake Forest Baptist.

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Poster Session

Preliminary results of a phase 1, first-in-human study of INA03, an anti-CD71 antibody-drug conjugate, in patients with relapsed or refractory (R/R) acute leukemias. *First Author: Sylvain Garciaz, Institut Paoli-Calmettes, Aix-Marseille University, Marseille, France*

Background: R/R acute leukemias (AL) represent major therapeutic challenges. Several reports have highlighted the role of iron metabolism in various proliferative tumor models including AL including the over-expression of the transferrin receptor (TfR1/CD71). Our strategy is thus to harness CD71 overexpression to specifically target cytotoxic agents to leukemic cells. INA03 is an antibody drug conjugate (ADC) constituted of a humanized monoclonal IgG₄ against CD71 and the microtubule disrupting agent monomethyl auristatin E (MMAE). We herein report the preliminary safety and efficacy data of INA03 from a phase 1/2 trial in patients (pts) with R/R AL (NCT03957915). **Methods:** INA03 is given as 30 minutes IV infusion on days 1 (Loading dose (LD)) followed by maintenance injections on D15 for cycle 1 and on D1 and D15 of cycle 2 and beyond. Eligibility criteria are: R/R AL after at least one line of treatment including high dose chemotherapy and/or Vidaza and Venetoclax, AlloSCT > 18y, with FEV₂ > 50%, Creatinine Clearance > 30ml/min, normal liver function, ECOG < 2. The study design is based on a continuous reassessment method and includes 2 parts: a LD Titration study (Part 1, completed), followed by a Dose Escalation Part 2. During Part 1, sequential cohorts of 2 pts were included to receive ascending LD of INA03 followed by subsequent fixed dose of INA03 to deal with a potential sink effect related to the high expression of CD71 in normal erythroblasts. During Part 2, sequential cohorts of 3 pts received escalating doses of INA03 Q2 weeks in 28-day cycles. The objectives were to establish the MTD for subsequent administration and both safety/tolerability and anti-leukemic activity. **Results:** With a cutoff date of January 18, 2023, 22 pts across 8 cohorts were included in the study. The median age was 73 (range: 39 – 83), 20 (91%) pts had AML and two (9%) had ALL. Three (13.6%) pts had a prior allo-SCT and 12 (54.5%) had prior VEN exposure. Pts received escalating doses of INA03 of 0.02 mg/kg to 2 mg/kg. MMAE pharmacokinetics (PK) appears dose-proportional with a small accumulation after repeated IV, while INA03 PK exhibits target-mediated drug disposition without accumulation. No DLT was observed among the 18 DLT-evaluable pts, up to the highest dose of 2 mg/kg. No grade 2-4 TEAEs were observed. One related grade 1 TEAE (hyperkalemia/phosphatemia) was reported. Transient decrease of reticulocyte count and erythroblasts percentage were observed at 0.5 mg/kg and above. Blasts reductions were seen in 3/18 evaluable pts at dose > 1 mg/kg including two partial responses. **Conclusions:** INA03 is well tolerated up to the dose of 2 mg/kg with some efficacy signals in R/R AL. The trial continues to accrue patients. Clinical trial information: NCT03957915. Research Sponsor: Institut Paoli Calmettes; Inatherys.

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Poster Session

Superior outcomes after allogeneic stem cell transplantation (SCT) among patients (Pts) ≥ 60 years (yrs) treated with cladribine (CLAD), low dose cytarabine (LDAC) plus venetoclax (Ven) for newly diagnosed acute myeloid leukemia (AML). *First Author: Jayastu Senapati, Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: CLAD/LDAC/VEN alternating with AZA-VEN has shown promising outcomes in older pts with AML (*Kadia, JCO Nov 2022*). Improved disease control and preserved performance status achieved with CLAD/LDAC/VEN treatment, may translate into superior post-SCT outcomes. **Methods:** We compared outcomes of pts ≥ 60 yrs of age treated on the phase II study of CLAD-LDAC-VEN who underwent SCT in 1st remission (CR1) to a retrospective cohort of pts ≥ 60 yrs treated with hypomethylating agent (HMA)-VEN based or intensive (INT) therapy who underwent SCT in CR1 between 2013-2022. Relapse free survival (RFS) was from response to relapse/death & overall survival (OS) from start of therapy to death. **Results:** 35 pts treated with CLAD-LDAC-VEN were compared to 42 pts treated with INT & 40 pts with HMA-VEN therapy for remission induction prior to SCT at our center (Table). The median age of pts in the low-intensity arms were similar (68 yrs), but lower on the INT arm (62 yrs). More pts post INT therapy received a myeloablative conditioning (MAC). At a median follow up of 17+ months (m) for CLAD-LDAC-VEN arm, 59 m for INT arm, and 30 m for HMA arm, the median RFS (NR vs. 50 m vs. 20 m respectively, $p < 0.01$) and OS (NR vs. 58 m vs. 32 m respectively, $p < 0.01$) was superior for the CLAD-LDAC-VEN arm. 3-yr cumulative incidence of relapse & NRM (as competing events) were both significantly lower with CLAD-LDAC-VEN (4% and 7%) compared to INT (17% and 23%) or HMA-VEN (41% and 27%) therapy. **Conclusions:** Older pts with AML proceeding to SCT after CLAD-LDAC-VEN therapy had significantly improved survival, characterized by significantly lower rates of NRM and relapse compared to HMA-VEN or INT therapies. Larger studies and longer follow up is needed to confirm its benefit. Research Sponsor: None.

Baseline parameters	CLAD-LDAC-VEN	INT	HMA-VEN
N	35	42	40
Median age (yrs)	68 (60-73)	62 (60-72)	68 (60-77)
	25 (71)	10 (24)	30 (75)
WBC ($\times 10^9/L$)	1.9 (0.6-22.5)	3.0 (0.4-107)	2.6 (0.3-131)
Platelet ($\times 10^9/L$)	49 (16-184)	50 (8-1069)	44 (10-242)
BM blasts (%)	34 (6-68)	52 (14-90)	42 (9-88)
Genomics			
CTG	4 (11)	10/38 (26)	11/30 (27)
Adverse	21 (60)	15/38 (39)	15/30 (50)
Diploid	0	2/38 (5)	0
CBF			
Mutations			
ASXL1	8 (23)	5 (12)	3 (8)
IDH	12 (34)	14 (33)	7 (18)
FLT3 (ITD $\pm$ TKD)	4 (11)	12 (29)	8 (20)
NPM1	11 (31)	11 (26)	6 (15)
RUNX1	5 (14)	3 (7)	7 (18)
TP53	4 (11)	4 (10)	8 (20)
Favorable	9 (26)	10/38 (26)	5/32 (16)
Intermediate	8 (23)	12/38 (32)	8/32 (25)
Adverse	18 (51)	16/38 (42)	19/32 (59)
Sec-AML	6 (17)	2 (5)	12 (30)
Best response	2 nd treated	0	0
	CR/CRi	35 (100)	42 (100)
	MRO negative	30 (86)	26 (62)
Time to SCT (m)	4.2 (2.5-11)	4.1 (3.0-16.8)	4.9 (2.2-30)
SCT details			
MAC			
Donor	10 (29)	14 (33)	7 (18)
MUD	19 (54)	21 (50)	26 (64)
Haplo	6 (17)	7 (17)	7 (18)
GVHD			
Acute	12 (34)	28 (67)	26 (64)
Chronic	7 (20)	12 (29)	5 (12)
Post SCT maintenance	12 (34)	7 (17)	13 (32)

7048

Poster Session

Treatment outcomes in adults with newly diagnosed B-cell acute lymphoblastic leukemia: A comparison between pediatric-inspired regimens and HyperCVAD at a Hispanic-serving cancer center. *First Author: Shawn Patrick Griffin, Department of Clinical Pharmacy Practice, School of Pharmacy & Pharmaceutical Sciences, University of California, Irvine, Irvine, CA*

Background: It is unknown if HyperCVAD is more favorable than pediatric-inspired regimens (PIRs) among adult Hispanic patients with newly diagnosed B-cell acute lymphoblastic leukemia. This analysis aims to determine the interaction of Hispanic ethnicity and treatment regimen on outcomes. **Methods:** Records of adults (≥ 18 years) treated with a PIR or HyperCVAD from January 2011 to November 2022 at our institution were reviewed. Patients were excluded if they received treatment modifications in a clinical trial or were lost to follow-up prior to 6 months. The primary endpoint was event-free survival (EFS) comprised of relapse, death, secondary malignancy, or failure to achieve complete remission. Secondary endpoints included overall survival (OS). Ph+ disease was not grouped into the poor-risk category. **Results:** 100 patients were included. Median age was 39 years, 57% were male, and 61% self-identified as Hispanic. 48 were included in the PIR and 52 in the HyperCVAD groups. 37 in the PIR group received CALGB 10403. There was no difference in race, ethnicity, rituximab use, WBC, LDH, bone marrow blast %, presence of CNS disease at diagnosis, or poor-risk genetics (Table) between the PIR and HyperCVAD groups. However, a lower rate of Ph+ disease (8.3% vs 58%) and younger median age (31 years vs 49 years) was observed in the PIR group. Allogeneic stem cell transplantation (ASCT) was pursued in 48% of PIR and 37% of HyperCVAD-treated patients. EFS at 5-years was lower among patients receiving a PIR compared to HyperCVAD (28% vs 41%; hazard ratio [HR], 1.89; $P = .022$). After censoring for ASCT there was no change ($P = .03$). Treatment group was the only significant predictor for EFS although a treatment-by-subgroup interaction ($P < .10$) with Hispanic ethnicity was found. OS at 5-years was 61% in PIR and 64% in HyperCVAD-treated patients (HR, 1.54; $P = .25$). In multivariable Cox regression analysis, Hispanic ethnicity (HR, 2.56; $P = .041$) and male sex (HR, 2.62; $P = .027$) were predictors for worse OS. Hispanic patients demonstrated worse EFS with a PIR compared to HyperCVAD (HR, 2.52; $P = .008$), which remained significant when evaluating only Ph- patients (HR, 2.20; $P = .048$). Non-Hispanics did not experience the same difference in EFS (HR, 0.88; $P = .81$). **Conclusions:** Treatment with a PIR resulted in worse EFS over HyperCVAD in adult Hispanic ALL patients. Future studies focusing on regimen intensity, adherence, and toxicities are needed to explore potential causes for this disparity. Research Sponsor: None.

	PIR (n = 48)	HyperCVAD (n = 52)
Poor-risk genetics, No. (%)	18 (38)	16 (31)
Hypodiploidy (< 44 chromosomes)	0	1 (1.9)
Complex karyotype	7 (15)	10 (19)
Ph-Like (CRLF2 mutation)	7 (15)	4 (7.7)
del(17p) (TP53 mutation)	1	1 (1.9)
KMT2A/MLL-rearrangement (t(4;11))	5 (10)	2 (3.8)
t(6;14q32)/IGH translocation	3 (6.3)	1 (1.9)
CDKN2A/B mutations	3 (6.3)	4 (7.7)

7050

Poster Session

Early in vivo generation of V γ 9V δ 2 T-cells after haploidentical stem cell transplant with post-transplant cyclophosphamide: Updated results of a monocentric phase 1 study. *First Author: Maxime Jullien, CHU de Nantes, Service d'hématologie Clinique, Nantes, France*

Background: The presence of donor V γ 9V δ 2 T-cells after haploidentical hematopoietic stem cell transplant (haplo-HSCT) has been associated with improved disease-free survival. These cells, that kill tumor cells in a non-MHC restricted manner and do not induce graft-versus-host disease (GVHD) can be generated by stimulation with bisphosphonate zoledronic acid (ZA), in combination with interleukin-2 (IL-2). **Methods:** A prospective monocentric phase 1 dose-escalating study aimed at demonstrating the possibility to generate V γ 9V δ 2 T-cells in vivo after haplo-HSCT with post-transplant cyclophosphamide (PTCY). A 3x3 protocol was designed to determine the maximum tolerated dose (MTD) of early administration of increasing low-doses of IL-2 in combination with a fixed dose of ZA, starting the first Monday after day+15 post-transplant. A single dose of 4 mg IV ZA was administered, followed, by subcutaneous injections of IL-2, 5 days/week, for 4 consecutive weeks. Three IL-2 doses were tested: 2, 4 and 6 million U/infusion. Main inclusion criteria were patients (pts) between 18-70 years old with a hematological disease eligible for haplo-SCT using a Baltimore-based conditioning, no HLA-matched sibling or unrelated donor, no contraindication to ZA nor IL-2 and informed consent. MTD was defined by the dose just below that which yielded 2/3 or 2/6 dose limiting toxicities (DLT), including severe or recurrent acute GVHD. V γ 9V δ 2 T-cells monitoring was performed in multiparameter flow cytometry on blood samples collected before conditioning, on the day of the first ZA and IL-2 injection, once a week+3 for 4 weeks and at day +70 post-graft. The protocol was registered at ClinicalTrials.gov as NCT03862833. **Results:** Twenty-six pts were included between April 2019 and September 2022 (including 7 controls). Three pts withdrew their consents in the experimental group, and 16 pts were treated with ZA and IL-2 (level 1 n = 7 including 1 not evaluable for DLT, level 2 n = 3, level 3 n = 6). First injections occurred at a median of 20 days after Day 0 (range: 17-21). One, 0 and 1 DLT and 4, 2, 2 acute GVHD (all grade II-III) were documented, and MTD was not reached. V γ 9V δ 2 T cells were clearly detectable in both controls and treated pts before conditioning. The median highest value (0.6x10⁶/L, range: 0.0-3.2) was observed at a median of 12 days (8-12) after first infusion of ZA+IL-2. A significantly higher proportion of V γ 9V δ 2 T cells was observed at days +22 and +29 in treated pts compared to controls. At the date of the submission, 3 relapse/progression occurred in treated pts, and 10 are alive in CR. Median OS is not reached. **Conclusions:** Early in vivo generation of V γ 9V δ 2 T cells is possible after haplo-SCT with PTCY by using a combination of ZA and repeated IL-2 infusions. The DMT has not been reached. This study lays the groundwork for future phase 2/3 studies. Clinical trial information: NCT03862833. Research Sponsor: Nantes University Hospital (public funds).

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Poster Session

Effect of disease status prior to T-cell depleted allogeneic stem cell transplantation on relapse-free and overall survival in patients with adverse-risk acute myeloid leukemia (AML). *First Author: Alexandra Ewa Rojek, Section of Hematology/Oncology, Department of Medicine, University of Chicago, Chicago, IL*

Background: Patients (pts) with adverse risk AML experience poor long term disease control. Some of these pts can be rescued with allogeneic stem cell transplantation (SCT). Adverse risk was defined by high risk cytogenetic and molecular markers (2017 European Leukemia Network criteria) and by disease status prior to SCT. We investigated outcomes of pts receiving *in vivo* T-cell depleted allogeneic SCT (TCD-SCT) at our center. **Methods:** We retrospectively analyzed 200 adverse-risk AML pts who received TCD-SCT from 2002-19. Pts were categorized into groups: untreated first relapse at SCT, primary induction failure with active disease at SCT, resistant to first induction but achieving morphologic complete remission (CR) by SCT, and induction sensitive CR with high-risk disease by ELN criteria. Outcomes were evaluated by 1-year (yr) and 3-yr relapse-free survival (RFS), overall survival (OS), and non-relapse mortality (NRM), and compared with log-rank tests of significance. **Results:** Baseline pt characteristics included a median age of 54 years (IQR, 44-61) with 62 (31%) pts older than 60, and 81 (41%) with HCT-CI score 3 or greater. All pts underwent *in vivo* TCD with alemtuzumab or ATG; 153 (77%) received reduced-intensity conditioning; 142 (71%) had 8/8 or 7/8 matched donors. Fourteen (7%) pts developed grade III-IV acute graft versus host disease (GVHD), and 25 (13%) developed chronic GVHD. With a median follow up of 14.3 months, cumulative incidence of relapse was 59% and NRM was 27%. Outcomes are summarized in the table. There was a statistically significant difference between categorized groups by RFS ($p < 0.01$) and OS ($p < 0.01$). **Conclusions:** We conclude that among adverse-risk AML pts, those in CR at time of TCD-SCT have superior survival outcomes to those with active disease. For those in CR at TCD-SCT, prior resistance to frontline induction was associated with inferior survival, suggesting that AML biology, treatment sensitivity, and remission status are important factors for TCD-SCT outcomes. The inferior outcomes observed for those with primary refractory disease suggest that while TCD-SCT can be effective with acceptable NRM, more work is needed to identify which pts can benefit from future transplant strategies. Better post-SCT therapy is needed to prevent relapses. Research Sponsor: None.

	1-yr RFS ^a (95% CI)	3-yr RFS ^a (95% CI)	1-yr OS ^b (95% CI)	3-yr OS ^b (95% CI)	1-yr NRM ^c (95% CI)	3-yr NRM ^c (95% CI)
All	200	36 (30-43)	21 (16-28)	53 (47-61)	29 (23-36)	33 (24-40)
Relapsed, active disease	48	29 (19-45)	13 (6-26)	38 (26-54)	19 (10-34)	23 (9-37)
Primary induction failure, active disease	71	28 (19-41)	16 (9-27)	49 (39-62)	20 (12-32)	27 (14-38)
Resistant to primary induction, CR	32	37 (24-59)	22 (11-42)	63 (48-82)	28 (16-49)	25 (7-41)
Induction sensitive, CR	49	55 (43-71)	39 (28-55)	69 (58-84)	53 (41-69)	19 (7-31)

7051

Poster Session

Myeloablative fractionated busulfan-based conditioning regimen in patients with AML and MDS: Results of a randomized clinical trial comparing 2 fractionation schedules. *First Author: Uday R. Popat, Department of Stem Cell Transplantation & Cellular Therapy, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Hematopoietic stem cell transplantation (HSCT) cures leukemias, but comes at a cost of higher toxicity and non-relapse mortality (NRM). We previously showed that fractionating the busulfan (Bu) dose and starting it on day -13 instead of day -6, leads to lower toxicity and permits delivery of a myeloablative regimen, even to older patients. We designed a single institution randomized trial to validate the concept of fractionation and to test the hypothesis that further fractionation by starting chemotherapy on day -20 further reduces toxicity and lowers NRM without increasing relapse risk. **Methods:** Patients with AML or MDS, 18 to 70 years old, with a matched related or unrelated donor were eligible if they had adequate organ function. Patients were randomized to one of two arms: The shorter arm consisted of outpatient Bu 80mg/m² on days -13 and -12, while the longer arm consisted of outpatient Bu 80mg/m² on days -20 and -13. The rest of the regimen and GVHD prophylaxis were similar in both arms: On days -6 to -3, fludarabine 10mg/m², cladribine 10mg/m² and Bu dosed to achieve total Bu exposure of 20,000 $\pm$ 12% μ Mol-min for the whole course, including outpatient doses. Additionally, the last 33 patients received venetoclax from days -22 to -3 in both arms. The GVHD prophylaxis was tacrolimus and mini-methotrexate in the first 29 patients and tacrolimus and cyclophosphamide in the remainder. The only difference between the two arms was if busulfan was started on day -20 or not. **Results:** A total of 116 patients were randomized, 59 to the shorter day -13 arm and 57 to the longer day -20 arm. Median age was 59 in the day -13 arm and 57 in the -20 arm. 70.7% had AML. 41.4% were transplanted in first complete remission. The characteristics of the two groups were well-balanced. The median follow-up in the 67 surviving patients was 48.9 months. More patients in the day -13 group experienced grade ≥ 3 toxicities than in the day -20 group (93.2% vs. 73.7%, $p = 0.005$). The difference in toxicity led to a reduction of the 3-year NRM (19% vs. 7%, $p = 0.067$). There was no difference in relapse rate ($p = 0.99$) (Table). **Conclusions:** Further fractionating busulfan and moving just one dose of busulfan 1 week earlier reduces toxicities and may lower NRM, without increasing relapse rate. Clinical trial information: NCT02250937. Research Sponsor: n/a.

Outcome	Day -13 arm (n=59)	Day -20 arm (n=57)	P value
Any non-hematologic G3 or higher AE	93.2%	73.7%	0.005
G3 or higher pneumonitis	18.6%	7%	0.1
G3 or higher sinusoidal obstruction syndrome	5.1%	0%	0.24
G3 or higher mucositis	33.9%	10.5%	0.003
Non-relapse mortality			
3 yrs	19% (8.7 – 29.2)	7% (0.3 – 13.7)	0.067
Relapse			
3 yrs	32.3% (22.1 – 47.2)	31.7% (21.5 – 47.6)	0.99
PFS			
Median	24.6 months (12.2 – NR)	NR (20.5 – NR)	0.19
3 yrs	48.7%	61.3%	
OS			
Median	50.2 (26.1-NR)	NR (58.6-NR)	0.13
3 yrs	56.1%	67.6%	
GRFS			
3 yrs	35.3%	52.5%	0.098

7052

Poster Session

Financial toxicity and quality of life in patients undergoing bone marrow transplant evaluation: A single center analysis. *First Author: S. M. Qasim Hussaini, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins Hospital, Baltimore, MD*

Background: The impact of pre-transplant financial toxicity on quality of life (QOL) outcomes following bone marrow transplant (BMT) is unknown. We investigated the prevalence of financial toxicity in a population undergoing evaluation for BMT and its impact on post-transplant clinical and health-related QOL outcomes. **Methods:** This is a cross-sectional study in patients undergoing evaluation for allogeneic BMT between 1/1/2018 and 9/23/2020 at a large academic medical center. Financial health at baseline was measured via the comprehensive score for financial toxicity (COST) survey. The cohort was divided into three groups: none, mild, and moderate-high financial toxicity. QOL was measured using Functional Assessment of Cancer Therapy (FACT)-based questionnaires at multiple timepoints. Multivariate logistic regression analysis evaluated factors associated with financial toxicity. Kaplan-Meier curves and log-rank tests evaluated overall survival and non-relapse survival. **Results:** Of 245 patients evaluated for BMT, 176 (71.8%) completed both questionnaires with 63.1% male, 72.2% white, and median age 57 years. Common diagnoses were myelodysplastic syndrome (39.2%), leukemia (38.1%), and lymphoma (13.6%). Overall, 83 (47.2%) patients reported no financial toxicity, 51 (29.0%) mild, and 42 (23.9%) with moderate-high financial toxicity at initial evaluation for BMT. Compared to those with no financial toxicity, those with mild or moderate-high financial toxicity reported significantly reduced spending on leisure, food/clothing, used all or a portion of savings, borrowed money or accumulated debt using a credit card, and did not fill a prescription due to costs ($p < 0.0001$ for all). In patients with baseline moderate-high financial toxicity, FACT-BMT scores were lower at 6 months (126 none vs 122 mild vs 92 moderate-high; $p = 0.0007$) and 1 year (133 none vs 117 mild vs 112 moderate-high; $p = 0.0075$) following BMT. Older age (> 62) (OR 0.4; 95% CI [0.17 – 0.94], $p = 0.03$) and income equal or greater than \$60,000 (OR 0.16; 95% CI [0.07 – 0.36], $p < 0.001$) were associated with lower odds of financial toxicity. No association was noted between financial toxicity and selection for BMT, overall survival, or non-relapse mortality. **Conclusions:** Financial toxicity was highly correlated with patient-reported changes in behavior affecting their daily activities and transplant care, with notable impact on QOL following transplant for up to 1 year. Early interventions by physician and social work-led teams may benefit patients who are at risk for financial toxicity. Research Sponsor: Supported by the American Society for Hematology Research Scholar Award and P30-AG028716-13 Mini#6.

Financial toxicity and QOL.			
Day 30	No Financial Toxicity	Mild	Moderate-High
BMTS	27	30	24*
FACTG	87	83	74
FACT BMT	114	109	98
Day 90			
BMTS	31	31	26**
FACTG	89	87	85
FACT BMT	118	117	112
Day 180			
BMTS	30	32	24*
FACTG	95	88	70*
FACT BMT	126	122	92*
Day 365			
BMTS	33	30	29*
FACTG	99	85	86*
FACT BMT	133	117	113*

* $p < 0.01$; ** $p < 0.05$.

7054

Poster Session

Report of a chronic myeloid leukemia registry in a low-and middle-income setting. *First Author: Nicolas Anthony Othieno-Abinya, Nairobi Hospital Cancer Centre, Nairobi, Kenya*

Background: Treatment of chronic myeloid leukaemia (CML) in Kenya has been supported since the year 2002 by a collaboration between the Max Foundation and Novartis Pharmaceuticals in the Glivec International Patient Assistance Program (GIPAP). In November 2020 this was transitioned to Max Access Solutions (MAS) that brought in the Ministry of Health as a partner. A broad range of BCR-ABL tyrosine kinase inhibitors are available. We wanted to describe epidemiology, treatment and outcome of CML in the country. **Methods:** Patients' records were reviewed and data entered in a database. Key variables included age, sex, BMI, diet, disease phase at diagnosis, treatment, and outcome. Continuous variables were summarized using mean (standard deviation) or median (interquartile range). Categorical variables were summarized using counts and percentages. Bivariate comparisons of treatment outcome were done using chi-square or Fisher's exact test. Analysis of variance (ANOVA) or Kruskal-Wallis test was used for continuous variables. **Results:** 1347 patients-males 748 (55.5%), females 599 (44.5%). Mean age was 44.5 years. Seventy (9.0%) were underweight, 88 (11.4%) obese. Mean body surface area (BSA) was 1.75m². Chronic phase cases were 1177 (96.2%), accelerated phase 46 (3.8%), blastic phase 1 (0.1%). Mean bone marrow blast count was 5.25%, BCR-ABL/ABL was 63.7%, haemoglobin 10.8g/dl, total wbc count 225 x 10⁹/litre, platelets 392.5 x 10⁹/litre. Imatinib was administered upfront to 1319 patients (99.8%). Two hundred and six (15.3%) were switched to second line; 100 (48.8%) to dasatinib, 50 (24.4%) to bosutinib. Transformation was registered in 26 cases (1.9%) - accelerated in 13 (72.2%), blastic in 5 (27.8%), 4 (80.0%) being myeloid and 1 (20%) lymphoblastic. Those alive are 1151 (85.4%) and 185 (13.7%) lost to follow-up. Deaths were recorded in 11 (0.8%). Those with lower BSA were more likely to die ($p = 0.01$). **Conclusions:** CML in Kenya occurs at a younger age-group with a slight male preponderance. With availability of a range of BCR-ABL tyrosine kinase inhibitors, treatment outcome is close to what is documented in high-income settings. Research Sponsor: Novartis Kenya Limited.

7053

Poster Session

Longitudinal, prospective cardiovascular and metabolic risk in treatment-naive patients with chronic myeloid leukemia in chronic phase (CML-CP) starting tyrosine kinase inhibitor (TKI) therapy in a real-world setting. *First Author: Javid J. Moslehi, University of California San Francisco, San Francisco, CA*

Background: Multiple TKIs used in the treatment (tx) of CML have been associated with the development of cardiovascular/metabolic (CV/Met) comorbidities, yet no study to date has prospectively and systematically assessed CV/Met parameters after TKI initiation. CA180-653 (NCT03045120) is a non-interventional, prospective, real-world study characterizing the effects of TKIs (dasatinib [DAS], imatinib [IM], nilotinib [NIL], and bosutinib [BOS]) on CV/Met risk factors in patients (pts) with CML-CP in routine care. Baseline CV/Met risks were previously reported (Mauro, GCOS 2019). Here, we report data from the final 2-year follow-up. **Methods:** Adult pts with newly diagnosed CML-CP due to start tx with DAS, IM, NIL, or BOS were enrolled; the BOS cohort was not analyzed independently due to small sample size. Pts were followed for 24 mo. Blood/urine samples, CV/Met assessments, coronary calcium scoring, echocardiography, and cytogenetic/molecular response assessments were collected at routine office visits at predetermined timepoints. The primary endpoint was change in CV/Met risk from baseline. **Results:** At the end of follow-up, 118 pts were enrolled; 49 received DAS, 47 IM, 16 NIL, and 6 BOS. Of these, 83 (70.3%) pts completed the study and 35 (29.7%) discontinued; the most common reason for discontinuation was withdrawal of consent ($n = 19$). No pts died from CML. At baseline, median age was 57 (range, 20–97) y; 59.3% of pts were male and 83.9% were White. Sixty-two (52.5%) pts had CV/Met risk factors at baseline, including hypertension ($n = 45/62$; 72.6%), hyperlipidemia ($n = 33/62$; 53.2%), diabetes ($n = 19/62$; 30.6%), and arrhythmia ($n = 10/62$; 16.1%). Over the study period, 1 (3.4%) patient receiving DAS and 2 (6.9%) receiving IM developed coronary artery calcification; 2 (9.1%) pts receiving IM developed pericardial effusion. Median left ventricular ejection fraction on 2D echocardiogram was normal for all TKIs at baseline (65.4% [range, 27–81]) and end of study (65.4% [range, 40–80]). Systolic and diastolic blood pressure increased from baseline only in pts who received NIL. Blood glucose levels increased from baseline for DAS, IM, and NIL (median: 1.9, 4.9, and 5.8 mg/dL, respectively), and low-density lipoprotein levels decreased from baseline in all 3 cohorts (median: 72.7, 52.1, and 56.3 U/L, respectively); data from the NIL group were limited by the small sample size. There was 1 death from myocardial infarction related to NIL. **Conclusions:** These findings suggest more than half of pts with CML-CP have CV/Met risk factors at baseline. At end of study, there was indication of CV/Met effects based on TKI selection. This highlights the importance of appropriate TKI selection based on pt comorbidity characteristics, along with close monitoring and management of CV/Met risks throughout tx. Clinical trial information: NCT03045120. Research Sponsor: Bristol Myers Squibb.

7055

Poster Session

Mortality rate and social disparity trends with tyrosine kinase inhibitory availability in chronic myelogenous leukemia: An analysis in the US from 1999 to 2020. *First Author: Tony Varughese, Hackensack University Medical Center, Hackensack, NJ*

Background: We analyzed CML mortality from 1999 to 2020 in the US in relation to FDA approval of tyrosine kinase inhibitors (TKIs). These agents were introduced in the 2000s, revolutionizing the treatment of CML and providing a paradigm for targeted therapy in oncology. Starting with imatinib in 2001, followed by dasatinib (2006), nilotinib (2007), and bosutinib (2012). TKIs have increased tolerability and efficacy for the treatment of CML as compared to previous treatment modalities. We investigated age-adjusted mortality rates (AAMR) and annual percent change (APC) in this population in relation to TKI approval. **Methods:** Using the CDC WONDER database, we examined mortality trends from 1999 to 2020 for CML in the US. AAMRs were calculated per 100,000 people and stratified by sex, race/ethnicity, and census region. AAMR groups were listed as pre-TKI era and 1 year post-FDA approval of different TKI agents. We computed the APC trends for the respective stratification with Joinpoint, a regression analysis program. **Results:** Between 1999 and 2020 there were 35,268 deaths from CML. In 1999, overall AAMR initially was 0.8, which improved to 0.5 by 2020 with a respective APC of -2.5%. In our subgroup analysis there was a consistent and significant decrease in AAMR since the introduction of Imatinib in 2001. With additional TKI releases, AAMR continued to decline in all subgroups. APC for mortality rates was similar between all subgroups [-2.0 to -2.8%] indicating a similar benefit regardless of subgroup. Male AAMR was consistently higher than female AAMR. Black and white patients (0.5, 2020) have a 2.5x higher AAMR (0.2, 2020) compared to Asian patients. Census region did not show a significant difference between each other. **Conclusions:** Since the FDA approval of imatinib in 2001 and the subsequent release of TKIs there has been a significant impact on reducing AAMR for patients with CML. The decline was seen in sex, race, and census region. The APCs were similar between all subgroups indicating a consistent improvement in survival. Possible etiologies of disparities in AAMR for males in comparison to females and for black and white patients in comparison to Asian patients include gender and race-associated gene polymorphisms possibly inducing differences in drug metabolism. Further gender and race specific pharmacokinetic studies would be useful to further elucidate etiology of the disparity and may lead to changes in TKI dosing strategies. Research Sponsor: None.

	AAMR, 1999 Pre-TKI	AAMR, 2002 Imatinib	AAMR, 2007 Dasatinib and Nilotinib	AAMR, 2013 Bosutinib	AAMR, 2020	APC Trends (1999 to 2020)
Women	0.6	0.4	0.3	0.3	0.3	-2.7%
Men	1.0	0.6	0.6	0.5	0.7	-2.4%
Black	0.8	0.7	0.4	0.4	0.5	-2.8%
White	0.8	0.6	0.4	0.4	0.5	-2.0%
Hispanic	0.8	0.4	0.2	0.3	0.4	-2.5%
Asian	0.6	0.4	0.2	0.2	0.2	-0.1%
Northeast	0.6	0.6	0.4	0.3	0.3	-2.6%
Midwest	0.7	0.6	0.4	0.4	0.4	-2.4%
South	0.6	0.6	0.4	0.4	0.3	-2.5%
West	0.6	0.6	0.5	0.4	0.3	-2.4%

7056

Poster Session

External validation of the Molecular International Prognostic Scoring System (IPSS-M) for myelodysplastic syndromes. *First Author: Brian Chernak, Columbia University Irving Medical Center, New York, NY*

Background: Myelodysplastic Syndromes (MDS) comprise a group of clonal diseases characterized by dysplastic hematopoietic progenitor cells, leading to cytopenias and in select cases transformation to acute myeloid leukemia (AML). In June 2022 the Molecular International Prognostic Scoring System (IPSS-M) was developed to build on the traditional IPSS-R and is reported to be prognostic even with incomplete molecular data. We aimed to validate this scoring system with an external dataset, and utilize a patient population which typically does not contain complete molecular testing at diagnosis. **Methods:** This single center study at a tertiary medical center in New York, NY was conducted as an external validation of the IPSS-M. Patients with MDS who had documented peripheral blood counts, bone marrow biopsies, and cytogenetic data were identified in the institutional tissue bank. After eliminating repetitive patient samples, 405 patient entries, collected between July 7, 2010 and March 29, 2022 were included in this study. 392 patients had previously been categorized by IPSS-R score. 332 patients had at least one subsequent follow-up event. 94 patients had bone marrow biopsies that were peri-diagnostic (within 12 months of diagnosis). **Results:** Patients in the entire cohort had a median age of 74 years (range, 30-96). The median follow-up duration was 1.5 years (range 0.0-9.9 years). Nearly all patients had at least partial molecular diagnostic data. Other than PRPF8 mutations (0%), all other mutations included in the IPSS-M scoring system were tested in a subset of the study population. The most common mutations in the patient population were SF3B1 (20.4%), ASXL1 (17.6%), and SRSF2 (15.9%); 12.2% of patients had the del5q cytogenetic abnormality, and 5.6% were found to have at least one TP53 mutation; 2.7% were TP53 (multi-hit). 29% of all patients were up-staged from IPSS-R to IPSS-M score, while 12% were down-staged. At the time of study evaluation, there were 84 events; 61.3% of patients were alive at the time of analysis. The median overall survival was 3.6 years (25-75% range: 2.75-5.50 years). When limited to patients with peri-diagnostic bone marrow biopsies, there were statistically significant differences in overall survival between IPSS-M categories ($p < 0.000001$) as well as IPSS-R categories ($p < 0.00001$). There was no statistical difference in survival between IPSS-M categories ($p = 0.6$) or IPSS-R categories ($p = 0.2$) if scores were calculated at any time point in the patient's disease course. **Conclusions:** This study validates the utility of both the IPSS-M and the IPSS-R scoring systems, and notably retains important risk stratification with incomplete diagnostic data. Importantly, the scoring systems are not effectively prognostic as the disease progresses, and thus should only be utilized at or near the time of diagnosis. Research Sponsor: None.

7058

Poster Session

Methylation-based prediction of myelodysplastic syndrome survival outcomes. *First Author: Alvin Shi, GRAIL, LLC, a subsidiary of Illumina, Inc., currently held separate from Illumina, Inc., under the terms of the Interim Measures Order of the European Commission dated 29 October 2021, Menlo Park, CA*

Background: Myelodysplastic syndromes (MDS) are a heterogeneous group of myeloid malignancies associated with a myriad of deleterious outcomes and a 5-year relative survival of 37%. MDS risk stratification is key for optimal treatment decisions. DNA methylation is associated with MDS biology due to frequent somatic mutations in genes (i.e. TET2, DNMT3A, IDH1, IDH2, and WT1) that affect DNA methylation. We hypothesized that methylation-based markers may help stratify risk and improve IPSS-R (the Revised International Prognostic Scoring System). Here, we evaluated the potential of both Bone Marrow (BM) Whole-genome Bisulfite Sequencing (WGBS) and Serum-based Targeted Methylation (TM) Sequencing to predict survival of MDS patients. **Methods:** We conducted paired BM WGBS and Serum-based TM sequencing on a cohort of 127 patients with MDS (N = 104) and secondary AML (N = 23) treated at the Columbia University Medical Center. We categorized patients based on an overall survival of > 3 ("long", N = 50) or < 3 years ("short", N = 77). We then identified differentially methylated regions (DMRs) differing between long and short survivor groups, and analyzed the biological pathways and functions enriched in these regions. To assess survival association, we trained a random forest classifier on principal components ("methylation classifier") on the methylation fractions from a subset of 96 Serum and 98 BM MDS patient samples to predict long vs. short survival, and compared this against a logistic regression IPSS-R model. We optimized the hyperparameters and assessed classifier performance using six-fold nested cross-validation. Finally, we conducted a multivariable cox regression with predicted scores from the methylation classifier, IPSS-R scores (recalculated at sample collection), age, and gender. **Results:** We identified a total of 7,742 DMRs in the BM WGBS and 14,093 DMRs in the Serum TM as significantly different between long and short survivor groups. Signaling pathways for calcium, cAMP, MAPK, Rap1, and PI3K-Akt were significantly enriched in DMRs. We also identified a previously-reported CpG island hypermethylation signature associated with AML progression in BM and Serum. The methylation classifier achieved a comparable AUROC compared to IPSS-R logistic regression for both BM WGBS (0.80 vs 0.78) and Serum TM (0.77 vs 0.73) samples. Multivariable Cox regression demonstrated that both predicted scores from the methylation classifier (Serum $p = 0.002$; BM $p = 0.016$) and IPSS-R scores (Serum $p = 0.003$; BM $p = 0.004$) are significant predictors of survival. **Conclusions:** We demonstrated methylation-based sequencing represents a promising new tool for MDS patient risk stratification. As IPSS-R relies on bone marrow aspirates, the Serum-based TM assay offers a less-invasive method for MDS risk stratification. Research Sponsor: GRAIL, LLC, a subsidiary of Illumina, Inc., currently held separate from Illumina, Inc., under the terms of the Interim Measures Order of the European Commission dated 29 October 2021.

7057

Poster Session

Hematologic and transfusion outcomes in patients (pts) with lower-risk myelodysplastic syndromes (LR-MDS) receiving luspatercept: Real-world assessment in the community practice setting. *First Author: Sudipto Mukherjee, Cleveland Clinic, Cleveland, OH*

Background: Erythropoiesis-stimulating agents (ESAs) are used as first-line (1L) treatment (tx) for the management of symptomatic anemia in LR-MDS. Luspatercept is approved for pts with LR-MDS with ring sideroblasts (RS) who experience ESA failure and are transfusion dependent. We assessed clinical outcomes of pts with LR-MDS with RS, or MDS/myelodysplastic neoplasms with RS and thrombocytosis, treated with luspatercept in US community practices. **Methods:** This retrospective, observational cohort study used physician-abstracted chart data from community oncology clinics and included adults diagnosed with LR-MDS (including Very low- to Intermediate-risk IPSS-R status) on/after Jan 1, 2015 who received luspatercept for ≥ 3 months (mos) with ≥ 3 mos of follow-up. Transfusion burden (TB) was defined by number of sessions (ses) received in the 8 weeks (wks) prior to luspatercept tx (baseline) and the lowest number for any consecutive period ≥ 8 wks during wks 1–24 of tx: transfusion independent (TI); low TB (LTB), 1–3 ses; and moderate TB (MTB), 4–5 ses. **Results:** Of 253 pts, 219 (87%) had 1 tx prior to luspatercept tx and 31 (12%) received ≥ 2 . ESAs were used as 1L tx in 210 pts (83%). Median follow-up was 5.7 mos. The most common reason for discontinuing initial MDS tx among patients who received ≥ 1 tx prior to luspatercept was lack of anemia improvement (133/250). At baseline, 21 (8%) pts were TI, 208 (82%) had LTB, and 24 (10%) MTB. Median duration of luspatercept tx was 10.8 mos. During wks 1–24, 20/21 (95%) pts remained TI and 201/232 (87%) pts with LTB/MTB at baseline achieved TI for ≥ 8 wks. The Table shows changes in median hemoglobin (Hb), absolute neutrophil count (ANC), and platelet (plt) count. **Conclusions:** Most pts with LR-MDS received 1L ESAs and over half discontinued the first tx prior to luspatercept due to lack of anemia improvement, highlighting the need for alternative options to improve clinical outcomes. Consistent with data from the MEDALIST trial, 87% of pts with LTB/MTB who received luspatercept achieved TI for ≥ 8 wks, supporting its clinical benefit in routine clinical practice. Research Sponsor: Bristol Myers Squibb.

Median p25–p75	Diagnosis	Luspatercept initiation	C1	C2	C3	C4	C5	C6	C7	C8
Hb, g/dL*	8.9	7.9	8.0	8.2	8.8	8.6	9.0	9.0	9.1	9.3
ANC, $\times 10^9/L^*$	7.8–9.6	7.2–8.5	7.3–8.8	7.6–9.1	7.9–9.9	7.8–9.5	8.1–9.9	8.5–9.9	8.5–9.9	8.5–9.9
Plt count, $\times 10^9/L^*$	230	200	190	200	210	200	210	210	210	210
	1500–3300	1250–3200	1310–2960	1350–3270	1400–3375	1436–3255	1400–3500	1390–3500	1400–3700	1370–3800
	175	157	143	151	167	155	160	147	153	158
	129–232	110–221	91–190	100–206	111–230	98–233	100–240	93–210	111–244	107–251

C, cycle; cycle every 3 wks p25–p75, 25th–75th percentile. * Results available for a range of 78–196 pts. * A range of 76–170 pts. * A range of 77–193 pts across C1–8.

7059

Poster Session

Outcome of TP53-mutated CCUS and the risk of progression to myeloid neoplasms. *First Author: Syed Naseem Shah, Mayo Clinic, Rochester, MN*

Background: TP53-mutated ($TP53^{mut}$) myeloid neoplasms (MN) are aggressive leukemia with poor survival. A subset of $TP53^{mut}$ MN is preceded by $TP53^{mut}$ CCUS that is conventionally considered to be high-risk premalignant condition, though evidence supporting the notion is lacking. We studied outcomes of $TP53^{mut}$ CCUS compared to $TP53$ wild-type ($TP53^{wt}$) CCUS. **Methods:** Mayo Clinic Molecular Hematology Database (N=7593) was queried to identify patients (pts) harboring pathogenic variant(s) in exons 4–11 of the $TP53$ gene with $\geq 2\%$ variance allele frequency (VAF). CCUS was defined using the 5th edition of the WHO Classification for MN. **Results:** Of 457 pts with $TP53^{mut}$, 29 (5.9%) had $TP53^{mut}$ CCUS. The median age at diagnosis was 67 years, 17 (59%) were female, and 20 (69%) had received cytotoxic therapies. One and ≥ 2 $TP53^{mut}$ were seen in 26 (89.6%) and 3 (10.3%) pts, respectively. Median $TP53^{mut}$ VAF was 9% (range 3–42), 3 had $TP53^{mut}$ VAF $\geq 20\%$, and 4 (14%) had non-MDS defining cytogenetic anomalies. Of 16 pts with available follow up evaluation (median interval 22 months, Table), 3 (10.3%) progressed to $TP53^{mut}$ MN at 5, 13, and 14 months from diagnosis. We next compared outcomes of $TP53^{mut}$ CCUS to $TP53^{wt}$ CCUS (n=138). The proportion of pts developing MN was not different between $TP53^{mut}$ and $TP53^{wt}$ CCUS (18.1 vs 10.3%, $P = .42$). Progression free survival of $TP53^{mut}$ CCUS was comparable to $TP53^{wt}$ CCUS at 1- (77 vs 83%), 2- (67 vs 67%), and 5-years (67 vs 59%, $P = .9$). Similarly, overall survival of $TP53^{mut}$ vs $TP53^{wt}$ CCUS at 1- (81 vs 89%), 2- (76 vs 76%), and 5-years (76 vs 67%) was comparable ($P = .94$). **Conclusions:** In contrast to the prevalent notion, $TP53^{mut}$ was not associated with a higher risk of MN progression or mortality compared to $TP53^{wt}$ CCUS. Majority of $TP53^{mut}$ clones showed remarkable stability over years. Research Sponsor: None.

Age/ Sex	Baseline		Last Follow-up		Interval (mo.)
	Cytogenetics	NGS (% VAF)	Phenotype	Cytogenetics	NGS (% VAF)
72F	46, XX	$TP53$ (6)	t-MDS	45, X, add (5)(q11.2), -7	$TP53$ (82)
73M	46, XY	$PHF6$ (12), $TP53$ (7)	t-MDS	46, XY	
61F	46, XX	$TP53$ (7.5), $TP53$ (5.5)	t-MDS	46, XY, del(7)(q22)/47, idem,+21	
65F	46, XX	$TP53$ (42), $IDH1$ (38), $SRSF2$ (43)	CCUS	46, XX	
65M	46, XY	$TP53$	CCUS	46, XY	
52F	46, XX	$TP53$ (10)	CCUS	46, XX	$TP53$ (8)
71M	46, XY	$TP53$ (6), $DNMT3A$ (7), $JAK2$ (10)	CCUS	46, XY	$TP53$ (11), $DNMT3$ (15), $JAK2$ (6)
67M	45, X,Y,t(1;15)(q23;q15)	$TP53$ (9)	CCUS	45, X, -Y,t(1;15)(q23;q15)	
71M	46, XY	$TP53$ (9)	CCUS		
40F	46, XX	$TP53$ (13)	CCUS	46, XX	$TP53$ (16)
58F	46, XX	$TP53$ (19), $TET2$ (17)	CCUS	46, XX	$TP53$ (24), $TET2$ (21)
84F	46, XX	$TP53$ (37)	CCUS	46, XX	$TP53$ (5)
65F	45, X, -X	$TP53$ (7)	CCUS	45, X, -X	$TP53$ (7)
16F	46, XX	$TP53$ (5)	CCUS	46, XX	$TP53$ (5), $TP53$ (16)
52F	46, XX	$TP53$ (7)	CCUS	46, XX	
60F	46, XX	$TP53$ (6), $TET2$ (6)	CCUS	46, XX	

CCUS: clonal cytopenia of undetermined significance, NGS: next-generation sequencing, F: female, M: male, t-MDS: therapy-related myelodysplastic syndrome.

7060 Poster Session

Defining the immune microenvironment in myelodysplastic syndrome and acute myeloid leukemia using machine learning. *First Author: Maher Albitar, Genomic Testing Cooperative, Irvine, CA*

Background: Changes in the bone marrow microenvironment are believed to play a major role in the biology of Myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML). To study the bone marrow microenvironment (BME) in MDS and AML and to compare it with normal BME, we studied the expression profile of 43 immune biomarkers and evaluated the differences in the BME between AML and MDS and compared it to that of normal BME. These 43 immune biomarkers included B- and T-cell markers, cytokines and chemokines. **Methods:** RNA was extracted from fresh bone marrow aspiration samples from 626 patients with AML, 564 patients with MDS, and 1449 individuals having bone marrow without any mutations or having low level mutations determined to be CHIP (clonal hematopoiesis of indeterminate potential) and considered normal. RNA levels of 42 immune biomarkers were quantified using next generation sequencing. Using a machine learning algorithm, we first selected the relative genes that distinguish between two classes using K-fold cross-validation (K = 12). The selected genes were used to predict one class from the other using random forest classifier. Samples were divided into a training set (67%) and testing set (33%) for each classification. **Results:** The random forest showed that MDS can easily be distinguished from normal using the expression of 15 genes (CYFIP2, CXCR4, IL1RAP, CD58, CD36, CD19, PAX5, CD79B, ID1, IL8, CD44, IL1R1, CD79A, IL21R, and CD74). The AUC for distinguishing MDS from normal was 0.996 in the training set and 0.931 (95% CI: 0.912-0.949) in the testing set. Distinguishing between AML and normal was also robust and achievable using the expression of only 10 genes (CYFIP2, IL1R1, CXCR4, IL8, IL21R, CD44, CD28, CD79A, and IL7R, and CD8A). The AUC for the training set was 0.994 and 0.972 (95% CI: 0.961-0.983) for the testing set. Eight of these 10 markers were shared with MDS algorithm. Only CD28 and IL7R were specifically needed for AML classification. Distinguishing between MDS and AML was achievable with high reliability with AUC of 0.994 (95% CI: 0.992-0.997) in training set and 0.924 (95% CI: 0.896-0.952) in testing set. Only 10 biomarkers were used for distinguishing MDS from AML, nine of which (IL1R1, CYFIP2, CD44, IL1RAP, CXCR4, IL21R, CD74, IL8, and CD36) were used in distinguishing MDS from normal. The only unique biomarker was CD28. Comparing levels of these biomarkers, most of which showed highest level in normal BM, significantly lower level in MDS but the level was even significantly lower in AML (deeper reduction) than in MDS. **Conclusions:** This data suggests that the BME is significantly different in MDS from AML and both are different from normal. Few immune biomarkers play major role in defining each BME. However, relative increase or decrease between these immune biomarkers dictate the uniqueness of each microenvironment. Research Sponsor: Genomic Testing Cooperative.

7062 Poster Session

Jaktinib in patients (pts) with myelofibrosis (MF) who were refractory to or relapsed after ruxolitinib: A single-arm, open-label, multicenter, phase 2 study. *First Author: Jie Jin, Department of Hematology, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China*

Background: Currently, ruxolitinib is the only marketed Janus kinase inhibitor (JAKi) for pts with MF in China, which demonstrated symptomatic and splenic benefit with increased cytopenias. However, at least 50% of pts develop resistance or intolerance to ruxolitinib in the long-term follow up, for whom life expectancy is largely reduced. There are few therapeutic options after ruxolitinib failure. Jaktinib, an oral novel JAK and AVCR1 inhibitor showed promising activity in Jaki-naïve pts with intermediate or high risk MF with mild side effects. Here we present the results of jaktinib in MF pts who were refractory or relapsed to prior ruxolitinib therapy. **Methods:** Pts who had primary or post-ET/PV MF and were previously treated with ruxolitinib for at least 3 months and with either inadequate efficacy response (defined as < 10% spleen volume reduction [SVR] by MRI/CT or < 30% decrease in spleen size by palpation from baseline) or spleen regrowth to < 10% SVR or < 30% decrease in spleen size from baseline following an initial response were recruited to receive jaktinib 100 mg twice daily. The primary endpoint was the proportion of pts with SVR ≥ 35% from baseline (SVR35) at week (wk) 24, measured by MRI/CT images and assessed by Independent Review Committee. Secondary endpoints included the best spleen response rate (defined as achieving SVR35 at any time), the proportion of pts with ≥ 50% reduction in MPN Symptom Assessment Form Total Symptom Score (MPN-SAF TSS), improvement of anemia and safety. **Results:** A total of 34 pts were enrolled. The median duration of previous ruxolitinib treatment was 18.6 months (range 3.4-70.1). The median baseline TSS was 19.5 (range 1-55), hemoglobin (Hb) was 101.5 g/L (range 61-149), and platelets was 159×10⁹/L (range 66-951). 11 pts (32.4%) achieved SVR35 at wk 24. The best spleen response rate was 38.2% (13/34). The median time to achieve the first SVR35 was 8.1 weeks, and the median duration of response was not reached. At wk 24, 13 pts (46.4%) achieved a ≥ 50% improvement in TSS from baseline. Of 16 transfusion-independent pts with Hb ≤ 100 g/L at baseline, 8 (50.0%) had a ≥20 g/L Hb increase by wk 24. Of 6 pts who required RBC transfusion at baseline, 2 had a 50% decrease in RBC infusion by wk 24. The median jaktinib exposure time was 231 days (range 96-371). 23 pts (67.6%) had one or more grade ≥3 treatment emergent adverse events (TEAEs). The most common grade ≥3 TEAEs were anemia (32.4%, n = 11), thrombocytopenia (32.4%, n = 11), leukocytosis (20.6%, n = 7) and leukopenia (11.8%, n = 4). Treatment discontinuation due to TEAEs occurred in 2 pts (5.9%). A dose reduction or temporary interruption due to TEAEs were reported in 9 pts (26.5%). **Conclusions:** MF pts who were refractory/relapsed to ruxolitinib attained substantial spleen response, and reduction in MF-related symptom burden with jaktinib, which could be a new option for MF pts who have failed ruxolitinib. Clinical trial information: NCT04851535. Research Sponsor: Suzhou Zelgen Biopharmaceuticals Co, Ltd.

7061 Poster Session

Jaktinib in patients (pts) with myelofibrosis (MF) who were intolerant to ruxolitinib (RUX): An open-label, single-arm phase 2b study. *First Author: Yi Zhang, The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, China*

Background: As the first approved Janus kinase inhibitor (JAKi) for pts with symptomatic MF, RUX showed superiority in spleen volume reduction with increased anemia and thrombocytopenia. However, there are few treatment options after RUX intolerance. Jaktinib, an oral novel JAK and AVCR1 inhibitor showed promising efficacy in Jaki-naïve pts with intermediate or high risk MF with mild side effects. Here we present the results of MF pts who were intolerant to RUX and received jaktinib 100 mg bid from a phase 2b study. **Methods:** Pts who had primary or post-ET/PV MF and were previously treated with RUX for ≥28 days who either required RBC transfusions or required more frequent transfusions on RUX, or had grade 3/4 anemia, thrombocytopenia or hematoma when receiving RUX, and with palpable spleen ≥5 cm were included. The primary endpoint was the proportion of pts with spleen volume reduction of ≥ 35% from baseline (SVR35) at week (wk) 24, assessed centrally on the basis of MRI/CT images. Secondary endpoints included the best spleen response rate (defined as achieving SVR35 at any time), the proportion of pts with ≥ 50% reduction in MPN Symptom Assessment Form Total Symptom Score (MPN-SAF TSS), anemia response, safety, etc. **Results:** A total of 45 patients received jaktinib 100 mg bid. The full analysis set (FAS) for efficacy included 44 pts who had completed the 24-week treatments and evaluations or terminated prior to wk 24, and excluded one pt because of incorrect diagnosis of MF. The median baseline TSS was 9.5, hemoglobin (Hb) was 79.5 g/L, and platelets was 132.5×10⁹/L. While on RUX, 21 pts (48%) required RBC transfusion and all pts experienced those grade 3 hematological toxicities. In FAS, the SVR35 rate at wk 24 was 43% (19/44). Over the study phase, the best spleen response rate was 55% (24/44). The median time to achieve the first SVR35 was 12 weeks. Response was maintained in 80% pts for at least 24 weeks and median duration was not reached. At wk 24, 62% of the evaluable pts achieved a ≥ 50% improvement in TSS from baseline. Of 31 pts with baseline Hb ≤ 100 g/L, 13 (42%) had a ≥20 g/L Hb increase. Of 19 pts who required RBC transfusion at baseline, 11 (58%) had a 50% decrease in RBC infusion frequency. Of 9 transfusion-dependent pts at baseline, one became transfusion-independent. In the safety set (n = 45), the median jaktinib exposure time was 280 days. The most common grade ≥3 TEAEs were anemia (31%), thrombocytopenia (22%), pneumonia (18%), neutropenia (16%) and leukopenia (16%). Treatment discontinuation due to TEAEs occurred in five pts (11%). A dose reduction or temporary interruption due to TEAEs were reported in 12 pts (27%). **Conclusions:** Jaktinib demonstrated promising activities in MF pts who was intolerant to RUX by substantially reducing spleen volume, ameliorating MF-related symptom burdens, and elevating Hb levels. Jaktinib could be a viable treatment for MF pts with anemia in this setting. Clinical trial information: NCT04217993. Research Sponsor: Suzhou Zelgen Biopharmaceuticals Co, Ltd.

7063 Poster Session

Selinexor (SEL) plus ruxolitinib (RUX) in JAK inhibitor (JAKi) treatment-naïve patients with myelofibrosis: Updated results from XPORT-MF-034. *First Author: Haris Ali, City of Hope, Duarte, CA*

Background: Myelofibrosis (MF) is a myeloproliferative neoplasm associated with splenomegaly, high symptom burden, and poor prognosis. Activity has been shown with the combination of SEL + the JAKi RUX in preclinical studies. Specific subgroups with lower response rates to RUX monotherapy, such as males vs females (25% vs 59%) and those with a lower (≤15 mg vs 20 mg) RUX starting dose (22-27% vs 43%), highlight unmet need in specific groups (grps). **Methods:** XPORT-MF-034 is a Phase 1/2, open-label study evaluating safety and efficacy of SEL at 40 mg and 60 mg once-weekly plus RUX per standard of care in 28-day cycles. Assessments included safety, spleen/symptom response, survival, and hemoglobin levels. The primary analysis population included those who had baseline assessment and were treated to at least Week 24 (W24) or discontinued before W24. Two pts with baseline total symptom score (TSS) = 0 were excluded from analysis of TSS reduction of ≥50% (TSS50). **Results:** As of Dec 21, 2022, 10 participants received 40 mg and 14 participants received 60 mg SEL; 22 of the 24 pts enrolled had reached at least W24 and were included in the efficacy analysis. The median duration of treatment was 28 wks overall, 33 wks for 60 mg and 22.5 wks for 40 mg grps. Most common adverse events (AEs) by dose (60/40 mg) were nausea (79%/70%); majority grade 1-2), anemia (79%/50%), and fatigue (57%/60%). Most common Grade ≥3 AEs were anemia (50%/40%), thrombocytopenia (29%/10%), and neutropenia (7%/20%). AEs were reversible with dose modifications. Two patients discontinued treatment due to treatment-related AEs (thrombocytopenia and neuropathy); 3 deaths have occurred in the study, none related to SEL. Overall, 64% (14/22) achieved SVR35 at W24, with 79% [11/14] vs 38% [3/8], in the 60 mg vs 40 mg grp, respectively. The 60 mg grp achieved a deeper median SVR response vs the 40 mg grp at W24 (49% vs 31%). At W24, TSS50 was achieved by 45% (9/20) overall, 58% [7/12] of the 60 mg, and 25% [2/8] of the 40 mg grp. Among 11 pts with baseline hemoglobin < 10 g/dL, median hemoglobin decreased by 0.5 g/dL from baseline to W12 and increased by 0.8 g/dL from baseline to W24. Similar efficacy was observed across all subgrps with 60 mg. Reduction of variant allele frequency from baseline to W24 was > 10% in 50% (4/8) and > 20% in 25% (2/8) of evaluable pts for 60 mg grp. **Conclusions:** Encouraging activity with 60mg SEL + RUX combination were observed in TSS50, SVR and hemoglobin levels overall, as well as in key subgroups including males, in pts started on low dose RUX (≤15 mg), and pts with larger baselines spleen size. Updated data will be available for presentation. Clinical trial information: NCT04562389. Research Sponsor: Karyopharm Therapeutics.

n/N (%)		RUX 15/20 mg BID		RUX 5/10 mg BID		Baseline Spleen Volume < 1800 cm ³		Baseline Spleen Volume ≥1800 cm ³	
		Female	Male	Female	Male	Female	Male	Female	Male
SVR35 at W24	SEL	1/2	2/6	3/6 (50)	0/2 (0)	2/6 (33)		1/2 (50)	
	40 mg	(50)	(33)						
	SEL	4/5	7/9	6/8 (75)	5/6 (83)	5/7 (71)		6/7 (86)	
	60 mg	(80)	(78)						

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Poster Session

Effects of ruxolitinib and magrolimab on calreticulin in myelofibrosis CD34+ cells in vitro: Proof of concept for combination therapy. *First Author: Ciro Roberto Rinaldi, University of Lincoln, Lincoln, United Kingdom*

Background: In solid tumours, calreticulin (CALR) overexpression produces a pro-phagocytic signal and is counteracted by concomitant expression of anti-phagocytic CD47, reflecting an apoptosis vs survival mechanism. We have previously found that CD47, not CALR, is overexpressed on the membrane of patients with MPN. Anti-CD47 Magrolimab, is currently being evaluated in clinical trials in AML, MDS but have yet to be tested, either in monotherapy or in combination in MF. **Methods:** Mononuclear cells were collected by Ficoll separation from bone marrow of 6 MF patients and from 2 controls. CD34+ cells and monocytes were purified using Dynabeads kits from ThermoFisher. Cells expression of CALR and CD47 was measured by flow cytometry, before and after incubation with ruxolitinib (Jak inhibitor) alone and in combination with magrolimab. Cells survival was calculated after combining CD34 with monocytes. Informed Consent was obtained for all samples collected. **Results:** CD47 membrane expression was 57% in untreated MF cells compared to 12% in the control samples and CALR membrane expression was 51.8% in untreated MF cell compared to 12.5% in the control samples. After incubation with ruxolitinib, MF CD34+ cell survival decreased to 98.2%. Following Incubation with magrolimab alone, MF CD34+ cells show no changes in survival (100% alive). The combination of ruxolitinib and magrolimab reduced slightly the MF CD34+ cell survival to 92%. A substantial membrane overexpression of CALR was observed in MF CD34+ cells when incubated with Ruxo and Magrolimab, 74.1%, vs Ruxo alone 52.6%, Magrolimab alone 53.4% and in untreated (51.8%). Interestingly, in the healthy controls, the exposure to combination therapy did not cause the same degree of CALR overexpression (20.7% vs 12.5%), indicating a much stronger pro-phagocytic effect following magrolimab/ruxolitinib combo in MF cancer cells. **Conclusions:** In vitro, treatment with ruxolitinib or ruxolitinib plus magrolimab, slightly reduce the overall cell survival rate in CD34+ MF samples, comparing with no significant changes in single agent magrolimab. However, the combination of Ruxolitinib and Magrolimab significantly increases CALR membrane expression comparing with Ruxo or Magrolimab alone, signalling a much stronger pro-phagocytic message in MF cells comparing with controls. The induced CALR over-expression, could stimulate a stronger immune response in vivo, where the presence of macrophages would allow removal of CALR rich cells and potentiate the cytoreductive activity towards MF clone. These data support the rational of combining Ruxolitinib with Magrolimab in the next clinical trial stage in myelofibrosis. Research Sponsor: Gilead.

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Poster Session

Impact of transfusion burden on health-related quality of life (HRQOL) and functioning in patients (pts) with myelofibrosis (MF): Post hoc analysis of SIMPLIFY-1 (S1) and -2 (S2). *First Author: Ruben A. Mesa, Wake Forest University School of Medicine, Winston-Salem, NC*

Background: MF is associated with substantial symptom burden that can negatively impact pt quality of life (QOL). Transfusions may reduce anaemia-associated symptoms, but can be burdensome and carry complications that may affect social, emotional, and general health; thus, QOL may be further negatively affected in transfusion-dependent (TD) pts. To characterize the relationship between transfusion burden and pt-reported outcomes (PROs), we report an exploratory post hoc analysis of the phase 3 S1 and S2 trials of the JAK1/JAK2/ACVR1 inhibitor momelotinib (MMB) in pts with MF. **Methods:** The pooled analysis set comprised both arms of the intent-to-treat populations of S1 (JAK inhibitor naive, MMB vs ruxolitinib [RUX]; N = 432) and S2 (JAK inhibitor exposed, MMB vs best available therapy [88% RUX]; N = 156). Transfusion independent (TI): no transfusions and hemoglobin (Hb) ≥ 8 g/dL in 12 wk; TD: ≥ 4 units transfused or Hb < 8 g/dL in 8 wk; transfusion requiring (TR): not meeting TI or TD criteria. PRO assessment: SF-36v2 (physical functioning [PF], role-physical [RP], general health [GH], vitality [VT], social functioning [SF], and mental health [MH]) domains; norm-based scores (NBS) range from 11.6 to 70.4 based on domain). PROs by transfusion status were described over the 24-wk randomized period. **Results:** SF-36v2 NBS were available from 503/588 pts in the pooled analysis set at baseline (BL); mean NBS in all domains were lower than the general population mean per the SF-36v2 Manual (50; SD, 10): PF, 39.6; RP, 39.0; GH, 39.8; VT, 43.6; SF, 43.2; MH, 46.3. Within the pooled analysis set, mean NBS in all domains at BL and week 24 (W24) were lower in TD vs TI pts. Among BL TD pts (n = 150) at W24, 75 remained TD (TD-TD), 40 became TI (TD-TI), 21 became TR, and 14 had no data. Pts who became TI experienced greater improvement (positive mean change from BL) in most domains vs pts who remained TD (Table). **Conclusions:** Among pts with MF in S1 and S2, TD pts had lower functioning and HRQOL than TI pts across SF-36v2 domains, suggesting that transfusion dependence has detrimental effects on multiple aspects of QOL. Among BL TD pts, those who became TI at W24 had greater improvement across most domains than those who remained TD, with mean changes for TD-TI pts near or above the minimally important difference (2 or 3, based on domain) for groups with low BL NBS. These analyses highlight transfusion dependence as a key pt-centered outcome and support further research into the impact of transfusions on QOL in MF. Clinical trial information: NCT01969838; NCT02101268. Research Sponsor: GSK plc.

SF-36v2 NBS, mean (SD)	BL TD (n = 150)	W24 TD-TI (n = 40)	W24 TD-TD (n = 75)	Mean change from BL at W24 (TD-TI vs TD-TD)
PF	36.8 (9.8)	42.9 (9.7)	38.9 (10.4)	4.8 vs 1.2
RP	37.4 (10.0)	41.8 (9.4)	38.4 (9.4)	2.2 vs 1.1
GH	38.2 (8.1)	44.1 (8.1)	39.6 (9.6)	4.3 vs 1.4
VT	42.1 (10.4)	47.8 (9.5)	44.6 (10.9)	2.5 vs 2.6
SF	42.6 (10.3)	48.6 (8.3)	43.6 (9.9)	5.0 vs -0.4
MH	46.0 (10.3)	48.8 (10.8)	47.1 (10.5)	3.5 vs 1.5

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Poster Session

Indirect treatment comparison (ITC) of momelotinib (MMB) vs fedratinib (FED) safety in patients (pts) with myelofibrosis (MF). *First Author: Lucia Masarova, Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: JAK inhibitors (JAKi) are a mainstay of MF treatment, with proven ability to improve symptoms and spleen volume for most pts; although safety profiles vary, some approved JAKi have associated hematologic toxicity. The JAK1/JAK2/ACVR1 inhibitor MMB has shown consistent benefit in improving anemia, symptoms, and spleen volume in pts with MF. Clinical trials have directly compared MMB with ruxolitinib, with MMB showing a more favorable hematologic toxicity profile. However, there are limited data comparing MMB vs other JAKi such as FED. We performed an ITC of safety outcomes between MMB and FED in pts with MF. **Methods:** A matching-adjusted indirect comparison (MAIC) was undertaken to compare outcomes from phase 2 and/or 3 MMB and FED trials. Adverse events (AEs) occurring in $> 10\%$ of a treatment arm over 24 weeks were evaluated; primary outcomes were grade 3/4 anemia and thrombocytopenia. Separate analyses were performed in JAKi-naive (SIMPLIFY-1 [S1] vs JAKARTa) and JAKi-experienced (pooled SIMPLIFY-2 [S2], MOMENTUM vs JAKARTa2) pts. Evaluable outcomes were limited by published aggregate data, so not all were feasible to compare. MAIC involved reweighting MMB pt data by matching baseline characteristics prioritized by expert clinical input (DIPSS/IPSS, Total Symptom Score, platelet counts, spleen volume/length, and/or hemoglobin levels) between trial arms, and determining odds ratios (ORs), risk ratios, and risk differences (RDs) between outcomes in resulting balanced populations. As nonrandomized groups were compared, results may be biased due to unmeasured/residual confounding, despite adjusting for prognostic factors/effect modifiers. **Results:** Effective MMB sample sizes after adjustment were 151.1 JAKi-naive and 79.4 JAKi-experienced pts. Risk of any or grade 3/4 anemia, diarrhea, nausea, and serious AEs leading to dose reductions were statistically less likely with MMB vs FED in both populations; any or grade 3/4 thrombocytopenia was also less likely with MMB vs FED, significantly so in JAKi-naive pts. Odds/risk of other outcomes assessed varied in significance (key OR/RD results presented in the Table). No identified outcomes were statistically less likely with FED. **Conclusions:** MMB showed a favorable safety profile vs FED in both JAKi-naive and experienced pts, including a significantly lower risk of key hematologic AEs, diarrhea, and nausea over 24 weeks. Clinical trial information: NCT04173494; NCT01969838; NCT02101268; NCT01523171; NCT01437787. Research Sponsor: GSK plc.

MMB vs FED	JAKi naive		JAKi experienced	
	S1 vs JAKARTa		S2, MOMENTUM vs JAKARTa2	
	OR	RD, %	OR	RD, %
Anemia				
Grade 3/4	0.09 ^a	-36.7 ^a	0.07 ^a	-34.3 ^a
Any	0.00 ^a	-85.3 ^a	0.08 ^a	-41.3 ^a
Thrombocytopenia				
Grade 3/4	0.48 ^a	-7.9	0.72	-5.1
Any	0.15 ^a	-42.2 ^a	0.79	-4.4
Diarrhea (any)	0.11 ^a	-47.8 ^a	0.29 ^a	-29.5 ^a
Headache (grade 3/4)	0.01 ^a	-13.4 ^a	0.97	-0.4
Nausea (any)	0.10 ^a	-48.8 ^a	0.15 ^a	-39.9 ^a
Serious AE				
Discontinuation	0.45	-7.0	0.16 ^a	-20.6 ^a
Dose reduction	0.02 ^a	-43.2 ^a	0.01 ^a	-38.5 ^a
Grade 3/4 AE	0.24 ^a	-34.1 ^a	0.67	-9.9

^a P < .05.

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Poster Session

Longitudinal assessment of cardiac involvement in Erdheim-Chester disease using cardiac magnetic resonance imaging. *First Author: Levi-Dan Azoulay, Hôpital Pitié-Salpêtrière, Paris, France*

Background: Erdheim-Chester disease (ECD) is a rare multi-systemic non-Langerhans cell histiocytosis that affects the heart in nearly half of patients. Atrial infiltration and pericardial effusion are the hallmarks of cardiac involvement and can lead to clinical complications (conduction disorders, coronary artery stenosis, tamponade, constrictive pericarditis). Evolution under treatment is poorly studied. We aimed to investigate the evolution of cardiac involvement in ECD using cardiac magnetic resonance (CMR) imaging. **Methods:** All ECD patients with a CMR imaging disclosing a cardiac involvement and who underwent at least one follow-up CMR imaging between 2005 and 2020 at a French tertiary center were retrospectively included. First and last CMR imaging were compared. Multivariable analysis was performed to search for independent predictors of cardiac involvement resolution. Variables were included in the model if their P-value was < 0.1 on univariable analysis. **Results:** Overall, 46 patients were included. Median age at first imaging was 63 years [53-69]. Median delay between the first and the last imaging was 4 years [2-7]. *BRAF*^{V600E} mutation was present in 43 patients (94%). Patients received a median of 2 [1-3] treatments. All patients (100%) had cardiac involvement at baseline. Right atrio-ventricular sulcus (RAVS) was infiltrated in 38 patients (83%) and was the main cardiac feature. Overall, complete regression was observed in 6 patients (13%), partial regression in 26 patients (56%), stable imaging in 12 patients (26%), and worsening in 2 patients (5%). In patients with RAVS infiltration, complete regression was observed in 5 patients (16%) and partial regression was seen 22 patients (58%) regression. On univariable analysis, patients with regression of their infiltration had a lower rate of death (16% versus 64%, $P = 0.002$), a higher rate of atrial infiltration late gadolinium enhancement (LGE) (97% versus 71%, $P = 0.01$), a higher rate of hydronephrosis (50% versus 14%, $P = 0.03$) and a lower rate of interferon prescription (69% versus 100%, $P = 0.02$). A similar rate of vemurafenib use was observed in both groups (69% versus 54%, $P = 0.3$). On multivariable analysis, death remained significantly associated with follow-up imaging status ($\beta = -2.3$ $P = 0.01$), while atrial infiltration LGE ($\beta = 2.7$, $P = 0.06$), hydronephrosis ($\beta = 1.6$, $P = 0.1$) and treatment with interferon ($\beta = -1.6$, $P = 1$) were no longer significantly associated with imaging status. **Conclusions:** Partial or complete resolution of cardiac involvement was observed in 69% of patients with ECD and was significantly associated with a lower rate of death on multivariable analysis. Research Sponsor: None.

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Poster Session

Consistency of pacritinib for spleen and symptom reduction in patients with myelofibrosis regardless of cytopenias. *First Author: Prithviraj Bose, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: In patients with myelofibrosis (MF), JAK inhibitor therapy can improve both splenomegaly and disease symptoms. Unfortunately, dosing – and thus efficacy – of available current JAK1/2 inhibitors is frequently limited in patients with cytopenic MF due to drug-induced exacerbation of cytopenias. Pacritinib is a novel JAK1-sparing inhibitor of JAK2/IRAK1/ACVR1 that has been studied at full dose in patients with MF regardless of cytopenias. Here, we present data on spleen and symptom benefit in pacritinib-treated patients across the cytopenic spectrum, stratified by both baseline platelet (PLT) count and hemoglobin (HB) level. **Methods:** Evaluable patients treated with pacritinib in the PERSIST-1 and PERSIST-2 studies were analyzed, stratified by baseline PLT (<100, ≥100x10⁹/L) and HB (<8, 8 to <10, ≥10 g/dL). Groups were analyzed for depth of spleen volume response (SVR), modified total symptom score (TSS) response, patient global impression of change (PGIC), and dose intensity. **Results:** Of 276 patients evaluable for spleen response, median age was 67 years, 51.5% had grade 3 fibrosis, 70% had primary MF, and 16% had prior JAK2 inhibitor exposure. Median dose intensity was >99.7% for the duration of the study across PLT and HB subgroups. Overall, 80% of patients had ≥10% SVR (SVR-10), 75.5% had TSS-10, and 78% reported that their symptoms were improved at week 24. Week 24 spleen reduction occurred consistently across PLT and HB strata, with 84-93% and 86-90% of patients respectively (Table). SVR-35 occurred in 23-25% of patients across PLT strata and in 21-28% of patients across HB strata. Symptom response was also consistent across strata, though TSS-50 occurred at highest rates (62.5%) in patients with HB <8 g/dL. There was no diminution in symptom burden reduction in patients with thrombocytopenia (Table). Across all subgroups, at least three-quarters of patients reported symptoms were “improved” at week 24. **Conclusions:** Pacritinib demonstrates consistent efficacy for spleen and symptom response in patients with MF regardless of blood counts. This consistent effect may be related to pacritinib’s unique kinome profile and its ability to be delivered at full dose in patients regardless of cytopenias. Clinical trial information: NCT01773187, NCT02055781. Research Sponsor: CTI BioPharma Corp.

Week 24 percent of evaluable patients responding by baseline PLT (x10 ⁹ /L), HB (g/dL).					
	PLT <100 N=136	PLT ≥100 N=137	HB <8 N=29	HB 8-9.99 N=94	HB ≥10 N=153
SVR-35	25%	23%	21%	28%	23%
SVR-10	77%	82%	79%	75.5%	82%
SVR-0	84%	93%	90%	86%	89.5%
TSS (N)*	N=100	N=56	N=24	N=55	N=80
TSS-50	43%	41%	62.5%	33%	44%
TSS-10	74%	79%	79%	73%	76%
PGIC (N)	N=112	N=120	N=24	N=84	N=127
“Much” / “very much improved” at week 24	43%	52.5%	54%	37%	55%
Any “improved” at week 24	75%	81%	79%	76%	79.5

*Only scores from TSS v2.0 were included in this analysis. Abbreviations: HG, hemoglobin; PGIC, patient global impression of change; PLT, platelets; SVR, spleen volume response; TSS, modified total symptom score.

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Poster Session

Outcomes of patients with a myeloproliferative neoplasm and atrial fibrillation. *First Author: Orly Leiva, New York University Grossman School of Medicine, New York, NY*

Background: Patients with myeloproliferative neoplasms (MPN), including essential thrombocythemia (ET), polycythemia vera (PV), and primary myelofibrosis (PMF), are associated with increased risk of cardiovascular (CV) disease including arterial thrombosis (AT). Atrial fibrillation (AF) is also associated with increased risk of AT and often co-exists with MPN. However, thrombotic and bleeding outcomes in patients with MPN compared with those without have not been thoroughly investigated. **Methods:** Patients aged ≥ 18 years with a hospital admission for AF with and without a history of MPN in 2017 and 2018 were identified using the National Readmission Database. Primary outcomes were 30-day (D) and 90-D any-cause, AT-related (including stroke, myocardial infarction, arterial thromboembolism), and bleeding-related readmissions. Propensity score weighting (PSW) was performed in order to adjust for imbalances between MPN and non-MPN patients. PSW Cox proportional hazards was performed to estimate risk of 90-D readmission in patients with MPN compared with patients without. **Results:** A total of 468,094 patients with AF were identified with 1,617 patients having a history of MPN. CHA₂DS₂-VASC (mean 3.8 vs 3.7) and HAS-BLED scores (mean 2.4 vs 2.3), risk scores for AT and bleeding in AF, were similar between MPN and non-MPN patients. After PSW Cox proportional hazards, patients with MPN had an increased risk of 30-D all-cause (HR 1.72, 95% CI 1.70 – 1.74), AT (HR 1.45, 95% CI 1.38 – 1.53), and bleeding (HR 2.21, 95% CI 2.01 – 2.44) re-admissions. MPN patients had an increased risk of 90-day any cause (HR 1.38, 95% CI 1.37 – 1.40) and bleeding (HR 1.76, 95% CI 1.65 – 1.88) but not AT (HR 1.03, 95% CI 0.99 – 1.08) readmissions. **Conclusions:** Among patients admitted for AF, MPN is associated with increased risk of 30-D and 90-D any-cause and bleeding readmissions and 30-D AT readmissions despite similar CHA₂DS₂-VASC and HAS-BLED risk scores. Further studies are needed to identify risk factors for bleeding and AT in patients with MPN and AF and improve on current risk scores, which do not include MPN status. Research Sponsor: None.

	Non-MPN N = 466,477	MPN N = 1,617
Age, mean (SD)	70.9 (12.9)	73.3 (12.1)
Female Sex, N (%)	227,303 (48.7)	870 (53.8)
Co-Morbidities, N (%)		
Coronary artery disease	173,677 (37.2)	545 (33.7)
Anemia	69,318 (14.9)	564 (34.9)
Thrombocytopenia	16,381 (3.5)	72 (4.5)
Chronic Lung Disease	111,837 (24.0)	417 (25.8)
Diabetes	133,347 (28.6)	359 (22.2)
Hypertension	368,470 (79.0)	1,221 (75.5)
Prior Stroke	43,945 (9.4)	186 (11.4)
Long-term Anticoagulation	155,332 (33.3)	492 (30.3)
Long-term Anti-Platelet	107,538 (23.1)	425 (26.3)
CHADS ₂ -VASC, mean (SD)	3.7 (1.8)	3.8 (1.8)
HAS-BLED, mean (SD)	2.3 (1.1)	2.4 (1.1)

CHA₂DS₂-VASC includes congestive heart failure, age, hypertension, diabetes, prior stroke, vascular disease, and sex. HAS-BLED includes age, hypertension, medications predisposing to bleeding, prior bleeding, alcohol use.

7069

Poster Session

Bromodomain and extra-terminal (BET) inhibitor INCB057643 (LIMBER-103) in patients (pts) with relapsed or refractory myelofibrosis (R/R MF) and other advanced myeloid neoplasms: A phase 1 study. *First Author: Justin M. Watts, Sylvester Cancer Center, University of Miami, Miami, FL*

Background: BET proteins are epigenetic readers that regulate expression of critical onco-proteins involved in the pathophysiology of hematologic malignancies, including MF. INCB057643 is a small-molecule BET inhibitor evaluated as monotherapy and in combination with ruxolitinib (RUX) in pts with advanced malignancies in 2 previous phase 1/2 clinical trials. **Methods:** This ongoing phase 1, 3+3 dose-escalation/expansion study (NCT04279847) evaluates safety and tolerability of INCB057643 (4 mg once daily [qd]; escalation up to 12 mg qd) in pts aged ≥18 years as (1) monotherapy (part 1) in R/R MF, myelodysplastic syndromes (MDS), or MDS/myeloproliferative neoplasm (MPN) overlap syndromes (MDS/MPN) or (2) added to RUX (part 2) in pts with MF and suboptimal response to RUX. The primary endpoint is safety and tolerability, including identification of dose-limiting toxicities (DLTs). **Results:** 13 pts have been treated in part 1 (4 mg, n=6; 8 mg, n=4; 10 mg, n=1; 12 mg, n=2), and 3 pts received 4 mg + RUX in part 2 (overall age range, 50–79 years; men, n=9; study treatment duration range, 15–314 days). 12 pts had MF, and 4 had MDS/MPN. All 6 pts in the 4-mg cohort discontinued treatment (3 for progressive disease [PD]; MF, n=2; MDS/MPN, n=1); 1 pt with MF in the 12-mg cohort discontinued for thrombocytopenia. The other 9 pts remain on treatment. Thrombocytopenia was the most common treatment-emergent adverse event (TEAE; n=9; Table) and the only TEAE leading to discontinuation (n=3). Grade ≥3 TEAEs occurring in ≥1 pt were thrombocytopenia (n=4), anemia (n=3), and hypokalemia (n=2). There were 8 serious AEs across 4 pts, with only COVID-19 occurring in >1 pt (n=2); all but one (pneumonia) were considered unrelated to study treatment. There were 2 DLTs (thrombocytopenia [MDS/MPN pt] and hyperbilirubinemia [MF pt]; both 12-mg cohort) and 2 deaths (both 4-mg cohort due to PD [MF, n=1; MDS/MPN, n=1]). **Conclusions:** Treatment with INCB057643 monotherapy (4 and 8 mg qd) and in combination (4 mg qd) with RUX was generally well tolerated in this pt population. The 12-mg qd monotherapy dose was not tolerated and caused 2 DLTs. There were no treatment-related fatal events. Dose finding in part 1 is ongoing with 10 mg qd, after which a recommended phase 2 dose will be declared. Combination dose escalation is also ongoing. Preliminary efficacy including spleen size and symptoms will be available for presentation. Clinical trial information: NCT04279847. Research Sponsor: Incyte Corporation.

TEAEs occurring in ≥3 patients.						
TEAE, n (%)	4 mg (n=6)	8 mg (n=4)	10 mg (n=1)	12 mg (n=2)	4 mg + RUX (n=3)	Total (N=16)
Thrombocytopenia	3 (50)	2 (50)	1 (100)	1 (50)	2 (67)	9 (56)
Dysgeusia	0	1 (25)	1 (100)	2 (100)	1 (33)	5 (31)
Nausea	1 (17)	2 (50)	0	1 (50)	0	4 (25)
Anemia	2 (33)	1 (25)	0	0	0	3 (19)
Blood bilirubin increased	1 (17)	2 (50)	0	0	0	3 (19)
Ejection fraction decreased	0	1 (25)	0	0	2 (67)	3 (19)
COVID-19	0	2 (50)	0	0	1 (33)	3 (19)

7071

Poster Session

Clinical outcomes by SF3B1 mutation status in patients (pts) with lower-risk myelodysplastic syndrome (LR-MDS) retreated with erythropoiesis-stimulating agents (ESAs). *First Author: Adeola Y. Makinde, Bristol Myers Squibb, Princeton, NJ*

Background: Pts with SF3B1-mutated LR-MDS often have a more favorable prognosis versus those with SF3B1 wildtype. A sizeable number of pts with LR-MDS undergo ESA treatment even after experiencing ESA failure in first line. This study evaluated the outcomes of pts with LR-MDS retreated with ESAs in routine clinical practice, stratified by SF3B1 status. **Methods:** This retrospective cohort study included pts with LR-MDS in the US community setting who initiated ESAs as first-line therapy between January 1, 2016 and June 30, 2019, and were followed through June 30, 2021. Eligible pts discontinued ESAs (treatment gap ≥ 3 wk for epoetin alfa or ≥ 6 wk for darbepoetin alfa) and subsequently reinitiated ESA therapy at least once during follow-up. Ring sideroblasts (RS) ≥ 15% served as a surrogate for pts with unknown SF3B1 mutation status. Outcomes included ESA switches, dose reductions and escalations, ESA failure, and overall survival (OS). Primary ESA failure was defined as no rise in hemoglobin (Hb) ≥ 1.5 g/dL or no decrease in RBC transfusion requirement by 8 wk of treatment. Transfusion-dependent (TD) status was evaluated for pts who were transfusion independent (TI) at baseline. **Results:** A total of 82 pts with LR-MDS and repeat ESA treatment were included. Median age at start of ESA treatment was 79 y (interquartile range [IQR], 72–85). Diagnosis of MDS-RS, MDS with isolated del(5q), MDS with multilineage dysplasia, and MDS with single lineage dysplasia was reported in 30 (36%), 7 (9%), 9 (11%), and 9 (11%) pts, respectively; 27 (33%) had unknown classification. Median follow-up was 26 mo (IQR, 13–38) with 65% failing ESA therapy by 8 wk. Table shows pts’ SF3B1 mutation status, median OS, pts who had an ESA switch, dose reduction or escalation, experienced ESA failure, and pts who were TI at baseline and became TD during follow-up. Results were similar when RS was not used as a surrogate, and when analyses were limited to pts who were treated with ESAs only throughout follow-up. **Conclusions:** In this study of pts with LR-MDS retreated with ESAs, primary ESA failure was high with nearly half of TI pts becoming TD during follow-up. OS was poor regardless of SF3B1 status – 2–4 times lower than the remaining life expectancy for a 79-y-old (108 mo for men; 125 mo for women). Although treatment options were limited during the study period, the high primary failure rate suggests that pts with LR-MDS may benefit from alternatives to ESAs. Research Sponsor: Bristol Myers Squibb.

Clinical outcomes by SF3B1 status.				
	Overall (n = 82)	SF3B1 positive (n = 19)	SF3B1 negative (n = 29)	Unknown (n = 34)
Pts who experienced, n (%)				
ESA switch	18 (22)	7 (37)	7 (24)	4 (12)
Dose reduction	29 (35)	6 (32)	11 (38)	12 (35)
Dose escalation	34 (41)	11 (58)	12 (41)	11 (32)
ESA failure	53 (65)	13 (68)	15 (52)	25 (74)
Pts who became TD during follow-up, n/N (%)				
OS, median, mo	26/54 (48)	7/17 (41)	10/19 (53)	9/18 (50)
	45	58	35	27

7072

Poster Session

Outcomes of individuals with clonal hematopoiesis evaluated at a cancer center. *First Author: Kelly Sharon Chien, Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Clonal hematopoiesis (CH) refers to the presence of somatic mutations in individuals without overt hematological disorders. CH, including CH of indeterminate potential (CHIP) and clonal cytopenia of undetermined significance (CCUS), is associated with hematologic malignancies and other systemic comorbidities. There are currently no established guidelines regarding the optimal monitoring and management of patients with CH, and the impact of CH in patients with concomitant underlying malignancies remains unknown. **Methods:** Patients seen at a tertiary cancer center with at least 1 somatic mutation detected by next generation sequencing on bone marrow aspirate or peripheral blood between January 2015 and March 2021 were included. Patients with donor-derived CH or any morphologic evidence of a myeloid neoplasm were excluded. **Results:** We evaluated 78 patients—76% had a history of malignancy and 73% had other comorbidities. The mutations most frequently observed were *DNMT3A* (40%), *TET2* (31%), *TP53* (26%), and *ASXL1* (18%). The median overall survival for all patients was not reached (2-year survival rate of 79%). Most deaths were related to primary malignancies (35%), comorbidities (20%), or myeloid neoplasms (20%). Due to concomitant use of antineoplastic therapy and other causes of cytopenia in 19 patients, we further categorized patients into 4 groups: CHIP on treatment (CHIP-T), other CHIP (CHIP-O), CCUS on treatment or with a non-myeloid hematologic malignancy (CCUS-T), and other CCUS (CCUS-O). Transformation to a myeloid neoplasm occurred in 12 patients (15%). The 3-year cumulative incidence of transformation was higher in CCUS-O (24%) and CCUS-T (21%) compared to the CHIP group (6%, $p = 0.48$). On univariate analysis, increasing age, variant allele frequency (VAF) ≥ 0.2 , hemoglobin < 10 g/dL, and any chromosomal abnormalities were associated with higher risk for transformation. By multivariate analysis, transformation was only significantly associated with VAF ≥ 0.2 (hazard ratio (HR) 18.25; 95% confidence interval (CI): 3.59, 92.73; $p = 0.0005$) and hemoglobin < 10 g/dL (HR 15.62; 95% CI: 3.29, 74.05; $p = 0.0005$). **Conclusions:** CH in predominantly cancer patients is associated with cardiovascular disease and transformation to myeloid neoplasms, especially in those with higher mutational burdens and anemia. However, patients die more frequently from their primary malignancy or comorbidities than from a myeloid neoplasm. Close monitoring of hematologic progression and extra-hematologic manifestations of CH is crucial. Further investigation into the identification of individuals at high risk of myeloid transformation and potential early therapeutic interventions for this population is warranted. Research Sponsor: The University of Texas MD Anderson Cancer Center Support Grant CA016672 and The University of Texas MD Anderson MDS/AML Moon Shot Program.

TPS7074

Poster Session

A randomized, open-label study of the efficacy and safety of galinpepimut-S (GPS) maintenance monotherapy compared to investigator's choice of best available therapy (BAT) in patients with acute myeloid leukemia (AML) who have achieved complete remission (CR) after second-line salvage therapy. *First Author: Omer Hassan Jamy, University of Alabama at Birmingham, Birmingham, AL*

Background: Patients with relapse/refractory (r/r) AML have poor outcomes. Allogeneic stem cell transplantation (allo-SCT) can potentially cure some patients with r/r AML who achieve second CR (CR2). However, barriers to transplantation such as advanced age, poor functional status/comorbidities or lack of donor exist and not all patients are able to proceed to allo-SCT. Therefore, novel strategies to decrease relapse risk in these patients are urgently needed. A National Cancer Institute consensus study on prioritization of cancer antigens ranked the Wilms tumor 1 (WT1) protein as the top immunotherapy target in cancer. WT1 has emerged as an encouraging vaccine target in AML due to its overexpression in leukemic blasts. Maintenance therapy with Galinpepimut-S (GPS), a multivalent heteroclitic WT1 peptide vaccine, has shown promising activity in patients with AML by inducing a strong innate immune response (CD4+/CD8+) against the WT1 antigen and across a broad range of HLA types. **Methods:** This is an open-label, multicenter, randomized, phase III study of GPS vs. BAT in patients with AML in CR2/CRp2 (CR2 with incomplete platelet recovery). BAT may include observation, low dose cytarabine and hypomethylating agents +/- venetoclax. The primary endpoint of the study is overall survival (OS). Secondary endpoints include safety and tolerability of GPS and leukemia-free survival. Exploratory endpoints include WT1-specific immune response dynamics in blood and bone marrow. Approximately 125–140 patients will enroll, in a 1:1 ratio, to provide at least 90% power under an assumed hazard ratio of 0.52, based on median OS of 8.0 m (BAT) and 15.4m (GPS). Randomization will be stratified by duration of CR1 (< 12 m vs. ≥ 12 m), Cytogenetics (poor-risk vs. all other), CR2 vs. CRp2 and measurable residual disease (MRD) after CR2 (MRD- vs. MRD+). Inclusion criteria consists of willing subjects ≥ 18 y with AML within 6m of achieving CR2/CRp2, ineligible for allo-SCT due to any reason, with ≥ 300 lymphocytes/ μ L and with adequate renal and hepatic function. Subjects with central nervous involvement, having received a live vaccine 30d prior to first dose of study drug, having a diagnosis of immunodeficiency, receiving ≥ 10 mg daily of prednisone equivalent (or any other systemic immunosuppressant) for any indication 7d prior to first dose of study drug, hypersensitivity to study agent and with a history of solid organ transplant would be excluded. The clinical trial is actively enrolling, and the registry number is NCT04229979. Clinical trial information: NCT04229979. Research Sponsor: Sella Life Sciences Group.

TPS7073

Poster Session

A phase 1b/2 study of pivekimab sunirine (PVEK, IMG632) in combination with venetoclax/azacitidine or magrolimab for patients with CD123-positive acute myeloid leukemia (AML). *First Author: Naval Guastad Daver, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Despite improved outcomes with azacitidine (AZA) and venetoclax (VEN) in frontline unfit AML (CR 37% and CR/CRi 66%), long-term survival for these patients remains inadequate (mOS < 15 m, DiNardo NEJM 2020). CD123 is expressed on the majority of AML blasts and leukemic stem cells while minimally expressed on normal hematopoietic stem cells (Kovtun Blood Adv 2018). Pivekimab sunirine (PVEK, IMG632) is an antibody-drug conjugate (ADC) comprising a high-affinity CD123 antibody, cleavable linker, and an indolinobenzodiazepine pseudodimer (IGN) payload. The IGN payload alkylates DNA and causes single strand breaks without crosslinking. IGNs are designed to have high potency against tumor cells, while demonstrating less toxicity to normal marrow progenitors than other DNA-targeting payloads. Clinical data in relapsed/refractory (R/R) AML (Daver ASH 2022) supported the continued clinical exploration of the PVEK+AZA+VEN triplet. The current enrolling dose expansion cohorts (Regimen C; Cohorts 1 and 2) in frontline AML will evaluate antileukemia activity and MRD levels in the combination of PVEK+AZA+VEN. Regimen E will enroll patients with R/R AML to evaluate the safety and antileukemia activity of PVEK in combination with magrolimab. **Methods:** This is an open-label, multicenter, Phase 1b/2 study of PVEK administered in combination regimens in patients with frontline and R/R CD123-positive AML. Patients will receive the established recommended phase 2 dose (RP2D) of PVEK 0.045 mg/kg IV, as a < 30 -minute outpatient infusion. In Regimen C, patients will receive PVEK 0.045 mg/kg IV on D7 + azacitidine 75 mg/m² SC or IV daily on days 1 to 7, and venetoclax up to 400 mg PO daily for at least 14 days (Cohort 1) or for up to 28 days (Cohort 2) in a 28-day cycle. In Regimen E, R/R AML patients will receive PVEK 0.045 mg/kg IV on D1 of the 28-day cycle in combination with magrolimab at 30 mg/kg Q2W, after the standard ramp up schedule. Regimen C will enroll adults with untreated AML, CD123+ by flow cytometry or IHC and no prior HMA treatments. The primary endpoints for Regimen C are composite CR rate, overall response rate (ORR), duration of remission (DOR), MRD levels and key secondary endpoints are safety, PK and immunogenicity. Regimen E will enroll adult patients with relapsed or refractory CD123+ AML with up to 2 prior lines of therapy. The primary endpoint for Regimen E is dose limiting toxicities (DLTs) and key secondary endpoints are safety, antileukemic activity, PK and immunogenicity. The PVEK+AZA+VEN triplet (Regimen C) is currently enrolling frontline unfit patients across sites in France, Germany, Italy, Spain, UK and USA. The PVEK+Magro doublet (Regimen E) is planned to be open for enrollment mid-2023 at sites in the USA. Clinical trial information: NCT04086264. Research Sponsor: ImmunoGen, Inc.

TPS7075

Poster Session

Iadademstat in combination with gilteritinib for patients with mutated FLT3 relapsed/refractory acute myeloid leukemia. *First Author: Amir Tahmasb Fathi, Massachusetts General Hospital, Harvard Medical School, Boston, MA*

Background: Epigenetic dysregulation is a hallmark of acute myeloid leukemia (AML) and is caused by recurrent translocations and/or mutations in chromatin regulators and transcription factors, resulting in myeloid differentiation blockade and leukemic stem cell renewal. Accordingly, about 70% of recurring mutations in AML patients (pts) target regulators of gene expression, underscoring the potential of epigenetic therapies to change the disease natural history. Iadademstat (iada/ORY-1001) is a specific, oral, potent, covalent inhibitor of the epigenetic Lysine-Specific Demethylase 1 (LSD1/KDMA1) enzyme. In preclinical and clinical studies iada decreased leukemic stem cell survival and induced macrophage/monocytic differentiation of blasts. ALICE, a Ph2 study of iada in combination with azacitidine (aza), showed high complete remission (CR/CRi) rates and durable responses in treatment naive, unfit AML pts without exacerbating the toxicity profile of aza (Salamero et al., Oral at ASH 2022). Despite improvements in AML therapy, relapsed and refractory (R/R) cases are frequent and contribute to the death of more than 50% of pts, particularly in those subpopulations with higher risk genetics, the largest of which (up to 30-40% AML pts) harbors fms-like tyrosine kinase 3 mutations (FLT3mut+). Use of the FLT3 inhibitor (FLT3i) gilteritinib as monotherapy for R/R pts resulted in improved outcomes but the duration of remission achieved is transient and often brief (CR rate: 20%; EFS: 2.8 months) per the ADMIRAL Ph3 study (Perl, et al., NEJM 2019). Preclinically, iada has marked synergy with FLT3i, particularly gilteritinib, in FLT3 wild-type and FLT3 mut+ AML cells and in derived cell lines resistant to venetoclax, azacitidine and FLT3is. **Methods:** Adult pts with ECOG 0-2 and FLT3 mut+ R/R AML, after 1 or 2 prior lines of therapy, will be enrolled. In escalation (3+3), up to 18 pts will receive iada at 75 to 150 μ g, orally, in 5 days ON-2 days OFF schedule, with gilteritinib SoC. Up to approximate 14 pts will be expanded from pharmacologically active dose/s (per Project OPTIMUS). Primary endpoints of the study are safety and RP2D determination. Bayesian posterior probability efficacy monitoring will be performed periodically for each dose cohort. Bayesian efficacy futility and early stopping boundary will be applied. Posterior probability criterion (Prob (CR > 0.3) ≥ 0.60) at the end of the study will warrant further research. Safety in expansion will be evaluated continuously with a Bayesian stopping rule. Secondary endpoints include OS, EFS, CR, CR/CRi, ORR, TTR, DoR, and transfusion rate. Exploratory endpoints include PK, PD, MRD and gene mutational analysis. The study will run in 15 US sites. Additional sites will be added for a subsequent Phase 2 randomized controlled double-blinded FRIDA 2 study to assess the efficacy of this combination in R/R FLT3 mut+ AML. Clinical trial information: NCT05546580. Research Sponsor: Oryzon Genomics.

TPS7076

Poster Session

A phase II study of vibecotamab, a CD3-CD123 bispecific T-cell engaging antibody, for MRD-positive AML and MDS after hypomethylating agent failure. First Author: Nicholas James Short, Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: CD123 is a marker of leukemic stem cells that is differentially overexpressed in most patients with acute myeloid leukemia (AML), myelodysplastic syndromes (MDS) and chronic myelomonocytic leukemia (CMML). In contrast, CD123 is expressed at negligibly low levels on normal hematopoietic progenitors, making it a potentially promising therapeutic target. Vibecotamab (formally XmAb14045) is a CD3-CD123 bispecific engaging antibody that has established clinical activity in relapsed/refractory AML. In a phase I study, the overall response rate was 14.8% in patients who received vibecotamab at a dose of $\geq 0.75 \mu\text{g/kg}$ (Ravandi F et al. ASH 2020 abstract #460). Response rates were notably higher in those with lower disease burden (bone marrow blasts $\leq 25\%$) where the overall response rate was 25.9%. In light of the activity of vibecotamab in relapsed/refractory low-blast AML, we designed this phase II study to evaluate vibecotamab in other low-blast states, including CD123-positive, MRD-positive AML and in MDS or CMML after failure of hypomethylating agents. **Methods:** This is a two-arm, open-label, phase II study of vibecotamab in patients with AML in first or second morphological remission with detectable MRD at a level of $\geq 0.1\%$ by flow cytometry and in patients with MDS (intermediate or higher-risk by IPSS-R) or CMML (CMML-1 or CMML-2) after failure of hypomethylating agents. CD123 expression $\geq 20\%$ on aberrant myeloid blasts is required for study eligibility. Vibecotamab is given IV in a ramp-up dose schedule on days 1, 3, 5 and 8 of cycle 1, followed by weekly doses of vibecotamab at a dose of $1.7 \mu\text{g/kg}$. Patients may receive up to 4 cycles of vibecotamab in 28-day cycles. The primary objective of the AML MRD cohort is to determine the MRD negativity rate after 4 cycles; the primary objective of the MDS/CMML cohort is to determine the response rate (CR + mCR + PR + HI + clinical benefit) after 4 cycles. The target MRD response in the AML MRD cohort is 50%, and the target response rate in the MDS/CMML cohort is 30%. Secondary endpoints include remission duration, duration of MRD response (AML MRD arm), CR rate (MDS/CMML arm), relapse-free survival, overall survival, and safety. Exploratory endpoints include correlation of clinical outcomes with CD123 expression and the dynamics of CD123 expression at treatment initiation and at the time of relapse. Additional immunological correlates will be performed, including 1.) determination of molecular immune states that predict response or resistance, 2.) functional interrogation of TCR-antigen interactions, and 3.) nomination of leukemic neo-antigens. The planned enrollment is 40 patients (20 in each of the two cohorts). To date, 13 patients have been enrolled (7 in the AML MRD cohort and 6 in the MDS/CMML cohort). The trial is actively accruing at MD Anderson Cancer Center. Clinical trial information: NCT05285813. Research Sponsor: MD Anderson Cancer Center; Xencor.

TPS7078

Poster Session

Phase 1B/2A safety, pharmacokinetics and pharmacodynamics study of foscicliprox alone and in combination with cytarabine in patients with relapsed/refractory acute myeloid leukemia. First Author: Tara L. Lin, Division of Hematologic Malignancies & Cellular Therapeutics, University of Kansas, Kansas City, KS

Background: Foscicliprox (CPX-POM) is a broad-spectrum anticancer agent being developed through a public-private partnership between CicloMed LLC and KU Cancer Center (KUCC). Following intravenous administration, foscicliprox is rapidly and completely metabolized to its active metabolite clidopirox (CPX). Given foscicliprox is a prodrug lacking pharmacologic activity, in vitro mechanistic studies were conducted utilizing CPX as the test article. In collaboration with Notable Labs (Foster City CA), we characterized ex vivo sensitivity to CPX in bone marrow and peripheral blood samples from ten newly diagnosed and relapsed acute myeloid leukemia (AML) patients. Reductions in blast counts were seen in each of the 10 patients studied at clinically relevant concentrations. In vitro experiments in AML cell lines (HL-60 and MV4-11) characterized the mechanism(s) of the anti-leukemia activity of CPX. CPX inhibited proliferation of AML cell lines in a dose- and time-dependent manner with IC50 values ranging from 2.5-4 μM . CPX induced cell cycle arrest in the subG0 phase and CPX-treated cells lost their ability to enter to G0-G1 phase. Moreover, CPX induced early and late phase apoptosis. CPX also activated Caspase 3/7 activity. This preclinical data led to the development of a multi-center Phase 1B/2A clinical proof of concept trial (NCT04956042) in AML patients. **Methods:** Eligible AML patients are adults with primary refractory (two prior regimens) or relapsed AML; ECOG PS 0-2; adequate end organ function. Prior allogeneic stem cell transplant is allowed if patient is more than 100 days post-transplant with no active graft-versus-host disease. CPX-POM is administered as 900 mg/m² once daily as an IV infusion on Days 1 to 5 of each 21-day cycle. Day 8 bone marrow sample is collected for correlative studies. Ex vivo Drug Sensitivity Screening (DSS) will be performed on samples obtained prior to treatment and C1 Days 8 and 21. 14 evaluable patients will be enrolled in Cohort 1a. If disease response is observed in at least 4 of 14 patients, an additional 14 patients will be enrolled in Cohort 1b. During Cohort 1a, patients who do not respond to CPX-POM alone may be switched to the combination of CPX-POM + cytarabine. Patients who respond to the combination treatment may continue until evidence of disease progression. If disease response to CPX-POM alone is not observed in at least 4 of 14 patients in Cohort 1a, the study may be terminated or a Cohort 2a may be initiated using the combination of CPX-POM and cytarabine. The trial is currently open at two sites with 14 patients enrolled and 8 evaluable for the primary endpoint. Clinical trial information: NCT04956042. Research Sponsor: CicloMed LLC.

TPS7077

Poster Session

A phase 1/2 dose escalation study of the BCL-2 inhibitor ZN-d5 and the WEE1 inhibitor azenosertib (ZN-c3) in patients (Pts) with acute myeloid leukemia (AML). First Author: Catherine Choy Smith, Division of Hematology/Oncology, Department of Medicine, Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco, CA

Background: B-cell lymphoma 2 (BCL-2) is an anti-apoptotic protein and pathway inhibition combined with chemotherapy and/or targeted therapeutics has led to significant clinical benefit in pts with AML. Disruption of cell cycle regulation may complement BCL-2 inhibition as many malignant cells are dependent on proteins that regulate cell cycle progression. The cell cycle checkpoint protein, WEE1, is highly expressed in genomically unstable malignancies and inhibition of WEE1 induces tumor cell apoptosis. It has been previously reported that the combination of ZN-d5 (an oral, selective BCL-2 inhibitor) and azenosertib (an oral, highly potent WEE1 inhibitor) synergistically enhance killing of AML cells both *in vitro* and *in vivo*, as well as in TP53-mutated models (Izadi, AACR 2022). Based on this strong pre-clinical rationale, a Phase 1/2 study was designed to evaluate the novel combination of ZN-d5 and azenosertib in pts with relapsed/refractory (R/R) AML. **Methods:** This phase 1/2 open-label study (ZN-d5-004C, NCT05682170) is determining the maximum tolerated dose (MTD), recommended phase 2 dose (RP2D), pharmacokinetics (PK), and clinical activity of ZN-d5 + azenosertib in pts with AML. The phase 1 dose-escalation stage is based on a Bayesian Optimal Interval design. Phase 2 is an open-label expansion to be conducted if supported by safety and efficacy data from the dose-escalation stage. Prior to initiating dose-escalation for the ZN-d5 + azenosertib combination, an azenosertib monotherapy cohort is being enrolled, as it has not been previously administered to pts with hematologic malignancies. For the dose-escalation azenosertib monotherapy (n=15) and ZN-d5 combination (n=40) cohorts, pts must have relapsed/refractory (R/R) disease after ≥ 1 line of AML therapy that may include the BCL-2 inhibitor, venetoclax. In phase 1, an azenosertib monotherapy cohort will be opened prior to investigation of ZN-d5 + azenosertib in combination. In phase 2, ZN-d5 + azenosertib will be given at the RP2D. Alternative dosing schedules may also be investigated based on emerging clinical data. The primary endpoints are adverse events and dose-limiting toxicities. Secondary endpoints include the rate and duration of remission according to the European LeukemiaNet 2017 criteria, including complete remission (CR), CR with incomplete hematologic recovery (CRi), morphologic leukemia-free state (MLFS), partial remission (PR), stable disease, progressive disease, relapse after remission (including molecular relapse), remission rate (CR + CRi), overall response rate (CR + CRi + MLFS + PR), and rate of and time to relapse. Pts will remain on study until disease progression, failure to respond, remission if additional therapy is clinically indicated, withdrawal of consent, loss to follow-up, or death. Clinical trial information: NCT05682170. Research Sponsor: Zentaris Pharmaceuticals.

TPS7079

Poster Session

Phase 1 study of ziftomenib (KO-539) in combination with venetoclax or venetoclax/azacitidine or standard induction cytarabine/daunorubicin (7+3) chemotherapy for the treatment of patients with acute myeloid leukemia. First Author: Amer Methqal Zeidan, Yale University, New Haven, CT

Background: Relapsed or refractory (R/R) acute myeloid leukemia (AML) with nucleophosmin 1-mutations (*NPM1*-m) or *KMT2A*-rearrangement (*KMT2A*-r) represent a high unmet need. Ziftomenib is a potent and selective inhibitor that targets the menin-mixed-lineage leukemia (MLL) lysine(K)-specific methyltransferase 2A (*KMT2A*) interaction driving leukemogenesis in these subtypes. An ongoing Phase 1/2 study (KO-MEN 001) has demonstrated meaningful clinical activity and tolerability with ziftomenib monotherapy in R/R AML. In preclinical testing, ziftomenib combined with venetoclax induced synergistic lethality in *KMT2A*-r and *NPM1*-m human AML cell lines and patient-derived cells. Moreover, treatment with ziftomenib plus venetoclax/azacitidine has induced prolonged durable remissions in mice with *KMT2A*-r AML xenografts. Therefore, administration of ziftomenib in combination with standard-of-care (SOC) therapies may provide additional clinical benefit for patients with newly diagnosed or R/R *NPM1*-m and *KMT2A*-r menin-dependent AML. **Methods:** KOMET-007 (KO-MEN-007, NCT#) is a 2-part dose escalation (Phase 1a) and expansion (Phase 1b) study to evaluate the safety, tolerability, and preliminary antileukemic activity of ziftomenib in combination with non-intensive chemotherapy (NIC) and intensive chemotherapy (IC) in patients with *NPM1*-m and *KMT2A*-r AML. During Phase 1a, the ziftomenib dose will be escalated with standard doses of either venetoclax and azacitidine (zifto/ven/aza) or cytarabine and daunorubicin (zifto/7+3) in defined genetic cohorts (*NPM1*-m and *KMT2A*-r) using a rule-based approach (n = 6 per cohort/dose level) to select ziftomenib doses for expansion/validation in Phase 1b. The Phase 1b portion will also evaluate zifto/ven/aza in newly diagnosed AML (*KMT2A*-r and *NPM1*-m) and zifto/ven in R/R AML (*NPM1*-m only). The overall primary objectives are to establish the minimum biologically effective, dose limiting toxicities, and recommended Phase 2 dose of ziftomenib combined with NIC and IC backbones in each genetically defined cohort. Additional secondary endpoints include preliminary antileukemic efficacy (including MRD-negative responses and number of patients able to transition to subsequent allogeneic stem cell transplant), pharmacokinetic, and pharmacodynamic data. Exploratory end points include biomarkers for efficacy and resistance, pharmacodynamic biomarkers and activity in isolated myeloid sarcoma. Clinical trial information: NCT04067336. Research Sponsor: Kura Oncology, Inc.

TPS7080

Poster Session

A phase 1b study to evaluate the efficacy, safety, and pharmacokinetics of an investigational microbiome therapeutic, SER-155, in adults undergoing hematopoietic stem cell transplantation. *First Author: Doris M. Ponce, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: In patients undergoing allogeneic hematopoietic cell transplantation (HCT), loss of gastrointestinal microbial diversity is associated with risk of bloodstream infections (BSI), acute graft-versus-host disease (aGVHD), and death. SER-155 is a rationally designed investigational cultivated microbiome therapeutic, hypothesized to improve clinical outcomes in HCT by restoring colonization resistance to potential pathogens, promoting epithelial barrier integrity, and reducing colonic inflammation. SER-155-001 is a Phase 1b study evaluating the efficacy, safety, and pharmacokinetics (PK) of SER-155 in adults undergoing HCT. **Methods:** This study will enroll approximately 70 subjects ≥ 18 years in an open-label Cohort 1 (n = 10) followed by a double-blind, placebo-controlled Cohort 2 (n = 60) randomized 1:1 to SER-155 or placebo. A variety of conditioning regimens, donor types, and GVHD-prophylaxis regimens are included. Exclusion criteria include history of severe colitis or active inflammatory bowel disease or total colectomy, umbilical cord blood or ex vivo T-cell depletion, exposure to fecal microbiota transplant or any live microbial therapeutic within 3 months prior to screening, and evidence of relapse or progression of hematologic malignancy (minimal residual disease is allowed). Following screening, participants in both cohorts receive 2 treatment courses (one before and one after HCT), each comprised of microbiome conditioning with oral vancomycin or placebo followed by SER-155 or placebo, plus a conditional 3rd treatment course if the subject receives antibiotics. Safety outcomes are followed through 52 weeks post HCT. The primary endpoint is the incidence and severity of adverse events, serious adverse events, and adverse events of special interest. Secondary endpoints include rates of BSI, gastrointestinal infections, aGVHD, febrile neutropenia and overall survival. Microbiome related endpoints include engraftment of SER-155 bacterial strains in the gastrointestinal tract (PK endpoint) and fecal microbiome diversity, composition and metabolites. **Results:** Cohort 1 enrollment is complete, with 13 participants receiving SER-155. In December 2022, the Data and Safety Monitoring Committee supported continuation to Cohort 2 enrollment following review of safety data from Cohort 1. Enrollment in Cohort 2 is underway. **Conclusions:** This Phase 1b study is designed to assess the safety, and clinical efficacy of SER-155 in allogeneic HCT, expanding the clinical experience of microbiome-directed interventions in allogeneic HCT recipients. Clinical trial information: NCT04995653. Research Sponsor: Seres Therapeutics.

TPS7082

Poster Session

ASC2ESCALATE: A US phase 2, single-arm, dose-escalation study of asciminib monotherapy in patients (pts) with chronic myeloid leukemia in chronic phase (CML-CP) previously treated with 1 prior tyrosine kinase inhibitor (TKI). *First Author: Ehab L. Atallah, Medical College of Wisconsin, Milwaukee, WI*

Background: ATP-competitive TKIs extend life expectancy in CML; yet up to 40% of newly diagnosed pts with CML-CP stop first-line (1L) therapy by 5 years due to resistance or intolerance and switch to second-line (2L) therapy. There is also an unmet need to overcome high rates of resistance in 2L. Studies show some pts with resistance achieve responses with higher doses of TKIs, while use of another second-generation (2G) TKI may not clinically benefit pts with resistance to a 2G TKI. Asciminib is the 1st BCR:ABL1 inhibitor that Specifically Targets the ABL Myristoyl Pocket (STAMP), giving it activity against most BCR:ABL1 mutations imparting resistance to ATP-competitive TKIs. Asciminib was 1st approved in the US for patients with CML-CP after ≥ 2 TKIs at 80 mg once daily (QD) and 40 mg twice daily (BID) and CML-CP with the T315I mutation at 200 mg BID. In the phase 3 ASCEMBL study, asciminib 40 mg BID showed superior efficacy vs bosutinib 500 mg QD in pts with CML-CP after ≥ 2 prior TKIs at weeks 24 (major molecular response [MMR], 25.5% vs 13.2%) and 96 (MMR, 37.6% vs 15.8%) and favorable tolerability with > 2 years' follow-up. The phase 1 dose-finding X2101 trial investigated asciminib doses of 80-200 mg QD and 10-200 mg BID; the maximum tolerated dose of asciminib was not reached and no differing safety signals were noted in patients receiving 200 mg BID vs the total treatment population. Here, we describe the phase 2 ASC2ESCALATE trial investigating efficacy and safety of 2L asciminib with dose escalation in pts with CML-CP (NCT05384587). **Methods:** This is a phase 2, open-label, multicenter, single-arm, dose-escalation study in the US. Adults with CML-CP without the T315I mutation with treatment resistance/failure (BCR:ABL1^{IS} > 10% with 6-12 months of 1L treatment or > 1% with > 12 months of 1L treatment) or intolerance (BCR:ABL1^{IS} > 0.1%) with ≥ 6 months of treatment with 1 prior ATP-competitive TKI are eligible. All pts start treatment with asciminib 80 mg QD. For pts not achieving BCR:ABL1^{IS} $\leq 1\%$ at 6 months, dose will be escalated to 200 mg QD if pts do not have grade ≥ 3 or persistent grade 2 toxicity refractory to optimal management. For those without MMR at 12 months, either dose escalation from 80 to 200 mg QD or from 200 mg QD to 200 mg BID will occur or pts can be switched to an investigator's agent of choice and taken off study treatment. Pts achieving MMR at 12 months will continue asciminib at their current dose. Pts continuing to derive clinical benefit from asciminib per investigator assessment may receive post-trial access. Recruitment for this study began August 2022 with an estimated enrollment of 92 pts with CML-CP across ≈ 40 sites. The primary endpoint is MMR at 12 months. Secondary endpoints include additional efficacy outcomes at 3, 6, 18, and 24 months and safety measures. Clinical trial information: NCT05384587. Research Sponsor: Novartis Pharmaceuticals Corporation.

TPS7081

Poster Session

A phase 1, multicenter, open-label, dose-escalation and dose-expansion study to evaluate the safety, tolerability, pharmacokinetics (PK), and efficacy of HS-10382 (TERN-701) in patients (pts) with chronic myeloid leukemia (CML). *First Author: Weiming Li, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China*

Background: There is a need for new treatment options for pts with CML who are intolerant/resistant to currently available BCR-ABL1 ATP-binding site targeted tyrosine kinase inhibitors (TKIs). HS-10382 (TERN-701) is a potent, oral small molecule allosteric inhibitor of BCR-ABL. By binding to the myristoyl site of the BCR-ABL1 protein, HS-10382 (TERN-701) locks BCR-ABL1 into an inactive conformation. This results in a mutation-driven resistance profile different from that of ATP-binding site TKIs, providing potential for both monotherapy and combination therapy with ATP-binding site TKIs. In preliminary nonclinical assays, HS-10382 (TERN-701) was highly potent against wild type BCR-ABL1 as well as most common mutations acquired by pts treated with second generation active site TKIs. This ongoing first-in-human phase 1 study is evaluating HS-10382 (TERN-701) in pts with CML. **Methods:** Eligible adult CML chronic phase (CP) or advanced phase (AP) pts who are resistant or intolerant to prior BCR-ABL1 TKI therapy are enrolled in an open-label Phase 1 study to evaluate the safety, tolerability, PK and efficacy of HS-10382 (TERN-701). This study is being conducted in two parts: Part 1 dose escalation utilizing a rolling six design and Part 2 dose expansion. In the dose escalation stage, CML-CP/AP pts who are resistant or intolerant to prior BCR-ABL1 therapy are being enrolled to determine the maximum tolerated dose (MTD) or maximum applicable dose. Doses selected from the escalation part will be evaluated in the expansion stage in CML-CP pts who are resistant or intolerant to prior BCR-ABL1 TKI therapy and have no T315I mutation. All pts will be carefully followed for adverse events for the duration of study treatment and for 28 days after the last dose of study drug. Pts will be permitted to continue therapy with assessments for progression if the study drug is well-tolerated and the pt has no objective evidence of disease progression. This study is ongoing (enrollment underway for Part 1, dose 3 as of February 2023) with 7 participating study sites in China. Clinical trial information: NCT05367700. Research Sponsor: Jiangsu Hansoh Pharmaceutical Co., Ltd.

TPS7083

Poster Session

A phase 2/3 trial of oral azacitidine (Oral-AZA) in patients (pts) with low- or intermediate-risk myelodysplastic syndromes (MDS). *First Author: Guillermo Garcia-Manero, MD Anderson Cancer Center, Houston, TX*

Background: MDS, a heterogeneous group of clonal myeloid malignancies, are characterized by ineffective hematopoiesis and peripheral blood cytopenias, which can often lead to red blood cell (RBC) transfusion dependence and a risk of progression to acute myeloid leukemia (AML). In early clinical trials, 14- and 21-day (d) dosing regimens of the hypomethylating agent Oral-AZA were well tolerated and induced hematologic improvement (HI) in pts with lower-risk (LR) MDS. In a phase 3 trial, Oral-AZA 300 mg QD for 21d per 28d cycle significantly improved the rate of RBC transfusion independence (TI) and induced durable HI versus placebo (PBO) in patients (pts) with LR-MDS with RBC-transfusion-dependent anemia and thrombocytopenia (Garcia-Manero, et al. *J Clin Oncol* 2021). Grade 3/4 cytopenias were common in the Oral-AZA arm. Given the substantial clinical benefit of Oral-AZA observed in this setting, a new phase 2/3 trial is ongoing to further evaluate the 14d Oral-AZA regimen in pts with International Prognostic Scoring System Revised (IPSS-R)-defined low or intermediate (int)-risk MDS. **Methods:** This ongoing, multicenter, randomized, phase 2/3 trial (CA055-026; NCT05469737) will evaluate the safety and efficacy of Oral-AZA in pts with IPSS-R low- or int-risk MDS. Key eligibility criteria include ≥ 18 years, ECOG performance status score ≤ 2 , and ≥ 1 cytopenia (anemia, thrombocytopenia, or neutropenia). Pts with an absolute neutrophil count < $0.5 \times 10^9/L$ within a week of randomization will be excluded. Informed consent will be obtained from all participants. The phase 2 portion will enroll and randomize ~ 42 pts 1:1 to receive open-label Oral-AZA 200 or 300 mg QD for 14d per 28d cycle, plus best supportive care (BSC), to determine the recommended phase 3 dose (RP3D). The primary endpoints are safety and rate of complete remission (CR) within 6 Tx cycles. The secondary endpoints are overall response rate (ORR), and packed (p) RBC-TI and platelet-TI sustained for 84d in ≤ 6 Tx cycles. ORR includes CR, partial remission (PR), marrow CR, and any HI, per IWG 2006 response criteria. In the phase 3 portion, ~ 188 additional pts will be enrolled and randomized 1:1 to Oral-AZA at the RP3D or PBO for 14d per 28d cycle, plus BSC. Pts in the PBO arm with stable disease at Tx cycle 6 disease assessment or with documented disease progression after ≥ 3 Tx cycles will have the option to cross over into the Oral-AZA arm. The primary endpoint is CR in ≤ 6 Tx cycles. The key secondary endpoint is 84d pRBC-TI. Other secondary endpoints include those described in the phase 2 portion plus overall survival, event-free survival, time to AML progression, iron parameters, health-related quality of life, healthcare resource utilization, and safety parameters. Pts who benefit from Oral-AZA in phase 2 or 3 may continue to receive Tx in an extension phase. Trial recruitment began in December 2022 and is ongoing. Clinical trial information: NCT05469737. Research Sponsor: Bristol-Myers Squibb.

TPS7084

Poster Session

A phase I study of MEK inhibitor selumetinib in combination with azacitidine in patients with higher-risk chronic myeloid neoplasia. *First Author: Gregory Roloff, University of Chicago, Chicago, IL*

Background: Myelodysplastic syndrome (MDS), Philadelphia chromosome-negative myeloproliferative neoplasms (MPNs), and MDS/MPN overlap syndromes present significant clinical challenges for patients deemed transplant ineligible, and who are relapsed or refractory to conventional therapies. RAS-pathway activating mutations in myeloid malignancies are associated with a proliferative phenotype and contribute to disease progression. Cooperation between RAS-dependent signaling and epigenetic dysregulation provides the basis for rationally designed combination studies. Selumetinib (AZD6244) is a potent, selective, orally bioavailable, and non-ATP competitive small molecule inhibitor of MEK1/2, downstream of RAS. **Methods:** This is an investigator-initiated, Phase I, open-label dose-escalation study of selumetinib in combination with azacitidine for patients with higher risk MDS, MDS/MPNs, and myelofibrosis. The trial will enroll patients with high-risk myeloid neoplasms that meet disease-specific criteria for MDS or MPNs and who require treatment. This phase I study follows a 3+3 dose-escalation design, with three planned dose levels across two different cohorts (A and B). The dose of azacitidine (75 mg/m²) will remain stable, with three planned selumetinib dose levels (50 mg, 75 mg, and 100mg, respectively) across the two cohorts. Azacitidine will be given on days 1-7 followed by selumetinib from days 7-21 of 28 day cycles. Cohort A includes subjects with MDS with relapsed/refractory disease requiring therapy and MDS/MPN overlap syndromes; Cohort B includes subjects with myelofibrosis refractory or intolerant to JAK inhibitor therapy or ineligible for ruxolitinib treatment given baseline cytopenias (thrombocytopenia < 50,000/uL, anemia < 9 g/dL, and/or red cell transfusion dependent). The trial has an enrollment goal of 18 to 24 subjects, and treatment will continue indefinitely if the patient continues to derive benefit. Dose escalation will proceed independently within both cohorts. Cohort A is nearing completion of enrollment and cohort B is actively enrolling. The primary objective is to determine the maximum tolerated dose of selumetinib in combination with azacitidine. Select secondary and exploratory objectives include describing the preliminary clinical response rates and observing relationships between the presence of RAS activating mutations, RAS pathway activation, and clinical response. Clinical trial information: NCT03326310. Research Sponsor: AstraZeneca; University of Chicago Personalized Cancer Care Consortium.

TPS7086

Poster Session

A phase I study of ruxolitinib in combination with abemaciclib for patients with primary or post-polycythemia vera/essential thrombocythemia myelofibrosis. *First Author: Jan Philipp Bewersdorf, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Patients (pts) with myelofibrosis (MF) have a reduced life-expectancy compared to age-matched controls. Several oral Janus Kinase (JAK) inhibitors such as ruxolitinib (RUX) have been approved by the US FDA based on improvements in symptom burden and spleen volume reduction compared to physician's choice of best available therapy. However, duration of response to these agents is generally time-limited and treatment with JAK inhibitors is not considered to have disease-modifying potential. Additionally, median overall survival after RUX discontinuation is only 11-14 months. Thus, novel mechanism-based therapies for pts with disease progression on RUX are needed. JAK2 V617F mutations promote transition from G1 to S-phase of the cell cycle via increased expression of CDC25A, which is also upregulated in primary MPN patient samples. Additional cell cycle regulators such as CDK6 and Cyclin D have also been implicated in MF pathogenesis. Finally, we and others have shown that combination of the CDK4/6 inhibitors and RUX had synergistic effects in murine models of MF (Rampal et al., CCR 2021) providing the preclinical rationale for this trial. **Methods:** This multicenter, phase I dose-escalation trial (NCT05714072) evaluates the safety of RUX + the CDK4/6 inhibitor abemaciclib in pts with primary or secondary MF with intermediate-1/2 or high-risk disease by DIPSS who require treatment and had an inadequate response to RUX. Among the currently FDA-approved CDK4/6 inhibitors, abemaciclib was chosen for combination therapy due to less myelosuppressive effects compared with other CDK4/6 inhibitors. Inadequate response to RUX is defined by (I) palpable splenomegaly ≥ 5 cm below the left costal margin at study entry AND/OR (II) active MPN symptoms, as defined by the presence of one symptom score ≥ 5 or two symptom scores ≥ 3 using the screening MPN-SAF TSS. Following a conventional "3+3" dose-escalation design, pts will be treated with increasing doses of abemaciclib and stable doses of RUX (10mg or 15mg BID). The primary endpoint is to determine the maximum tolerated dose of RUX + abemaciclib. Secondary endpoints include measures of efficacy. Exploratory endpoints include changes in allele fraction of driver mutations, gene expression profiling, and clonal architecture to identify biomarkers of response, mechanisms of resistance, and to assess for any disease-modifying effects of the combination therapy. This trial is open to enrollment at Memorial Sloan Kettering Cancer Center and MD Anderson Cancer Center. Clinical trial information: NCT05714072. Research Sponsor: None.

TPS7085

Poster Session

Phase 1b clinical study of IRAK 1/4 inhibition for low-risk myelodysplastic syndromes refractory/resistant to prior therapies. *First Author: Guillermo Garcia-Manero, Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Chronic stimulation of both interleukin-1 receptor (IL-1R) and toll-like receptors (TLRs) in myeloid progenitors is thought to cause a bone marrow proinflammatory environment responsible for persistent cytopenia in patients with low-risk (LR)-MDS. IRAK1 and IRAK4 are serine/threonine kinases that are critical for the downstream signaling of IL-1R and most TLRs resulting in the production of proinflammatory cytokines and NLRP3 inflammasome-driven pyroptosis leading to bone marrow inflammation and cell death. Thus, IRAK1/4 inhibition is a potential target for the treatment of LR-MDS by decreasing inflammation and cell death within the bone marrow allowing the restoration of hematopoiesis. R289 is a prodrug that is converted to the active drug R835 in the gastrointestinal (GI) tract. R835 is a potent and selective inhibitor of IRAK1 and IRAK4 kinases and inhibits TLR and IL-1R-dependent proinflammatory cytokine production in multiple cell types. *In vivo*, R835 blocks TLR4 and IL-1R-dependent systemic cytokine release in mice. The safety and pharmacokinetic properties of R289/R835 were evaluated in a phase 1 healthy volunteer study (Study C-906289-001). R289 was well tolerated with no serious or severe adverse events (AEs) reported. Most AEs were mild and transient; the most common AEs (mild/moderate) were headache and GI disturbance. Overall, the trial supported the advancement of R289 into further studies. An open-label Phase 1b study to determine the tolerability and preliminary efficacy of R289 for patients with LR-MDS refractory to prior therapies is currently enrolling patients. **Methods:** The current study (NCT05308264) includes a dose escalation phase (up to 12 patients) and a dose expansion phase (up to 10 patients). Inclusion criteria for both phases will include patients ≥ 18 years with a definitive diagnosis of LR-MDS. Exclusion criteria will include prior treatment for MDS that concluded <4 weeks prior to study treatment. Dose Escalation Phase: Dose escalation will utilize a 3+3 design to determine the maximum tolerated dose (MTD). R289 tablets can be taken orally with or without food. Dose limiting toxicity (DLT) will be assessed at each dose level. The DLT evaluation period will be 28 days. After completion of the DLT evaluation period, patients who do not experience DLTs may remain on treatment at their respective dose level if they continue to demonstrate clinical benefit without toxicity. Dose Expansion Phase: Up to 10 additional patients with LR-MDS will be enrolled; the primary endpoint of the study will be the safety and tolerability of R289. The secondary endpoints will include an assessment of preliminary efficacy and characterization of the pharmacokinetics of R289. R289 will be administered to all patients at a dose not to exceed the MTD determined in the Dose Escalation Phase. The trial is currently recruiting at 8 US sites. Clinical trial information: NCT05308264. Research Sponsor: Rigel Pharmaceuticals.

TPS7087

Poster Session

Phase 1b, open-label study of add on therapy with CK0804 in participants with myelofibrosis, with suboptimal response to ruxolitinib. *First Author: Lucia Masarova, Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Drugs targeting JAK2 inhibition including ruxolitinib have led to significant improvement in quality of life and survival of myelofibrosis (MF) patients, however almost 30% have suboptimal response and disease remains incurable. Novel therapies are urgently needed. In addition to mutation-driven stem cell-derived clonal myeloproliferation, recent data support role of reactive cytokine- and chemokine-driven inflammatory fibrosis that contribute to MF pathogenesis, specifically, abnormal CXCR4/CXCL12 axis can drive disease progression and extra-medullary hematopoiesis. Targeting bone marrow inflammation is emerging as potential therapeutic strategy for MF. Adoptive therapy with allogeneic, cord blood (CB) derived Regulatory T cells (Tregs) have shown to be safe in bone marrow failure patients. CXCR4 enriched CB Tregs (CK0804) show faster egress across transwell membrane in response to SDF1 α and preferential homing to bone marrow, *in vivo*. We hypothesize that multiple infusions of CK0804 may decrease inflammation and improve clinical outcomes in MF. **Methods:** Single arm study consisting of safety run-in of 9 participants followed by expansion cohort of additional 15 participants using 3+3+3 study design. MF patients receiving ruxolitinib therapy > 3 months prior to enrollment with stable dose for at least 8 weeks prior to Day 1, unlikely to benefit from further ruxolitinib monotherapy in opinion of investigator would be eligible. Each participant will receive single infusion of CK0804 at fixed dose of 100 million Treg cells administered every 28 days. Participants will continue their ruxolitinib therapy. Participants with no treatment limiting toxicity (TLT) after 28 days or those with toxicity with clear alternative explanation (e.g. disease progression) or transient (≤ 72 hrs) abnormal laboratory values without associated clinically significant signs or symptoms based on investigator determination will receive up to six 28-day treatment cycles AND 6 months of follow up after last infusion of CK0804. Primary Objective: Determine safety and tolerability of CK0804 as add-on therapy in MF, with suboptimal response to ruxolitinib. Primary endpoint: Safety, tolerability and TLTs of CK0804 as assessed by incidence and severity of AE and SAEs determined by NCI CTCAE Version 5.0. Secondary Objective: Determine efficacy of CK0804 as add-on therapy in MF, with suboptimal response to ruxolitinib. Secondary endpoint: Assessment of overall response rate and its duration, using modified International Working Group Myeloproliferative Neoplasm Research and Treatment and European Leukemia Net consensus report; Rate of anemia response and Rate of spleen response by imaging at and after 24 weeks; Symptom burden assessed using Myeloproliferative Neoplasms Symptom Assessment Form Total Symptom Score scale. Safety data from cohort 1 will be presented. Clinical trial information: NCT05423691. Research Sponsor: Cellenkos Inc.

TPS7088

Poster Session

EXCEED-ET: A single-arm multicenter study to assess the efficacy, safety, and tolerability of ropeginterferon alfa-2b-njft (P1101) in North American adults with essential thrombocythemia. *First Author: Lucia Masarova, MD Anderson Cancer Center, Houston, TX*

Background: Essential thrombocythemia (ET) is a myeloproliferative neoplasm (MPN) characterized by a high platelet count due to an overacting JAK-STAT pathway as a result of the most common mutations in JAK2, CALR and MPL genes. There is a high, unmet clinical need for safe and effective treatment options for patients with ET who require cytoreduction, both naïve and previously exposed to hydroxyurea (HU) or anagrelide (ANA). In addition to blood count control and thrombohemorrhagic risk reduction, treatment for ET should also halt/prevent disease progression to post-ET myelofibrosis. Reduction in variant allele frequency and changes in marrow morphology may lead to the elimination of the malignant clone, and treatment with an interferon may achieve this outcome. Interferons have been used in the treatment of MPNs for over 30 years with well-established improvements in hematological and molecular rates, but interferons are not approved by a regulatory agency for the treatment of ET. The objective of this study is to assess the efficacy of ropeginterferon alfa-2b-njft, a new generation interferon alfa, in adults with ET who live in the US or Canada. **Methods:** This single-arm, open-label study includes a 28-day screening period, a 12-month treatment phase, and a 28-day follow-up period, for a total trial duration of 14 months. An extension phase will supply ropeginterferon alfa-2b-njft to patients deriving benefit for a total of 3 years of treatment. Adults diagnosed with ET according to the WHO 2016 criteria with a platelet count at screening $> 450 \times 10^9/L$, cytoreductive treatment naïve, or with prior use or currently on HU and/or ANA may participate. Prior treatment with an interferon is an exclusion factor. Patients with a history or presence of clinically relevant depression, risk of suicide, or autoimmune disease may not participate. Ropiginterferon alfa-2b-njft will be administered subcutaneously every 2 weeks at the starting dose of 250 mcg (Week 0), 350 mcg (Week 2), and target dose of 500 mcg (Week 4) and remain fixed for the 12-month treatment period. Subjects currently on HU or ANA will follow a pre-specified dose-tapering schedule. All subjects will receive low-dose aspirin unless contraindicated. The primary endpoint is a durable response defined as the proportion of subjects who achieve simultaneous peripheral blood count remission (platelets $\leq 400 \times 10^9/L$ and WBC $< 10 \times 10^9/L$) for at least 80% of bi-weekly measurements consecutively between weeks 32-52, a durable resolution of disease-related symptoms according to the MPN Symptom Assessment Form Total Symptom Score (MPN-SAF TSS), and absence of bleeding or thrombotic events. This study is being sponsored by PharmaEssentia USA. Clinical trial information: NCT05482971. Research Sponsor: PharmaEssentia.

TPS7089

Poster Session

Phase 1 study to determine the safety and efficacy of onvansertib, a novel, oral, PLK1 inhibitor in patients with proliferative chronic myelomonocytic leukemia relapsed/refractory or intolerant to available therapies. *First Author: Kristen McCullough, Division of Hematology, Mayo Clinic, Rochester, MN*

Background: Chronic myelomonocytic leukemia (CMML) is a myelodysplastic/myeloproliferative overlap neoplasm (MDS/MPN) that can be further divided into MD (WBC $< 13 \times 10^9/L$) and MP ($\geq 13 \times 10^9/L$) subtypes. MP-CMML is enriched in RAS pathway mutations (*NRAS*, *CBL*, *KRAS*, *PTPN11* and *NFI*), has a shorter median survival (19 vs 36 months), has a higher rate of acute myeloid leukemia (AML) transformation (40% vs 10%) and has a unique transcriptomic and epigenetic composition. These RAS pathway mutations promote selective PLK1 overexpression, a mitotic checkpoint kinase. Given the relative inefficacy of hypomethylating agents (HMA) in MP-CMML and previously demonstrated in vitro and in vivo efficacy data for PLK1 inhibition on MP-CMML with RAS pathway mutations, we designed a phase 1 clinical trial testing the safety of onvansertib, a novel, orally bioavailable, PLK1 inhibitor in relapsed/refractory MP-CMML. **Methods:** This is an investigator-initiated, prospective, open-label, phase I study of onvansertib in MP-CMML relapsed/refractory (RR) or intolerant to existing therapies including HMA and hydroxyurea. The primary endpoint is characterization of safety. Secondary endpoints include efficacy as defined by the 2015 MDS/MPN International Working Group criteria, volumetric spleen response and symptom response via assessment with MPN-SAF-TSS. Inclusion criteria include MP-CMML RR following hydroxyurea or at least 4-cycles of HMA or intolerance of treatment with either, platelets $\geq 20,000/m^3$ and Cockcroft-Gault creatinine clearance $\geq 60 \text{ mL/min/m}^2$. Hydroxyurea may continue for the first 28 days on study. Onvansertib will be given orally on days 1 through 21 of a 28-day cycle with a Bayesian optimal interval design to assess the safety and recommended phase II dose. Exploratory endpoints include targeting efficacy, impact of PLK1 and KMT2A expression and interactions with ASXL1 and TET2 mutations. Twenty-five patients will be enrolled at Mayo Clinic in Minnesota, with enrollment open since November 2022. Clinical trial information: NCT05549661. Research Sponsor: Cardiff Oncology; Benefactor.

7500

Oral Abstract Session

Results of a phase 3 study of IVO vs IO for previously untreated older patients (pts) with chronic lymphocytic leukemia (CLL) and impact of COVID-19 (Alliance). *First Author: Jennifer Ann Woyach, The Ohio State University Comprehensive Cancer Center, Columbus, OH*

Background: The Bruton's tyrosine kinase inhibitor (BTKi) ibrutinib +/- anti-CD20 antibody obinutuzumab (IO) is a standard frontline regimen for older adults with CLL. BTKi alone do not often lead to complete response (CR) or undetectable minimal residual disease (uMRD), thus are given indefinitely. Smaller trials showed that IO plus venetoclax (IVO) can induce uMRD CRs which may allow successful discontinuation. **Methods:** Alliance for Clinical Trials in Oncology A041702 is a multicenter trial designed to evaluate if IVO with response-guided discontinuation of I improves progression free survival (PFS) versus IO with indefinite I in treatment-naïve, older CLL pts. IO is given in standard fashion, and in the IVO arm V is added at C3D1 and continued until C14D28. After 14 cycles, pts undergo response evaluation including CT scans and bone marrow biopsy with central MRD assessment by flow cytometry. Pts in IVO arm with uMRD CR discontinue I; all others continue I until progression or unacceptable toxicity. Eligible pts were age ≥70 years (amended to ≥65). Pts had CrCl ≥ 40 mL/min, bilirubin ≤ 1.5 x ULN, and no other life-limiting intercurrent illness. Pts were stratified based on Rai stage and +/- del17p13.1 by FISH, and randomized 1:1 to IO:IVO. With 431 evaluable pts, the trial had 90% power to detect significant improvement in PFS using a one-sided log-rank test with one-sided type 1 error rate of 2.5%. The Alliance DSBM approved release of data on Nov 4, 2022 after meeting the protocol defined futility threshold at the second planned event-driven interim analysis. Data were locked on December 15, 2022. **Results:** Between January 4, 2019 and July 15, 2022, 465 pts were registered (IO:232, IVO:233). Median age was 74; 67% of pts were men. Rai stage 3-4 was seen in 55% and del17p in 13%. With median follow-up of 14 months, PFS of IO was 87.5% compared to 85% on IVO. Events were observed in 29 pts on IO (4 progressions, 23 deaths, 2 pts started other therapy) and 35 on IVO (7 progressions, 28 deaths). The predefined futility boundary was crossed, with a hazard ratio (HR) of 1.20 (95% CI: 0.73-1.97) in favor of IO. COVID-19 was the leading cause of death in both arms, (11 COVID-19 deaths on IO, 19 on IVO), with 13 and 11 additional deaths from other causes, respectively. Censoring pts with COVID-19 related deaths, PFS HR is 0.82 (95% CI: 0.44-1.53) in favor of IVO. Grade 3+ toxicity and discontinuation in year 1 of therapy were similar between arms. **Conclusions:** This study demonstrates that PFS for IVO is not superior to IO for treatment-naïve older CLL pts in the setting of the COVID-19 pandemic. Study treatment is ongoing, and long-term follow-up will determine if there are advantages to IVO, with special attention to MRD and therapy discontinuation. Support: U10CA180821, U10CA180882, U24 CA196171; <https://acknowledgments.alliancefound.org>. Clinical trial information: NCT03737981. Research Sponsor: U.S. National Institutes of Health.

7502

Oral Abstract Session

Results of MOLTO, a multicenter, open label, phase II clinical trial evaluating venetoclax, atezolizumab and obinutuzumab combination in Richter syndrome. *First Author: Anna Maria Frustaci, Department of Hematology, Niguarda Cancer Center, ASST Grande Ospedale Metropolitano Niguarda, Milano, Italy*

Background: Chemoimmunotherapy is the standard first line of patients (pts) with diffuse large B-cell lymphoma (DLBCL) variant of Richter syndrome (RS). Response rate and duration are unsatisfactory. The biology of RS (high rate of DNA damage response pathway defects, high tumor mutation burden coupled with the expression of the PD1/PDL1 axis) prompts investigation of non-chemo combinations leveraging agents that circumvent TP53 abnormalities and trigger anti tumor immune response. MOLTO is a multicenter international ph 2 study (NCT04082897) evaluating activity and safety of atezolizumab (humanized monoclonal antibody blocking PD-L1), venetoclax (BCL2 inhibitor) and obinutuzumab (anti-CD20 MoAb) combination in untreated DLBCL-RS. **Methods:** Treatment consisted of 35 cycles with obinutuzumab (1000 mg C1-8), atezolizumab (1200 mg C1-18) and venetoclax (400 mg/d C1-35), q21. Primary endpoint was ORR ≥67% at C6. RS diagnosis was centrally revised. RS mutation profile was tested on pre-treatment cell free DNA. Minimal residual disease (MRD) was tested by 12 colors flow cytometry and NGS on peripheral blood mononuclear cells and plasma. **Results:** 28 planned pts were enrolled from Oct 2019 to Oct 2022 (Table). Three were not evaluable for primary endpoint due to G5 infection (n=1) or early withdrawn (n=2). As per intention-to-treat ORR was 67.9% (19/28) thus meeting primary endpoint. CR rate was 28.6%. No clinical characteristics influenced C6-ORR. After a median follow-up of 11.6 mo, 11/19 pts (57.9%) are in continuous remission (8 on active therapy, 2 received allogeneic transplant, 1 discontinued due to MDS) among them, 6 for ≥24 mo. Of the remaining 8 pts, 7 progressed after a median of 14 cycles, 1 died from sepsis at C9 in remission. Median duration of response, PFS and OS were 11.7, 16.2 and 31.6 mo, respectively. Out of the 13 patients who progressed, 4 received a salvage therapy and are alive at a median follow-up of 24.3 mo. Bulky disease and ECOG PS >1 affected PFS. Rate of unmeasurable MRD, impact of mutations and chronic lymphocytic leukemia-RS clonal relation on outcomes will be presented at the meeting. Overall 43 G3-4 adverse events (AE) were recorded in 17 pts (60.7%), mostly hematological (51.2%). Any grade immune-related AEs were reported in 6 pts (G3-4 in 2), none led to discontinuation. No tumor lysis syndrome observed. Infections ≥G3 occurred in 6 pts, including 2 G5. One pt developed MDS. **Conclusions:** Atezolizumab, obinutuzumab and venetoclax combination is active in pts with untreated DLBCL-RS. This regimen led to durable remissions, longer than 2yrs in one third of responders. Clinical trial information: NCT04082897. Research Sponsor: Roche.

Pts' characteristics.	
	N (%)
Age median (range)	70 y (32-81)
Age ≥65 y	22 (78.6)
ECOG 1-2	16 (57.1)
Pts pretreated for CLL	20 (71.4)
n prior CLL treatments (range)	1 (0-3)
Prior BTKi/GIT	11 (39.3) (32.1)
Bulky	16 (57.1)
del17p/TP53mut	11 (42.9)
Ann Arbor III-IV	22 (78.6)

7501

Oral Abstract Session

Lisocabtagene maraleucel (liso-cel) in R/R chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL): Primary analysis of TRANSCEND CLL 004. *First Author: Tanya Siddiqi, City of Hope National Medical Center, Duarte, CA*

Background: In patients (pts) with R/R CLL/SLL that progressed on BTKi and failed venetoclax (ven)-based regimens, achieving CR with current treatment is uncommon. New therapies that achieve deep and durable responses are needed. We report the primary analysis of the phase 1/2, single-arm, multicenter TRANSCEND CLL 004 (NCT03331198) study evaluating liso-cel in pts with R/R CLL/SLL. **Methods:** Pts must have received at least 2 prior lines of therapy, including a BTKi. Eligible pts received liso-cel at a target dose of either 50 (DL1) or 100 (DL2) × 10⁶ CAR⁺ T cells. The primary endpoint was rate of CR and CR with incomplete marrow recovery (CRI) by IRC per 2018 iwCLL criteria in the prespecified subset of efficacy-evaluable pts with disease progression on BTKi and ven failure (primary efficacy analysis set [PEAS]) at DL2 (null hypothesis [H₀]: ≤ 5%). Key secondary endpoints were ORR (H₀: ≤ 40%) and rate of undetectable minimal residual disease (uMRD; 10⁻⁴) in blood (H₀: ≤ 5%). **Results:** Of 137 leukapheresed pts, 117 received liso-cel (safety set), 96 (DL1 = 9; DL2 = 87) were efficacy evaluable, and 53 (DL1 = 4; DL2 = 49) were in the PEAS. In the safety set, median (range) age was 65 y (49-82), 83% had high-risk features, median (range) lines of prior therapy was 5 (2-12), and all pts had prior BTKi. Median (range) on-study follow-up was 21.1 mo (0.4-55.6) for the safety set. In the PEAS at DL2, the primary endpoint of CR/CRI rate was met at 18.4% (95% CI, 8.8-32.0; 1-sided P = 0.0006; Table). ORR was 42.9% and was not statistically significant (95% CI, 28.8-57.8; 1-sided P = 0.3931). The uMRD rate was 63.3% in blood and 59.2% in marrow. Median (95% CI) DOR was 35.3 mo (11.01-not reached [NR]) with a median follow-up of 19.7 mo. Median duration of CR/CRI was NR. In the safety set, rate of any-grade CRS was 84.6% (gr 3, 8.5%; no gr 4/5) and neurological events (NE) was 45.3% (gr 3, 17.9%; gr 4, 0.9%; no gr 5); 69.2% received tocilizumab and/or corticosteroids for CRS/NEs. Rate of gr ≥ 3 infections, hypogammaglobulinemia, and prolonged cytopenia was 17.1%, 15.4%, and 53.8%, respectively. One death related to liso-cel was due to hemophagocytic lymphohistiocytosis. Liso-cel exhibited rapid in vivo expansion and was detected by qPCR in blood up to 36 mo after infusion. **Conclusions:** Liso-cel demonstrated durable CR/CRI, high uMRD rates, and a manageable safety profile in pts with heavily pretreated, high-risk R/R CLL/SLL and high unmet need. Clinical trial information: NCT03331198. Research Sponsor: This study was funded by Juno Therapeutics, a Bristol-Myers Squibb Company.

Efficacy	PEAS at DL2 (n = 49)	Full efficacy set at DL2 (n = 87)
CR/CRI rate ^a	9 (18.4) [8.8-32.0]; P = 0.0006	16 (18.4) [10.9-28.1]
ORR ^a	21 (42.9) [28.8-57.8]; P = 0.3931	41 (47.1) [36.3-58.1]
uMRD in blood ^a	31 (63.3) [48.3-76.6]	56 (64.4) [53.4-74.4]
uMRD in marrow ^a	29 (59.2) [44.2-73.0]	51 (58.6) [47.6-69.1]
DOR ^b	35.3 (11.01-NR)	35.3 (19.78-NR)
Duration of CR/CRI ^b	NR (NR-NR)	NR (12.22-NR)
PFS ^b	11.9 (5.72-26.18)	18.0 (9.43-30.13)

^an (%) [95% CI]; ^bMedian (95% CI), mo.

7503

Oral Abstract Session

Golidocitinib in treating refractory or relapsed peripheral T-cell lymphoma: Primary analysis of the multinational pivotal study results (JACKPOT8). *First Author: Qingqing Cai, Sun Yat-sen University Cancer Center (China), Guangzhou, China*

Background: Currently there is no consensus on the treatment of relapsed/refractory (r/r) PTCL, and patient prognosis was poor. Golidocitinib is an orally available, JAK1-selective inhibitor currently being evaluated in a multinational, pivotal study in r/r PTCL (JACKPOT8 Part B, NCT04105010). Here we reported the primary analysis of efficacy and safety results of this study. **Methods:** PTCL patients who had relapsed from or had been refractory/intolerant to ≥ 1 (but ≤ 3) prior systemic therapy(ies) were enrolled to receive golidocitinib at 150 mg once daily until disease progression or pre-defined discontinuation criteria were met. The primary endpoint was CT-based objective response rate (ORR) assessed by an independent review committee (IRC) according to Lugano 2014 classification. The efficacy analysis set included patients whose pathological diagnosis of PTCL had been retrospectively confirmed by a central laboratory and who had at least one measurable lesions at baseline. The safety analysis set included all dosed patients. **Results:** As of November 30, 2022, a total of 104 patients with r/r PTCL were enrolled and dosed with golidocitinib. Baseline characteristics: median age was 58 years old; 64.4% were male; 20.2% had baseline bone marrow involvement. Major subtypes included NOS (46.2%), AITL (15.4%) and ALCL (9.6%). The median prior lines of therapies were two. All of the patients had been treated with chemotherapies, and 48.1% had also been treated with histone deacetylase inhibitors. By the data cut-off (DCO) date, a total of 80 patients had both IRC assessment and central pathology review results available, and thus were included in the efficacy analysis. Among them, 35 patients achieved tumor response (ORR = 43.8%), including 20 patients (25.0%) achieved complete responses. Tumor response was observed in various subtypes, including AITL (56.3%), NOS (45.7%), ALCL (11.1%) and others (44.4%). In patients who relapsed from HDAC inhibitor treatment, 54.8% achieved tumor response. With a median follow-up of 5.5 months for responders, the median duration of response (DoR) has not been reached. Golidocitinib was tolerated in patients with r/r PTCL. By the DCO date, the longest duration on treatment was 15.7 months (still responding). The most common ≥ grade 3 treatment-related adverse events (TRAEs) were hematological in nature, including neutrophil count decreased (26.0%), white blood cell count decreased (25.0%), platelet count decreased (16.3%) and lymphocyte count decreased (16.3%). TRAEs leading to dose interruption, reduction, and discontinuation were 37.5%, 5.8%, and 7.7%, respectively. The majority of TRAEs were reversible or clinically manageable. **Conclusions:** Golidocitinib demonstrated its potential as a novel targeted therapy for the treatment of r/r PTCL. The updated data will be presented at the conference. Clinical trial information: NCT04105010. Research Sponsor: Dizal Pharmaceutical.

7504

Oral Abstract Session

A phase 2 trial of CHOP with anti-CCR4 antibody mogamulizumab for elderly patients with CCR4-positive adult T-cell leukemia/lymphoma. *First Author: Ilseung Choi, Department of Hematology and Cell therapy, National Hospital Organization Kyushu Cancer Center, Fukuoka, Japan*

Background: No standard of care for elderly patients with aggressive adult T-cell leukemia/lymphoma (ATL) has been established yet. We assessed the efficacy of an anti-CCR4 antibody, mogamulizumab (Moga) combined with biweekly cyclophosphamide (CPA), doxorubicin (DXR), vincristine (VCR), and prednisone (PSL) (Moga-CHOP-14) for untreated elderly patients with aggressive ATL. **Methods:** In this phase 2 trial conducted at 21 centers in Japan, untreated CCR4-positive aggressive ATL patients aged 66 years or older and 56-65 years who were not candidates for allogeneic hematopoietic stem cell transplantation (allo-HSCT) received six cycles of Moga-CHOP-14, followed by two cycles of Moga monotherapy. The primary endpoint was 1-year progression-free survival (PFS), defined as the time from enrollment to the progression/relapse of ATL or death due to any cause, whichever occurred first. Secondary endpoints were complete response rate (CR), overall response rate (ORR), overall survival (OS), 1-year event-free survival (EFS), and the incidence of adverse events. The necessary number of patients calculated by setting the threshold 1-year PFS at 16% and the expected 1-year PFS at 31% using the exact method based on binomial distribution under the conditions of one-sided level of significance of 5% ($\alpha = 0.05$) and power of 70% was 43. **Results:** A total of 50 patients were enrolled from October 2015, until September 2020. Among the 48 evaluable patients, the median age was 74 years (interquartile range [IQR], 70-78). ATL subtypes included 31, 9, and 8 patients for the acute, lymphoma, and unfavorable chronic type, respectively. ATL-PI included 9, 31, and 8 patients for high, intermediate, and low risk, respectively. With a median follow-up of 1.6 years (IQR, 0.7-2.4), 1-year PFS was 36.2% (90% confidence interval [CI], 24.9-47.6), and a median PFS was 0.7 years (95% CI, 0.5-1.0). CR and ORR were noted in 64.6% (95%CI, 49.5-77.8), and 91.7% (95% CI, 80.0-97.7), respectively. One-year OS was 66.0% (95% CI, 50.6-77.6) and median OS was 1.6 years (95%CI, 1.1-2.8). One-year EFS was 29.9% (95% CI, 17.6-43.2) and median EFS was 0.5 years (95%CI, 0.4-0.7). The most frequent adverse events grades 3/4, which occurred in > 10% of patients were lymphocytopenia (97.9%), leukopenia (93.8%), neutropenia (89.6%), febrile neutropenia (64.8%), anemia (58.3%), thrombocytopenia (45.8%), infection (27.1%), skin rash (20.8%), and hyperglycemia (20.8%). Relative dose intensity (RDI) was calculated for each drug: the mean RDI for Moga was 82.1%, for CPA 71.7%, for DXR 72.7%, for VCR 72.0%, and for PSL 77.3%. **Conclusions:** This study demonstrated that Moga-CHOP-14 significantly improved PFS in elderly patients with aggressive CCR4-positive ATL who were ineligible for allo-HSCT. Moga-CHOP-14 is now considered for the preferred first-line treatment in those patients. Clinical trial information: jRCTs041180130. Research Sponsor: Kyowa Kirin; Japan Agency for Medical Research and Development.

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Oral Abstract Session

Epcoritamab + R² regimen and responses in high-risk follicular lymphoma, regardless of POD24 status. *First Author: Reid Merryman, Dana-Farber Cancer Institute, Boston, MA*

Background: Follicular lymphoma (FL) is a heterogeneous disease. Early progression after initial treatment (tx) with chemoimmunotherapy (CIT), POD24, occurs in around 20% of patients (pts) and strongly predicts poor outcomes. There is no standard tx approach for high-risk, relapsed or refractory (R/R) FL (high-risk subgroups in Table). Novel options are needed to improve efficacy in pts with high unmet need. Epcoritamab, a subcutaneous (SC) T-cell-engaging bispecific antibody, demonstrated impressive single-agent antitumor activity and a manageable safety profile in R/R FL (Hutchings et al, *Lancet* 2021) and shows promise combined with standards of care. Here we present pooled analyses from cohorts 2a and 2b of the ongoing phase 1/2 EPCORE NHL-2 trial (NCT04663347) of epcoritamab with rituximab + lenalidomide (R²). **Methods:** Pts with R/R CD20⁺ FL received epcoritamab SC + R² for 12 cycles (Cs; 28 d each). Epcoritamab was dosed QW in C1-3, Q2W in C4-9, and Q4W in C≥10 (2a) or QW in C1-2 and Q4W in C≥3 (2b) for ≤2 y. **Results:** As of Oct 31, 2022, 109 R/R FL pts had received epcoritamab 48 mg + R² in 2a and 2b. Median age was 65 y, 56% of pts had FLIPI 3-5, 61% had stage IV disease, and 59% had only 1 prior tx. Most had received alkylating agents (92%) or anthracyclines (62%); 2 had prior CAR T. At a median follow-up of 8.8 mo (range, 1.2-18.5), 82% were still on tx. The most common tx-emergent AEs were: CRS and neutropenia, 48% each; injection-site reactions, 38%; and fatigue, 33%. CRS events were mostly low grade (G; 46% G1-2, 2% G3) and mostly occurred following the first full dose on C1D15; all resolved and none led to discontinuation. ICANS occurred in 2 pts (G1, G2) and resolved. In 101 efficacy-evaluable pts, overall response rate (ORR) was 97%, with complete metabolic response (CMR) in 86%. Notably, pts achieved higher ORR/CMR rates with epcoritamab + R² vs their immediate prior tx line (ORR, 97% vs 85%; CMR, 86% vs 60%). Estimated 6-mo progression-free survival was 93%. In second-line (2L) pts with POD24, ORR/CMR rates were 95%/90% (additional high-risk subgroup data in Table). Additional data with longer follow-up will be presented. **Conclusions:** Epcoritamab + R² showed potent antitumor activity and a manageable safety profile in a large R/R FL population. Encouraging responses were seen in pts with high-risk disease, suggesting epcoritamab SC may abrogate negative effects of high-risk features. A separate POD24 cohort is planned, and epcoritamab + R² is being studied in the phase 3 EPCORE FL-1 trial (NCT05409066). Clinical trial information: NCT04663347. Research Sponsor: This study was funded by Genmab A/S and AbbVie.

ORR and CMR in high-risk R/R FL subgroups.

	n (%)	ORR %	CMR %
Primary refractory ^a	39 (39)	97	87
Double refractory ^b	39 (39)	92	79
Refractory to prior anti-CD20 tx	49 (49)	94	84
POD24 ^c	38 (38)	95	82
POD24 ^c 2L ^d	20 (20)	95	90

^aNo response or relapse within 6 mo after first-line tx. ^bRefractory to anti-CD20 and an alkylating agent. ^cProgression within 2 y of initial tx with CIT. ^dPts received epcoritamab in 2L.

LBA7505

Oral Abstract Session

Observation vs. radiotherapy in primary mediastinal B-cell lymphoma patients with complete response to standard immunochemotherapy: The IELSG37 randomized trial. *First Author: Emanuele Zucca, Institute of Oncology Research; Clinic of Hematology, Oncology Institute of Southern Switzerland, Ente Ospedaliero Cantonale; Faculty of Biomedical Science, Università della Svizzera italiana; International Extranodal Lymphoma Study Group (IELSG), Bellinzona, Lugano, Switzerland*

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2023, issue of the Journal of Clinical Oncology.

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Oral Abstract Session

Real-world outcomes of brexucabtagene autoleucel (brexu-cel) for relapsed or refractory (R/R) mantle cell lymphoma (MCL): A CIBMTR subgroup analysis by prior treatment. *First Author: Swetha Kambhampati, City of Hope National Medical Center, Duarte, CA*

Background: Brexu-cel is a CAR T therapy approved for adult patients (pts) with R/R MCL. In a 3-year follow-up of ZUMA-2 (Wang et al., 2022), ORR was 91% (CR 68%). Median DOR, PFS and OS were 28.2, 25.8 and 46.6 mo respectively. Here, we describe real-world outcomes of brexu-cel by receipt of prior BTK inhibitor (BTKi), bendamustine, autoHCT, and 1-2 vs ≥ 3 prior lines of therapy. **Methods:** From 07/2020-08/2022, 397 pts receiving brexu-cel for R/R MCL from 79 US centers were registered in the CIBMTR observational database. In this analysis, 272 were included (median follow-up 6.6 mo; range 0.3-16.5), excluding pts with prior non-HCT cellular therapy (n = 7), missing data on prior treatment, or no follow-up. Descriptive analyses were used for all outcomes. **Results:** Median age was 65.8 years (range 34.1-84.9); pts were mostly male (78%). Prior to infusion, 7% had ECOG PS ≥ 2; 76% had clinically significant comorbidities; 4% had extranodal CNS involvement. At diagnosis, Ki-67 ≥ 30%, Ki-67 ≥ 50% and TP53/17p deletion were seen in 69% (n = 111/160), 44% (n = 70/160) and 19% (n = 29/153) of pts respectively. Pts had a median of 4 lines of prior therapy (range 1-12; 6% as 2L). Prior to leukapheresis, 87% were BTKi-exposed; 54% received bendamustine; 31% were autoHCT recipients. Median time from leukapheresis to infusion was 28 d (IQR 26-34 d), during which 18% received bridging therapy. ORR for all was 89% (CR 78%). At 6 mo, cumulative incidence of relapse/PD was 21%; DOR, PFS and OS were 76%, 73% and 83% respectively. Grade ≥ 3 (ASTCT consensus) CRS and ICANS occurred in 9% and 27% of pts (88% and 62% for any grade). Most CRS (94%) and ICANS (79%) resolved within 3 weeks. Prolonged cytopenia by 30 d occurred in 23% pts. NRM at 100 d and 180 d were 3% and 6% respectively, mainly due to infections. ORR for BTKi-naïve (n = 36) vs -exposed (n = 233) pts was 85% (CR 79%; 6-mo DOR 84%) vs 89% (CR 77%; 6-mo DOR 74%); for pts with (n = 145) vs without (n = 124) prior bendamustine was 88% (CR 75%; 6-mo DOR 75%) vs 89% (CR 80%; 6-mo DOR 77%); for pts with (n = 83) vs without (n = 188) prior autoHCT was 90% (CR 82%; 6-mo DOR 83%) vs 88% (CR 76%; 6-mo DOR 72%). Higher CR rates were seen in pts with brexu-cel as 2/3L (n = 56) vs 4L+ (n = 213) (91% vs 74%; ORR 92% vs 88%; 6-mo DOR 77% vs 75%). Similar safety profiles were seen regardless of prior BTKi or autoHCT. Pts with prior bendamustine had fewer Grade ≥ 3 ICANS (19% vs 36%) but more prolonged cytopenia (29% vs 16%) vs pts without. **Conclusions:** These early findings suggest that real-world outcomes of brexu-cel are consistent regardless of prior BTKi, bendamustine, or autoHCT. Use of brexu-cel in earlier lines may help achieve a higher CR rate. Further studies with longer follow-up are warranted to contextualize response rates in relation to long-term clinical benefits of brexu-cel. Updated data with longer follow-up will be reported at the time of presentation. SK and NA contributed equally. Research Sponsor: Kite, a Gilead Company; NCI grant: National Cancer Institute (CIDR [U24 CA233032]).

7508

Oral Abstract Session

Very long-term follow-up of rituximab maintenance in young patients with mantle cell lymphoma included in the LYMA trial, a LYSA study. *First Author: Cl  mentine Sarkozy, Institut Curie, Saint Cloud, Paris, France*

Background: The phase III LYMA trial demonstrated the efficacy (OS, PFS, EFS) and safety of rituximab maintenance (RM) post autologous stem cell transplant (ASCT) in first line for young patients with mantle cell lymphoma (MCL) (Le Gouill et al, NEJM). Herein, we present the first long-term analysis of the LYMA trial. **Methods:** 299 patients were included in LYMA trial of whom 240 were randomized to receive 3 years of RM (n = 120) or no RM (observation; n = 120). Primary endpoint was 3 years EFS. We updated the outcome of all patients enrolled in this trial. Treatment at relapse and cause of death were collected. **Results:** At the time of the present analysis, the median follow-up is 7 years (0.2-10). The median EFS and PFS were still statistically superior in favor of RM (not reached (NR), versus 5.8 years, p < .0001 for EFS and NR versus 6.1 years for PFS in RM and observation arm respectively). The 7 years estimated EFS and PFS were 76.2% (95% CI 67.4-82.9%) versus 46% (95% CI 36.6-54.9%) and 78.5% (95% CI 69.9-85.0%) versus 47.4% (95% CI 37.9-56.3%), for RM and observation respectively, p < .0001). In the RM arm, 22 patients had died (18.3%) versus 33 (27.5%) in the observation arm with a 7-year OS estimate of 83.2% (95% CI: 74.7-89.0%) and 72.2% (95% CI 62.9%-79.5%) in RM and observation arm, respectively (p = 0.087). Causes of death were not significantly distinct between the 2 groups, lymphoma being the leading cause in both (50% in both arm), with less than 10% of infectious related death. The end of RM was not associated with an increase in the relapse incidence, since in the RM arm, 17/21 (81%) of the progression occurred during the theoretical 3 years of RM and only 19% after the end of RM. On the contrary, in the observation arm, 32/53 (60%) of the progression/relapses occurred during the theoretical 3 years of maintenance part, and 40% after. Salvage treatments were not different between the RM and observation arm, including anti CD20 and BTK inhibitors administered in 75% versus 79% and 10% versus 15% of the relapsing patients in the RM and observation arms, respectively. Post relapse OS was significantly impacted by previous RM, with a median OS-2 of 1.1 years (95%CI 0.7-2.1) for the 21 relapsing patients in the RM arm versus 4.6 years (95%CI 2-NA) for the 53 relapsing patients in the observation arm. Given the timing of relapses in RM arm, this reflects the aggressiveness of early disease progression during RM. **Conclusions:** The benefice in favor of RM in term of EFS (the primary objective), PFS remains after 7 years of FU, but not in OS. The end of RM was not associated with an increase in relapse rate. RM was not associated with an increase in infectious related mortality, making of this strategy a safe standard of care with long term FU. Patients relapsing during RM have a particularly poor outcome and represent an unmet medical need. Clinical trial information: NCT00921414. Research Sponsor: Roche and AMGEN.

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Poster Discussion Session

Five-year follow-up update of defined-composition CD19 CAR T-cell therapy for relapsed/refractory CLL. *First Author: Emily C. Liang, Fred Hutchinson Cancer Center, Seattle, WA*

Background: We have described high response rates in patients (pts) with relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL) treated with CD19-targeted CAR T cells. We now report comprehensive analyses of factors associated with duration of response (DOR) with a 68-month median follow-up. **Methods:** We included 49 pts with R/R CLL and/or Richter's transformation (n = 10) treated on a phase I/II clinical trial of defined-composition CD19 CAR T-cell therapy (1:1 ratio of CD8+:CD4+). Response rates were investigator-assessed by 2018 iwCLL criteria. Measurable residual disease (MRD) in bone marrow (BM) was evaluated by multiparameter flow cytometry (MFC) and *IGH* next-generation sequencing (NGS; clonoSEQ assay). CAR T-cell enumeration was assessed by MFC. Serum cytokine concentrations (20 analytes) were measured by Luminex assay. Univariate associations between duration of response (DOR) and patient, disease, CAR T-cell manufacturing, and treatment-related variables were estimated using Cox regression (50+ variables). Association between CAR T-cell in vivo persistence and DOR was modeled with a time-dependent Cox model including blood CAR transgene levels (copies/ μ g genomic DNA). **Results:** Median age was 61 years (IQR, 55-67). Forty-six pts (94%) had complex karyotype and/or 17p deletion; 46 (94%) received cyclophosphamide/fludarabine lymphodepletion. In the response-evaluable cohort (n = 47), median follow-up was 68.3 months (IQR, 54.3-81.6). Overall and complete response rates at day+28 were 70% and 17%, respectively, and the median DOR was 22.2 months (95% CI, 10.7-not reached [NR]). MRD-negativity at day+28 by MFC occurred in 33/47 (70%). In pts with MRD-negativity by MFC and available data, MRD negativity by NGS was seen in 18/29 (62%). In NGS MRD-negative responders, the median DOR was 56.8 months (95% CI, 39.5-NR). In all evaluable patients, the 5-year OS and PFS were 35.5% (95% CI, 24.0%-52.5%) and 21.5% (95% CI, 12.0%-38.5%), respectively. In univariate Cox regression, day+28 MRD-negativity by MFC (HR = 0.03, 95% CI, 0.01-0.18, p < 0.001), day+28 MRD-negativity by NGS (HR = 0.21, 95% CI, 0.07-0.61, p = 0.004), peak CD8+ CAR T-cell expansion (HR = 0.49, 95% CI, 0.24-1.00, p = 0.05), CAR T-cell persistence (HR = 0.71, 95% CI, 0.54-0.91, p = 0.01), and lower peak MIP-1 β (HR = 3.12, 95% CI, 1.13-8.65, p = 0.03) were associated with longer DOR. Peak MIP-1 β remained associated with DOR (HR = 3.83, 95% CI, 1.35-10.9, p = 0.012) in a multivariable model including pre-LD CLL cells in BM, tumor cross-sectional area, peak CD8+ CAR T-cell expansion, and day+28 MRD by MFC. **Conclusions:** CD19 CAR T-cell therapy achieved durable remissions in R/R CLL pts. Day+28 MRD, CAR T-cell peak expansion, and CAR T-cell persistence were strongly associated with DOR. Lower peak serum levels of MIP-1 β , a cytokine known to be produced by CLL cells upon BCR activation, was strongly and independently associated with DOR. Clinical trial information: NCT01865617. Research Sponsor: U.S. National Institutes of Health; Bezos Family Foundation; U.S. National Institutes of Health; Life Sciences Discovery Fund; University of British Columbia Clinical Investigator Program, National Gene Vector Biorepository at Indiana University; Juno Therapeutics, a Bristol-Myers Squibb company.

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Poster Discussion Session

Real-world early outcomes of axicabtagene ciloleucel for relapsed or refractory (R/R) follicular lymphoma (FL). *First Author: Caron Alyce Jacobson, Dana-Farber Cancer Institute, Boston, MA*

Background: Axicabtagene ciloleucel (axi-cel) is an autologous CAR T approved for adult patients (pts) with r/r FL after $\geq$ 2 lines of systemic therapy. In the primary analysis of the pivotal ZUMA-5 trial, 94% of pts who received axi-cel to treat r/r FL achieved an objective response, with a 79% CR rate (Jacobson et al. 2022). Grade $\geq$ 3 cytokine release syndrome (CRS) and neurologic events occurred in 6% and 15% of pts, respectively. Here, we present the real-world outcomes of pts receiving axi-cel for r/r FL, including those who would have been ineligible for ZUMA-5. **Methods:** A total of 230 pts from 72 US centers receiving first axi-cel for r/r FL in the real-world setting between March 2021 and October 2022 were identified from the CIBMTR registry. The following pts were excluded: no consent, prior non-transplant cellular therapy, and FL grade 3b or 3a/3b unspecified. Of the 230 pts, 151 pts had post-infusion assessments and were included in the analysis of outcomes. Effectiveness outcomes were ORR, CR, DOR, PFS and OS. Adverse events included CRS, immune effector cell-associated neurotoxicity syndrome (ICANS) and prolonged cytopenia. **Results:** Of the 230 pts, median age was 62 years and 60% were male. Prior to infusion, 98% had an ECOG performance score of 0-1, 33% had elevated LDH, and 66% were chemo-resistant. Clinically significant comorbidities were present in 74% of the pts. Ninety-two (40%) pts would have been ineligible for ZUMA-5, mainly due to comorbidities. Pts had a median of 4 (range 1-13) lines of prior therapy including 14% who also underwent prior ASCT. Median time from leukapheresis to infusion was 28 days (IQR 26-34). 9% of pts received bridging therapy. Outcomes were analyzed among the 151 pts with follow-up (median 6.2 mo). ORR and CR rates were 93% (95% CI 88-97%) and 84% (95% CI 77-89%), respectively. Estimated PFS and OS at 6 mo were 88% (95% CI 81-92%) and 96% (95% CI 91-98%), respectively. Grade $\geq$ 3 CRS (ASTCT consensus) and ICANS (ASTCT consensus) occurred in 2% (95% CI 0-6%) and 13% (95% CI 8-19%) of pts, respectively. Median cumulative incidence estimates of CRS resolution was 5 days and ICANS resolution was 4 days. Among pts alive at Day 30 (n = 150), 11% experienced prolonged cytopenia (4% neutropenia, 9% thrombocytopenia). PFS and OS at 6 mo were comparable regardless of ZUMA-5 eligibility, while pts eligible for ZUMA-5 had fewer Grade $\geq$ 3 ICANS (10% vs 16%) and more rapid ICANS resolution (92% vs 71% resolved within 2 weeks). Pts aged $\geq$ 65 vs < 65 years had comparable effectiveness and safety profiles. **Conclusions:** This is the first report on axi-cel to treat r/r FL in real-world settings. Despite a broader pt population, early results demonstrate effectiveness and safety profiles consistent with those observed in the ZUMA-5 trial. The intent is to present findings from an updated dataset with longer follow-up at ASCO. Overall, these findings support the continued broad use of axi-cel to treat r/r FL. Research Sponsor: Kite, a Gilead company; National Cancer Institute Grant: National Cancer Institute (CIDR U24 CA233032J).

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Poster Discussion Session

SAVE (Safe Accelerated Venetoclax Escalation): Initial results of a prospective, phase Ib study of venetoclax with an accelerated dose ramp-up in patients with CLL. *First Author: Jennifer Leigh Crombie, Dana-Farber Cancer Institute, Boston, MA*

Background: Venetoclax (VEN)-based regimens are highly effective for patients (pts) with treatment naive (TN) and relapsed/refractory (R/R) CLL. Despite high rates of undetectable minimal residual disease (uMRD) and durable responses even with time-limited therapy, uptake of VEN in routine clinical practice has been relatively low, in part due to the inconvenient 5-week dose ramp-up used to reduce the risk of tumor lysis syndrome (TLS). Accelerated ramp-up schedules have been evaluated in retrospective studies (Davids et al., AJH, 2022), but prospective studies are lacking. Here we present initial results of SAVE: Safe Accelerated Venetoclax Escalation, a phase Ib study of VEN with an accelerated dose ramp-up in pts with CLL. **Methods:** This is an ongoing phase Ib investigator-sponsored trial for pts with TN and R/R CLL (NCT04843904). Key eligibility include CLL requiring therapy per 2018 iwCLL criteria and adequate renal function. The primary endpoint is the highest risk TLS group that can safely tolerate an accelerated VEN ramp-up. Secondary endpoints include safety and tolerability and rates of ORR/CR/uMRD after 3 months of VEN-based therapy. Patients are treated inpatient with a 5-day daily VEN ramp-up schedule (20-50-100-200-400 mg). TLS labs are monitored pre-dose and at 4, 8, 12, and 24 hours following each dose. Anti-CD20 antibody is given per SOC. At least 5 pts from cohort A (low TLS risk using standard assessment) were required to enroll prior to opening cohort B (medium and high TLS risk). Efficacy is assessed using 2018 iwCLL criteria, toxicity using iwCLL and CTCAE v5, and MRD using central 8-color flow at 10^{-4} . **Results:** As of 2/2/2023, 20 pts have been treated (10 each from cohort A and B) (Table). 19 pts received obinutuzumab with VEN, and 1 pt received VEN monotherapy. All pts completed an accelerated VEN ramp-up without any clinical TLS. One pt with medium TLS risk had lab TLS (phos and uric acid peaked at 8.7 mg/dL) after the first VEN 400 mg dose, which resolved with sevelamer and rasburicase, thereby prolonging the ramp-up to 6 days. Median inpatient time was 6 days (range 5-8). All grade hemo tox: neutropenia (45%; 20% G3/4), thrombocytopenia (35%; 10% G3/4). One pt died 2 months into treatment due to complications of a bowel obstruction unrelated to study treatment. ORR after 3 mo. was 89% in 19 evaluable pts including 2 CRs. Among 19 evaluable patients after 3 mo., 74% and 42% had uMRD in PB and BM, respectively. **Conclusions:** Our early data suggest that an inpatient, accelerated 5-day VEN ramp-up is feasible in CLL, with a low rate of TLS, even among patients with medium or high risk of TLS. The study is currently ongoing. Clinical trial information: NCT04843904. Research Sponsor: Dana-Farber Cancer Institute; U.S. National Institutes of Health.

	Total N=20	Cohort A N=10	Cohort B N=10
Baseline Characteristics			
Median Age (range)	69 (66-77)	68 (66-69)	71 (68-77)
TN	13 (65%)	5 (50%)	8 (80%)
R/R	7 (35%)	5 (50%)	2 (20%)
TP53-aberrant	4 (20%)	3 (30%)	1 (10%)
Unmutated IGHV	9 (45%)	3 (30%)	6 (60%)

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Poster Discussion Session

Long-term safety with ≥ 12 months of pirtobrutinib in relapsed/refractory (R/R) B-cell malignancies. *First Author: Catherine Callaghan Coombs, UCI Health, Orange, CA*

Background: While Bruton tyrosine kinase inhibitors (BTKi) can induce sustained remissions, ongoing response requires continuous treatment and thus long-term safety/tolerability is critical for adherence, maintaining dose intensity, and delivering maximum efficacy. Pirtobrutinib is a highly selective, non-covalent (reversible) BTKi approved by the FDA in January 2023 for R/R mantle cell lymphoma after 2 prior lines of therapy including a BTKi. Pirtobrutinib has demonstrated promising efficacy with low discontinuation and dose reduction rates in patients (pts) with multiple subtypes of R/R B-cell malignancies. However, the long-term safety and tolerability of pirtobrutinib has not yet been reported. Here we report the clinical safety in pts with long-term (≥ 12 months) pirtobrutinib treatment from the phase 1/2 BRUIN trial. **Methods:** Pts with R/R B-cell malignancies who received ≥ 12 months of pirtobrutinib were included. Median time to onset, dose reduction, discontinuation, and cumulative incidence rates were determined for treatment emergent adverse event (TEAE) that occurred in $\geq 20\%$ of pts and select AE of interest associated with BTKi. **Results:** As of 29 July 2022, 773 pts were enrolled, and 326 (42%) pts received treatment for ≥ 12 months. Among these 326 pts, median time on treatment was 19 months (IQR: 16,25), with 231 (71%) remaining on pirtobrutinib. The most common TEAE (all grade, regardless of attribution) in this long-term 326 pt cohort were fatigue (32%), diarrhea (31%), Covid-19 (29%), contusion (26%), cough (25%), and back pain (21%). TEAE leading to dose reduction or discontinuation occurred in 23 (7%) and 11 (3%) pts, respectively. Four (1%) pts discontinued due to a treatment-related AE, and 1 pt had a fatal treatment-related AE (Covid-19 pneumonia). Select AE of interest for the long-term pts are shown in the Table. Comprehensive safety analyses describing the frequency of TEAE over time will be presented. **Conclusions:** Prolonged pirtobrutinib therapy continues to demonstrate a safety profile amenable to long-term administration at the recommended dose without evidence of new or worsening toxicity signals. The safety and tolerability observed in pts on therapy for ≥ 12 months was similar to previously published safety analyses on all pts enrolled regardless of follow-up. Clinical trial information: NCT03740529. Research Sponsor: Loxo@ Lilly.

Select AE of interest associated with BTKi in pts with ≥ 12 months exposure (N = 326).

AE	Any Grade TEAE %	Grade ≥ 3 TEAE %	Median time (months) to first dose reduction occurrence (Q1, Q3)	Leading to dose reduction %	Leading to drug discontinuation %	Cumulative incidence rate (6, 12, 24 months)
Bruising ^a	31	0	1.8 (0.5, 5.6)	< 1	0	23, 27, 29
Arthralgia	21	1	7.4 (2.9, 12.0)	0	0	9, 16, 20
Rash ^a	20	< 1	2.4 (0.7, 9.1)	0	0	13, 15, 18
Hemorrhage/ ^a Hematoma ^a	17	2	5.8 (1.9, 13.7)	0	0	9, 11, 16
Hypertension	16	3	6.9 (2.1, 11.6)	< 1	0	7, 12, 16
Atrial fibrillation/ ^a flutter ^a	3	1	10.2 (3.8, 15.0)	0	0	1, 2, 2

^aConsolidated Terms.

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Poster Discussion Session

Response-adapted therapy (tx) with nivolumab plus brentuximab vedotin (nivo + BV) without autologous hematopoietic cell transplantation (auto-HCT) in children, adolescents, and young adults (CAYA) with low-risk relapsed/refractory (R/R) classic Hodgkin lymphoma (cHL): CheckMate 744. *First Author: Paul David Harker-Murray, Children's Wisconsin, Milwaukee, WI*

Background: Outcomes are poor for patients (pts) with cHL who develop R/R disease after first-line (1L) chemotherapy $\pm$ radiotherapy (RT). Salvage tx that attain high event-free survival (EFS) rates and minimize late toxicity by omitting high-dose chemotherapy (HDCT)/auto-HCT are needed. CheckMate 744 (NCT02927769) is the first multicenter phase 2 study evaluating a risk-stratified, response-adapted salvage tx with nivo + BV in CAYA with R/R cHL. In the standard-risk cohort, complete molecular response (CMR) rate before consolidation with HDCT/auto-HCT was 94% (Harker-Murray et al. *Blood* 2022). With highly active salvage tx, pts in low-risk cohort could achieve high EFS without HDCT/auto-HCT; we report data from this cohort. **Methods:** Pts were aged 5–30 y and had ≤ 3 cycles (C) of 1L anthracycline-based systemic tx. Risk stratification was described in Harker-Murray et al. Pts received 4C of nivo + BV induction. Pts with CMR received additional 2C nivo + BV before involved-site radiation therapy (ISRT) consolidation (dose, 30–30.6 Gy). Pts with suboptimal response received 2C BV + bendamustine intensification; pts with CMR proceeded to ISRT consolidation. Primary endpoints: CMR rate (Lugano 2014) any time before ISRT and 3-y EFS rate, both per blinded independent central review (BICR). For CMR and overall response rate (ORR), a 90% confidence interval (CI) was used per statistical plan. **Results:** Among 28 pts treated with nivo + BV, median (range) age was 17 (6–27) y; 64% of pts were aged < 18 y. Most (64%) pts had stage II disease at relapse; 82% had relapse ≥ 12 mo after 1L tx, 2 pts had prior RT. Median (range) follow-up was 31.9 (2.2–55.3) mo. CMR, ORR, 3-y EFS and PFS rates are shown in Table. Median duration of response was not reached; 87% of pts had sustained response at 36 mo' follow-up. Efficacy outcomes were comparable in the pediatric population (CMR per BICR before ISRT, 88.9%; 3-y EFS rate, 78.3%). During induction, 22 (78.6%) pts had treatment-related adverse events (TRAEs; grade 3/4, 25.0% pts; hematologic, < 10% pts; immune-mediated, 21.4%). Serious AEs leading to discontinuation included rash, pyrexia, and acute kidney injury (1 pt each). **Conclusions:** The findings demonstrate that most CAYA with low-risk R/R cHL can be salvaged with chemoimmunotherapy with a favorable toxicity profile, and do not require HDCT/auto-HCT. Clinical trial information: NCT02927769. Research Sponsor: Bristol Myers Squibb.

CMR and ORR per BICR and investigator (INV) in low-risk cohort.

	BICR	INV
Any time before ISRT		
CMR, n (%) [90% CI]	26 (92.9) [79.2–98.7]	25 (89.3) [74.6–97.0]
ORR, n (%)	28 (100.0)	28 (100.0)
After 4C nivo + BV		
CMR, n (%)	23 (82.1)	24 (85.7)
ORR, n (%) [90% CI]	27 (96.4) [84.1–99.8]	28 (100.0) [89.9–100.0]
3-y EFS, n (%) [90% CI]	86.9 [69.5–94.7]	88.0 [71.8–95.2]
3-y PFS, n (%) [90% CI]	95.0 [76.7–99.0]	95.7 [79.4–99.1]

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Poster Discussion Session

Pirtobrutinib in covalent BTK-inhibitor (cBTKi) pre-treated mantle cell lymphoma (MCL): Updated results and subgroup analysis from the phase 1/2 BRUIN study with > 3 years follow-up from start of enrollment. *First Author: Nirav Niranj Shah, Medical College of Wisconsin, Milwaukee, WI*

Background: Pirtobrutinib is a highly selective, non-covalent (reversible) BTKi. Here, we report updated results of pirtobrutinib in patients (pts) with cBTKi pre-treated relapsed/refractory (R/R) MCL and more than 3 years follow-up from start of enrollment. **Methods:** Pts with cBTKi pre-treated R/R MCL received pirtobrutinib monotherapy in a multicenter phase 1/2 BRUIN trial (NCT03740529). Efficacy was assessed in the prespecified primary efficacy cohort that comprised the first 90 enrolled pts who had measurable disease, had received a prior cBTKi, and had no known central nervous system involvement. The primary endpoint was overall response rate (ORR) as assessed by independent review committee. Secondary endpoints included duration of response (DOR) and safety. A data cut of 29 July 2022 was utilized. **Results:** Among MCL pts who received a prior cBTKi (n=90), median age was 70 years (range, 46–87), median prior lines of therapy were 3 (range, 1–8), 82% discontinued a prior cBTKi due to disease progression, and 78% had intermediate/high risk SMPI score. Of samples available, 17/36 (47%) had TP53 mutations and 25/34 (74%) had Ki67 $\geq 30\%$. The ORR was 57% (95% CI, 46–67), including 19% complete responses (n=17) and 38% partial responses (n=34). At a median follow-up time of 13 months, the median DOR among the 51 responding pts was 17.6 months (95% CI, 7.3–27.2). The 12- and 18-month estimated DOR rates were 58% (95% CI, 41–72) and 45% (95% CI, 27–61), respectively. ORR and DOR by subgroups are shown in the Table. The median progression-free survival was 7.4 months (95% CI, 5.3–13.3). The median overall survival was 23.5 months (95% CI, 15.9–NE). In the MCL safety cohort (n=166), the most frequent treatment-emergent adverse events (TEAE) were fatigue (31%), diarrhea (22%), and anemia (17%). The most common Grade ≥ 3 TEAE was neutropenia (15%). Grade ≥ 3 TEAE of hemorrhage (3%) and atrial fibrillation/flutter (2%) were infrequent. Only 5 (3%) pts discontinued due to a treatment-related AE. **Conclusions:** Pirtobrutinib continues to show durable efficacy and a favorable safety profile in heavily pre-treated R/R MCL pts with prior cBTKi therapy. Responses were observed in pts with high-risk disease features including pts with blastoid/pleomorphic variants, elevated Ki67 index, and TP53 mutations. Clinical trial information: NCT03740529. Research Sponsor: Loxo@Lilly.

ORR and DOR in cBTKi pre-treated MCL pts and high-risk subgroups.

	cBTKi pre-treated MCL, n	ORR, % (95% CI)	DOR, median (95% CI)
Overall	90	56.7 (45.8–67.1)	17.6 (7.3–27.2)
MCL histology			
Classic/Leukemic	70	58.6 (46.2–70.2)	17.6 (7.5–NE)
Blastoid	8	50.0 (15.7–84.3)	NE (1.4–NE)
Pleomorphic	12	50.0 (21.1–78.9)	27.2 (3.7–NE)
TP53 mutation			
Yes	17	47.1 (23.0–72.2)	17.6 (1.7–NE)
No	19	57.9 (33.5–79.7)	14.8 (1.9–NE)
Ki-67			
$< 30\%$	9	66.7 (29.9–92.5)	17.6 (1.6–NE)
$\geq 30\%$	25	56.0 (34.9–75.6)	21.6 (1.7–NE)

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Poster Discussion Session

Circulating tumor DNA of classical Hodgkin lymphoma. *First Author: Maria Cristina Piroso, Institute of Oncology Research, Bellinzona, Switzerland*

Background: Classical Hodgkin lymphoma (cHL) is the most common lymphoma in young adults. The morphologic peculiarity that makes cHL unique are the few tumor cells surrounded by a polyclonal inflammatory microenvironment. It is also the cancer with the highest sensitivity to immune checkpoint inhibitors. But why is it so immunogenic and how it escapes the immune control at the same time have only been partially elucidated. Although cure rates of cHL have constantly increased over the years there is still a high need for identification of biomarkers for more precise treatment decisions. The need for enriching tumor cells before assaying has limited cHL biological studies. Patients with cHL have significant amounts of circulating tumor DNA (ctDNA), suggesting an alternative approach for studying this enigmatic tumor. **Methods:** IOSI-EMA003 (NCT03280394) is a prospective, observational, multi-center study of adult patients with previously untreated cHL aiming at: i) identifying subgroups of patients with phenotype- and outcome-associated molecular signatures; ii) testing and validating baseline ctDNA load as a prognostic biomarker; iii) testing if ctDNA can be used for the early identification of chemoresistance. Blood samples were collected at staging and disease response assessment. PET scans were centrally and blindly reviewed. ctDNA was analyzed by using deep targeted and shallow whole genome sequencing to measure ctDNA load, capture mutations and profile ctDNA fragmentation patterns. The composition of the tumor microenvironment of cHL was probed by single cell RNA-seq. **Results:** A total of 215 patients were enrolled. Based on ctDNA fragmentation patterns reflecting chromatin accessibility in the regulatory region of germinal center (GC) B-cell genes, we segregated cHL into two subgroups that we named SNCD (for sub-nucleosomal cDNA) and NCD (for nucleosomal cDNA). We hypothesized that SNCD cHL stems from a cell that is closer to the GC B-cell differentiation stage than NCD cHL. SNCD cHL and NCD cHL differed in many aspects, including activation induced cytidine deaminase (AID)-hypermutation profile, neoantigen load, immune editing mechanism and response to chemotherapy and checkpoint inhibitors. Clinically, SNCD cHL displayed less sensitivity to both chemotherapy and anti-PD1 antibodies. Immune editing of SNCD cHL points loss of MHC-I, recruitment of Treg and upregulation of LAG3 as prominent immune checkpoint. High load of pre-treatment ctDNA nominated high-risk patients more accurately than clinico-radiological features. In addition, persistence of residual ¹⁸FDG avid lesions and measurable ctDNA was a better proof of chemoresistance than the sole persistence of residual ¹⁸FDG avid lesions. **Conclusions:** Our results provide a roadmap for cHL subtyping and molecular classification. We also propose ctDNA as a quantifiable and radiation-free biomarker to be used in clinical trials testing a more personalized treatment approach. Clinical trial information: NCT03280394. Research Sponsor: European Research Council (ERC) Consolidator Grant CLCLONE, ID: 772051; Swiss Cancer Research Foundation, ID 3746, 4395, 4660, 5257, Bern, Switzerland; Swiss National Science Foundation, ID 320030_169670/1, 310030_192439, 320036_179318.

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Poster Discussion Session

Efficacy and safety of pembrolizumab every six weeks in relapsed/refractory classical Hodgkin lymphoma or primary mediastinal B-cell lymphoma: The phase 2 KEYNOTE-B68 trial. *First Author: Andrew Bruce McDonald, Alberts Cellular Therapy, Netcare Pretoria East Hospital, Pretoria, South Africa*

Background: Pembrolizumab (pembro) 200 mg Q3W demonstrated robust antitumor activity and manageable safety in relapsed/refractory (R/R) classical Hodgkin lymphoma (cHL) and R/R primary mediastinal B-cell lymphoma (PMBCL), resulting in FDA approval. Recently, the FDA granted accelerated approval of pembro 400 mg Q6W in all approved indications based on data from solid tumor trials in solid tumors. The global Phase 2 trial (NCT04875195) evaluates the efficacy and safety of pembro 400 mg Q6W in R/R cHL and R/R PMBCL. We present, for the first time, data from 66 patients (pts) with approximately 9 months (mo) of follow up. **Methods:** In this nonrandomized, open-label trial, pts aged ≥ 18 years with PD-1 inhibitor naïve R/R cHL or PMBCL received 400 mg pembro Q6W for ≤ 18 cycles, until progression, unacceptable toxicity, or withdrawal. Eligible pts with cHL must have relapsed or failed to respond after ≥ 1 prior lines of therapy (LOT) or relapsed or failed to respond after ≥ 1 prior multiagent LOT or autologous stem cell transplant (ASCT). Eligible pts with PMBCL must have relapsed or failed to respond after ≥ 2 prior LOT including rituximab and relapsed or failed to respond to or were ineligible for ASCT. The primary endpoint was ORR per Lugano criteria by investigator (Lugano, INV). Secondary endpoints were DOR (Lugano, INV) and safety. Exploratory endpoints were PFS (Lugano, INV) and OS. Data cut-off date was October 18, 2022. **Results:** At data cut-off, 66 pts (60 R/R cHL, 6 R/R PMBCL) were enrolled. Median follow-up (range) was 8.9 mo (1–15.9) for pts with R/R cHL and 10.6 mo (5.1–15.4) with R/R PMBCL. The ORR was 65% (95% CI, 51.6–76.9 [33.3% CR; 31.7% PR]) for pts with R/R cHL, and 50% (95% CI, 11.8–88.2 [33.3% CR; 16.7% PR]) for R/R PMBCL. Drug-related adverse events (AE) occurred in 24 pts (40%) with R/R cHL and 2 pts (33.3%) with R/R PMBCL. Grade ≥ 3 drug-related AEs occurred in 3 pts (5%) with R/R cHL and 1 pt (16.7%) with R/R PMBCL. Immune-mediated AEs occurred in 13 pts (21.7%) with R/R cHL and 1 pt (16.7%) with R/R PMBCL. Grade ≥ 3 immune-mediated AEs occurred in 2 pts (3.3%) with R/R cHL. Antitumor activity is summarized in the Table. **Conclusions:** With approximately 9 mo of follow up, pembro 400 mg Q6W demonstrates robust antitumor activity in pts with R/R cHL and R/R PMBCL. The ORR observed is similar to pembro 200 mg Q3W in R/R cHL and R/R PMBCL. Pembro 400 mg Q6W had no new safety concerns, confirming Q6W dosing in hematologic indications. Clinical trial information: NCT04875195. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

	R/R cHL N = 60	R/R PMBCL N = 6
ORR, n (%) [95% CI]	39 (65.0) [51.6, 76.9]	3 (50.0) [11.8, 88.2]
CR	20 (33.3)	2 (33.3)
PR	19 (31.7)	1 (16.7)
Median* DOR mo (range)	NR (0.0+, 8.6+)	9.7 (2.6, 9.7)
9-mo DOR rate, %	NR	66.7
Median OS mo (95% CI)*	NR (NR, NR)	NR (0.1, NR)
12-mo OS rate, %	91.8	62.5
Median PFS mo (95% CI)*	6.3 (5.6, NR)	4.1 (0.1, NR)
12-mo PFS rate, %	37.9	33.3

NR = Not reached; *Kaplan-Meier estimates; *+ no progressive disease at time of last assessment.

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Poster Discussion Session

Metabolic response rates of epcoritamab + R-CHOP in patients with previously untreated (1L) high-risk diffuse large B-cell lymphoma, including double-hit/triple-hit lymphoma: Updated EPCORE NHL-2 data. *First Author: Lorenzo Falchi, Lymphoma Service, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Patients (pts) with 1L diffuse large B-cell lymphoma (DLBCL) typically receive rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP); however, around 40% relapse. Complete response rates and long-term outcomes are worse for high-risk pts with International Prognostic Index (IPI) 3–5 or double-hit/triple-hit lymphoma, representing an underserved pt population requiring better curative options. Data from the pivotal study of single-agent epcoritamab, a T-cell-engaging bispecific antibody, demonstrated impressive efficacy and a manageable safety profile (Thieblemont et al, JCO 2022). Preliminary data for epcoritamab + R-CHOP in 1L DLBCL (NCT04663347) showed encouraging efficacy. Here we present results for a larger cohort with longer follow-up. **Methods:** Pts with 1L CD20+ DLBCL and IPI ≥ 3 received subcutaneous epcoritamab (cycle [C] 1–4, QW; C5–6, Q3W) + R-CHOP for 6 Cs (21 d each) followed by epcoritamab monotherapy Q4W (28-d Cs) up to a total of 1 y. **Results:** As of Oct 31, 2022, 47 pts (median age, 64 y) had received epcoritamab 48 mg + R-CHOP with a median follow-up of 11.5 mo (range, 0.8–15.5). All pts had IPI 3–5, 37 (79%) had stage IV disease, and of 25 pts with FISH data available, 11 (44%) had double-hit/triple-hit DLBCL. Median time from diagnosis to first dose was 28 d (range, 3–423). Median dose intensity for R-CHOP was $\geq 95\%$. The most common treatment-emergent AEs (TEAEs) of any grade (G) were neutropenia (64%), anemia (62%), CRS (60%), fatigue (40%), pyrexia (40%), injection-site reactions (38%), and nausea (38%). TEAEs led to epcoritamab discontinuation in 3 pts; 1 pt had a G5 TEAE (COVID-19, unrelated to treatment). CRS was predominantly low grade (57% G1–2, 2% G3) and occurred mostly after the first full dose (C1D15); all cases resolved. One pt experienced G2 ICANS, which resolved. All response-evaluable pts (100%) had a response, and 76% had a complete metabolic response (CMR; Table). Notably, response rates were similar for double-hit/triple-hit pts (CMR rate, 82% [9/11]). The median durations of response, progression-free survival, and overall survival were not reached. Responses were durable; at 9 mo, an estimated 96% of pts with CMR remained in CMR. Updated data will be presented. **Conclusions:** Subcutaneous epcoritamab + R-CHOP induces high CMR rates with a manageable safety profile in pts with 1L high-risk DLBCL, including double-hit/triple-hit pts. These results support the ongoing phase 3 study of epcoritamab + R-CHOP in 1L pts (NCT05578976). Clinical trial information: NCT04663347. Research Sponsor: This study was funded by Genmab A/S and AbbVie.

Antitumor activity.	Total evaluable n=46	Double-hit/triple-hit n=11
n (%)		
Overall response	46 (100)	11 (100)
Complete metabolic response	35 (76)	9 (82)
Partial metabolic response	11 (24)	2 (18)
Stable/Progressive disease	0	0

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Poster Discussion Session

Subgroup analysis of elderly patients (pts) with diffuse large B-cell lymphoma (DLBCL) in the phase 3 POLARIX study. *First Author: Bei Hu, Levine Cancer Institute, Charlotte, NC*

Background: In the Phase 3 POLARIX study (NCT03274492), polatuzumab vedotin with rituximab, cyclophosphamide, doxorubicin, and prednisone (Pola-R-CHP) significantly improved progression-free survival (PFS) compared with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP), with a similar safety profile in pts aged 18–80 years with previously untreated DLBCL (Tilly et al. 2022). Combination regimens may be associated with higher rates of toxicity in elderly pts. We report the efficacy and safety of Pola-R-CHP vs R-CHOP in pts aged ≥ 70 years enrolled in POLARIX. **Methods:** POLARIX methods were described by Tilly et al. (2022). Pts with previously untreated DLBCL were randomized 1:1 to receive 6 cycles of Pola-R-CHP or R-CHOP, plus 2 cycles of rituximab. This analysis focused on pts aged ≥ 70 years at enrollment. **Results:** Overall, 284 pts were analyzed for efficacy (Pola-R-CHP, n=141; R-CHOP, n=143) and 280 pts were analyzed for safety (Pola-R-CHP, n=137; R-CHOP, n=143). Median age was 74 years (range 70–80), and 69.7% had an International Prognostic Index score of 3–5. Most pts in either arm received all 6 doses of polatuzumab vedotin or vincristine (88.3% and 91.6% in the Pola-R-CHP and R-CHOP arms, respectively). At data cutoff (June 28, 2021; median follow-up: 24.2 months), the risk of progression, relapse or death was lower with Pola-R-CHP vs R-CHOP (hazard ratio [HR] 0.64; 95% confidence interval [CI]: 0.41–0.99) (Table). Death by any cause occurred in 14.2% and 19.6% of pts treated with Pola-R-CHP and R-CHOP, respectively. Overall survival (OS) and disease-free survival (DFS) results are presented in the Table. Safety profiles were generally comparable for Pola-R-CHP vs R-CHOP, including rates of Grade 3–5 adverse events (AEs), Grade 5 AEs, serious AEs, peripheral neuropathy (any grade), neutropenia (Grade 3–4), and infection (Grade 3–4) (Table). **Conclusions:** Pola-R-CHP and R-CHOP demonstrated similar safety profiles in pts aged ≥ 70 years with previously untreated DLBCL. The risk-benefit profile favored Pola-R-CHP vs R-CHOP. Clinical trial information: NCT03274492. Research Sponsor: The POLARIX study (NCT03274492) was sponsored by F. Hoffmann-La Roche Ltd and Genentech, Inc. Third-party editorial assistance was provided by Leen Al-Mohammad, BSC, of Ashfield MedComms, an Inizio company, and was funded by F. Hoffmann-La Roche Ltd.

	Pola-R-CHP (efficacy-evaluable n=141; safety-evaluable n=137)	R-CHOP (efficacy-evaluable n=143; safety-evaluable n=143)	HR (95% CI)*
2-year PFS rate, % (95% CI)	77.1 (69.98–84.19)	67.0 (59.15–74.79)	0.64 (0.41–0.99)
2-year OS rate, % (95% CI)	86.2 (80.47–91.98)	82.8 (76.51–89.05)	0.74 (0.41–1.31)
2-year DFS rate, % (95% CI)	80.6 (73.37–87.78)	73.4 (65.11–81.72)	0.65 (0.38–1.11)
Total no. pts with Grade 3–5 AE, n (%)	101 (73.7)	100 (69.9)	
Total no. pts with Grade 5 AE, n (%)	5 (3.6)	7 (4.9)	
Total no. pts with serious AE, n (%)	59 (43.1)	55 (38.5)	
Total no. pts with peripheral neuropathy, any grade, n (%)	72 (52.6)	67 (46.9)	
Total no. pts with Grade 3–4 neutropenia, n (%)	42 (30.7)	50 (35.0)	
Total no. pts with Grade 3–4 infection, n (%)	22 (16.1)	18 (12.6)	

*Unstratified analysis; *DFS-evaluable population, n=125 (Pola-R-CHP); n=124 (R-CHOP).

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Poster Discussion Session

Impact of imaging frequency on progression free survival in Alliance clinical trials enrolling patients with untreated follicular lymphoma. *First Author: Sarah C. Rutherford, Weill Cornell Medicine, New York, NY*

Background: With goal of simplifying clinical trials in lymphomas, we reported that bone marrow biopsies are irrelevant for response assessment in most patients (pts) with follicular lymphoma (FL) on trials (Rutherford JCO 2023). We then investigated impact of imaging frequency in FL clinical trials. We hypothesized that progression free survival (PFS) would not be different when imaging is performed less frequently than required by trials. **Methods:** We identified all trials through Alliance for Clinical Trials in Oncology that enrolled untreated pts with FL from 2008–2016. We considered 2 imaging schedules: protocol specified (control) vs relaxed (X) in which response assessments at every other required time point were omitted. For each trial, we estimated PFS using Kaplan Meier methods for the 2 schedules then determined difference in PFS between schedules as % change from control schedule in 2 year (yr) PFS rate. We performed simulation studies to approximate impact of less frequent imaging on PFS estimation using 50901 (low-intermediate risk FL) and 50904 (intermediate-high risk FL, control arm). We assumed exponential distribution for PFS, where rate parameter was calculated based on observed median PFS with uniform censoring distribution. Protocols for 50901 and 50904 mandated imaging every 4 months (mos) for 2 yrs then every 6 mos (SO). We ran 1000 iterations of 100 observations using 3 tumor assessment follow up schedules: every 6 mos for 2 yrs then yearly (S1), every 8 mos for 2 yrs then yearly (S2), or yearly (S3) for simulated progression times. We calculated deviation of PFS using simulated schedules from truth (SO). **Results:** Across 5 FL trials, median percent change of schedule X from control schedule in estimated 2yr PFS was 2.1% (0.0–30.8%) and in estimated 4yr PFS was 0.9% (-8.6–25.7%). Disparate result in 50901 is due to small shift in events with low number of pts at risk for progression. Simulation study results by trial were: for 50901, true median PFS 1.9 yrs and average median PFS for S1, S2, and S3 of 2.05, 2.11, and 2.21 yrs; for 50904 (control arm), true median PFS 4.1 yrs and average median PFS for S1, S2, and S3 of 4.16, 4.12, and 4.05 yrs. **Conclusions:** Our findings support decreased frequency of imaging studies in FL clinical trials, which would improve resource use and decrease pt burden. We plan a larger analysis to confirm results. <https://acknowledgments.alliancefound.org>. Clinical trial information: NCT00553501, NCT01145495, NCT01190449, NCT01286272, NCT01829568. Research Sponsor: U10CA180821, U10CA180882; Celgene, GSK.

Trial	Events/ N	Median Followup (yr)	2yr PFS rate (%; 95% CI)		
			Control Schedule	Schedule X	% Change from Control Schedule
50904 (control)	22/65	2.7	79.4 (69.6–90.6)	81.0 (71.4–91.9)	2.0
50904 (experimental)	17/60	3.2	75.8 (65.0–88.3)	80.1 (70.2–91.4)	5.7
50901 (1000mg dose)	21/30	4.2	46.8 (31.5–69.5)	61.2 (45.6–82.1)	30.8
A051103	6/22	3.8	70.7 (53.5–93.6)	70.7 (53.5–93.6)	0
50701	37/58	6.5	75.5 (65.1–87.5)	77.3 (67.1–88.9)	2.3
50803	16/61	6.1	88.2 (80.4–96.8)	89.9 (82.6–97.9)	1.9

Effectiveness and safety outcomes in patients with EBV⁺ PTLD treated with allogeneic EBV-specific T-cell immunotherapy (tabellecleucel) under an expanded access program (EAP) in Europe. *First Author: Sylvain Choquet, Hôpital de la Pitié-Salpêtrière, Paris, France*

Background: Pts with relapsed or refractory (r/r) EBV⁺ post-transplant lymphoproliferative disease (PTLD) in Europe have had historically poor overall response rates and median overall survival (OS) with no approved treatment options. Tabelecleucel, an off-the-shelf, allogeneic EBV-specific T-cell immunotherapy has shown clinical benefit and favorable safety profile in the treatment of EBV⁺ PTLD failing rituximab ± chemotherapy (Prockop EBMT 2021, ATC 2021, ASH 2022). Its recent European marketing authorization (EMA) represents the first approval of an allogeneic T-cell immunotherapy globally. **Methods:** Atara Bio supported expanded access requests for tabellecleucel in Europe. Here we report updated effectiveness and safety data for r/r EBV⁺ PTLD pts who provided consent for research between Sep 2020 and Dec 2022. **Results:** 74 EAP requests were received from 10 countries for pts with r/r EBV⁺ diseases. 27 EBV⁺ PTLD pts consented to secondary use of data and 24 pts had received ≥1 dose of tabellecleucel, including 4 pts with primary central nervous system (PCNS) PTLD. 16 of 24 (66.7%) PTLD pts achieved a partial (PR) (33.3%) or complete (CR) (33.3%) response, with median time to response (TTR) of 1.0 mo (0.8–2.2). Response rate for PCNS PTLD pts was 75% (1 CR, 2 PR). 1-yr OS Kaplan–Meier (KM) estimate rates were 73.7% (95% CI: 47.3, 88.3) overall, 87.5% in allogeneic hematopoietic stem cell transplant (HCT) and 66.5% in solid organ transplant (SOT), with a median follow-up time of 9.9 (2.4–13.9) and 6.0 (0.7–18.0) mo, respectively. Serious treatment-emergent adverse events (TESAEs) were reported in 7 (29.2%) pts, including 1 fatal event of disease progression. Predefined risks for tabellecleucel were reported in 3 pts; 1 (4.2%) SOT pt had a TESAE of liver transplant rejection (grade 2) and 2 (8.3%) HCT pts had non-serious TEAEs of chronic graft-versus-host disease (grade 1 and 2). No cases of cytokine release syndrome or tumor flare reaction were reported. No AEs were reported as related to tabellecleucel by the treating physician. **Conclusions:** These updated real-world results for pts with r/r EBV⁺ PTLD post-HCT or post-SOT treated in the European EAP continue to reinforce the favorable risk:benefit profile of tabellecleucel and are in line with clinical study data supporting its recent EMA approval. Research Sponsor: None.

Effectiveness outcomes in tabellecleucel treated r/r EBV⁺ PTLD pts.

	EBV ⁺ PTLD post-HCT (N=8)	EBV ⁺ PTLD post-SOT (N=16)	All (N=24)
Responders*	7 (87.5)	9 (56.3)	16 (66.7)
95% CI	(47.3, 99.7)	(29.9, 80.2)	(44.7, 84.4)
CR	4 (50.0)	4 (25.0)	8 (33.3)
PR	3 (37.5)	5 (31.1)	8 (33.3)
Median TTR, mo (range)	1.0 (0.9–1.6)	1.0 (0.8–2.2)	1.0 (0.8–2.2)
Median follow-up, mo (range)	9.9 (2.4–13.9)	6.0 (0.7–18.0)	7.4 (3.4–11.8)
1-yr OS KM rate (95% CI)	87.5 (38.7, 98.1)	66.5 (32.7, 86.2)	73.7 (47.3, 88.3)

*Best overall response, n (%); CI, confidence interval.

Circulating tumor DNA (ctDNA) status and clinical outcomes in patients (pts) with previously untreated diffuse large B-cell lymphoma (DLBCL) in the POLARIX study. *First Author: Alex Francisco Herrera, Department of Hematology and Hematopoietic Cell Transplantation, City of Hope, Duarte, CA*

Background: the POLARIX study, pts with previously untreated DLBCL were randomized to Pola-R-CHP or R-CHOP (NCT03274492; Tilly et al. 2022). We previously validated the prognostic value of ctDNA at baseline and after one cycle of therapy in POLARIX (Herrera et al. 2022); here, we evaluate the relationship between ctDNA clearance and PFS and OS. **Methods:** Pts were included if baseline and longitudinal ctDNA results were available. Plasma ctDNA was measured at baseline, Cycle (C) 5 Day (D) 1, and end of treatment (EOT), with the AVENIO NHL CAPP-Seq assay (Stokowski et al. 2022). ctDNA clearance was determined as previously described (Herrera et al. 2022). PFS and OS according to ctDNA status were reported as landmarked hazard ratios (HR) and 3-yr rates. HRs were adjusted for IPI score (>2), region, bulky disease (>7.5cm), age (>60 years), and cell of origin. **Results:** At baseline, 654 pts had ctDNA results; 494 (76%) and 519 (79%) pts were evaluable at C5D1 and EOT, respectively. Undetectable ctDNA (ctDNA–) was achieved by 57% (152/265) of Pola-R-CHP-treated pts and 59% (135/229) of R-CHOP-treated pts at C5D1 (p=0.79), and by 66% (172/262) of Pola-R-CHP-treated pts and 67% (172/257) of R-CHOP-treated pts at EOT (p=0.83). Achieving ctDNA– was prognostic for PFS and OS in each treatment arm at C5D1 and EOT (Table). Pts in the Pola-R-CHP arm who had complete response (CR) with PET-CT and ctDNA– at EOT had superior PFS and OS compared with pts with CR and detectable ctDNA (ctDNA+) at EOT (PFS HR 0.30, 95% confidence interval [CI]: 0.14–0.66; OS HR 0.20, 95% CI: 0.07–0.60). This was not observed with R-CHOP (PFS HR 0.74, 95% CI: 0.34–1.63; OS HR 1.11, 95% CI: 0.30–4.16). Among pts with CR and ctDNA– at EOT, pts treated with Pola-R-CHP had superior PFS vs R-CHOP (HR 0.41, 95% CI: 0.21–0.82); this was not observed with OS (HR 0.41, 95% CI: 0.14–1.18). There was no statistically significant difference in PFS between treatment arms in pts with CR and ctDNA+ at EOT (PFS HR 1.20, 95% CI: 0.49–2.83). **Conclusions:** Achieving ctDNA– at C5D1 and EOT was prognostic for longer survival. Although no difference was observed in the number of pts with ctDNA– at EOT between arms, pts achieving CR and ctDNA– at EOT had superior PFS in the Pola-R-CHP vs the R-CHOP arm, suggesting deeper molecular responses in pts treated with Pola-R-CHP beyond the detection sensitivity of the assay used in this analysis. Clinical trial information: NCT03274492. Research Sponsor: The POLARIX study (NCT03274492) was sponsored by F. Hoffmann-La Roche Ltd and Genentech, Inc. Third-party editorial assistance was provided by Carla Smith, MSc, of Ashfield MedComms, an Inizio company, and was funded by F. Hoffmann-La Roche Ltd.

	Landmarked PFS, HR (95% CI)	3-yr PFS, % (95% CI)	Landmarked OS, HR (95% CI)	3-yr OS, % (95% CI)
Pola-R-CHP C5D1: ctDNA+ ctDNA–	0.38 (0.23–0.63)	58 (49–70) 83 (76–90)	0.36 (0.17–0.76)	79 (72–87) 93 (89–97)
R-CHOP C5D1: ctDNA+ ctDNA–	0.52 (0.31–0.87)	61 (52–72) 76 (68–85)	0.50 (0.23–1.10)	82 (74–90) 93 (89–98)
Pola-R-CHP EOT: ctDNA+ ctDNA–	0.25 (0.14–0.46)	55 (46–66) 85 (79–92)	0.12 (0.05–0.28)	70 (61–81) 96 (93–99)
R-CHOP EOT: ctDNA+ ctDNA–	0.43 (0.25–0.74)	48 (38–60) 78 (70–85)	0.21 (0.10–0.45)	76 (67–86) 95 (91–98)

A phase 1 study of AT101, a novel anti-CD19 CAR-T cell therapy targeting a membrane-proximal epitope of CD19, in patients with relapsed or refractory B cell non-Hodgkin lymphoma. *First Author: Dok Hyun Yoon, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea*

Background: All the FDA-approved CD19 CAR-T products are based on FMC63 scFv, which binds to the membrane-distal region of CD19. We developed a novel anti-CD19 antibody clone (1218) that binds to a membrane-proximal epitope of CD19, thereby not competing with FMC63. AT101 is an autologous CAR T cell transduced with a lentiviral vector, including the CD19-CAR with a humanized scFv of 1218, 4-1BB costimulatory, and CD3zeta domain. **Methods:** In this phase 1 trial, patients (n = 3 per dose level; up to n = 18 in total) are treated with AT101 in 3 dose-escalation cohorts based on a standard 3 + 3 design. Each patient received a single intravenous dose of AT101 at dose level (DL) 1 (0.2 × 10⁶ cells/kg), DL2 (1.0 × 10⁶ cells/kg), or DL3 (5.0 × 10⁶ cells/kg). The primary objective is to determine the safety, the maximum tolerated dose (MTD), and the recommended phase 2 dose (RP2D) of AT101. The secondary objective is to evaluate the pharmacokinetics of AT101 and the preliminary efficacy, such as overall response rate (ORR), duration of response (DOR), progression-free survival (PFS), event-free survival (EFS), and overall survival (OS). Key eligibility criteria include patients aged ≥19 with histologically confirmed relapsed or refractory B-cell non-Hodgkin lymphoma (NHL). **Results:** Fourteen patients were enrolled from March 2022 to December 2022, and nine were treated. The median age of treated patients was 61.6 years (ranged from 39 to 84) after a median of 4 prior lines of therapy (range 2–10). Their subtypes of NHL were as follows: diffuse large B cell lymphoma (n = 4), follicular lymphoma (n = 3), mantle cell lymphoma (n = 1), or marginal zone lymphoma (n = 1). The dosing of AT101 at DL1 and DL2 was completed. The dosing at DL3 is ongoing. Across cohorts 1 and 2, no grade 3 or higher cytokine release syndrome (CRS) was reported. Among the first three patients at DL1, one dose-limiting toxicity (DLT) of grade 4 neurotoxicity was observed but resolved in a week without sequelae. No other DLTs were observed in the additional three patients at the DL1 and three at the DL2 cohort. Another one at DL2 experienced grade 1 CRS with grade 1 neurotoxicity. Five patients experienced Grade ≥3 hematologic toxicities. An ORR is 66.7% (4/6) in cohort 1 and 100% (3/3) in cohort 2, including six complete responses (CR, 50.0% [3/6] in cohort 1 and 100% [3/3] in cohort 2). As of February 13, 2023, all six CRs are ongoing, including two patents exceeding six months after the treatments. Updated results will be presented at the meeting, including the cohort of DL3. **Conclusions:** In this phase I study, AT101 was well tolerated at the first two dose levels and showed promising efficacy in relapsed or refractory B-cell NHL patients. The majority of adverse effects were transient and manageable. The administrations of DL3 are currently ongoing, and updated results will be presented at the meeting. Clinical trial information: NCT05338931. Research Sponsor: AbClon Inc.

High complete response rate with TNB-486 in relapsed/refractory follicular lymphoma: Interim results from an ongoing phase 1 study. *First Author: Ranjit Nair, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Follicular lymphoma (FL) is incurable with a relapsing/remitting pattern and decreasing progression-free survival (PFS) interval per recurrence. In the relapsed/refractory (R/R) setting, patients (pts) failing CAR T or CD20 bispecific T-cell engagers (TCE) have few options. TNB-486 is a novel bispecific CD19xCD3 TCE that induces T-cell-mediated cytotoxicity with reduced cytokine release via a low-affinity αCD3 moiety. We present interim data from a phase 1 dose-escalation study of TNB-486 (NCT04594642). **Methods:** Third-line+ R/R FL pts (grade [G] 1–3a) were enrolled (prior CD19 therapy allowed). Escalating fixed TNB-486 doses (0.03–2.4 mg) without priming were evaluated prior to implementing single (day [D] 1) and double priming doses (D1 & 8) prior to target dose (D15). TNB-486 was given IV every 2 weeks in 28-d cycles (C) for up to 2 y. Response was assessed with REC1L 2017 by central image review. Adverse events (AEs) and CRS/ICANS were graded by CTCAE v5.0 and 2019 ASTCT criteria. **Results:** As of Dec 31, 2022, 17 pts received TNB-486 at target doses 0.03–10 mg (median age 68 y [range 33–86]; 53% male; 65% stage III/IV; 25% CD20– disease; median prior lines of therapy [LOT] 3 [range 2–9]). Prior therapies included αCD20 Ab (100%), alkylator (76%), IMiD (47%), CD20 TCE (12%), CD19 CAR T (12%), and ASCT (6%); 53% progressed or started 2nd LOT within 24 mo of initiating 1st LOT (POD24). Median time on study was 7 mo (range 1–22). Eleven pts were response evaluable for efficacy at target doses ≥2.4 mg. Objective response rate (ORR) and complete response (CR) rate were 91% (Table). ORR/CR for pts with CD20– disease, prior CD20 TCE, and POD24 was 100%. One pt progressed at C6 with preserved CD19 expression; all others remain in remission to date. The 6-mo PFS rate was 91%. No G3+ CRS occurred (59% G1, 12% G2). Neurologic events consistent with ICANS were reported in 24%, all G1–2 except 1 with a G3 event (confusion). All CRS/NT were transient, resolving in a median of 1.5 d (range 1–5). G3+ treatment-related AEs in >10% of pts included decreased lymphocytes (35%) and neutropenia (12%). No treatment-related deaths or AEs leading to discontinuation occurred (1 pt died and 1 discontinued due to COVID-19). One pt received double step-up priming dosing to date with no CRS/NT. **Conclusions:** TNB-486 induces high complete remission rates during early phase dose escalation. With limited follow-up, responses appear durable in heavily pretreated FL pts, with a manageable safety profile. Dose escalation is ongoing to identify the RP2D. Clinical trial information: NCT04594642. Research Sponsor: AstraZeneca; TeneoTwo.

Select AEs and efficacy.

Select G3+ AEs of Interest (N=17)	Response Assessment (n=11)		
Non-COVID infections (unrelated)	2 (12%)	ORR (≥2.4-mg target doses)	91%
Decreased neutrophils	2 (12%)	CR	91%
Anemia	1 (6%)	Post-CD20 TCE (n=2)	100%
ICANS	1 (6%)	CD20– FL (n=2)	100%
CRS	0	POD24 (n=5)	100%
Febrile neutropenia	0		

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Poster Session

Effect of follow-up time on the ability of subcutaneous epcoritamab to induce deep and durable complete remissions in patients with relapsed/refractory large B-cell lymphoma: Updated results from the pivotal EPCORE NHL-1 trial. *First Author: Yasmin Karimi, University of Michigan Comprehensive Cancer Center, Ann Arbor, MI*

Background: Outcomes are poor for patients (pts) with relapsed/refractory (R/R) large B-cell lymphoma (LBCL). Effective treatments (tx) that drive deep, durable responses and long-term benefit are needed. In the pivotal EPCORE NHL-1 trial (NCT03625037), single-agent epcoritamab (epcor) showed high complete response (CR) and MRD-negativity rates, a median duration of response (mDoR) not reached (NR) in pts who achieved CR, and a manageable safety profile as an off-the-shelf, subcutaneous (SC), CD3xCD20 T-cell-engaging bispecific antibody (Thieblemont et al, *JCO* 2022). We present updated results with longer follow-up in a challenging-to-treat population. **Methods:** Pts with R/R CD20⁺ LBCL received SC epcor (step-up priming and intermediate doses followed by 48-mg full doses) in 28-d cycles (Cs): QW, C1–3; Q2W, C4–9; Q4W, C≥10 until PD or unacceptable toxicity. **Results:** As of Nov 18, 2022, of 157 pts (median age, 64 y) with LBCL (including DLBCL [n=139], HGBCL [n=9], PMBCL [n=4], and FL grade 3B [n=5]; 13/99 double/triple-hit by FISH), 36 remain on tx. Pts had a median of 1.6 y from initial diagnosis to first dose and a median of 3 (range, 2–11) prior tx lines; 61% of pts had primary refractory disease, and 39% had prior CAR T, of whom 75% progressed ≤6 mo of tx. Median follow-up was 20 mo (range, 0.3+ to 28.2). Pts received a mean of 9.1 cycles. LBCL overall response and CR rates were 63.1% and 39.5%, respectively, and were consistent for DLBCL (61.9% and 39.6%). The mDoCR was 20.8 mo. Median time to CR was 2.7 mo; 8 pts converted from partial response to CR at ≥36 wk. Median overall survival (mOS) was 18.5 mo (95% CI, 11.7–NR), with an estimated 58% of pts alive at 12 mo. mOS was NR in pts who achieved CR. Additional outcomes for pts with CR are shown in Table. The most common TEAEs of any grade (G) were: CRS 51%, neutropenia 24%, pyrexia 24%, fatigue 23%, nausea 22%, and diarrhea 21%. Nine pts (6%) had G1–2 ICANS, and 1 pt had a G5 event with confounding factors. Fatal TEAEs occurred in 15 pts; 2 were considered related (COVID-19, ICANS). CRS was predominantly low grade (48% G1–2; 3% G3) and occurred following the first full dose (C1D15). One pt discontinued tx due to G1 CRS. Total metabolic tumor volume (TMTV) data will be presented. **Conclusions:** These data with longer follow-up reaffirm single-agent SC epcor induces durable CRs with improved outcomes and a manageable safety profile. No new safety signals were observed in these hard-to-treat pts. These impressive data support the ongoing phase 3 studies evaluating epcor across different lines of tx and in various combinations. Clinical trial information: NCT03625037. Research Sponsor: This study was funded by Genmab A/S and AbbVie.

Outcomes for pts with CR (n=62).					
mDoR among CR pts,	DoR among CR pts at 9, 12, 15 mo	mPFS	PFS at 9, 12, 15 mo	mOS	OS at 9, 12, 15 mo
mo	%	NR	%	NR	%
20.8	91.2	NR	91.1	NR	98.3
95% CI,	85.2	95% CI,	87.2	95% CI,	95.0
17.3–NR	79.0	18.5–NR	81.3	NR–NR	88.3

Kaplan-Meier estimates.

7527

Poster Session

Preliminary results from a phase I/II study of IMM0306, a CD47 and CD20 bispecific monoclonal antibody-trap, in patients with relapsed or refractory CD20-positive B-cell non-Hodgkin's lymphoma. *First Author: Jianliang Yang, Department of Medical Oncology, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing Key Laboratory of Clinical Study on Anticancer Molecular Targeted Drugs, Beijing, China*

Background: IMM0306 is a fusion protein of CD20 monoclonal antibody with the CD47 binding domain of SIRPα on both heavy chains. It has a higher affinity for CD20 than for CD47, thus enabling its preferential and simultaneous binding to CD20 and CD47 on malignant B cells rather than to CD47-positive normal tissues. Here, we report the safety, pharmacokinetics (PK), pharmacodynamics (PD), and efficacy results of the dose escalation stage in a phase I/II study in patients (pts) with relapsed or refractory CD20-positive B-cell non-Hodgkin's lymphoma. **Methods:** This is a first-in-human, open-label, phase I/II study of IMM0306. The ongoing Phase I part (0.04, 0.1, 0.25, 0.5, 0.8, 1.2, 1.6, 2.0 mg/kg, IV) followed an accelerated titration and standard 3+3 design. IMM0306 was administered once per week after a 2-week single-dose period, until disease progression or intolerable toxicity. Dose-limiting toxicity (DLT) was evaluated in the first 28 days. Safety was evaluated per CTCAE 5.0, tumor assessments performed once every 8 weeks, PK and PD were also assessed. **Results:** As of the data cut-off date on Dec 15th, 2022, 42 pts were enrolled. 18 (43%) pts received 3 or more prior lines of therapy, all pts received prior anti-CD20 therapy. No DLTs were observed up to 2.0 mg/kg. The most frequent treatment-related adverse events (TRAEs) were lymphocyte decreased (61.9%), white blood cell (WBC) decreased (61.9%), anemia (59.5%), neutrophil (ANC) decreased (40.5%), platelet (PLT) decreased (40.5%), infusion-related reactions (31.0%). Grade ≥ 3 TRAEs occurred in 30 (71.4%) pts, the most frequent grade ≥ 3 TRAEs were lymphocyte decreased (59.5%), WBC decreased (16.7%), ANC decreased (11.9%). Three treatment-related SAEs were PLT decreased (grade 4), chest pain (grade 2) and diarrhea (grade 3). In 38 response evaluable pts, 2 follicular lymphoma (FL) pts achieved CR, 1 marginal zone lymphoma (MZL) pt and 2 FL pts achieved PR and 13 pts showed SD. 26 pts were treated at doses ≥ 0.8 mg/kg, among whom 11 were FL pts. Of these 11 FL pts, 4 (36%) responded including 2 CR both at 1.2 mg/kg and 2 PR at 1.2 and 1.6 mg/kg respectively. IMM0306 exhibited approximate dose-proportional increase in PK exposure from 0.5 to 2.0 mg/kg and no obvious accumulation was observed after repeated dosing. B-cell counts depleted rapidly at doses ≥ 0.8 mg/kg. Elevated cytokines levels were observed after first dosing of IMM0306, but multiple dosing did not stimulate further cytokine activation. **Conclusions:** IMM0306 was well-tolerated and with a robust preliminary anti-tumor activity especially in pts with R/R FL and MZL. The phase I/II study is ongoing. Clinical trial information: CTR20192612. Research Sponsor: ImmuneOnco Biopharmaceuticals (Shanghai) Inc.

7526

Poster Session

Subgroup analyses of primary refractory (refr) vs early relapsed (rel) large B-cell lymphoma (LBCL) from the TRANSFORM study of isocabtagene maraleucel (liso-cel) vs standard of care (SOC) as second-line (2L) therapy. *First Author: Loretta J. Nastoupil, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: The TRANSFORM primary analysis (PA; NCT03575351) confirmed the superior efficacy of liso-cel vs SOC as 2L therapy in patients (pts) with primary refr or early rel LBCL (Abramson et al. *Blood* 2022). Response to first-line (1L) therapy (refr vs rel), which was a study randomization stratification factor, may influence future treatment response. Here, we present results for refr and rel LBCL subgroups from the TRANSFORM PA. **Methods:** TRANSFORM is a randomized phase 3 study of liso-cel vs SOC (salvage chemotherapy [CT] followed by high-dose CT [HDCT]/autologous SCT [ASCT]) in adults ≤ 75 y with LBCL primary refr to or rel ≤ 12 mo after 1L therapy and eligible for HDCT/ASCT. The primary endpoint was event-free survival (EFS); key secondary endpoints were CR rate, PFS, and OS. In this predefined subgroup analysis, refr was SD, PD, PR, or CR with rel < 3 mo after 1L therapy; rel was CR with rel ≥ 3 mo and ≤ 12 mo after 1L therapy. **Results:** 92 pts were randomized to each arm. Most pts in the liso-cel and SOC arms had refr disease (73% and 76%, respectively; rel disease, 27% and 24%). Baseline characteristics in the refr and rel subgroups, respectively, were generally balanced: median LDH (U/L; liso-cel, 228.5 and 225; SOC, 259 and 259); median SPD (cm²; liso-cel, 11 and 12; SOC, 15.5 and 18); high-grade B-cell lymphoma (liso-cel, 27% and 16%; SOC, 27% and 9%); diffuse LBCL not otherwise specified (liso-cel, 58% and 56%; SOC, 49% and 73%). Consistent with the overall study population, EFS, CR rate, and PFS favored liso-cel vs SOC in both subgroups (Table). Safety was also consistent. Grade ≥ 3 cytokine release syndrome (CRS) and neurological events (NE) were low in refr (1% and 4%) and rel (0 and 4%) subgroups, respectively, with no grade 4/5 CRS or NEs. **Conclusions:** In TRANSFORM, liso-cel showed benefits in EFS, PFS, and CR rate vs SOC irrespective of prior response to 1L therapy. As refr LBCL is historically difficult to treat, outcomes for liso-cel in this subgroup are encouraging. Clinical trial information: NCT03575351. Research Sponsor: This study was funded by Celgene, a Bristol-Myers Squibb Company.

	Refr: liso-cel arm (n = 67)	Rel: liso-cel arm (n = 25)	Total liso-cel arm ¹ (n = 92)	Refr: SOC arm (n = 70)	Rel: SOC arm (n = 22)	Total SOC arm ¹ (n = 92)
EFS ^a HR (95% CI)	12.0 (6.0–NR) 0.371 (0.244–0.565)	NR (15.6–NR) 0.294 (0.117–0.739)	NR (9.5–NR) 0.356 (0.243–0.522)	2.2 (2.1–2.7)	8.3 (2.9–NR)	2.4 (2.2–4.9)
CR rate, n (%) [95% CI]	46 (69) [56.2–79.4]	22 (88) [68.8–97.5]	68 (74) [63.7–82.5]	23 (33) [22.1–45.1]	17 (77) [54.6–92.2]	40 (43) [33.2–54.2]
PFS ^a HR (95% CI)	19.2 (6.6–NR) 0.441 (0.275–0.708)	NR (NR–NR) 0.266 (0.089–0.739)	NR (12.6–NR) 0.400 (0.261–0.615)	4.9 (2.3–7.5)	9.0 (6.0–NR)	6.2 (4.3–8.6)
OS ^a HR (95% CI)	29.5 (22.2–NR) 0.754 (0.447–1.273)	NR (NR–NR) 0.535 (0.126–2.266)	NR (29.5–NR) 0.724 (0.443–1.183)	20.9 (15.1–NR)	NR (17.9–NR)	29.9 (17.9–NR)

^aData are median (95% CI), mo; ^bvs SOC. NR, not reached. ¹Abramson et al. *Blood* 2022.

7528

Poster Session

Rates of cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) from Center for International Blood and Marrow Transplant Research (CIBMTR) data on US subjects (SUBJ) with lymphoma following chimeric antigen receptor T cell therapy (CAR-T). *First Author: Matthew J. Frigault, Massachusetts General Hospital, Boston, MA*

Background: The engineered T-cell products axicabtagene ciloleucel (axi-cel) and brexucabtagene autoleucel (brexu-cel) are FDA approved for relapsed/refractory diffuse large B-cell lymphoma (DLBCL) and mantle cell lymphoma (MCL), respectively. This study investigated real-world rates of CRS and ICANS following CAR-T. **Methods:** This study analyzed CIBMTR data of US SUBJ receiving axi-cel or brexu-cel for any indication from Oct 2020–Dec 2021 with ≥1 follow-up visit. CRS and ICANS were graded per American Society for Transplantation and Cellular Therapy consensus guidelines. **Results:** 927 SUBJ (median age, 63 y; men, 65%) from 87 centers were analyzed. Most received axi-cel (76%), 83% of whom had DLBCL or transformed follicular lymphoma (tFL); 24% received brexu-cel (MCL). Most SUBJ had Ann Arbor stage III/IV (63%), no active central nervous system disease (84%), and refractory disease at CAR-T infusion (66%). Among all 589 SUBJ with DLBCL/tFL who received axi-cel, 54% achieved complete response, 17% partial response, and 6% stable disease. 89/715 SUBJ with available data received treatment for CRS prevention, mostly tocilizumab alone (80% [71/89]) or in combination (3% [3/89]). Overall, 766 SUBJ (83%) developed CRS (grade ≥3, 64 [8%]; Table). Of the 89 SUBJ who received CRS prevention treatment, 78% developed CRS, with 3% (3/89) having grade ≥3. 77% of SUBJ with CRS received CRS treatment, 97% of whom received tocilizumab (alone or in combination [eg, with corticosteroids]). Most (64%) SUBJ with grade 1 CRS received treatment, 63% of whom received tocilizumab alone. ICANS occurred in 424/876 SUBJ with ICANS data (48%; Table), of whom 205 (48%) had grade ≥3. ICANS treatment was reported and administered to 86% of SUBJ with ICANS, 92% of whom received corticosteroids. **Conclusions:** CRS and ICANS incidence rates were consistent with previously published literature and highlight potential burdens of CAR-T. In addition, the treatment landscape for CRS is changing; SUBJ with grade 1 CRS often received treatment. These data will inform the design of future studies aimed at preventing and treating CAR-T toxicities. Research Sponsor: Incyte Corporation.

	CRS*			ICANS [†]		
	All SUBJ n=927	Axi-cel n=707	Brexu-cel n=220	All SUBJ n=876	Axi-cel n=664	Brexu-cel n=212
Median (range) age, y	63 (19–89)	62 (19–88)	65 (34–89)	63 (19–89)	62 (19–88)	65 (34–89)
Incidence, %	83	81	86	48	45	60
Grade 1/2/3	44/39	45/36	39/47	14/35	13/32	17/43
Grade 3/4/5	4/2/1	3/2/1	5/3/1	15/6/1	14/6/1	18/9/2
Time to onset, median (range), d	4 (1–157)	4 (1–157)	5 (1–46)	7 (1–101)	7 (1–101)	7 (1–31)
<72 h onset, %	32	32	32	7	8	6
Grade ≥2, %	17	16	20	6	6	4
Duration, median (range), d	5 (0–175)	5 (0–40)	4 (0–175)	7 (1–98)	6 (1–67)	8 (1–98)

All SUBJ with data available for *CRS or [†]ICANS.

7529

Poster Session

AB-101, an allogeneic, non-genetically modified, natural killer (NK) cell therapy, evaluated as monotherapy or in combination with rituximab in R/R non-Hodgkin lymphoma. *First Author: Rashmi Khanal, Fox Chase Cancer Center, Philadelphia, PA*

Background: AB-101 is a non-genetically modified, cord blood-derived, allogeneic, cryopreserved, NK cell therapy for use in combination with monoclonal antibody (mAb) or innate cell engager therapies. AB-101 is being developed to enhance response to mAb therapy through the antibody-dependent cellular cytotoxicity (ADCC) mechanism. Many cancer patients (pts) are unable to mount a robust ADCC response, rendering mAb therapy less effective for these pts. AB-101 has attributes that enhance NK cell activity: Consistent phenotype for tumor engagement and cytotoxicity; Selected killer immunoglobulin-like receptor B (KIR B) haplotype; V/V CD16 polymorphism at F158 for enhanced ADCC. AB-101 outpatient administration provides optimized NK cells to pts, potentially enhancing their anti-tumor activity in combination with mAb that utilize the ADCC mechanism. We have initiated a Ph 1/2 clinical trial evaluating the combination of AB-101 with rituximab (RTX) in pts with R/R NHL of B-cell origin. **Methods:** Two AB-101 dose levels, 1 or 4e9 cells, will be evaluated as monotherapy or combination with RTX. All enrolled pts will receive at least 1 cycle of 4 weekly AB-101 doses, with cyclophosphamide/fludarabine lymphodepletion (LD). Pts receiving the combination may receive up to 4 treatment cycles. **Results:** Dose escalation is ongoing with 17 pts enrolled. Pts were elderly (median of 68 yrs) and heavily pretreated (median of 4 prior lines) with 64% having had prior CD19 CAR-T. Pts had DLBCL (9), FL (5), MCL (2), and LPL/WM (1). 11 monotherapy pts and 6 RTX combination pts were treated at time of abstract. 16 pts received AB-101 at 1e9 cells/dose; 1 pt received 4e9 cells/dose. 4 of 6 combination pts have received > 1 cycle. AB-101 was generally well tolerated. The most common G3+ AEs were LD-related neutropenia and lymphopenia. All AB-101 related AEs were G1/2. ICANs and GVHD, events associated with allogeneic cell therapy, were not reported; Gr 1 CRS occurred in 2 pts and resolved within 24h. SAEs were reported in 9 pts. The most common SAEs were associated with either infections (n = 3) or PD (n = 3) and one related SAE of Gr 1 fever was reported. No pts discontinued treatment due to an AB-101-related AE. ORR for the RTX cohort was 67% (4/6) with a CR rate of 50% (3/6). 3 of 4 responses were observed in pts who failed prior CAR-T therapy. ORR for the monotherapy cohorts was 27% (3/11). **Conclusions:** 4 weekly doses of AB-101 given alone or with RTX appeared to be safe and well tolerated without the serious/severe toxicities associated with CAR-T therapies. Preliminary efficacy of the combination treatment is encouraging. The study is ongoing and continues to enroll the combination cohorts and the 4e9 cells/dose level. Updated safety, efficacy, and exploratory PK/PD/immunogenicity results will be provided during the presentation. Clinical trial information: NCT04673617. Research Sponsor: Artiva Biotherapeutics.

7531

Poster Session

Zilovetamab vedotin (MK 2140) in relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL): Early results from the phase 2 waveLINE-004 study. *First Author: Muhit Ozcan, Ankara University School of Medicine, Ankara, Turkey*

Background: Treatment options are limited for patients (pts) with R/R DLBCL who are not candidates for autologous stem cell transplant (ASCT). ROR1 is an oncofetal protein pathologically expressed in hematologic malignancies including DLBCL. In the phase 1 first-in-human study in hematologic malignancies (waveLINE-001), the ROR1-targeting antibody-drug conjugate zilovetamab vedotin (ZV) showed promising activity and manageable safety in R/R DLBCL. The single-arm, open-label, phase 2 waveLINE-004 study (NCT05144841) is designed to evaluate activity of ZV monotherapy in pts with R/R DLBCL. Early data are reported. **Methods:** Eligible pts were ≥18 y old, had histologically confirmed DLBCL by WHO classification, measurable disease per Lugano 2014 criteria, PET-positive disease, and ECOG PS of 0-2. Pts must have received ≥2 prior lines of therapy (including an alkylating agent, anthracycline, and an anti-CD20 antibody) with progression after or ineligibility for ASCT and CAR T-cell therapy. All pts received ZV 2.5 mg/kg IV Q3W until disease progression, unacceptable toxicity, or withdrawal. Primary end point was ORR per Lugano 2014 criteria. Safety and tolerability was a secondary end point. Safety was evaluated in all pts who received ≥1 dose of treatment; efficacy was reported for pts with ≥3 mo follow-up. **Results:** At data cutoff (Nov 16, 2022), 40 pts enrolled and received ≥1 dose of treatment; 23 (58%) had discontinued and 17 (43%) were ongoing. Median age was 68.0 y, 29 (73%) pts were male, 37 (93%) had an ECOG PS of 0 or 1, 24 (60%) had ≥3 prior lines of therapy, and 10 (25%) received prior ASCT. 11 (28%) pts received prior CAR-T. Median follow-up (range) was 2.6 mo (0.3-7.9) for all pts and 6.0 mo (3.0-7.9) for pts in the efficacy analysis (n = 20). ORR by investigator review was 30% (95% CI, 11.9-54.3), with 2 pts having a CR and 4 a PR; 5 pts had SD (DCR, 55% [95% CI, 31.5-76.9]). Treatment related AEs (TRAES) occurred in 28 (70%) pts, most commonly (≥15%) diarrhea (9 [23%]), anemia (8 [20%]), neutropenia (7 [18%]), neutrophil count decreased (7 [18%]), and alopecia (6 [15%]). Grade 3/4 TRAES occurred in 16 (40%) pts, most commonly (≥10%) neutropenia (7 [18%]), anemia (6 [15%]), and neutrophil count decreased (4 [10%]). Discontinuation due to a TRAE of diabetic ketoacidosis occurred in 1 (3%) pt. Grade 1/2 treatment-related peripheral neuropathy occurred in 6 (15%) pts; no grade 3/4 AEs occurred. Dose reduction due to treatment-related peripheral neuropathy occurred in 3 (8%) pts. No infusion reaction or tumor lysis syndrome due to treatment occurred and no pts died because of TRAES. **Conclusions:** Early results show that ZV had clinically meaningful antitumor activity in pts with R/R DLBCL who progressed after or have been ineligible for ASCT and/or CAR-T. Additionally, the safety profile was manageable and consistent with other monomethyl auristatin E-containing agents. Clinical trial information: NCT05144841. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

7530

Poster Session

Systemic VSV-IFNβ-NIS oncolytic virotherapy in patients with relapsed refractory T-cell lymphoma. *First Author: Nabila Nora Bennani, Division of Hematology, Mayo Clinic, Rochester, MN*

Background: Oncolytic virotherapy is a novel immunomodulatory therapeutic approach currently under study for relapsed refractory (R/R) hematologic malignancies. The engineered Vesicular Stomatitis Virus VSV-IFNβ-NIS used in this study encodes interferon beta (IFNβ) and sodium iodine symporter (NIS). Virally-encoded IFNβ serves as an index of viral proliferation and enhances host anti-tumor immunity. Herein, we report the updated results of the phase 1 clinical trial NCT03017820 of a one-time administration of systemic VSV-IFNβ-NIS among patients (pts) with R/R multiple myeloma (MM), T cell Lymphoma (TCL) and Acute myeloid Leukemia (AML) with particular focus on the TCL cohort treated at the highest dose level (DL4) without Ruxolitinib. **Methods:** VSV-IFNβ-NIS was administered as a single IV dose following a classical 3+3 phase I trial, starting at 5e9 TCID50 DL1 through 1.7e11 TCID50 DL4. A dose expansion cohort of 8 additional R/R TCL pts was added at DL4 in view of an initial signal of activity. The primary objective was to determine the maximum tolerated dose of VSV-IFNβ-NIS as a single agent. Secondary objectives were determination of safety profile and preliminary efficacy of VSV-IFNβ-NIS. Adverse events (AEs) are reported based on CTCAE V4; cytokine release syndrome (CRS) grading was based on Lee (Blood 2014) criteria. **Results:** To date, a total of 43 pts received VSV-IFNβ-NIS: MM (N=21), TCL (N=21) and AML (N=1). In the TCL cohort: at DL4 Group A (no Ruxolitinib), 12 pts were registered, but only 11 pts were treated (mycosis fungoides (MF) N=3; ALK- ALCL N=1; PTCL-NOS N=2; AITL N=4; Nodal PTCL, TFH N=2; ages 33-79). These pts received a median of 3 lines of therapy (range: 1-5). No dose limiting toxicities were observed. Grades 3 and higher AEs were hematologic with transient lymphopenia (63.6%), neutropenia (36.4%) being the most common. The non-hematologic AEs observed included unique toxicities such as CRS grades 1-2 (81.8%); the transient transaminitis grade 1-2 (36.4%) and grade 3 (27.3%) along with thrombocytopenia grade 1-2 (63.6%) and grade 3 (18.2%) were a reflection of IFNβ toxicity. All the AEs observed were short lived. Responses were seen in pts with PTCL. At DL4, in pts with systemic PTCL (N=9), there were 5 responses including 3 complete responses (CR) with two long-lasting at 24 months, an ongoing 15 month CR, and a 5 month CR, and 2 partial responses (PR) lasting 5 months in one pts and 6 months in the other. **Conclusions:** These updated results of single agent VSV-IFNβ-NIS which include pts with PTCL treated at the highest dose level and a dose expansion cohort demonstrates not only the safety of VSV-IFNβ-NIS but also a strong efficacy signal in pts with PTCL with impressive durable responses. Two expansion cohorts at DL4 have been added (20 additional PTCL, 10 B-cell lymphoma pts) to obtain additional data on tolerability and efficacy and biomarkers of response in these pts. Clinical trial information: NCT03017820. Research Sponsor: U.S. National Institutes of Health; Vyriad.

7532

Poster Session

Efficacy of COVID vaccinations in patients with chronic lymphocytic leukemia. *First Author: Kaitlin Annunzio, The Ohio State University, Columbus, OH*

Background: Chronic lymphocytic leukemia (CLL) is the most prevalent leukemia in the western world. Primarily affecting older patients, CLL increases the risk of infection due to immunosuppression from underlying disease and treatments. With the COVID19 pandemic now in its third year, vaccines remain one of our best protections against infection. However, people with CLL historically have decreased vaccine efficacy; hence protection from the COVID19 vaccines is uncertain. Furthermore, it is unknown if antibodies generated in response to vaccination confer immunity. Therefore, we tested for presence of SARS-CoV-2 antibodies post vaccination to determine if a response was generated and led to a decreased risk of breakthrough infections. **Methods:** We performed a retrospective cohort study of patients with CLL who received at least one COVID19 vaccine. Spike protein antibodies were assessed in a CLIA-approved laboratory. Detectable spike protein antibodies after vaccination were assessed, excluding those detected any time after Cilgavimab-Tixagevimab administration, within 90 days after any monoclonal antibody or convalescent plasma, or after covid infection post vaccine to best capture antibody responses from the vaccine. Logistic regression model was used to assess the odds of antibody development. Fine-Gray model was used to assess risk of breakthrough infections. **Results:** 477 patients were included in this study with median age of 60.4 years. Patients were predominately male (64.8%) and white (97.3%). 70.4% of patients had received at least one treatment for CLL. 45.5% of patients were on CLL treatment at time of vaccination, with the majority (87.6%) of these treated with BTK inhibitors either as monotherapy or with a BCL2 inhibitor or anti CD-20 therapy. Three hundred thirteen (68.2%) of the patients had a detectable antibody after vaccination. Those who received CLL treatment were less likely to have detectable antibody response compared to those not on treatment (OR = 0.19, p < 0.0001). Compared with patients who received Moderna vaccine, Pfizer (OR = 0.15, p < .01) and Janssen (OR = 0.46, p = 0.29) vaccine receivers were less likely to have detectable antibodies. Eighty (17.2%) patients developed COVID19 infection after vaccination, with 5% mortality from COVID19. Those who received Pfizer vaccines had a higher risk of infection (HR = 2.25, p = 0.0016). Regardless of vaccine type, those who had antibodies post vaccination had a decreased risk for infection (HR = 0.38, p < 0.0001). **Conclusions:** Among patients who were vaccinated against COVID19, those who received CLL treatment were less likely to develop antibodies compared to untreated patients, indicating that treatment decreases vaccine efficacy. We show that detectable antibodies after vaccination decrease risk for infection. Moderna appears to have greater efficacy, with more patients having positive antibody titers and a lower risk of developing COVID19. Research Sponsor: None.

7533

Poster Session

Analysis of racial disparities accounting for treatment received in chronic lymphocytic leukemia: A real-world cohort analysis. *First Author: Adam Kittai, Division of Hematology, The Ohio State University Comprehensive Cancer Center, Columbus, OH*

Background: Recent population-based studies have shown that Black patients (pts) with CLL have worse overall survival (OS) than White pts with CLL. These studies could not account for the use of modern therapies, CLL prognostic variables, or comorbidity and thus the root cause of this disparity remains unclear. Here, we use the Flatiron Health Database (FHD) to study this disparity, while accounting for disease-specific variables and treatment (tx) received. **Methods:** Retrospective analysis of pts with CLL in the FHD treated between 2002 to 2022 was performed. Pt characteristics such as age at diagnosis (dx), year (yr) of dx, months (mos) from dx to first tx, race, sex, IGHV status, ECOG performance status (PS), and use of small molecule inhibitors at any time (including BTK inhibitors, venetoclax, PI3K inhibitors, and lenalidomide) were collected and analyzed. OS was measured from tx start. Multivariable cox regression (MVA) was used to determine adjusted odds of survival. **Results:** 13646 pts with CLL were identified. Mean age at dx was 65.3 yrs, and mean time from dx to tx was 32.3 mos. 81.2%, 8.4%, and 10.4% of pts were White, Black, or other race, respectively, and 63.2% of pts were male. 61.4% of pts were IGHV unmutated, and 89.1% of pts had a ECOG PS 0/1. 58.7% of pts were treated with a small molecule inhibitor at any point during their tx. After a median follow-up of 5.3 yrs, the median OS was 10.5 yrs (95% CI: 10.2-10.8). Black pts were younger at dx (63.1 vs 65.4), had shorter time to first tx (23.6 mo vs 34 mo), were more likely to be IGHV unmutated than White pts (83% vs 60.1%), and had more small molecule inhibitor use (69% vs 58.5%). These differences were all statistically significant (p <0.01). 90.8% and 89.1% of Black and White pts had an ECOG PS of 0/1, respectively. Median OS for Black pts was 10 yrs (95% CI: 9.1-11.1) vs 10.5 yrs (95% CI: 10.2-10.8) for White pts. On MVA, Black pts had higher risk of death than White pts of the same age despite increased use of small molecule inhibitor (Table). However, the interaction between age and race was also significant, indicating a decreasing disparity between Black and White race as pts aged. Time to first tx, IGHV unmutated status, and ECOG PS were also independently associated with worse OS. **Conclusions:** Black race especially at younger age was independently associated with worse OS despite the use of small molecule inhibitors, IGHV status, and ECOG PS. Research Sponsor: AstraZeneca.

MVA of pt characteristics on OS.			
	N=10152*		
	HR (95% CI)		P-value
Age, 5-yr older			<.01
White	1.50 (1.46-1.54)		
Black	1.32 (1.24-1.41)		
Mos from dx to tx start, 6 more mos	1.03 (1.03-1.04)		<.01
Race, Black vs White at age			<.01
30	2.93 (1.74-4.93)		
50	1.76 (1.36-2.28)		
70	1.06 (0.93-1.20)		
IGHV vs Mutated			<.01
Unmutated	1.29 (1.13-1.47)		
missing	1.41 (1.26-1.58)		
ECOG PS vs 0-1			<.01
2-4	2.08 (1.85-2.33)		
missing	0.89 (0.83-0.96)		
Use small molecule inhibitor vs No	0.80 (0.75-0.86)		<.01

*Controlled for gender and region.

7534

Poster Session

Patient perspectives on CLL treatment side effects: A sub-analysis of the VOICE survey. *First Author: Constantine Si Lun Tam, Alfred Health, Melbourne, Victoria, VIC, Australia*

Background: Treatment for chronic lymphocytic leukemia (CLL), including chemo-immunotherapy and targeted drugs, is associated with various adverse events. We surveyed patients with CLL about their knowledge and attitudes regarding treatments and “side effects” (SEs), a more widely understood term for adverse events. **Methods:** Clinicians and patient advocacy group representatives developed and distributed a survey from March through December 2022 in 12 countries to patients with CLL who underwent ≥1 line of treatment. The anonymous survey was available via an electronic platform, digital questionnaires (.pdf), or paper forms. This sub-analysis includes items regarding SEs during treatment intervals, although the SEs queried were not comprehensive. **Results:** Treatment SEs had a moderate or high impact on 27%–43% of patients in every domain queried (Table). Most patients (300/370; 81%) discussed SEs with their physicians “always” or “sometimes”, but (117/277) were seeking more information about the benefits and SEs associated with their treatment, primarily via the internet. When asked how they would respond to common SEs, most patients would consult their physician first. Notably, >10% of them would continue treatment normally if they experienced arrhythmias or cardiac problems, and 21% would continue if they developed hypertension (Table). A similar proportion (11%) would continue treatment if they had an infection, while 23% of them would consider stopping treatment without medical advice if they developed skin cancer. **Conclusions:** These results show the impacts of SEs from CLL treatment affect substantial numbers of patients in multiple life areas. The responses suggest that despite patient-physician communication about SEs, there is a need to help patients find reliable information about their treatments online as well. Finally, patients’ willingness to stop or continue treatment in the event of various SEs, including cardiovascular or oncologic events, indicates a critical knowledge gap regarding the risk associated with these events. The real-world data presented herein highlights areas in which improved patient education initiatives could directly improve patient outcomes. Research Sponsor: MphaR; AstraZeneca.

Impact of treatment side effects (N = 322)	No impact (%)	Little impact (%)	Moderate/high impact (%)	Other (%)
Physical	96 (30)	79 (24)	137 (43)	10 (3)
Psychological	111 (35)	83 (26)	117 (36)	11 (3)
Social	139 (43)	83 (26)	88 (27)	12 (4)
Emotional	132 (41)	84 (26)	97 (30)	9 (3)
Work	155 (48)	58 (18)	98 (31)	11 (3)
Patient response to side effects (N = 329)	Continue treatment (%)	Consult physician (%)	Consider stopping (%)	Other (%)
Hypertension	70 (21)	243 (74)	13 (4)	3 (1)
Cardiac problems	44 (13)	251 (76)	29 (9)	5 (2)
Arrhythmia	41 (12)	256 (78)	29 (9)	3 (1)
Skin cancer	38 (12)	210 (64)	77 (23)	4 (1)
Infections	37 (11)	264 (80)	24 (8)	4 (1)
Headache	107 (32)	210 (64)	9 (3)	3 (1)
Weight loss	88 (27)	230 (70)	8 (2)	3 (1)

7535

Poster Session

Fixed-duration ibrutinib + venetoclax for first-line treatment of chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL): 4-y follow-up from the FD cohort of the phase 2 CAPTIVATE study. *First Author: Paul M. Barr, Wilmot Cancer Institute, University of Rochester Medical Center, Rochester, NY*

Background: CAPTIVATE (PCYC-1142) is a multicenter phase 2 study of first-line ibrutinib (I) + venetoclax (V) in CLL/SLL. Follow-up results from the fixed duration (FD) cohort showed 3-y PFS rate of 88% overall and rates ≥80% in patients (pts) with high-risk features (Wierda, ASCO 2022). Here we present updated results from the FD cohort with 4-y follow-up. **Methods:** Pts aged ≥70 y with previously untreated CLL/SLL received 3 cycles of I then 12 cycles of I+V (I 420 mg/d orally; V ramp-up to 400 mg/d orally). Responses were investigator assessed per iwCLL 2008 criteria. Undetectable minimal residual disease (uMRD; <10⁻⁴) was assessed by 8-color flow cytometry. **Results:** 159 pts were enrolled, including pts with high-risk features of unmutated IGHV (uIGHV) (56%) or del(17p) and/or TP53 mutation (17%). Median time on study was 50 mo (range 1–53). At 4 y of follow-up, the best CR rate was 58% and ORR was unchanged at 96%. At 4 y, PFS rate was 79% (95% CI 71–84) and OS rate was 98% (95% CI 94–99). 4 y PFS rates were numerically lower in pts with uIGHV (73%) or del(17p) and/or TP53 mutation (63%), while OS rates remained consistently high (Table). 4 y PFS rates by MRD status 3 mo after stopping treatment (EOT+3) were significantly higher overall in pts with uMRD vs detectable MRD (dMRD) in PB (90% vs. 66%, Table); this difference was minimal at 24 mo (100% vs 91%). Median TTNT was not reached overall (range 1–53 mo); the 4 y rate of freedom from next treatment was 84% (95% CI 77–89). Second malignancies continue to be collected off treatment; 1 AE of prostate cancer occurred during this y of follow-up. To date, 19 pts with PD after completing fixed duration I+V in either the FD cohort or MRD cohort placebo arm initiated retreatment with I. Responses in 17 pts with available data were 1 CR, 13 PR, and 1 each PR with lymphocytosis, SD, and PD. Median time on retreatment was 11 mo (range 0–39). The most common AEs (≥10%) with retreatment were diarrhea (n=3), COVID-19 (n=3), and anemia (n=2). In addition, 4 pts have started I+V retreatment to date. **Conclusions:** Results of the CAPTIVATE study support I+V as an all-oral, once-daily fixed-duration regimen for previously untreated pts with CLL/SLL. With 4 y follow-up, fixed-duration I+V continues to provide deep, durable remissions with clinically meaningful PFS and time off treatment, including in pts with high-risk disease features. New safety findings off-treatment were expectedly negligible, highlighting the benefits of a fixed duration regimen. Promising responses were observed upon retreatment with I in progressing pts. Clinical trial information: NCT02910583. Research Sponsor: Pharmacyclics LLC, an AbbVie Company.

	4 y PFS, % (95% CI)	4 y OS, % (95% CI)
FD Cohort (N=159)	79 (71–84)	98 (94–99)
del(17p) and/or TP53 (n=27)	63 (41–79)	96 (76–99)
uIGHV (n=89)	73 (62–81)	97 (90–99)
uMRD at EOT+3, PB (n=90)	90 (81–95)	100
dMRD at EOT+3, PB (n=57)	66 (52–77)	100

7536

Poster Session

Real-world outcomes by race in patients (pts) with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL): Final analysis results from the informCLL registry. *First Author: Jacqueline Claudia Barrientos, Mount Sinai Comprehensive Cancer Center, Miami Beach, FL*

Background: informCLL is a large, US-based, prospective, observational registry of pts with CLL/SLL initiating treatment (tx) in the era after approval of ibrutinib (Ibr). Here, we report real-world tx patterns and outcomes by race and line of therapy (LOT) from the final analysis of informCLL. **Methods:** Pts with CLL/SLL who initiated FDA-approved tx were enrolled between 10/2015 and 6/2019. Baseline characteristics, tx patterns, time to next tx (TTNT), OS, and safety are summarized by race (focus on Black and White pts) and LOT (first-line [1L] or relapsed/refractory [R/R], with focus on 1L). **Results:** Of 1459 eligible pts enrolled, 105 were Black (1L, n=58; R/R, n=47), 1323 were White (1L, n=779; R/R, n=544), and 31 were of other races (Asian [n=6], Native American [n=4], other/not reported [n=21]). Relative to White pts, 1L-treated Black pts were younger (median age 65 vs 70 y) and had worse performance status (ECOG status ≥1: 59% vs 50%), more advanced disease (Rai stage III-IV: 55% vs 46%), shorter time from diagnosis to 1L tx (median 7 vs 19 mo), and lower rates of del(17p) among tested pts (6% vs 13%). Across race, Ibr was the most common 1L tx (Black, n=29 [50%]; White, n=346 [44%]) followed by CIT (Black, n=25 [43%]; White, n=331 [42%]). With median follow-up of approximately 32 mo in 1L-treated pts, the estimated rate of freedom from next-line therapy at 36 mo was similar between Black and White pts across all-treated pts and among Ibr-treated subgroups (Table). Estimated 36-mo OS rates in all-treated pts were also similar by race, with a high OS rate observed among Ibr-treated Black pts (97% at 36 mo). In multivariate analyses (MVA) in 1L-treated pts, male gender, poorer ECOG status, and increased comorbidity burden were independent predictors of decreased OS while race was not associated with OS. In 1L Ibr-treated pts, the only factor associated with decreased OS in MVA was longer time from diagnosis to 1L tx. Rates of serious AEs and AEs leading to tx discontinuation appeared similar across race (Table). **Conclusions:** Although historical retrospective studies from the pre-novel agent era have shown poorer clinical outcomes among Black pts with CLL relative to non-Black pts, results from informCLL show similar or potentially improved outcomes, including OS, among 1L Ibr-treated Black pts relative to White pts. These results suggest that access to novel agents such as Ibr may in part overcome historical disparities in clinical outcomes by race in pts with CLL. Clinical trial information: NCT02582879. Research Sponsor: Pharmacyclics LLC, an AbbVie Company.

	Black all-treated	White all-treated	Black Ibr-treated	White Ibr-treated
Outcomes with 1L tx				
# of pts, n	58	779	29	346
Median follow-up, mo	32.5	31.7	33.5	31.3
Median duration of 1L tx, mo	5.5	4.9	25.2	23.5
36-mo estimate of freedom from next-line therapy, %	73	72	72	75
36-mo OS rate, %	87	83	97	85
Serious AEs, %	28	29	45	38
AEs leading to tx discontinuation, %	14	25	24	36

7537

Poster Session

Real-world (RW) dosing patterns and outcomes among chronic lymphocytic leukemia (CLL) patients (pts) with or without an ibrutinib (IBR) dose adjustment (DA) in first-line (1L). *First Author: Kerry Anne Rogers, Division of Hematology, The Ohio State University, Columbus, OH*

Background: Pts treated for CLL with IBR, a once-daily Bruton's tyrosine kinase inhibitor with dosing flexibility options, may adjust their daily dose to help prevent recurrence or worsening of adverse events, while preserving efficacy. This RW study describes outcomes for CLL pts treated with 1L IBR who did or did not have a DA. **Methods:** Electronic medical records from the Acentrus database (1/1/2016-4/30/2022) were used to identify CLL pts initiated on 1L IBR (index date). The first 6 months post-index were used to identify pts who remained on a starting dose of 420mg/day or with a DA (reducing to a dose lower than 420mg/day; reasons for DA not available). Treatment adherence (measured by proportion of days covered [PDC] and medication possession ratio [MPR]) and time to next treatment (TTNT) were described for patients with and without a DA. Descriptive analyses are reported for all pts and among a subgroup of pts with high cardiovascular (CV) risk, defined as having a pre-existing CV comorbidity or a high CV risk score (CV subgroup). **Results:** 1,171 CLL patients were initiated on 1L IBR at the recommended dose of 420mg/day (Table). Of those, 1,038 (88.6%) remained on 420 mg for ≥ 6 months (mean age=70.2 years, 33.6% female, median follow-up: 30.5 months); 229 (19.6%) had a DA at any time post-index (median time to DA: 5.5 months) and 126 had the DA during the first 6 months (mean age=72.2 years, 42.9% female, median follow-up: 35.1 months). Mean PDC and MPR were descriptively higher in pts with a DA (overall: PDC=0.81, MPR=0.84; CV subgroup: PDC=0.78, MPR=0.81) relative to pts with no DA (overall: PDC=0.70, MPR=0.73; CV subgroup: PDC=0.69, MPR=0.72). Median TTNT was not reached for pts with or without a DA; 12-month Kaplan-Meier (KM) rates were similar for pts with a DA (overall: 89.1%; CV subgroup: 92.7%) and with no DA (overall: 92.5%; CV subgroup: 92.0%). **Conclusions:** Among CLL pts initiating 1L with standard-of-care IBR, 19.6% had a DA. Those with a DA had descriptively higher treatment adherence with no detriment to TTNT, relative to those who maintained 420mg/day starting dose, regardless of baseline CV risk. These findings are consistent with other RW studies and suggest that IBR DA can be an effective treatment strategy that does not negatively affect efficacy while being well-tolerated outside of clinical trials. Research Sponsor: Janssen Scientific Affairs, LLC.

	Overall N=1,171	CV subgroup N=724
DA at any time, n (%)	229 (19.6%)	154 (21.3%)
Time to first DA, months, mean $\pm$ standard deviation [median]	9.0 $\pm$ 9.2 [5.5]	8.5 $\pm$ 8.7 [5.4]
Staying on reduced dose for the remainder of 1L, n (%)	138 (60.3%)	93 (60.4%)
Returning to 420 mg, n (%)	25 (10.9%)	14 (9.1%)
Further reduced dose following initial DA, n (%)	22 (9.6%)	17 (11.0%)
Other dosing patterns following DA, n (%)	44 (19.2%)	30 (19.5%)
DA within first 6 months, n (%)	126 (55.0%)	88 (57.1%)
No DA during first 6 months, n (%)	1,038 (88.6%)	634 (87.6%)

7540

Poster Session

A matching-adjusted indirect comparison (MAIC) of the efficacy and safety of acalabrutinib (acala) versus zanubrutinib (zanu) in relapsed or refractory chronic lymphocytic leukemia (RR CLL). *First Author: Adam Kittai, Division of Hematology, The Ohio State University Comprehensive Cancer Center, Columbus, OH*

Background: The BTKi ibrutinib is the standard of care in RR CLL and was compared in head-to-head randomized clinical trials (RCTs) with second-generation BTKi: acala in ELEVATE-RR and zanu in ALPINE. However, major differences in these RCT's populations prevents comparison of acala and zanu. Acala was also assessed in the ASCEND RCT, which had a similar population to ALPINE but a different comparator. Thus, we used unanchored MAIC to compare the efficacy and safety of acala vs zanu using individual patient data (IPD) from ASCEND and published aggregate data from ALPINE. **Methods:** In the unanchored MAIC, acala IPD from ASCEND were weighted to match zanu baseline data from ALPINE. This reduced between-study differences in variables that were prognostic/effect-modifying of progression-free survival (PFS) in an exploratory multivariate cox regression analysis of ASCEND. These included sex, ECOG PS, bulky disease, prior chemoimmunotherapy, del(11p), del(17p), TP53 without del(17p), IGHV status, region, age, prior lines of therapy and Rai stage. An efficacy analysis assessed investigator-assessed PFS (INV PFS) in randomized patients with baseline data (acala, n = 149; zanu, n = 327). Pseudo IPD for INV PFS for zanu were obtained from Kaplan-Meier curves. A safety analysis assessed odds ratios (ORs) of AEs in treated patients with baseline data (acala, n = 148; zanu, n = 324). To allow comparison of the incidence of AEs, an artificial data cut-off (Feb 21, 2020) was imposed for acala to match the zanu median treatment exposure (both 28.4 months). **Results:** After matching, the effective sample size of acala was 99 (66.6%; 65% male; median age 66 years). 12- and 24-month INV PFS are shown below. The MAIC hazard ratio (HR) for INV PFS is similar for acala vs zanu (HR 0.90, 95% CI 0.60–1.36). The risk of having grade ≥ 3 AE (OR 0.66, 95% CI 0.41–1.05), atrial fibrillation (AF; OR 1.32, 95% CI 0.56–3.08), grade ≥ 3 AF/atrial flutter (OR 0.60, 95% CI 0.12–2.89), grade ≥ 3 hemorrhage (OR 0.61, 95% CI 0.19–2.03) or an AE leading to discontinuation (OR 1.14, 95% CI 0.61–2.13) was similar with acala vs zanu. The risk of having a serious AE (OR 0.61, 95% CI 0.39–0.97), hypertension (any grade: OR 0.18, 95% CI 0.09–0.37; grade ≥ 3 : OR 0.22, 95% CI 0.09–0.54), any grade hemorrhage (OR 0.54, 95% CI 0.34–0.87) or an AE leading to dose reduction (OR 0.30, 95% CI 0.14–0.67) was lower with acala vs zanu. **Conclusions:** Acala and zanu have a similar efficacy in patients with RR CLL, while acala has a lower risk of grade ≥ 3 hemorrhage, any grade and grade ≥ 3 hypertension and dose reduction due to AEs vs zanu. Limitations of MAIC analyses mean the results should be viewed as hypothesis-generating. Research Sponsor: AstraZeneca.

Landmark INV PFS.		
Treatment	12-month INV PFS % (95% CI)	24-month INV PFS % (95% CI)
Acala pre-matching	89 (83–93)	75 (68–81)
Acala post-matching	91 (84–95)	76 (66–84)
Zanu	92 (88–94)	78 (73–83)

7538

Poster Session

Ibrutinib dose modifications for management of cardiac adverse events in patients with B-cell malignancies: Pooled analysis of 10 clinical trials. *First Author: Deborah Marie Stephens, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT*

Background: Continuous therapy with once-daily ibrutinib (Ibr) is associated with long-term PFS in pts with B-cell malignancies. Dose reduction is a potential AE management approach that may optimize treatment outcomes. We evaluated outcomes with dose reductions in Ibr-treated pts with cardiac AEs. **Methods:** Data were pooled for Ibr-treated pts from 10 studies of CLL (n=781), mantle cell lymphoma (MCL; n=250), marginal zone lymphoma (MZL; n=63) or Waldenström macroglobulinemia (WM; n=169). Cardiac AEs, initial and recurrent, were identified by preferred terms within the cardiac disorders system organ class. Recurrence was defined as an AE of same or worse grade, and was measured up to 30 days after last dose of ibrutinib or start of next-line therapy, whichever occurred earlier. **Results:** Overall, 234/1263 pts (19%) had cardiac AEs of any grade. Twelve pts were excluded from the analysis: 9 who had a dose reduction prior to a cardiac AE (0.7%) and 3 who had a fatal cardiac AE with no prior cardiac AE (0.2%). Of the remaining 222 pts with grade 1–4 cardiac AEs, 22 (10%) had Ibr dose reduction to 420 mg (n=3), 280 mg (n=10), or 140 mg (n=9) after a cardiac AE. These pts (n=22) tended to be older (≥ 75 y: 45% vs 29%), less heavily pretreated (≥ 1 prior therapy: 45% vs 73%), and with a lower Ibr discontinuation rate (23% vs 48%) than those without dose reduction (n=200). Recurrence of the same cardiac AEs at the same or worse severity was less frequent in pts with dose reductions, both overall (14% vs 18%) and as serious AEs (5% vs 10%). No pt died due to cardiac AE recurrence. Among pts with cardiac AEs who started with the 420 mg Ibr dose (177/222; excludes 45 patients with MCL or MZL who per label start with 560 mg dose), no cardiac AE recurred at same or worse severity in the subset with dose reductions (Table). PFS was not negatively impacted by dose reduction, both overall (n=22; median PFS not reached [NR], 24-mo PFS: 91%), and in those who started with the 420 mg dose (n=18; median PFS NR; 24-mo PFS, 94%). **Conclusions:** Dose reduction for cardiac AEs may enable pts to continue to benefit from long-term Ibr and mitigate the risk of cardiac AE recurrence or worsening. Clinical trial information: NCT01105247, NCT01236391, NCT01578707, NCT01722487, NCT01611090. Research Sponsor: Pharmacyclics LLC, an AbbVie Company.

Recurrence of cardiac AEs by dose reduction in patients with Ibr 420 mg starting dose.		
Pts with recurrence of same AE at same or worse grade, n/N (%)	With dose reductions (N=18)	Without dose reductions (N=159)
Any grade 1-4 cardiac AE	0/18 (0)	30/159 (19)
Cardiac arrhythmias	0/15 (0)	23/122 (19)
Cardiac failure	0/1 (0)	3/13 (23)
Other cardiac disorders	0/5 (0)	4/41 (10)
Any serious cardiac AE	0/18 (0)	17/159 (11)
Cardiac arrhythmias	0/15 (0)	11/122 (9)
Cardiac failure	0/1 (0)	3/13 (23)
Other cardiac disorders	0/5 (0)	3/41 (7)

7541

Poster Session

Utility of pharmacogenomic testing in predicting intolerance to BTK inhibitors. *First Author: Fahmin Basher, Duke Cancer Institute, Durham, NC*

Background: Oral inhibitors of Bruton's tyrosine kinase (BTKi) are used for a number of B-cell malignancies, including chronic lymphocytic leukemia (CLL), mantle cell lymphoma (MCL), marginal zone lymphoma (MZL) and lymphoplasmacytic lymphoma (LPL). Real-world data has demonstrated that BTKi discontinuation is commonly due to intolerance, but contributing factors are not fully understood. Prior work suggests that cytochrome P450 (CYP) polymorphisms may increase the risk of targeted therapy discontinuation in CLL. We utilized pharmacogenomic (PGx) testing in Veterans treated with BTKi to evaluate the potential contribution of CYP polymorphisms to intolerance and responses to BTKi. **Methods:** We identified Veterans receiving care through the Veterans Administration (VA) who were prescribed a BTKi and underwent testing through the Pharmacogenomic Testing for Veterans (PHASER) program, currently offered at 22 VA facilities. We analyzed factors including time on BTKi therapy, reasons for discontinuation, and use of concomitant medications known to strongly inhibit CYP. Event-free survival (EFS) was defined as time from BTKi initiation to discontinuation. **Results:** Eighty-nine Veterans treated with BTKi who had PGx testing were identified, of which 97% (86) were male and 85% (76) were diagnosed with CLL. Other diagnoses included LPL (4), MCL (3), and MZL (3). Seventy-seven patients (pts) were treated with ibrutinib, nine with acalabrutinib and three with zanubrutinib. Three pts had poor metabolizer genotype (PMG) for CYP2C19 and 25 pts received strong CYP2C19 inhibitors (inh). Thirty-two pts had PMG for CYP2D6, and 12 pts received strong CYP2D6 inh. With a median follow up time of 38.9 months, 25 pts (28%) permanently discontinued due to intolerance and 10 pts (11%) progressed on BTKi therapy. Another 25 pts temporarily discontinued therapy. Median duration of BTKi therapy was 11.0 months for pts discontinuing for intolerance, 23.2 months for pts discontinuing for progression, and 38.5 months for pts not discontinuing therapy. Reasons for intolerance included arrhythmia, bleeding, and infections. EFS due to intolerance or progression was not statistically different between pts who were either CYP2C19 PMG or who received strong CYP2C19 inh, compared to all other pts. Interestingly, EFS due to intolerance alone was statistically different comparing these groups (p = 0.014, median 49.4m vs NR), but EFS due to progression was not (p = 0.76, median 79.6m vs NR). EFS was not significantly different comparing pts who were either receiving strong CYP2D6 inh or were PM to those who were not. **Conclusions:** We found that Veterans who were treated with BTKi and who either took concomitant strong CYP2C19 inh or had a CYP2C19 PMG were more likely to have intolerable side effects of BTKi therapy leading to discontinuation. Our results suggest that evaluating polypharmacy and PGx factors should be considered when prescribing BTKi. Research Sponsor: None.

7542

Poster Session

Brentuximab vedotin + AVD for newly diagnosed classic Hodgkin lymphoma (cHL): Incidence and management of peripheral neuropathy in a multi-institution cohort. First Author: Jackson Bowers, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

Background: Brentuximab vedotin (BV) in combination with doxorubicin, vinblastine, and dacarbazine (AVD) is the new standard of care for newly diagnosed stage III/IV cHL. In the pivotal ECHELON-1 trial, peripheral neuropathy (PN) was the most common toxicity, seen in 67% of patients (pts) and leading to discontinuation of BV in 6.6%. However, PN from BV+AVD in cHL has not been studied in a non-trial setting, where clinicians may have different strategies for managing it. **Methods:** We conducted a multi-site, retrospective study to characterize PN in pts who were planned to receive 6 cycles of BV+AVD for newly diagnosed cHL before 9/2022. Data was obtained from medical records and PN was graded retrospectively using CTCAE v5.0 criteria. Multivariable logistic regression was used to assess factors associated with PN. Progression-free survival (PFS) and overall survival (OS) were calculated using the Kaplan Meier method. A Cox proportional hazards model was used to test the effect of discontinuation on PFS. **Results:** 153 pts from 10 US institutions were eligible. Median age was 35 years (range 18-76) with 22% of pts over 60 years old. Thirty-four pts (22%) had at least 1 ineligibility criteria for ECHELON-1, including stage (8% stage I/II), performance status (3% ECOG 3+), preexisting PN (6%), or other comorbidities including HIV and other malignancies (10%). Of advanced stage pts, 41% had IPS 4-7. Median no. BV+AVD cycles was 6 (range 1-6). PN was reported by 80% of pts during treatment; 39% experienced grade (G) 1, 31% G2, and 10% G3. In total, BV was modified in 44% of pts due to PN leading to BV discontinuation in 23% with median no. of doses omitted of 4 (range 1-10), dose reduction in 17% and temporary dose hold in 4%. Vinblastine was modified in 17% of pts due to PN including discontinuation or temporary hold in 10% and dose-reduction in 7%; in 35% of pts with vinblastine modification, BV was continued. None of the factors assessed (age, sex, baseline PN, diabetes mellitus) predicted development of any grade PN. However, higher initial dose of BV in mg (based on weight) was associated with increased risk of grade 2+ PN (OR 1.03, 95% CI 1.01-1.05, $p = 0.002$). With median follow up of 24 months (range 0.33-87), PN resolution was documented in 36% and improvement in 33% at last follow up. Ongoing G2+ PN was present in 13% of pts at last follow up. 2-year PFS for the advanced stage patients was 82.7% (95% CI 0.76-0.90) and OS was 97.4% (95% CI 0.944-1). Discontinuation of BV due to neuropathy did not affect PFS (HR 1.1, 95% CI 0.45-2.5). **Conclusions:** In the non-trial setting, BV+AVD was associated with a high incidence of PN. In our cohort, which includes pts who would not have been eligible for the pivotal ECHELON-1 trial, BV discontinuation rates were higher than previously reported, but 2-year outcomes remain comparable; discontinuation of BV was not associated with inferior PFS. Research Sponsor: None.

7544

Poster Session

Identifying racial and ethnic disparities in patients diagnosed with mycosis fungoides/Sézary syndrome in the United States: A contemporary SEER analysis. First Author: Maria Elena Fierro, University of Texas Health Science Center at San Antonio, San Antonio, TX

Background: Mycosis fungoides (MF) and Sézary syndrome (SS) are rare cutaneous T-cell lymphomas. In this study, we compare demographics, treatment, and survival patterns in Hispanic (HI) vs. Non-Hispanic (NH) patients diagnosed with MF and SS. **Methods:** Data were analyzed on MF and SS patients in the US reported to SEER 18 database between 2000 and 2018. SEER 18 contains the most comprehensive population-based cancer information in the US, covering approximately 27% of the total US population, and up to 36% of HI. Racial groups analyzed included NH whites, HI whites, blacks, and Asians/Pacific Islanders. Patient characteristics, age-adjusted incidence rate, and survival rate were compared across ethnic groups, HI vs NH. Stratification by age, gender, and stage at diagnosis were considered. Kaplan-Meier and Cox regression analyses were used to compare overall survival (OS) between HI and NH. Multivariate analysis and propensity score matching were performed with adjustment for age, stage, and B-symptoms. **Results:** 8578 patients with MF and 275 patients with SS were identified. Of patients with MF, 11% were HI and 89% were NH; of patients with SS, 12% were HI and 88% were NH. In NH patients with MF, most patients were male (58%); for HI patients with MF, a male predominance was not observed ($p < 0.001$). In patients with SS, most patients were male in both NH and HI (56% NH, 56% HI; $p = 0.989$). In both MF and SS, HI were diagnosed at younger ages compared to NH, 49 y.o vs 60 y.o ($p < 0.001$) and 59 y.o vs 71 y.o ($p = 0.009$) respectively. Most HI and NH with MF and SS did not receive radiotherapy (91% of NH and 92% of HI for MF; 92% of NH and 91% of HI for SS; p values 0.166 and 0.760, respectively). On survival analysis, for patients with MF, the survival probability (SP) at 2, 5, and 10 years for HI vs NH were 94%, 87%, and 77% vs. 91%, 81%, and 69%, respectively. The survival difference observed favored HI ($p < 0.001$). For patients with SS, there was no statistically significant survival difference between HI and NH with 2, 5, and 10 year SP at 65%, 42%, and 17% for HI and 62%, 36%, and 16% for NH, respectively ($p = 0.99$). In patients with SS, the median survival time in years was 3.3 and 3.2 in NH and HI patients, respectively. In patients with MF, the median survival time was not reached. On multivariate analysis, when adjusted for age, those patients with MF and SS who were older than 80 y.o and between 60 to 80 y.o, had worse OS compared to those younger than 60 y.o, with HR 17.6 (95%: 13.8 – 22.3) and 4.2 (95% CI: 3.6 – 5) respectively for MF; and HR 1.8 (95% CI: 0.9 – 3.7) and 1.64 (CI 95% 1 – 2.8) respectively for SS. **Conclusions:** We identified ethnic differences in incidence, age at diagnosis, sex, and survival outcomes in patients with MF and SS. Notably, we identified a survival advantage in patients with MF that favored HI. In patients with SS, there was no ethnic difference in survival. Research Sponsor: None.

7543

Poster Session

Depth of metabolic response at interim PET and survival outcomes among patients with primary refractory and early relapsing diffuse large B-cell lymphoma (DLBCL). First Author: Allison Marie Bock, Mayo Clinic, Rochester, MN

Background: Total metabolic tumor volume (TMTV) and maximum standardized uptake value (SUVmax) may improve upon standard 18F-fluorodeoxyglucose positron emission tomography/computed tomography (PET-CT)-based assessment of advanced DLBCL during treatment. We report the association of TMTV and SUVmax changes at interim PET-CT (PET2) on survival outcomes in patients with primary refractory DLBCL (prDLBCL) and early relapsing DLBCL (erDLBCL). **Methods:** Adult patients with prDLBCL (less than a complete response (CR) or progression by the end of treatment (EOT)) or erDLBCL (CR at EOT with relapse within 12 months) between 2005 and 2019 at Mayo Clinic Rochester were included. The % change (Δ) from baseline to PET2 (after 2 cycles of 1L therapy) of TMTV and SUVmax were measured. A PET segmentation threshold of 1.5 liver mean SUV + two standard deviations with a minimum volume constraint of 0.5 mL was utilized (MIM Software, Inc., Cleveland OH, USA) with manual input as needed. Functional splines analysis determined SUVmax and TMTV threshold for analysis. **Results:** 131 patients had complete PET-CT data (N=79 prDLBCL, N=52 erDLBCL). Baseline median TMTV and SUVmax were 767.4 cm³ (range 0.9-6840.4) and 20.5 (2.0-52.6), respectively. At a median follow up of 77.6 months, 81 patients had died. 2-year OS rate was 53% (95% CI: 42-67) for patients with a PET2 Δ SUVmax decline $\geq 65\%$ compared to 15% (95% CI: 7-29) for patients with a PET2 Δ SUVmax decline $< 65\%$ ($p < 0.001$). prDLBCL had a 2-year OS rate of 48% (95% CI: 31-74) for a Δ SUVmax $\geq 65\%$ compared to 7% (95% CI: 2-21) for a Δ SUVmax $< 65\%$ ($p < 0.001$), which captured 58% of prDLBCL patients (N=46). Two-year OS rate was 43% (95% CI: 34-54) for patients with a Δ TMTV $\geq 75\%$ compared to 5% (95% CI: 1-35) for patients with Δ TMTV $< 75\%$ ($p < 0.001$). All patients with a Δ TMTV $< 75\%$ had prDLBCL. prDLBCL had a 2-year OS rate of 28% (95% CI: 18-44) for a Δ TMTV $\geq 75\%$. The outcomes for Δ SUVmax $< 65\%$ and Δ TMTV $< 75\%$ at PET2 remained significant in a cox regression model adjusted for IPI and bulky disease (> 10 cm)(Table). **Conclusions:** A Δ TMTV decline $< 75\%$ or a Δ SUVmax decline $< 65\%$ at PET2 identified an ultra-high-risk subgroup of DLBCL with particularly poor outcomes, that captured a high percentage of prDLBCL patients, and was significant after adjusting for IPI and bulky baseline disease. These patients may benefit from clinical trials evaluating alternative PET-adapted treatment strategies, but further evaluation among all patients with DLBCL is needed. Research Sponsor: None.

Multivariate analysis of TMTV and SUVmax response at interim PET (PET2) on OS from time of relapse after 1L therapy, adjusted for baseline bulky disease and IPI.

PET2	Overall Survival (OS)		
	2-Year Rate	HR (95% CI)	P-Value
Δ SUVmax $\geq 65\%$	53%	(reference)	< 0.001
Δ SUVmax $< 65\%$	15%	3.58 (2.15-5.97)	
Δ TMTV $\geq 75\%$	43%	(reference)	< 0.001
Δ TMTV $< 75\%$	5%	2.97 (1.69 - 5.20)	

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Poster Session

Zanubrutinib plus obinutuzumab versus obinutuzumab in patients with relapsed/refractory follicular lymphoma: Updated analysis of the ROSE-WOOD study. First Author: Christopher Flowers, Department of Lymphoma/Myeloma, MD Anderson Cancer Center, Houston, TX

Background: In an early-phase study, the combination of zanubrutinib plus obinutuzumab (ZO) was well tolerated and associated with an early signal of efficacy in patients (pts) with follicular lymphoma (FL) (Tam et al. *Blood Adv* 2020). ROSE-WOOD (NCT03332017) is a phase 2, randomized study designed to assess efficacy and safety of ZO vs obinutuzumab (O) in pts with relapsed/refractory (R/R) FL. Here, we present an updated analysis with a median follow-up of 20.2 mo. **Methods:** Pts with R/R FL (grade 1–3a) who received ≥ 2 lines of therapy including an anti-CD20 antibody and alkylating agent were randomized 2:1 to receive ZO or O. Zanubrutinib was given at 160 mg twice daily until progression or unacceptable toxicity. The primary endpoint was overall response rate (ORR) by independent central review. Secondary endpoints included duration of response (DOR), progression-free survival (PFS), time to next treatment (TTNT), overall survival (OS), and safety. **Results:** A total of 217 pts were randomized (145 for ZO; 72 for O). Median age was 64 years. Of the 217 pts, 114 (52.5%) had a high Follicular Lymphoma International Prognostic Index (FLIPI) score at screening and 123 (56.7%) pts had high tumor burden criteria according to Groupe d'Etude des Lymphomes Folliculaires (GELF) criteria. Median number of prior lines of therapy was 3 (range, 2–11). A total of 114 (52.5%) pts were refractory to rituximab; 214 (98.6%) pts received prior immunochemotherapy. Prior exposure to anticancer drugs included anthracyclines (80.6%), cyclophosphamide (94.0%), and bendamustine (54.8%). ORR was 69.0% (ZO) vs 45.8% (O) ($P = 0.0012$). Complete response rate was 39.3% (ZO) vs 19.4% (O); 18-mo DOR rate was 69.3% (ZO) vs 41.9% (O); median PFS was 28.0 mo (ZO) vs 10.4 mo (O) (hazard ratio [HR], 0.50 [95% CI: 0.33, 0.75]; $P = 0.0007$). Median TTNT was not evaluable for ZO and 12.2 mo for O (HR, 0.34 [95% CI: 0.22, 0.52]; $P < 0.0001$). Estimated OS rate at 24 mo was 77.3% (ZO) and 71.4% (O), with median OS not reached in either arm. Nonhematologic treatment-emergent adverse events of any grade that occurred more frequently for ZO vs O ($> 5\%$ difference) were petechiae (6.3% vs 0%) and herpes zoster infection (6.3% vs 0%); in contrast, pyrexia (13.3% vs 19.7%) and infusion-related reaction (2.8% vs 9.9%) occurred more frequently in pts on O. When adjusted for duration of treatment exposure, incidences of infection and cytopenia were similar, and incidence of all grades of hemorrhage was 2.4 (ZO) vs 1.3 (O) persons per 100 person-months. Two pts in each treatment group reported major hemorrhage. Incidences of atrial fibrillation and hypertension were low and similar in both treatment arms. **Conclusions:** ZO demonstrated meaningful activity and a manageable safety profile in pts with heavily pretreated R/R FL, representing a potential novel therapy. Clinical trial information: NCT03332017. Research Sponsor: BeiGene.

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Poster Session

Safety and efficacy of ABR in pts with TN or R/R MCL: Ph Ib trial. *First Author: Tycel Jovelle Phillips, University of Michigan Comprehensive Cancer Center, Ann Arbor, MI*

Background: Acalabrutinib (A) is a next-generation Bruton tyrosine kinase inhibitor approved for relapsed/refractory (R/R) mantle cell lymphoma (MCL). Bendamustine (B) + rituximab (R) is used for treatment-naïve (TN) and R/R MCL. We present updated data on safety and efficacy of ABR in patients (pts) with TN or R/R MCL. **Methods:** Eligible adults received ABR in this phase 1b study (NCT02717624) as follows: ABR for 6 28-d cycles, maintenance A+R for up to 2 y (TN cohort responders), then oral A continuously until progressive disease (PD) or treatment discontinuation due to toxicity (both cohorts). The primary endpoint was safety. Secondary endpoints were overall response rate (ORR), progression-free survival (PFS), and duration of response (DOR), all per Lugano. **Results:** Overall, 38 pts were enrolled (TN, n=18; R/R, n=20) with median age 66 y (range, 47–86). Baseline characteristics were (TN and R/R cohorts, respectively): stage IV disease in 88.9% and 95.0%, high-risk simplified MPI score in 11.1% and 15.0%, bulky disease >5 cm in 16.7% and 30.0% or ≥10 cm in 5.6% and 10.0%, and blastoid morphology in 5.6% and 15.0%; R/R pts had a median of 2 prior lines of therapy. As of the data cutoff date (6/15/22), 6 (33.3%) TN pts and 4 (20.0%) R/R pts were receiving A monotherapy (Table). Most common any-grade AEs were nausea (n=14, 77.8%; TN) and neutropenia (n=11, 55.0%; R/R). Grade 3–4 AEs occurred in 13 (72.2%) TN pts and 17 (85.0%) R/R pts, most commonly neutropenia in both cohorts (n=7, 38.9% [TN]; n=10, 50.0% [R/R]). Serious AEs occurred in 11 (61.1%) TN pts and 13 (65.0%) R/R pts. There were no reports of ventricular tachyarrhythmia. Grade 3 atrial fibrillation occurred in 1 pt outside the safety reporting period and was not related to study treatment. Grade ≥3 major hemorrhage was reported in 2 (11.1%) TN pts and 3 (15.0%) R/R pts. Grade ≥3 hypertension was reported in 3 (16.7%) TN pts and 2 (10.0%) R/R pts. Five TN pts died (AE: pneumonitis, n=1; unknown, n=4) and 6 R/R pts died (AE: COVID and cerebrospinal meningitis, n=2; PD, n=2; unknown, n=2). ORR was 94.4% (n=17) in the TN cohort and 85.0% (n=17) in the R/R cohort, with CR rates of 77.8% (n=14) and 70.0% (n=14), respectively. Median DOR was not estimable (NE) in the TN cohort and 43.5 mo in the R/R cohort. Median PFS and overall survival were NE in the TN cohort (median follow-up 47.6 mo) and 28.6 mo and NE, respectively, in the R/R cohort (median follow-up 20.4 mo). **Conclusions:** Triple-combination ABR was tolerable and effective in pts with TN or R/R MCL. Clinical trial information: NCT02717624. Research Sponsor: AstraZeneca.

Disposition.

	TN (n=18)	R/R (n=20)	Total (N=38)
Patients, n (%)			
Time on study, median (min–max), mo	47.6 (0.6–72.4)	20.4 (1.2–64.2)	26.4 (0.6–72.4)
Completed 6 cycles of BR	15 (83.3)	10 (50.0)	25 (65.8)
Completed 6 cycles of ABR	14 (77.8)	10 (50.0)	24 (63.2)
Receiving A at end of study	6 (33.3)	4 (20.0)	10 (26.3)
Discontinued A	12 (66.7)	16 (80.0)	28 (73.7)
AE	6 (33.3)	9 (45.0)	15 (39.5)
Disease progression	2 (11.1)	5 (25.0)	7 (18.4)
Withdrawal by PI	2 (11.1)	1 (5.0)	3 (7.9)
Other	2 (11.1)	1 (5.0)	3 (7.9)

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Poster Session

Final three-year follow-up analysis of phase I/II study on tirabrutinib in patients with relapsed or refractory primary central nervous system lymphoma. *First Author: Katsunori Asai, Department of Neurosurgery, Osaka International Cancer Institute, Osaka, Japan*

Background: Primary central nervous system lymphoma (PCNSL) is known as an uncommon and extremely aggressive type of non-Hodgkin lymphoma of brain tumors. Tirabrutinib (TIR), a second-generation oral Bruton's tyrosine kinase inhibitor, was approved for the treatment of relapsed or refractory PCNSL (rPCNSL) based on the results of phase I/II study in Japan (Trial registration: JapicCTI-173646) in 2020. **Methods:** In this study, 44 Japanese patients with rPCNSL received TIR QD at doses of 320 mg (n = 20), 480 mg (n = 7), or 480 mg while fasting (480 mg fasted: n = 17). The International PCNSL Collaborative Group criteria were used to assess the primary endpoint, which was the overall response rate (ORR). We previously reported the interim results with 14.9 (range: 1.4–27.7) months of median follow-up in 2020 (Mishima et al., the 25th Society for Neuro-Oncology 2020). The final analysis results with a three-year follow-up are reported here (data cutoff: April 27th, 2022). **Results:** For the entire population, the ORR was 63.6% with 36.4% of complete response, the median duration of response was 9.2 months, the median progression-free survival was 2.9 months, and the median overall survival was not reached (median follow-up: 37.1 months). The most frequent adverse events (AEs) were skin and subcutaneous tissue disorders and blood and lymphatic system disorders at any grade, including rash (36.4%) and neutropenia (27.3%), leukopenia (25.0%), lymphopenia (18.2%), and thrombocytopenia (11.4%). Grade ≥3 AEs were neutropenia (9.1%), leukopenia (9.1%), lymphopenia (6.8%), and erythema multiforme (6.8%). One patient with 480 mg had grade 5 AEs (Pneumocystis jirovecii pneumonia and Interstitial lung disease), while neither new grade 5 AEs nor new safety profiles were observed since the last data cutoff. As of the current data cutoff, 15 and 6 of 44 patients had been receiving TIR for more than one and three years, respectively, and 5 of the 6 patients continued receiving TIR, including 4 patients who were receiving 480 mg fasted. **Conclusions:** In conclusion, TIR showed long-lasting effectiveness in a subset of patients with a tolerable safety profile of rPCNSL. Clinical trial information: JapicCTI-173646. Research Sponsor: ONO PHARMACEUTICAL CO., LTD.

	All (N = 44)	320 mg QD (N = 20)	480 mg QD (N = 7)	480 mg fasted QD (N = 17)
ORR (CR + CRu + PR), n (%) [95% CI]	28 (63.6) [47.8–77.6]	12 (60.0) [36.1–80.9]	7 (100.0) [59.0–100.0]	9 (52.9) [27.8–77.0]
Complete response (CR + CRu), n (%) [95% CI]	16 (36.4) [22.4–52.2]	5 (25.0) [8.7–49.1]	4 (57.1) [18.4–90.1]	7 (41.2) [18.4–67.1]
Median TTR, months [range]	0.9 [0.3–1.3]	0.9 [0.3–1.3]	0.9 [0.3–1.0]	0.9 [0.8–1.0]
Median DOR, months [range]	9.2 [0.6–45.9]	3.7 [0.6–45.9]	10.2 [0.6–28.8]	12.1 [0.9–38.7]
Median PFS, months [95% CI]	2.9 [1.8–11.1]	2.1 [1.8–18.2]	11.1 [1.4–22.0]	5.8 [1.0–13.0]
Median OS, months [95% CI]	Not reached [21.0–NE]	37.9 [11.2–NE]	Not reached [1.4–NE]	Not reached [5.5–NE]

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Poster Session

Circulating tumor DNA (ctDNA) by clonoSEQ to monitor residual disease after axicabtagene ciloleucel (axi-cel) in large B-cell lymphoma (LBCL). *First Author: Brodie Miles, Kite, a Gilead Company, Santa Monica, CA*

Background: Most patients (pts) with LBCL respond to axi-cel, but many will eventually experience disease progression (Jacobson et al. JCO. 2020). Monitoring of ctDNA from blood, a minimally invasive diagnostic tool, has been used to assess measurable residual disease (MRD) with prognostic value, including in pts with diffuse LBCL treated with axi-cel in the third line of therapy (3L; Frank et al. JCO. 2019). Here, we explored the value of ctDNA to predict outcomes in LBCL after axi-cel across lines of treatment. **Methods:** Pts with LBCL from ZUMA-12 (Phase 2 axi-cel in 1L), ZUMA-7 (Phase 3 axi-cel or standard of care [SOC] in 2L), and ZUMA-14 (Phase 2 axi-cel + rituximab in 3L) were included. All studies included initial MRD testing ≈30 days post axi-cel infusion. ClonoSEQ MRD assay (limit of detection=0.0001%-0.00001%) was used to define the lymphoma B-cell clonotype in formalin-fixed, paraffin-embedded (FFPE) biopsy tissue prior to axi-cel infusion and to track ctDNA in blood after treatment. Positive predictive value (PPV; MRD+ pts who relapsed or were nonresponders/total MRD+ pts ×100) and negative predictive value (NPV; MRD- pts in ongoing response/total MRD- pts ×100) were assessed at Day 28, Month (Mo) 3, and Mo 5 for 3L; Days 50, 100, 150, Mo 9, and Mo 24 for 2L; and Day 28, Mo 3, and Mo 6 for 1L. **Results:** In 3L, the PPV at Day 28 was 88% (7/8) and NPV was 83% (10/12). NPV remained 83% at Mo 3 (10/12) and increased to 100% (8/8) at Mo 5. Overall, 83% (5/6) of relapsed pts had MRD detected at any time; of those 5, 100% (5/5) had MRD detected at any time prior to or at progression with a median detection of 43 days prior to progression. In 2L, the MRD+ detection rate among evaluable pre-infusion samples was only 69% (11/16). At Day 50, PPV was 100% (7/7) in the SOC arm, whereas it was only 57% (4/7) in the axi-cel arm. PPV increased over time in the axi-cel arm, reaching 100% by Mo 9 (2/2). At Day 50, NPV was 53% (8/15) in the axi-cel arm and 38% (5/13) in the SOC arm. Overall, 47% (9/19) of relapsed pts on the axi-cel arm had MRD detected at any time; of those 9, 78% (7/9) had MRD detected prior to or at progression with a median of 35 days prior to progression. In 1L, most pts (11/14) remained in ongoing response by data cut off. The PPV at Day 28 was 50% (1/2): of the two pts who had detectable MRD at Day 28, one subsequently became MRD negative at Mo 3 yet relapsed just after Mo 3, while the second became negative by Mo 3 and had ongoing response up to Mo 24. The NPV at Day 28 was 88% (7/8). **Conclusions:** The prognostic value of MRD assessment by clonoSEQ varied across lines of therapy in pts with LBCL treated with axi-cel. A relatively high rate of undetectable MRD at baseline in the 2L setting and prior to relapse in the 2L and 1L settings warrants exploration of more sensitive ctDNA monitoring methods. Clinical trial information: NCT03391466 NCT03761056 NCT04002401. Research Sponsor: Kite, a Gilead Company.

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Poster Session

Glofitamab + Pola-R-CHP in patients with previously untreated diffuse large B-cell lymphoma (DLBCL): Results from a phase Ib study. *First Author: Michael Dickinson, The Peter MacCallum Cancer Centre, Royal Melbourne Hospital and The University of Melbourne, Melbourne, Vic, VIC, Australia*

Background: Polatuzumab vedotin plus rituximab, cyclophosphamide, doxorubicin and prednisone (Pola-R-CHP) has shown a significant progression-free survival benefit versus R-CHOP as first line (1L) therapy for DLBCL (Tilly et al. 2022). Glofitamab is a bispecific antibody with a novel 2:1 (CD20:CD3) format; bivalency for CD20 on B cells enables combination with anti-CD20 antibodies, including rituximab. Glofitamab monotherapy induced durable responses in patients (pts) with relapsed/refractory DLBCL and its incorporation in the 1L setting may further improve outcomes (Dickinson et al. 2022). We present results from the expansion stage of an ongoing Phase Ib study (NCT03467373) of glofitamab (Glofit) + Pola-R-CHP in pts with 1L DLBCL. **Methods:** Pts received Pola-R-CHP on Day (D) 1 of each 21-day cycle (C; max. 6 cycles) and glofitamab in C2–C6 (C2 step-up dosing [2.5mg CD28, 10mg CD215]; target dose [30mg] C3D8 and onwards). Response was assessed by PET-CT using Lugano criteria (Cheson et al. 2014). Efficacy-evaluable pts were those that reached end of treatment (EOT), progressed or died by data cut-off (EOT population). Cytokine release syndrome (CRS) events were graded by ASTCT criteria (Lee et al. 2019) and other adverse events (AEs) by CTCAE (v4.0). **Results:** As of Nov 14, 2022, 24 pts had enrolled and received study treatment (safety population). Median age was 65 years (range: 32–85), 96% of pts had stage III–IV disease and median IPI score was 3 (IPI 1: 4% [1/24], IPI 2: 33% [8/24], IPI 3: 38% [9/24], IPI 4: 25% [6/24]). Of 24 pts, 17 were efficacy evaluable. After a median follow up of 5.1 (range: 3–8) months, complete metabolic response rate was 76.5% (13/17) and overall response rate was 100% in the EOT population (best overall response). In safety-evaluable pts, Grade (Gr) ≥3 AEs occurred in 15 (63%) pts and Gr ≥3 AEs related to glofitamab in 9 (38%) pts. One Gr 5 AE was reported (acute respiratory distress syndrome, unrelated to study treatment). Serious AEs (SAEs) were reported in 12 (50%) pts and SAEs related to glofitamab in 4 (17%) pts. AEs leading to glofitamab dose interruption occurred in 5 (21%) pts; median dose intensity was 100% for all Glofit + Pola-R-CHP components. Only Gr 1 CRS (n = 3, 13%) was reported, with no treatment or hospitalization required. Neurological AEs (NAEs) occurred in 11 (46%) pts and were mostly Gr 1/2 (10 pts, 42%); one patient had a Gr 3 NAE (hypomania). No NAEs potentially consistent with immune effector cell-associated neurotoxicity syndrome were reported. Neutropenia was reported in 12 (50%) pts (Gr 3, n = 6; Gr 4, n = 6), febrile neutropenia in 2 (8.3%) pts and Gr 3/4 infection in 4 (17%) pts (Gr 3, n = 2; Gr 4, n = 2). **Conclusions:** Early data suggest that Glofit + Pola-R-CHP has promising efficacy and a similar safety profile to Pola-R-CHP and Glofit + R-CHOP for 1L DLBCL treatment. Glofit + Pola-R-CHP dose intensity was maintained in all pts. Updated data will be presented. Clinical trial information: NCT03467373. Research Sponsor: This study was sponsored by F. Hoffmann-La Roche Ltd. Third-party medical writing assistance, under the direction of all authors, was provided by Dikeledi Mathebjeane, MSc of Ashfield MedComms, an Inizio company, and was funded by F. Hoffmann-La Roche Ltd.

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Poster Session

Glofitamab monotherapy in pts with relapsed/refractory (R/R) large B-cell lymphoma (LBCL): Extended follow-up and landmark analyses from a pivotal phase II study. *First Author: Lorenzo Falchi, Lymphoma Service, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Glofitamab is a CD3xCD20 bispecific antibody delivered in a fixed course of 12 three-weekly cycles. In a Phase II study (NCT03075696), glofitamab induced high complete response (CR) rates and had manageable toxicity in pts with R/R LBCL (Dickinson et al. 2022). We present an extended follow-up and a landmark analysis to assess the outcomes of pts in CR. **Methods:** Pts with LBCL and ≥ 2 prior therapies received 1000mg obinutuzumab pretreatment 7 days prior to the first glofitamab dose. IV glofitamab was given as step-up doses: 2.5mg on Day (D) 1 of Cycle (C) 1, 10mg on C1D8 and 30mg (target dose) on D1 of C2–12 (21-day cycles). The primary endpoint was independent review committee (IRC)-assessed CR rate. PFS and OS post-hoc analyses were performed in responders (landmark for CR at C3 or end of treatment [EOT]). **Results:** As of Oct 10, 2022, 154 pts had received ≥ 1 dose of study treatment; baseline characteristics were as previously presented. Median number of prior therapies was 3 (range: 2–7); 33% had received prior CAR T-cells and 85% were refractory to their most recent regimen. Median time on study was 20.1 months (range: 0–32). The investigator (INV)-assessed CR rate (BOR) was 38% (40% by IRC) and overall response rate was 59% (52% by IRC). CR rates were consistent in pts with and without prior CAR-Ts (37% vs 39%). After a median follow-up of 18.3 months (range: 0–30) in pts with a CR (BOR), most CRs (39/59; 66%) were ongoing. Median duration of CR (DoCR) was 24.1 months (95% CI: 19.8–NE); an estimated 70% of pts with a CR at any time remained in remission at 18 months. The 18-month OS rate was 41% (95% CI: 32.1–49.3). Landmark analyses at 1 year in pts with a CR pre-C3 (PFS rate: 71%, OS rate: 92%) and in pts with a CR at EOT (PFS rate: 80%, OS rate: 94%) showed that most pts were progression free and alive. In a cohort of 101 pts treated with glofitamab doses below the recommended Phase II dose but ≥ 10 mg with longer median CR follow-up (31 months, range: 1–49), the median DoCR was 30.1 months (95% CI: 5.5–NE) and 55% of pts were still in remission at data cut-off. This further confirms the highly durable responses achieved with glofitamab. CRS (by ASTCT) remained the most common adverse event (AE), occurring in 64% of pts, and was mostly Grade (Gr) 1 (48%) or Gr 2 (12%); Gr 3 (3%) and Gr 4 (1%) events were uncommon. The incidence of AEs and serious AEs was stable compared with earlier analyses, with one new Gr 3 AE (acute kidney injury), one new Gr 2 neurologic AE (agitation) and no new glofitamab-related Gr 5 AEs reported. **Conclusions:** Glofitamab continued to demonstrate durable responses, with most pts in CR at EOT still in remission without new AEs. These data support the potential for favorable long-term outcomes with fixed-duration glofitamab for R/R LBCL. Updated analyses, including a larger population with a median CR follow up of approximately 20 months post-EOT, will be presented. Clinical trial information: NCT03075696. Research Sponsor: NP30179 is sponsored by F. Hoffmann-La Roche Ltd. Third-party medical writing assistance, under the direction of all authors, was provided by Dikeledi Mathebjeane, MSc of Ashfield MedComms, an Inizio company, and was funded by F. Hoffmann-La Roche Ltd.

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Poster Session

Real-world outcomes with novel therapies in R/R DLBCL. *First Author: Jennifer Leigh Crombie, Dana-Farber Cancer Institute, Boston, MA*

Background: Outcomes have historically been poor for patients with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL). Despite an increase in approved R/R DLBCL treatment options, clinical outcomes of these therapies remain less certain. Novel treatments for R/R DLBCL patients include chimeric antigen receptor T-cell (CAR T) therapy, polatuzumab vedotin plus bendamustine and rituximab (pola-BR), tafasitamab plus lenalidomide (tafa-len), loncastuximab (lonca), and selinexor. The objective of this study was to examine real-world outcomes of these novel therapies. **Methods:** US patient data from the COTA electronic health records database (2010–2021) were used for this retrospective study. Patients had a diagnosis of DLBCL after 1/1/2010, with ≥ 1 prior line of systemic antineoplastic therapy (including an anti-CD20 antibody), and treatment with any of these novel therapies. Patients receiving variations of pola-BR or tafa-len regimens were included. Outcomes included overall response rate (ORR), complete response (CR) rate, median progression-free survival (mPFS), and median overall survival (mOS). Outcomes were also analyzed for those treated with any novel therapy following prior CAR T exposure. **Results:** A total of 175 R/R DLBCL patients were included (median age 63 y, 60.6% male, median of 2 prior therapies); 29.1% had an international prognostic index score ≥ 3 , 61.7% had stage III/IV disease, and 65.7% had primary refractory disease. A total of 73, 69, and 27 patients were treated with CAR T, pola-BR, and tafa-len regimens, respectively. Only 6 patients were treated with lonca and no patients received selinexor. Among 169 patients treated in the 2L+ setting with tafa-len, pola-BR, and CAR T, the CR rate was 11.1%, 18.8%, and 52.1%, respectively (Table). A total of 112 patients were treated in the 3L+ setting with CR rate of 10.0%, 13.5%, and 41.8%, for tafa-len, pola-BR, and CAR T, respectively. Outcomes in the 18% of patients treated with any novel agent following CAR T exposure were ORR of 19.1%, CR of 4.8%, and mPFS and mOS of 1.4 mo and 2.3 mo, respectively. **Conclusions:** Outcomes of pola-BR and tafa-len regimens in the 2L+ and 3L+ R/R DLBCL setting remain suboptimal, with worse outcomes as patients advance through lines of therapy. Outcomes are particularly poor when these agents are used following CAR T therapy. Research Sponsor: This study was funded by Genmab A/S and AbbVie.

Clinical outcomes by line of therapy and treatment type.

	Treatment in the 2L+ setting			Treatment in the 3L+ setting		
	CAR T (n=73)	Pola-BR (n=69)	Tafa-len (n=27)	CAR T (n=55)	Pola-BR (n=37)	Tafa-len (n=20)
Outcome (95% CI)						
ORR (%)	76.7 (65.4, 85.8)	59.4 (46.9, 71.1)	40.7 (22.4, 61.2)	74.6 (61.0, 85.3)	62.2 (44.8, 77.5)	35.0 (15.4, 59.2)
CR (%)	52.1 (40.0, 63.9)	18.8 (10.4, 30.1)	11.1 (2.4, 29.2)	41.8 (28.7, 55.9)	13.5 (4.5, 28.8)	10.0 (1.2, 31.7)
mPFS (mo)	6.7 (4.0, 10.0)	3.1 (1.9, 3.8)	1.9 (0.8, 3.5)	5.6 (2.9, 7.4)	3.4 (2.1, 4.4)	1.7 (0.7, 4.4)
mOS (mo)	26.5 (13.6, NE)	7.8 (5.6, 11.4)	6.3 (1.6, 16.2)	17.8 (9.6, NE)	7.4 (4.3, 10.9)	6.3 (1.6, 16.2)

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Poster Session

A phase 1a/b study of BR101801, a PI3K γ and DNA PK triple inhibitor, in adult patients with advanced hematologic malignancies. *First Author: Bong-Seog Kim, Boryung Corporation., Seoul, South Korea*

Background: BR101801, a triple inhibitor of PI3K γ and DNA PK, inhibits not only the signal affecting cell growth caused by PI3K γ but also efficiently induces cell cycle arrest and apoptosis through inhibition of DNA-PK activation, and finally decreases the stability of oncogenic protein, c-Myc(AACR2020 abstract #655). We initiated a first-in-human study to investigate BR101801 across advanced hematologic malignancies that had relapsed or was refractory to the standard therapies. **Methods:** This is a phase 1, open-label, multi-center, dose escalation (1a), and expansion (1b) study of BR101801 in adult patients with advanced hematologic malignancies including relapsed/refractory (R/R) B-cell lymphoma, CLL/SL, and PTCL (NCT04018248). Dose was escalated at 50, 100, 200 and 325 mg QD. PTCL-NOS, AITL, FTCL and Nodal PTCL with TFH phenotype were included for dose expansion study at 200mg as RP2D. **Results:** 12 patients with advanced hematologic malignancies were enrolled in phase 1a study and treated with 50-325mg of BR101801. The median age was 63 years (range 30-76 years). Histological subtypes include AITL (n = 5, 41.7%), PTCL-NOS (n = 3, 25.0%), DLBCL (n = 2, 16.7%), MZL (n = 1, 8.3%) and MF (n = 1, 8.3%). Of 7 evaluable patients with PTCL (PTCL-NOS and AITL), ORR was 42.9% (95% CI, 9.9-81.6) and CBR was 85.7% (95% CI, 42.1-99.6). In median follow-up duration of 22.5 months, mPFS was 22.2 months (95% CI, 3.6-22.2) and mOS has not yet reached. Duration of response of the 3 responders were 9.2, 14.1+ and 20.7+ months, respectively. Safety was analyzed in 12 patients. 10 patients (83.3%) experienced ≥ 1 ADRs. The most common ($\geq 10\%$) ADRs were Rash (33.3%), ALT increased (33.3%), AST increased (25.0%), and Diarrhea (16.7%). Grade 3 ADRs occurred in 6 patients (50.0%) and those were ALT increased (25.0%), AST increased (16.7%), Rash (16.7%), erythema multiforme (8.3%), and neutropenia (8.3%). All ADRs were manageable and has recovered. There were no Grade 4 or 5 ADRs and no treatment related death observed. DLTs were occurred at 325mg; thus, 200mg QD was determined as the MTD and RP2D. The pharmacokinetics data showed an ideal profile in general. The PK results did not remarkably deviate from the non-clinical studies, and a more thorough interpretation will be performed in phase 1b. In phase 1b study, 7 PTCL patients were enrolled and it is ongoing till enrollment of total 12 patients. **Conclusions:** The results for the phase 1a study evaluated the safety, efficacy results and pharmacokinetic characteristics, 200 mg QD was shown to provide target exposure for clinical efficacy with the tolerable and safe profile. BR101801 showed of antitumor activity, especially in R/R PTCL patients. Hence, the phase 1b study of BR101801 is warranted in R/R PTCL patients and we expect BR101801 would become a promising therapeutic option for these patients. Clinical trial information: NCT04018248. Research Sponsor: Boryung.

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Poster Session

Safety and efficacy profile of a very low dose of MC-1-50 for treatment of r/r NHL. *First Author: Shiqi Li, 920th Hospital of Joint Logistics Support Force of People's Liberation Army of China, Kunming, China*

Background: CD19 chimeric antigen receptor (CAR) T cell therapy has shown promising efficacy in the r/r B-NHL. However, many patients fail to respond, or quickly relapse after the initial response. To improve efficacy, we established a novel PrimeCAR platform (PRIMCAR) that shortens the manufacture time to about 2 days and enriches more stem cell-like memory T (T_{scm}) cells in the product. The MC-1-50 CAR-T cells produced by the PRIMCAR platform have exhibited a promising efficacy for B-ALL (Shiqi Li, et al. J Clin Oncol 2022; 40 [suppl 16]. Abstract 7008). Here, we report the preliminary safety and efficacy data of MC-1-50 for r/r B-NHL. **Methods:** In this Phase I/II study (NCT04271410), MC-1-50 CAR T cells were manufactured by the PRIMCAR platform. T cells were infected with a lentiviral vector encoding a humanized CD19 specific scFv following 4-1BB and CD3 ζ cytoplasmic domain. Patients (pts) received single-dose of MC-1-50 at dose ranged 0.5-5 $\times 10^5$ CAR+/kg (Level 1, 0.5 $\times 10^5$ CAR+/kg; Level 2, 3 $\times 10^5$ CAR+/kg; Level 3, 5 $\times 10^5$ CAR+/kg). Pts were pre-conditioned with fludarabine (25-30 mg/m²) and cyclophosphamide (200-300 mg/m²) daily for 3 days. Toxicity was graded by CTCAE, CRS and ICANS were graded by ASTCT criteria. Primary endpoints are the dose-limiting toxicities (DLTs) rate in the first 28 d and safety to determine a recommended Phase II dose (RP2D). **Results:** As of May 2022, thirteen pts with r/r B-NHL were infused with MC-1-50. Disease characteristics and outcomes are shown in the table. No DLTs were reported. 3 pts (23.08%) experienced CRS, including 2 (15.38%) at grade 1, and 1 (7.69%) at grade 2, no ≥ 3 CRS were observed, and no ICANS occurred. A preliminary dose-dependent response was observed. At dose Level 1 (DL1), none of the 3 patients showed a good response. At DL2, two patients showed PR response, and 3 of the 5 patients achieved CR response. At DL3, 5 of 5 patients achieved CR response. These patients with CR response did not experience a relapse during the followed-up (ranging from 5-18 months). CAR-T expansion was observed in all dose levels, although long-term persistence cannot be evaluated yet, 4 of 5 patients in DL2 and 3 of 5 patients in DL3 had detectable CAR expression by qPCR (≥ 50 copy/ug DNA) in the 6-month follow-up. **Conclusions:** The PRIMCAR platform could produce CAR T cells quickly with a high percentage of T_{scm} . Treatment of r/r B-NHL at very low dose resulted in excellent safety profiles while exhibiting a high and durable efficacy. Clinical trial information: NCT04271410. Research Sponsor: ChongQing Precision Biotech Co., Ltd.

Disease characteristics and safety outcomes.

ID	Age	Gender	Lymphoma type	Disease stage	Dose level ($\times 10^5$ /kg)	CRS	ICANS
NHL01-01	29	M	DLBCL	IV	0.5	2	/
NHL01-02	45	F	DLBCL	IV	0.5	1	/
NHL01-03	63	M	CLL	IV	0.5	/	/
NHL02-01	64	M	FL	III	3	/	/
NHL02-02	62	M	FL	IV	3	/	/
NHL02-03	72	M	DLBCL	II	3	/	/
NHL02-04	64	M	MCL	IV	3	/	/
NHL02-05	52	M	HGBL	IV	3	/	/
NHL03-01	78	M	MCL	IV	5	/	/
NHL03-02	49	M	MCL	III	5	1	/
NHL03-03	46	F	DLBCL	IV	5	/	/
NHL03-04	46	M	FL	III	5	/	/
NHL03-05	67	M	DLBCL	IV	5	/	/

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Poster Session

Phase II trial of split-dose R-CHOP for older patients with diffuse large B-cell lymphoma (DLBCL). *First Author: Nirav Niranjan Shah, Medical College of Wisconsin, Milwaukee, WI*

Background: Management of elderly DLBCL is limited by age associated comorbid conditions and decreased tolerance of chemotherapy regimens. Many elderly or unfit/frail patients (pts) with DLBCL receive either non-anthracycline based treatment (bx) or attenuated regimens such as Rituximab (R)-miniCHOP which is ~50% dose reduction from standard R-CHOP-21. Split-dose (SD) R-CHOP is an alternative approach where pts receive CHOP at a 50% dose reduction on Days 1 and 15 of each 28-day cycle with full dose Rituximab on Day 1 for 6 cycles. The cumulative dose of SD R-CHOP delivered over each 28 day cycle is equivalent in dose intensity to one cycle of standard R-CHOP-21. **Methods:** This is a Phase II, prospective, open label study conducted through the Wisconsin Oncology Network and included two academic centers (NCT03943901). Older pts aged ≥75 years or 70-74 years plus elevated cumulative illness rating scale for geriatrics score with untreated de-novo or transformed Stage IIX-IV DLBCL were eligible. Treatment consisted of two months (4 doses) of SD R-CHOP with growth factor support followed by interim response assessment with PET/CT and peripheral blood cell-free clonoSEQ minimal residual testing (MRD). Pts with interim PET/CT score of Deauville 1-3 and MRD negativity were offered abbreviated therapy with two additional months of SD-R-CHOP. All others completed 6 cycles. The primary endpoint was end of tx (EOT) complete response (CR) rate. We utilized a Simon 2-stage design with interim analysis requiring at least 8 EOT CR in the first 16 pts (Stage I) to proceed to stage II. **Results:** To date, 14 pts have completed tx. The median age was 81 years (73-88) and 57% (n = 8) were male. Most pts had stage 4 disease (n = 8, 57%). 8 of 14 pts were interim PET/CT negative and 8 of 12 MRD evaluable pts were interim MRD negative. 10/14 (71%) pts achieved EOT CR exceeding our minimal threshold to continue the study early. The remaining 4 pts had progressive disease (PD) either during tx or at EOT evaluation. 6 pts were both interim MRD and PET negative; 5 de-escalated to the abbreviated arm with all achieving CR with no relapses to date. 7 pts (50%) had Grade 3+ non-hematologic toxicities and 4 pts (29%) had Grade 3-4 neutropenia. There were 2 deaths, one from COVID-19 with concurrent PD and the other from PD. Median PFS or OS have not been reached with a median follow-up of 13 months for surviving pts. **Conclusions:** SD-R-CHOP offers older pts with DLBCL equivalent dose intensity as R-CHOP-21 through a fractionated dosing schedule improving tolerability. Prespecified interim efficacy endpoint was met early with 10/14 pts with EOT CR. Interim stratification by MRD and PET/CT allowed de-escalation of tx in early responding pts without compromising efficacy. Clinical trial information: NCT03943901. Research Sponsor: Froedtert Foundation Grant; Adaptive Biotechnology.

Outcome Data	N = 14 pts
Interim MRD status	MRD Neg = 8 pts MRD Pos = 2 pts MRD N/A = 2 pts
Interim PET Response	CR = 8 pts PR = 6 pts
EOT MRD Status	MRD Neg = 9 pts MRD Pos = 3 pts MRD N/A = 2 pts
EOT PET Response	CR = 10 pts PD = 4 pts

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Poster Session

Evaluation of outcomes between rituximab-abbs and reference product rituximab in adult patients with newly diagnosed diffuse large B-cell lymphoma in a non-inferiority study. *First Author: Vivian Nguyen, Kaiser Permanente, San Diego, CA*

Background: Rituximab in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) is the standard of care for diffuse large B-cell lymphoma (DLBCL). However, adding rituximab has increased treatment costs. Thus, development of biosimilars help provide more affordable care. Though rituximab-abbs was studied primarily in the follicular lymphoma population, in 2018 the FDA approved this drug as the first biosimilar for all indications of the reference product based on extrapolation. However, there are no clinical trials studying the effectiveness and safety of rituximab-abbs in DLBCL in the U.S. **Methods:** This is a data-only, non-inferiority study to compare two-year overall survival (OS) and the incidence of serious adverse events (AEs) between rituximab-abbs and its reference product (RP) as R-CHOP among adult patients with newly diagnosed DLBCL, with an index date from December 1, 2018-December 31, 2020. Non-inferiority will have a margin set to the upper limit of 5% for serious AEs, and a lower limit of 5% for OS. To assess for safety, we are following up on AEs until end of patient's Kaiser Permanente (KP) membership, death, six months after last rituximab dose, or December 2022 for all AEs except infusion reactions. For infusion reactions only, the follow up is 1 day. To assess for efficacy, we are following up on OS until end of patient's KP membership, death, December 2022, or two years. **Results:** 535 patients were enrolled; 240 patients received RP rituximab and 295 patients received rituximab-abbs. The median time of follow up was 730 days, or 2 years (range in days, 2.0-730). Complete response was similar in the RP rituximab group and the rituximab-abbs group (70.4% vs. 77.3% respectively, p = 0.07). Additionally, partial response was also similar among the two products (19.2% vs. 16.9%, p = 0.51). The Kaplan-Meier two-year survival curve was also similar between the two products (p = 0.52), demonstrating no difference. Further statistical analysis confirmed the non-inferiority of the biosimilar products for survival. Infusion reaction adverse events (13.8% vs. 11.2%, p = 0.37) and non-infusion adverse events (68.3% vs. 71.2%, p = 0.47) were also similar in the two groups, with a survival curve demonstrating no difference between the two products and data analysis meeting the non-inferiority criteria. **Conclusions:** Rituximab and rituximab-abbs are non-inferior to each other in both efficacy and safety. Long term follow up would be needed to confirm these results. Research Sponsor: None.

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Poster Session

Six-year safety and efficacy results from the CHRONOS-1 study of the PI3K inhibitor copanlisib in patients with relapsed or refractory follicular lymphoma. *First Author: Martin H. Dreyling, LMU University Hospital, Munich, Germany*

Background: The efficacy of copanlisib, an intravenous pan-class I phosphatidylinositol 3-kinase (PI3K) inhibitor, was demonstrated in the Phase II CHRONOS-1 study in patients with relapsed or refractory indolent B-cell lymphoma (Dreyling et al. *J Clin Oncol* 2017). Copanlisib was approved by the US Food and Drug Administration in 2017 for the treatment of patients with follicular lymphoma (FL) who have received ≥2 therapies. Here, we describe updated efficacy and safety data from patients with FL at the 6-year follow-up of CHRONOS-1. **Methods:** CHRONOS-1 included patients with relapsed or refractory indolent FL (grades 1-3a) who had received ≥2 lines of therapy. Copanlisib 60 mg was administered via intravenous infusion on days 1, 8, and 15 of a 28-day cycle. Objective tumor response rate (ORR) was assessed by independent radiologic review (Cheson et al. *J Clin Oncol* 2007) as the primary efficacy endpoint. Safety analysis included adverse events graded using CTCAE v4.03. **Results:** 104 patients with FL were treated in CHRONOS-1, of whom 99.0% (n = 103) discontinued treatment at the time of database cut-off on June 30, 2022. 72% of patients (n = 75) received ≥1 line of subsequent systemic anti-cancer therapy during follow-up, with 40% receiving a rituximab-based regimen. At the cut-off, ORR (primary endpoint) was 57.7% (n = 60), with 19.2% (n = 20) of patients achieving a complete response. Median duration of response was 12.2 months (range 1.1-48.1). Median progression-free survival (PFS) was 11.2 months (range 0.2-51.5) with a median follow-up of 20.7 months (95% confidence interval [CI] 11.5, 31.5); PFS rate was 32% at 2 years. Median overall survival was 46.3 months (range 0.7-82.9) with a total of 56 events and a median follow-up of 82.4 months (95% CI 79.3, 84.9); survival rate was 43% at 6 years. Median duration of treatment was 6.0 months (range 0.23-80.9). No patients experienced transformation to aggressive lymphoma (diffuse large B-cell lymphoma). The primary reasons for stopping treatment included radiologic disease progression (42.3%; n = 44) and adverse events not associated with clinical disease progression (29.8%; n = 31). The safety profile was consistent with the reported 2-year follow-up data (Dreyling et al. *Am J Hematol* 2020). The most common treatment-emergent adverse events (all grades/grades 3-4) were infusion-related hyperglycemia (50.0%/39.5%), diarrhea (36.5%/8.7%), hypertension (28.8%/23.1%), pyrexia (27.9%/4.8%), and neutropenia (26.0%/23.0%). **Conclusions:** Copanlisib continued to induce robust response and durable survival in patients with relapsed or refractory indolent FL at 6 years of follow-up. Copanlisib was well tolerated, with no new safety signals and no evidence of malignant transformation. These results further support the long-term use of copanlisib in this patient population. Clinical trial information: NCT01660451. Research Sponsor: Funded by Bayer AG, medical writing support provided by Complete HealthVizion.

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Poster Session

First interim analysis of a phase 1 study of zanubrutinib (zanu) plus lenalidomide (len) in patients (pts) with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL). *First Author: Huilai Zhang, Tianjin Medical University Cancer Institute & Hospital, Tianjin, China*

Background: Effective therapies for R/R DLBCL are limited in China, especially for pts ineligible for high-dose therapy/stem cell transplantation (HDT/SCT). Preclinical data suggest synergy of len with zanu, a potent and selective Bruton tyrosine kinase inhibitor approved for various B-cell malignancies. Here, we present interim analysis results of an ongoing phase 1, open-label, dose-escalation/expansion study of zanu + len in R/R DLBCL (NCT04436107). **Methods:** Pts with R/R DLBCL ineligible for HDT/SCT with ≥1 prior line of adequate systemic therapy were enrolled. Dose escalation (part 1): Len 15 mg, 20 mg, or 25 mg orally once daily on days 1-21 of each 28-day cycle. Dose expansion (part 2): Len 25 mg. Zanu 160 mg was given orally twice daily continuously in parts 1 and 2. Primary endpoints were safety and recommended phase 2 dose (RP2D) of len (part 1) and overall response rate (ORR) by investigator based on Lugano classification (part 2). Interim analysis was performed when the 19th pt in part 2 completed first tumor assessment. Pts who received len 25 mg (RP2D) in parts 1 and 2 were analyzed separately. **Results:** As of November 8, 2022, 46 pts were treated and included in interim analysis (27 in part 1; 19 in part 2; 30 at RP2D). Median age was 60 years (range, 29-82), 83% had stage III-IV disease, 37% had refractory disease, 70% had non-germinal center B-cell (non-GCB) like disease; median number of prior systemic therapies was 1 (range, 1-5). Median exposure to zanu and len was 3.9 months (mo) (range 0.4-24.9), median follow-up was 6.6 mo (range 0.5-25.5). ORR was 46% overall (95% CI: 30.9-61.0; complete response [CR]: 24%) and 57% at RP2D (95% CI: 37.4-74.5; CR: 30%). At RP2D, ORR was 61% (95% CI: 38.5-80.3; CR: 35%) for pts with non-GCB disease and 50.0% (95% CI: 11.8-88.2; CR: 17%) for GCB. At RP2D, median duration of response was not reached and 6-mo event-free rate was 59% (95% CI: 23.8-82.8). Median progression-free survival was 5.5 mo (95% CI: 2.8-not estimable) with a 9-mo event-free rate of 37% (95% CI: 17.6-57.4). Overall, 46 (100%) pts experienced ≥1 treatment-emergent adverse event (TEAE). At RP2D, grade ≥3 TEAEs occurred in 60% of pts, most commonly neutrophil count decreased (43%), white blood cell count decreased (23%), and pneumonia (13%). One pt (2%) had febrile neutropenia (grade 3) but recovered within 2 days. TEAEs led to discontinuation of both len and zanu in 2 pts (cardiopulmonary failure unrelated to treatment [part 1, len 20 mg], pulmonary embolism [part 1, len 25 mg]) and discontinuation of len in 2 pts (platelet count decreased [part 1, len 20 mg], rash [part 2]). Two TEAEs leading to death were reported, unrelated to treatment. **Conclusions:** Zanu 160 mg plus len 25 mg combination showed an acceptable safety profile with promising efficacy. Further evaluation of the combination in a larger sample size is planned in future analysis. Clinical trial information: NCT04436107. Research Sponsor: BeiGene.

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Poster Session

A phase 1 study evaluating the safety, tolerability, pharmacokinetics, and preliminary antitumor activity of Bcl-2 inhibitor BGB-11417 in adult patients with mature B-cell malignancies. *First Author: Caixia Li, The First Affiliated Hospital of Soochow University, Suzhou, China*

Background: BGB-11417 is a potent and highly selective Bcl-2 inhibitor. Phase 1 study results showing high activity and good tolerability in patients (pts) with mature B-cell malignancies were previously reported (Abstract 2989, ASH 2022). We present here results of BGB-11417 monotherapy in B-cell malignancies with a longer follow up. **Methods:** BGB-11417-102 (NCT04883957) is an ongoing, multicenter, phase 1, open-label, dose-finding study in China. Primary objectives: safety, maximum tolerated dose (MTD), and recommended phase 2 dose (RP2D) of BGB-11417 monotherapy for selected cohorts. Pts with relapsed/refractory (R/R) B-cell malignancies received escalating doses (80, 160, 320, or 640 mg once daily) with weekly or daily ramp-up to intended target dose. Dose-limiting toxicity (DLT) for each cohort was evaluated during ramp-up through day 21 at the intended dose. AEs were reported per CTCAE v5.0 (or Grading Scale for Hematologic Toxicity in chronic lymphocytic leukemia [CLL] Studies). **Results:** As of 1 Oct 2022, 54 pts (34 R/R non-Hodgkin lymphoma [NHL; 20 diffuse large B-cell lymphoma, 7 follicular lymphoma, 4 marginal zone lymphoma, 3 transformed NHL], and 20 R/R CLL/small lymphocytic lymphoma [SLL]) received $\leq$ 640 mg/d. 640mg was the highest dose pre-defined in the study and MTD was not reached. Median (range) values: age, 61 y (31-84); prior lines of systemic therapy, 2 (1-7); follow-up duration, 6.6 m (0.2-13.0). Study discontinuation: 23 pts (22 NHL; 1 CLL/SLL); reasons: 18 progressive disease, 4 withdrew, 1 investigator decision. Tx-emergent AEs (TEAEs): all grades, 92.6%; grade $\geq$ 3, 53.7%. Most common TEAE: all grades, white blood cell count decreased (48.1%); grade $\geq$ 3, neutropenia (25.9%). DLTs occurred in 3 patients at 80 mg/d or 160 mg/d; 14.8% had serious TEAEs and 14.8% had TEAEs leading to drug interruption. No pts had TEAEs leading to death/tx discontinuation or clinical tumor-lysis syndrome events. Of 39 pts available for tumor assessment (27 NHL; 12 CLL/SLL), 5 with NHL and 9 with CLL/SLL achieved responses (NHL: 3 partial responses [PR] at 160 mg/d, 1 PR at 320 mg/d, 1 complete response [CR] at 640 mg/d; CLL/SLL: 2 CR and 2 PR at 80 mg/d, 3 PR at 160 mg/d, 2 PR at 320 mg/d). Nine pts with R/R CLL/SLL (5 at 80mg/d, 4 at 160 mg/d) had minimum residual disease (MRD) assessment; 3 had undetectable MRD with CLL cell/total nucleated cells $< 10^{-4}$ (uMRD4; 1 pt achieved blood and bone marrow aspirate uMRD4 after 4.5 months at 80 mg/d; 2 pts had blood uMRD4 after 7.1 months at 160 mg/d). The monotherapy RP2D for R/R CLL/SLL was 320 mg/d. **Conclusions:** These results demonstrated that BGB-11417 monotherapy was well tolerated at all tested doses up to 640 mg/d, with no dose-dependent toxicity increase. BGB-11417 monotherapy showed promising initial efficacy results in R/R CLL/SLL, with pts achieving responses at lower dose levels. Clinical trial information: NCT04883957. Research Sponsor: BeiGene.

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Poster Session

Long-term efficacy and safety of pembrolizumab with R-CHOP as first-line therapy for DLBCL. *First Author: Carrie Ho, Fred Hutchinson Cancer Center, Seattle, WA*

Background: Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) represents the historical 1st line treatment standard for DLBCL but fails to cure about 1/3 of patients. While generally ineffective in relapsed DLBCL-NOS, checkpoint inhibitors may have greater promise in untreated, immunocompetent patients. We previously reported safety and early efficacy of pembrolizumab plus RCHOP, noting objective responses in 90% of patients (CR 77%) and a 2-year progression-free survival (PFS) of 83%. We now report 5 year follow up of our study. **Methods:** Patients age > 18 with untreated DLBCL or grade 3b follicular lymphoma, intended to receive 6 cycles of R-CHOP, were eligible. Pembrolizumab 200 mg IV with R-CHOP was given in 21-day cycles for 6 cycles. For this updated analysis, progression and survival events, and immune-related toxicities, are reported. Additionally, prognostic factors including tumor PD-L1 expression (Qualtek/Merck) were re-analyzed. **Results:** 30 patients were treated (13/30 with IPI 3-5). Median follow up is now 4.8 years (95% CI, 4.5-5.4). Since our initial report (Smith BJH 2019) we have observed 1 additional relapse (alive after CAR-T therapy) and 2 deaths in remission (1 urothelial carcinoma, 1 respiratory failure in the setting of progressive ILD). 5-year PFS is 71% (CI, 54-94%) and 5-year overall survival 83% (CI, 71-98%). During the study period and at long term follow up, there were 8 total immune-related adverse events (IRAEs) among 7 patients (23%) (Table). Four were treatment-emergent AE (occurred within 90 days of completing treatment): grade 1 hyperthyroidism, grade 2 hyperthyroidism, grade 3 pneumonitis, and grade 3 rash. There were 4 late IRAEs: colitis, paraneoplastic pemphigus, rheumatoid arthritis, and Graves' disease, occurring at 3, 5, 8, and 46 months after completing treatment, respectively. PD-L1 tumor expression was documented in 19 of 23 (83%) tested patients. At long-term follow up, none of the 19 patients who had any PD-L1 expression have relapsed. Two out of the 4 patients with no PD-L1 expression have relapsed. On univariate analysis, PD-L1 H-score > 0 ($p < 0.0001$) was associated with improved PFS. **Conclusions:** At 5 year follow-up, pembrolizumab plus R-CHOP has led to durable responses in most patients with the best outcomes in PDL1-expressing disease. Furthermore, the safety profile was manageable, with a low rate of grade 3 or higher IRAEs (10%) and no consistent pattern of late events. These data support ongoing strategies incorporating PD-1/PDL-1 inhibitors in 1st line DLBCL therapy and confirmation of predictive biomarkers including tumor PD-L1 expression. Clinical trial information: NCT02541565. Research Sponsor: Merck; U.S. National Institutes of Health.

IRAEs.		
Treatment-emergent IRAE	Any Grade, N (%)	Grade $\geq$ 3, N (%)
Hyperthyroidism	2 (6.7)	0
Rash	1 (3.3)	1 (3.3)
Pneumonitis	1 (3.3)	1 (3.3)
Late IRAE		
Rash (paraneoplastic pemphigus)	1 (3.3)	1 (3.3)
Colitis	1 (3.3)	0
Hyperthyroidism (Graves' Disease)	1 (3.3)	0
Rheumatoid arthritis	1 (3.3)	0

ABSTRACT
WITHDRAWN

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Poster Session

Updated clinical results of first-in-human study of CD19/BCMA dual-targeting fast CAR-T GC012F for patients with relapsed/refractory B-cell non-Hodgkin's lymphoma. *First Author: Xinfeng Chen, Biotherapy Center, the First Affiliated Hospital of Zhengzhou University, Zhengzhou, China*

Background: CD19-directed CAR-T cell therapy has been demonstrated to be a valuable treatment option for relapsed/refractory B-cell non-Hodgkin's lymphoma (r/r B-NHL). It has been shown that 39% to 97% of clinical samples of B-NHL also express BCMA. To further improve safety and efficacy, we have developed a CD19 and BCMA dual-targeting CAR-T, GC012F, manufactured on the novel next-day Fast CAR-T process, for the treatment of r/r B-NHL. The initial 3-patient data of an investigator-initiated trial (ChiCTR2100047061) was reported at EHA 2022 (#2938). Here, we present updated results of this ongoing IIT trial. **Methods:** From October 2021 to January 2023, nine eligible r/r DLBCL pts were enrolled and treated with a single infusion of GC012F in escalating dosing cohorts after a standard lymphodepletion regimen. The primary objectives of this study were safety and tolerability; the secondary were pharmacokinetics and efficacy. Cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) were graded by ASBMT 2019, adverse effects were evaluated according to CTCAE 5.0. Efficacy assessment of GC012F was referred to the Lugano criteria. Expansion of CAR-T cells and CAR copy numbers were measured by flow cytometry and qPCR, respectively. **Results:** As of data cut-off of January 16th, 2023, with a median of 207 days (range 94-460) of follow-up, all nine pts received single GC012F infusions at dose levels from 3.7×10^4 to 3×10^5 CAR-T/kg, and completed at least 3 months of follow-up. All pt lymphoma samples expressed CD19, and 6 out of 7 expressed BCMA. The median SPD was 2690.81 mm² (408.3-13325.96). Pts received a median of 2 prior lines (range 2-3) of therapy including rituximab and anthracyclines. Two pts received prior auto-HSCT. The ORR in nine pts was 100% (9/9) at month 3, CR rate was 77.8% (7/9) at month 3 and 71.4% (5/7) at month 6, respectively. To date, the longest duration of remission was 14.4 months. No dose-limiting toxicities were observed. One pt had grade 3 CRS over 2 days. No ICANS were observed. Of the 9 treated pts, $\geq$ grade 3 TEAEs were neutropenia (7/9), leukopenia (5/9) and thrombocytopenia (3/9). All TEAEs were resolved after treatment with standard of care and supportive care. The median peak copy number of CAR-T cells in peripheral blood was 71,000 copies/ μ g DNA (range 9263 -185,039), and the median peak time was 14 days (range 9 - 21). CAR-T cells were also detected in tumor biopsies from all five pts tested. **Conclusions:** This first-in-human trial of GC012F for the treatment of r/r B-NHL showed a manageable safety profile and promising clinical responses. The ORR was 100% at M3 with 77.8% (7/9) achieving CR. GC012F CAR-T cells were detectable in the tumor biopsies, indicating the infiltration of CAR-T cells into the tumor lesions. Study with larger cohort and longer follow-up is ongoing. Clinical trial information: ChiCTR2100047061. Research Sponsor: Gracell Biotechnology (Shanghai) Co., LTD.

A multi-institutional prospective cohort study of minimal residual disease in peripheral T-cell lymphoma: Impact of autologous stem cell transplant. *First Author: Nicole C. Foley, Washington University School of Medicine, St. Louis, MO*

Background: Roughly 80% of pts with peripheral T-cell lymphomas (PTCL) respond to CHOP-based therapy but 5-yr survival ranges between 20-40%. The high relapse rate after complete response (CR) suggests more sensitive response assessment, such as minimal residual disease (MRD) testing, could have prognostic or predictive value. Next generation sequencing (NGS) of the T-cell receptor (TCR) can detect a known TCR clonotype at 10^{-5} . In a prospective study, we evaluated the utility of MRD testing via TCR NGS in PTCL (NCT03297697). Here we report results for pts pre- and post-autologous stem cell transplant (ASCT). **Methods:** This investigator-initiated, multi-institutional, prospective cohort study assessed MRD testing by TCR NGS in PTCL. Pts with previously untreated PTCL not otherwise specified (NOS), angioimmunoblastic T-cell lymphoma (AITL), anaplastic large cell lymphoma (ALCL), PTCL with T-follicular helper (TFH) phenotype, or monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL) treated with anthracycline-based curative-intent therapy were eligible. Baseline TCR (TRG or TRB) clonotypes were established from diagnostic tissue or peripheral blood if tissue was not available. TCR clonality was determined positive via the LymphoTrack TRG/TRB Assays – MiSeq (Invivoscribe, San Diego, CA) when top % reads were $\geq 2.5\%$ and $\geq 2\times$ above background. Samples were obtained at diagnosis (pre-treatment), following induction therapy (EOT/pre-ASCT), and serially post-ASCT. **Results:** Of 43 enrolled pts, 19 underwent consolidative ASCT, of which 10 had post-ASCT samples available for MRD testing (Table). Median age at ASCT was 62 years (range: 38-77). Baseline TCR clonotypes were identified in 10/10 pts. At pre-ASCT evaluation, 7/10 pts had detectable TCR MRD ('pos') and 3/10 pts had TCR MRD below the level of detection ('neg'). Of the 3 MRD neg pts pre-ASCT, 2 had CR and 1 had PR by PET-CT. All 7 TCR MRD pos pts pre-ASCT had CR by PET-CT. Of 7 MRD pos pts pre-ASCT, 6 remained MRD pos and 1 became MRD neg post-ASCT. Of the 4 MRD neg pts post-ASCT, none have relapsed at 52, 31, 34, and 31 mo post-ASCT. Of 7 MRD pos pts pre-ASCT, 3 have relapsed following ASCT (at 3, 9, and 29 mo post-ASCT). **Conclusions:** In this cohort of patients with PTCL receiving consolidative ASCT in CR1, all 4 pts with negative TCR MRD post-ASCT remain in remission at median follow up of 32.5 mo post-ASCT. The negative predictive value of TCR NGS MRD post-ASCT should be further evaluated. Clinical trial information: NCT03297697. Research Sponsor: Lymphoma Research Foundation; T-cell Leukemia/Lymphoma Society.

Pt #	Age	Dx	Induction	Pre-ASCT MRD	Pre-ASCT PET/CT	Post-ASCT MRD	Relapse post-ASCT	Follow-up Post-ASCT (mo)
1	52	ALK-ALCL	CHOEP	-	PR	-	No	52
2	39	AITL	BV+CHP	-	CR	-	No	31
3	69	PTCL NOS	BV+CHP	-	CR	-	No	34
4	71	AITL	Aza + CHOP	+	CR	-	No	31
5	68	AITL	CHOEP	+	CR	+	No	51
6	77	AITL	Aza + CHOP	+	CR	+	Yes (3 mo)	10 (died)
7	70	MEITL	CHOEP	+	CR	+	Yes (9 mo)	11 (died)
8	68	PTCL NOS	CHOEP	+	CR	+	No	20
9	38	AITL	Aza + CHOP	+	CR	+	No	28
10	67	TFH PTCL	Aza + CHOP	+	CR	+	Yes (29 mo)	29

Treatments and outcomes of patients with localized extranodal NK/T-cell lymphoma (ENKL) diagnosed between 2014 and 2021: A cooperative study in Japan. *First Author: Kana Miyazaki, Mie University Graduate School of Medicine, Tsu, Japan*

Background: A previous cooperative study of patients (pts) with ENKL who were diagnosed between 2000 and 2013 in 31 institutes in Japan reported that the most common first-line treatment for localized ENKL was radiotherapy with dexamethasone, etoposide, ifosfamide, and carboplatin (RT-DeVIC) (66%). The 2-year (yr) overall survival (OS) and progression-free survival (PFS) of pts with localized ENKL were 78% and 68%, respectively (JCO 2017). RT-DeVIC has been included as a preferred regimen of combined modality therapy in the NCCN guidelines. The treatments and outcomes of pts with localized ENKL in recent clinical practice are unknown. **Methods:** We conducted a cooperative study (NKEA-Next; UMIN000046300) by hemato-oncologists and radiation oncologists of pts with ENKL who were diagnosed between 2014 and 2021 in 45 institutes in Japan. The results were compared with those from the 2000-2013 cohort (JCO 2017). The primary endpoint was OS of pts with ENKL who received next-generation treatment in 2014-2021 at participating institutes. We analyzed the data of localized ENKL. **Results:** Of 351 pts in the 2014-2021 cohort, 235 (67%) had localized ENKL. First-line therapy was RT-DeVIC in 185 (79%) pts, sequential chemoradiotherapy in 17, RT alone in 15 pts, and chemotherapy alone in 12 pts. Six pts received no treatment due to poor performance status (PS). Only two pts (1%) received anthracycline-containing regimens. With a median follow-up of 3.4 yrs, the 2-yr OS and PFS of localized ENKL were 83% and 75%, respectively. Pts treated with RT-DeVIC showed the following clinical features: median age, 58 yrs (range, 13-82); age > 60 yrs, 45%; stage IIE, 34%; B symptoms present, 27%; elevated serum lactate dehydrogenase, 23%; ECOG PS 2, 4%; and soluble interleukin-2 receptor (sIL-2R) level > upper limit of normal (ULN), 31% (57/183). The complete response rate was 88% among the 179 pts who were evaluated for response. The 2-yr OS and PFS of RT-DeVIC were 87% and 79%, respectively. There was no treatment-related death due to RT-DeVIC. G3/4 mucositis was recorded in 32% (G3, n = 59; G4, n = 0). G3/4 febrile neutropenia occurred in 18% (G3, n = 32; G4, n = 2). sIL-2R > ULN was associated with worse OS ($P < 0.01$). In comparison with pts with localized disease in the 2000-2013 cohort, pts in the 2014-2021 cohort received RT-DeVIC more frequently ($P < .001$). There was no significant difference in OS ($P = 0.24$) or PFS ($P = 0.10$) between the two cohorts. **Conclusions:** RT-DeVIC was more frequently used for first-line treatment of localized ENKL, and its efficacy has been maintained, with 87% 2-yr OS in recent clinical practice in Japan, providing further evidence of RT-DeVIC as a preferred first-line regimen for localized ENKL. No obvious improvement in OS and a reduction in G3 mucositis were observed, suggesting that more efficacious and less toxic regimens need to be introduced. Research Sponsor: the Japan Society for the Promotion of Science Grant-in-Aid for Scientific Research (JSPS KAKENHI) (26461418, 17K09924).

Impact of neighborhood deprivation on disability free survival in patients with aggressive B cell non-Hodgkin lymphoma. *First Author: Madelyn Burkart, Feinberg School of Medicine; Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Chicago, IL*

Background: Advancements in treatment over the last decade have greatly improved survival in B cell non-Hodgkin's lymphoma (NHL), yet not all patients (pts) benefit the same. Non-Hispanic Black (NHB), uninsured and lower socioeconomic status pts continue to suffer worse survival. However, the impact of neighborhood deprivation on disability has not been explored. We aimed to assess the association between neighborhood deprivation and disability free survival (DFS) in NHL pts. **Methods:** 258 aggressive NHL pts treated between 2005-2020 were included. Pts without documented follow up were excluded. Race/ethnicity was categorized as non-Hispanic white (NHW), Hispanic, NHB and other. Primary outcomes included progression free survival (PFS), overall survival (OS) and DFS. DFS was defined as time to needing any rehabilitative, home-health or skilled nursing services immediately following induction therapy, indicating disability and lack of functional independence. Neighborhood deprivation was assigned using the national Area Deprivation Index (ADI), a validated measure classifying neighborhood adversity. Pts were categorized into high (67-99), intermediate (34-66) or low (1-33) ADI scores, with least disadvantaged designated by lower scores. Kaplan-Meier analyses were used to compare PFS, OS and DFS. **Results:** Demographic data is shown in the table; 45% were female, 65% were NHW, 10% were NHB, 8% were Hispanic and 10% were other. Median age at diagnosis was 57 years. There was no difference in PFS or OS between racial/ethnic groups ($p=0.91$ and $p=0.23$ respectively). Payor source influenced both PFS and OS ($p<0.001$ and $p<0.001$ respectively), with self-pay associated with worse PFS and OS. Neighborhood deprivation based on ADI did not influence PFS ($p=0.33$) or OS ($p=0.76$). High ADI score was associated with worse DFS compared to lower ADI scores ($p=0.03$). ADI score differed significantly based on race/ethnicity ($p<0.0001$), with more NHB pts residing in areas of high ADI scores (40% vs 5% NHW vs 10% Hispanic). There was no association between ADI score and a pt's ECOG performance status, IPI score or albumin at diagnosis ($p=0.87$, $p=0.78$ and $p=0.59$ respectively). **Conclusions:** NHL pts with higher neighborhood adversity experience more disability after treatment despite similar survival. Further work is needed to better understand how neighborhood factors are contributing to disability before community-level strategies for improvement can be developed. Research Sponsor: None.

	Total N (N=258)	Low ADI (N=133)	Intermediate ADI (N=76)	High ADI (N=29)	P-value
Gender (%)					P=0.25
Male	142	57	34	9	
Female	116	62	53	13	
Age (%)					P=0.09
>= 60 years old	133	53	35	12	
< 60 years old	124	66	24	10	
Race/ethnicity (%)					P<0.0001
NHW	168	65	29	5	
NHB	25	24	36	40	
Hispanic	21	52	38	10	
Other	27	52	33	15	
Diagnosis (%)					P=0.69
DLBCL	197	99	51	10	
MCL	61	61	26	13	
IPI score (%)					P=0.78
Low	74	59	27	14	
Low-intermediate	89	61	31	8	
High-intermediate	54	54	31	15	
High	41	63	29	7	

Final analysis of the phase IB part of the LOC-R01 trial, a non-comparative randomized phase IB/II study of escalating doses of lenalidomide and ibrutinib in association with R-MPV for patients with a newly diagnosed primary central nervous system lymphoma (PCNSL). *First Author: Marion Alcantara, Institut Curie, Saint-Cloud, France*

Background: Results of conventional induction chemotherapies in PCNSL need to be improved. Ibrutinib, a BTK inhibitor, and lenalidomide, an immunomodulatory drug, have shown promising results in the relapse setting, supporting to further assess their combination with standard high-dose methotrexate-based chemotherapy. **Methods:** Patients (pts) with newly diagnosed PCNSL, aged 18 to 60, were randomized to receive four 28-day cycles of either ibrutinib or lenalidomide in combination with R-MPV (rituximab, methotrexate, procarbazine, vincristine and prednisone) in a 3+3 design for ibrutinib 420/560/280 mg (D3 to D14 and D17 to D28) and lenalidomide 20 mg D1 to 14/20 mg D1 to 21/15 mg D1 to 21. Responder pts then received a consolidation with R-Cytarabine and an intensive chemotherapy with autologous stem cell transplantation. The objective of the phase IB study was to define the recommended phase II dose (RP2D) based on the dose-limiting toxicity (DLT) occurring during the first induction cycle. We present the results of the phase IB, including the toxicities that occurred throughout induction therapy. **Results:** 26 pts (median age 52) were randomized, 13 in each treatment group. Four DLTs (/21 evaluable pts) have been observed: grade 5 aspergillosis and pneumocystosis (N=1, ibrutinib 560 mg and concurrent high-dose corticosteroids without prophylaxis), grade 4 catheter-related infection > 7 days (N=1, lenalidomide 20 mg D1-14) and grade 3 increased alanine aminotransferase > 7 days (N=1, lenalidomide 20 mg D1-14 and N=1, lenalidomide 15 mg D1-21). RP2D of ibrutinib and lenalidomide were 560 mg (D3-14 and D17-28) and 15 mg (D1-21) respectively, in combination with R-MPV. One Yell's syndrome was reported as a serious adverse event (AE) at cycle 2 in the lenalidomide arm. Grade ≥ 3 treatment-related AEs occurring in ≥ 2 pts at any time during induction treatment are detailed in the table. After 4 induction cycles, 3/11 evaluable pts had CR/CRu and 7/11 had partial response (PR) in the ibrutinib group. In the lenalidomide arm, 6/10 evaluable pts had CR/CRu and 4/10 had PR. Survivals will be presented. **Conclusions:** Targeted induction immunotherapy with ibrutinib or lenalidomide and R-MPV is feasible for newly diagnosed PCNSL and shows promising response rates. Adverse events should be monitored carefully. The phase II part of the study is ongoing and opened to patients up to 65 years old. Clinical trial information: NCT04446962. Research Sponsor: French government funding (PHRC-K: programme hospitalier de recherche clinique national en cancérologie).

Grade ≥ 3 treatment-related AEs (≥ 2 pts).	Lenalidomide + R-MPV N = 13	Ibrutinib + R-MPV N = 12	Overall N = 25
Hepatic cytotoxicity	5 (38%)	4 (33%)	9 (36%)
Neutropenia	3 (23%)	3 (25%)	6 (24%)
Thrombocytopenia	0	2 (17%)	2 (8%)
Anemia	0	2 (17%)	2 (8%)
Lymphocytopenia	2 (15%)	0	2 (8%)
Sepsis	0	5 (42%)	5 (20%)
Catheter-related infection	2 (15%)	0	2 (8%)

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Poster Session

Racial and ethnic disparities in risk of second primary malignancies among diffuse large B-cell lymphoma survivors. *First Author: Pragati Gole Advani, Roswell Park Cancer Institute, Buffalo, NY*

Background: Previous studies have shown an increased risk of second primary malignancies (SPMs) among diffuse large B-cell lymphoma (DLBCL) survivors; however, this has not been comprehensively examined by race/ethnicity. We utilized a large population-based database to examine disparities in SPM risk by race/ethnicity. **Methods:** From 17 United States population-based Surveillance, Epidemiology and End Results (SEER) program cancer registry areas, we identified 57,262 $\geq$ 12-month first-primary DLBCL survivors diagnosed between 2000-2019. Standardized incidence ratios (SIRs) and accompanying 95% confidence intervals (CIs) quantified SPM risk by race/ethnicity (non-Hispanic White, Black, Asian/Pacific Islander [API] and Hispanic), compared with the general population. **Results:** Overall, we observed 4,719 SPMs after DLBCL representing a 1.2-fold significantly increased risk (95% Confidence Interval [CI] = 1.16-1.23) compared to the general population and an excess of 23 cases per 10,000 person-years. SIRs for all second cancers combined varied significantly by race/ethnicity with APIs and Hispanics presenting higher overall SPM risk [SIR_{API}: 1.42 (CI = 1.27-1.59), and SIR_{Hispanic}: 1.31 (CI = 1.19-1.43)] compared to the White or Black patients [SIR_{White}: 1.17 (CI = 1.13-1.21), SIR_{Black}: 1.16 (CI = 1.03-1.30)] (p-heterogeneity < 0.001). Heterogeneity by race/ethnicity in SIRs was even more pronounced in DLBCL survivors diagnosed at a younger age, those who were $\geq$ 5 years into their survivorship, those who had received chemotherapy, or those who had received no radiation as their initial treatment. Although SIRs for SPM was significantly higher for advanced stage DLBCL survivors (compared to those with a localized/regional disease), heterogeneity by race/ethnicity in SPM risk was significant regardless of the stage. Results from site specific analyses reported significantly higher overall SIRs for second hematological malignancies compared to solid cancers [SIR_{hemat}: 3.52 (CI = 3.22-3.85), and SIR_{solid}: 1.08 (CI = 1.04-1.11)]. Patterns by race/ethnicity also varied significantly by second cancer type, particularly for second primary anal cancer, Hodgkin's lymphoma (HL), and Acute Non-Lymphocytic Leukemia (ANLL) (p < 0.001 for each). Strikingly elevated SPM risks (SIRs > 10) were observed for second primary anal cancer, HL and ANLL among the Black patients, and HL among the APIs and Hispanic DLBCL survivors, compared to the white patients. **Conclusions:** Using a large-scale population-based data, we observed substantial disparities in SPM risk by race/ethnicity, with patients belonging to minority groups experiencing higher risks. SPMs have emerged as an important challenge for DLBCL survivors, therefore, further research to understand drivers of the observed race/ethnicity heterogeneity is warranted. Research Sponsor: None.

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Poster Session

Preliminary data of a phase 1b/2 study of BCL-2 inhibitor lisaftoclax (APG-2575) alone or combined with ibrutinib or rituximab in patients (pts) with Waldenström macroglobulinemia (WM). *First Author: Sikander Ailawadhi, Mayo Clinic, Jacksonville, FL*

Background: B-cell lymphoma 2 inhibitors (BCL-2i) are well tolerated and effective in treating B-cell lymphoproliferative disorders such as CLL. Investigational agent lisaftoclax is a novel, oral, highly selective and potent BCL-2i. Preclinical data show a strong synergistic effect of lisaftoclax plus ibrutinib in an ibrutinib-insensitive PDXWM1 model. **Methods:** This global, open-label, multicenter study evaluates the safety and efficacy of lisaftoclax alone and combined with ibrutinib or rituximab in pts with WM. Pts were enrolled in 3 arms: Arm A (lisaftoclax), BTKi-resistant/intolerant pts; Arm B (lisaftoclax plus ibrutinib), treatment-naïve pts; and Arm C (lisaftoclax plus rituximab), BTKi-naïve relapsed/refractory pts. Lisaftoclax was escalated from 400 to 1,200 mg using a modified toxicity probability interval design. A 3-day ramp-up was used for pts at high TLS risk. Primary objectives were pharmacokinetics (PK), safety, and efficacy assessments; responses were assessed per IWWM criteria. **Results:** As of January 25, 2023, 46 pts were enrolled (Arm A [n = 14]; up to 1,000 mg; Arm B [n = 24]; up to 1,200 mg; Arm C [n = 8]; up to 800 mg). Baseline characteristics are shown in the table. Median (range) treatment duration was 6 (1-18; Arm A), 14 (1-27; B), and 8 (2-26; C) months. Overall response rates (ORRs) were: Arm A, 25% (median time to response [MTTR], 4.3 months); Arm B, 90.9% (MTTR, 1.9); Arm C, 37.5% (MTTR, 4.4). No significant difference was observed between pts with and without CXCR4-mut. At 1,200 mg, 1 DLT (grade 3 clinical TLS), due to pre-existing renal impairment, was reported. At 1,000 mg, 1 grade 3 laboratory TLS occurred in Arm B because of dehydration and active symptomatic therapies; abnormal electrolytes resolved after 1 day of drug interruption, without recurrence. Grade $\geq$ 3 lisaftoclax-related AEs included neutropenia (13%), leukocytopenia (4.3%), anemia (2.2%), weight loss (2.2%), and septic shock (2.2%). Ventricular arrhythmias were not observed. Only 1 pt required dose reduction (due to neutropenia). MTD has not been reached. A total of 14 pts discontinued study treatment because of disease progression (n = 5) and AE (n = 1). Lisaftoclax plus ibrutinib showed a PK exposure comparable to ibrutinib alone, indicating no potential DDIs. **Conclusions:** Lisaftoclax alone or combined with ibrutinib/rituximab demonstrated measurable effects in pts with naïve or BTKi-treatment-failed WM. Internal study identifier: APG2575WU101. *SA and ML are co-first authors. Clinical trial information: NCT04260217. Research Sponsor: Ascentage Pharma Group Corp Ltd.

Arm	A (n = 14)	B (n = 24)	C (n = 8)
Median age, y (range)	67.5 (48-75)	65.0 (51-92)	65.0 (54-72)
Male, no. (%)	11 (78.6)	18 (75.0)	6 (75.0)
IPSSWM high, no. (%)	8 (57.1)	4 (16.7)	2 (25.0)
Lines of prior therapies, median (range)	4.0 (1-7)	0	1.5 (1-7)
MYD88+CXCR4+	3	7	1
MYD88+CXCR4-	5	14	6
MYD88-CXCR4+	0	1	0
MYD88-CXCR4-	5	1	1

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Poster Session

Uncertainty and coping in patients with newly diagnosed indolent non-Hodgkin's lymphoma (iNHL). *First Author: Richard Newcomb, Massachusetts General Hospital, Boston, MA*

Background: iNHLs are a heterogeneous group of incurable diseases with prolonged illness courses requiring intermittent periods of surveillance and treatment. Due to illness uncertainty, patients with iNHL struggle with immense psychological distress. Yet, studies exploring coping, prognostic uncertainty and distress in this population are limited. **Methods:** We conducted a cross sectional study of adults (age $\geq$ 18) newly diagnosed with iNHL at a single academic center. We enrolled consecutive patients who were diagnosed $\leq$ 3 months prior to study enrollment. At baseline, we collected patient reported outcomes to assess QOL (Functional Assessment of Cancer Therapy), psychological symptoms (Hospital Anxiety and Depression Scale), prognostic understanding (Prognostic Awareness Impact Scale), and coping (Brief COPE). We categorized coping as approach-oriented (active coping, use of emotional support, positive reframing, acceptance) and avoidant (behavioral disengagement, denial, and self-blame). We used median split to differentiate between low and high utilizers of approach or avoidant coping. **Results:** We enrolled 70.6% (48/68) of eligible patients newly diagnosed with iNHL (mean age 66.8 yrs; 39.6% chronic lymphocytic leukemia/ lymphoma; 33.3% follicular lymphoma). At baseline, nearly one-third (31.2%) experience clinically significant symptoms of anxiety and depression. 45.8% of patients identified prognostic uncertainty as the "the most stressful part of being a patient," and 31.2% reported having "difficulty letting go of thoughts about their prognosis." Notably, patients had significant misperceptions about their prognosis with incurable iNHL, as 47.9% reporting that a cure was at least 'somewhat' likely. Patients with iNHL most often used acceptance (56.3%), denial (47.9%), and emotional support (47.9%) as coping strategies. Patients who were high utilizers of multiple approach-oriented coping strategies experienced fewer anxiety (B = -2.66, p = 0.01) and depression (B = -1.73, p = 0.02) symptoms and improved QOL (B = 9.43, p = 0.001). Patients who highly utilized any avoidant-oriented coping strategies experienced increased anxiety symptoms (B = 2.16, p = 0.05), but no difference in depression symptoms or QOL. **Conclusions:** Patients with iNHL report immense prognostic uncertainty and psychological distress. Use of multiple approach oriented coping strategies was associated with decreased psychological distress and improved QOL. Interventions to address prognostic uncertainty and to promote approach oriented coping in patients with iNHL are sorely needed and have the potential to ameliorate psychological distress and improve QOL in this vulnerable population. Research Sponsor: None.

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Poster Session

Epidemiologic characteristics, treatment patterns, and survival analysis of plasmablastic lymphoma in the US. *First Author: Alec Hansen, Department of Internal Medicine, University of Utah, Salt Lake City, UT*

Background: Plasmablastic Lymphoma (PBL) is a rare aggressive subtype of diffuse large B-cell lymphoma primarily affecting the immunocompromised, including those living with HIV. There is no established standard of care, and current survival estimates range from 8-15 months (mos). With the largest previous study of PBL limited to 590 patients (pts), we aimed to evaluate epidemiologic characteristics, treatment patterns and survival trends on a national scale. **Methods:** Pts diagnosed with PBL from 2010-2020 were identified in the National Cancer Database (NCDB) and the Surveillance, Epidemiology, and End Results (SEER) Program. Age-adjusted incidence rates (IR) were calculated using SEER. Demographic and treatment characteristics and overall survival were evaluated in the NCDB using Kaplan-Meier and multivariate Cox regression analysis. **Results:** For the 1,153 pts identified in SEER, the incidence of PBL was 0.07 per 100,000 person-years, with higher IR in males (0.12) and pts age > 75 years (0.23). IR increased on average by 4.2% per year from 2010 to 2020 (95% CI 1.51-6.96). Of the 1,822 PBL pts in NCDB, the median age at diagnosis was 57 years. PBL was more common in male (77.2%) and White pts (76.8%). Most pts presented at an advanced (III or IV) Ann Arbor stage (59.9%). Pts were HIV+ in 50.2% of cases and 51.2% had extranodal disease. The median OS (mos) was 22.4 mos (95% CI 16.2-28.6), with a 1-, 5-, and 10-yr OS of 56%, 40%, 32%, respectively. PBL pts treated with multiagent chemotherapy (N = 862, 66%) had mos of 58.6 mos (95% CI 43.0-74.3). Pts who received no systemic treatment (N = 456, 25%) had mos of 1.9 mos (95% CI 1.2-2.5). Pts with Stage I disease had a mos of 86.2 mos, Stage II of 51.1 mos, Stage III of 35.9 mos, and Stage IV of 8.8 mos. Pts with HIV had a greater mos (44.0 mos [95% CI 28.7-59.3]) than HIV- pts (21.7 mos [95% CI 12.4-30.9]). On multivariate Cox regression adjusted for age, race, and socioeconomic status, factors associated with worse OS included age (HR 1.03 [95% CI 1.02-1.04], p < 0.001), B symptoms (HR 1.35 [95% CI 1.11-1.65], p = 0.003) and advancing stage. Factors associated with improved OS included Hispanic ethnicity (HR 0.70 [95% CI 0.52-0.93], p = 0.014) and extranodal disease (HR 0.77 [95% CI 0.63-0.93], p = 0.001). HIV+ status had no significant impact on survival (HR 1.09 [95% CI 0.87-1.38], p = 0.443). **Conclusions:** We present the largest study to date describing the epidemiologic, survival, and treatment patterns of PBL. In contrast to prior studies, we found a longer mos of 58.6 mos among those treated. This may represent a large real-world population providing more accurate estimates or reflect improved outcomes from a growing number of novel therapeutic options. Notably, HIV+ status did not have a significant impact on OS. While OS remains poor, advances in treatment over the last decade are promising and highlight the need for clinical advances to improve front line therapeutic options for PBL. Research Sponsor: None.

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Poster Session

Outcomes among adult recipients of CD19 CAR T-cell therapy for Burkitt lymphoma. *First Author: Laura S. Samples, Fred Hutchinson Cancer Research Center, Seattle, WA*

Background: Burkitt lymphoma (BL) is a rare, but highly aggressive B-cell lymphoma associated with especially poor outcomes in patients with relapsed/refractory disease. Multiple CD19 chimeric antigen receptor (CAR) T-cell products have been FDA approved to treat relapsed/refractory B-cell non-Hodgkin lymphoma in the second-line setting, however little is known about CAR T-cell responses in patients with BL. This multicenter study aims to assess real-world outcomes among patients with BL treated with CAR T-cell therapy across the United States. **Methods:** This multicenter, retrospective chart review was conducted by abstracting data from the medical charts of patients with BL who received CAR T-cell therapy. Demographic characteristics were assessed along with pre-CAR treatments, bridging therapies, infusion-related complications, CAR-T responses, and the use of post-CAR systemic therapy and/or hematopoietic stem cell transplant. **Results:** A total of 13 patients with relapsed/refractory BL received CAR T-cell therapy after a median of 3 prior therapies (range 1-6). Most patients received axi-cel (n = 8), although tisa-cel (n = 3) and liso-cel (n = 2) were also represented. The median age of these patients was 38 (range 24-68). A total of 6 (46.2%) had evidence of central nervous system involvement at diagnosis and 5 (38.5%) had a prior history of autologous stem cell transplant. The overall response rate 1 month after infusion was 69.2% with a complete response rate of 53.8%. All patients experienced grade 1-2 cytokine release syndrome (CRS). No one experienced grade ≥ 3 CRS, but 2 patients developed grade ≥ 3 immune effector cell-associated neurotoxicity syndrome (ICANS). Twenty-eight-day mortality was 23%, including one patient who died from grade 4 ICANS. Regarding long term data, only 4 (30.8%) patients sustained a complete response for more than 6 months. Median progression-free survival was 4.2 months (95% CI 28.2-257.6), and the 1-year overall survival rate was 61.5% (95% CI 0.56-0.67). Two (15.4%) patients received consolidative allogeneic stem cell transplants after CAR T-cell therapy, but both ultimately developed progressive disease. **Conclusions:** Relapsed/refractory BL is a rare and aggressive disease that remains challenging to treat despite the advent of CAR T-cell therapy. Further investigation is needed to determine the most effective management of these patients. We expect to include additional patients in this analysis over the coming months. Research Sponsor: None.

7572

Poster Session

Unveiling the prognostic significance of BCL6+/CD10+ mantle cell lymphoma: A systematic analysis. *First Author: Dan Ran Castillo, Division of Medical Oncology and Hematology, Loma Linda University School of Medicine, Loma Linda, CA*

Background: Mantle cell lymphoma (MCL) is heterogenous B-cell neoplasm that characterized by the presence of the IgH/CCND1 translocation. The significance of CD10 expression in MCL is not fully understood. The co-expression of CD10 and BCL6 in MCL is rare requiring further investigation to determine its clinical significance. This meta-analysis aims to examine the relationship between MCL variants and their cellular behaviors and clinical outcomes. **Methods:** A search of the GDC and dbGaP database was conducted using the PICOS model and PRISMA guidelines to retrieve survival data. Overall survival (OS) data was pooled from multiple studies and analyzed using the R programming package survival and a log-rank test was performed to compare OS. Mean differences between BCL6+ vs. BCL6- for individual studies were calculated and combined to minimize batch effects. Summary statistics across studies were obtained by averaging mean differences and pooling individual standard deviations. The correlation between CD10 and BCL6 was tested using Fisher's exact test, with a significance level of 0.05. **Results:** The analysis included a total of 537 patients (425 males and 112 females), with a median age at diagnosis of 69 years in CD10+ MCL and 61.5 years in CD10- MCL. Out of the 537 patients, 70 were CD10+ positive, and BCL6 positivity had an odds ratio of 5.11 [95% CI [2.49, 10.46]; p = 0.000286] for CD10 positivity compared to CD10 negativity. The subgroup analysis revealed a higher frequency of blastoid/pleomorphic/small variants in BCL6+/CD10+ MCL. BCL6 positivity was associated with worse OS, independent of CD10 expression (median OS of 14 months in BCL6+ MCL vs. 43 months in BCL6- MCL; p = 0.01). The co-expression of BCL6 and CD10 was associated with a shorter median OS (22 months in BCL6+/CD10+ vs. 55 months in BCL6-/CD10+, p = 0.01) and significantly higher mitotic index (Ki67%) compared to BCL6-/CD10+ MCL (mean Ki67% of 63.13 $\pm$ 19.45% vs. 45 $\pm$ 21.69%, p < 0.01). The forest plot analysis showed that BCL6 expression was correlated with a significantly higher Ki67% (difference of 24.29; p = 0.0094). **Conclusions:** Our meta-analysis found that BCL6 expression correlates with CD10 positivity in MCL variants and has a negative impact on prognosis, independent of CD10 expression. Higher Ki67% levels in BCL6+ MCL compared to BCL6- MCL support the prognostic value of the BCL6+ immunophenotype in MCL variants. Prognostic scoring systems adjusted for BCL6 expression should be incorporated into MCL management. Targeted therapies against BCL6 may offer potential treatment options for MCL subtypes. Research Sponsor: None.

	CD10+ n = 70	CD10- N = 467
Male/Female	1.5:1(42/28)	4.6:1(383/84)
Median Age (years)	69	61.5
Classic	47.1% (33)	74.7% (374)
Blastoid/Pleomorphic/Small	48.6% (34)	16.8% (79)
BCL6+	22	112
BCL6-	41	349
Ki67% difference BCL6+ vs BCL6-: 24.29 (5.97-42.62), p = 0.0094		
Median OS in BCL6+/CD10+	22	p = 0.01
Median OS in BCL6-/CD10+	55	

7573

Poster Session

Investigating the impact of demographic disparities on clinical outcomes in cutaneous T-cell lymphoma (CTCL): A multicenter retrospective cohort analysis. *First Author: Tim Niyogusaba, Emory University School of Medicine, Atlanta, GA*

Background: Black patients have been shown to have a higher incidence of cutaneous T-cell lymphomas (CTCL) and display unique clinicopathologic features at diagnosis, however, drivers of these disparities and the role of social determinants of health (SDoH) remain poorly understood. **Methods:** To further characterize the prognostic relevance of racial and demographic disparities in CTCL, we performed a retrospective review of 1,198 patients seen at 8 different academic treatment centers in the United States between 2000-2020. Clinical variables included demographics, disease characteristics, and survival. Race and ethnicity were stratified into 2 groups for this analysis: non-Hispanic Black (B) and Non-Black (NB). Distance to center was stratified into short, intermediate, or long commute (< 10, 10-50, > 50 miles, respectively) based on home zip code. The primary endpoint was overall survival (OS). Univariate association and multivariable analyses were assessed using Cox proportional hazards models. **Results:** Among 1,198 total patients, 42.4% identified as B and 58.6% as NB. B patients presented younger, had a shorter commute, lower income, but no difference in insurance compared to NB patients. There was no difference in survival by race (Median OS 74 months [95% CI 65-84] compared to 65 [95% CI 58-75] for NB patients). Distance to center was strongly associated with survival and remained significant on multivariate analyses after controlling for age, race, and other SDoH. Longer commute was associated with worse OS compared to short commute for both B and NB counterparts (median 55 months [95% CI 49-66] vs. 79 [95% CI 69-90] and 75 [95% CI 63-86], respectively, p = 0.006). **Conclusions:** We characterized the impact of race and SDoH on overall survival (OS) in a diverse, multicenter cohort of patients with CTCL. We found that distance to cancer center was the most important factor contributing to disparities in OS in this study. This highlights the importance of improving access to care, particularly in rare and clinically heterogeneous diseases such as CTCL. Research Sponsor: None.

7574

Poster Session

A phase 2 study of HLX208, a BRAF^{V600E} inhibitor, in adult patients with Langerhans cell histiocytosis and/or Erdheim-Chester disease harboring BRAF^{V600E} mutation. *First Author: Xin-xin Cao, Department of Hematology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China*

Background: HLX208 is a novel BRAF^{V600E} inhibitor, exhibiting excellent antitumor efficacy in preclinical studies. This phase 2 study aimed to evaluate the efficacy, safety, and pharmacokinetics of HLX208 in adult patients with Langerhans cell histiocytosis (LCH) and/or Erdheim-Chester disease (ECD) harboring BRAF^{V600E} mutation. **Methods:** This was a single-arm, open-label, multicenter, phase 2 study. Patients with histologically confirmed LCH and/or ECD were enrolled and received oral administration of HLX208 at 450 mg twice every day. HLX208 was given in 28-day cycles until disease progression, experiencing intolerable toxicity, withdrawal of consent, initiation of new antitumor therapy, or death, whichever occurred first. The primary endpoint was the objective response rate (ORR) assessed by independent review committee (IRC) per PET Response Criteria in Solid Tumors (PERCIST) 1.0. Secondary endpoints included safety, other efficacy measures, and pharmacokinetics of HLX208. **Results:** As of January 15, 2023, 22 patients with LCH and/or ECD were enrolled. All patients have received at least one dose of HLX208 and were included in the current analysis. The median age was 39 (range 18-69) years. Nine (40.9%) patients were male. 12 (54.5%) patients were diagnosed with LCH, 9 (40.9%) were diagnosed with ECD, and 1 (4.5%) had combined LCH and ECD. 6 (27.3%) patients had single system multifocal disease, while 16 (72.7%) had multisystem disease. The median follow-up duration was 4.8 months (95% CI 2.7-5.7). Among the 10 efficacy evaluable patients, ORR (unconfirmed) assessed by IRC per PERCIST 1.0 was 90.0% (95% CI 55.5-99.7%) (9/10, including 2 complete metabolic response [CMR] and 7 partial metabolic response [PMR]), while that by investigators per PERCIST 1.0 was 100.0% (95% CI 69.2-100.0%) (10/10, including 3 CMR and 7 PMR). Disease control rate was 100.0% (95% CI 69.2-100.0%) as assessed by both IRC and investigators per PERCIST 1.0. The median duration of response, median progression-free survival, and median overall survival were not reached. Of the 22 patients who received the drug, 17 (77.3%) patients experienced treatment-emergent adverse events (TEAEs); 12 (54.5%) reported treatment-related adverse events (TRAEs), most commonly alanine aminotransferase increased (36.4%), aspartate aminotransferase increased (22.7%), γ -glutamyltransferase increased (18.2%), and blood lactate dehydrogenase increased (18.2%). Most TRAEs were grade 1 (27.3%) and 2 (18.2%). Only 2 (9.1%) patients experienced grade ≥ 3 TRAEs and 1 (4.5%) experienced treatment-related serious adverse event. There were no TRAEs that led to treatment discontinuation or death. **Conclusions:** In summary, HLX208 was safe and well tolerated, and showed promising efficacy in patients with LCH and/or ECD. Clinical trial information: NCT05092815. Research Sponsor: Shanghai Henlius Biotech, Inc.

7575

Poster Session

Clinical characteristics, survival outcomes, and prognostic factors in extra-nodal natural killer/T-cell lymphoma, nasal type: The National Cancer Database study (2004-2019). *First Author: Firas Baidoun, Hematology Oncology Division, Mayo Clinic-Florida, Jacksonville, FL*

Background: Extranodal natural killer/T-cell lymphoma (ENKTL), nasal type, is a rare and aggressive Epstein-Barr virus driven lymphoma, which is most prevalent in East Asia and Latin America. There have been very few large studies outside of Asia. Therapeutic and survival outcomes have not been well characterized in the US. **Methods:** The National Cancer Database was queried for patients who were diagnosed at aged ≥ 18 years between 2004 and 2019. Patients who were lost to follow-up were excluded. Kaplan-Meier and multivariate Cox regression analyses were performed. **Results:** The cohort consists of 2,036 evaluable patients with 68% males, 74% Caucasian, 22% Hispanic Caucasian and 9% African American. The median age at diagnosis was 54 (18-90) years. The median follow up was 71 months (95% CI 66.8-75.7). Early-stage disease (I and II) was reported in 64% while advanced stage disease (III and IV) constituted 36%. Treatment groups include chemotherapy alone (29%), radiation alone (10%), combined modality therapy (CMT-chemoradiation) (42%). The median overall survival (OS) for the whole cohort was 27 months (95% CI 20.6-33.7). Median OS was better in patients with early stage compared to advanced stage disease (90 vs. 6 months, $P < 0.001$). Among therapeutic groups in early-stage disease, CMT ($N = 616$) had significantly better median OS than radiation alone ($N = 152$) or chemotherapy alone ($N = 168$) (194 vs. 34 vs. 14 months, $P < 0.001$). No significant difference was seen between radiation alone and chemotherapy alone ($P = 0.617$). Among patients treated with CMT, chemotherapy-first CMT ($N = 134$) had better OS than radiation-first CMT ($N = 347$) (median OS not reached vs. 194 months, $P = 0.017$). In the advanced stage disease, chemotherapy-treated patients ($N = 418$) had better median OS compared to patients who did not receive chemotherapy ($N = 103$) (7.6 vs 1.3 months, $P < 0.001$). Among patients who received chemotherapy, patients consolidated with SCT ($N = 59$) had better median OS compared to the patients who received chemotherapy only ($N = 353$) (63 vs 6 months, $P < 0.001$). In multivariate analysis, factors associated with worse OS were age (HR 1.021 95% CI 1.015-1.026; $P < 0.001$) and B-symptoms (HR 1.463 95% CI 1.276-1.678; $P < 0.001$). Whereas factors associated with better OS were early stage (HR 0.450 95% CI 0.387-0.524, $P < 0.001$), radiation therapy (HR 0.526 95% CI 0.458-0.603, $P < 0.001$) and chemotherapy (HR 0.546 95% CI 0.473-0.630, $P < 0.001$). **Conclusions:** The study represents one of the largest studies on ENKTL in the US. Early-stage disease is highly curable with CMT with chemotherapy-first sequencing being superior to radiation-first sequencing. Advanced stage disease is associated with extremely poor prognosis overall but is associated with a significant improvement in OS with consolidative SCT with possible role of consolidative RT in advanced stage. Research Sponsor: None.

7577

Poster Session

Risk of incident melanoma among individuals with low-count monoclonal B-cell lymphocytosis (MBL). *First Author: Bryan Alexis Vallejo, Division of Computational Biology, Mayo Clinic, Rochester, MN*

Background: Prior research has consistently shown that patients with chronic lymphocytic leukemia (CLL) have an ~ 2 -fold increased risk of developing melanoma compared to controls. MBL is a common condition affecting 8-10 million adults over the age of 40 years in the United States and is a precursor to CLL. Little is known about the association between MBL and melanoma. Herein, we evaluated the risk of incident melanoma in a large cohort of individuals screened for MBL. **Methods:** Participants from the Mayo Clinic Biobank who had no prior history of hematologic malignancy, were 40 years or older, were residents of counties surrounding Mayo Clinic, and who provided blood samples between 7/2009 and 4/2022 were included in the study. Peripheral blood mononuclear cells were screened for MBL using highly sensitive eight-color flow cytometry. Individuals with MBL were classified as CLL-like MBL (CD5+, CD20dim) or atypical MBL (CD5+, CD20+) based on immunophenotypes, and also classified as low-count MBL (LCMBL) or high-count MBL (HCMBL) based on whether the percent clonal B-cell count was $< 85\%$ or $\geq 85\%$, respectively. Diagnosis of melanoma was ascertained using ICD codes and review of the electronic health records. All individuals were followed from date of sample upon which MBL screening was performed to the earliest of incident melanoma, loss to follow-up, withdrawal from the study, or September 30, 2022. We used Cox regression to estimate hazard ratios (HR) and 95% confidence intervals (CI), adjusting for age, sex, and history of melanoma in previous 5 years. **Results:** A total of 7,334 participants were screened for MBL, of which 1,151 (16%) individuals had MBL. Among those with MBL, 1,107 (96.2%) had CLL-like MBL and 1098 (95.4%) had LCMBL. The median age at entry into the MBL screening cohort was 67 years (range 40-101) and 37% were male; individuals with MBL were older (median age 72 vs 65 years) and male (49% vs 35%). After a median follow-up of 2.9 years (range 0-13.2), 121 of the 7,334 (1.6%) participants developed incident melanoma after the date of MBL screening. The 10-year cumulative incidence of melanoma among individuals with MBL was 7.8% (95% CI 4.5-13.5%) compared to 3.4% (2.7-4.4%) in those who screened negative for MBL. After adjusting for age, sex, and history of prior melanoma, we found a 1.81-fold increased risk of incident melanoma (95% CI 1.19-2.76) among individuals with MBL. The increased risk of melanoma persisted when the analysis was restricted to individuals with LCMBL (HR = 1.84; 95% CI 1.21-2.82). **Conclusions:** In the largest MBL screening cohort to date, we found that LCMBL, a common condition, was associated with an 84% elevated risk of melanoma, similar to the ~ 2 -fold increased risk observed in patients with CLL. These data, together with our prior findings of a heightened risk of serious infections and lymphoid malignancies, suggest that individuals with LCMBL are at increased risk for adverse health outcomes. Research Sponsor: U.S. National Institutes of Health.

7576

Poster Session

Association of pharmacist interventions with adherence upon targeted anticancer oral therapy initiation. *First Author: Richard Mcshinsky, VA Salt Lake City, Salt Lake City, UT*

Background: Oncology pharmacists (OPs) increasingly play a role in managing cancer patients, with the availability of targeted oral anticancer agents (TOAs). OPs ensure appropriate indications upon initiation; screen for, anticipate, and mitigate potential drug-drug interactions; manage side effects; and promote adherence. The impact of OPs on adherence to TOAs has not been described. **Methods:** The Veterans Affairs Corporate Data Warehouse and Cancer Registry were used to: 1. identify Veterans with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL), marginal zone lymphoma (MZL), lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia (WM), and/or mantle cell lymphoma (MCL) who received single agent TAO for the first time between 2018 and 2021; 2. retrieve patient demographics, disease characteristics, and TAO dispensation information; and 3. identify visits with OPs within a 30-day window of initial dispensation. Dispensation information was used to calculate the proportion of days covered (PDC) during the first 4, 8, and 12 week milestones after initial dispensation. Non-adherence was defined as a PDC < 0.9 . A two-sample proportion test and a Wilcoxon rank-sum test were used to compare milestone adherence between patients who visited with an OP at treatment initiation vs those who did not. **Results:** 1,944 patients were identified, with a median age of 75 years; 98% were male; 1,498 (77%) were white, 244 (13%) were black, and 53 (3%) were Hispanic, rest were other, or unknown. CLL was the most common diagnosis at 1,578 patients (81%), followed by MCL at 162 (8%), WM at 135 (7%), and MZL at 69 (4%). 1,702 patients (88%) received ibrutinib, 110 (6%) venetoclax, 91 (5%) acalabrutinib, and 32 (2%) lenalidomide. Fewer than 5 patients received either idelalisib, zanubrutinib, umbralisib, and/or duvelisib. 1,757 patients had an initial dispensation supply of either < 28 days or 28-30 days and were used to conduct the adherence analysis; of those 702 had met with an OP at therapy initiation. In the 239 patients with a dispensation day supply < 28 days, patients who met with an OP had higher 4, 8, and 12 week adherence rates (97%, 96% and 92%) compared to those who did not (82%, 75%, 72%); odds ratios (OR) 8.8, 7.7 and 4.7 respectively (all with $p < 0.01$). In the 1,518 patients with a dispensation day supply of 28-30 days, patients who met with an OP also had higher 8-, and 12-week adherence rates (96% and 91%, resp) compared to those that did not (87%, 79%); OR 3.4 and 2.6 resp, both with $p < 0.01$. **Conclusions:** Visiting with an OP upon TAO therapy initiation was associated with a clinically and statistically significant increase in adherence at 4, 8, and 12 weeks after first dispensation. To our knowledge, this is the first study to quantify the impact of an OP on non-adherence in a real-world setting. Our findings suggest a critical need to integrate OPs TAO therapy initiation workflows. Research Sponsor: AbbVie.

TPS7578

Poster Session

ZUMA-23: A global, phase 3, randomized controlled study of axicabtagene ciloleucel versus standard of care as first-line therapy in patients with high-risk large B-cell lymphoma. *First Author: Jason Westin, Department of Lymphoma/Myeloma, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: The nearly 40% of patients (pts) with large B-cell lymphoma (LBCL) who are refractory to or relapse after current first-line (1L) standard-of-care (SOC) regimens, such as R-CHOP (rituximab [R] + cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]) and DA-EPOCH-R (dose-adjusted etoposide [DA-E]), have poor prognoses. High International Prognostic Index (IPI) score and the subtype of high-grade B-cell lymphoma (HGBL) are associated with shorter progression-free and overall survival (PFS and OS; Nastoupil LJ and Bartlett NL. *J Clin Oncol*. 2023). Strategies to improve outcomes in these subgroups have been largely unsuccessful; therefore, therapeutic options with a different mechanism of action are needed. Axicabtagene ciloleucel (axi-cel) is an autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy approved to treat pts with relapsed/refractory (R/R) LBCL after demonstrating significant clinical benefit as 2L (ZUMA-7; Locke FL, et al. *N Engl J Med*. 2022) and ≥ 3 L (ZUMA-1; Neelapu SS, et al. *N Engl J Med*. 2017) therapy. Additionally, in the Phase 2 ZUMA-12 study in pts with refractory 1L LBCL, axi-cel showed a high rate of durable responses with an objective response rate of 89% (complete response rate, 78%) and an ongoing response rate of 73% (median follow-up, 15.9 mo; Neelapu SS, et al. *Nat Med*. 2022). ZUMA-23 is the first Phase 3, randomized controlled study to evaluate CAR T-cell therapy as a 1L regimen for any cancer and will assess axi-cel versus SOC in pts with high-risk LBCL, defined as IPI 4-5. **Methods:** The Phase 3 trial design will enroll ≈ 300 adult pts with high-risk, histologically confirmed LBCL based on the 2016 WHO classification, including diffuse large B-cell lymphoma (DLBCL), HGBL, and transformed follicular or marginal zone lymphoma (Swerdlow SH, et al. *Blood*. 2016). Eligible pts will receive 1 cycle of R-chemotherapy and then be randomized 1:1 to receive axi-cel or continue with SOC. Pts in the axi-cel arm will undergo leukapheresis and then receive R-CHOP or DA-EPOCH-R as bridging therapy, followed by lymphodepleting chemotherapy (fludarabine/cyclophosphamide), and a single axi-cel infusion (2×10^6 CAR T cells/kg). Prophylactic corticosteroids may be administered to reduce the incidence and severity of cytokine release syndrome at the investigator's discretion. Pts in the SOC arm will receive 5 additional cycles of R-CHOP or DA-EPOCH-R (investigator's choice). The primary endpoint is event-free survival by blinded central review. Key secondary endpoints are OS and PFS. Safety, quality of life, and pharmacokinetics will also be assessed. Pts with a history of HIV and/or hepatitis B or C and undetectable viral loads may enroll. Key exclusion criteria include LBCL of the central nervous system. ZUMA-23 is open for enrollment (NCT05605899). Clinical trial information: NCT05371093. Research Sponsor: Kite, a Gilead Company.

TPS7579

Poster Session

ZUMA-22: A phase 3, randomized controlled study of axicabtagene ciloleucel (axi-cel) versus standard-of-care therapy in patients with relapsed or refractory (R/R) follicular lymphoma (FL). *First Author: Ian W. Flinn, Sarah Cannon Research Institute, Tennessee Oncology, Nashville, TN*

Background: Patients with R/R FL experience progressively shorter remissions with each successive line of therapy, and the disease is largely considered incurable (Batlevi et al. *Blood Cancer J.* 2020). Patients who relapsed < 24 months after initiating first-line chemoimmunotherapy (POD24) have inferior overall survival compared with those who did not experience POD24 (Casulo, Barr. *Blood.* 2019). However, outcomes of R/R FL have improved with the introduction of novel options including chimeric antigen receptor (CAR) T-cell therapy, a highly effective approach with potential to change the treatment paradigm (Jacobson et al. *Lancet Oncol.* 2021; Freedman, Jacobson. *Am J Hematol.* 2020). Axi-cel, an autologous anti-CD19 CAR T-cell therapy, is approved for the treatment of R/R FL. In ZUMA-5, a single-arm, Phase 2 study of axi-cel in indolent non-Hodgkin lymphoma, patients with FL (n = 127) had a median progression-free survival of 40.2 months and median overall survival not yet reached after median follow-up of 41.7 months, with manageable long-term safety (Neelapu et al. ASH 2022. Abstract 4660). In ZUMA-5, POD24 did not adversely affect progression-free survival or overall survival. ZUMA-22 is a Phase 3, open-label, multicenter, randomized controlled trial that will evaluate the efficacy and safety of axi-cel compared with standard-of-care therapy in patients with R/R FL. **Methods:** The study will enroll approximately 230 adult patients with FL (Grades 1-3a) who have either had 1 prior line of therapy and experienced POD24 or had ≥2 prior lines of systemic therapy. Patients will be randomized 1:1 to receive axi-cel or standard-of-care therapy. Patients in the standard-of-care therapy arm will receive investigator's choice of either rituximab + lenalidomide, rituximab + CHOP, or rituximab + bendamustine. Patients in the axi-cel arm will undergo leukapheresis, followed by optional bridging therapy, lymphodepleting chemotherapy (fludarabine/cyclophosphamide), and a single axi-cel infusion (2×10^6 CAR T cells/kg). The primary endpoint is progression-free survival by blinded central assessment per Lugano classification (Cheson et al. *J Clin Oncol.* 2014). Secondary endpoints include complete and overall response rates, duration of response, overall survival, event-free survival, time to next treatment, safety, and quality-of-life assessments. Additional key inclusion criteria are ECOG 0-1, presence of ≥1 measurable lesion, and adequate bone marrow and organ function. Those with HIV or hepatitis B or C and an undetectable viral load are eligible. Key exclusion criteria are a history of large B-cell lymphoma or transformed FL, and FL Grade 3b. The study is currently open and actively accruing patients at several sites globally (NCT05371093). Clinical trial information: NCT05371093. Research Sponsor: Kite, a Gilead Company.

TPS7581

Poster Session

Phase 1b open-label study of loncastuximab tesirine in combination with other anticancer agents in patients with relapsed/refractory B-cell non-Hodgkin lymphoma (LOTIS-7). *First Author: Brian T. Hess, Division of Hematology and Medical Oncology, Department of Medicine, Medical University of South Carolina, Charleston, SC*

Background: Combining agents with different mechanisms of action may enhance treatment (Tx) efficacy in patients (pts) with relapsed/refractory (R/R) B-cell non-Hodgkin lymphoma (B-NHL). Loncastuximab tesirine (loncastuximab tesirine-lyl; Lonca), an FDA-approved, CD19-directed, antibody-drug conjugate indicated for R/R diffuse large B-cell lymphoma (DLBCL), showed significant efficacy and manageable toxicity in a phase 2 trial in pts with R/R DLBCL. In preclinical models, Lonca + polatuzumab vedotin (Pola) showed improved efficacy. CD20×CD3 T-cell engaging antibodies and Lonca target different antigens; combining these is expected to increase efficacy. The safety and activity of Lonca combined with other agents in pts with R/R B-NHL will be evaluated in LOTIS-7. **Methods:** LOTIS-7, a phase 1b, open-label, multicenter, multiarm study (NCT04970901), will enroll ~200 pts with B-NHL in part 1 (dose escalation, 60 pts) and part 2 (dose expansion, 140 pts). Part 2 may include specific subpopulation(s) of B-NHL informed by part 1. Primary endpoints are frequency and severity of adverse events (AE), serious AE, dose-limiting toxicities, and frequency of AE-related dose modifications. Secondary endpoints are overall response rate; duration of response; complete response rate; progression-free, relapse-free, and overall survival; Lonca concentrations; and antidrug antibody titers. Planned arms include Lonca + Pola (arm C), glofitamab (arm E), or mosunetuzumab (arm F). Arm C enrollment is open: pts are treated with Lonca + Pola as an outpatient infusion. In part 1, arm C pts receive Lonca at escalating doses (90-150 µg/kg) and Pola (1.8 mg/kg) on day 1 of each 3-week cycle; pts in arms E and F will receive Lonca 150 µg/kg for 2 cycles, then 75 µg/kg for subsequent cycles + glofitamab (2.5 mg on cycle [C]1 day [D]8, 10 mg on C1D15, 10 or 30 mg for C2-12 D1, arm E) or mosunetuzumab SC (5 mg on C1D1, 15 or 45 mg for C1D8, and 45 mg for C1D15 and C2-8 D1, arm F) after initial step-up dosing. Lonca Tx may continue for up to 1 year or until disease progression, unacceptable toxicity, or other discontinuation criteria. Key eligibility criteria include age ≥18 years, pathologic diagnosis of R/R B-NHL (2016 WHO classification), measurable disease (2014 Lugano classification), Tx failure/intolerance, ≥2 lines of prior therapy (LOT) for part 1 (≥1 LOT for part 2), and ECOG performance status of 0-2. Pts previously receiving a study drug could not enroll in that respective study arm. Pts who received a stem-cell transplant within 60 days (100 days for arms E/F) before study Tx; received allogeneic stem cell or solid organ transplant (arms E/F); have lymphoma with active CNS involvement, ascites, edema, or effusion; or have significant comorbidities are excluded. The study opened in December 2021; 12 pts have been enrolled and 9 treated in the Lonca + Pola arm. Clinical trial information: NCT04970901. Research Sponsor: ADC Therapeutics SA.

TPS7580

Poster Session

The ELIPSE-1 study: A phase 1, multicenter, open-label study of CNTY-101 in subjects with relapsed or refractory CD19-positive B-cell malignancies. *First Author: Krish Patel, Center for Blood Disorders and Cellular Therapy, Swedish Cancer Institute, Seattle, WA*

Background: Century Therapeutics' foundational technology is built on induced pluripotent stem cells, differentiated from allogeneic approaches that utilize non-renewable donor-derived cells. This approach allows production of a clonal cell bank of precisely edited cells that can be expanded and differentiated to supply large amounts of homogeneous allogeneic therapeutic products for off-the-shelf use. CNTY-101 is an allogeneic Chimeric Antigen Receptor NK (CAR-NK) cell product with genetic modifications designed to specifically target CD19-expressing B-cell malignancies, reduce alloreactivity in the recipient allowing for repeat dosing, increase persistence, and enable cell elimination in the event of unexpected adverse events. CNTY-101, as a CAR-NK product, has the potential for improved safety over T-cell based cellular therapies. **Methods:** This first-in-human study will determine the MTD and recommended Phase 2 regimen (RP2R) of CNTY-101 in combination with subcutaneous (SC) IL-2 in patients with R/R aggressive and indolent CD19-positive B-cell Non-Hodgkin lymphomas including diffuse large B-cell lymphoma, mantle cell lymphoma, primary mediastinal large B-cell lymphoma, follicular lymphoma and marginal zone lymphoma, who are without other treatment options. Part 1 of the study (dose escalation using the BOIN design) will start with a dose of CNTY-101 cells without IL-2 (1 to 3 subjects), followed by dose escalation up to four dose cohorts administering a single dose of CNTY-101 cells in combination with IL-2 daily for 8 days (Sched A). After the single-dose MTD (or the maximal single dose) has been reached, a fractionated schedule of 3 doses per 28-day cycle, administered on Days 1, 8, and 15 (Sched B), will also be explored, starting with approximately one-third the maximum single dose level of CNTY-101, followed by escalation/de-escalation. Subjects in whom CNTY-101 shows signs of clinical benefit (i.e. stable disease or better per Lugano 2014 criteria) may receive additional cycles of CNTY-101 if the Investigator, Sponsor, and appropriate regulatory authorities, as required, concur that the benefit-risk is positive. One overall CNTY-101 RP2R will be declared in Part 1. Part 2, expansion, will further evaluate the safety, pharmacokinetics (PK), and efficacy of the CNTY-101 regimen, treating up to an additional 12 subjects to reach a total of approximately 20 subjects treated at the RP2R. In addition to safety and efficacy endpoints, the trial will evaluate exploratory PK, immunogenicity and pharmacodynamic endpoints including evaluations of tumor cfDNA, iNK tumor trafficking and serum cytokines. Clinical trial information: NCT05336409. Research Sponsor: Century Therapeutics.

TPS7582

Poster Session

BRUIN CLL-321: A phase 3 open-label, randomized study of pirtobrutinib versus investigator's choice of idelalisib plus rituximab or bendamustine plus rituximab in BTK inhibitor pretreated chronic lymphocytic leukemia/small lymphocytic lymphoma. *First Author: George Follows, Department of Haematology, Addenbrooke's Hospital NHS Trust, Cambridge, United Kingdom*

Background: Covalent (c) Bruton tyrosine kinase inhibitors (BTKi) have transformed the management of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), but these agents are not curative. cBTKi share pharmacologic liabilities such as low oral bioavailability and a short half-life that may lead to suboptimal BTK target coverage, especially in rapidly proliferating tumors with high BTK protein turnover, which can manifest as acquired resistance to cBTKi. Novel therapeutic agents addressing both intolerance and resistance while also improving efficacy are needed. Pirtobrutinib, a highly selective, non-covalent (reversible) BTKi, inhibits both wildtype and C481-mutant BTK with equal low nM potency, and has favorable oral pharmacology that enables continuous BTK inhibition throughout the dosing interval, regardless of intrinsic rate of BTK turnover. In the phase 1/2 BRUIN study, pirtobrutinib demonstrated promising durable overall response rates (ORR) and was well tolerated in patients with CLL/SLL regardless of prior therapy (including cBTKi), number of prior lines of therapy, BTK C481 mutation status, or reason for prior cBTKi discontinuation. The objective of this study is to determine whether pirtobrutinib is superior to conventional therapy in patients previously treated with cBTKi. **Methods:** BRUIN CLL-321 (NCT04666038) is a randomized, open-label, global phase 3 study comparing pirtobrutinib monotherapy (200mg QD) to investigator's choice of idelalisib plus rituximab (IdelaR) or bendamustine plus rituximab (BR). Approximately 250 CLL/SLL patients previously treated with a covalent BTKi will be randomized 1:1 and stratified by both del(17p) status (yes/no) and prior venetoclax treatment (yes/no). Patients on the control arm can crossover to pirtobrutinib monotherapy if they experience progressive disease per iwCLL 2018 as confirmed by an independent review committee (IRC). Adults with CLL/SLL who require therapy per iwCLL 2018 criteria and have received prior covalent BTKi are eligible. An unlimited number of prior lines of therapy, including venetoclax, are allowed. Key exclusion criteria include CNS involvement by CLL/SLL, a major bleeding event on prior cBTKi, Richter's Transformation at any time, prior therapy with a non-covalent BTKi, or a history of either allogeneic or autologous stem cell transplant (SCT), or chimeric antigen receptor (CAR) T-cell therapy within 60 days prior to randomization. The primary end point is progression-free survival (PFS) per iwCLL 2018 criteria as assessed by IRC. Secondary endpoints include investigator assessed PFS, overall survival, ORR, duration of response, safety and tolerability, and patient reported outcomes. Enrollment for this study is ongoing. Clinical trial information: NCT04666038. Research Sponsor: Loxo/Lilly.

TPS7583

Poster Session

BRUIN CLL-322: A phase 3 open-label, randomized study of fixed duration pirtobrutinib plus venetoclax and rituximab versus venetoclax and rituximab in previously treated chronic lymphocytic leukemia/small lymphocytic lymphoma. *First Author: Toby A. Eyre, Oxford University Hospitals NHS Foundation Trust, Churchill Cancer Center, Oxford, United Kingdom*

Background: Covalent (c) Bruton tyrosine kinase inhibitors (BTKi) have reshaped the treatment landscape for chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and are now often used as initial therapy. The MURANO study established 2-year fixed duration venetoclax plus rituximab as a standard of care regimen for patients with relapsed or refractory CLL/SLL. However, its efficacy has not been formally assessed in CLL/SLL patients treated with a cBTKi, a common setting where this regimen is used in contemporary practice. Pirtobrutinib, a highly selective, non-covalent (reversible) BTKi, inhibits both wildtype and C481-mutant BTK with equal low nM potency, and has favorable oral pharmacology that enables continuous BTK inhibition throughout the dosing interval regardless of intrinsic rate of BTK turnover. In the phase 1/2 BRUIN study, pirtobrutinib demonstrated promising durable overall response rates (ORR) and was well tolerated in patients with pre-treated CLL/SLL regardless of prior therapy (including cBTKi), number of prior lines of therapy, BTK C481 mutation status, or reason for prior cBTKi discontinuation. The study's objective is to assess the superiority of adding time-limited pirtobrutinib to the MURANO regimen, hypothesized to prolong disease control in a largely BTKi-pretreated population. **Methods:** BRUIN CLL-322 (NCT04965493) is a randomized, open-label, global, phase 3 study comparing time-limited pirtobrutinib (200mg QD) plus venetoclax and rituximab versus venetoclax and rituximab in previously treated CLL/SLL patients. Approximately 600 patients, 80% who have been previously treated with cBTKi, will be randomized 1:1 and stratified by del(17p) status (yes/no) and prior BTKi experience (discontinuation due to progressive disease vs due to other reasons vs no prior BTKi exposure). Eligible patients are adults diagnosed with CLL/SLL and require therapy per iwCLL 2018 criteria who have received prior therapy that may or may not include a cBTKi. There are no restrictions on the number of lines of prior therapy. Key exclusion criteria include CNS involvement by CLL/SLL, Richter transformation at any time, prior BCL2 inhibitor or non-covalent BTK inhibitor, or a history of either allogeneic or autologous stem cell transplant, or chimeric antigen receptor T-cell therapy within 60 days prior to randomization. The primary endpoint is progression-free survival (PFS) per iwCLL criteria assessed by an independent review committee. Secondary endpoints include investigator assessed PFS, ORR, overall survival, time to next treatment, event-free survival, safety and tolerability, and patient-reported outcomes. Enrollment is ongoing for patients previously treated with BTKi and completed for BTKi naïve patients. Clinical trial information: NCT04965493. Research Sponsor: Loxo@Lilly.

TPS7584

Poster Session

BRUIN CLL-314: A phase 3, open-label, randomized study of pirtobrutinib versus ibrutinib in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma. *First Author: Jennifer Ann Woyach, Ohio State University Comprehensive Cancer Center, Columbus, OH*

Background: Covalent (c) Bruton tyrosine kinase inhibitors (BTKi) have transformed the management of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), but these agents are not curative. cBTKi share pharmacologic liabilities such as low oral bioavailability and a short half-life that may lead to suboptimal BTK target coverage, especially in rapidly proliferating tumors with high BTK protein turnover, such as accelerating CLL/SLL, which can manifest as acquired resistance to cBTKi. Novel therapeutic agents addressing both intolerance and resistance while also improving efficacy are needed. Pirtobrutinib, a highly selective, non-covalent (reversible) BTKi, inhibits both wildtype and C481-mutant BTK with equal low nM potency and has favorable oral pharmacology that enables continuous BTK inhibition throughout the dosing interval regardless of intrinsic rate of BTK turnover. In the phase 1/2 BRUIN study, pirtobrutinib demonstrated promising durable overall response rates (ORR) and was well tolerated in patients with CLL/SLL irrespective of prior therapy (including cBTKi), number of prior lines of therapy, BTK C481 mutation status, or reason for prior cBTKi discontinuation. The objective of this study is to compare efficacy and tolerability of pirtobrutinib versus ibrutinib in patients with CLL/SLL. **Methods:** BRUIN CLL-314 (NCT05254743) is a global, phase 3, open-label, randomized study comparing pirtobrutinib with ibrutinib. Approximately 650 BTKi-naïve patients, either treatment-naïve (up to 30%) or previously treated with other non-BTKi agents, will be randomized 1:1 to receive daily 200 mg pirtobrutinib once daily or 420 mg ibrutinib as continuous monotherapy. Randomization will be stratified by del(17p) status (yes/no) and number of prior lines of therapy (0 vs 1 vs ≥2). Enrollment for this study is ongoing. Adults with CLL/SLL who require therapy per iwCLL 2018 criteria are eligible. Key exclusion criteria include prior exposure to any BTKi, use of some concomitant therapies including anticoagulants, such as warfarin and other vitamin K antagonists, significant cardiovascular disease, active infections, and other clinically significant conditions. The primary objective is to establish non-inferiority of pirtobrutinib versus ibrutinib by comparing the ORR per iwCLL guidelines assessed by an independent review committee. Superiority of pirtobrutinib versus ibrutinib in progression-free survival is a key secondary outcome. Other endpoints include duration of response, overall survival, time-to-next treatment, tolerability, and patient-reported outcomes. Trial efficacy and safety will be monitored by an independent data monitoring committee. Clinical trial information: NCT05254743. Research Sponsor: Loxo@Lilly.

TPS7585

Poster Session

KEYFORM-008: Coformulated favezelimab and pembrolizumab (MK4280A) versus chemotherapy in relapsed/refractory classical Hodgkin lymphoma. *First Author: David Lavie, Hadassah Medical Center, Jerusalem, Israel*

Background: PD-1 inhibitors are highly effective in patients (pts) with relapsed or refractory (R/R) classical Hodgkin lymphoma (cHL), but treatment options are limited for pts who have progressed after PD1 blockade. There is an unmet need for effective therapies for anti-PD1 resistant cHL. Upregulation of lymphocyte-activation gene 3 (LAG-3) expression in cHL is proposed to contribute to anti PD-1 resistance (Veldman J et al. Cancer Treat Rev. 2020; 82:101931). The anti-LAG3 antibody favezelimab plus the anti-PD-1 therapy pembrolizumab, has shown promising antitumor activity and manageable safety in pts with R/R cHL after anti-PD1 therapy (Timmerman J et al. Blood 2022; 140). In this ongoing trial, we evaluate the efficacy and safety of MK-4280A in pts with R/R cHL that are refractory to anti-PD1 therapy (ClinicalTrials.gov, NCT0508867). **Methods:** This randomized, open-label, parallel group, active-controlled phase 3 trial will enroll approximately 360 pts aged ≥ 18 years. Eligible pts will have histologically confirmed R/R cHL, which has progressed on anti-PD-1 mAb and have exhausted all available treatment options with clinical benefit including ineligibility for or failed auto-SCT. In addition, pts must have relapsed after treatment with or failed to respond to brentuximab vedotin (BV), were ineligible for BV or discontinued BV due to toxicity, have ECOG performance status (PS) 0-2, adequate organ function, and availability of archival or newly obtained tissue sample. Pts will be randomized 1:1 to receive MK-4280A (coformulated favezelimab 800 mg/pembrolizumab 200 mg; Arm A) IV Q3W or physician's choice of gemcitabine (800-1200 mg/m²) IV or bendamustine (90-120 mg/m²) IV (Arm B). Randomization will be stratified by prior auto-SCT (yes vs no), and ECOG PS (0/1 vs 2). Treatment will continue for up to 35 cycles of MK-4280A, or until unacceptable toxicity, disease progression (PD), or withdrawal from trial. Pts in Arm B with PD confirmed by blinded independent central review (BICR) per Lugano criteria may be eligible to crossover to receive up to 35 cycles of MK-4280A. Disease response assessments by PET and CT or MRI will be performed Q12W during the trial. The primary endpoint is progression free survival (PFS) by BICR per Lugano criteria. Secondary endpoints are overall survival (OS), objective response rate (ORR) and duration of response (DOR) (by BICR per Lugano criteria), and safety. Exploratory endpoints include PFS on subsequent oncologic therapy, and pt reported quality of life. Adverse events will be monitored throughout the trial and graded per NCI CTCAE v5.0. PFS, OS and DOR will be estimated using Kaplan-Meier method. ORR with 95% CI will be estimated using the Clopper-Pearson method. Efficacy will be assessed in the intention-to-treat population and safety assessed in all treated pts. Enrollment in this trial is ongoing. Clinical trial information: NCT0508867. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

TPS7586

Poster Session

SUNMO: A phase III trial evaluating the efficacy and safety of mosunetuzumab in combination with polatuzumab vedotin vs rituximab plus gemcitabine and oxaliplatin in patients with relapsed/refractory aggressive B-cell non-Hodgkin lymphoma. *First Author: Jason Westin, MD Anderson Cancer Center, Houston, TX*

Background: Aggressive non-Hodgkin lymphomas (aNHL) are a diverse group of neoplasms, of which diffuse large B-cell lymphoma (DLBCL) is the most common subtype (Thandra, 2021). Patients (pts) with relapsed/refractory (R/R) DLBCL after one prior therapy who are unable to receive, or relapse after an autologous stem cell transplant (ASCT) and/or chimeric antigen receptor T-cell therapy have a poor prognosis (Salles, 2019; Di Blasi, 2022). Mosunetuzumab (Mosun) is an off-the-shelf CD20xCD3 T-cell engaging bispecific antibody that redirects T cells to eliminate malignant B cells (Sun, 2015), with promising efficacy and safety as a single agent, as shown in a Phase I trial in pts with B-cell NHL, including aNHL (Budde, 2022). Mosun has also shown promising safety and efficacy in combination with polatuzumab vedotin (Pola), a CD79b targeted antibody-drug conjugate that delivers the microtubule-disrupting agent monomethyl auristatin E directly to B cells (Dornan, 2009), in a Phase Ib/II trial in pts with R/R aNHL (Budde, ASH 2021). **Methods:** SUNMO (NCT05171647) is a randomized, open-label, global Phase III trial evaluating the efficacy and safety of subcutaneous Mosun + intravenous (IV) Pola (M-Pola) vs IV rituximab + gemcitabine and oxaliplatin (R-GemOx) in pts with R/R aNHL. Eligible pts have CD20-positive R/R aNHL (DLBCL not otherwise specified [NOS], high-grade B-cell lymphoma double/triple hit or NOS, transformed follicular lymphoma [trFL], or Grade 3B FL), ECOG performance status 0-2, and ≥1 prior systemic therapy (if only one prior line of therapy, pts must be ineligible for ASCT). Exclusion criteria include prior treatment with CD20-directed bispecific antibodies, R-GemOx, or GemOx; prior allogeneic stem cell transplant; and any central nervous system involvement of lymphoma. Pts will be randomized 2:1, stratified by the number of prior lines of therapy (1 vs > 1) and response to last therapy (relapsed vs refractory) to receive M-Pola or R-GemOx IV for a fixed duration of up to 8 cycles (6 cycles for Pola; M-Pola, 21-day cycles; R-GemOx, 14-day cycles). The primary endpoint is progression-free survival (PFS) determined by an independent review facility (IRF). Secondary endpoints include overall survival; IRF- and investigator (INV)-assessed complete response (CR) rate, objective response rate, and duration of response/CR; INV-assessed PFS; patient-reported outcomes; and safety. Biomarker analyses include pre-specified prognostic subsets from baseline biopsies and circulating tumor DNA at baseline and during treatment. Enrollment is ongoing, and an estimated 75 sites globally will enroll approximately 222 pts (M-Pola, 148 pts; R-GemOx, 74 pts). Clinical trial information: NCT05171647. Research Sponsor: This study was sponsored by F. Hoffmann-La Roche Ltd. Third-party editorial assistance was provided by Martha Warren, MSci, and Cheryl Wright, PhD, of Ashfield MedComms, an Inizio company, and was funded by F. Hoffmann-La Roche Ltd.

TPS7587

Poster Session

BRUIN MCL-321: A phase 3, open-label, randomized study of pirtobrutinib versus investigator choice of BTK inhibitor in patients with previously treated, BTK inhibitor naïve mantle cell lymphoma. *First Author: Michael Wang, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Covalent (c) Bruton tyrosine kinase inhibitors (BTKi) have transformed the management of MCL, but these agents are not curative. cBTKi share pharmacologic liabilities (e.g., low oral bioavailability, short half-life), which collectively may lead to suboptimal BTK target coverage especially in rapidly proliferating tumors with high BTK protein turnover such as MCL, which can manifest as acquired resistance to BTKi. Pirtobrutinib, a highly selective, non-covalent (reversible) BTKi, has favorable oral pharmacology that enables continuous BTK inhibition throughout the dosing interval regardless of intrinsic rate of BTK turnover. In the phase 1/2 BRUIN study, pirtobrutinib demonstrated promising durable overall response rates and was well tolerated in patients (pts) with MCL regardless of prior therapy (including cBTKi), number of prior lines of therapy, or reason for prior cBTKi discontinuation. Pirtobrutinib was approved by the FDA in January 2023 for R/R MCL after 2 prior lines of therapy including a BTKi. The objective of this study is to establish whether pirtobrutinib is superior to investigator's choice of cBTKi in pts with previously treated, BTKi naïve MCL. **Methods:** BRUIN MCL-321 (NCT04662255) is a randomized, open-label, global phase 3 study comparing pirtobrutinib monotherapy versus investigator's choice of cBTKi monotherapy (ibrutinib, acalabrutinib, or zanubrutinib) in pts with previously treated, BTKi naïve MCL. Approximately 500 pts will be randomized 1:1 and stratified by sMIPI risk (low/intermediate vs high), comparator BTKi (ibrutinib vs acalabrutinib/zanubrutinib), and number of prior lines of therapy (1 vs ≥ 2). Enrollment for this study is ongoing. Adults with a diagnosis of MCL who have received ≥ 1 prior line of systemic therapy for MCL and are BTKi naïve are eligible. Pts must have measurable disease by imaging per Lugano criteria and have progressed on or relapsed following the most recent line of therapy. A history of current or prior CNS involvement, significant cardiovascular disease, stroke or intracranial hemorrhage within 6 months of randomization, and autologous stem cell transplant (SCT), allogeneic SCT or chimeric antigen receptor (CAR) T-cell therapy within 60 days of randomization are key exclusion criteria. Progression-free survival (PFS) per Lugano criteria assessed by an independent review committee is the primary endpoint. Overall response rate, duration of response, investigator-assessed PFS per Lugano criteria, overall survival, event-free survival, time to treatment failure, time to next treatment, PFS2 (time from randomization to disease progression on next line of treatment or death from any cause), safety and tolerability, and pt reported outcomes are secondary endpoints. Clinical trial information: NCT04662255. Research Sponsor: Loxo@Lilly.

TPS7589

Poster Session

waveLINE-007: Phase 2 study of zilovetam vedotin (ZV) in combination with cyclophosphamide, doxorubicin, and prednisone plus rituximab (R-CHP) in previously untreated diffuse large B-cell lymphoma (DLBCL). *First Author: David Lavie, Hadassah Medical Center, Jerusalem, Israel*

Background: The preferred first-line regimen for DLBCL is rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP); but novel therapies are needed. A recent phase 3 study showed that replacing vincristine with an antibody-drug conjugate (ADC) is a viable approach (Tilly H et al. *N Engl J Med*. 2022;386:351-363). Receptor tyrosine kinase-like orphan receptor 1 (ROR1) is an oncofetal protein that is minimally expressed in adult tissues and overexpressed in DLBCL. ZV is an ADC comprising a humanized IgG1 monoclonal anti-ROR1, a proteolytically cleavable linker, and the antimicrotubule agent, monomethyl auristatin E. The single-arm, open-label, phase 2 waveLINE-007 study (NCT05406401) will investigate ZV combined with R-CHP in patients with previously untreated DLBCL. Part 1 is being conducted to determine safety and tolerability and recommended phase 2 dose (RP2D) of ZV in combination with R-CHP. Part 2 will be conducted to investigate efficacy of ZV at the RP2D with R-CHP. **Methods:** Eligible patients will be ≥ 18 years of age and have previously untreated histologically confirmed DLBCL, positron emission tomography (PET)-positive disease verified by blinded independent central review (BICR), an ECOG PS of 0 or 1, and adequate organ function. Patients diagnosed with primary mediastinal B-cell lymphoma, with a history of transformation of indolent disease to DLBCL, or active central nervous system lymphoma will be excluded. Approximately 60 patients will be enrolled (part 1, n = 45; part 2, n = 15). Part 1 will use a modified toxicity probability interval design to establish the RP2D of ZV when administered with R-CHP. The starting dose of ZV will be 1.75 mg/kg (modified to 1.5, 2.0, 2.25, or 2.5 mg/kg) administered as an intravenous infusion every 3 weeks (Q3W) in combination with R-CHP. In part 2, an additional 15 patients will receive ZV at RP2D plus R-CHP Q3W for up to 6 cycles until disease progression per Lugano 2014 criteria, unacceptable toxicity, or withdrawal. Disease response assessment, computed tomography, and PET will occur at baseline and cycles 3 and 6. Adverse events (AEs) will be monitored up to 30 days after cessation of treatment (90 days for serious AEs, or 30 days if new anticancer therapy is initiated). AEs will be graded per National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0. Primary end points are safety and tolerability and RP2D for ZV in combination with R-CHP, and complete response rate per Lugano 2014 criteria as assessed by the investigator. Secondary end points are objective response rate and duration of response per Lugano 2014 criteria by investigator review. Exploratory end points include progression-free survival per Lugano 2014 criteria by BICR and overall survival. Recruitment is currently underway. Clinical trial information: NCT05406401. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

TPS7588

Poster Session

A phase 2 trial of mosunetuzumab with lenalidomide augmentation as first-line therapy for follicular (FL) and marginal zone lymphoma (MZL). *First Author: Adam J Olszewski, Brown University, Providence, RI*

Background: First-line therapy for high-burden FL and MZL includes immunochemotherapy (most commonly rituximab with bendamustine), which is associated with toxicities, is not curative, and leads to a prolonged T-cell depletion. The alternative of rituximab with full-dose lenalidomide did not improve efficacy or toxicity [Morschhauser et al., *NEJM* 2018]. However, lower-dose, short-course lenalidomide (15mg) may enhance cytotoxic T-cell immunity and efficacy of rituximab [Zucca et al, *Blood* 2019]. Mosunetuzumab is a CD20xCD3-binding, T-cell-engaging bispecific antibody approved for relapsed/refractory FL after 2 lines of therapy. It results in a complete response (CR) rate of 60% in that setting [Budde et al., *Lancet Oncol*, 2022], despite prior exposure to immunosuppressive therapies. This trial proposes a novel therapeutic approach to first-line treatment of FL/MZL, exploring 3 hypotheses: 1) that mosunetuzumab will lead to a high rate of CR, and possibly eradication, of FL/MZL when applied before exposure to immunosuppressive modalities; 2) that low-dose lenalidomide can augment the cytotoxic T-cell response when CR is not achieved with mosunetuzumab alone, and 3) that baseline host immune environment measured in treatment-naïve state can predict CR to bispecific antibody therapy. **Methods:** The Brown University Oncology Research Group BrUOG-401/ML43251 (NCT04792502) is an investigator-initiated, multi-center, single-arm, phase 2 clinical trial for patients (pts) with FL and MZL in need of first-line systemic therapy. Pts with FL must meet the Groupe d'Etude des Lymphomes Folliculaires (GELF) criteria of high-burden disease, whereas pts with MZL must require therapy in the investigators' opinion. As of January 2023, 7 of the planned 52 pts have been enrolled. The trial uses a response-adapted design: pts start with 4 courses of subcutaneous mosunetuzumab monotherapy, using step-up dosing during Cycle 1 (5mg $\rightarrow$ 45mg $\rightarrow$ 45mg) to mitigate the risk of cytokine release syndrome (CRS). Pts attaining CR (by Lugano criteria) after Cycle 4 continue for a total of 8 cycles of mosunetuzumab monotherapy. Pts attaining partial response or stable disease receive 4 additional cycles of mosunetuzumab with low-dose lenalidomide augmentation (10mg daily), with further 4 cycles of mosunetuzumab/lenalidomide if CR after C8 is still not attained. The primary endpoints include the ORR and CR rate at final assessment, and rates of toxicities, particularly CRS, tumor flare, and immune-mediated events. PFS and rate of progression of disease at 24 months (POD24) are among secondary endpoints. The study uses Simon's two-stage design, with the null hypothesis that the CR rate is 53% (based on prior RELEVANCE trial). Correlative studies aim at determining predictive biomarkers of response, including immune signatures and dynamics of circulating tumor DNA during study therapy. Clinical trial information: NCT04792502. Research Sponsor: Genentech; Leukemia and Lymphoma Society.

TPS7590

Poster Session

MAHOGANY: A phase 3 trial of zanubrutinib plus anti-CD20 antibodies vs lenalidomide plus rituximab in patients with relapsed or refractory follicular or marginal zone lymphoma. *First Author: Loretta J. Nastoupil, MD Anderson Cancer Center, Houston, TX*

Background: Inhibition of Bruton tyrosine kinase (BTK) has emerged as a strategy for treatment of patients (pts) with B-cell malignancies including indolent non-Hodgkin lymphomas. Zanubrutinib is a second-generation, potent, and specific BTK inhibitor and has shown to be more effective and better tolerated than first-generation BTK inhibitors in several diseases including chronic lymphocytic leukemia/small lymphocytic lymphoma and Waldenström macroglobulinemia. Zanubrutinib is approved in >15 countries, including the United States and European Union, for pts with relapsed or refractory (R/R) marginal zone lymphoma (MZL) who received ≥ 1 anti-CD20-based regimen, based on the single-arm MAGNOLIA trial (Opat et al. *Clin Cancer Res* 2021). In R/R follicular lymphoma (FL), ROSEWOOD, a phase 2 randomized study of zanubrutinib plus obinutuzumab (ZO) vs obinutuzumab, met its primary endpoint of increased overall response rate (ORR) at primary analysis (Zinzani et al. *J Clin Oncol* 2022). In this trial, ZO in pts with R/R FL demonstrated deep and durable responses with a favorable safety profile. **Methods:** MAHOGANY (BGB-3111-308, NCT05100862) is a phase 3 randomized, open-label trial that compares efficacy and safety of a combination of zanubrutinib plus anti-CD20 monoclonal antibody vs lenalidomide plus rituximab in 2 independent cohorts, for pts with either R/R FL or MZL. Key eligibility criteria include histologically confirmed FL (grades 1-3A) or MZL, previously treated with ≥ 1 anti-CD20-based regimen, relapsed after or refractory to the most recent systemic therapy, in need of treatment, no prior BTK inhibitor exposure, and no prior resistance to a lenalidomide-based regimen. In the FL cohort, pts will be randomized 1:1 to ZO (N = 300) and lenalidomide plus rituximab (N = 300). Randomization is stratified by age (≥ 60 years vs < 60 years), number of prior lines of therapy (1-2 vs > 2) and rituximab-refractory status (yes vs no). The primary endpoint is progression-free survival (PFS) assessed by an independent review committee (IRC), according to Lugano 2014 criteria. Key secondary endpoints are ORR by IRC assessment and overall survival. In the MZL cohort, pts will be randomized 1:1 to zanubrutinib plus rituximab (N = 75) and lenalidomide plus rituximab (N = 75). Randomization is stratified by age (≥ 60 years vs < 60 years) and number of prior lines of therapy (1-2 vs > 2). The primary endpoint is PFS assessed by IRC according to Lugano 2014 criteria. The key secondary endpoint is ORR by IRC assessment. Zanubrutinib is given at 160 mg twice daily or 320 mg once daily according to investigator, until progression or unacceptable toxicity. Obinutuzumab or rituximab are given for up to 8 infusions. Lenalidomide is given according to approved label for up to 12 cycles. Recruitment is ongoing. Clinical trial information: NCT05100862. Research Sponsor: BeiGene.

TPS7591

Poster Session

A phase 1/2 study of STP938, a first-in-class inhibitor of CTP synthase 1, in patients with relapsed/refractory B or T cell lymphoma. *First Author: Manish R. Patel, Florida Cancer Specialists/Sarah Cannon Research Institute, Sarasota, FL*

Background: The rate limiting step in *de novo* pyrimidine synthesis is catalyzed by two homologous enzymes, CTPS1 and CTPS2. CTPS1 is essential for lymphocyte proliferation, whereas CTPS2 is sufficient in non-haemopoietic cells. STP938 is a first in class oral CTPS1 inhibitor showing > 1,300-fold selectivity over CTPS2. In preclinical studies, STP938 induced death of cancer cells by apoptosis at nanomolar concentrations, and inhibited tumor growth in *in vivo* models of hematological malignancies. **Methods:** The study employs a seamless dose escalation, dose expansion design. The phase 1 dose escalation follows a standard 3+3 approach. Intra-patient dose escalation will be permitted. The recommended phase 2 dose (RP2D) will be nominated based on safety, target engagement and early signs of efficacy. An additional six patients will be treated at the RP2D with a preliminary assessment of food effect. Key phase 1 endpoints are safety and tolerability. Key phase 2 endpoints are objective response rate and duration of response. The study is open to adult patients following at least 2 prior lines of therapy who have no treatment options known to provide clinical benefit. The phase 1 study is recruiting patients with B or T cell lymphoma; the phase 2 study will be limited to cohorts of patients with specific lymphoma subtypes, which may include T cell lymphoma (peripheral or cutaneous), mantle cell lymphoma, indolent B cell lymphoma and diffuse large B cell lymphoma. Standard exclusion criteria apply; patients with ECOG performance score > 2 or known CNS involvement by lymphoma are not eligible. The phase 2 study will follow a Simon two-stage design with an interim analysis for futility based on predefined, lymphoma subtype specific response rates. In the case of STP938 showing promising efficacy, provision is included in the protocol to expand a cohort using an adaptive approach based on early efficacy signals (Mehta and Pocock, 2011). Target engagement is assessed by measuring cytokine release (TNF α , IFN γ , IL2, IL8) from *ex vivo* stimulated patient T cells. Exploratory studies include pre- and on-treatment lymphoma biopsies to assess biomarkers of response and mechanism of action. Tumor genomics will be assessed by sequencing of circulating tumor DNA prior to treatment and at disease progression using a bespoke genomic assay designed to elucidate biomarkers of response and understand mechanisms of resistance. The phase 1 study (NCT05463263) opened to enrollment in the US and UK in September 2022. No dose limiting toxicities were observed in the first cohort of 3 patients. The phase 2 study will include additional centers in France. Clinical trial information: NCT05463263. Research Sponsor: Step Pharma.

TPS7593

Poster Session

BELLWAVE-003: A phase 2 dose escalation, confirmation, and cohort expansion study of nemtabrutinib in hematologic malignancies. *First Author: Guilherme Fleury Perini, Hospital Paulistano and Instituto Américas, São Paulo, Brazil*

Background: Bruton tyrosine kinase (BTK) inhibitors (BTKi) have transformed the treatment of several hematologic malignancies. However, acquired resistance, commonly associated with *BTK* C481S mutations, can develop. Nemtabrutinib (MK-1026, formerly ARQ 531) is a noncovalent, competitive inhibitor of both wild type and C481S-mutant BTK that has shown promising antitumor activity at 65 mg once daily (QD) in relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL). BELLWAVE-003 (NCT04728893) is an open-label, phase 2 study investigating the safety and efficacy of nemtabrutinib in patients (pts) with R/R B-cell malignancies. **Methods:** BELLWAVE-003 includes a dose escalation and confirmation phase (part 1) and a cohort expansion phase (part 2). Enrollment of 450 pts is planned. Part 1 will enroll approximately 30 pts, with a minimum of 6 and maximum of 20 per dose level. Part 2 will enroll approximately 420 pts. All pts must be ≥ 18 years and have an ECOG performance status of 0 to 2. Part 1 will enroll pts with CLL/SLL that was R/R after ≥ 2 prior therapies. Part 2 will enroll pts in 8 cohorts: CLL/SLL that is R/R to a covalent irreversible BTKi and a BCL2 inhibitor, and, for pts with CLL, R/R to or ineligible for a PI3K inhibitor (cohort A); R/R CLL/SLL that is BTKi-naïve (cohort B); del17p or *TP53*-mutant R/R CLL/SLL (cohort C); R/R Richter transformation (cohort D); R/R mantle cell lymphoma, including prior covalent BTKi (cohort E); R/R marginal zone lymphoma, including prior covalent BTKi (cohort F); R/R follicular lymphoma (cohort G); and R/R Waldenström's macroglobulinemia, including prior covalent BTKi (cohort H). Initially, pts received nemtabrutinib 80 mg QD orally at dose level 1. Data from BELLWAVE-001 and BELLWAVE-003 subsequently established nemtabrutinib 65 mg QD as the recommended phase 2 dose (RP2D) for future pt enrollment. Treatment will continue until unacceptable toxicity, disease progression, or withdrawal. Adverse events will be monitored throughout and graded using NCI CTCAE version 5.0. Hematologic toxicities in pts with CLL will be assessed using iwCLL 2018 criteria. CT/MRI and/or PET will be performed every 12 weeks, unless needed more frequently. For part 1, the primary end points are safety and tolerability and establishing the RP2D; secondary end points are pharmacokinetics (PK), ORR, and DOR. For part 2, the primary end point is ORR; secondary end points are safety and tolerability, PK, and DOR; and exploratory end points include PFS, OS, and health-related quality of life. Safety and efficacy will be assessed in all pts who receive ≥ 1 dose of study drug. Pts receiving nemtabrutinib 80 mg and 65 mg QD will be analyzed separately. Safety will be summarized descriptively. ORR and 95% CI will be estimated using an exact binomial method. DOR, PFS, and OS will be estimated using the Kaplan-Meier method. Enrollment for this study is ongoing. Clinical trial information: NCT04728893. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

TPS7592

Poster Session

Phase 3 trial of subcutaneous epcoritamab + R-CHOP versus R-CHOP in patients (pts) with newly diagnosed diffuse large B-cell lymphoma (DLBCL): EPCORE DLBCL-2. *First Author: Laurie Helen Sehn, BC Cancer Centre for Lymphoid Cancer and University of British Columbia, Vancouver, BC, Canada*

Background: In pts with newly diagnosed DLBCL, standard treatment with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) has a 5-year progression-free survival (PFS) rate of 67.0%, 58.4%, and 45.8% for International Prognostic Index (IPI) 2, 3, and 4-5, respectively (Ruppert et al, *Blood* 2020). Epcoritamab is a subcutaneously administered, bispecific antibody that binds CD3 on T cells and CD20 on B cells, inducing potent and selective T-cell-mediated killing of malignant CD20+ B cells (Hutchings et al, *Lancet* 2021). Epcoritamab monotherapy demonstrated deep and durable responses (overall response rate [ORR], 63%; complete response rate, 39%) and was generally well tolerated in pts with relapsed/refractory (R/R) aggressive, large B-cell lymphoma (LBCL) (Thieblemont et al, *J Clin Oncol* 2022). Results from an ongoing phase 1/2 study in high-risk pts with newly diagnosed DLBCL (EPCORE NHL-2 arm 1; NCT04663347) show that epcoritamab + R-CHOP has promising efficacy and a manageable safety profile in high-risk pts with IPI 3-5. Among efficacy-evaluable pts (n = 31), ORR was 100% and complete metabolic response (CMR) was 77%; cytokine release syndrome (CRS) events (n = 17/33; 52%) were mostly low-grade, had predictable timing, and did not lead to treatment discontinuation (Falchi et al, ASCO 2022, abstract 7523). These encouraging data support further evaluation of epcoritamab + R-CHOP for the treatment of newly diagnosed DLBCL. **Methods:** This phase 3, global, multicenter, open-label study (NCT05578976) evaluates the efficacy and safety of epcoritamab + R-CHOP in adults newly diagnosed with one of the following CD20+ DLBCL (de novo or transformed from follicular lymphoma [FL]): 1) DLBCL, not otherwise specified (NOS); 2) high-grade B-cell lymphoma with *MYC* and *BCL-2* and/or *BCL-6* rearrangement; 3) T-cell/histiocyte-rich LBCL; 4) Epstein-Barr virus-positive DLBCL, NOS; or 5) FL grade 3b. Other key eligibility criteria include IPI ≥ 2 (pts with IPI 2 not to exceed ~30% of total pts), ECOG PS 0-2, and ≥ 1 measurable disease site. Approximately 900 pts will be randomized 2:1 to either epcoritamab + R-CHOP (6 cycles, followed by 2 cycles of epcoritamab) or R-CHOP (6 cycles, followed by 2 cycles of rituximab). The primary efficacy endpoint is PFS in pts with IPI 3-5 (based on IRC assessment per Lugano criteria). The secondary efficacy endpoints are PFS in pts with IPI 2-5, event-free survival, CMR, overall survival, and minimal residual disease negativity. Safety endpoints include incidence and severity of treatment-emergent adverse events (AEs), serious AEs, and AEs of special interest (CRS, immune cell-associated neurotoxicity syndrome, and clinical tumor lysis syndrome. Enrollment began in January 2023 globally. Clinical trial information: NCT04663347, NCT05578976. Research Sponsor: Epcoritamab is jointly developed by Genmab A/S and AbbVie Inc.; AbbVie and Genmab are sponsoring this study.

TPS7594

Poster Session

BELLWAVE-008: A phase 3 study of the efficacy and safety of nemtabrutinib in previously untreated patients (pts) with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) without TP53 aberrations. *First Author: Ömür Gökmen Sevinç, Istanbul Medipol University, International School of Medicine, Istanbul, Turkey*

Background: Targeting the Bruton's tyrosine kinase (BTK) pathway has been a revolutionary treatment option for first-line treatment of CLL/SLL. Nemtabrutinib is a non-covalent, reversible, potent BTK inhibitor that targets both wild-type and C481S-mutant BTK. Results of an ongoing phase 1/2 dose-escalation study (BELLWAVE-001) have demonstrated manageable safety and preliminary antitumor activity of nemtabrutinib in pts with CLL/SLL. BELLWAVE-008 is a randomized, open-label, phase 3 study (NCT05624554) designed to evaluate efficacy and safety of nemtabrutinib compared with investigator's choice of chemoimmunotherapy (FCR or BR) in pts with previously untreated CLL/SLL without TP53 aberrations. **Methods:** Eligible pts are ≥ 18 years old with previously untreated CLL/SLL with active disease and without TP53 aberrations (17p deletion and/or *TP53* mutation), with ECOG PS of 0-2 and adequate organ function. Pts with Richter transformation or active central nervous system involvement are excluded. Approximately 300 pts will be enrolled and randomly assigned 1:1 to receive nemtabrutinib (65 mg orally once daily until progressive disease, unacceptable toxicity, or discontinuation) or intravenous infusion of the investigator's choice of chemoimmunotherapy for 6 cycles lasting 28 days each (FCR: fludarabine 25 mg/m² and cyclophosphamide 250 mg/m² on days 1, 2, and 3 of each cycle, plus rituximab 375 mg/m² initially, followed by 500 mg/m² on day 1 of each cycle; or BR: bendamustine 70-90 mg/m² on days 1 and 2 of each cycle plus rituximab 375 mg/m² initially, followed by 500 mg/m² on day 1 of each cycle). Randomization will be stratified by risk (high risk: 11q deletion and/or IGHV unmutated vs low risk: absence of high-risk factors) and age (< 65 years vs ≥ 65 years). Treatment response (imaging, physical examination, constitutional symptoms, hematologic evaluation, and bone marrow biopsy, as required) will be performed every 12 weeks up to and including cycle 25, and every 24 weeks thereafter. Adverse events (AEs) will be monitored up to 30 days after treatment cessation (90 days for serious AEs) and will be graded per National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0, and hematologic toxicities will be evaluated according to International Workshop on Chronic Lymphocytic Leukemia (iwCLL). Primary end point is progression-free survival per the iwCLL 2018 criteria as assessed by blinded independent central review. Secondary end points include overall survival, objective response rate (ORR), duration of response, and safety. Exploratory efficacy end points include resistance evaluations, ORR including partial response with lymphocytosis as a response category, pharmacokinetics/pharmacodynamics, and health-related quality of life. Enrollment is ongoing. Clinical trial information: NCT05624554. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

TPS7595

Poster Session

waveLINE-006: A phase 2 study of the safety and efficacy of zilovetamab vedotin as monotherapy or in combination in patients (pts) with aggressive and indolent B-cell malignancies. *First Author: Pier Luigi Zinzani, IRCCS Azienda Ospedaliero-Universitaria di Bologna Istituto di Ematologia "Seràgnoli", Bologna, Italy*

Background: ROR1 is a transmembrane protein expressed in hematologic malignancies. Zilovetamab vedotin (ZV) is an antibody-drug conjugate comprising a humanized IgG1 monoclonal anti-ROR1, a proteolytically cleavable linker, and the antimicrotubule agent monomethyl auristatin E. Nemtabrutinib is a reversible inhibitor of Bruton's tyrosine kinase (BTK). The combination of ZV and a BTKi has the potential for improved responses in B-cell malignancies. The waveLINE-006 study (NCT05458297) is designed to investigate safety and efficacy of ZV as monotherapy or in combination with nemtabrutinib in pts with B-cell malignancies. **Methods:** Eligible pts are ≥ 18 years old with biopsy-proven and/or histologically confirmed mantle cell lymphoma (MCL), Richter's transformation (RT), chronic lymphocytic leukemia (CLL), or follicular lymphoma (FL), relapsed or refractory (R/R) disease, ECOG performance status of 0 to 2, and adequate organ function (table). Approximately 275 pts will be enrolled in 6 cohorts (A-F; see table). In cohorts A and B, patients will receive ZV 2.5 mg/kg IV Q3W. In cohort C, 30 patients will be enrolled in a safety run-in phase of ZV in combination with nemtabrutinib, then an additional 15 patients will receive the RP2D of the combination. Patients in cohort D (schedule optimization) will be randomized 1:1 to receive ZV 2.5 mg/kg IV Q3W (arm 1) or ZV 2.0 mg/kg IV Q2/3W (arm 2). Patients in cohorts E and F (efficacy expansion) will receive the dose and schedule of ZV determined during schedule optimization. Each recipient of ZV or nemtabrutinib will receive the assigned intervention until disease progression, unacceptable toxicity, or other discontinuation criteria are met. Tumor scans will be performed at baseline, then Q12W up to week 108, then Q24W thereafter. Adverse events (AEs) will be monitored and will be graded per NCI CTCAE version 5. The primary end points are the safety and tolerability of ZV alone (cohort D) and in combination with nemtabrutinib (cohort C), and the objective response rate of ZV alone (cohorts A, B, D, E, and F) and in combination with nemtabrutinib (cohort C). The secondary end points are the duration of response of ZV alone (cohorts A, B, D, E, and F) and in combination with nemtabrutinib (cohort C) and the safety and tolerability of ZV alone (cohorts A, B, E, and F). Clinical trial information: NCT05458297. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

Cohort	Inclusion Criteria	n	Treatment
A	R/R MCL after ≥ 2 therapies including a BTKi and either received or was ineligible for CAR-T cell therapy	40	ZV 2.5 mg/kg IV Q3W
B	R/R RT after ≥ 1 prior therapy	50	
C	R/R MCL to ≥ 1 prior therapy and no prior exposure to noncovalent BTKi	45	ZV 2.0 to 2.5 mg/kg IV Q3W
D	R/R CLL or FL after ≥ 2 prior therapies	80	Nemtabrutinib 65 mg PO QD Randomized 1:1 to receive: ZV 2.5 mg/kg IV Q3W (arm 1) or ZV 2.0 mg/kg IV Q2/3W (arm 2)
E	R/R FL after ≥ 2 prior therapies	30	ZV on dose and schedule determined in cohort D
F	R/R CLL after ≥ 2 prior therapies	30	

8000

Oral Abstract Session

Carfilzomib, lenalidomide, and dexamethasone (KRd) versus elotuzumab and KRd in transplant-eligible patients with newly diagnosed multiple myeloma: Post-induction response and MRD results from an open-label randomized phase 3 study. *First Author: Stefan Knop, Wuerzburg University Medical Center, Wuerzburg, Germany*

Background: In medically fit patients with newly diagnosed (ND) multiple myeloma (MM), triplet or quadruplet induction regimens, high-dose chemotherapy (HDT) and autologous stem cell transplant (ASCT) remain a standard of care. Carfilzomib (K), lenalidomide (R) and dexamethasone (d, KRd) induction/consolidation has proven exceptionally effective. Elotuzumab (E), an anti-SLAMF-7 monoclonal antibody bears favorable tolerability in relapsed/refractory MM while its role in NDMM remains unclear. **Methods:** Transplant-eligible (TE) NDMM patients (pts) up to 70 years (yrs) were randomized 1:1 to receive six cycles (C) of KRd or E-KRd, (chemomobilisation for ASCT after C3), single (tandem, if <CR/high risk NDMM) HDT/ASCT, followed by four consolidation C (KRd/E-KRd) and R or ER maintenance. Induction (IND, 28-day C) consisted of K on D1/2, 8/9 and 15/16 (20 mg/m² IV on D 1/2 in C1 and 36 mg/m² thereafter), R (25 mg PO, D1-21) and d (36/40 mg D 1, 8, 15, 22). E was given on D 1, 8, 15, and 22 (C1/C2) and on D 1 and 15 (C3-6; 10 mg/kg IV). After IND, pts underwent restaging when bone marrow was analyzed for minimal residual disease (MRD) by next-generation flow cytometry. The first co-primary endpoint of the study was the rate of pts who were in $\geq$ VGPR and were MRD negative. The study is registered as NCT03948035. **Results:** 579 pts (574 of whom received treatment) were randomized between 08/2018 and 10/2021 at 52 sites and included in the intent-to-treat analysis. Median age was 60 (range, 31-71) yrs. 15.4% had ISS stage III disease. 108/459 evaluable pts (23.5%) had high-risk cytogenetics (del(17p); t(4;14); t(14;16); $\geq$ 3 1q21 copies). 525/574 pts (91.5%) completed 6 IND cycles. MRD negativity and $\geq$ VGPR was achieved in 145 of E-KRd (49.8%) and 102 (35.4%) of KRd patients, respectively (p=.0005). 212 (72.9%) of E-KRd versus 177 (62.5%) of KRd patients experienced treatment-emergent AEs (TEAEs) of $\geq$ grade 3. Febrile neutropenia occurred in 26 (6.4%) E-KRd versus 14 (4.9%) KRd pts. Grade 3/4 thrombocytopenia was seen in 36 (12.4%) E-KRd and 30 (10.6%) KRd pts. Pneumonia occurred in 24 E-KRd (8.2%) and 18 KRd (6.4%) pts. Grade 3/4 cardiac events occurred in 16 E-KRd (5.5%) and of grades 3 to 5 in 16 (5.7%) of KRd pts. 12 E-KRd (4%) and 9 KRd (3.2%) pts had COVID-19 infections with one grade 5 event each (0.3% and 0.4%, respectively). Three pts on E-KRd (1.0%) versus 7 on KRd (2.5%) died on induction due to infections (N=3), MM progression (2), AML (1), a cardiac event (N=1), other (N=3). **Conclusions:** In this study, the addition of elotuzumab to KRd significantly improved the rate of early, deep ($\geq$ VGPR) MRD-negative remission in TE NDMM. E-KRd pts had slightly more TEAEs. Events were mainly hematotoxicity. To the best of our knowledge, this is the first study to show a benefit for the addition of elotuzumab to a front-line regimen. Clinical trial information: NCT03948035. Research Sponsor: AMGEN, Celgene, BMS.

8002

Oral Abstract Session

First results from the RedirecTT-1 study with teclistamab (tec) + talquetamab (tal) simultaneously targeting BCMA and GPRC5D in patients (pts) with relapsed/refractory multiple myeloma (RRMM). *First Author: Yael C Cohen, Tel-Aviv Sourasky (Ichilov) Medical Center, and Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel*

Background: Tec is the first BCMA-directed bispecific antibody approved for the treatment of triple-class exposed RRMM. Tal, a bispecific antibody targeting the novel myeloma antigen GPRC5D, has shown promising efficacy in pts with RRMM. Simultaneously targeting 2 validated myeloma target antigens, using tec + tal in combination may lead to improved outcomes by overcoming resistance mechanisms, such as antigen escape. Here, we report the first results from the phase 1b RedirecTT-1 trial (NCT04586426) in pts with RRMM. **Methods:** Enrolled pts had MM per International Myeloma Working Group 2016 criteria; were RR or intolerant to the last line of therapy (LOT); were exposed to a proteasome inhibitor, immunomodulatory drug, and anti-CD38 therapy; and had measurable disease. The primary objectives are to evaluate safety and to identify a recommended phase 2 regimen (RP2R) for the combination. Responses were investigator assessed. AEs were graded per CTCAE v5.0. Cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) were graded per ASTCT criteria. **Results:** As of Dec 12, 2022, 63 pts received tec + tal. Median (range) age was 67 y (39–81); median (range) prior LOT was 5 (1–11); 33% (15/45) had high-risk cytogenetics; 78% (49/63) were triple-class refractory; 63% (40/63) were penta-drug exposed; and 43% (27/63) had extramedullary disease (EMD; all bone independent). Median (range) duration of follow-up was 14.4 mos (0.5–21.9). The most common treatment-emergent AEs were CRS (81%; grade [gr] 3, 3%, no gr 4), neutropenia (76%; gr 3/4, 75%), and anemia (60%; gr 3/4, 43%). Dose-limiting toxicities (DLTs) were reported at dose level 1 (gr 3 herpetic stomatitis) and dose level 3 (gr 3 AST/ALT elevation). One ICANS event was reported at dose level 3. No DLTs were reported at the RP2R. Across all dose levels, overall response rate (ORR) was 84% (52/62) among all evaluable pts and 73% (19/26) among evaluable pts with EMD; rate of CR or better ($\geq$ CR) was 34% (21/62) and 31% (8/26), respectively. At the RP2R, ORR was 92% (12/13) among all evaluable pts and 83% (5/6) among evaluable pts with EMD; rate of $\geq$ CR was 31% (4/13) and 33% (2/6), respectively. Median duration of response has not been reached. Updated data, with 19 additional pts at the RP2R, will be presented. **Conclusions:** In this first combination study of a BCMA- and GPRC5D-targeted bispecific antibody, tec + tal at the RP2R has a manageable safety profile consistent with each of the monotherapies. A 92% ORR was observed in pts with advanced RRMM at the RP2R, and an ORR of 83% was achieved in pts with EMD, a high-risk population with unmet need, supporting further evaluation of the combination. Clinical trial information: NCT04586426. Research Sponsor: Janssen Research & Development.

8001

Oral Abstract Session

Maintenance therapy with carfilzomib, pomalidomide, and dexamethasone (KPD) in high-risk myeloma patients (pts): A phase 2 study with a safety run-in. *First Author: Ajay K. Nooka, Winship Cancer Center of Emory University, Atlanta, GA*

Background: High-risk pts derive survival benefit from combination maintenance (PI and IMiD) strategies. We have evaluated the safety and efficacy of the next generation PI (carfilzomib) and IMiD (pomalidomide) in combination with dexamethasone in high-risk myeloma (NCT03756896). **Methods:** Newly diagnosed high-risk myeloma pts that have achieved $\geq$ PR post-ASCT were included. High-risk myeloma was defined by the presence of t(4;14) in 27.6%, t(14;16) in 17.2%, del17p in 58.6% pts by FISH or CTG or presence of $\geq$ 20% circulating cells (pPCL) in 6.9%. Double-hit myeloma (as defined by presence of $\geq$ 2 high-risk cytogenetic abnormalities including gain of 1q) was seen in 58.6% of pts. Each cycle is 28 days. Carfilzomib 20/56 mg/m² IV was given on days 1, 8, 15 and pomalidomide 2 mg PO on days 1 to 21 and dexamethasone 40 mg PO was administered on days of carfilzomib. Statistical analysis was conducted using SAS Version 9.4. **Results:** After the safety run in the first 3 pts, 26 additional pts were enrolled. Median age was 60 years (range, 46–75); 58.6% male and 58.6% black. At diagnosis, 65.5% had RISS stage 3 disease. 54.5% of whites and 64.7% of blacks had double-hit disease. Median time from diagnosis and from transplant to study entry was 9.3 (range, 6.08-12.42) and 2.89 (range, 2.8-51) months, respectively. At study entry, $\geq$ CR and $\geq$ VGPR rates were 24.1% and 68.9%, respectively, which deepened to 79.3% and 100% while on study. The median time to best response was 2.07 months (range, 1.22-14.26). Of the 15 pts with available MRD data, MRD (10^{-5}) and (10^{-6}) were achieved in 80% and 53.3%, respectively. After a median follow-up of 25.8 months, 36 month PFS was 63.2% (95% CI 38.3-80.3%) and 36 month OS was 72.4% (44.2-88.0%). Double-hit disease was an independent predictor for progression and death. Among these high risk patients, RISS did not show any statistical significance. While there is no PFS difference by race, the 36 month OS for black pts was inferior compared to whites (61.1% [23.1-84.7%] vs 85.7% [33.4%-97.9%], log rank 0.05). At data cut-off, 37.9% of pts were still receiving treatment; most common reason for permanent treatment discontinuation was progressive disease (27.6%). Among the 6 pt deaths, the most common cause of death was progressive disease (83.3%). Most common ($\geq$ 20%) TEAEs were fever (37.9%), fatigue (34.5%), diarrhea (27.6% [G3/4, 3.4%]), nausea (24.1%), cough (20.7%), muscle cramps (20.1%), acneiform rash (20.1%). TEAEs of interest were cardiac (10.3% [G3/4, 3.4%]), cataracts (17.2% [G3/4, 17.2%]), neutropenia (6.9% [G3/4, 6.9%]) and anemia (10.3% [G3/4, 0%]). **Conclusions:** In pts with high-risk myeloma, KPD maintenance deepened responses. MRD negativity (10^{-5}) was attained in 80% of pts. Despite the encouraging results in this cohort of high-risk patients, PFS and OS among double-hit pts remains poor, warranting newer strategies aimed at remission sustenance. Clinical trial information: NCT03756896. Research Sponsor: Amgen.

8003

Oral Abstract Session

Talquetamab (tal) + daratumumab (dara) in patients (pts) with relapsed/refractory multiple myeloma (RRMM): Updated TRIMM-2 results. *First Author: Bhagirathbhai R. Dholaria, Vanderbilt University Medical Center, Nashville, TN*

Background: Tal is a T-cell redirecting bispecific antibody (BsAb) targeting G protein-coupled receptor family C group 5 member D. Dara is an anti-CD38 mAb with direct on-tumor and immunomodulatory actions. Combining immunomodulatory effects of tal + dara may lead to synergistic efficacy. Initial TRIMM-2 (NCT04108195) results showed that SC tal RP2Ds, 0.4 mg/kg QW or 0.8 mg/kg Q2W, + SC dara had promising efficacy and increased CD38+/CD8+ T cells and proinflammatory cytokines. We report updated results with additional pts and longer follow-up. **Methods:** Pts had MM, $\geq$ 3 prior lines of therapy (LOT; including a proteasome inhibitor [PI] and immunomodulatory drug [IMiD]) or were double refractory to a PI and IMiD, and had not received anti-CD38 therapy in $\leq$ 90 d. Pts received tal RP2Ds with step-up dosing + dara 1800 mg per approved schedule. AEs were graded per CTCAE v5.0; cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) were graded per ASTCT guidelines. Responses were assessed per IMWG criteria. **Results:** As of Dec 12, 2022 (N = 65), median follow-up was 11.5 mo (range 1.0–27.3). Median age was 63 y (range 37–81); 18% of pts had high-risk cytogenetics; 25% had extramedullary plasmacytomas. Median prior LOT was 5 (range 2–16); 63% penta-drug exposed; 58% triple-class refractory. Prior treatments included anti-CD38 (88% [77% refractory]), anti-BCMA (54% [38%]), BsAb (25% [25%]), and anti-BCMA CAR-T (17% [2%]) therapy. All pts had $\geq$ 1 AE (grade [Gr] 3/4 78%), most commonly CRS (78%; all Gr 1/2), dysgeusia (75%), dry mouth (55%), anemia (52%), fatigue (45%), and skin exfoliation (45%). CRS had a median time to onset of 1 d after the most recent dose with median duration of 2 d. 63% of pts had infections (Gr 3/4 22%; Gr 5 3% [n = 2 pneumonia, possibly related to tal + dara]). 38% of pts had neutropenia (Gr 3/4 26%). 85% had postbaseline IgG < 500 mg/dL; of these, 32% received IVIg. ICANS occurred in 3 pts (5%; all Gr 1/2 and resolved in 1–2 d). ORR was 78% (66% $\geq$ VGPR; 45% $\geq$ CR) across RP2Ds (100% in anti-CD38 naïve pts), and responses deepened over time. In pts exposed/refractory to prior therapy, ORRs were 75%/76% for anti-CD38, 74%/64% for anti-BCMA, and 75%/75% for BsAb. Median time to first response was 1 mo (range 0.9–8.3); at 12 mo, 86% of responders (89% of pts with $\geq$ CR) still had responses. At data cutoff, 84% of responders remain on therapy (83%/82% anti-CD38 exposed/refractory). mPFS was 19.4 mo; 12-mo PFS and OS rates were 76% and 93%, respectively. **Conclusions:** Steroid-sparing tal + dara showed deep and durable responses with promising mPFS in heavily pretreated pts with RRMM, including pts refractory to anti-CD38/BCMA and T-cell redirecting therapy, suggesting combined immunomodulatory actions can yield robust responses in pts with refractory disease. The safety profile was clinically manageable; no new signals were identified with longer follow-up. Research Sponsor: Janssen Research & Development, LLC.

8004

Oral Abstract Session

Updated phase I study results of PHE885, a T-Charge manufactured BCMA-directed CAR-T cell therapy, for patients (pts) with r/r multiple myeloma (RRMM). *First Author: Adam Samuel Sperling, Dana-Farber Cancer Institute, Boston, MA*

Background: B cell maturation antigen (BCMA) targeted CAR-T cells are approved for RRMM. Long manufacturing time and high clinical demand limit access. T-Charge, an innovative platform that reduces manufacturing time to <2 days and preserves T cell stemness, results in robust expansion and prolonged CAR T cell persistence. Here we report updated results from the Phase I trial of T-Charge manufactured, fully human, BCMA CAR-T PHE885 (NCT04318327). **Methods:** Eligible pts had RRMM after ≥2 prior lines of therapy (tx). Pts received fludarabine and cyclophosphamide (or bendamustine) for lymphodepletion (LD) prior to PHE885 infusion. Primary objective was safety. Secondary objectives were clinical response and cellular kinetics. **Results:** As of December 22, 2022, 46 pts received PHE885 at the following doses: 2.5e6 (n=4), 5e6 (n=13), 10e6 (n=20), 14.3e6 (n=1), and 20e6 (n=8) CAR T cells. PHE885 was manufactured for 61% of pts at a single academic institution; these pts proceeded from apheresis to LD in a median of 16 days. Median age at enrollment was 65 y (range [R] 45-81), median prior lines of tx was 4 (R 2-10). 37% of pts had extramedullary disease; 96% were triple refractory. Despite aggressive disease, only 28% of pts required bridging chemotherapy, predominantly influenced by quick production time. 96% of pts experienced any gr cytokine release syndrome (CRS); 11% had gr 3 CRS. Median time to CRS onset was 8 (R 2-16) days and median duration was 4 (R 1-19) days. Immune effector cell-associated neurotoxicity syndrome (ICANS) occurred in 22% of pts; 7% had gr 3 ICANS. Dose limiting toxicities were experienced by 13% of pts and included gr 4 neutropenia, gr 4 lipase increase, gr 3 serum amylase increase, gr 3 neurotoxicity, gr 3 transaminitis, and gr 3 ejection fraction reduction. The most common tx-related gr ≥3 AEs included anemia (54%), neutropenia (50%), and thrombocytopenia (37%). Geo-mean peak PHE885 expansion (C_{max}) was 276,000 copies/μg by qPCR and 70.6% of CD3+ T cells by flow cytometry (n=41). The PHE885 transgene was detected in 13/14 (93%) pts at 6 mo and 5/7 (71%) at 12 mo post infusion. T cells with early memory phenotype were preserved in the final product and persisted in pts post infusion. In 43 efficacy-evaluable pts, the ORR was 98%. At 10e6 dose (n=19), ORR was 100% and CRR was 42% (median follow-up of 4.9 mo [R 1.4-11.8]); 60% of 10 evaluable pts were MRD negative at 10^{-5} by NGS. Initial efficacy data at 20e6 and longer follow-up at active doses will also be presented. **Conclusions:** T-Charge manufactured PHE885 produced high response rates with no unexpected safety findings in heavily pretreated RRMM pts with aggressive disease. PHE885 expanded rapidly and showed durable persistence in vivo. Since conversion to CR/sCR has occurred as late as 18 months after infusion in this study, longer follow-up is ongoing to identify a recommended dose for future development. Clinical trial information: NCT04318327. Research Sponsor: Novartis.

8006

Oral Abstract Session

LINKER-MM1 study: Linvoseltamab (REGN5458) in patients with relapsed/refractory multiple myeloma. *First Author: Hans C. Lee, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Linvoseltamab is a BCMAxCD3 bispecific antibody with encouraging efficacy and a manageable safety profile in patients (pts) with relapsed/refractory multiple myeloma (RRMM) (Bumma et al. ASH 2022). Two Phase (Ph) 2 full dose cohorts (50 mg and 200 mg) in the LINKER-MM1 (NCT03761108) trial were studied to optimize dose selection. **Methods:** Ph 2 enrolled adults with MM who progressed on/after ≥3 lines of therapy (LoT) including a proteasome inhibitor (PI), an immunomodulatory drug (IMiD), and an anti-CD38 antibody (Ab), or were at least triple class (IMiD/PI/anti-CD38 Ab) refractory. A protocol amendment permitted pts who progressed during 4–12 wks on 50 mg to dose escalate to 200 mg. Primary endpoint was objective response rate (ORR). Key secondary endpoints included duration of response (DoR) and minimal residual disease status. **Results:** As of 1 Sept 2022, 252 pts have enrolled (Ph 1: 73; Ph 2: 179 [200 mg: 75; 50 mg: 104]). Median age was 66 yrs (range 37–90), 12% had extramedullary plasmacytomas, 12% high-risk cytogenetics, 37% bone marrow plasma cell percentage (BMPC) ≥50%. Median soluble BCMA concentration (sBCMA) was 0.43 mg/L (range 0–10.2), median prior LoT: 5 (range 1–16), and 81% were ≥triple class refractory. Numerically higher efficacy was observed with 200mg, including in high disease burden subgroups; ORR was 64% (200 mg cohort; n = 58, includes 12 Ph 1 pts) and 50% (50 mg cohort; n = 104). Subgroup analyses showed higher ORR in the 200 mg cohort versus 50 mg for sBCMA ≥0.4 mg/L (52% vs 37%), BMPC > 67% (64% vs 35%) and revised ISS stage III (71% vs 27%). Median DoR was not reached for both cohorts (median follow-up: 2.3 months [200 mg], 4.7 months [50 mg]). Probability of maintaining response at 6 months was 89% (200 mg) and 85% (50 mg). Eight pts dose escalated from 50 to 200 mg; 6 (75%) achieved a response. Treatment-emergent adverse events (TEAEs) occurred in 95% (Grade [Gr] ≥3: 66%) of pts in the 200 mg cohort (n = 87, includes 12 Ph 1 pts) and 100% (Gr ≥3: 80%) in the 50 mg cohort. The most common TEAEs were cytokine release syndrome (200 mg: 37% [Gr 3: 1%]; 50 mg: 53% [Gr 3: 2%]), fatigue (200 mg: 32% [Gr ≥3: 0]; 50 mg: 33% [Gr ≥3: 0]) and anemia (200 mg: 28% [Gr ≥3: 24%]; 50 mg: 40% [Gr ≥3: 36%]). Grade ≥3 ICANS occurred in 2 pts (2%) in the 200 mg cohort and 1 pt (1%) in the 50 mg cohort. TEAEs leading to treatment discontinuation occurred in 7% (200 mg cohort) and 8% (50 mg cohort) of pts. Infections occurred in 43% (Gr ≥3: 26%) in the 200 mg cohort and 59% (Gr ≥3: 31%) in the 50 mg cohort. **Conclusions:** Linvoseltamab 200 mg showed better efficacy compared with 50 mg, including in pts with high disease burden. The 200 mg dose had consistent efficacy across high-risk subgroups and induced responses in pts who progressed on 50 mg. Safety was consistent across Ph 2 doses. The recommended linvoseltamab dose for further development is 200 mg. Updated data with longer follow-up and complete enrollment of the 200 mg cohort will be presented at the meeting. Clinical trial information: NCT03761108. Research Sponsor: Regeneron Pharmaceuticals, Inc.

8005

Oral Abstract Session

Updated results of a phase I, open-label study of BCMA/CD19 dual-targeting fast CAR-T GC012F for patients with relapsed/refractory multiple myeloma (RRMM). *First Author: Juan Du, Shanghai Changzheng Hospital, Shanghai, Shanghai, China*

Background: GC012F is a chimeric antigen receptor (CAR)-T cell therapy with B cell maturation antigen (BCMA) and CD19 dual-target developed on the novel FasT CAR-T platform enabling 22–36 h manufacturing. Our previous results were presented at ASCO and EHA 2022 for 29 pts (NCT04236011; NCT04182581), which demonstrated GC012F treatment led to deep and durable response in RRMM pts. Furthermore, initial results showed that GC012F showed considerable efficacy and safety in high-risk transplant-eligible newly diagnosed MM pts (Blood 2022; 140 (Supplement 1): 889–890). Here we present update on RRMM study with a longer median follow-up. **Methods:** From October 2019 to January 2022, 29 heavily pretreated RRMM pts (age 27–76) with a median of 5 prior lines therapies (range 2–9) received GC012F. 26 (89.7%) pts were high risk (HR- mSMART), 8 (27.6%) pts had EM disease, 24 (82.8%) pts were refractory to last therapy. 10 (34.5%) pts had received prior anti-CD38 and 11 (37.9%) pts were treated with auto-HSCT. After lymphodepletion over 2–3 days (30 mg/m²/d, 300mg/m²/d Flu/Cy), GC012F was administered as single infusion at 3 dose levels: 1x10⁵/kg (DL1) n=2, 2x10⁵/kg (DL2) n=10 and 3x10⁵/kg (DL3) n=17. **Results:** At the time of data cut-off (January 30, 2023), 29 eligible pts had been evaluated for response with the last patient completed 12 months efficacy follow up. Overall response rate was 93.1% (27/29), stringent complete response rate was 82.8% (24/29), ≥very good partial response rate was 89.7% (26/29). All patients dosed (29/29) achieved MRD negativity by flow cytometry (sensitivity 10⁻⁴–10⁻⁶). To date 24/29 patients (82.8%) achieved MRD- sCR across all dose levels. According to the Kaplan-Meier method, the median duration of response (DOR) was 37.0 months (95%CI, 11.0–NR) and the median progression free survival (PFS) was 38.0 months (95%CI, 11.8–NR). Cytokine Release Syndrome (CRS) was reported in 25 (86.2%) pts, which was mostly ≤grade 2 (n=23, 79.3%) and 2 (6.9%) pts were grade 3. No ICANS was observed (Graded by ASBMT criteria). Median duration of CRS was 3 days (1–8 d). PK results showed no difference amongst dose levels DL1 to DL3. The median time of persistence was 41.0 days (range: 51–1183) and GC012F was still detectable in 23 (79.3%) pts at 6 months and in 16 (55.2%) pts at 12 months after infusion. sBCMA plasma levels started declining at day 4 in 80% (8/10) patients, falling sharply at day 10 in 100% (19/19), and reaching minimal levels from 30 to 60 days post infusion in 100% (29/29) patients. **Conclusions:** The updated results showed GC012F continues to provide deep and durable responses, and a very high MRD negativity rate in RRMM pts, including in pts refractory to anti-CD38, PIs and IMiDs. Based on these promising results of the study of GC012F for RRMM, further clinical studies will be conducted to confirm the efficacy of GC012F. Clinical trial information: NCT04236011; NCT04182581. Research Sponsor: Gracell Biotechnologies Ltd, Shanghai, China.

8007

Oral Abstract Session

A phase 3, open-label, randomized study to evaluate the efficacy and safety of single-agent belamaf mafodotin (belamaf) compared to pomalidomide plus low-dose dexamethasone (Pd) in patients (pts) with relapsed/refractory multiple myeloma (RRMM): DREAMM-3. *First Author: Katja Weisel, University Medical Center of Hamburg-Eppendorf, Hamburg, Germany*

Background: Belamaf, an antibody-drug conjugate targeting B-cell maturation antigen, induces cell death by direct cell kill and immune-mediated mechanisms. The DREAMM-2 trial (NCT03525678) showed rapid, deep and durable responses to belamaf monotherapy in pts with RRMM. The Phase 3, open-label, randomized, multicenter DREAMM-3 trial (NCT04162210) evaluated belamaf monotherapy vs Pd in adult pts with RRMM at second relapse (third line) or later. **Methods:** Pts were randomized (2:1) to belamaf 2.5 mg/kg Q3W or Pd (pom 4 mg PO daily on days 1–21 of 28 day cycle; dex, 40mg PO [20mg if >75 years]) Q1W. The primary endpoint was progression free survival (PFS). **Results:** 325 pts were enrolled (belamaf n=218, Pd n=107). Median (range) age was 68 (38–90) years; 57% were male. Median (range) duration of exposure for belamaf was 4.1 (0.4, 22.9) months (mo) and 5.3 (0.4, 24.0) for Pd. Median (range) duration of follow-up was 11.5 (0.6, 24.2) mo for belamaf and 10.8 (0.0, 26.4) mo for Pd. Median PFS was longer for belamaf (11.2 [6.4, 14.5] mo) vs. Pd (7.0 [4.6, 10.6] mo). There was no statistically significant difference in PFS between the 2 treatment groups, (HR 1.03 [95% CI: 0.72, 1.47]), based on the stratified Cox model (p=0.558). Belamaf induced deeper responses vs Pd (Table). Median duration of response (DoR) was more durable for belamaf than for Pd (Table). At 12 mo, the probability (95% CI) of maintaining response was 0.768 (0.641, 0.854) for belamaf and 0.484 (0.258, 0.679) for Pd. Median PFS2 was 18.7 mo (95% CI 14.5, NR) for belamaf and 12.7 mo (9.3, 21.1) for Pd. PFS2 rate at 6 mo was 73% for belamaf and 76% for Pd. Overall survival (OS) data were immature (37.5% overall maturity) at this analysis; median OS was 21.2 mo (95% CI 18.7, NR) for belamaf and 21.1 mo (15.1, NR) for Pd (HR 1.14 [95% CI 0.77, 1.68]; p=0.746). Adverse events (AEs) were reported in 97% and 93% of patients (Table). The safety profile was consistent with previous reports for belamaf and Pd. **Conclusions:** Belamaf monotherapy did not demonstrate PFS superiority when compared to a doublet (Pd). However, median PFS was longer for belamaf monotherapy and belamaf induced deeper, more durable responses than Pd. No new safety signals were observed. Subgroup analyses and PRO outcomes will be reported. Belamaf continues to be investigated in combination with established and novel agents. Research Sponsor: GSK(207495).

Efficacy and safety.

	Belamaf (ITT n=218, safety n=217)	Pd (ITT n=107, safety n=102)
ORR, n (%)	89 (41)	38 (36)
≥VGPR, n (%)	55 (25)	9 (8)
MRD- ≥VGPR, n (%)	15 (7)	0
DoR, months, median (95% CI)	NR (17.9, NR)	8.5 (7.6, NR)
Any AE, n (%)	211 (97)	95 (93)
Serious AEs, n (%)	94 (43)	40 (39)
Fatal AEs, n (%)	16 (7)	11 (11)
Grade 3–4 AEs, n (%)	164 (76)	71 (70)
AEs leading to discontinuation, n (%)	33 (15)	17 (17)

8008

Oral Abstract Session

Efficacy and safety of elranatamab in patients with relapsed/refractory multiple myeloma (RRMM) and prior B-cell maturation antigen (BCMA)-directed therapies: A pooled analysis from MagnetisMM studies. *First Author: Ajay K. Nooka, Winship Cancer Institute, Emory University Hospital, Atlanta, GA*

Background: Studies in the MagnetisMM program (MM-1, NCT03269136; MM-3, NCT04649359; MM-9, NCT05014412) enrolled pts treated with prior BCMA-directed therapies. A pooled analysis from these studies evaluated the efficacy and safety of elranatamab in pts with RRMM and prior exposure to BCMA-directed therapy. **Methods:** Eligible pts received at least 1 PI, 1 IMiD, 1 anti-CD38 antibody, and 1 BCMA-directed therapy (ADC and/or CAR-T cells). Pooled analysis included pts in MM-1 (n = 13) who received SC elranatamab 215–1000 µg/kg; MM-3 (n = 64) and MM-9 (n = 9) who received the RP2D, SC 76 mg QW. Efficacy endpoints were assessed by investigator per IMWG criteria. TEAEs were graded by CTCAE (MM-1, v4.03; MM-3 & MM-9, v5.0); CRS and ICANS were graded by ASTCT criteria. Results include data up through ~10 months after last pt initial dose in all pooled studies. **Results:** In total, 86 pts were included. Median age was 66.0 y (range, 40–84); 47.7% male. At baseline, 69.8% had an ECOG PS ≥1; 24.4% had high risk cytogenetics; 54.7% had extramedullary disease. Pts received a median of 7.0 (3–19) prior lines of therapy, including BCMA-directed ADC (67.4%), CAR T-cells (41.9%), 9.3% received both. 96.5% and 54.7% of pts were triple-class and penta-drug refractory, respectively; among pts who received ADC and CAR-T cells respectively, 79.3% and 27.8% were refractory to ADC and CAR-T cells. After a median follow-up of 10.3 mo (0.3–32.3), median duration of treatment was 3.3 mo (0.03–30.4). At data cut-off, 24.4% of pts remained on treatment; most common reason for permanent treatment discontinuation was progressive disease (44.2%). ORR was 45.3% (95% CI 34.6–56.5), with ≥CR achieved in 17.4% of pts. ORR for pts with prior BCMA-directed ADC and CAR-T cells was 41.4% (95% CI 28.6–55.1) and 52.8% (95% CI 35.5–69.6), respectively. Among responders, median time to objective response was 1.9 mo (0.3–9.3). Median DOR was not reached by 10 mo; the DOR rate at 9 mo was 72.4% (95% CI 54.7–84.2). DOR rate (95% CI) for pts with prior BCMA-directed ADC and CAR-T cells were 67.3% (43.1–83.0) and 78.9% (53.2–91.5) at 9 mo, respectively. Median PFS was 4.8 mo (95% CI 1.9–7.7), and median OS was not reached by 10 mo, with a rate of 60.1% (95% CI 48.9–69.6) at 9 mo. Most common (≥25% of pts) TEAEs were CRS (65.1% [G3 1.2%]), anemia (59.3% [G3/4, 46.5%]), neutropenia (44.2% [G3/4, 40.7%]), thrombocytopenia (40.7% [G3/4, 29.1%]), diarrhea (33.7% [G3/4, 0%]), and lymphopenia (32.6% [G3/4, 30.2%]). ICANS was reported in 5.8% (G3, 2.3%) of pts. **Conclusions:** In pts with RRMM and prior exposure to BCMA-directed therapies, elranatamab was efficacious and well tolerated; no new safety signals were observed vs the BCMA-naïve population. Results support treatment with elranatamab in pts with RRMM post BCMA-directed therapy. Clinical trial information: NCT03269136, NCT04649359, NCT05014412. Research Sponsor: Pfizer.

8010

Poster Discussion Session

Long-term remission and survival in patients with relapsed or refractory multiple myeloma after treatment of LCAR-B38M CAR-T: At least 5-year follow-up in LEGEND-2. *First Author: Jian-Qing Mi, State Key Laboratory of Medical Genomics, National Research Center for Translational Medicine, Shanghai Institute of Hematology, Ruijin Hospital Affiliated With Shanghai Jiao Tong University School of Medicine, Shanghai, China*

Background: LCAR-B38M CAR-T cells express a structurally differentiated CAR construct containing a 4-1BB costimulatory domain and 2 BCMA-targeting single-domain antibodies designed to confer avidity. LEGEND-2 was a first-in-human phase 1 study of LCAR-B38M conducted in China, which showed encouraging efficacy and manageable safety in 74 patients (pts) with RRMM. The US phase 1b/2 CARTITUDE-1 and Chinese phase 2 CARTIFAN-1 trials of ciltacabtagene autoleucl, which expresses the same CAR as LCAR-B38M, confirmed the efficacy observed in LEGEND-2. Here, we present ≥5-y FU data from LEGEND-2, the longest FU for any BCMA-targeted CAR-T cell therapy study. **Methods:** Study design was previously published. Pts underwent lymphodepletion with cyclophosphamide (cy) 300 mg/m² (n=66) or cy 250 mg/m² plus fludarabine 25 mg/m² (n=8) prior to receiving LCAR-B38M at a median dose of 0.51 × 10⁶ (range, 0.07–2.10 × 10⁶) CAR-positive T cells/kg in a single (n=9) or 3 split (n=65) infusions. **Results:** Pts were enrolled from 30 Mar 2016 to 26 Nov 2017. As of 30 Nov 2022, median FU was 65.4 mo (range, 0.4–78.8). 74 pts had received LCAR-B38M (median age, 54.5 y; 60.8% male; median [range] 3 [1–9] prior lines of therapy [LOT]; 44.6% ISS stage I; 28.4% ISS stage II; 29.7% with extramedullary disease [EMD]; 35.7% cytogenetic high risk). No new CAR-T cell-related toxicities were reported in the analysis. ORR (87.8%), CR rate (73.0%), MRD-negative CR rate (67.6%), median DOR (23 mo), and median PFS (18 mo) were mature and the same as previously reported; median OS was previously not reached. At 65.4-mo median FU, median OS was 55.8 mo, with 33 (44.6%) pts alive and 13 (17.6%) still disease-free. Compared with pts with progressive disease (PD) or who died, pts without PD were more likely to have baseline ECOG performance status (PS) 0, IgG type MM, ISS stage I MM, numerically shorter time from diagnosis, fewer prior LOT, no light chain MM, and no EMD (Table). **Conclusions:** At ≥5-y FU in LEGEND-2, median OS was 55.8 mo and 18% of pts with RRMM were disease-free, raising the possibility of a cure in this heavily pretreated pt population. Our data suggest that pts who are less heavily pretreated or have good functional status may experience greater benefit, potentially being cured, from LCAR-B38M CAR-T cell therapy. Clinical trial information: NCT03090659. Research Sponsor: Key Research and Development Plan of ShaanXi Province, Project 2018SF-002 awarded to W-H Zhao, Project 2017ZDXM-SF-25-6 (Approval No. 2018ZDXM-SF-039) awarded to A-L He; National Natural Science Foundation of China (No. 81970189) awarded to J Xu.

Baseline characteristics of pts with and without PD/death.	Without PD n=13	With PD/Death n=61
	median FU, 66.8 mo (range, 61.1–76.1)	median FU, 64.6 mo (range, 0.4–78.8)
Male / female	61.5% / 38.5%	60.7% / 39.3%
Median age (range), y	53 (35–68)	55 (27–74)
ECOG PS 0	61.5%	36.1%
MM type: IgG / light chain	76.9% / 0%	37.7% / 31.1%
EMD	0%	36.1%
ISS stage I	61.5%	41.0%
Median time from diagnosis (range), y	3 (1–9)	4 (1–9)
Median # prior LOT (range)	2 (1–6)	3 (1–9)
Median dose (range), ×10 ⁶ cells/kg	0.432 (0.16–1.58)	0.523 (0.07–2.10)

8009

Poster Discussion Session

CARTITUDE-1 final results: Phase 1b/2 study of ciltacabtagene autoleucl in heavily pretreated patients with relapsed/refractory multiple myeloma. *First Author: Yi Lin, Mayo Clinic, Rochester, MN*

Background: Heavily pretreated patients (pts) with relapsed/refractory multiple myeloma (RRMM) treated with standard of care therapy have median overall survival (OS) of ~12 months (mo). In the single-arm, phase 1b/2 CARTITUDE-1 study (NCT03548207), pts received a single infusion of ciltacabtagene autoleucl (cilta-cel), a CAR-T cell therapy targeting BCMA. At the final protocol-specified analysis (27.7-mo median follow-up [MFU]), overall response rate (ORR) was 98%, with 83% stringent complete response (CR); 27-mo rates of progression-free survival (PFS) and OS were 55% and 70%, respectively. Here, we report study closeout results. **Methods:** Eligible pts received ≥3 prior lines of therapy (LOT) or were double refractory to a proteasome inhibitor (PI) and immunomodulatory drug (IMiD); and had received prior PI, IMiD, and anti-CD38 antibody therapy. Primary endpoint was ORR and safety; secondary endpoints included PFS, OS, and minimal residual disease (MRD) negativity at 10⁻⁵. **Results:** 97 pts received cilta-cel (median age 61 years [y]; median 6 prior LOT; 42% penta-drug refractory; 88% triple-class refractory; 99% refractory to last LOT). As of October 14, 2022, MFU was 33.4 mo (range, 1.5–45.2). Median (m) duration of response was 33.9 mo (95% CI, 25.5–not estimable [NE]). mPFS was 34.9 mo (95% CI, 25.2–NE), with an estimated 47.5% progression free and alive at 36 mo. mOS was not reached (NR), with an estimated 62.9% survival at 36 mo. Of 49 MRD-evaluable pts, 26 had MRD negativity sustained for ≥12 mo, of which 20 had sustained MRD-negative ≥CR. mPFS was NR in these subgroups (Table). 18 pts were MRD negative with ≥CR at 24 mo post infusion. No new safety signals and no new neurotoxicity events were reported since the 27.7-mo MFU. 6 new cases of second primary malignancy were reported, including 2 cases of basal cell carcinoma and 1 case each of myelodysplastic syndrome, B-cell lymphoma, melanoma, and prostate cancer. 5 additional deaths occurred (progressive disease [PD], n=3; pneumonia and sepsis, n=1 each [both unrelated to cilta-cel]), for a total of 35 (PD, n=17; unrelated to cilta-cel, n=12; related, n=6). **Conclusions:** Longer mPFS was observed after a single infusion of cilta-cel than any previously reported therapy in heavily pretreated pts with RRMM. Achieving CR and/or sustained MRD negativity was associated with prolonged PFS. Pts continue to be followed for safety and survival in the 15-y CARTINUE long-term study (NCT05201781; MMY4002). Clinical trial information: NCT03548207. Research Sponsor: Janssen Research & Development, LLC; Legend Biotech USA Inc.

PFS at ~3-y MFU.				
Subgroup	n	mPFS (95% CI), mo	30-mo PFS rate	36-mo PFS rate
All pts	97	34.9 (25.2–NE)	54.2%	47.5%
≥CR	76	38.2 (34.9–NE)	66.8%	59.8%
6-mo sustained MRD negativity ^a	34	32.2 (25.1–NE)	68.6%	45.7%
12-mo sustained MRD negativity ^a	26	NR (NE–NE)	74.9%	NE
12-mo sustained MRD-negative CR ^a	20	NR (NE–NE)	78.5%	NE

^a≥2 MRD-negative assessments, 6 or 12 mo apart, with no MRD-positive samples in that interval.

8011

Poster Discussion Session

Long-term follow-up from MajesTEC-1 of teclistamab, a B-cell maturation antigen (BCMA) x CD3 bispecific antibody, in patients with relapsed/refractory multiple myeloma (RRMM). *First Author: Niels W.C.J. van de Donk, Amsterdam University Medical Center, Vrije Universiteit Amsterdam, Amsterdam, Netherlands*

Background: Teclistamab is the first approved off-the-shelf BCMA×CD3 bispecific antibody for the treatment of patients (pts) with RRMM based on data from the pivotal phase 1/2 MajesTEC-1 study (NCT03145181/NCT04557098). Moreau et al (*NEJM* 2022) reported rapid, deep, and durable responses: overall response rate (ORR) was 63% (39% ≥complete response [CR] rate), with a median duration of response (mDOR) of 18.4 mo, and median progression-free survival (mPFS) of 11.3 mo after a median follow-up (mFU) of 14.1 mo. Here, we present updated results with extended follow-up of ~2 y (22 mo). **Methods:** Eligible pts were aged ≥18 y, had documented MM (per IMWG 2016 criteria), and had received ≥3 prior lines of therapy (LOT), including a proteasome inhibitor, an immunomodulatory drug, and an anti-CD38 antibody. Prior BCMA-targeted therapy was not allowed in this cohort. Pts received teclistamab 1.5 mg/kg QW (the recommended phase 2 dose [RP2D]), with the option to switch to Q2W dosing if they achieved ≥partial response after ≥4 cycles of therapy in phase 1 or ≥CR for ≥6 months in phase 2. The primary endpoint was ORR (assessed per IMWG 2016 criteria by computerized algorithm). AEs were graded per CTCAE v4.03. Cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) were graded per ASTCT guidelines. **Results:** As of Dec 9, 2022, 165 pts had received teclistamab at the RP2D (median age, 64 y; 58% male; 26% high-risk cytogenetics; 12% International Staging System stage III). Pts had a median of 5 prior LOT (range, 2–14): 92% daratumumab exposed; 78% triple-class refractory; 81% daratumumab-refractory; and 90% refractory to last LOT. At 22 mo mFU, 43% of pts achieved ≥CR, mDOR was 24 mo (95% CI, 16.2–not estimable [NE]), mDOR in pts achieving ≥CR was not reached (95% CI, 24.0–NE), mPFS was 12.5 mo (95% CI, 8.8–17.2), and median overall survival was 21.9 mo (95% CI, 16.0–NE). Hematologic AEs (any grade [gr]/gr 3/4) included neutropenia (72%/65%), anemia (54%/38%), thrombocytopenia (42%/22%), and lymphopenia (35%/33%). Infections occurred in 78% of pts (52% gr 3/4); key infections included respiratory (56%), COVID-19 (27%), other viral (10%), GI (8%), fungal (5%), PJP (4%), and hepatitis B (0.6%). CRS occurred in 72% of pts (0.6% gr 3; no gr 4/5); 5 (3%) pts reported 9 ICANS events (all gr 1/2; all resolved). 1 pt in phase 1 required a teclistamab dose reduction due to neutropenia. 6 treatment-related deaths have occurred (3 due to COVID-19). Of the 49 pts who remain on study, ~90% have received Q2W dosing. **Conclusions:** After ~2 y mFU, pts receiving teclistamab demonstrated deep and durable responses regardless of refractory status, with mPFS of 12.5 mo and mDOR of 24 mo (not reached in those achieving ≥CR). These long-term follow-up data support teclistamab as a safe and effective off-the-shelf BCMA bispecific therapy for pts with RRMM. Clinical trial information: NCT03145181, NCT04557098. Research Sponsor: Janssen Research & Development.

8012

Poster Discussion Session

Safety and efficacy of standard of care (SOC) ciltacabtagene autoleucel (Cilta-cel) for relapsed/refractory multiple myeloma (RRMM). *First Author: Doris K. Hansen, Department of Blood & Marrow Transplant and Cellular Immunotherapy, Moffitt Cancer Center, Tampa, FL*

Background: Cilta-cel was FDA approved in 2022 for the treatment of RRMM. We evaluated the outcomes of patients treated with intended SOC cilta-cel. **Methods:** 12 US academic medical centers contributed data to this retrospective study. As of 12/31/2022, 177 patients were leukapheresed and 139 received cilta-cel. **Results:** The table describes the study population compared to the CARTITUDE-1 trial. More patients in our study had extramedullary disease (EMD, 35%) and high-risk cytogenetics (41%). 55% of the patients would not have met eligibility criteria for CARTITUDE-1. Common reasons for ineligibility were cytopenias (19%), prior BCMA therapy (14%), organ dysfunction (12%), oligosecretory disease (13%), and plasma cell leukemia (8%). 83% of the patients received bridging chemotherapy (overall response rate, ORR: 28%). Lymphodepletion included fludarabine (Flu) + cyclophosphamide (Cy): 81%, bendamustine: 11%, Cy: 4%, and cladribine + Cy: 4%. Median CAR-T cells infused were 0.6 million/kg (range: 0.1-0.9), and 19% of patients were treated on an expanded access protocol (EAP). Median follow-up was 2.3 months (range: 0-8). Cytokine release syndrome (CRS) was seen in 81% ($\geq$ grade 3: 7%) and immune effector cell-associated neurotoxicity syndrome (ICANS) in 22% ($\geq$ grade 3: 8%) of patients. Tocilizumab, steroids, and anakinra were used in 61%, 44%, and 10% of patients, respectively. Delayed neurotoxicity (NT) was seen in 9% (cranial nerve palsy: 8, Parkinsonism: 2, others: 3). Grade $\geq$ 3 cytopenias at day $\geq$ 30 were seen in 75% of patients. Infections were seen in 32% of patients. Day 30 (N=115) and best response rates (N=118) were: $\geq$ partial response (PR), 75/80%; $\geq$ very good PR, 44/62%; and $\geq$ complete response (CR), 26/40%, respectively. In the non-EAP FluCy population (N=88), best ORR $\geq$ CR were 89/49%. 17 patients died by data cut-off, 4 due to disease progression and 13 (9%) due to non-relapse mortality (NRM) (grade 5 CRS: 3, infection: 6, CRS/infection: 1, grade 5 ICANS: 1, delayed NT: 2). **Conclusions:** Patients treated with intended SOC cilta-cel had a favorable ORR (80%) despite a larger proportion of patients having high-risk features relative to trial patients and limited follow-up. Response rates were higher in patients receiving conforming products with FluCy conditioning (89%). Delayed NT and NRM were seen in 9% of patients. Results will be updated with continued follow-up. D.K.H., K.K.P., M.J., Y.L. & S.S. contributed equally. Research Sponsor: None.

Comparison of patient characteristics and outcomes by intended SOC vs. CARTITUDE-1 trial participants.

	Intended SOC, N=139	CARTITUDE-1, N=97
Median age, yrs	64	61
ECOG PS 0 or 1	91%	96%
Extramedullary disease	35%	13%
High-risk cytogenetics	41%	24%
Median prior regimens	6 (2-18)	6 (4-8)
Penta-refractory disease	36%	42%
Grade $\geq$ 3 CRS and ICANS	7%, 8%	4%, 2%
Delayed NT/Parkinsonism	9%/1.4%	12%/6%
Best ORR $\geq$ CR	All: 80%/40%	98%/83%
	Non-EAP FluCy: 89%/49%	

8014

Poster Discussion Session

Plasma cell leukemia: A multicenter retrospective study of 150 patients. *First Author: Iloabueke Gabriel Chineke, The University of Arizona Cancer Center, Arizona, AZ*

Background: Despite the use of novel induction regimens, stem cell transplantation (SCT), and maintenance therapy, plasma cell leukemia (PCL) remains a challenging disease with a dismal prognosis. Currently, there is no agreed standard of care management for PCL. We conducted a multicenter retrospective analysis of the clinical presentation, treatment, and outcomes of 150 patients with PCL. **Methods:** Data of patients diagnosed with pPCL or sPCL between 01/2010 and 01/2021 were entered into a study-specific REDCap database from 7 different U.S. academic sites. PCL was defined as $\geq$ 5% circulating plasma cells. Clinical data included baseline patient characteristics, clinical presentation, treatment, therapeutic response, and survival outcomes. Overall survival (OS) curves were plotted using the Kaplan-Meier method. Cox proportional hazards regression tested associations between patient characteristics and OS, generating hazard ratios (HR) and 95% confidence intervals (CI), adjusted for PCL type (primary or secondary) and SCT. **Results:** The analytical cohort included 93 pPCL and 57 sPCL patients. Median age at diagnosis was 60 years. High-risk cytogenetics were found in 56.7% of the patients where it was documented. Of the 79 patients with a documented induction regimen, 58.2% received a proteasome inhibitor triplet, 22.8% received a VTD-Pace like conventional chemotherapy, and 3% received a daratumumab quadruplet regimen. SCT (autologous or allogeneic) was done in 56.1% of the patients. The median OS for all patients, those with pPCL, and those with sPCL was 20.3, 36.6, and 3.2 months, respectively. Secondary PCL was associated with worse survival outcomes compared with pPCL (HR, 2.46; 95% CI, 1.51-3.98; $p < 0.001$) (Table). Median OS was better in patients treated with a proteasome inhibitor triplet regimen vs VTD PACE-like combination (28.2 versus 12.6 months). OS was prolonged among patients who underwent any type of SCT compared with those who did not undergo SCT (44.0 versus 5.7 months, $p < 0.001$). **Conclusions:** This multicenter retrospective study is one of the largest PCL analyses performed to date and reveals the clinical practice patterns of treatment and survival of PCL patients across the U.S. in the novel treatment era. The survival analysis reinforces the poor prognosis in sPCL patients and the continued need for novel treatment approaches in this patient population. While limited by retrospective design, this analysis suggests prolonged survival with transplantation in both pPCL and sPCL. Research Sponsor: None.

Associations with survival (any survival, n=150).

Characteristics	Crude HR (95% CI)	Adjusted HR (95% CI)	p-value
PCL type (primary/secondary)	4.69 (3.10 - 7.10)	2.46 (1.51 - 3.98)	< 0.001
Any transplant	0.17 (0.11 - 0.28)	0.23 (0.14 - 0.38)	< 0.001
Extramedullary disease	1.57 (0.98 - 2.50)	1.09 (0.64 - 1.88)	0.749

8013

Poster Discussion Session

Impact of bridging therapy (BT) on outcome of relapsed refractory multiple myeloma (RRMM) with Ide-cel CAR T-cell therapy: Real-world experience from the US myeloma CAR T consortium. *First Author: Aimaz Afrough, Simmons Comprehensive Cancer Center, UT Southwestern Medical Center, Dallas, TX*

Background: Ide-cel is an FDA-approved treatment for RRMM patients (pts). However, there is limited data on how BT for disease control during its manufacturing process affects clinical outcomes. **Methods:** Eleven US academic centers contributed data to this analysis without involvement from the manufacturer. By 5/1/2022, 235 pts had undergone leukapheresis, with 214 infused with a median follow up of 9 months (mos). BT was given between leukapheresis and CAR-T infusion. **Results:** In this analysis, 79% of pts (n = 170) received BT, which included alkylator-based in 35.5%, steroid and/or IMiD/Ab combos (IMiD combos) in 14%, PI combinations (PI combos) in 12%, and selinexor in 10%. BT recipients had higher ECOG PS 2-4, R-ISS 2-3, ferritin, and CRP before lymphodepleting (LD) chemo, however, no difference among BT subgroups. No difference in prior lines of therapy or penta-refractory between BT and No BT (NBT) groups or BT subgroups. Median cycle of the BT was 1 (1-7), with overall response rate (ORR) of 12%, with no difference among BT subgroups. Incidence and severity of CRS and ICANS were comparable in BT and NBT. However, pts who received BT had a longer median hospital stay compared to NBT, particularly in the alkylator/selinexor subgroups. There were no significant difference in cytopenias at day 90 post CAR-T between the BT and NBT or BT subgroups. For the 73% (n = 157) evaluable for day 90 response, there was no difference in the complete or ORR between the BT and NBT groups (41% vs. 52%; $p = .2$ and 84% vs. 87.5%, $p = .8$, respectively). Median PFS was worse at 8.1 mos in BT vs 11.5 mos in NBT ($p = .03$). Among BT subgroups, PFS was the longest with IMiD combos with median PFS not reached (NR), comparable to NBT, and was significantly longer than all other BT subgroups ($p = 0.01$). The median OS was 13.8 mos with BT and NR in NBT ($p = .002$). In BT subgroup analysis, alkylators had a shorter OS, although, this was not significant ($p = .06$). There was no significant difference in PFS and OS in relationship to response to BT ($p = .6$ and $p = .9$, respectively). **Conclusions:** Pts without BT had longer PFS and OS post ide-cel, likely reflective of less aggressive disease. Those who received BT with steroid/IMiD and Ab combos had similar PFS as NBT. However, BT choice is complicated by disease severity and should be evaluated per patient circumstances. Research Sponsor: None.

Patient's characteristics and outcomes based on BT.

	BT			Type of BT				
	Yes (N = 170)	No (N = 44)	P	Alkylator (N = 76)	IMiD combos (N = 30)	PI combos (N = 25)	Selinexor (N = 21)	P
Median Age, yrs	63	65	.4	63	63.5	63	66	.8
ECOG ≥ 1	21%	2%	.002	24%	13%	13%	19%	.5
EMD	47%	36%	.2	54%	27%	48%	57%	.052
R-ISS ≥ 3	82%	55%	.002	82%	95%	90%	79%	.4
High-risk cytogenetic	36%	19%	.07	39%	38%	37.5%	31.5%	.9
Ferritin > 300 ng/mL prior LD	59%	32%	.001	59%	50%	52%	62%	.5
CRP > 5 mg/dL prior LD	25%	9%	.02	30%	20%	32%	10%	.1
Median hospital stay, days	10	8	< .001	10.5	9	9	11	.6
Median PFS, mos	8.1	11.5	.03	6.9	NR	6.4	9.7	.01

8015

Poster Discussion Session

Disparities in multiple myeloma: A global perspective on drug toxicity trends. *First Author: Majid Jaberi-Douraki, DATA Consortium, Computational Comparative Medicine, Department of Mathematics, Kansas State University-Olathe, Olathe, KS*

Background: The FDA Adverse Event Reporting System (FAERS) is one of the largest pharmacovigilance databases containing information on adverse events (AEs) received from manufacturers, consumers and healthcare professionals. The purpose of this study is to evaluate the global disparities in multiple myeloma (MM) through data mining of FAERS. **Methods:** We examined AEs associated with FDA-approved MM drugs from 2003-2022 from FAERS and the Medical Dictionary for Regulatory Activities. Patient data were then stratified based on age, sex (F/M) and 6 geographical regions. We evaluated the reporting odds ratio (ROR) combined with a 95% confidence interval for the elevated incidence of AEs. **Results:** The data curation provided 381,378 patients with information from North America (NA), Europe (EU), Asia (AS), Africa (AF), Oceania (OC) and Latin America & the Caribbean (LA), merged from 129 countries and 27 phenotypic systems and organs categories when the number of AEs happened more than 0.1% of the total. Cardiotoxicities (n=23160) and vascular toxicities (n=26716) were seen more in NA (M) (ROR=1.16 $\pm$ 0.02 and EU (M) (ROR=1.11 $\pm$ 0.03) compared to the rest of the World. Nephrotoxicity (n=17486) was reported more in AF (M) (ROR=2.92 $\pm$ 0.41) compared to AS (M) (ROR $\geq$ 1.17 $\pm$ 0.12), EU (M) (ROR $\geq$ 1.34 $\pm$ 0.13) and NA (M) (ROR=1.09 $\pm$ 0.03). Peripheral neuropathies (n=14786) were frequent among EU (F) (ROR=1.09 $\pm$ 0.07) and OC (M) (ROR=1.08 $\pm$ 0.04). Mortality was higher among AS and EU (ROR $\geq$ 2.15 $\pm$ 0.93) compared to NA and OC. There were 18,222 secondary neoplasms in FAERS. Skin neoplasms (n=4650) more frequently occurred in OC and EU (ROR $\geq$ 1.70 $\pm$ 0.16). Breast neoplasms (n=694) were the highest in EU (F) (ROR=4.01 $\pm$ 0.63) and lowest in OC (F) (ROR<1). Gastrointestinal neoplasms (n=1564) were more common among AS, EU and OC (M) with (ROR $\geq$ 2.23 $\pm$ 0.47). Lymphomas (n=542) were predominant in AS(M) (ROR=2.21 $\pm$ 0.98) and OC (M) (ROR=3.35 $\pm$ 2.23). Leukemias (n=3896) cases were significantly higher in EU (M) (ROR=4.08 $\pm$ 0.40) and EU (F) (3.11 $\pm$ 0.26). Respiratory tract and mediastinal neoplasms (n=796) were more common in AS, EU and OC(M) where ROR $\geq$ 1.36 $\pm$ 0.33. More phenotypic characterization are tabulated below. **Conclusions:** FAERS can be used to assess cancer disparity from a global perspective. Our results indicates that certain AEs are influenced by gender and geographical location. These disparities in MM AEs may be the result of factors such as genetics, dosing/regimen, comorbidities, age and sex. These variables must be investigated for improved patient care, strategies for AE reduction, mortality reduction and optimal allocation of healthcare resources. Research Sponsor: None.

Phenotypic Characterization	Sex	NA (n=308177)	EU (n=40761)	AS (n=16467)	AF (n=363)	OC (n=2166)	LA (n=3919)
Age	F	70	69	71	59.5	68	67
	M	69	68	69	60	68	65
Reproductive neoplasms	F	2.1 $\pm$ 1.2	4.95 $\pm$ 2.5	4.2 $\pm$ 1.6	Data not available	1.34 $\pm$ 1.1	1.69 $\pm$ 1.2
Prostate neoplasms	M	2.11 $\pm$ 0.98	4.39 $\pm$ 0.65	1.25 $\pm$ 0.39	2.80 $\pm$ 2.40	3.53 $\pm$ 0.49	1.35 $\pm$ 0.84

8016

Poster Discussion Session

Investigation into aberrant B cell repertoire in myeloma on humoral immunity and patient survival. *First Author: Lakshmi Bhavani Potluri, Wayne State Univ/DMC Sinai Grace Hospital, Detroit, MI 48235, Detroit, MI*

Background: B cells are critical to inhibiting tumor progression, as they generate tumor-reactive antibodies; promote anti-tumor killing capacity of NK cells and phagocytosis of macrophages/DCs; and enrich priming of T cells against the tumor. Multiple myeloma (MM) is a B-cell-derived malignancy, and its survival is partly driven by a deficiency in the immune response. Yet, the abnormalities of the B-cell-mediated humoral responses in MM are ill defined. **Methods:** We investigated B cell composition in bone marrow (BM) from patients with newly diagnosed MM (NDMM, N = 170), relapsed/refractory MM (RRMM, N = 140) and healthy donors (HD, N = 21) by multi-color flow cytometry. **Results:** We observed that B1b cells were significantly reduced by 45% (p = 0.004) in NDMM patients compared to HD. B1b cells are important in generating long-lasting protective antibodies, particularly against vaccines, in a T cell independent fashion. Similarly, B2 cells, which can produce all antibody types, were significantly reduced in the periphery of NDMM and RRMM patients. Within the B2 cell population, germinal center (GC) matured B cells were significantly reduced in both BM and periphery of MM patients, as shown by significantly higher expression of Fas receptor. Because of deficiencies in the GC-maturation of these B cells, their ability to switch from IgM to IgG was also significantly decreased. On the other hand, the population of regulatory B cells (Bregs) were significantly elevated by 2.3-fold (p < 0.05) in the BM and periphery of NDMM and periphery of RRMM patients. However, the ability of Breg cells to produce suppressive cytokines, like IL-10, was significantly reduced (p = 0.03), indicating impaired suppressive functional capacity. We investigated whether this dysregulated B cell homeostasis impacts myeloma patient survival following treatment. We found that a higher proportion of Bregs and a lower percent of B1a in BM and periphery prior to treatment was associated with favorable progression-free survival (PFS) in both NDMM and RRMM patients. We hypothesized that reduction of B2 cells and their inability to have GC-based maturation could impair antibody generation against acute infections and tumor neoantigens. Therefore, we evaluated MM patients' ability to produce antibodies against hepatitis B surface antigen-based vaccination. We observed that only 31% of MM patients (N = 32) respond to the vaccine compared to 90% of HD. Furthermore, MM patients' antibody titers were significantly lower (< 120 IU/L) compared to > 5000IU/L in HD. **Conclusions:** All together, these results show that in MM patients, vaccine-responsive populations of B cells are reduced, with fewer mature B cells with limited repertoires in GC to fight against acute infections, and with a high number of dysregulated regulatory B cells. These results indicate that compromised B cell functionality in MM patients could impact therapeutic outcome. Research Sponsor: U.S. National Institutes of Health.

8018

Poster Discussion Session

A phase 1 study of belantamab mafodotin in combination with standard of care in newly diagnosed multiple myeloma: An interim analysis of DREAMM-9. *First Author: Saad Zafar Usmani, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Belantamab mafodotin (belamaf) is a B-cell maturation antigen-binding antibody-drug conjugate that eliminates myeloma cells via direct cell killing and anti-myeloma immune responses. DREAMM-9 (NCT04091126) is an ongoing Phase 1, randomized, dose and schedule evaluation study. It aims to evaluate belamaf plus bortezomib, lenalidomide, and dexamethasone (VRd) in adult patients (pts) with transplant-ineligible (TI) newly diagnosed MM (NDMM) and to establish the recommended dose for future development of belamaf combination therapies in the 1st-line setting. Herein, we report updated interim-analysis data. **Methods:** Belamaf dose cohorts (Co1–7) are shown in the Table. VRd was given every 3 weeks (Q3W) until cycle 8, and Rd Q4W thereafter. Following safety data from Co2–5, Co6–7 were opened in parallel (randomized 1:1) and have shorter follow-up (Table). Safety was the primary endpoint; efficacy and tolerability were secondary endpoints. Minimal residual disease (MRD) was assessed by next-generation sequencing (10⁻⁵). **Results:** As of data cutoff (Oct 20, 2022), 93 pts were treated across Co1–7. Median age (range) was 73 (51–88) years, 55% of pts were male, and 84% were white. The most commonly reported non-ocular adverse events (AEs) across all Co were thrombocytopenia (46%), constipation (36%), diarrhea (34%), and peripheral sensory neuropathy (31%). Overall, belamaf-related Grade ≥3 AEs occurred in 35% of pts and led to belamaf dose reductions in 7% and dose delays in 63% of all treated patients. Grade ≥3 ocular AEs (keratopathy and visual acuity [KVA] scale) occurred in 53% of all pts and led to dose reductions in 12% and dose delays in 52% of overall pts. Fatal AEs occurred in 7 pts, all unrelated to study treatment. Efficacy results and ocular AEs are summarized in the Table: 100% of pts responded in Co1 (1.9 mg/kg Q3/4W) and Co3 (1.9 mg/kg Q6/8W). Median time to very good partial response or better (≥VGPR) ranged from 2.1 to 3.1 months (mo) across cohorts. Highest MRD negativity (MRD-I) rates (≥VGPR) were seen in Co1 (83%) and Co3 (67%). **Conclusions:** This updated interim analysis demonstrates that belamaf plus VRd has no new safety signals and provides early and deep anti-myeloma responses in pts with TI NDMM, with high MRD-I rates. Clinical trial information: NCT04091126. Research Sponsor: GSK (209664).

Summary.							
Cohorts	1	2	3	4	5	6	7
	1.9 mg/kg Q3/4W	1.4 mg/kg Q6/8W	1.9 mg/kg Q6/8W	1.0 mg/kg Q3/4W	1.4 mg/kg Q3/4W	1.4 mg/kg then 1.0 mg/kg Q9/12W	1.9 mg/kg then 1.4 mg/kg Q9/12W
	n=12	n=12	n=12	n=15 (Safety popula- tion n=14)	n=13	n=14	n=15 (Safety popula- tion n=14)
Grade ≥3 ocular AEs (KVA; N=91), %	83	58	92	57	85	7	0
Median follow-up, mo	27.6	16.0	16.2	15.3	15.2	2.5	2.0
ORR, %	100	92	100	80	92	79	53
≥CR	75	83	83	53	62	14	7
VGPR	17	8	17	20	23	21	27
PR	8	0	0	7	8	43	20
MR/SD	0	8	0	7	0	7	7
MRD-I, %							
≥CR	75	33	58	33	46	7	0
≥VGPR	83	33	67	33	46	14	7

8017

Poster Discussion Session

Final results of pilot trial to evaluate anti-PD1 and 8 Gy in 1 fx for relapsed refractory multiple myeloma. *First Author: Mohammad Khurram Khan, Emory University, Atlanta, GA*

Background: Single agent Immune-Checkpoints, such as Anti-PD1, have not been successful. A pilot phase 1, 2 trial (NCT03267888) was conducted to see if radiotherapy (RT) and anti-PD1 (Pembrolizumab) could provide early signals of safety and response. **Methods:** Inclusion criteria included patients > 18 years of age, ECOG 0-1, able to give informed consent, have relapsed/refractory myeloma, and have ≥1 osseous and/or extra-osseous lesion that could undergo RT. Patients had to be candidates for anti-PD1 based on organ function testing, have measurable disease per International Myeloma Working Group Criteria (IMWG), and/or have progressive disease on serial staging PET/CT. IRB approval was obtained. RT (8 Gy in 1 fx) was given on day 0, cycle 1 followed by pembrolizumab (200 mg/kg iv on day 2 or 3, then every 3 weeks +/- 7 days) for 2 years or until progression. Primary endpoint was toxicity. Secondary endpoints were IMWG response, abscopal response, overall survival (OS), and immunological changes on serial blood collections. Patients were assessed at 3, 6, and 12 months for progression free survival (PFS) using IMWG and serial PET/CT scans. Patients with stable disease were continued on the trial. Patients that progressed were censored. Standard statistical analysis was performed, and included Kaplan-Meier to estimate OS and PFS. **Results:** From June, 2018 until October, 2021, 32 patients were screened and 25 were enrolled. Of the enrolled patients, 76% were Caucasian, 64% had ECOG 1, and the mean age was 60 years. Prior to enrollment, the median number of prior lines of therapy that a patient had filed was 5.0 (range: 2 – 11). There was no grade 2 or higher radiation related toxicity within the irradiated volume using CTCAE 4.0. Only one case of ≥ grade 3 (fevers) pembrolizumab-related toxicity was noted. Abscopal response, defined as improvement of a non-targeted lesion, was noted in 5 of 25 patients (20%). IMWG showed robust reduction in the paraproteins and other myeloma labs, suggesting response to radiotherapy and anti-PD1. A total of 8 patients showed response. Of those responding patients, 5 were post CarT cell patients, suggesting that the most benefit may be in post CarT cell patients. None of the post CarT cell patients were noted to have cytokine release syndrome and/or neurotoxicity. Of the responding patients, some of these were associated to have a robust CD 8 T cell activation. The 6 and 12 month PFS for the entire cohort was 31.8% and 22.7%, respectively. The 6 and 12-month OS for the entire cohort was 68% and 64%, respectively. Those that were post CarT, there was a higher 6 month PFS (50%) and OS (71.4%). **Conclusions:** Combination therapy of single-fraction, low-dose radiation therapy with pembrolizumab appears to be safe and shows early promise of efficacy in MM pts progressing following CarT therapy. Larger trials are warranted in the relapsed/refractory myeloma patients. Clinical trial information: NCT03267888. Research Sponsor: Merck Pharmaceutical.

8019

Poster Discussion Session

Changing spectrum of infection with BCMA and GPRC5D targeting bispecific antibody therapy in patients with relapsed refractory multiple myeloma (RRMM). *First Author: Abhishek Janardan, Medical College of Wisconsin, Milwaukee, WI*

Background: There is a paucity of granular data on infection risk with bsAb targeting BCMA and GPRC5D in RRMM. **Methods:** We identified and followed 80 patients treated with bsAb therapy at 3 institutions in early-phase clinical trials between 2019 and 2022. Baseline demographic, disease and infection-specific variables were collected from the beginning of treatment to the last follow-up or 3 months after the study exit. **Results:** A total of 86 treatment courses were included, 56 patients received BCMA bsAb, 15 GPRC5D bsAb combination with CD38MoAb + / - IMiD (GPRC5Dc), and 15 GPRC5D bsAb monotherapy (GPRC5Dm). The median age was 70 (45-91) years and 48% (n = 41) were females. Racial/ethnic minorities accounted for 27% (n = 24) of patients included. A total of 117 infections were observed, 89 in the BCMA group, 24 in the GPRC5Dc group and 4 with GPRC5Dm. The infection rate per 100 days in recipients of BCMA bsAb and GPRC5D bsAb were 0.56 and 0.40 (p = 0.34), respectively. There was a greater incidence of high-grade infections (≥ grade 3) with BCMA bsAb treatment compared to GPRC5D bsAb (p = 0.01). Grade 5 events were observed in 8% (n = 7) of patients treated with BCMA bsAb compared to none with GPRC5D bsAb. The proportion of bacterial, viral, and fungal infection in the BCMA group were 56% (n = 50), 37% (n = 37), and 7% (n = 6) respectively and that in GPRC5D group were 46% (n = 13), 43% (n = 12), 11% and (n = 3) respectively. Of the infections during BCMA bsAb therapy, 76% (n = 67) required hospitalization compared to 54% (n = 15) with GPRC5D bsAb (p = 0.02). At 18 months, the cumulative incidence of all-grade infection in the BCMA and GPRC5D group were 72% and 47%, respectively (p = 0.05). The cumulative incidence of ≥ grade 3 infection at 18 months was higher at 60% with BCMA bsAb compared to 29% with GPRC5D bsAb (p = 0.01). The cumulative mean number of recurrent infections by 18 months with BCMA bsAb was 3.2 (95% CI 2.33-4.58) and 1.4 (95% CI 0.77-2.60) with GPRC5D bsAb (p = 0.25). In multivariate analysis, the use of BCMA bsAb, GPRC5D combination therapy and prior infections with bsAb therapy was associated with a significantly higher risk of all-grade and grade ≥3 infections. **Conclusions:** There is a significant risk of infections with bsAb therapy in RRMM with higher cumulative incidence of infection, higher grade infection and infections that require hospitalization with BCMA bsAb compared to GPRC5D bsAb. There were seven grade 5 events noted, all in patients treated with BCMA bsAb. Additionally, GPRC5D combination therapy with CD38MoAb +/- IMiDs conferred a higher risk of infections compared to GPRC5D monotherapy. Research Sponsor: None.

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Poster Discussion Session

Analysis of infections and parameters of humoral immunity in patients (pts) with relapsed/refractory multiple myeloma (RRMM) treated with talquetamab (tal) monotherapy in MonumenTAL-1. *First Author: Paula Rodríguez-Otero, Clínica Universidad de Navarra, CIMA, CIBERONC, IDISNA, Pamplona, Spain*

Background: Infection, a key complication of MM, may be due to patient, disease, or treatment-related factors. Immunotherapies that impact normal immune cells may increase risk of infection. Tal, a bispecific antibody with clinical benefit in pts with RRMM, targets G protein-coupled receptor family C group 5 member D (GPCR5D), a protein of unknown function with significantly higher expression on malignant versus normal plasma cells. We report the infection profile and immune function with tal in the phase (ph) 1/2 MonumenTAL-1 study (NCT03399799/NCT04634552). **Methods:** Pts had RRMM, were intolerant to/progressed on established therapies (ph 1), or had ≥ 3 prior lines of therapy (ph 2; ≥ 1 proteasome inhibitor/immunomodulatory drug/anti-CD38 antibody). Subcutaneous tal was given at 0.4 mg/kg QW or 0.8 mg/kg Q2W. Infections (graded by CTCAE v4.03) were treated per local guidelines. B-cell subpopulations and IgG levels were assessed from whole blood and serum samples, respectively. **Results:** We evaluated 339 pts on tal QW or Q2W, of whom 51 had prior T-cell redirection therapy (pTCRT); infection rates are shown in the table (median follow-up, 15.9, 10.1, and 13.1 mo, respectively). New-onset infections were most prevalent during cycles 1–2. Grade (gr) 3/4 infections observed in >2 pts were pneumonia (3.5%) and UTI (2.1%) on tal QW; pneumonia (2.1%) and COVID-19 (2.1%) on tal Q2W; and pneumonia (5.9%) with pTCRT. Opportunistic infections were observed in 3.5%, 4.1%, and 5.9% of pts, respectively. Less than 1.5% of pts died from infections: COVID-19 pneumonia (n=2) and one each due to septic shock, fungal sepsis, and unknown etiology. Hypogammaglobulinemia rates by IgG values were 64.3% (tal QW), 65.5% (tal Q2W), and 70.6% (pTCRT); IVIg use was 14.7%, 12.4%, and 15.7%, respectively. CD19+ B-cell levels were stable, and there was a trend toward increased non-clonal IgG over time. **Conclusions:** Roughly 20% of pts had gr 3/4 infections on tal (most frequently cycles 1–2), with low rates of opportunistic infections, discontinuation, and death. Infection rates, particularly rates of fatal infections, appear lower with tal than with BCMA-targeted T-cell-based therapies. A trend toward increased non-clonal IgG suggests potential recovery of humoral immunity accompanies rapid, deep, and durable responses to tal. These results distinguish tal as an important emerging therapy for RRMM. Clinical trial information: NCT03399799, NCT04634552. Research Sponsor: Janssen Research & Development, LLC.

Pts, n (%)	Tal 0.4 mg/kg QW (n=143)	Tal 0.8 mg/kg Q2W (n=145)	pTCRT (n=51)
Infections			
Any Gr	83 (58.0)	94 (64.8)	36 (70.6)
Gr 3/4	31 (21.7)	23 (15.9)	13 (25.5)
Led to death	3 (2.1)	2 (1.4)	0
Led to discontinuation	2 (1.4)	0	1 (2.0)
Led to dose interruption	44 (30.8)	43 (29.7)	16 (31.4)
Gr 3/4 neutropenia	44 (30.8)	32 (22.1)	27 (52.9)
Any infection + concomitant Gr 3/4 neutropenia	11 (7.7)	3 (2.1)	9 (17.6)
Gr 3/4 infection + concomitant Gr 3/4 neutropenia	4 (2.8)	1 (0.7)	1 (2.0)

8022

Poster Session

Treatment patterns for extramedullary multiple myeloma and outcomes with CAR-T therapy and bispecific antibodies. *First Author: Saurabh Zanwar, Mayo Clinic, Rochester, MN*

Background: Extramedullary Multiple Myeloma (EMM) is an aggressive entity with a dismal prognosis. Immune effector therapies (IETs), including chimeric antigen receptor T-cell (CAR-T) therapies and bispecific T-cell engaging antibodies (BsAb), have demonstrated excellent efficacy in relapsed/refractory MM with limited data for efficacy in EMM. Here, we report the treatment outcomes for patients with EMM. **Methods:** We identified 299 patients with EMM diagnosed between 01/01/2000 and 12/31/2021 after excluding solitary plasmacytomas, paraneoplastic MM and primary plasma cell leukemia. The IMWG criteria were used for response definition. **Results:** Of the 299 patients, 204 (68%) patients had secondary EMM (sEMM) and 95 (32%) patients had primary EMM (pEMM). For sEMM (n=204), the median progression free survival (PFS) with initial therapy was 2.9 (95% CI: 2.4-3.2) months. Initial treatment strategies for sEMM were heterogeneous and demonstrated in the table; 44% patients achieved $\geq$ partial response (PR) with initial treatment for sEMM. The median PFS in patients with $\geq$ PR was 5.8 (95%CI: 4.5-6.9) months vs 1.8 (95%CI: 1.4-2; $p < 0.0001$) months for $<$ PR. For patients with pEMM (n=95), the median PFS was 12.9 (95% CI: 6.7-18) months; the median PFS was 17.4 (95%CI: 12.9-25.4) months for patients with $\geq$ PR versus 1 month (95%CI: 0.8-2) in patients with $<$ PR. Thirty patients (all sEMM and triple class refractory) were treated with IET after development of EMM: 18 with BCMA-directed CAR-T, 10 with BsAbs, and 2 with both CAR-T and BsAbs. In patients receiving CAR-T therapy, 75% (15/20) achieved $\geq$ PR with 40% (n=8) achieving MRD negative (by flowcytometry) complete response. Fifteen (75%) patients receiving CAR-T had progressive disease (PD); 7 with systemic and EMM PD and 4 patients each with isolated EMM or systemic PD. The median PFS for patients treated with CAR-T was 4.9 months [3.1- not reached (NR)]. Among patients achieving a $\geq$ PR with CAR-T, the median PFS was 5.8 (95%CI: 4.7-NR) months vs 1.4 months [95%CI: 0.8-NR], $p < 0.001$ for $<$ PR. Among patients treated with BsAbs (10-BCMA, 1 each against FcRH5 and GPRC5D), 33% (4/12) achieved a $\geq$ PR. Ten (83%) patients had PD on BsAb; 8 with both EMM and systemic PD and 1 patient each with isolated EMM or PD. The median PFS with BsAb was 2.9 months (95%CI: 2.2-NR). **Conclusions:** Patients with EMM continue to have dismal outcomes with conventional therapies. High response rates were noted with CAR-T therapy, but these tend to be short-lived. Research Sponsor: None.

PFS with initial treatment for secondary EMM.

Groups	n	Median PFS (95%CI), months	P value
Proteasome Inhibitor (PI) plus IMiD based combination without CD38 antibody (Ab)	24	2.2 (1.9-5.2)	0.078
CD38 Ab-combination (including with PI or IMiD)	36	4.5 (2.5-7.6)	
CAR-T or BsAb	12	3.9 (1.9-NA)	
VDT-PACE like and alkylator combinations	59	2.9 (2.4-3.5)	
Either PI or IMiD-based combination without CD38 Ab	34	3.1 (2.2-5.1)	
Other therapies	13	1.5 (0.8-NA)	

8021

Poster Session

Busulfan, melphalan, and carfilzomib (BuMelCar) conditioning for autologous stem cell transplant (ASCT) in multiple myeloma: Phase I/II data. *First Author: Joseph Allan Norton, Loyola University Medical Center, Maywood, IL*

Background: Melphalan-200 high dose chemotherapy for ASCT has been the standard of care for multiple myeloma (MM) for over 30 years. Newer combination regimens such as Busulfan and Melphalan (BuMel) have demonstrated improved progression free survival (PFS) but with increased transplant related morbidity including mucositis and infections. Our group previously demonstrated that adding a proteasome inhibitor (bortezomib) to BuMel further increased PFS with mucositis ameliorated by Palifermin. Building on this effectiveness, we added carfilzomib to the BuMel backbone in a Phase I/II manner focused on safety and initial effectiveness of this novel regimen. **Methods:** This phase I/II open-label dose-escalation/expansion study (NCT03795597) enrolled patients with relapsed or high risk first remission MM. Patients received Busulfan over 4 days at a target total AUC of 20,000 mM-min followed by melphalan at 140mg/m². Patients received 4 total doses of IV carfilzomib, 2 before melphalan and 2 after, with the final 2 doses escalated based on toxicity. Palifermin was given on days -11, -10, 0, and +1. Once MTD was determined, 10 more patients were treated at that level. Primary objective was safety and secondary outcomes were response to treatment at day 100 including MRD, engraftment kinetics, PFS, and OS. **Results:** Patients were predominantly male (79%) with median age 60.95 years. Median KPS was 80 and median HCT-CI was 2. The carfilzomib MTD was 36 mg/m². One SAE of grade V ischemic colitis was seen at the 45 mg/m² dose level. Toxicity at 36 mg/m² yielded a similar pattern to our prior bortezomib containing regimen with grade 1 NSVT in 2 patients and hypertension in another. With a median follow up of 22 months, only 1 of the 13 MTD patients has progressed at 33mo. 2-year PFS and OS are both 100%. Analysis at D+100 showed 69% of MTD patients were MRD negative regardless of genetics. **Conclusions:** This novel BuMelCar ASCT regimen is safe and tolerable and appears to lead to a high % of MRD negative disease at D+100, which other studies correlate to a high PFS at 2 years. A comparison study with mel 200 is warranted to test whether BuMelCar can improve transplant outcomes especially in high-risk patients. Clinical trial information: NCT03795597. Research Sponsor: Amgen.

Toxicity of BuMelCar by dose levels.

Toxicity		Carfilzomib Dose Level				
		27	27	36	36	45
		All Grades	Grade III/IV	All Grades	Grade III/IV	All Grades
GI	All Grades	27 (76.92)	4 (30.76)	2 (15.38)	3 (100)	1 (33.33)
	Grade III/IV	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Mucositis/Eso-phagitis	2 (6.67)	0 (0)	10 (76.92)	2 (66.67)	0 (0)
	Infection	0 (0)	0 (0)	3 (23.08)	0 (0)	1 (33.33)
	FN	2 (6.67)	2 (66.67)	10 (76.92)	10 (76.92)	3 (100)
Cardiac Toxicity	All Grades	0 (0)	0 (0)	2 (15.38)	0 (0)	1 (33.33)
	Grade III/IV	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Electrolyte Abnormality	All Grades	3 (100)	0 (0)	13 (100)	1 (7.69)	3 (100)
	Grade III/IV	3 (100)	0 (0)	12 (92.30)	1 (7.69)	2 (66.67)
Other	All Grades	3 (100)	0 (0)	12 (92.30)	1 (7.69)	0 (0)
	Grade III/IV	3 (100)	0 (0)	12 (92.30)	1 (7.69)	1 (33.33)

8023

Poster Session

Plinabulin to shorten neutropenia and improve quality of life peri-autologous hematopoietic cell transplant. *First Author: Gunjan L. Shah, Adult Bone Marrow Transplant Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Plinabulin is a selective immunomodulating microtubule-binding agent, which prevents chemotherapy induced neutropenia (CIN) via a mechanism of action different from that of G-CSF analogues. It has been studied for CIN and anti-solid tumor activity in phase 3 trials. To decrease the period of myelosuppression and obligate neutropenia after high dose melphalan with autologous hematopoietic stem cell transplantation (AHCT) for patients with multiple myeloma, we studied the addition of plinabulin to standard growth factors. **Methods:** To achieve the primary objective of reducing the duration of absolute neutropenia post AHCT, 40mg of intravenous plinabulin was given 1-3 hours after stem cell infusion (Day 0) with pegfilgrastim on Day +1 in this pilot trial (NCT05130827). Secondary objectives include the safety, tolerability, and toxicity profile of plinabulin in combination with pegfilgrastim, neutrophil and platelet engraftment rate, disease response, progression free and overall survival, patient reported outcome (PRO) assessment of symptom burden, and plinabulin pharmacokinetic profiling. Exploratory objectives include transfusion requirements, phenotypic characterization of neutrophil population through day 30, and analysis of cytokine levels early post AHCT. **Results:** Between January 2022 and February 2023, 15 patients with median age of 64 (range 54-74) and 33% female received plinabulin after melphalan 140 (n = 4) or 200mg/m² (n = 11). Median CD34+ cells/kg infused was 4.12 x 10⁶ (range 2.18 – 7.85). Half of the patients had hypertension immediately after the plinabulin infusion, which is a known toxicity and resolved within a few hours. Median WBC on Day 0, 1, and 2 was 7.67(3.6 – 11.5), 5.2 (3.2 – 13.6), and 17.1 (5.1-59.1), respectively. Of the 14 patients who have engrafted to date, median time to ANC $> 0.5 \times 10^9$ cells/L was 11 days (range 9-16) with median days from AHCT to ANC < 0.5 of 5 days (range 5-6). The median number of days of ANC < 0.1 and < 0.5 were 2 (range 1-5) and 5 days (range 4-9), respectively. For the 7 patients who had a fever, the median time to fever was 8 days from AHCT (range 8-12), and all except one were peri-engraftment. Median length of stay was 17 days (range 15-21). Median pRBC and platelet transfusions were 0 (range 0-3) and 3 (range 0-11), respectively. **Conclusions:** Plinabulin appears well tolerated without additional major toxicities post AHCT and provided a high WBC on Day +2 and decreased rate of neutropenic fever. Plinabulin PK, quality of life data, and PROs will be presented. Adjusting the schedule of plinabulin to later post AHCT pre engraftment may further shorten the duration of neutropenia using this novel mechanism of action. Clinical trial information: NCT05130827. Research Sponsor: Beyond Spring; Institutional Funds.

8024

Poster Session

Prognostic value of month 1 bone marrow and PET MRD status in CAR-T therapy for myeloma. *First Author: Radhika Bansal, Division of Hematology, Mayo Clinic, Rochester, MN*

Background: Minimal residual disease (MRD) is prognostic for survival in multiple myeloma (MM). MRD is usually assessed in the bone marrow (BM) by flow cytometry or NGS. MRD by FDG PET/CT provides a global representation of the tumor burden, including response assessment of extramedullary disease. We examined MRD status in MM pts using both BM and PET/CT at Mayo Clinic. **Methods:** Medical records were reviewed retrospectively for MM pts who received CAR-T between 4/2018 and 12/2022. All PET/CT scans were assessed by radiologists. BM MRD was assessed by flow cytometry with a sensitivity of 10⁻⁵. Progression-free survival (PFS) and overall survival (OS) were analyzed by Kaplan-Meier method. **Results:** Among the 157 CAR-T pts, including 89 pts who received FDA-approved CAR-T, median age was 63 years, 59% (92/157) were males, 42% (66/157) had high risk cytogenetics with median of 5 prior lines of therapy, 36% (57/157) had plasmacytoma. Incidence of CRS was 83%, 5% grade ≥ 3 CRS. Incidence of ICANS was 19%, 4% grade ≥ 3 ICANS. CR/sCR rate was 37%. One hundred and thirty-seven pts (87%) had evaluable BM at month (mo) 1, 85% (117/137) were BM MRDneg at mo 1. Baseline demographics were comparable between the two groups except age, % BM plasma cells and use of bridging therapy. Among the MRDneg pts, CR/sCR rate was 44% (51/117) and 95% (111/117) had sFLC below normal. At median follow-up of 13.8 months, median PFS among pts with BM MRDneg at 1 mo was 12 mo (95% CI: 11, 30) vs 3 mo (95%CI: 2, 7) for BM MRDpos (p<0.001). Median OS among pts with BM MRDneg at 1 mo was 34 mo (95% CI: 24, NR) vs 22 mo (95%CI: 7, NA) for BM MRDpos (p<0.01). At month 1, 112 pts had both BM and PET/CT assessments available, 64/112(57%) were both BM MRDneg/PET MRDneg, 38/112 (34%) were MRDneg for either BM or PET and 10/112 (9%) were positive for both BM and PET (MRDpos/PET MRDpos). Baseline demographics except age were comparable between the 2 groups (Table). Rate of conversion from MRDpos to MRDneg was low. Rate of sustained BM and PET MRDneg at mo 12 was 44% (8/18). The median PFS and OS for BM MRDneg/PET MRDneg was significantly longer as compared to others (Table). **Conclusions:** Achieving FLC below normal, BM MRDneg and PET MRDneg at 1 month, regardless of IMWG response at that time, is prognostic for both PFS and OS in MM pts receiving CAR-T. Failure to achieve any of these confers poor prognosis. Research Sponsor: None.

Pt characteristics.					
	BMneg/PETneg (N=64)	BMpos/PETpos (N=10)	BMneg/PETpos OR BMpos/PETneg (N=58)	Total (N=112)	p value
Age, yrs, median (Range)	65 (45, 82)	55 (43, 67)	64 (33, 81)	64 (33, 82)	0.02
Clita-cel, n(%)	14 (22)	0 (0)	6 (16)	20 (18)	0.12
Ide-cel, n(%)	31 (48)	4 (40)	13 (34)	48 (43)	
Trial (2-Phase II), n(%)	19 (30)	6 (60)	19 (50)	44 (39)	
sFLC <normal, n(%)	64 (100)	3 (30)	31 (82)	98 (87)	<0.001
Best response, CR/sCR, n(%)	27 (42)	0 (0)	13 (34)	40 (36)	<0.001
PFS, mo, median (95% CI)	13 (12, NR)	2 (12, NR)	9 (6, NR)	12 (12, 16)	<0.0001
OS, mo, median (95% CI)	NR (NR, NR)	7 (4, NR)	37.9 (22, NR)	29 (22, NR)	<0.01

8026

Poster Session

Updated OS of patients with AL amyloidosis after CAEL-101. *First Author: Michael Sang Hughes, Columbia University Medical Center, New York, NY*

Background: Morbidity and mortality remain high in immunoglobulin light chain (AL) amyloidosis due to organ involvement despite hematologic remission. Few anti-amyloid fibril therapies for AL amyloidosis exist. We previously published the results of the phase 1a/1b study of CAEL-101 in AL amyloidosis showing significant improvement in organ response rates.¹ We report long-term outcomes. **Methods:** Patients enrolled in NCT02245867 with relapsed/refractory AL amyloidosis received in phase 1a, a one-time dose-finding CAEL-101 infusion and in phase 1b, 4 weekly CAEL-101 infusions with preplanned dose escalation. Patients were evaluated for organ response for 12 weeks after last infusion. We extracted clinical, laboratory, and pathology data regarding clinical course beyond 12 weeks after last treatment. We performed a review of all AL amyloidosis patients at our center not treated with CAEL-101 1/01/2012-12/30/19 as clinical comparisons. **Results:** 22 patients were enrolled in CAEL-101. 5 patients were treated in both phase 1a and phase 1b. With median follow-up of 81.3 months (IQR 60.4-87.7), long term follow-up data are available for 19/22 patients. 5 patients died during long term follow-up: 3 from progressive AL amyloidosis; 1 from organ transplantation complication; and 1 from venous thromboembolism sequelae. Among patients with organ data available, 10/17 had hematologic progression and received next line therapy. 5/17 patients had organ progression. All patients with organ PD had previous/concomitant hematologic PD. Median OS was not reached; median organ PFS was 93.3 months (38.9-NR). No delayed adverse events occurred. Comparison with historical control groups revealed trends toward improved OS: HR 0.42 (0.09-1.81 p=0.23) in all comers AL amyloid controls, and HR 0.20 (0.03-1.16 p=0.07) in cardiac controls. Kaplan-Meier analysis and Cox regression were performed. **Conclusions:** Patients with relapsed/refractory AL amyloidosis who received a low cumulative amount of the novel anti-amyloid CAEL-101 in a phase 1a/1b study had lengthy overall and progression-free survival compared to historical controls. Patterns of organ progression after initial response may reflect intrinsic differences in organ vulnerability. The CAEL101-301 and CAEL101-302 phase 3 clinical trials are underway to confirm these findings. Reference: 1. Edwards CV, Rao N, Bhutani D, et al: Phase 1a/b study of monoclonal antibody CAEL-101 (11-1F4) in patients with AL amyloidosis. Blood 138:2632-2641, 2021. Research Sponsor: None.

Baseline patient characteristics.			
	CAEL-101 (N=22)	Control (N=86)	Cardiac control (N=62)
Age	66	63	62
Gender (M/F)	14/8	46/40	32/30
Cardiac involvement	54%	72%	100%
Renal involvement	45%	61%	51%
NT-proBNP	1377 (662-13131)	1040 (89-17000)	2289 (191-17000)
Creatinine	1.03 (0.8-1.3)	1.07 (0.53-5.4)	1.01 (0.59-5.4)
Light chain type (K/L)	11/11 (50%/50%)	19/67 (78%/22%)	14/48 (22%/78%)
24h urine protein (mg)	3062 (1200-7260)	2346 (600-23,000)	3700 (330-23,000)

8025

Poster Session

CT103A, a novel fully human BCMA-targeting CAR-T cells, in patients with relapsed/refractory multiple myeloma: Updated results of phase 1b/2 study (FUMANBA-1). *First Author: Chunrui Li, Department of Hematology, Tongji Hospital of Tongji Medical College, Huazhong University of Science, Wuhan, China*

Background: CT103A, which is designed with a fully human BCMA-specific CAR structure, has shown sustained efficacy and durable safety in heavily pretreated relapsed and refractory multiple myeloma patients. Here, we report updated efficacy and safety data of its phase 1b/2 study (FUMANBA-1) with longer duration of follow-up. **Methods:** FUMANBA-1 is conducted in 14 centers in China. This study enrolled RRMM patients who received ≥ 3 lines of prior therapies containing at least a proteasome inhibitor and an immunomodulatory agent and were refractory to their last line of treatment. Patients who have progressed on previous BCMA CAR-T cell therapy were also included. All patients received a single infusion of CT103A at the dose of 1.0 x 10⁶ CAR-T cells/Kg. The objective is to evaluate the efficacy, safety and PK/PD of CT103A. **Results:** As of the September 9th, 2022, 103 patients [53.4% male; median age 58.0 years (range 39-70)] with RRMM received CT103A (17 in phase 1b; 86 in phase 2) with a median follow-up of 13.8 months (range 0.4 to 27.2). The treated patients had received a median of 4 (range 3-23) lines of prior therapy. 101 patients were evaluable for efficacy assessment. The median time to first response was 16 days (range 11-179). A 96% ORR was observed, with 74.3% ≥ CR. Median DOR and median PFS have still not reached. The 12-month PFS rate was 78.8% (95% CI: 68.6–85.97). For patients without prior BCMA CAR-T therapy (N = 89), ORR was 98.9% with 78.7% ≥ CR. For patients without prior BCMA CAR-T therapy and received CT103A for more than 6 months as of the cutoff date (N = 81), ORR was 98.8% with 80.2% ≥ CR. For patients with prior BCMA CAR-T cell therapy, 4/5 (80%) of those who achieved sCR still sustained sCR over 18 months post infusion. Of the 101 patients, 95% achieved MRD-negativity with a median time to MRD-negative of 14 days (range 13-185), and all patients with CR/sCR were MRD-negative. Furthermore, 82.4% (95%CI 70.90-89.72%) achieved sustained MRD negativity over 12 months. Since the previous publication in 64th ASH meeting, no new events of CRS and ICANS occurred. The most common ≥ grade 3 treatment-related AEs were still hematologic. The expansion of CT103A reached the median peak level of 87570.6 copies/μg gDNA at a median of 12 days. CT103A was still above lower limit of qualification (100 copies/μg gDNA) in 50.0% (28/56) patients at 12 months and 40.0% (4/10) patients at 24 months after infusion. In addition, only 20 of 103 patients (19.4%) with evaluable samples were detected to be positive for the anti-drug antibody. **Conclusions:** At a longer median follow-up of 13.8 months, CT103A achieved deep and long-lasting responses in heavily pretreated patients with MM. Furthermore, patients with prior BCMA CAR-T cell therapy who achieved sCR had sustained sCR over 18 months. CT103A demonstrated a favorable safety profile with no new risk observed with longer follow-up. Clinical trial information: NCT05066646. Research Sponsor: None.

8027

Poster Session

Population pharmacokinetic-pharmacodynamic model of nirogacestat effects on B-cell maturation antigen in healthy subjects. *First Author: Todd Shearer, SpringWorks Therapeutics, Inc., Stamford, CT*

Background: B-cell maturation antigen (BCMA) is expressed on the membrane of normal plasma cells (PCs) and multiple myeloma (MM) cells and is the target of several investigational agents and approved products for MM treatment. Mechanistically, BCMA is cleaved from the cell surface by the enzyme gamma secretase, resulting in reduced levels of membrane-bound BCMA (mbBCMA) and release of soluble BCMA. Gamma secretase inhibitors (GSIs) have been shown to increase BCMA receptor density and potentiate the activity of several BCMA-targeted therapies in both clinical trials and *in vitro* studies. Although the effect of GSIs on BCMA receptor density has been well characterized *in vitro*, their effect on BCMA dynamics is incompletely understood in humans. This study sought to evaluate the pharmacodynamics (PD) of the GSI nirogacestat on mbBCMA in healthy subjects. **Methods:** A total of 23 healthy subjects were administered single doses of 50, 150, or 300 mg nirogacestat or multiple doses of 100 mg every 12 hours. Density of mbBCMA on PCs isolated from whole blood and bone marrow was measured by flow cytometry at baseline and 1, 2, 4, 8, 24, and 48 hours after single doses and 24 and 48 hours after the first dose in subjects receiving multiple doses. Nirogacestat serum concentrations were also measured at multiple time points to fully characterize the pharmacokinetics (PK). A population PK-PD model of the effect of nirogacestat on BCMA dynamics in humans was developed and used to simulate various administration dose levels and schedules to find an optimal nirogacestat regimen that continually increases mbBCMA over the dosing interval. **Results:** A 2-compartment model with linear absorption and elimination described serum nirogacestat in healthy subjects. A sequential PK-PD model that included an effect compartment and drug effect on mbBCMA cleavage rate described mbBCMA values. Simulations indicated that a 100-mg dose administered twice daily sufficiently maintained elevated and clinically relevant mbBCMA levels. Exposure and efficacy benchmarks from *in vitro* experiments and published clinical studies were used to contextualize simulations and hypothesize various dose and schedule scenarios to minimize dose of the BCMA-targeting therapy while maximizing BCMA potentiation. **Conclusions:** These results suggest that nirogacestat dose and schedule may have direct implications on the potentiation of BCMA-targeting therapies. Simulations suggest that the 100-mg, twice-daily nirogacestat dose results in elevated mbBCMA levels that could even allow for use of lower doses of BCMA-targeted agents while maintaining or improving efficacy. Study results along with this PK-PD model will be used to support nirogacestat dose and schedule in ongoing and planned studies in patients with MM. Research Sponsor: SpringWorks Therapeutics.

8028

Poster Session

Measurable residual disease (MRD) and clonal diversity for multiple myeloma treatment monitoring. *First Author: Joaquin Martinez-Lopez, Departamento de Hematología, Hospital 12 de Octubre, Complutense University, CNIO, Madrid, Spain*

Background: MRD assessment is a known surrogate marker for survival in multiple myeloma (MM). However, some patients with non-detectable MRD, do relapse, and some MRD-positive patients with an extensive follow-up, do not relapse. Clonal diversity is defined as the number of unique Immunoglobulin (H, K, or L) sequences in each sample. Here, we present a single institution experience assessing MRD by NGS of Ig genes and the long-term impact of depth of response as well as clonal diversity on the clinical outcome of a large population of MM patients. **Methods:** 482 MM patients at University of California, San Francisco (UCSF) diagnosed from 2008 to 2020. Of them, 304 were newly diagnosed and 178 in ≥ 2 nd line. MRD was assessed in patients achieving VGPR or better by IMWG criteria. MRD assessment was performed by NGS (Adaptive Biotechnologies, Seattle, WA). PFS curves were plotted by the Kaplan-Meier method, and the log-rank test was used to estimate statistical significance. **Results:** 1098 MRD samples were analyzed. MRD was available at 3 time points for 118 patients. Median follow-up was 26m. Overall, 181 of 482 patients (38%) achieved MRD- ($< 10^{-6}$) on one or more samples. Clonal diversity was available in 87 of those patients. In the newly diagnosed group, 84 of 120 (39%), achieved MRD- at the level of 10^{-6} at least once. These patients had a prolonged PFS versus patients who were persistently MRD+ at different levels ($p > 0.0001$). Notably, patients achieving a MRD $< 10^{-5}$ have longer OS than those with MRD $> 10^{-5}$ ($p = 0.009$). Of the 178 patients who received therapy for relapsed disease, 64 achieved MRD- at 10^{-6} (36%) and PFS was also prolonged versus patients who remained MRD+ (44 m v NR, $p = 0.03$). Then, we analyzed the effect of repeated MRD monitoring on PFS. Three categories were defined: (A) patients with ≥ 3 MRD- samples, (B) patients with continuously declining detectable clones, and (C) patients with a stable number of clones. Groups A and B had a more prolonged PFS than group C (NR vs NR vs 38m, $p < 0.0001$). Finally, we analyzed clonal diversity at the moment of maximum response: patients MRD+ who have not relapsed have higher clonal diversity than MRD+ patients who relapsed. Moreover, patients who were MRD- who have not relapsed have higher clonal diversity than patients who were MRD- who did relapse. This was also observed independently for the 3 receptors analyzed (IgH $p = 0.026$; IgK $p = 0.036$ and IgL $p = 0.036$). Patients with more than 66000 IgH unique sequences at the moment of maximum response had a prolonged PFS ($p = 0.05$). **Conclusions:** MRD assessment in a real-world setting has the same predictive power as that seen in clinical trials even on OS. MRD dynamics can accurately predict disease evolution and drive clinical decision-making. Clonal Diversity could complement MRD assessment in the prediction of the outcome in MM. Research Sponsor: CRIS against cancer.

8030

Poster Session

Phase 2 study of abatacept, ixazomib, and dexamethasone in patients with relapsed/refractory multiple myeloma. *First Author: Khalid Shalaby, Roswell Park Comprehensive Cancer Center, Buffalo, NY*

Background: Multiple myeloma (MM) usually responds to induction therapy but relapses with therapy-resistant disease. CD28 expressed on MM cells is correlated with worse outcomes. Bone marrow stromal cells expressing CD28 ligands CD80 and/or CD86 are cellular partners in the MM niche transducing a pro-survival signal to MM cells contributing to therapy resistance in relapsed disease. We have previously shown in vitro and in vivo preclinical studies that blocking the pro-survival CD28 activation on MM cells with abatacept (CTLA4 IgG binding to CD80/CD86 and blocking engagement to CD28) reverses chemotherapy resistance and re-sensitizes MM cells to drugs they previously were resistant to. **Methods:** We tested efficacy and safety of combining Abatacept with the proteasome inhibitor (PI) Ixazomib (Ixa) and Dexamethasone (Dex) in patients with MM who had relapsed (or primary refractory) disease following treatment with first line PI Bortezomib based regimen. Previous studies found that Ixa/Dex alone only had an 11% overall response rate (ORR) and 11% Clinical Benefit Rate (CBR) in patients with prior Bortezomib exposure. In our trial, patients with MM cells positive for CD28 or CD86 by flow cytometry or immunohistochemistry in any proportion were eligible. From September 11, 2018 to August 5, 2021, 15 patients received Abatacept loading dose cycle 1 day 1 followed by 125 mg subcutaneously on day 2 and then weekly. Patients received Ixa 4 mg on days 1, 8, and 15 and Dexamethasone 40 mg weekly of a 28-day cycle. The primary endpoint was ORR (partial response (PR) or better) according to International Myeloma Working Group criteria. Secondary end points were toxicity profile, progression-free (PFS), and overall survival (OS). **Results:** Median age was 62.8 years (range 50-83.9). Ten (66.6%) patients received prior autologous stem cell transplant. The ORR was 33.33% (90% CI 16.58%-54.46%) (one-sided Binomial exact test 0.4845). Complete remission (CR) was achieved in 6.7%, and 26.7% achieved PR with 53.3% of patients having stable disease (SD). Median time to best response among patients with CR and PR was 8.9 weeks (95% CI 4–21). Median time on treatment was 23 weeks (95% CI 12.143-48.143) for all patients and 52.5 weeks (95% CI 39.286-68) for patients with response. One-year PFS was 45% (90% CI 21%-66%), median PFS 12 months (90% CI 5.7-25.9) and 1-year OS 100%, median OS not reached. Two grade 3 treatment emergent adverse events (TEAE) (diarrhea and low platelets) occurred requiring hospitalization. Grade 1/2 GI TEAEs were most common. No grade 3/4 treatment related infections were observed and 2 grade 3 infections occurred. **Conclusions:** Despite prior exposure to Bortezomib, one third of patients had response to Ixa with Abatacept and Dex. Patients with response stayed on treatment for almost 1 year on average with limited AEs. Most patients on trial gained benefit with a clinical benefit rate (CR+PR+SD) of 86.66%. Clinical trial information: NCT03457142. Research Sponsor: Bristol-Myers Squibb.

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Poster Session

Long-term outcomes with isatuximab-carfilzomib-dexamethasone (Isa-Kd) in relapsed multiple myeloma patients with 1q21+ status: Updated results from the phase 3 IKEMA study. *First Author: Thierry Facon, Department of Hematology, Lille University Hospital, Lille, France*

Background: Gain or amplification of 1q21 (1q21+, ≥ 3 copies), a chromosomal abnormality frequently observed in multiple myeloma (MM), has a negative impact on prognosis due to its potential involvement in resistance to MM therapy and disease progression. In the prespecified, long-term analysis of the Phase 3 IKEMA trial in relapsed MM patients (pts), treatment with Isa-Kd showed continued, significant improvement in progression-free survival (PFS) vs Kd (HR 0.58; 95.4% CI 0.42–0.79), with meaningful increase in depth of response (complete response or better [$\geq$ CR]) 44.1% vs 28.5%; minimal residual disease negativity [MRD-] 33.5% vs 15.4%, MRD- $\geq$ CR 26.3% vs 12.2%), and a manageable safety profile. In this subgroup analysis of IKEMA, we evaluated efficacy of Isa-Kd in pts with 1q21+ status (with or without high-risk chromosomal abnormalities [HRCAs]) and related subgroups— isolated 1q21+ (≥ 3 copies without HRCAs), gain(1q21), amp(1q21) — at long-term follow-up (44.2 months). **Methods:** Pts with 1–3 prior lines of therapy were randomized to Isa-Kd (n=179) or Kd (n=123). Assessment was prespecified (at 30% cut-off by FISH) for 1q21+ status as ≥ 3 copies, gain(1q21) as 3 copies, and amp(1q21) as ≥ 4 copies. **Results:** In the Isa-Kd and Kd arms, 41.9% and 42.3% of pts had 1q21+ status, 26.3% and 25.2% isolated 1q21+, 24.0% and 30.1% gain(1q21), 17.9% and 12.2% amp(1q21) respectively. Greater PFS benefit was achieved with Isa-Kd vs Kd in pts with 1q21+ status (HR 0.58, 95% CI 0.37–0.92) and in pts with isolated 1q21+, gain(1q21), or amp(1q21) (Table). Responses deepened by adding Isa to Kd, with increased rates of very good partial response or better ($\geq$ VGPR), $\geq$ CR, MRD-, and MRD- $\geq$ CR (Table). **Conclusions:** 1q21 abnormalities affect PFS in MM pts. Our results at long-term follow-up of pts with 1q21+ status (with or without HRCAs) in the IKEMA study continue to show greater PFS benefit and deeper responses with Isa-Kd than Kd, consistent with the overall population and earlier 1q21+ subgroup interim analyses. Thus, they support Isa-Kd as an effective treatment option also for difficult-to-treat, 1q21+ pts with relapsed MM. Clinical trial information: NCT03275285. Research Sponsor: Sanofi.

	Standard risk		1q21+		Isolated 1q21+ (w/o HRCAs)		Gain(1q21)		Amp(1q21)	
	Isa-Kd	Kd	Isa-Kd	Kd	Isa-Kd	Kd	Isa-Kd	Kd	Isa-Kd	Kd
n	85	43	75	52	47	31	43	37	32	15
ORR, %	36.3	35.0	41.9	42.3	26.3	25.2	24.0	30.1	17.9	12.2
CR, %	42.4	20.3	27.8	16.2	38.2	16.2	30.2	18.2	18.4	14.5
PFS HR vs Kd (95% CI)	(26.3-36.3)	(11.2-28.2)	(17.1-38.2)	(10.2-24.8)	(18.8-38.2)	(10.2-25.1)	(20.8-38.2)	(10.2-25.0)	(13.1-38.2)	(2.8-38.2)
PFS HR vs Kd (95% CI)	(0.50-0.93)	(0.34-0.51)	(0.38-0.57)	(0.27-0.40)	(0.50-0.93)	(0.27-0.40)	(0.50-0.93)	(0.27-0.40)	(0.33-0.61)	(0.13-0.40)
ORR %	90.8	86.0	86.7	82.7	91.5	87.1	90.7	86.5	81.3	73.3
VGPR %	79.9	73.9	73.3	71.9	80.9	79.1	79.1	76.6	65.6	40.0
MRD %	44.6	18.6	34.7	15.4	40.4	12.9	34.9	13.5	34.4	20.0
MRD- $\geq$ CR %	33.8	11.6	29.3	15.4	36.2	12.9	27.9	13.5	31.3	20.0

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Poster Session

Baseline and early post-infusion biomarkers associated with optimal response to idecabtagene vicleucel (ide-cel) in the KarMMA-3 study of triple-class-exposed (TCE) relapsed and refractory multiple myeloma (RRMM). *First Author: Julia Piasecki, Bristol Myers Squibb, Princeton, NJ*

Background: Ide-cel, a B-cell maturation antigen (BCMA) chimeric antigen receptor T cell therapy, significantly improved median progression-free survival (mPFS) and overall response rate (ORR) vs standard regimens (SRs) in patients (pts) with TCE RRMM in the KarMMA-3 study (NCT03651128; Rodríguez-Otero et al. *NEJM* 2023). Previous analyses in KarMMA-3 (Munshi et al. *NEJM* 2021) of pts with later-line (4L+) TCE RRMM identified low baseline (BL) levels and complete clearance of soluble BCMA (sBCMA, a measure of tumor burden) and early minimal residual disease (MRD) negativity as correlates of durable response to ide-cel. The current analysis explored the association between biomarkers and efficacy or severity of inflammatory adverse events of ide-cel in KarMMA-3. **Methods:** sBCMA levels were measured in blood samples collected from pts in KarMMA-3 at BL and regular intervals from treatment (tx) initiation until confirmed progression. MRD status was assessed in bone marrow aspirate (clonoSeq; 10^{-5} sensitivity) at 6 and 12 mo post infusion and reported in all pts, regardless of response. Biomarker analyses were based on pts who received ide-cel or ≥ 1 dose of SR. Post hoc analyses assessed correlations between biomarkers and efficacy endpoints or cytokine release syndrome (CRS) and investigator-identified neurotoxicity (iINT); associations of interest were identified using a ranked sum test and nominal P value < 0.05 . **Results:** Lower BL sBCMA levels were associated with higher ORR ($<$ partial response [PR] vs $\geq$ PR) in both tx arms (ide-cel, $P = 0.0223$; SR, $P = 0.0395$), indicating this may be agnostic of the BCMA-directed modality. Lower BL sBCMA was also associated with higher complete response (CR) rate ($<$ CR vs $\geq$ CR) in the ide-cel arm ($P = 0.0038$). Additionally, lower BL sBCMA levels in the ide-cel arm were associated with lower grade (gr) of CRS (gr 0–1 vs 2 vs ≥ 3 ; $P = 0.0022$) and iINT (gr 0–1 vs ≥ 2 ; $P = 0.0113$); however, overlapping ranges may limit predictive utility. Further analyses will be presented. In the ide-cel arm, landmark mPFS was longer in pts with undetectable versus detectable sBCMA at 2 mo post infusion (16.3 vs 5.2 mo; HR, 0.26) or at 6 mo (16.8 vs 9.6 mo; HR, 0.62). Furthermore, landmark mPFS was also longer in pts with MRD negativity versus pts with positive/indeterminate MRD status at 6 mo (17.2 vs 5.8 mo; HR, 0.288) or at 12 mo (13.8 vs 4.6 mo; HR, 0.121). **Conclusions:** BL sBCMA levels correlated with response and CRS and iINT grade in the ide-cel arm of KarMMA-3, potentially reinforcing the importance of management of BL tumor burden for optimal response to ide-cel. Early clearance of sBCMA at 2 mo, sustained clearance of sBCMA at 6 mo, and MRD negativity at 6 or 12 mo, regardless of clinical response, may be useful biomarkers for identifying pts likely to achieve a complete and durable response to ide-cel. Clinical trial information: NCT03651128. Research Sponsor: Celgene, a Bristol-Myers Squibb Company, and 2seventy bio.

8032

Poster Session

Health related quality of life (HRQoL) in patients with triple-class-exposed relapsed/refractory multiple myeloma (TCE RRMM) treated with idecabtagene vicleucl (ide-cel) versus standard regimens: Patient-reported outcomes (PROs) from KarMMA-3 phase 3 randomized controlled trial (RCT). *First Author: Michel Delforge, University of Leuven, Leuven, Belgium*

Background: Patients (pts) with TCE RRMM have few treatment (Tx) options and poor HRQoL. Ide-cel, the first in class CAR T cell Tx for pts with TCE RRMM, improved PFS versus standard (std) regimens in the KarMMA-3 trial. We report the PRO results comparing the Tx arms. PROs provide further understanding of Tx benefit of ide-cel from the pts' perspective. **Methods:** KarMMA-3 (NCT03651128) is an open-label phase 3 RCT comparing the efficacy and safety of ide-cel with std regimens in pts with TCE RRMM, who had received 2–4 prior regimens. In addition to clinical endpoints, we evaluated the impact of ide-cel compared with std regimens on the changes in HRQoL, measured by the EORTC QLQ-C30, EORTC QLQ-MY20, and the EQ-5D-5L questionnaires. PROs were collected at baseline (screening), day of infusion and monthly from 2–24 months (mo) and thereafter every 3 mo. This interim analysis reports PROs through 20 mo. Comparisons were performed on least squares mean (LSM) changes from baseline over time between arms using constrained longitudinal data analysis (cLDA). **Results:** In total, 386 pts were randomized (ide-cel, 254; std regimens, 132). PRO compliance was high over time (> 80%). At baseline, PROs were similar between arms. LSM changes from baseline to 20 mo showed significant differences ($P < 0.05$), with effect sizes of 0.3–0.7, in favor of ide-cel for most domains, including global health status/QoL, cognitive functioning, fatigue, and pain (EORTC QLQ-C30); side effects of Tx (EORTC QLQ-MY20); and the EQ-5D-5L VAS. The difference in overall LSM change reached or exceeded the pre-specified between-groups minimal importance difference (MID) for improvement in most domains in favor of ide-cel (Table). **Conclusions:** Ide-cel showed statistically significant and clinically meaningful improvements in HRQoL, including key MM symptoms and functioning, for pts with TCE RRMM compared with std regimens. The PRO data for ide-cel expands upon the clinical outcomes observed in the KarMMA-3 trial. Clinical trial information: NCT03651128. Research Sponsor: Bristol Myers Squibb.

Instrument/Domain	Diff Between Arms LSM (95% CI)		MID	Hedges' g (95% CI)
	Ide-cel versus Std Regimens			
EORTC QLQ-C30				
Global health status/QoL	6.17* (3.35, 8.99)	4		0.46 (0.25, 0.68)
Physical functioning	4.32* (1.66, 6.98)	5		0.34 (0.13, 0.56)
Cognitive functioning	5.64* (3.02, 8.27)	3		0.46 (0.24, 0.67)
Fatigue	-6.24* (-9.52, -2.96)	-5		-0.40 (-0.62, -0.19)
Pain	-5.68* (-9.36, -1.99)	-6		0.33 (-0.54, -0.11)
EORTC QLQ-MY20				
Side effects of Tx	-6.08* (-7.89, -4.26)	-10		-0.71 (-0.93, -0.49)
EQ- 5D-5L VAS	7.26* (4.70, 9.83)	7		0.60 (0.39, 0.82)

* P value < 0.05; Results favor ide-cel with - values for symptoms (fatigue, pain) and side effects and + values for functioning/health.

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Poster Session

Durability of responses with biweekly dosing of teclistamab in patients with relapsed/refractory multiple myeloma achieving a clinical response in the majesTEC-1 study. *First Author: Saad Zafar Usmani, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Teclistamab is the first B-cell maturation antigen (BCMA) bispecific antibody approved for the treatment of relapsed/refractory multiple myeloma (RRMM) at a dose of 1.5 mg/kg weekly (QW) given subcutaneously. A less frequent dosing schedule offers added convenience and flexibility to patients, physicians, and caregivers. We evaluated the ability of patients to maintain their responses after transitioning from QW to every other week (Q2W) dosing schedules in the pivotal phase 1/2 MajesTEC-1 trial (NCT03145181/NCT04557098). **Methods:** Eligible patients had RRMM and received ≥ 3 prior lines of therapy including a proteasome inhibitor, immunomodulatory drug, and anti-CD38 antibody. Prior BCMA-targeted therapy was not allowed in this cohort. Patients received the recommended phase 2 dose (RP2D) of 1.5 mg/kg teclistamab QW, with the option to switch to Q2W dosing if patients achieved a confirmed partial response or better after ≥ 4 cycles of treatment (phase 1) or a confirmed complete response (CR) or better for ≥ 6 months (phase 2). Response was assessed per IMWG 2016 criteria. **Results:** As of Dec 9, 2022, 165 patients in the pivotal cohort had received teclistamab at the RP2D. Of 104 responders, 60 patients switched to Q2W dosing; 50 met the protocol-defined criteria for switching, and 10 switched who did not meet the criteria (4 due to adverse events [AEs]; 6 due to other reasons). Patients who switched had a median age of 64 years, 58% were male, 25% had high-risk cytogenetics, 7% had extramedullary plasmacytomas, and 3% had International Staging System stage III disease at baseline. Patients received a median of 4 prior lines of therapy, and 75% were triple-class refractory. At the time of switch, 49 (82%) patients achieved $\geq$ CR, and 11 (18%) had a very good partial response. Median time to switch from QW to Q2W dosing was 11.1 months (range, 3–20). At median 11.1-month (range, 2–24) follow-up since switching, the median duration of response from the date of switch was 20.5 months (range, 1–23), with 40/60 patients still in response and ongoing treatment. Of the remaining patients, 13/60 have progressed (median time from switch to progression not estimable), 2 discontinued due to AEs, 1 discontinued for other reason, and 4 died. Additional results will be presented. **Conclusions:** Overall, patients from the MajesTEC-1 study who transitioned from QW to less frequent Q2W dosing of teclistamab had sustained remission, with a median duration of response of 20.5 months from the date of switch. Clinical trial information: NCT03145181, NCT04557098. Research Sponsor: Janssen Research & Development.

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Poster Session

Evaluation of prophylactic tocilizumab (toci) for the reduction of cytokine release syndrome (CRS) to inform the management of patients (pts) treated with teclistamab in MajesTEC-1. *First Author: Niels W.C.J. van de Donk, Amsterdam University Medical Center, Vrije Universiteit Amsterdam, Amsterdam, Netherlands*

Background: Teclistamab is the first BCMA $\times$ CD3 bispecific antibody approved for the treatment of relapsed/refractory multiple myeloma (RRMM). In MajesTEC-1, CRS occurred in 72.1% of pts treated at the recommended phase 2 dose (RP2D) of weekly teclistamab 1.5 mg/kg (50.3% grade [gr] 1; 21.2% gr 2; 0.6% gr 3), and was successfully managed using toci in 36.4% of pts ($\pm$ other interventions) without affecting response to teclistamab. Emerging data show that prophylactic administration of toci prior to first dose of bispecific antibodies reduces CRS incidence and severity, which may facilitate outpatient initiation of therapy. The current analysis includes the first prospective study of effects of prophylactic toci on incidence and severity of CRS with teclistamab. **Methods:** Eligible pts were aged ≥ 18 y with RRMM and had previously received a PI, IMiD, and anti-CD38 antibody. Pts received subcutaneous teclistamab (following 2 step-up doses) in a prospective exploratory cohort at the RP2D or in a fixed-dose cohort. Toci (single 8 mg/kg IV dose) was given ≤ 4 hours before the first teclistamab step-up dose. CRS was graded per Lee et al 2014 and managed per institutional guidelines. **Results:** 14 pts were included: median age 64 y (range 50–82); all pts had ECOG score ≤ 1 and ISS I/II; 91% had standard cytogenetic risk; 21% had extramedullary plasmacytomas; 31% had $\geq 30\%$ BMPCs; median 4 prior lines of therapy (range 2–7); 64% triple-class refractory. Median follow-up was 1.2 mo (range 0.2–4.6). CRS occurred in 4 pts (29%; no gr ≥ 3 CRS); 1 had a subsequent CRS event (table). Median time to onset was 2 d (range 1–3); median duration was 2 d (range 2–4); all events were managed with toci and resolved without teclistamab discontinuation. 7 of 14 pts had gr 3/4 neutropenia (consistent with the overall MajesTEC-1 population). 2/14 had a gr 3/4 infection. 2/14 had a neurotoxicity AE. Of the response evaluable patients, 4/7 responded. Cytokine and PK data in additional pts with longer follow-up will be presented to further inform pt management. **Conclusions:** A single dose of toci before teclistamab treatment appeared to reduce the incidence of CRS relative to the overall MajesTEC-1 study population with no new safety signals and no evidence of impact on response to teclistamab considering the short follow-up. Prophylactic toci has the potential to reduce CRS risk in pts with disease profiles suitable for outpatient dosing, reducing the burden of hospitalization during teclistamab step-up dosing. Clinical trial information: NCT03145181, NCT04557098. Research Sponsor: Janssen Research & Development.

Pt	CRS grade	Dose after which CRS occurred	Disease characteristics in pts with CRS
1	1	Step-up dose 1	40% BMPCs (biopsy); 0 plasmacytomas
2	2	Step-up dose 2	30% BMPCs (aspirate); 2 plasmacytomas
3	1	Step-up dose 2	70% BMPCs (biopsy); 0 plasmacytomas; 11.6% circulating plasma cells at baseline
4	2	Cycle 1 Day 1	80% BMPCs (biopsy); 0 plasmacytomas
4	2	Step-up dose 1	

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Poster Session

Tumor-intrinsic features associated with progression-free survival (PFS) in patients (pts) with relapsed and refractory multiple myeloma (RRMM) treated with idecabtagene vicleucl (ide-cel). *First Author: Nicholas Stong, Bristol Myers Squibb, Princeton, NJ*

Background: Ide-cel, a B-cell maturation antigen chimeric antigen receptor T cell therapy, has demonstrated frequent, deep, and durable responses in pts with RRMM in the KarMMA (NCT03361748), KarMMA-2 (NCT03601078), and KarMMA-3 (NCT03651128) trials. A previous analysis of KarMMA showed comparable efficacy of ide-cel across molecular high-risk/resistance (HR/R) features such as biallelic p53 inactivation, 1q amplification, t(4;14), and *CRBN* dysregulation, and identified a baseline gene expression pattern (PC4) associated with PFS (Martin N, et al. *Hemasphere* 2022;6:(S6):1452). We aim to identify additional genomic features associated with ide-cel efficacy in KarMMA and KarMMA-2, and evaluate samples from KarMMA-3 pts as an independent validation cohort. **Methods:** Transcriptional and genomic profiles were assessed at baseline in CD138+ cells from bone marrow from pts in KarMMA, KarMMA-2 cohort 1, and KarMMA-3. Gene copy number aberrations were evaluated for associations with response. Analyses were post hoc and exploratory, and a P -value, or false discovery rate (FDR), of < 0.05 was used to identify associations of interest. **Results:** In evaluable pts in KarMMA ($n = 70$), single copy number loss was observed at 2 loci that associated with PFS, a broad region across 14q ($n = 16$) and deletion at 1p31.2 ($n = 6$). These were generally independent and collectively represented 30% (21/70) of pts. Both were associated with shorter median PFS (mPFS) in KarMMA (cohort mPFS, 8.8 mo, $n = 128$; Munshi et al. *N Engl J Med* 2021;384:705-16) after FDR correction (del 14q, mPFS, 4.0 mo; del 1p31.2, mPFS, 2.3 mo). No pt with 1p loss achieved a best overall response (BOR) better than partial response. Pts with loss vs non-loss of 14q had similar BOR distribution, but poorer mPFS within each BOR (10.4 vs 29.7 mo for loss vs non-loss in pts with complete response/stringent complete response). Due to small sample size in KarMMA-2 cohort 1 ($n = 18$), these data were aggregated with those from KarMMA. When combined, previously described associations with HR/R features were maintained except for biallelic p53 inactivation, which showed a stronger association with shorter PFS in the aggregate dataset ($n = 83$, $P = 0.04$) than in KarMMA ($n = 65$, $P = 0.09$). KarMMA-3 ($n = 210$) analysis is ongoing and will be used as a validation cohort for these findings. Consistent trends for the association of the PC4 gene signature with PFS were observed in KarMMA-2 but were not statistically significant and limited by sample size. **Conclusions:** Two novel genomic HR/R features associated with PFS were identified using samples from KarMMA; validation is ongoing using samples from KarMMA-3. The PC4 gene signature was consistent in 2 RRMM cohorts. A modest association between biallelic p53 disruption and PFS emerged with increased sample size and will be studied in KarMMA-3. Research Sponsor: Celgene, a Bristol-Myers Squibb Company, and 2seventy bio.

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Poster Session

Pivotal phase 2 MonumenTAL-1 results of talquetamab (tal), a GPRC5DxCD3 bispecific antibody (BsAb), for relapsed/refractory multiple myeloma (RRMM). *First Author: Carolina D. Schinke, Myeloma Center, University of Arkansas for Medical Sciences, Little Rock, AR*

Background: Tal is a first-in-class BsAb targeting the novel antigen G protein-coupled receptor family C group 5 member D. In MonumenTAL-1 (NCT03399799/NCT04634552), tal showed promising efficacy and clinically manageable safety in patients (pts) with RRMM. We report pivotal phase 2 results in pts with and without prior T-cell redirection therapy. **Methods:** Eligible pts were intolerant to or progressed on established therapies (phase 1) or had ≥ 3 prior lines of therapy (LOT), including ≥ 1 proteasome inhibitor, ≥ 1 immunomodulatory drug, and ≥ 1 anti-CD38 antibody (phase 2). Pts received RP2Ds of SC tal 0.4 mg/kg QW or 0.8 mg/kg Q2W with step-up doses. CRS and ICANS were graded by ASTCT criteria; all other AEs were graded by CTCAE v4.03. Response was assessed by IMWG criteria. Data cut-off was Sep 12, 2022 for efficacy and Oct 19, 2022 for safety. Data will be updated for the meeting. **Results:** From the pivotal cohorts, 288 pts received tal 0.4 mg/kg QW (n = 143) or 0.8 mg/kg Q2W (n = 145), and 51 pts with prior T-cell redirection therapy received either dose. In the QW, Q2W, and prior T-cell redirection cohorts, respectively, median prior LOT was 5–6; 74%, 69%, and 84% were triple-class refractory and 29%, 23%, and 41% were penta-drug refractory; 15%, 11%, and 12% received prior belantamab. In the prior T-cell redirection cohort, 71% received CAR-T therapy, 35% received a BsAb, and 6% received both. In the pivotal cohorts, ORR was 74% (QW, 14.9 mo median follow-up [mF/U]) and 73% (Q2W, 8.6 mo mF/U), with very good partial response or better ($\geq$ VGPR) in 59% (QW) and 57% (Q2W). ORR was consistent across subgroups, including baseline ISS stage III disease, cytogenetic risk, number of prior LOT, and belantamab exposure. In pts with baseline plasmacytomas, ORR was 49% in both pivotal cohorts. In the prior T-cell redirection cohort, ORR was 63% (53% $\geq$ VGPR) at 11.8 mo mF/U. Median PFS was 7.5, 11.9 (61% censored), and 5.1 mo in the QW, Q2W, and prior T-cell redirection cohorts, respectively. Common AEs included CRS (79%, 75%, 77%), skin-related AEs (56%, 71%, 69%), nail-related AEs (54%, 53%, 61%), and dysgeusia (50%, 48%, 61%); most were grade 1/2 and clinically manageable. ICANS occurred in 11%, 11%, and 3% of pts. Infections occurred in 58%, 65%, and 71% (grade 3/4: 22%, 16%, 26%) of pts, with low rates of opportunistic infections. AEs resulted in dose reductions in 15%, 8%, and 10% of pts and discontinuation in 5%, 8%, and 6%. There were no tal-related deaths. Responders to tal had higher T cell counts and lower frequencies of exhausted T cells and CD38+ Tregs vs non-responders. **Conclusions:** Pivotal phase 2 tal data showed $> 70\%$ ORR in heavily pretreated pts with RRMM. High response rates were also seen in pts with prior T-cell redirection therapy. The safety profile was clinically manageable with low rates of high-grade infections and tal discontinuations. Clinical trial information: NCT03399799, NCT04634552. Research Sponsor: Janssen Research & Development, LLC.

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Poster Session

Results from a first-in-human phase I study of F182112, a B-cell maturation antigen (BCMA)-CD3 bispecific antibody, in patients with relapsed/refractory multiple myeloma. *First Author: Mingyuan Sun, State Key Laboratory of Experimental Hematology, National Clinical Research Center for Hematological Disorders, Institute of Hematology and Blood Diseases Hospital, Tianjing, China*

Background: F182112 is a BCMA x CD3 bispecific antibody that redirects CD3+ T cells to mediate T-cell activation and subsequent lysis of BCMA-expressing myeloma cells. NTP-F182112-001 is a First-in-human, Open-label, Multiple center Phase 1 Dose-Escalation Study to Evaluate Safety, Tolerability, Pharmacokinetic, Immunogenicity, and Preliminary Efficacy of F182112 in Patients with Relapsed or Refractory Multiple Myeloma. Clinical trial information: NCT04984434. **Methods:** Eligible patients aged ≥ 18 years had received at least 2 prior multiple myeloma treatment regimens (not including autologous stem cell transplant) including a proteasome inhibitor, an immunomodulatory agent. Three dose cohorts (0.01, 0.1, and 0.3 μ g/kg) were planned for accelerated titration phase and the following dose cohorts (3, 10, 20, and 30 μ g/kg) were planned for the i3+3 dose escalation phase. F182112 were administered as QW or Q2W IV infusion. The primary endpoint was safety and tolerability assessed throughout the study by monitoring AEs per the CTCAE 5.0, except CRS per ASTCT 2018. **Results:** As of Feb 2, 2023, 16 pts in the first 7 cohorts received F182112 (0.01–20 μ g/kg). Median follow-up was 3.1 mo (range 0.9–11.7; median age 64 y [range 52–74]; 68% female). 9 (56%) pts had received ≥ 4 prior lines of therapy and 12 (75%) pts were refractory to last lines of therapy. The ORR was 43.8% (95% CI 19.8–70.1) among all enrolled patients (7/16). Of the 9 pts treated with ≥ 10 μ g/kg F182112, 6 pts achieved a partial response (PR) or better (overall response rate; 66.7%), including 2 (22.2%) with a very good partial response or better. The most common treatment-related AEs were CRS (81%), lymphopenia (75%; grade 3/4: 69%), neutropenia (63%; grade 3/4: 44%), leukopenia (56%; grade 3/4: 50%), and anemia (31%). CRS and anemia events were all grade 1–2 and median duration time to CRS was 2 days (1–5). One dose-limiting toxicities (transient ALT elevation, grade 3) occurred at the dose group of 10 μ g/kg. No pts required a F182112 dose reduction due to AEs. **Conclusions:** F182112 provides a novel immunotherapy approach for the treatment of Relapsed/Refractory Multiple Myeloma that may yield improved clinical efficacy in heavily pretreated pts. Clinical trial information: NCT04984434. Research Sponsor: Shan Dong New Time Pharmaceutical Co. Ltd.

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Poster Session

Adjusted indirect treatment comparison of progression-free survival (PFS) associated with DRd and VRd based on MAIA and SWOG S0777 individual patient-level data. *First Author: Brian G. Durie, Samuel Oschin Comprehensive Cancer Center, Los Angeles, CA*

Background: Both daratumumab in combination with lenalidomide and dexamethasone (DRd) and bortezomib in combination with lenalidomide and dexamethasone (VRd) are endorsed by NCCN guidelines as preferred regimens for the treatment of transplant-ineligible (TIE) patients with newly diagnosed multiple myeloma (NDMM). DRd and VRd have each demonstrated superior efficacy relative to lenalidomide and dexamethasone (Rd) alone in the MAIA and SWOG S0777 trials, respectively, but have not been compared directly in a head-to-head trial. Naive comparisons of efficacy across the 2 trials may be biased because MAIA enrolled only TIE patients (median age 73 years), whereas S0777 enrolled a mixed transplant-not-intended (TNI) population, which included both TIE patients and patients choosing to defer/refuse frontline stem cell transplantation (median age 63 years). **Methods:** The present study leveraged individual patient-level data (IPD) from both trials to perform an anchored indirect treatment comparison of DRd vs VRd, adjusting for differences in trial eligibility criteria and baseline patient characteristics. Harmonized inclusion criteria (NDMM, age ≥ 65 years, ECOG performance status ≤ 2) were applied to both trial populations. Age ≥ 65 years served as a proxy for TIE status since S0777 enrolled a mixed TNI population. Propensity score (PS) reweighting was used to balance the 2 trial populations on key baseline prognostic factors including age, sex, ISS stage, ECOG performance status, hemoglobin, eGFR, lactate dehydrogenase (LDH) level, and cytogenetic risk. Missing data were addressed with multiple imputation. After alignment of inclusion criteria and PS reweighting, an anchored indirect comparison was performed wherein within-trial progression-free survival (PFS) hazard ratios (HRs) for DRd vs Rd and VRd vs Rd were estimated and used to make indirect inference about PFS for DRd vs VRd. **Results:** 727 MAIA participants and 198 S0777 participants were eligible for inclusion. After PS reweighting, the trial populations were balanced on the key baseline prognostic factors identified above (standardized difference < 0.1 for each). The adjusted PFS HRs were 0.53 (95% CI: 0.41–0.68; $P < 0.0001$) for DRd vs Rd in MAIA and 0.88 (0.63–1.23; $P = 0.46$) for VRd vs Rd in S0777. In the adjusted Rd-anchored indirect comparison, the PFS HR for DRd vs VRd was 0.60 (0.39–0.90; $P = 0.02$). **Conclusions:** In this adjusted indirect treatment comparison based on IPD from the MAIA and S0777 trials, PFS was significantly longer for DRd relative to VRd. In the absence of a head-to-head trial comparing DRd and VRd, the present study may help to inform treatment selection in TIE patients with NDMM. Research Sponsor: Janssen.

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Poster Session

Elranatamab, a B-cell maturation antigen (BCMA)-CD3 bispecific antibody, for patients (pts) with relapsed/refractory multiple myeloma (RRMM): Extended follow up and biweekly administration from the MagnetisMM-3 study. *First Author: Mohamad Mohty, Sorbonne University, Hôpital Saint-Antoine, and INSERM UMRs938, Paris, France*

Background: MagnetisMM-3 (NCT04649359) is an open-label, multicenter, registration phase 2 study evaluating the efficacy and safety of elranatamab monotherapy in pts with RRMM; pts naive to BCMA-directed therapies were enrolled in Cohort A. **Methods:** Eligible pts were refractory to at least 1 PI, 1 IMiD, and 1 anti-CD38 antibody. Pts received SC elranatamab in 28-d cycles with step-up doses of 12 mg on C1D1 and 32 mg on C1D4 followed by 76 mg QW beginning C1D8. Pts treated for 6 cycles and achieving partial response (PR) or better with response persisting ≥ 2 mo were switched to 76 mg Q2W, 46 and 58 pts are included in the Q2W efficacy and safety analyses, respectively. **Results:** Overall, 123 pts received elranatamab. Median pt age was 68.0 y (range, 36–89), 63.4% of pts had an ECOG PS ≥ 1 and median prior lines of therapy was 5.0 (2–22); 96.7% and 42.3% of pts were triple-class- and penta-drug refractory, respectively. At data cutoff (~12 mo after last pt initial dose), the median follow up was 12.8 mo (0.2–22.7); 34.1% of pts remained on treatment. Most common reasons for permanent treatment discontinuation were progressive disease (39.0%) and adverse events (AE; 13.8%). Objective response rate per blinded independent central review (BICR) was 61% (95% CI 51.8–69.6), with 39 (31.7%) pts with complete response (CR) or stringent CR (sCR); very good partial response (VGPR) and PR were achieved in 29 (23.6%) and 7 (5.7%) pts, respectively. MRD-negativity (threshold 10^{-5}) was achieved by 92.0% (n = 23/25) of evaluable pts. Median duration of response (mDOR) has not been reached (95% CI 12.9–NE) and DOR at 12 mo was 74.1% (95% CI 60.5–83.6). In pts with CR/sCR or VGPR, mDOR was not reached by 12 mo; in pts with PR, mDOR was 5.2 mo (95% CI 1.6–NE). There were 46 responders by BICR who switched to Q2W dosing ≥ 24 wk prior to the data cut-off; among these pts, 80.4% maintained/improved their response ≥ 24 wk after the switch. Median progression-free and overall survival have not been reached by 12 mo, and the respective rates (95% CI) at 12 mo were 57.1% (47.2–65.9) and 62.0% (52.8–70.0). Most common Grade 3/4 treatment emergent AEs were hematologic; Grade 3/4 non-hematologic events reported in $\geq 5\%$ of pts were COVID-pneumonia (10.6%), hypokalemia (9.8%), pneumonia (7.3%), sepsis (6.5%), hypertension (6.5%), ALT increased (5.7%), and SARS-CoV-2 test positive (5.7%). Among pts who switched to Q2W dosing, the incidence of Grade 3/4 AEs decreased by $> 10\%$ after the switch. **Conclusions:** Elranatamab remains efficacious and well tolerated in pts with RRMM after > 1 y of follow-up. Updated analysis with a median follow up of ~15 mo, the longest of all phase 2 BCMA-CD3 bispecific antibody studies, including the outcome of pts who switched to the Q2W dosing, will be presented. These results support continued elranatamab development for pts with MM. Clinical trial information: NCT04649359. Research Sponsor: Pfizer.

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Poster Session

Efficacy and safety of elranatamab by age and frailty in patients (pts) with relapsed/refractory multiple (RRMM): A subgroup analysis from MagnetisMM-3. First Author: Noopur S. Raje, Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA

Background: Multiple myeloma is predominantly a disease of elderly and frail pts, who are often ineligible for intensive therapies. Data from the ongoing Phase 2 MagnetisMM-3 (NCT04649359) study demonstrated the efficacy and safety of elranatamab in pts with RRMM and no prior BCMA-directed therapy (Cohort A). Here we report results for subgroups of pts by age and frailty. **Methods:** Eligibility criteria, dosing and administration were previously reported (Bahlis, ASH 2022). Subgroups of pts within Cohort A (n = 123) were analyzed by age: < 65 (n = 43) vs ≥65 years (n = 80), and frailty: non-frail (n = 84) vs frail (n = 39). A simplified frailty scale was used (Facon et al, Leukemia 2020). Results include data up through ~12 months after last pt initial dose. **Results:** The median treatment duration was 8.2 vs 5.5 mo in the < 65 vs ≥65 years, and 6.4 vs 5.6 mo in the non-frail and frail subgroups, respectively. Discontinuation occurred in 62.8% vs 67.5% of pts aged < 65 vs ≥65 years and in 63.1% vs 71.8% of the non-frail vs frail groups, respectively. The most common reason for discontinuation in all subgroups was progressive disease, 51.2%, 32.5%, 42.9%, and 30.8% of < 65, ≥65 years, non-frail, and frail subgroups, respectively. The objective response rate (ORR) (95% CI) was 58.1% (42.1%, 73.0%) vs 62.5% (51.0%, 73.1%) for pts aged < 65 vs ≥65 years. Median duration of response was not reached in either age subgroup. The probability of maintaining response (95% CI) at 12 mo was 74.1% (51.0%, 87.5%) vs 73.8% (55.7%, 85.4%) for pts aged < 65 vs ≥65 years. The ORR (95% CI) for non-frail pts was 63.1% (51.9%, 73.4%) vs 56.4% (39.6%, 72.2%) for frail pts. Median duration of response was not reached in either frailty subgroup. The probability of maintaining response at 12 mo (95% CI) was 76.0% (60.2%, 86.2%) vs 70.5% (41.9%, 86.9%) for non-frail vs frail pts. Any Grade treatment-emergent adverse events (TEAEs) were reported in 100% of pts in the study. Grade 3/4 TEAEs were reported in 74.4%, 68.8%, 73.8% and 64.1% of pts in < 65, ≥65, non-frail and frail subgroups, respectively. Infections (Any Grade; Grade 3/4; Grade 5) were reported in 72.1%, 32.6% and 4.7% vs 68.8%, 40.0% and 6.3% in < 65 and ≥65 pts, respectively, and in 70.2%, 38.1% and 4.8% vs 69.2%, 35.9% and 7.7% in non-frail and frail pts, respectively. The rate of cytokine release syndrome was similar in patients with respect to age (< 65, 58.1%; ≥65 years, 57.5%) and frailty groups (non-frail, 57.1%; frail, 59.0%). Immune effector cell-associated neurotoxicity syndrome was reported in 2.3%, 6.3%, 6.0% and 2.6% of pts in < 65, ≥65, non-frail and frail subgroups, respectively. **Conclusions:** Elranatamab is efficacious and has a manageable safety profile in elderly or frail pts with RRMM and may be a treatment option for those ineligible for more intensive myeloma therapies. Clinical trial information: NCT04649359. Research Sponsor: Pfizer.

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Poster Session

Phase 1 study of tasquinimod, an S100A9 inhibitor, alone and in combination with IRd for relapsed and refractory multiple myeloma (RRMM). First Author: Dan T. Vogl, Abramson Cancer Center, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

Background: S100A9, a protein produced by myeloid-derived suppressor cells (MDSCs) in the bone marrow microenvironment, promotes multiple myeloma (MM) progression and confers therapeutic resistance. Tasquinimod (tasq), an oral S100A9 inhibitor, has pre-clinical anti-myeloma effects alone and combined with proteasome inhibitor (PI) and immunomodulator (ImiD) therapy (Lin C, EHA 2020; EP896). Tasq previously improved PFS in prostate cancer patients (pts) (JCO 2016;34(22):2636-43). We are conducting a phase 1 trial (NCT04405167) of tasq as a single agent and in combination with ixazomib (ixa), lenalidomide (len), and dexamethasone (dex) (IRd) in pts with RRMM. **Methods:** We enrolled pts with RRMM refractory to, intolerant of, or with contraindication to len, pomalidomide (pom), bortezomib, carfilzomib (cfz), and a CD38 monoclonal antibody. Tasq was given in 28-day cycles as shown below, with a 3+3 dose escalation scheme. For combination therapy, pts received ixa (4 mg days 1/8/15), len (25 mg days 1-21, with adjustments for renal dysfunction), and dex (40 mg qwk). **Results:** Of 15 pts, median age was 70y (range 56-84); 53% were male; 27% were African American and 73% Caucasian. Pts had received a median of 8 prior lines of therapy (range 4-17), and all were refractory to ≥1 ImiD, 87% to ≥1 PI, and 100% to a CD38 mAb, with 87% triple class refractory and penta-exposed. 10 pts received single-agent tasq at dose levels 1 (3 pts), 2 (3 pts), and 3 (4 pts). The most common treatment-emergent adverse events (TEAEs) were fatigue (all grade [gr] 1/2), anemia (5 pts, gr 3 in 2), anorexia (5 pts, gr 3 in 2), pain (5 pts, all gr 1/2), nausea/vomiting (4 pts, all gr 1/2), and neuropathy (3 pts, all gr 1/2). No dose-limiting toxicities (DLTs) were observed, but at dose level 3, 2 pts stopped for intolerable toxicities, and we identified dose level 2 as the single-agent MTD. 5 pts have received tasq with IRd at dose levels 1 (3 pts) and 2 (2 pts). Gr ≥ 3 TEAEs were gr 4 thrombocytopenia in 1 pt (improved with dose reductions of ixa and len), gr 3 insomnia in 1 pt, and gr 5 COVID pneumonia in 1 pt. No tasq-related DLTs were observed. On single-agent tasq, 3 pts with progressive disease at study entry had stabilization of serum markers while on study. Of 5 pts on the IRd combination, 1 has had a partial response that is ongoing after 10 months, despite being previously refractory to ixa/pom and cfz/pom combinations. **Conclusions:** Tasquinimod, an S100A9 inhibitor, is well tolerated in pts with RRMM as a single-agent and in combination with IRd, with a single-agent MTD of 1 mg daily after a 1-week dose escalation. Tasq has anti-myeloma activity in combination with IRd, as evidenced by a partial response in a patient previously refractory to ImiD/PI combination therapy. Enrollment continues to tasq with IRd at dose level 2. Clinical trial information: NCT04405167. Research Sponsor: The Leukemia & Lymphoma Society; Active Biotech.

Dose level	Tasquinimod dose
1	0.25 mg qd x1 wk, 0.5 mg qd x1 wk, then 1 mg qd
2	0.5 mg qd x1 wk, then 1 mg qd
3	1 mg qd
4	1.25 mg qd
5	1.5 mg qd

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Poster Session

Efficacy, safety, pharmacokinetic (PK), and pharmacodynamic (PD) support for talquetamab (tal) QW and Q2W dosing in patients (pts) with relapsed/refractory multiple myeloma (RRMM): Analyses from MonumentAL-1. First Author: Xuewen Ma, Janssen Research & Development, Spring House, PA

Background: Tal is a first-in-class bispecific antibody targeting the novel antigen G protein-coupled receptor family C group 5 member D. In MonumentAL-1 (NCT03399799/NCT04634552), tal demonstrated an overall response rate (ORR) of > 70%, with clinically manageable safety in pts with RRMM. We summarize efficacy, safety, PD, and PK results supporting the recommended phase 2 doses (RP2Ds) of tal: 0.4 mg/kg QW and 0.8 mg/kg Q2W SC. **Methods:** In MonumentAL-1, pts received IV (0.5–180 µg/kg) or SC (5–1600 µg/kg) tal doses in phase 1 and at the RP2Ds in phase 2, preceded by step-up doses. Blood samples were collected for the measurement of tal serum concentration and anti-tal antibodies (ADAs). Covariate effects on PK and efficacy were characterized. Efficacy and safety exposure-relationships (E–R) were evaluated using predicted PK metrics, ORR, and key treatment-emergent adverse events (TEAEs), including neurotoxicity, infections, cytopenia, ageusia, dysgeusia, weight loss, and cytokine release syndrome (CRS). **Results:** PK exposure was approximately dose proportional across IV and SC doses, with a SC bioavailability of 61.9%. At the RP2Ds, the mean concentration–time profiles were comparable and maintained at or above the concentration associated with the 90% maximal drug effect identified in an ex vivo cytotoxicity assay. The incidence of ADAs was 29% (QW) and 20% (Q2W). Presence of ADAs had no apparent impact on PK, safety (CRS, systemic administration-related reaction, or injection site reaction), or efficacy (ORR). At the RP2Ds, PD changes indicative of the proposed mechanism of action, such as T-cell activation, induction of cytokines, and T-cell redistribution, were comparable. Body weight, myeloma subtype, and International Staging System stage were identified as covariates for tal PK; however, there was no clinically relevant impact of age, sex, race, or mild/moderate hepatic or renal impairment on PK. Across SC doses in phase 1, ORR increased with exposure and reached a plateau at or above the RP2Ds, supporting the selected RP2Ds. Baseline myeloma subtype and extramedullary plasmacytoma status were identified as prognostic factors for ORR at the RP2Ds. There were no observed E–R for key TEAEs, including grade ≥3 infections or cytopenia, grade ≥2 weight loss, or grade 2 ageusia. No E–R for grade ≥1/≥2 CRS and peak tal exposure for any step-up doses, irrespective of tocilizumab administration, was observed. Dysgeusia rates were comparable between the 2 RP2Ds. **Conclusions:** Efficacy, safety, PK, and PD analyses support the selection of tal 0.4 mg/kg QW and 0.8 mg/kg Q2W SC regimens as RP2Ds. The RP2Ds provided comparable PK, PD, efficacy, and safety profiles. Covariates for PK exposure had no impact on E–R, and dose adjustment was not warranted. Clinical trial information: NCT03399799, NCT04634552. Research Sponsor: Janssen Research & Development, LLC.

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Poster Session

Clinical characteristics, markers of adverse prognosis, and predictors of development of extramedullary multiple myeloma. First Author: Saurabh Zanwar, Mayo Clinic, Rochester, MN

Background: Extramedullary Multiple Myeloma (EMM) has an aggressive clinical course and can present at diagnosis [primary EMM, (pEMM)] or relapse [secondary EMM, (sEMM)]. Here, we report clinical characteristics and outcomes of EMM, and predictive factors for the development of sEMM. **Methods:** We identified 299 patients with biopsy-proven EMM between 01/01/2000 and 12/31/2021. Patients with solitary plasmacytoma, paraneoplastic MM and primary plasma cell leukemia were excluded. A 1:1 matched pair analysis (matched for year of diagnosis of MM for comparable follow-up and treatment eras) was performed to compare clinical characteristics and outcomes for patients with and without sEMM. **Results:** The median follow-up from the diagnosis of MM was 11.5 years (95%CI: 9.3-14.8). Of 299 patients, 204 (68%) patients had sEMM and 95 (32%) had pEMM, with largely comparable baseline characteristics (Table). The median overall survival (OS) from the diagnosis of sEMM was 0.7 (95% CI: 0.6-0.9) years compared to 3.6 (95%CI: 2.4-5.6) years for pEMM (p<0.0001). For sEMM, multivariable analysis (MVA) for OS identified visceral organ involvement (eg. liver, lung/pleura, brain, pancreas, etc.) to be associated with inferior OS [HR 1.6 (95% CI: 1.1-2.4), p=0.01]; high-risk cytogenetics (HR-CTG), ISS-3 stage, and age did not impact OS from sEMM. For pEMM, HR-CTG [HR 2.3 (95% CI 1.1 -4.8), p=0.03] and ISS-3 stage [HR 3.1 (95% CI 1.5-6.7), p=0.003] were associated with inferior OS on MVA whereas visceral EMM or age did not impact OS from pEMM. On univariate analysis, patients with sEMM were younger (median age 58.7 vs 61 years, p=0.006), had a higher proportion of 1q duplication (32% vs 17%, p=0.001), t(4;14) [16% vs 9%, p=0.047] and elevated LDH (30% vs 19%, p=0.04), compared to the matched cohort of patients without sEMM. On MVA, younger age at diagnosis, t(4;14) and 1q duplication at diagnosis of MM were independent predictors of development of sEMM. The median OS from diagnosis of MM was 5.4 years (95%CI: 4.1-6.2) for patients with sEMM versus 7.5 years (95% CI: 6.4-10.1; p<0.001) for the matched cohort. Secondary EMM was an independent poor prognostic marker for OS from the diagnosis of MM [HR 1.6 (95%CI: 1.2-2.1); p=0.004] in addition to age, ISS3 disease and HR-CTG. **Conclusions:** Outcomes of patients with EMM, especially sEMM, remain dismal. Patients with sEMM have higher rates of 1q duplication and t(4;14) at diagnosis of MM and carried an independent adverse prognosis in a matched cohort. Research Sponsor: None.

Parameter at Diagnosis of MM	Primary EMM (n=95)	Secondary EMM (n=204)	p-value
Median age, years, (range)	61 (18-83)	58.7 (35-89)	0.09
ISS Stage 3, %	21	32	0.22
High-risk cytogenetics, %	53	54	0.89
17p deletion	18	16	0.7
1q duplication	26	31	0.44
t(4;14)	15	16	0.84
MAF translocations	15	8	0.15
Visceral site of disease, %	52	52	0.9
LDH > ULN at MM diagnosis, %	33	30	0.7
Marrow plasma cell infiltrate, median, %	30	50	0.005

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Poster Session

Identification of cytokines associated with response and cytokine release syndrome: Analysis of MagnetisMM-3 cohort A. *First Author: Hang Quach, St. Vincent's Hospital, University of Melbourne, Melbourne, VIC, Australia*

Background: MagnetisMM-3 (NCT04649359) is a phase 2 study of elranatamab monotherapy in patients with multiple myeloma refractory to at least 1 proteasome inhibitor, 1 immunomodulatory drug, and 1 anti-CD38 antibody. Promising efficacy and safety have been observed in patients who were naïve to B-cell maturation antigen (BCMA)-directed therapy (Cohort A) in MagnetisMM-3 (Bahlis et al., ASH 2022). **Methods:** In MagnetisMM-3, patients received subcutaneous elranatamab in 28-day cycles with step-up doses of 12 mg on C1D1 and 32 mg on C1D4 followed by 76 mg QW beginning C1D8. Serum samples were collected on C1D1 prior to first priming dose, and on C1D2, pre-dose C1D4, C1D5, pre-dose C1D8, C1D15, and C1D22. Levels of 45 peripheral cytokines were analyzed by proximity extension assay and a longitudinal mixed effects model was applied to each cytokine separately. Cytokines with a significant 2-fold differential expression (responders [defined as patients with best overall response of very good partial response or better] vs non-responders [defined as patients with best overall response of partial response or worse]; cytokine release syndrome [CRS] vs no CRS) at any timepoint are reported. Clinical data cutoff was in Oct 2022 with median follow up of 10.4 months. **Results:** Baseline levels of IL-6 (2.6-fold), IL-17C (2.0-fold), and MIP-1 α (2.1-fold) were lower in patients who achieved a response. After the first priming dose, 13 cytokines in the panel, including CCL8, IFN- γ , IL-2, and IL-27, were differentially expressed in responders vs non-responders. At baseline, no cytokines were found to predict CRS. After the first priming dose, 18 cytokines in the panel, including CCL8, IFN- γ , IL-10, IL-2, IL-27, IL-6, and IL-17A, were differentially expressed in patients with CRS vs no CRS. The maximal differential expression for 17/18 cytokines occurred at C1D2, ~24 hours post the first priming dose. **Conclusions:** Lower baseline levels of IL-6, IL-17C, and MIP-1 α correlated with a response of VGPR or better in BCMA-naïve patients from MagnetisMM-3, suggesting that lower levels of these cytokines might reflect a favorable immune environment. Many cytokines were differentially expressed at higher levels in patients who experienced CRS vs those who did not; the most prominent cytokines included CCL-8, IFN- γ , and IL-10. The timing of induction of CCL-8, IFN- γ , and IL-10 occurred by C1D2 suggesting a potential contribution of these cytokines in driving CRS. Clinical trial information: NCT04649359. Research Sponsor: Pfizer.

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Poster Session

ISAMAR: Multicenter phase II single arm trial of isatuximab (ISA) with/without lenalidomide (LEN) in pts with high risk smoldering multiple myeloma (HRSM). *First Author: Elisabet Esteve Manasanch, Department of Lymphoma/Myeloma, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: HRSM patients (pts) have a median time to progression of < 2 years. ISA is a monoclonal antibody that binds to highly expressed CD38 on myeloma cells and is approved in RRMM. We designed a phase II study to test the efficacy of ISA +/- LEN in HRSM (NCT02960555). **Methods:** The primary endpoint of the study was the overall response rate (ORR) after 6 months of ISA 20 mg/kg IV days 1, 8, 15, 22 cycle 1; days 1, 15 cycles 2-6; day 1 cycles 7-30 monotherapy (stage 1, n = 25) or with LEN 25 mg po daily on days 1-21 every 28 days, cycles 1-6 (stage 2, n = 36). Secondary endpoints are progression free survival (PFS), overall survival (OS) while exploratory endpoints included quality of life (QoL), flow and sequencing. **Results:** 61 HRSM pts (+immunoparesis and $\geq 95\%$ abnormal plasma cells in bone marrow) (stage 1 n = 25; stage 2 n = 36) were accrued 02/2017-10/2022. The study met its primary endpoint of ORR $\geq 70\%$ after 6 cycles of therapy [Stage 2 ORR (89%) = VGPR 9 (25%), PR 23 (64%), MR 3 (8%), PD 1 (3%)]. Median time to response was 1 cycle. In stage 2, 17/36 (47%) patients had grade 3 treatment related adverse events (AEs): 1 pt related to ISA (myalgia, 3%) and 16 pts related to LEN (44%) [ANC decrease (36%), skin rash (8%), ALC decrease (11%), WBC decrease (8%), fatigue (6%)] and 1/36 pts a grade 4 (related to LEN) [ANC decrease 3%]. Most common grade 1-2 AEs: WBC decrease (53%), ANC decrease (56%), skin rash (28%), fatigue (39%), ALC decrease (42%), thrombocytopenia (28%), diarrhea (39%), constipation (28%). There were no grade 5 AEs. No patients discontinued treatment due to AEs. There were 3 deaths in stage 1 unrelated to therapy: 1 patient progressed to and died while on systemic AL amyloidosis therapy, one patient (with COPD) died of COVID19 while in sustained PR, one heavy smoker died of squamous cell cancer of the tongue. Pre- and post-treatment BM flow showed that ISA/LEN increased CD4+/CD8+ and effector memory cytotoxic T cells. QoL measures (n = 32; 15 in stage 1, 17 in stage 2 and 21 with both BL/after 6 months data) showed that ISA +/- LEN resulted in decreased cancer worry/anxiety and improved future perspective at 6 months compared to BL in both stages. QoL was favorable and conserved throughout treatment, suggesting minimal effects of treatment on patient assessment of well-being. For stage 1, median PFS was 49.3 months (95% CI: 40.8-NA months); median OS not reached at a median f/u of 49 months (range 6.3-68 months). Stage 2 median PFS/OS is not reached. **Conclusions:** ISA/LEN results in high ORR without decrease in patient well-being. ISA monotherapy also results in prolonged PFS when compared to historical data. ISA/LEN therapy remodels the BM TME with increase in memory cytotoxic T cells. The results of this study give rationale for the ongoing phase 3 ITACHA evaluating ISA +/- LEN/DEX with the potential to change the standard of care in HRSM (NCT04270409). RO and OL have equal contribution. Clinical trial information: NCT02960555. Research Sponsor: High-risk Multiple Myeloma Moon Shot Program at UT MD Anderson Cancer Center; SANOFI; Miriam and Sheldon Adelson Medical Research Foundation; The Paula and Rodger Riney Foundation.

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Poster Session

Genomic analysis to identify determinants of inherent response and resistance to elranatamab in MagnetisMM-3 cohort A. *First Author: Nizar J. Bahlis, Arnie Charbonneau Cancer Institute, University of Calgary, Calgary, AB, Canada*

Background: MagnetisMM-3 (NCT04649359) is an open-label, multicenter, non-randomized phase 2 study of elranatamab monotherapy in patients (pts) with multiple myeloma refractory to at least 1 proteasome inhibitor, 1 immunomodulatory drug and 1 anti-CD38 antibody. This analysis examined molecular correlates of elranatamab response and resistance in pts naïve to B-cell maturation antigen (BCMA)-directed therapy (Cohort A). **Methods:** Bone marrow aspirate (BMA) samples collected at screening were analyzed by whole exome and whole transcriptome sequencing. To investigate the contribution of the tumor microenvironment (TME) in elranatamab response, the abundance of cell types in the BMA samples collected at screening was estimated using single sample gene set enrichment analysis (ssGSEA) of LM22 cell type signatures. Response was defined as a best overall response of very good partial response or better (partial response was considered non-response for this analysis). **Results:** *TNFRSF17* (BCMA encoding gene) expression correlated with markers of disease burden: levels increased with disease stage (with progressively higher levels in R-ISS stages I, II, and III; $p = 0.014$), were higher in pts with high-risk cytogenetics ($p = 0.002$) and correlated with plasma cell content in BMA samples ($p = 0.80$; $p < 10^{-10}$). *TNFRSF17* expression trended higher in non-responders ($p = 0.08$), but this trend was diminished when adjusting for disease burden. These findings suggest *TNFRSF17* expression in bulk BM samples is associated with higher disease burden and likely poorer response. According to ssGSEA of LM22 cell types, plasma cells in BMA were associated with non-responders ($p = 0.03$). Further multivariable modeling (controlling for plasma cell content) revealed additional cell types associated with response, including macrophages and monocytes, which were associated with poor outcome. Pts with both low plasma and low myeloid cells were most likely to respond. Genome wide copy number analysis showed that *TNFRSF17* locus amplification was associated with non-response ($p = 0.008$). Chromosomal alterations associated with non-response were identified, including genomic loci known to define high-risk MM (eg, 1q21+) and loci not known to be associated with high-risk MM (eg, 17q21+ and 6p21+). **Conclusions:** Genomic analysis of BMA samples from MagnetisMM-3 identified an association between higher *TNFRSF17* expression in the TME and unfavorable outcomes, likely due to its surrogacy with increased tumor burden. Features of high-risk disease were also associated with lack of response to elranatamab. Adjusting for tumor cell content revealed additional aspects of the TME associated with poor response, including increased myeloid cell populations. Lastly, alterations in specific genomic loci were also associated with response, consistent with tumor intrinsic features influencing elranatamab response. Clinical trial information: NCT04649359. Research Sponsor: Pfizer.

8047

Poster Session

Patient-derived MicroOrganoSpheres (MOS) and precision clinical decision-making for patients with multiple myeloma. *First Author: Rui Xi, Xilis, Inc, Durham, NC*

Background: There are many multiple myeloma (MM) treatments and nearly all patients undergo continual cycles of treatment, response, and resistance. Selecting an effective therapeutic strategy is of critical importance; but there is currently a lack of patient-derived MM models that can enable functional precision medicine to help real-time clinical decision-making to guide individual patient treatment. **Methods:** We show a method to rapidly establish MM patient-derived MicroOrganoSpheres (MOS), which are microscale, droplet-sized patient avatars that sustain the native tumor niche, including both stromal and immune compartments. We generated first-of-its-kind data showing that MM MOS predicted patient treatment outcomes and have the potential to guide clinical treatment decisions. We further developed high-throughput drug screen to demonstrate MM MOS response to FDA-approved single and combination therapies and developed MOS assays to predict patient responses to immunotherapies including bispecific and phagocytosis-inducing antibodies. **Results:** MM MOS established from patient bone marrow (BM) biopsies preserved CD138/CD38 tumor cells, stromal (e.g., osteoblast) cells, and all major immune cell populations (T, NK, B, macrophage, dendritic, and myeloid-derived suppressor cells) for 11 days in culture. We performed single and combo drug testing on MOS derived from 7 MM patients within 10 days of biopsy collection. Patients went on receiving treatments and their responses were assessed using International Myeloma Working Group response criteria. The MOS assay predicted responses of both treatment-naïve and refractory patient to standard-of-care regimens, including combinations of proteasome inhibitors (bortezomib, carfilzomib), immunomodulatory agents (lenalidomide) and DCEP. Moreover, the BM biopsy-derived MOS enabled high-throughput drug testing of single agents and combinations in 9-dose titrations, providing clinicians the ability to evaluate alternative treatment options. Furthermore, because MOS retain the immune compartments of the original tumor niche, we were able to evaluate patients' response to bispecific T cell engagers and developed a phagocytosis assay to measure anti-tumor phagocytosis activity, which showed efficacy in both single-agent and combo settings. Multi-modal profiling and an AI image analysis pipeline provided robust measurements that confirmed the unique phenotypic profile of each patient sample, highlighting the critical unmet need to guide each patient to the optimal treatment. **Conclusions:** Based on this groundbreaking feasibility study, a subsequent clinical trial of 40 patients is current under IRB review to further validate the clinical power of MM MOS to predict patient outcome and to demonstrate utility as a viable functional precision medicine approach to inform treatment decisions in the clinic. Research Sponsor: None.

8048

Poster Session

Retrospective analysis of the relationship between time to anti-resorptive therapy and incidence of skeletal related events in patients with multiple myeloma. *First Author: Adam F Binder, Sidney Kimmel Cancer Center at Thomas Jefferson University, Philadelphia, PA*

Background: Patients with multiple myeloma (MM) often have bone disease at diagnosis and are at risk of developing skeletal related events (SRE) (pathological fractures, spinal cord compression, and/or need for radiotherapy or surgery to bone). It is well established that for patients with lytic bone lesions at diagnosis, the use of anti-resorptive agents lead to a lower incidence of SREs. However, it is common for initiation of anti-resorptive therapy to be delayed. Recent studies have demonstrated that anti-resorptive therapy is underutilized in patients with MM. However, the effect of time to initiation of anti-resorptive agent after diagnosis of MM on SREs has not been well studied. Herein, we conducted a multi-center retrospective analysis to determine if time to anti-resorptive agent has an adverse impact on the risk of SREs. **Methods:** We performed a retrospective cohort study using our Electronic Health Record system to identify patients with newly diagnosed MM between July 1st, 2016 and June 30th, 2019 at two large academic centers. Patients previously treated or patients not treated with anti-resorptive therapy were excluded. The study's primary endpoint was hazard ratio of developing a SRE based on time to anti-resorptive therapy. The relationship between incidence of SREs and time to anti-resorptive therapy, gender, age, International Staging System (ISS) stage at diagnosis, and prior SRE present at diagnosis was analyzed by using a multivariable Cox proportional hazards model. The cutoff point of anti-resorptive therapy delay was based on the recursive partitioning of univariable Cox model. **Results:** 759 patients were included in the study (Thomas Jefferson University: n = 232; The Ohio State University: n = 527). Median age at diagnosis is 60.2 years (IQR: 12.4 years). 57% of patients were male. 77.9% and 20.3% of patients identified as white and black respectively. 210 patients (27.7%) were noted to have osteopenia, 45 (5.9%) had osteoporosis, 229 (30.2%) were vitamin D deficient, and 319 (42%) were obese at diagnosis. A skeletal related event was present at diagnosis in 338 (45.1%) of patients. 180 (34%) patients received anti-resorptive agents within 31 days. A delay in initiating anti-resorptive agents of greater than 31 days from diagnosis had an increased risk for SRE with a hazard ratio 1.654 (1.054–2.598; p-value: 0.029). **Conclusions:** This large multicenter retrospective study demonstrated that time to anti-resorptive therapy MM patients has a significant impact on the risk of SRE. Given many of the challenges in starting anti-resorptive therapy in a timely manner, this study emphasizes the need for inter-professional, multi-disciplinary collaborations to streamline the workflow and start therapy within the first month of diagnosis. Ongoing efforts are underway to develop quality improvement processes to achieve this goal. Research Sponsor: None.

8050

Poster Session

Safety and clinical activity of belantamab mafodotin plus lenalidomide and dexamethasone in transplant ineligible patients with newly diagnosed multiple myeloma: The phase 1/2, prospective, open-label, BelARd study. *First Author: Evangelos Terpos, Department of Clinical Therapeutics, National and Kapodistrian University of Athens, School of Medicine, Athens, Greece*

Background: We present the updated safety and efficacy of upfront belantamab mafodotin (belamaf) plus lenalidomide and dexamethasone (Rd) in transplant ineligible (TI) pts with newly diagnosed multiple myeloma (NDMM). **Methods:** The ongoing, prospective, open-label, phase 1/2 BelARd study (NCT04808037) aims to enroll 66 pts with TI NDMM, with ECOG PS < 2 and adequate organ function. In Part 1, 36 pts are randomized (1:1:1) to receive belamaf 2.5, 1.9, or 1.4 mg/kg Q8W plus Rd. Eye exams include Snellen best corrected visual acuity (BCVA) and corneal exam (slit lamp examination). Ocular adverse events (OAEs) are classified by CTCAE v5.0. This descriptive analysis presents the updated safety and efficacy findings for all Part 1 pts (cutoff date 15/12/22). **Results:** The analysis included 36 pts [median age: 73 years (64–86); male: 19 (53%)], of whom 31 (86%) were still on treatment and 5 (14%) had discontinued [4 pts due to belamaf-unrelated adverse events (AEs); 1 pt withdrew consent]. At baseline, 32 (89%) pts were intermediate fit as per International Myeloma Working Group frailty score and 34 (94%) had ECOG PS ≤ 1. Median follow up was 15 months (3–23); median belamaf administrations and number of cycles reached were 6 (2–10) and 15 (3–22). Thirty-four (94%) pts experienced ≥ 1 grade (Gr) ≥ 3 treatment-emergent AEs (TEAEs). Most common (≥ 10% of pts) non ocular Gr ≥ 3 TEAEs were fatigue (21 pts, 58%), rash (6 pts, 17%), diarrhoea (5 pts, 14%) and COVID-19 infection (4 pts, 11%); no Gr ≥ 3 thrombocytopenias and any Gr infusion-related reactions were reported. Regarding pts visual acuity, out of a total of 499 BCVA assessments, 164 (33%) were Gr 2 and 54 (11%) were Gr 3. Notably, a meaningful BCVA decline (worse than 20/50 in better seeing eye) was observed in 38 (8%) assessments, with a median time to resolution of 1 month. Regarding clinically relevant Gr ≥ 2 ocular symptoms, blurred vision, dry eye and visual impairment were observed in 38 (8%), 96 (20%) and 98 (20%) assessments, with a median time to resolution of 2, 3 and 2 months. Slit lamp examinations by the ophthalmologist (N = 501) revealed a Gr 2 keratopathy in 55 (11%) assessments and Gr 4 keratopathy in 2 (< 1%) assessments, with a median time to resolution of 4 months. Overall response rate [partial response (PR) or better] was 100.0% [36 pts; stringent complete response: 14% (5 pts); complete response: 19% (7 pts); very good partial response: 47% (17 pts); PR: 19% (7 pts)]. Median time to first response was 1 month. **Conclusions:** Part 1 of the BelARd study showed that in TI pts with NDMM, the safety profile of belamaf plus Rd was manageable and a meaningful BCVA decline was noted in a minority (< 10%) of assessments which resolved quickly (1 month). The combination induced rapid and deep responses, with all pts achieving ≥ PR and first response observed at a median of 1 month. Clinical trial information: NCT04808037. Research Sponsor: GSK.

8049

Poster Session

Evaluating the efficacy of commercial teclistamab in relapsed refractory multiple myeloma patients with prior exposure to anti-BCMA therapies. *First Author: Ross Firestone, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Teclistamab (Tec) is the first CD3 x BCMA bispecific antibody (BsAb) receiving accelerated FDA approval for treatment of relapsed or refractory multiple myeloma (RRMM) in patients who have received ≥ 4 prior lines of therapy, including a PI, IMiD and an anti-CD38 monoclonal antibody. The approval was based on the results of the MajesTec-1 study (Usmani S et al Lancet 2021, Moreau P et al NEJM 2022), demonstrating a 63% overall response rate in a heavily pretreated RRMM population. Patients with prior exposure to anti-BCMA therapies, such as BCMA targeted ADCs, CAR T-cell products and BsAbs were excluded from this study. Herein, we present our institutional experience with commercial Tec for RRMM including patients with prior BCMA and GPRC5D directed therapies. **Methods:** We have performed an IRB-approved, retrospective analysis of clinical outcomes of all patients who have received commercial Tec at MSKCC since its approval on 10/26/2022 using the PCD research database. Descriptive analyses were performed for baseline characteristics. The IMWG criteria (Kumar S et al, Lancet Oncol 2016) were used to assess response and define prior therapy refractoriness. Immune profile was assessed via high-dimensional flow cytometry using lineage, exhaustion, and activation markers. Serum soluble BCMA levels were assessed using an immunoassay. **Results:** As of 2/4/2023, 24 patients have received commercial Tec and 15 are response evaluable with ≥ 1 month of clinical follow-up. Median age was 66 (51–80), prior lines of therapy was 7 (4–13), time from diagnosis was 7 years (1.5–16), 53% had high-risk cytogenetics, and 40% had EMD. All patients were triple class refractory and 80% were penta-drug refractory. Ten had prior anti-BCMA therapy (7 Belamaf, 8 BCMA CART, 1 BCMA BsAb, 5 with ≥ 2 anti-BCMA therapies). With a median follow-up time of 1.3 months, the median time to response was 16 days. ORR was 60% (9/15) in all patients and 50% (5/10) in the prior anti-BCMA therapy group. Pts with ≥ 2 anti-BCMA therapies had a 40% (2/5) response rate to Tec. Clinical benefit rate (CBR) in all patients was 73% (11/15). None of the responders have progressed at this short follow-up time. Cytokine release syndrome was observed in 7/15 patients (41%) during step-up dosing (5/7 with g1 and 2/7 with g2 CRS) and CBR was 100% in patients with CRS (71% ORR). Other notable toxicities include 2 patients with grade 2 neurotoxicity that improved with therapy discontinuation. **Conclusions:** To our knowledge, this is the first report of commercial Tec in RRMM. Tec remains effective in RRMM despite prior exposure to anti-BCMA therapies, though exposure to multiple prior anti-BCMA therapies may be predictive of diminished efficacy. Clinical data on additional patients will be presented at the meeting. Ongoing translational investigations on soluble BCMA levels and patient-specific immune phenotype will also be presented at the meeting. Research Sponsor: MSKCC.

8051

Poster Session

Outcomes of patients with primary refractory multiple myeloma in the era of triplet and quadruplet induction therapy. *First Author: Charalampos Charalampous, Mayo Clinic, Rochester, MN*

Background: Patients with multiple myeloma (MM) that do not respond to initial therapy have worse outcomes compared to primary responders, and effective treatments are lacking in this population. However, the outcomes of primary refractory disease in the modern treatment era have not been studied. **Methods:** From 2007–2019, we reviewed MM patients treated with triplet/quadruplet therapy in our institution to assess the incidence of primary refractory disease and the impact of salvage therapies in this population. Primary refractory disease was defined as either progressive disease or stable disease at 4–6 cycles. The Kaplan-Meier estimates were used for survival probabilities. PFS and OS were calculated from MM diagnosis to progression, escalation/change of treatment, or death, respectively. For the primary refractory group, the second PFS and second OS were measured from the start of second-line therapy. The Cox regression model was used for multivariable analysis with the following variables (age, ISS, induction therapy, FISH, and bone marrow plasma cells at diagnosis). **Results:** We identified 1127 patients, of which 1086 were evaluated for hematologic response after 4–6 cycles. Of these, 93.3% (1013) had evidence of response, while 6.7% (73) had primary refractory disease. With a median OS of 50.7 months, patients with primary refractory disease had an increased risk for shorter survival in univariable and multivariable analysis (HR: 3.6, 95% CI = 2.61 – 4.96, HR = 3.89, 95% CI = 2.68 – 5.65, respectively). In subgroup analysis of primary refractory patients, the median second PFS and second OS from the first relapse were 11.9 months (95% CI: 8.7 – 17.3 months) and 43.4 (95% CI: 31.4– 75.9 months), respectively. Patients that received 2nd line ASCT had increased second PFS (20.9 vs. 8.1 months, respectively, p < 0.01) and second OS (74.7 vs. 31.3 months, respectively, p = 0.02) compared to patients that did not. Patients that took daratumumab as the second line did not have any significant survival differences compared to those who did not, p = NS. **Conclusions:** We conclude that early progression remains a significant factor for shorter OS in the current era, and salvage ASCT could be the most beneficial option for this population. Research Sponsor: None.

	No salvage ASCT (N = 33)	Salvage ASCT (N = 34)	Total (N = 67)	p-value
Age (years)				0.051
Median (range)	67.2 (27.1 - 85.5)	60.9 (30.8 - 71.6)	63.2 (27 - 85.5)	
ISS				0.778
1	9 (32.1%)	7 (25.9%)	16 (29.1%)	
2	8 (28.6%)	10 (37.0%)	18 (32.7%)	
3	11 (39.3%)	10 (37.0%)	21 (38.2%)	
R-ISS				0.666
1	7 (28.0%)	4 (17.4%)	11 (22.9%)	
2	12 (48.0%)	12 (52.2%)	24 (50.0%)	
3	6 (24.0%)	7 (30.4%)	13 (27.1%)	
Induction regimen				
VRd	32 (97.0%)	29 (85.3%)	61 (91.0%)	
KRd	0 (0.0%)	4 (11.8%)	4 (6.0%)	
Quadruplets	1 (3.0%)	1 (2.9%)	2 (3.0%)	
FISH (mSMART)				0.688
Standard-Risk	12 (42.9%)	14 (42.4%)	26 (42.6%)	
High-Risk	13 (46.4%)	13 (39.4%)	26 (42.6%)	
Double-Hit	3 (10.7%)	6 (18.2%)	9 (14.8%)	

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Poster Session

Determinants of overall survival of young adults with multiple myeloma: A National Cancer Database (NCDB) analysis of years 2004-2017. *First Author: Chakra Pani Chaulagain, Cleveland Clinic Florida, Weston, FL*

Background: There is paucity of real-world data on the outcomes of younger patients with multiple myeloma (MM). In this IRB approved retrospective analysis, the NCDB was used to evaluate the determinants of overall survival (OS) of young adults ≤ 50 years with MM who were treated at commission on cancer (CoC) accredited facilities across the USA. **Methods:** Using the NCDB, we identified $N = 16,792$ patients ≤ 50 years old diagnosed and treated for MM from 2004 to 2017. Multivariable cox regression analysis with backward elimination was utilized to identify the independent survival factors, using significance level of $p < 0.05$. Kaplan-Meier survival curves were generated and SAS version 9.4 was used to analyze the data. **Results:** Overall median survival time was 119 months; while survival rates of 1, 3, and 5-year were 90.6%, 78.0%, and 67.8%, respectively. Multivariable cox regression analysis with backward elimination method revealed that there were 13 significant independent survival factors: age, sex, race, ethnicity, Charlson-Deyo score, insurance status, facility type, median income, education level, distance to facility, year of diagnosis, hematopoietic stem-cell transplantation (HSCT), and treatment-regimen. Male patients were more likely to die compared to female patients (HR = 1.22, $p < 0.0001$). Black patients were predicted to have less death events compared to White patients (HR = 0.91, $p = 0.004$). In addition to that, Hispanic patients were more likely to die compared to non-Hispanics (HR = 1.2, $p = 0.0006$). Subjects who were treated in non-academic facilities were more likely to die compared to the ones who received care in academic centers (HR = 1.2, $p < 0.0001$). Moreover, patients with Medicare (HR = 1.65, $p < 0.0001$), Medicaid (HR = 1.49, $p < 0.0001$), and no insurance (HR = 1.63, $p < 0.0001$) had higher chance of death compared to those with private insurance. Patients with lower income $< \$38,000$ were more likely to die compared to income $\geq \$63,000$ (HR = 1.19, $p = 0.0007$). Only 6.8% of patients underwent HSCT and 93.2% did not. Patients undergoing HSCT had worse OS compared to those treated without HSCT (HR = 0.36, $p < 0.0001$). Detailed analysis will be presented. **Conclusions:** In this large cohort of real-world data analysis of very young MM patients, we found that White and Hispanic patients age ≤ 50 years had significantly inferior survival compared to Black and non-Hispanic patients. Patients with lower income, lower education level, non-private insurance, and those without access to academic centers for MM care had worse survival outcomes. The findings can be useful for designing prospective studies addressing disparity and equitable access to MM care. Despite being a pivotal part of MM therapy, HSCT utilization in the real-world setting is minimal. The barriers to HSCT utilization and the reason why it is inferior to no-HSCT in real-world setting need to be identified and addressed. Research Sponsor: Maroon Cancer Center, Cleveland Clinic Florida.

8055

Poster Session

Lenalidomide-based monotherapy versus augmented therapy for maintenance in standard risk multiple myeloma patients with no complete response post autologous hematopoietic cell transplantation. *First Author: Hussein Awada, Department of Translational Hematology and Oncology Research, Lerner Research Institute, Cleveland Clinic, Cleveland, OH*

Background: Standard risk (SR) multiple myeloma (MM) is typically characterized by the absence of poor prognostic cytogenetic aberrations, and better outcomes. However, outcomes in SR MM remain far from homogeneous, especially in patients undergoing autologous hematopoietic cell transplant (AHCT). While many patients do well initially, relapse is inevitable. Here, we studied the role of lenalidomide (R) maintenance therapy in determining outcomes in SR MM with no complete response (non-CR) post-AHCT. **Methods:** We retrospectively reviewed all MM patients who underwent AHCT at the Cleveland Clinic between January 1, 2011 and January 15, 2021. Electronic medical charts were accessed to retrieve data on demographic characteristics, comorbidities, International Scoring System (ISS) staging, cytogenetic risk categorization, serum and bone marrow studies, as well as maintenance therapy. SR MM was considered in patients who did not have t(4;14), t(14;16), t(14;20), del(17p), or gain(1q). Remission status was determined by serum studies at 3 months post-AHCT. The primary endpoint was median time to either progression or death, reported as time to event (TTE) determined by Kaplan Meier analysis. **Results:** A total of 517 patients were reviewed, of whom 279 were determined as SR MM. Further stratification yielded 100 non-CR SR patients on lenalidomide-based maintenance, of whom 87 were on R monotherapy and 13 on R combination. Comparison between the R-monotherapy and combination groups showed similar age at AHCT (60.5 vs 56 years, $P=0.07$), time to transplant (23.5 vs 30.8, $P=0.7$), albumin levels (<3.5 g/dL 25 vs 25%, $P=1$), Hematopoietic Cell Transplantation-specific Comorbidity Index (HCT-CI) score (≥ 3 43.5 vs 30.8%, $P=0.5$), Male preponderance (58.8 vs 69.2%, $P=0.6$), ethnicity (White 82.4 vs 76.9%, $P=0.7$), ISS stages (I 41 vs 45.5%, II 41 vs 36.4%, III 17.9 vs 18.2%, $P=0.9$), pre-AHCT lines of therapy (≥ 2 31.8 vs 38.5%, $P=0.8$), and pre-AHCT bone marrow plasma cells ($\geq 10\%$: 9.5 vs 7.7%, $P=1$), respectively. The only significant difference between the two groups was in the MM immunoglobulin subtype (IgG 80 vs 50%, $P=0.02$). Kaplan-Meier analysis for median TTE revealed that the R monotherapy group had a significantly shorter median TTE at 38.1 months versus 68.6 months ($P=0.03$) for the R combination group. **Conclusions:** SR MM patients who do not achieve a CR post-AHCT have better outcomes with R-combination rather than monotherapy. Research Sponsor: None.

8054

Poster Session

Ixazomib and daratumumab without dexamethasone (I-Dara) in elderly frail patients with RRMM: Results of the multicenter phase 2 study (IFM 2018-02) of the Intergrroupe Francophone du Myélome (IFM). *First Author: Cyrille Touzeau, University Hospital of Nantes, France, Nantes, France*

Background: Frailty is associated with inferior outcome in older myeloma patients, especially in the relapse setting.^{1,2} This adverse prognosis is mainly related to a high discontinuation rate for treatment (Tx) related adverse events (AE). Dexamethasone is responsible of a high rate of infections and metabolic AE. We present here the updated results from the phase 2 study I-Dara evaluating efficacy and tolerability of Ixazomib-Daratumumab without Dexamethasone in elderly frail patients with relapsed myeloma (RRMM) (NCT03757221). **Methods:** Ixazomib-naïve RRMM patients received oral Ixazomib (4 mg: days 1, 8, 15), IV Daratumumab (16 mg/kg; days 1, 8, 15, 22, cycles 1-2; days 1, 15, cycles 3-6; days 1, cycles 7+) and IV Methylprednisolone before Daratumumab (100 mg at day 1, 8, cycle 1 and then 60 mg). They were enrolled after 1 or 2 prior therapy if their frailty score was ≥ 2 by IMWG score. The primary endpoint was $\geq$ very good partial response rate (VGPR) at one year. Secondary endpoints included ORR, PFS, OS & toxicity according to NCI-CTCAE version 5. **Results:** Sixty-three patients were screened and 55 enrolled between 03/2018 and 09/2021. Patient were at first ($n = 36$) or second relapse ($n = 19$). Thirty-five patients (64%) were previously exposed to bortezomib, 37 (67%) were previously exposed to lenalidomide (Len) and 23 (42%) were refractory to Len. Median age was 82 (72-93). All patients had a frailty score ≥ 2 and 13 (24%) had a 3 or 4 frailty score. In 41 patients ISS at diagnosis was stage I ($n = 11$), II ($n = 18$) or III ($n = 12$). Seventeen (36%) patients harbored high-risk (HR) cytogenetic, including t(4;14) ($n = 8$) or del17p ($n = 10$). The median duration of Tx (DOT) in 14 pts with ongoing Tx was 22 mos [min-max: 16-40] at data cutoff (January, 19). The median DOT in 41 pts who stopped Tx was 10 mos [min-max: 0-31]; 28 had progressive disease (PD). Fourteen patients died during the study: Daratumumab-related bronchospasm (D1C1); Ixazomib-related overdose (C2), sepsis ($n = 3$), pneumonia ($n = 2$), PD ($n = 7$). Regarding toxicity, 31 pts had $\geq$ grade 3 AE (55%). The most common grade 3-4 AE were thrombocytopenia ($n = 10$), other cytopenias ($n = 5$), anemia ($n = 3$), infection ($n = 6$), gastrointestinal disorders ($n = 5$) and hypertension ($n = 3$). The $\geq$ VGPR rate is 32% @ 1 year (34% overall) with an ORR of 70% @ 1 year (74% overall). In Len refractory patients the $\geq$ VGPR rate is 40% @ 1 y and the ORR 70%, in HR patients the $\geq$ VGPR rate is 60% and ORR 80%. With a median follow-up of 23.0 mos median PFS is 18.5 mos and median OS NR (75% OS estimated at 27.9 mos). **Conclusions:** In this elderly frail population Ixazomib-Dara is a feasible combination with favorable efficacy profile even in Len refractory and HR cytogenetic patients. Early toxicity remains a concern in this population even though more manageable with Dara SC. Late benefit is consistent with one third of patients still on treatment. Clinical trial information: NCT03757221. Research Sponsor: Takeda and Janssen.

8056

Poster Session

Three-dimensional telomere profiling to predict risk of progression in smoldering multiple myeloma. *First Author: Shaji Kumar, Division of Hematology, Mayo Clinic, Rochester, MN*

Background: Multiple myeloma (MM) is preceded by monoclonal gammopathy of undetermined significance (MGUS). A transitional stage of smoldering multiple myeloma (SMM) can be identified between MGUS and MM. While MGUS carries a steady risk of progression of 1% per year, SMM is more heterogeneous with nearly 40% of patients progressing in the first 5 years, 15% in the next 5 years, reaching the same low risk as MGUS after 10 years. SMM with its high risk of progression in the initial years after diagnosis presents a viable opportunity for early intervention. For implementing early intervention, the ability to identify SMM patients at the highest risk of progression is critical. This has led to the development of several risk stratification systems. Using these systems high risk SMM patients studied in phase 3 trials demonstrated delayed progression to MM and improved overall survival with early initiation of therapy. However, these approaches showed limited specificity exposing patients at lower risk of progression to therapy. To date, identifying high risk SMM patients and confirming disease stability in low risk SMM patients remain an important clinical need. Genomic instability has been shown to be a sensitive indicator of disease progression in cancer. Telomere dysfunction is an early event in genomic instability. The 3-dimensional spatial profiling of telomeres using TeloView technology allows for quantification of telomere dysfunction, and was shown to be instrumental in risk stratification of cancer patients generally, but particularly in selected hematological malignancies. Importantly, in a previous SMM proof-of-concept study telomeric parameters measured by TeloView technology was found to be significantly different between SMM patients who progressed to active MM within 2 years and those who remained stable for over 5 years. **Methods:** We analyzed a total of 162 SMM patients using TeloView technology. 88 patients were employed as training dataset in Receiver Operating Curve (ROC) modeling to develop a scoring model that stratifies individual SMM patients based on risk of progression to full stage MM. An additional cohort of 74 SMM patients was used for blind validation of the developed scoring model. **Results:** We report area-under-the-curve (AUC) in the ROC analysis of 0.8 (accuracy 80%) achieved by the scoring model developed using the training dataset. Furthermore, the independent blind validation achieved positive predictive value of 83% and negative predictive value of 71%, with sensitivity and specificity of 80% and 76% respectively. **Conclusions:** The result of this study supports presenting TeloView as an accurate prognostic biomarker which appears able to stratify SMM patients into their respective risk groups with high sensitivity and specificity. This will potentially allow for evidence-based treatment decisions for high risk SMM patients and confident monitoring of stable patients. Research Sponsor: Telo Genomics Corp.

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Poster Session

A phase 2 evaluation of daratumumab-based induction therapy in patients with multiple myeloma with severe renal insufficiency. *First Author: R. Donald Harvey, Emory University School of Medicine and Winship Cancer Institute, Atlanta, GA*

Background: Myeloma patients (pts) with renal insufficiency (RI) have inferior disease outcomes; up to 50% present with acute kidney injury (AKI). AKI results from light chain-induced cast nephropathy; physicochemical properties (self-association, aggregate formation) may determine severity. Daratumumab has extensive data in myeloma, reduces circulating light chains, preserves renal function in AL amyloidosis, and has non-renal clearance. We hypothesized early therapy with daratumumab and VRD normalize myeloma-induced AKI in a population rarely included in trials. **Methods:** We used a Simon's two-stage design in newly diagnosed pts with severe AKI (CrCl <30 mL/min) of 4 x 21-D cycles of daratumumab 16mg/kg IV QW x 3 (C1-3, C4D1 only), bortezomib 1.3 mg/m² SQ D1, 4, 8, and 11, and dexamethasone 40mg (reduced to 20mg at C2 for ≥75 yrs.) D1-4 (C1 only, D1 only C2-4), 8, and 15, with add-on lenalidomide at C2 (25mg if CrCl ≥30 mL/min). Standard antitumor, antiemetic, premedications were used. Eligibility criteria were broad (CrCl <30 mL/min, PS 0-2, ANC>1000/mm³, Hgb>7 g/dL, plt>75,000/mm³) with liberal dose reductions for generalizability. Primary objective: determine proportion with renal recovery (CrCl ≥50 mL/min) after 2 cycles; secondary objectives: best response (IMWG), renal function at end of treatment, dose density/tolerability, adverse events (AE), renal function change by estimates [Cockcroft-Gault (C-G), MDRD, 24-hour urine, CKD-EPI], and daratumumab PK. If ≥7 responses seen in the first 11 pts, 14 more would be accrued. These data are the planned analysis of the initial cohort. **Results:** Thirteen pts enrolled: 8 male, 7 white/6 black, median age 69 yr (46-82), 11 treated/evaluable for the primary endpoint. Median baseline CrCl 13.8 mL/min (4.9-20.2), median serum creatinine (SCr) 4.92 mg/dL (3.53-9.93). One withdrew consent, 1 was inevaluable (rapid disease progression and death). Seven achieved CrCl of ≥50 mL/min (median C3D1 CrCl 61 mL/min, 22-151) after 2 cycles, all had SCr improvement at C3D1. Lenalidomide dose was 25 mg on C2D1 in 9/11 pts. Median (range) dose density (delivered/planned): daratumumab 100% (40-100), bortezomib 100% (25-100), dexamethasone 80% (67-100), lenalidomide 100% (0-100). The overall response rate was 100%, ≥VGPR rate 82%. Best responses were CR (3), VGPR (6), PR (2). Treatment-emergent grade ≥3 hematologic AEs: anemia (90.9%), lymphopenia (81.8%), thrombocytopenia (36.4%), neutropenia (9.1%). **Conclusions:** Early, aggressive therapy with a daratumumab-based induction regimen in myeloma pts with severe AKI improves renal function, with the majority achieving CrCl ≥50 mL/min after 2 cycles; all responded. AEs seen were consistent with prior experience with the 4-drug regimen. Per protocol, 14 additional patients will be accrued in the second stage. Clinical trial information: NCT04352205. Research Sponsor: Janssen.

8059

Poster Session

Curability of multiple myeloma (MM) based on relative survival rate (RSR) in patients (pts) treated on earlier total therapy (TT) protocols. *First Author: Samer Al Hadidi, University of Arkansas for Medical Sciences, Little Rock, AR*

Background: Long term overall survival (OS) follow-up data in pts with MM treated on clinical trials is limited. TT approach uses all MM-active drugs upfront to target drug-resistant subclones during initial treatment to prevent later relapse. We report the longest follow up of MM trials (TT1 (NCT00580372), TT2 (NCT00083551), TT3a (NCT00081939) and TT3b (NCT00572169)) reported to date with RSRs to assess for curability. **Methods:** Pts treated on TT1, TT2, TT3a and TT3b were followed at the University of Arkansas for Medical Sciences after completion of therapy including multi-agent chemotherapy, high dose melphalan followed by tandem autologous stem cell transplantation (ASCT) and fixed duration maintenance therapy with introduction of thalidomide (thal) (TT2+thal vs TT2-thal), bortezomib (TT3a) and lenalidomide (TT3b). Expected survival rate was defined as probability of a population surviving from yr to yr. RSR was defined as ratio between observed survival of trials to expected survival in population adjusting for age and sex based on enrollment year. Data cut-off was October 10, 2022. **Results:** 1379 pts were enrolled (TT1:231, TT2:668, TT3a:303, TT3b:177) with median follow up duration of 16.6 years (yrs) (TT1:25 yrs, TT2:18.4 yrs, TT3a:16.2 yrs, TT3b:14.2 yrs). 10-yr PFS increased from 8.8% (TT1) to 15.5% (TT2-thal) to 25.1% (TT2+thal) to 32.9% (TT3a) to 42.4% (TT3b). Median OS improved over time (TT1:5.8 yrs, TT2:10.4 yrs, TT3a:11.9 yrs, TT3b:10.1 yrs). 15-yr OS improved from 24.2% in TT1, 33% in TT2, 40% in TT3a and 37% in TT3b. 20-yr OS is 24.4% for pts treated on TT2 protocol. Outcomes were better for standard risk disease defined by low-risk gene expression profiling (GEP) with 20-yr OS of 30% in TT2 and 15-yr OS of 45% in TT3a. RSRs approach 1 at 10-15 yrs for TT1, but this occurs earlier, at 5-10 yrs, for TT2+Thal, TT3a and TT3b [Table]. No difference in RSR between TT3a and TT3b was noted. Relative excess risk (RER) showed an estimated 23%, 44% and 54% lower excess mortality when comparing TT2 (+ thal), TT2 (-thal) and TT3a with TT1, respectively. **Conclusions:** In the longest follow up duration of any MM clinical trial, a subset of MM pts are cured as evidenced by RSRs approaching 1. Approximately one third of pts treated on TT2 protocol and one-half pts treated on TT3a are alive at 20 year and 15 yrs from initial diagnosis, respectively. Incorporation of immunomodulatory drugs and proteasome inhibitors along with tandem ASCT resulted in cumulative improvement of OS as evidenced by lower RER of mortality. Clinical trial information: NCT00580372, NCT00083551, NCT00081939, NCT00572169. Research Sponsor: None.

RSRs.					
No. of yrs from diagnosis	TT1	TT2+thal	TT2-thal	TT3a	TT3b
1	0.9214	0.9355	0.9347	0.9415	0.8965
5	0.9181	0.9602	0.9176	0.9751	0.9903
10	0.937	0.9507	0.9435	0.9582	0.9627
11	0.9316	0.9573	0.9205	0.9796	0.926
12	0.9252	0.9729	0.9744	0.9245	0.9478
13	0.9649	0.9605	0.9006	0.8959	0.9816
14	0.9637	0.9406	0.9266	0.9896	
15	0.9623	0.85	0.881	0.9744	
17	0.954	0.9371	0.9256		

8058

Poster Session

Genomic landscape of multiple myeloma with extramedullary disease: Results from a large patient database. *First Author: Mateo Mejia Saldarriaga, Weill Cornell Medicine, New York, NY*

Background: Extramedullary disease (EMD) is associated with poor outcomes and the biological mechanisms driving this phenotype are poorly understood. We used the CoMMpass registry data to explore the genomic characteristics of EMD. **Methods:** The CoMMpass study is a prospective, international registry of newly diagnosed MM. 1143 patients had clinical data. Patients were classified as EMD if they had EMD at any point. Genomic data from bone marrow (BM) samples at diagnosis (whole genome sequencing, whole exome sequencing (WES), and RNA sequencing (RNAseq)) were compared between EMD and non-EMD. A multivariable model was constructed based on univariable results. Differential expression (DEA) and gene set enrichment analysis (GSEA) were performed after normalization using Hallmark and MM transcriptomic subgroups. The top 24 most mutated genes in MM were selected. **Results:** The median overall survival (mOS) and progression free survival (PFS) was shorter for EMD. The presence of EMD, anemia at diagnosis, age >65 years at diagnosis, ISS stage, and use of ASCT at the first line were independently associated with worse mOS and PFS. EMD was associated with worse mOS (HR 1.7, 95% CI 1.3 - 2.2 p <0.01) and PFS (HR 1.5, 95% CI 1.23 - 1.8, p <0.01) in multivariable analysis and was not abrogated by ASCT, triplet induction or maintenance. Results did not vary when landmark analysis was used. *MYC* amplification, deletion 18q and 1q amplification were enriched in EMD cases. *TP53* mutations and *TP53* bi-allelic inactivation (mutation and deletion) were enriched in EMD (Table). DEA identified 1552 genes with increased and 3344 with decreased expression (2.7%, 5.4% of total genes respectively) in EMD when compared to non-EMD. On GSEA, EMD cases were enriched for the CD-1, PR, and CTA myeloma gene expression signatures, in addition to the Hallmark pathways MYC target, E2F targets, G2M checkpoint and unfolded protein response, while the adhesion molecules pathway and MM gene signatures LB, MS, and MF were down-regulated in EMD. **Conclusions:** EMD cases were enriched for *TP53* mutations and bi-allelic *TP53* inactivation, both of which are prognostic. In addition, *MYC* amplification, 18q deletion and 1q gain were enriched in EMD which are novel CNA associated with EMD. EMD is also enriched for distinct molecular subgroup, including enrichment for CD-1, PR, and CTA signatures, the latter two are associated with poor outcomes, and the Hallmark pathways MYC, E2F and G2M checkpoints consistent with *MYC* amplification and PR molecular subgroup. WES and RNAseq of matching BM and EMD tissue samples from our institution is currently being performed. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology.

	Status	EMD n=130	No EMD n=778	P value
Del 17p	Present	15 (11.9)	75 (10.0)	0.62
Gain 1q	Present	55 (43.7)	277 (36.9)	0.16
Amp 8q24 (MYC)	Present	35 (27.8)	116 (15.5)	0.001
Del 18q	Present	29 (23.0)	106 (14.1)	0.015
TP53 status and Deletion (%)	Mutated	13 (9.6)	35 (4.4)	0.020
	CNA + Mutation	9 (7.3%)	21 (2.9%)	0.016

8060

Poster Session

T cell exhaustion markers in multiple myeloma patients before and after physical activity intervention. *First Author: Janine Joseph, Department of Cancer Prevention and Control, Roswell Park Comprehensive Cancer Center, Buffalo, NY*

Background: There is substantial evidence that the immune system is dysfunctional in multiple myeloma (MM). Adaptive immune cells, such as CD4⁺ and CD8⁺ T cells, are ineffective at controlling MM progression, suggesting immunosuppression. Therefore, efforts to overcome immunosuppression are likely key to more effective tumor control. Recent evidence from pre-clinical models suggests that exercise represents a non-pharmaceutical means to reduce immune exhaustion, but few studies have examined the relationship between an exercise intervention and biomarkers of immune exhaustion in cancer patients, especially in MM – the objective of this study. **Methods:** In this feasibility trial, 24 MM patients participated in a six-month physical activity intervention. The strength training arm (n=12) performed twice weekly supervised resistance trainings. The walking arm (n=12) engaged in an unsupervised, home-based wearable activity tracker intervention. Subjects provided peripheral blood samples before the start and at the conclusion of the intervention. Comprehensive flow cytometry was utilized to assess the frequency of mononuclear cells of interest, including CD4⁺ and CD8⁺ T cells and subpopulations expressing the markers of exhaustion PD-1 and/or TIGIT, which are the two exhaustion markers with the highest expression in this study sample. Ratios of exhausted cells (expressing any, one, or both of those markers) to non-exhausted cells (expressing no exhaustion markers) were calculated. Changes in the median values of these ratios were compared using Wilcoxon signed-rank tests. **Results:** Results from the immune panels are shown for the combined sample (n=24). All ratios of exhausted to non-exhausted cells were lower at the end of the six-month intervention, compared to baseline. The ratio of CD4⁺ TIGIT⁺ to non-exhausted CD4⁺ cells was significantly reduced, from 0.71 to 0.57 (p=0.04). The ratio of CD8⁺ PD-1⁺ to non-exhausted CD8⁺ cells was borderline significantly reduced, from 1.81 to 1.48 (p=0.06). **Conclusions:** This pilot study suggests that physical activity induces changes in MM patients' immune systems, potentially rendering a less exhausted T cell state. Larger studies are warranted to examine how exercise alters activation vs exhaustion phenotypes within specific T cell subsets (naïve, central memory, effector memory, regulatory) and to elucidate the effects of strength-based vs aerobic exercise on T cell function. Research Sponsor: Roswell Park Comprehensive Cancer Center.

Ratio ^a	Baseline	Final	p-value
CD4 ⁺ PD-1 ⁺ or TIGIT ⁺	1.33 (1.18)	1.15 (1.04)	0.14
CD4 ⁺ PD-1 ⁺	1.18 (1.02)	0.92 (0.91)	0.17
CD4 ⁺ TIGIT ⁺	0.71 (0.58)	0.57 (0.39)	0.04
CD4 ⁺ TIGIT ⁺ and PD-1 ⁺	0.48 (0.47)	0.41 (0.31)	0.10
CD8 ⁺ PD-1 ⁺ or TIGIT ⁺	2.36 (3.82)	2.13 (2.71)	0.09
CD8 ⁺ PD-1 ⁺	1.81 (2.56)	1.48 (2.00)	0.06
CD8 ⁺ TIGIT ⁺	1.91 (3.36)	1.67 (2.67)	0.18
CD8 ⁺ TIGIT ⁺ and PD-1 ⁺	1.25 (2.16)	1.01 (1.38)	0.17

^aMedians, interquartile ranges of ratios of exhausted CD4+ or CD8+ non-exhausted populations.

8061

Poster Session

Utilizing a two-step frailty assessment strategy in older adults with multiple myeloma (MM): A decision curve analysis. *First Author: Andrew Gahagan, Department of Hematology and Oncology, University of Alabama at Birmingham, Birmingham, AL*

Background: The International Myeloma Working Group Frailty Index (IMWG-FI) has been shown to predict risk of toxicity and mortality in older adults with MM (Palumbo et al., *Blood* 2015). However, IMWG-FI requires a geriatric assessment (GA) that is not routinely done in clinical practice due to time constraints. A simplified frailty index (SFI; Facon et al., *Leukemia* 2020) has been proposed as an alternative using ECOG PS as a proxy to functional status. We previously reported a moderate concordance between these two frailty indices (Kappa statistic 0.50; Gahagan et al., *ASH* 2022). Here, we examined if SFI can be utilized as a screening tool to identify patients who would benefit from a formal GA and frailty assessment. We hypothesized that a two-step approach would minimize the need for unnecessary GAs, while saving time in clinical practice. **Methods:** For this analysis, we included patients ≥ 50 yo with newly diagnosed (ND) or Relapsed/Refractory (RR)-MM at a single institution initiating a new treatment regimen (1st to 6th line) who are enrolled in a prospective registry (NCT05556928). All patients underwent a GA prior to a new line of therapy. ECOG PS and comorbidities were abstracted from medical records. We calculated IMWG-FI and SFI using published methods. Sensitivity, specificity along with their 95% CI were calculated for both SFI and IMWG-FI, using published SFI cutpoints. Lastly, we used decision curve analysis (DCA) as described by Vickers et al. to calculate the benefit of frailty screening using SFI for detection of non-frail patients and avoiding unnecessary GAs. We assumed that reasonable threshold probabilities were 0.25 and 0.33 respectively indicating that missing an unfit patient was 3 and 2 times worse than exposing a fit patient to an unnecessary GA (odds of 1:3 and 1:2 respectively). We quantified the net benefit (NB) of this two-step frailty assessment versus GA-for-all in terms of net reduction in unnecessary GAs. **Results:** A total of 146 adults with MM (49 ND-MM, 51 pre-transplant, and 46 RR-MM) starting a new line of therapy between 8/2020-1/2022 were included in this study. The median age was 62 (IQR 57-70) with 53% males and 36% blacks. The distribution by IMWG-FI was 43% fit, 32% intermediate-fit, and 25% frail. Using SFI, 32% of patients were frail. Using a cutpoint of ≥ 2 , SFI as a screening tool had a sensitivity of 89.2% (95% CI 75-96%) and a specificity of 65% (95% CI 56% to 73%). DCA showed that selecting candidates for GA based on a two-step strategy (SFI followed by IMWG-FI) led to an absolute 40-45% reduction in the number of unnecessary GAs without missing any frail patients. **Conclusions:** Our results suggest that using a two-step frailty assessment strategy of SFI as a screening tool followed by confirmation with IMWG-FI reduces the need for unnecessary GAs by 40-45% and may be more suitable for integration in busy oncology practice. Research Sponsor: None.

TPS8063

Poster Session

A first-in-human phase 1, multicenter, open-label study of CB-011, a next-generation CRISPR-genome edited allogeneic anti-BCMA immune-cloaked CAR-T cell therapy, in patients with relapsed/refractory multiple myeloma (CAMMOUFLAGE trial). *First Author: Jesus G. Berdeja, Sarah Cannon Research Institute, Nashville, TN*

Background: Autologous CAR-T cell therapies have shown significant benefit in the treatment of adults with relapsed/refractory multiple myeloma (r/r MM). However, these CAR-T cell therapies may have inherent challenges, including functional deficiencies in the patient's T cells, that could yield an inconsistent or impaired product, as well as require extended time and complexity in manufacturing, thereby limiting patient access and potentially requiring bridging therapy. CB-011 is an allogeneic, off-the-shelf anti-BCMA CAR-T cell therapy derived from healthy donor T cells. A next-generation CRISPR-Cas12a genome-editing technology using CRISPR hybrid RNA-DNA (chrDNA) guides, developed at Caribou to significantly reduce off-target editing, was implemented to generate 4 genome edits in the manufacture of CB-011: (i) the *TRAC* gene was knocked out to eliminate T cell receptor (TCR) expression and prevent graft versus host disease (GvHD), (ii) the BCMA-specific CAR was site-specifically inserted into the genome at the *TRAC* locus to eliminate random integration and serves to target the tumor antigen, (iii) the *B2M* gene was knocked out to eliminate expression of HLA class I molecules to mitigate host T cell cytotoxicity, and (iv) a B2M-HLA-E fusion transgene was site-specifically inserted into the genome at the *B2M* locus to overcome host NK cell-mediated killing following recognition of "missing self." This immune cloaking strategy has the potential to allow persistent antitumor activity of the CAR-T cells in the context of antigen engagement. Significant preclinical efficacy in vitro and in vivo supports the clinical evaluation of CB-011. **Methods:** CB-011 is being evaluated in a multicenter, Phase 1 clinical trial in patients with r/r MM. A 3+3 dose escalation design followed by expansion at the maximum tolerated dose (MTD) and/or the recommended Phase 2 dose (RP2D) is being utilized. Primary objectives are to determine the safety and tolerability of CB-011, and the recommended Phase 2 dose (RP2D). Additional key objectives include preliminary antitumor activity and pharmacokinetics (PK). After concurrently receiving lymphodepletion therapy with cyclophosphamide (300 mg/m²/d) and fludarabine (30 mg/m²/d) for 3 days, patients receive a single dose infusion of CB-011 and are followed for safety and efficacy. Antitumor activity and disease response are measured by International Myeloma Working Group criteria. The CAMMOUFLAGE Phase 1 trial is actively enrolling patients and additional information is available on clinicaltrials.gov (NCT05722418). Clinical trial information: NCT05722418. Research Sponsor: Caribou Biosciences.

8062

Poster Session

Presence of hyperdiploidy and history of tobacco use in African American patients with SMM. *First Author: Rujul H Parikh, Emory University, Winship Cancer Institute, Atlanta, GA*

Background: Smoldering multiple myeloma (SMM) has a clinically variable course in progression to active myeloma (MM). Accurate risk stratification is essential in identifying which patients may benefit from early therapeutic intervention. Current models do not account for the potential impact of race on risk of progression to SMM. Here, we seek to identify independent risk factors for progression in African American (AA) versus white patients in a real-world single institutional database of SMM patients. **Methods:** We retrospectively identified 224 patients (pts) with untreated SMM from 2007 to 2021 treated at our institution. Patient demographics and disease characteristics were obtained from our IRB-approved myeloma database. TTP was defined as the time from diagnosis of SMM to diagnosis of active MM, estimated by Kaplan-Meier and compared by log-rank test. Univariate analyses were performed using Cox proportional hazard models for TTP. **Results:** A total of 224 pts (AA 35%, white 47%, other/unknown 17%) were identified with median age 62y (range 32-82). Median follow-up was 4.3y in Whites and 5y in AA pts. Notable characteristics include M/F 45%/54%, IgG/IgA/FLC 76%/17%/6%, 30% current/past smoker (median 15 pack-years), 12% alcohol use (≥ 10 drinks/wk), 45% with BMI > 30 . Multiple cytogenetic abnormalities were defined as presence of ≥ 2 of the following: t(4;14), t(14;16), gain(1q21), del(1p), del(13), or del(17p). The median TTP (mTTP) was 6.8 [95% CI (3.7, 8.2)] years in whites and 5.6 [95% CI (4.6, 11.8)] years in AA. On univariate analysis, M-spike > 1.5 , involved K/L ratio > 12 , and bone marrow PC $> 20\%$ were associated with increased risk of progression for both AA and whites (all $p < 0.05$). As expected, gain of 1q21 was associated with increased risk of progression for both groups, though more pronounced in AA (HR 2.94, $p = 0.025$) versus whites (HR 2.33, $p = 0.013$). Hyperdiploidy was associated with shorter mTTP in AA (HR 3.03, $p = 0.004$) compared to whites (HR 1.39, $p = 0.3$). Multiple cytogenetic abnormalities was associated with shorter mTTP in whites (HR 2.63, $p = 0.004$) but was not statistically significant in AA (HR 2.63, $p = 0.104$). Interestingly, tobacco use was associated with shorter mTTP in Blacks (HR 2.94, $p = 0.005$) but not in whites (HR 0.96, $p = 0.85$). **Conclusions:** Understanding the potential impact of racial background on progression from SMM to MM is critical in the appropriate management of all patients with SMM. In this database, with a large proportion of AA patients, hyperdiploidy and +1q portend high risk of progression in AA patients. Further study is needed to better classify these potential differences to ensure risk stratification models are applicable to all patients. Research Sponsor: None.

TPS8064

Poster Session

CAMMA 2: A phase I/II trial evaluating the efficacy and safety of cevostamab in patients with relapsed/refractory multiple myeloma (RRMM) who have triple-class refractory disease and have received a prior anti-B-cell maturation antigen (BCMA) agent. *First Author: Shaji Kumar, Mayo Clinic, Rochester, MN*

Background: Multiple myeloma (MM) remains an incurable disease. Combinations of established agents, including proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs), and anti-CD38 antibodies, are used in all lines of therapy, but re-exposure to previously received classes of therapy is associated with decreasing response rates and duration of response (Moreau et al. 2021). BCMA-targeted agents have recently been approved for the treatment of patients with RRMM whose disease has been exposed or become refractory to PIs, IMiDs and anti-CD38 antibodies (triple-class exposed or refractory MM). Although effective, the majority of patients who respond to anti-BCMA agents eventually relapse. Proven salvage therapies for these patients are currently lacking and represent a new unmet medical need. Cevostamab is an immunoglobulin G1-based T-cell-engaging bispecific antibody that targets Fc receptor-homolog 5 (FcRH5) on myeloma cells and CD3 on T cells. Dual binding results in T-cell activation and potent killing of MM cells. In an ongoing Phase I study (G039775; NCT03275103), cevostamab monotherapy showed promising activity in heavily pre-treated patients with RRMM, including those with prior exposure to anti-BCMA agents (Trudel et al. 2021). **Methods:** CAMMA 2 (CO43476; NCT05535244) is an open-label, multicenter Phase I/II trial evaluating cevostamab monotherapy in patients with RRMM who are triple-class refractory and have previously received an anti-BCMA agent. Prior anti-BCMA antibody-drug conjugates or chimeric antigen receptor (CAR) T cells are permitted in Cohorts A1 and B1, while prior anti-BCMA bispecific antibodies are allowed in Cohorts A2 and B2. In A1 and A2, cevostamab is administered by intravenous infusion and is initiated with step dosing (0.3mg on Cycle [C] 1 Day [D] 1 and 3.3mg on C1D2, D3, or D4 depending on the emergence and resolution of cytokine release syndrome [CRS] after the initial administration), with the target dose of 160mg given on C1D8 and on D1 of each subsequent 21-day cycle. Patients are hospitalized for the C1 administrations only and treatment is continued until disease progression or unacceptable toxicity occurs. CRS is managed per protocol based on the clinical presentation and may involve corticosteroid and tocilizumab treatment. Primary objectives are evaluation of efficacy (primary endpoint: objective response rate by investigator assessment using IMWG criteria) and safety. Secondary objectives include assessment of quality of life, pharmacokinetics, pharmacodynamics, and immunogenicity. Cohorts B1 and B2 will evaluate the efficacy and safety of cevostamab at the recommended Phase II dose in this setting. As of February 2023, enrollment into Cohorts A1 and A2 is ongoing. Clinical trial information: NCT05535244. Research Sponsor: CAMMA 2 is sponsored by F. Hoffmann-La Roche Ltd. Third-party medical writing assistance, under the direction of all authors, was provided by Helen Cathro, PhD, of Ashfield MedComms, an Inizio company, and was funded by F. Hoffmann-La Roche Ltd.

TPS8065

Poster Session

MagnetisMM-6: An open-label, multicenter, randomized phase 3 study of elranatamab + daratumumab + lenalidomide (EDR) versus daratumumab + lenalidomide + dexamethasone (DRd) in transplant ineligible (TI) patients with newly diagnosed multiple myeloma (NDMM). *First Author: Sebastian Grosicki, Department of Hematology and Cancer Prevention, Medical University of Silesia, Katowice, Poland*

Background: Elranatamab, a humanized bispecific antibody targeting B cell maturation antigen (BCMA) on myeloma cells and CD3 on T cells, has shown promising efficacy and acceptable safety in clinical studies, as monotherapy (MagnetisMM-3, NCT04649359) and in combination with daratumumab (MagnetisMM-5, NCT05020236), in the treatment of patients with relapsed/refractory multiple myeloma (RRMM). Despite recent advances in the treatment of NDMM, MM remains incurable and more effective treatment options are needed. The aim of the MagnetisMM-6 study (NCT05623020) is to evaluate EDR versus DRd for TI patients with NDMM. **Methods:** MagnetisMM-6 is an ongoing, open-label, 2-arm, multicenter, randomized phase 3 study estimated to enroll ~646 patients. There are 2 parts: Part 1 evaluates the safety and recommended phase 3 dose (RP3D) of EDR; Part 2 evaluates the efficacy and safety of EDR at RP3D vs DRd in TI patients with NDMM. TI is defined as age ≥ 65 or age < 65 with comorbidities impacting the possibility of transplant. The primary endpoints of Part 2 are minimal residual disease (MRD) at 12 mo and progression-free survival. Secondary endpoints include overall and sustained MRD negativity rates, duration of MRD negativity, objective response rate, complete response (CR) rate, time to response, duration of response, duration of CR, overall survival, safety, quality of life, immunogenicity, and pharmacokinetics. Part 1 includes TI patients with NDMM as well as patients with RRMM who have received 1–2 prior lines of therapy including ≥ 1 immunomodulatory drug and ≥ 1 proteasome inhibitor. Part 2 includes only TI patients with NDMM. Key inclusion criteria are: ≥ 18 y; a diagnosis of MM (according to International Myeloma Working Group [IMWG] criteria); an ECOG performance status ≤ 2 ; and measurable disease based on IMWG criteria (serum M-protein ≥ 0.5 g/dL, urinary M-protein excretion ≥ 200 mg/24 hr, or involved serum free light chain [FLC] ≥ 100 mg/L and abnormal serum immunoglobulin $\kappa:\lambda$ FLC ratio [< 0.26 or > 1.65]). Key exclusion criteria are: smoldering MM; monoclonal gammopathy; Waldenström's macroglobulinemia; plasma cell leukemia; active, uncontrolled bacterial, fungal, or viral infections; previous systemic treatment for MM (NDMM patients only); previous treatment with a BMCA-directed therapy or anti-CD38-directed therapy ≤ 6 mo of the first dose of study treatment (RRMM patients only); or stem cell transplant ≤ 3 mo of the first dose of study treatment or active graft versus host disease (RRMM patients only). As of February 2023, the study is open and enrolling at 9 sites in 5 countries. Clinical trial information: NCT05623020. Research Sponsor: Pfizer.

TPS8067

Poster Session

MajesTEC-9: A randomized phase 3 study of teclistamab versus pomalidomide, bortezomib, and dexamethasone or carfilzomib and dexamethasone in patients with relapsed/refractory multiple myeloma. *First Author: Cyrille Touzeau, Centre Hospitalier Universitaire de Nantes, Nantes, France*

Background: Despite the advance in therapeutic options for patients with relapsed/refractory multiple myeloma (RRMM) over recent years, there remains a significant unmet medical need for new, well-tolerated therapies in earlier lines for patients who have previously received an anti-CD38 monoclonal antibody and lenalidomide. Teclistamab is the first B-cell maturation antigen (BCMA)-directed bispecific antibody approved for the treatment of triple class-exposed RRMM. Teclistamab redirects CD3+ T cells to mediate T-cell activation and subsequent lysis of BCMA-expressing myeloma cells. MajesTEC-9 (NCT05572515) is a phase 3, randomized, open-label, multicenter study comparing teclistamab with investigator's choice of pomalidomide, bortezomib, and dexamethasone (Pvd) or carfilzomib and dexamethasone (Kd) in patients with RRMM. **Methods:** Patients aged ≥ 18 years with RRMM (International Myeloma Working Group [IMWG] criteria) must have evidence of progressive disease or failure to achieve a response to last line of therapy and an Eastern Cooperative Oncology Group performance status score of 0–2. All patients must have received 1–3 prior lines of therapy, including ≥ 2 consecutive cycles of an anti-CD38 monoclonal antibody and ≥ 2 consecutive cycles of lenalidomide. Those treated with prior BCMA-directed therapy will be excluded. Approximately 590 patients will be randomized 1:1 to receive either teclistamab (28-day cycles) or Pvd (21-day cycles) or Kd (28-day cycles). Stratification factors include investigator's choice of Pvd or Kd, stage of disease, number of prior lines of therapy, and anti-CD38 monoclonal antibody refractory status. Treatment will continue until disease progression, death, intolerance, withdrawal of consent, or end of study, whichever occurs first. The primary endpoint is progression-free survival (IMWG 2016 criteria); secondary endpoints include overall response rate, duration of response, and overall survival. Adverse events (AEs) will be graded by Common Terminology Criteria for AEs v5.0; cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome will be graded by American Society for Transplantation and Cellular Therapy criteria. The study opened in January 2023 and enrollment is ongoing. Clinical trial information: NCT05572515. Research Sponsor: Janssen Research & Development.

TPS8066

Poster Session

MagnetisMM-7: An open-label, multicenter, randomized phase 3 study of elranatamab versus lenalidomide in post-transplant patients with newly diagnosed multiple myeloma. *First Author: Maria Victoria Mateos Manteca, Salamanca University Hospital, Salamanca, Spain*

Background: Elranatamab is a humanized bispecific antibody targeting B cell maturation antigen (BCMA) on myeloma cells and CD3 on T cells. Elranatamab has shown promising efficacy and acceptable safety in pts with relapsed and/or refractory multiple myeloma (MM). The aim of the MagnetisMM-7 study is to evaluate elranatamab monotherapy vs lenalidomide monotherapy in pts with newly diagnosed MM (NDMM) after undergoing autologous stem cell transplant (ASCT). **Methods:** MagnetisMM-7 is an ongoing, open-label, 2-arm, multicenter, randomized phase 3 study estimated to enroll ~700 pts. ClinicalTrials.gov ID: NCT05317416. Pts are randomized to receive either subcutaneous elranatamab or oral lenalidomide once daily. After initial step-up dosing, two alternative dosing regimens of elranatamab are examined. The primary endpoint is progression-free survival (PFS) assessed by blinded independent review per International Myeloma Working Group (IMWG) criteria (up to ~5 y). Secondary endpoints include overall survival, minimal residual disease (MRD) negativity rate at 12 mo after randomization per IMWG criteria as assessed via next-generation sequencing (NGS), sustained MRD negativity rate at 24 mo after randomization as assessed via NGS, PFS by investigator, duration of MRD negativity, complete response (CR) rate, duration of CR, safety, quality of life, immunogenicity, and pharmacokinetics. Key inclusion criteria are: ≥ 18 y; a diagnosis of MM with measurable disease according to IMWG criteria; history of induction therapy for NDMM, followed by high dose therapy and ASCT with or without consolidation; partial response or better according to IMWG criteria; identification of the dominant malignant clone; and Eastern Cooperative Oncology Group performance status ≤ 1 . Randomization must occur ≤ 120 d from ASCT; for pts who receive consolidation therapy after ASCT, randomization must occur ≤ 60 d of consolidation and ≤ 7 mo of ASCT. Key exclusion criteria are: plasma cell leukemia; amyloidosis; Waldenström's macroglobulinemia; POEMS syndrome; known active CNS involvement or clinical signs of myelomatous meningeal involvement; previous MM maintenance treatment; prior treatment with BCMA-targeted therapy; any other active malignancy ≤ 3 y of enrollment; active, uncontrolled bacterial, fungal, or viral infection; and previous administration of an investigational drug or vaccine ≤ 30 d or 5 half-lives preceding the first dose of study treatment. As of February 2023, the study is open and enrolling at 29 sites in 13 countries. Clinical trial information: NCT05317416. Research Sponsor: Pfizer.

TPS8068

Poster Session

OMNIA-2: Phase I/II study of ANV419, an IL-2R- $\beta\gamma$ targeted antibody-IL-2 fusion protein, in patients with relapsed or refractory multiple myeloma. *First Author: Dagmar Hess, Kantonsspital St. Gallen, St. Gallen, Switzerland*

Background: ANV419 is a potent, selective IL-2R $\beta\gamma$ targeted antibody IL-2 fusion protein, designed to enable the delivery of high dose interleukin-2 (IL-2) to patients, in order to stimulate anti-tumour response and minimise toxicities. The ANV419-001 first-in-human study (NCT 04855929) demonstrated that ANV419 preferentially stimulates cytotoxic CD8+ T and natural killer (NK) cells over immunosuppressive regulatory T cells, with a significantly longer half-life than that of conventional IL-2. The safety and tolerability data from this study confirmed that ANV419 delivers high molar equivalents of IL-2 in a tolerable and convenient way. In patients with multiple myeloma, the critical role of NK cells has been well described. ANV419 is expected to promote antitumor response via the preferential stimulation of cytotoxic CD8+ T and NK cells. **Methods:** The OMNIA-2 study (ANV419-102; NCT 05641324) will evaluate safety and preliminary efficacy of ANV419 as monotherapy and in combination with daratumumab (dara), or lenalidomide with low dose dexamethasone (lena/dex), in patients with relapsed or refractory multiple myeloma. OMNIA-2 is a Phase I open-label, multi-center study in adult patients ($n = 52$) with symptomatic multiple myeloma who responded to previous treatment and received autologous stem cell transplant, or at least 2 lines of therapy including an immunomodulator, proteasome inhibitor, and/or dara. The study is conducted in 2 stages using a Bayesian Optimal Phase 2 approach. Stage 1 consists of a run-in phase with subsequent randomization to ANV419 243mcg/kg or ANV419 108mcg/kg for 8 weeks, followed by a second randomization to ANV419 108mcg/kg in combination with lena/dex or dara for a further 8 weeks. Stage 2 follows a similar design as stage 1 and consists of a monotherapy run-in phase with either high or low dose ANV419, with a second randomisation to ANV419 108mcg/kg in combination with either lena/dex or dara, according to the safety and efficacy observed in Stage 1. ANV419 is administered intravenously over 15 to 20 minutes every two weeks. Lena, dex and dara are administered at their respective approved dosing regimens. Tumour response is determined using IMWG (2016) response criteria. AEs are assessed according to CTCAE V5.0. OMNIA-2 is being conducted in Denmark, France, Germany, Spain, Switzerland, UK and enrolment began in January 2023 and preliminary data are expected in Q1 2024. Clinical trial information: NCT05641324. Research Sponsor: ANAGEON AG.

TPS8069

Poster Session

EXCALIBER-RRMM: A phase 3, two-stage study of iberdomide, daratumumab, and dexamethasone (IberDd) versus daratumumab, bortezomib, and dexamethasone (DvD) in patients (pts) with relapsed/refractory multiple myeloma (RRMM). *First Author: Sagar Lonial, Winship Cancer Center of Emory University, Atlanta, GA*

Background: New treatments (Tx) are needed to achieve deep and durable responses in RRMM. Iberdomide (IBER) is a novel, potent oral cereblon E3 ligase modulator (CELMoD) with enhanced tumoricidal and immune-stimulatory effects compared with immunomodulatory drugs (IMiDs). IBER has synergy with dexamethasone (DEX), daratumumab (DARA), and bortezomib (BORT) in vitro. In a phase 1/2 trial, IberDd demonstrated efficacy with a manageable safety profile in pts with RRMM (Lonial S, et al. *HemaSphere* 2021;5(S2):S187). The EXCALIBER-RRMM phase 3 trial (NCT04975997) will compare the efficacy and safety of IberDd with that of DvD in pts with early RRMM. **Methods:** This multicenter, open-label study will be conducted in 2 stages: in Stage 1, ≥ 200 pts will be randomized 1:1:1 to 1 of 3 IBER doses (1.0, 1.3, or 1.6 mg) + DARA and DEX or to the DvD arm to identify optimal IBER dose when combined with DARA + DEX; in Stage 2, ≈ 664 additional pts will be randomized 1:1 to IberDd at the selected IBER dose or to DvD, for efficacy and safety analyses (Stage 1 pts in IBER selected dose cohort and DvD arm to be also included). Pts will be stratified by number of prior Tx lines (1 vs 2), age (≤ 70 vs > 70 y), and ISS stage at study entry (I-II vs III). Primary efficacy endpoint is progression-free survival (PFS), which is defined as the time from randomization to progressive disease (PD) or death. Assuming a decrease in PFS risk by 25% (HR = 0.75) with IberDd, under exponential distribution assumption of PFS (1-sided $\alpha = 0.025$) and adjusted for 3 interim analyses, 458 PFS events will have $\approx 84\%$ power to detect an improvement in Tx effect. The 3 planned interim analyses are: for IBER dose selection at end of Stage 1; and to examine PFS futility and superiority when ≈ 138 (30%) and ≈ 344 (75%) events, respectively, have been accumulated. Secondary endpoints include overall survival, duration of response, time to progression, overall response rate, measurable residual disease negativity rate, safety, and quality of life. Tx in the IberDd arm will consist of 28-day (D) cycles (C) with IBER on D1–21; 1800 mg subcutaneous (SC) DARA on D1, 8, 15, and 22 of C1–2, D1 and 15 of C3–6, and D1 of $\geq C7$; and 40 mg oral DEX (20 mg in pts > 75 y of age) on D1, 8, 15, and 22. Tx in the DvD arm will consist of 21-D cycles for C1–8 and 28-D cycles for $\geq C9$; 1800 mg SC DARA on D1, 8, and 15 for C1–3, D1 for $\geq C4$; 1.3 mg/m² SC BORT on D1, 4, 8, and 11 for C1–8; and 20 mg oral DEX (10 mg in pts > 75 y of age) on D1, 2, 4, 5, 8, 9, 11, and 12 for C1–8. Tx will continue until confirmed PD, unacceptable toxicity, or consent withdrawal. Key eligibility criteria include age ≥ 18 y, 1–2 prior lines of anti-myeloma Tx, partial response or better to ≥ 1 prior Tx, and documented PD during or after the last regimen. Prior anti-CD38 Tx is allowed only in Stage 2 ($\leq 10\%$ of pts). Enrollment began in June 2022 and is currently ongoing. Clinical trial information: NCT04975997. Research Sponsor: Bristol Myers Squibb.

TPS8070

Poster Session

A phase 3, two-stage, randomized study of mezigdomide, carfilzomib, and dexamethasone (MeziKd) versus carfilzomib and dexamethasone (Kd) in relapsed/refractory multiple myeloma (RRMM): SUCCESSOR-2. *First Author: Paul G. Richardson, Dana-Farber Cancer Institute, Boston, MA*

Background: Mezigdomide (MEZI), a novel oral cereblon E3 ligase modulator (CELMoD), induces maximal degradation of Ikaros/Aiolos leading to increased MM cell apoptosis and immune-stimulatory effects. MeziKd has shown potent synergistic antiproliferative activity in MM cell lines resistant to lenalidomide (LEN), and in a phase 1/2 study showed promising preliminary efficacy and safety in RRMM. The SUCCESSOR-2 phase 3 trial (NCT05552976) will compare the efficacy and safety of MeziKd vs Kd in patients (pts) with RRMM. **Methods:** This multicenter, open-label study comprises 2 stages. In Stage 1, ≥ 128 pts will be randomized 3:3:3:2 to 1 of 3 MEZI doses (1.0, 0.6, or 0.3 mg) + Kd, or to the Kd arm to select the optimal MEZI dose in combination with Kd for Stage 2. In Stage 2, ≈ 397 additional pts will be randomized 3:2 to MeziKd at the selected MEZI dose or to Kd, for efficacy and safety analyses (Stage 1 pts in the selected MeziKd dose cohort and Kd arm will also be included in these analyses). Pts will be stratified by age (≤ 70 vs > 70 y), number of prior lines of treatment (Tx; ≤ 2 vs > 2), and ISS stage at screening (I vs II vs III). MEZI dose selection will be based on Stage 1 efficacy, safety, pharmacokinetic and pharmacodynamic data, and exposure-response analyses. Primary efficacy endpoint is progression-free survival (PFS). Assuming a decrease in PFS risk by 33.3% (HR = 0.667) with MeziKd, under exponential distribution assumption of PFS (1-sided $\alpha = 0.025$) and adjusted for 3 interim analyses, ≥ 273 PFS events will have $\approx 89\%$ power to detect improvement in Tx effect. The planned interim analyses are for: MEZI dose selection at end of Stage 1, and to examine PFS futility and superiority when ≈ 82 (30%) and ≈ 205 (75%) events, respectively, have been accumulated. Secondary endpoints include determination of the recommended MEZI dose plus Kd (Stage 1 only), and assessment of overall survival, overall response rate, time to response, duration of response, time to progression, safety, and quality of life. MeziKd arm Tx consists of 28-day (D) cycles (C) with MEZI on D1–21; 20 mg/m² intravenous (IV) carfilzomib (CFZ) on D1 of C1, then 56 mg/m² on D8 and 15 of C1, on D1, 8, and 15 of C2–12, and on D1 and 15 of $\geq C13$; and 40 mg oral/IV DEX (20 mg optional in certain pt groups) on D1, 8, 15, and 22. Tx in the Kd arm consists of 28-D cycles with 20 mg/m² IV CFZ on D1 and 2 of C1, then 56 mg/m² on D8, 9, 15, and 16 of C1, and on D1, 2, 8, 9, 15, and 16 of $\geq C2$; and 20 mg oral/IV DEX (10 mg optional in certain pt groups) on D1, 2, 8, 9, 15, 16, 22, and 23. Tx will continue until progressive disease (PD) or unacceptable toxicity. Key eligibility criteria include age ≥ 18 y, ≥ 1 prior line of anti-MM Tx including LEN and an anti-CD38 monoclonal antibody, minimal response or better to ≥ 1 prior Tx, documented PD during or after last regimen, and no prior CFZ Tx. Enrollment began in October 2022 and is ongoing. Clinical trial information: NCT05552976. Research Sponsor: Bristol Myers Squibb.

TPS8071

Poster Session

Enrolling patients in Cardiac Amyloid Reaching for Extended Survival (CARES) trials: Two placebo-controlled, double-blind, randomized, international phase 3 trials assessing CAEL-101 in patients with Mayo stage IIIa or stage IIb AL amyloidosis. *First Author: Michaela Liedtke, Stanford Cancer Center, Stanford, CA*

Background: Light-chain (AL) amyloidosis is a rare, progressive, systemic disorder caused by plasma cell dyscrasia (PCD). Amyloid fibrils deposit in organs leading to progressive organ damage and death. Prognosis is poor for patients with cardiac involvement. Median survival is 24 and 4 months for patients in Mayo Stages IIIa and IIb (based on the 2013 European Modification of the Mayo 2004 staging criteria), respectively. The standard of care (SoC) is anti-PCD therapy to suppress amyloid fibril generation. As yet, there are no therapies that remove deposited fibrils. CAEL-101 is a monoclonal antibody that binds to amyloid fibrils and may facilitate their systemic removal, improve organ function, and patient survival. These ongoing trials will evaluate the efficacy and safety of CAEL-101 as first-in-class treatment to reduce amyloid burden in patients with cardiac AL amyloidosis. Notably, 301 (Mayo Stage IIb) is the first randomized, placebo-controlled efficacy clinical trial to formally assess the effects of a pharmacological in this severely ill population. Because the median expected survival for Mayo Stage IIb patients is far shorter than for Mayo Stage IIIa patients, the resulting sample size required for the Mayo Stage IIb study is less than for the Mayo Stage IIIa study. The objective of these trials is to evaluate the efficacy and safety of CAEL-101 when administered concurrently with SoC anti-PCD therapy in treatment-naïve patients with cardiac AL amyloidosis in Mayo Stages IIb (NCT04504825; 301) or IIIa (NCT04512235; 302). **Methods:** These international, multicenter, double-blind, randomized, phase 3 trials, initiated in 2020, are enrolling patients at > 100 sites in > 20 countries. Newly diagnosed adults with AL amyloidosis stage IIb or IIIa measurable hematologic disease, and histopathological diagnosis of amyloidosis with cardiac involvement are eligible. Patients with other forms of amyloidosis, symptomatic orthostatic hypotension, or supine systolic blood pressure < 90 mm Hg are ineligible. Patients in Mayo Stages IIb (N = 124) and IIIa (N = 267) are being randomized 2:1 to receive once-weekly IV infusions of CAEL-101 (1000 mg/m²) or placebo for 4 weeks, followed by maintenance dosing every 2 weeks. In these event-driven studies, treatment will continue to a minimum of 101 and 79 events for 301 and 302, respectively. Patients will receive concurrent institutional SoC anti-PCD therapy at the discretion of the investigator. Overall survival (primary endpoint) will be analyzed via time-to-event log-rank statistics. Secondary endpoints include functional outcomes, quality of life, and echocardiography. Clinical trial information: NCT04504825, NCT04512235. Research Sponsor: Alexion, AstraZeneca Rare Disease.

8500

Oral Abstract Session

Surgical outcomes of patients with resectable non-small-cell lung cancer receiving neoadjuvant immunotherapy with nivolumab plus relatlimab or nivolumab: Findings from the prospective, randomized, multicentric phase II study NEOpredict-Lung. *First Author: Clemens Aigner, West German Cancer Center, University Medicine Essen - Ruhrlandklinik, Essen, Germany*

Background: Feasibility of surgical resection for non-small-cell lung cancer (NSCLC) after preoperative immune checkpoint inhibitor therapy (PICIT) with PD-1/PD-L1 and CTLA-4 inhibitors has been established. This study reports the first data on surgery after preoperative LAG-3 inhibition in NSCLC patients. **Methods:** Patients with histologically confirmed NSCLC stage IB, II or IIIA (UICC 8th edition) were randomized to receive two preoperative doses (q14d) of nivolumab (240 mg, arm A), or nivolumab (240 mg) plus relatlimab (80 mg, arm B). Primary study endpoint was the number of patients undergoing curatively intended surgery within 43 days of initiation of PICIT. Surgery was performed following the institutional standards. Outcomes and peri-operative events were prospectively recorded. **Results:** 60 patients (29 female) were randomized 1:1 from 4/2020 to 7/2022. All patients were operated within 43 days after initiation of PICIT. Median age in arm A was 65 (43-78) years and 67 (44-81) years in arm B. Clinical UICC stages were similar between both arms. Central tumor location was present in 50% in arm A and 45% in arm B. R0 resection was achieved in 57 patients (95% ITT population, 98,3% curatively resected population). Two patients had pleural carcinosis only detected at surgery, and 1 patient had R1 resection. Resection was performed by lobectomy (n=23 and 24), bilobectomy (2 and 1), sleeve lobectomy (5 and 4) and combined lobectomy+segmentectomy (0 and 1). Surgical approach was either by videothoracoscopy (n=60% and 63,3%) or thoracotomy (n=40% and 36,6%). Conversion was required in 3 vs. 2 patients. Median operation time was 149 (77-234) and 165 (61-205) minutes. Median number of resected lymph nodes was 15 (3-52) and 10 (3-50). Intraoperative bleeding from the pulmonary artery was observed in 1 patient in each arm and was managed without sequelae. Post-operative complications occurred in 33,3% and 26,6%. Median hospital stay was 7 (2-22) and 5,5 (2-24) days. Complete or major histopathological response was observed in 27% and 30%. Overall perioperative 30-day mortality was 0%. No negative impact on adjuvant therapy was observed. The 12 months OS rate across both arms was 96% (95% CI: 83-99%), the DFS rate was 91 % (78-97%). **Conclusions:** Curative surgical resection following neoadjuvant combined PD-1/LAG-3 inhibition was equally safe and feasible as after PD-1 inhibition alone. Perioperative course, complications rate and outcome are comparable to other neoadjuvant regimens. Standard adjuvant therapies can be safely administered in this setting. Clinical trial information: NCT04205552. Research Sponsor: Bristol Myers Squibb.

8502

Oral Abstract Session

First-in-human dose-escalation trial of BI 764532, a delta-like ligand 3 (DLL3)/CD3 IgG-like T-cell engager in patients (pts) with DLL3-positive (DLL3+) small-cell lung cancer (SCLC) and neuroendocrine carcinoma (NEC). *First Author: Martin Wermke, Technical University Dresden, NCT/ UCC Early Clinical Trial Unit, Dresden, Germany*

Background: The inhibitory Notch ligand, DLL3, is highly expressed on the cell surface of SCLC and NEC tumors and is a promising drug target. BI 764532 is a DLL3/CD3 T cell engaging bispecific antibody that has shown potent preclinical anti-tumor activity in DLL3+ cells and xenograft models. NCT04429087 is an ongoing phase I first-in-human, open-label, dose-escalation trial of BI 764532 in adults with locally advanced/metastatic DLL3+ (confirmed centrally) SCLC, NEC or small cell carcinoma of any other origin (grouped as NEC), or large cell NEC (LCNEC). **Methods:** BI 764532 was administered intravenously using three different regimens: Regimen (R) A (fixed iv dose q3w); RB1 (fixed iv dose qw); RB2 (step-in doses followed by a fixed dose). Treatment (Tx) continued until progressive disease (PD), unacceptable toxicity, other withdrawal criteria, or maximum Tx duration (36 mos). The main objective was to determine the maximum tolerated dose (MTD) and/or recommended dose for expansion of BI 764532, based on dose-limiting toxicities (DLTs) during the MTD evaluation period. Further objectives were safety, tolerability, PK/PD and preliminary efficacy based on investigator review (RECIST v1.1). **Results:** As of 28th Dec 2022, 90 pts received ≥ 1 dose of BI 764532 (RA: n = 24, 8 dose levels; RB1: n = 10, 3 dose levels; RB2: n = 56, 6 dose levels; starting dose: 0.03 µg/kg). Median age: 60 years (32–78); ECOG PS 0/1: 24/74%; prior PD1/PD-L1 Tx: 40%; ≥ 2 prior lines of Tx: 69%. SCLC/NEC/LCNEC: 52/41/4%. Median Tx duration: 43 days (range 1–443); 25 pts are ongoing. DLTs were seen in 1 pt on RA (Grade 3 confusion) and 4 pts on RB2 (Grade 4 cytokine release syndrome [CRS]; Grade 3 CRS, Grade 3 nervous system disorder, Grade 2 infusion-related reaction). MTD has not been reached and dose escalation is ongoing. Overall, the most common treatment-related AEs were (any/Grade 3+): CRS (58/2%); pyrexia (19/0%); decreased lymphocytes (18/14%); asthenia (17/1%); dysgeusia (14/0%). CRS was managed with supportive care, corticosteroids, and/or anti-IL-6R antibodies. With RB2, most CRS and neurological events occurred early, and were reversible. Tumor response data were available for 70 pts (RA/RB1/RB2: n = 19/8/43). In pts with SCLC (n = 24) or NEC (n = 23) who received ≤ target dose of BI 764532, ORR was 33% and 22% across all regimens, respectively. One pt with LCNEC was also evaluable for response and achieved PR. **Conclusions:** BI 764532 showed clinically manageable tolerability and MTD has not been reached at the doses administered to date. Promising efficacy has been observed, not only in SCLC but also in difficult to treat entities such as NEC and LCNEC. The study is ongoing; updated data will be presented. Clinical trial information: NCT04429087. Research Sponsor: Boehringer Ingelheim.

8501

Oral Abstract Session

Perioperative toripalimab + platinum-doublet chemotherapy vs chemotherapy in resectable stage II/III non-small cell lung cancer (NSCLC): Interim event-free survival (EFS) analysis of the phase III NEOTORCH study. *First Author: Shun Lu, Shanghai Chest Hospital, Jiao Tong University, Shanghai, China*

Background: Adjuvant and neoadjuvant immunotherapy have been approved by US FDA to treat early-stage NSCLC. However, the optimal neoadjuvant and adjuvant treatment, including duration of treatment, are unknown. We present the interim results of a randomized, double-blind, placebo-controlled, Phase III trial to evaluate the efficacy and safety of perioperative toripalimab plus chemotherapy followed by toripalimab maintenance vs chemotherapy in resectable stage III NSCLC. **Methods:** Patients with stage II/III resectable NSCLC, without EGFR/ALK alterations for non-squamous NSCLC, were randomized 1:1 to receive 240 mg toripalimab or placebo combined with chemotherapy Q3W for 3 cycles before surgery and one cycle after surgery, followed by toripalimab or placebo monotherapy Q3W for 13 cycles. Stratification variables for randomization included disease stage, histopathologic subtype, PD-L1 expression and surgical procedure. Primary endpoints were EFS by investigator and major pathological response (MPR) rate by a blinded independent pathologic review (BIPR) in the stage III and the ITT populations. Secondary endpoints included overall survival (OS), pathologic complete response (pCR) rate, EFS by independent review committee (IRC), and safety. A planned interim analysis was performed on the primary endpoint of EFS in the stage III subjects. **Results:** A total of 404 stage III NSCLC patients were randomized to toripalimab (n=202) or placebo (n=202). By the data cutoff date (November 30, 2022), the median follow-up was 18.3 months. Baseline characteristics were well balanced between the two arms. EFS was significantly improved in the toripalimab arm, HR=0.40, 95% CI (0.277-0.565), P<0.0001, and crossed the pre-specified efficacy boundary. The median EFS was not reached in the toripalimab arm and 15.1 months in the placebo arm. A consistent effect on EFS, favoring toripalimab, was observed in all subgroups. The MPR and pCR rates per BIPR were also higher in the toripalimab arm, 48.5% vs 8.4% and 24.8% vs 1.0%, respectively. The OS results showed a trend favoring toripalimab. The incidence of Grade ≥ 3 adverse events (AEs) (63.4% vs 54.0%), fatal AEs related to toripalimab/placebo (0.5% vs 0%) and AEs leading to discontinuation of toripalimab/placebo (9.4% vs 7.4%) were comparable between the two arms. However, the incidence of immune-related AEs (42.1% vs 22.8%) was more frequent in the toripalimab arm. **Conclusions:** The addition of toripalimab to perioperative chemotherapy showed statistically significant improvements in EFS for stage III NSCLC patients with a manageable safety profile. Patients will be followed for overall survival. Clinical trial information: NCT04158440. Research Sponsor: Shanghai Junshi Biosciences Co.,Ltd.

8503

Oral Abstract Session

Exploratory biomarker analysis of the phase 3 KEYNOTE-604 study of pembrolizumab plus etoposide for extensive-stage SCLC. *First Author: Charles M. Rudin, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: In the phase 3 KEYNOTE-604 study of extensive-stage small-cell lung cancer (ES-SCLC; NCT03066778), first-line pembrolizumab (pembro) plus etoposide and platinum (EP) significantly improved PFS vs placebo (pbo) plus EP (HR, 0.75; P = 0.0023), with favorable OS (significance threshold not met; HR, 0.80; P = 0.0164). PFS/OS were similar regardless of PD-L1 CPS. In this exploratory analysis, tumor mutational burden (TMB), 18-gene T cell-inflamed gene expression profile (Tcell_{infl}GEP) and SCLC transcriptional subtypes were assessed as correlates of survival. **Methods:** Patients (pts) eligible for this analysis of KEYNOTE-604 had previously untreated ES-SCLC with evaluable pretreatment tumor samples. TMB was assessed by whole-exome sequencing (WES) of tumor and matched normal DNA. RNA-seq was used to determine Tcell_{infl}GEP and SCLC transcriptional subtypes (ASCL1, POU2F3, NEUROD1, YAP1, or inflamed). Associations of TMB, Tcell_{infl}GEP, and SCLC subtype with OS were analyzed using an adjusted Cox proportional hazards model. 1-sided (pembro + EP) and 2-sided (pbo + EP) P values were calculated for TMB and Tcell_{infl}GEP (prespecified α = 0.05); 2-sided P values were calculated for SCLC subtype (multiplicity-adjusted, α = 0.10). Clinical utility was assessed using prespecified cutoffs of ≥ 175 mut/exome for TMB and the first tertile for Tcell_{infl}GEP. Clinical data cutoff date was Dec 2, 2019. **Results:** Of 453 pts randomized in KEYNOTE-604 (ITT), 318 had WES data (pembro + EP, n = 167; pbo + EP, n = 151), and 316 had RNA-seq data (pembro + EP, n = 159; pbo + EP, n = 157). High TMB was positively associated with OS in the pbo + EP group (P = 0.005) but not the pembro + EP group (P = 0.450). There was a positive association between higher Tcell_{infl}GEP and OS in the pembro + EP (P = 0.003) and pbo + EP (P < 0.005) groups. SCLC subtypes were not associated with OS in either group (pembro + EP, P = 0.960; pbo + EP, P = 0.999). Clinical benefit of pembro + EP over pbo + EP was demonstrated for TMB < 175 mut/exome, but not for TMB ≥ 175 mut/exome. Pembro + EP benefit over pbo + EP was consistent across Tcell_{infl}GEP subgroups. **Conclusions:** In this exploratory analysis of biomarker subgroups of KEYNOTE-604, TMB and SCLC subtypes were not associated with OS in the pembro + EP group in pts with ES-SCLC. While Tcell_{infl}GEP was positively associated with OS in both treatment groups, no additional OS benefit was observed with pembro + EP. Further research is warranted to better identify predictive biomarkers to immunotherapy. Clinical trial information: NCT03066778. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

		n	Median OS (95% CI), mo	HR (95% CI)
TMB <175 mut/exome	Pembro + EP	87	10.2 (8.5–14.4)	0.60 (0.43–0.85)
	Pbo + EP	73	7.7 (6.6–9.3)	
TMB ≥175 mut/exome	Pembro + EP	80	12.3 (8.3–15.5)	1.02 (0.72–1.45)
	Pbo + EP	78	12.0 (9.8–13.9)	
Tcell _{infl} GEP <1st tertile	Pembro + EP	49	8.5 (8.1–12.5)	0.74 (0.49–1.11)
	Pbo + EP	56	7.9 (6.5–9.8)	
Tcell _{infl} GEP ≥1st tertile	Pembro + EP	110	13.1 (9.7–17.5)	0.77 (0.56–1.06)
	Pbo + EP	101	10.6 (8.2–12.9)	

8504

Oral Abstract Session

SWOG S1929: Phase II randomized study of maintenance atezolizumab (A) versus atezolizumab + talazoparib (AT) in patients with SLFN11 positive extensive stage small cell lung cancer (ES-SCLC). *First Author: Nagla Fawzy Abdel Karim, Inova Schar Cancer Institute, University of Virginia, Fairfax, VA*

Background: In unselected patients (pts) with extensive-stage small cell lung cancer (ES-SCLC), the addition of immune checkpoint inhibitors (ICI) to chemotherapy resulted in a modest improvement in OS. In a retrospective analysis of a study with veliparib (PARP inhibitor [PARPi]) and temozolomide in patients with SCLC, Schlafen-11 (SLFN11) predicted PFS and OS benefit for the addition of PARPi. We evaluated whether the addition of PARPi (talazoparib) to standard-of-care maintenance ICI (atezolizumab) following frontline chemoimmunotherapy improved outcomes in pts with SLFN11-positive ES-SCLC. **Methods:** Participants with ES-SCLC expressing SLFN11 (H-score ≥ 1 , evaluated centrally at MDACC) were randomized to maintenance atezolizumab (A) versus atezolizumab plus talazoparib (AT) following frontline chemotherapy and A. Randomization was stratified by Zebrod PS (0-1 vs 2) and use of consolidation thoracic radiation. The primary endpoint was PFS, and secondary endpoints included ORR, OS, and toxicity. The primary analysis was done using a 1-sided 10% level stratified log-rank test. Target sample size was 94 pts. **Results:** From June 2020 to December 2022, 309 pts were screened, of which 204 of 259 (79%) with evaluable tissue were SLFN11 positive, and 106 were randomized (52 A, 54 AT). Median follow up time is 5 months. Median age was 67 (45-84); 51 (48%) were females; 94 (89%) were white, 102 (96%) were PS 0-1, and 26 (25%) had radiation prior to randomization. With 80 PFS events reported, PFS was significantly improved with AT (hazard ratio [80% CI]: 0.70 [0.52-0.94]; $p = 0.056$). Median PFS was 2.8 months (80% CI 2.0-2.9) for A and 4.2 months (80% CI 2.8-4.7) for AT. OS was not different (hazard ratio [80% CI]: 1.17 [0.80-1.71]; $p = 0.30$). Median OS was 8.5 months (80% CI 7.4-12.7) for A and 9.4 months (80% CI 8.1-14.2) for AT. ORR was 16% (5/32, 80% CI 8-27%) for A and 12% (4/34, 80% CI 5-22%) for AT. Grade 3 or greater treatment related non-hematological adverse events (AEs) occurred in 13% pts in A and 15% in AT. Hematological AEs occurred 4% in A compared to 50% pts in AT (Expected for T) ($p < 0.001$). There were no treatment related grade 5 events. One participant on AT experienced grade 3 febrile neutropenia. The majority of grade 3 AEs were due to anemia (2% in A and 37% in AT). Only three pts discontinued treatment due to toxicity (2 in A and 1 in AT). **Conclusions:** This study met its primary endpoint demonstrating that maintenance AT improved PFS in SLFN11-selected patients with ES-SCLC. Hematologic toxicity was increased with AT as expected, with majority being grade 3 anemia. This study demonstrates the feasibility of conducting biomarker selected trials in SCLC, paving the way for future evaluation of novel therapies in selected SCLC populations. Clinical trial information: NCT04334941. Research Sponsor: U.S. National Institutes of Health; Genentech, Inc; NIH/NCI grants U10CA180888, U10CA180819, U10CA180820, U10CA180821; in whole or in part by funding from the Biomarker, Imaging, & QOL Studies Funding Program (BIQSFP) awarded by the National Cancer Institute; and in part by Genentech, a member of Roche Group. U01 CA213273, R01 CA207295, P50 CA070907. The University of Texas MD Anderson Cancer Center Lung Cancer Moonshot Program. The Andrew Sabin Family Fellowship.

LBA8505

Oral Abstract Session

IND227 phase III (P3) study of cisplatin/pemetrexed (CP) with or without pembrolizumab (pembro) in patients (pts) with malignant pleural mesothelioma (PM): A CCTG, NCIN, and IFCT trial. *First Author: Quincy S. Chu, Cross Cancer Institute, Edmonton, AB, Canada*

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2023, issue of the *Journal of Clinical Oncology*.

8506

Oral Abstract Session

Efficacy, cellular and molecular determinants of PD-1 checkpoint inhibition in relapsed mesothelioma. *First Author: Dean Anthony Fennell, University of Leicester and Leicester University Hospitals, Leicester, United Kingdom*

Background: Leveraging adaptive immunity to control mesothelioma is now a standard approach, however the factors that underpin clinical response are poorly understood. Here we report the final analysis of the CONFIRM trial (NCT03063450), a double-blind phase III randomized study of the PD-1 inhibitor nivolumab (N) versus placebo (P) in patients (pts) with unresectable mesothelioma. Genomic, transcriptomic and multiplex spatial phenotypic correlates were explored in mesotheliomas exhibiting either partial response or progressive disease as their best outcome. **Methods:** Pts with relapsed pleural or peritoneal mesothelioma with ECOG performance status 0-1 were randomized 2:1 to N (3 mg/kg) or P once every 2 weeks until progression, or a maximum of 12 months. Pts were stratified by epithelioid (E) vs non-epithelioid (NE) histology. Co-primary endpoints were progression-free survival (PFS) and overall survival (OS); key secondary endpoints included best overall response, safety and tolerability. PD-L1 tumour proportion score (TPS, Dako22C3) was evaluated. To decipher correlates response to N, blinded multi-omic analysis was conducted in a subset of responders (R, n=16) versus progressors (NR, n=13). Whole exomes (WES) and transcriptomes were sequenced, with immune landscapes profiled by 19x depth 4-panel multiplex immunofluorescence. Acquired resistance was explored by WES in a biopsied responder at the time of progression. **Results:** Between April 2017-March 2020, 332 pts were randomised to N (n=221) or P (n=111). Median follow up was 37.2m. Baseline characteristics were balanced between arms. Histology: E 88.3%, 3rd line or greater 69.9%. PFS was longer for N vs P (events=324; median, 2.9 vs 1.6 months; HR 0.65; 95% CI, 0.51 – 0.82; $P < 0.001$). Crossover from P was 18.0% (due to widespread availability of N during the covid19 pandemic). OS curves crossed at 32m; 9.5 vs 6.8 months; HR, 0.81; 95% CI, 0.64 – 1.04; $P = 0.096$). Grade 3-4 treatment-related toxicity occurred in 20.4% vs 7.2% of pts; discontinuation occurred in 13.6% (N) versus 9.9%. PD-L1 TPS was not predictive of PFS or OS. The R-subgroup had longer PFS versus NR (319 versus 30 days, Hazard ratio, HR 0.02, $p < 0.001$) and OS (670 vs 122 days HR 0.19, $p < 0.001$). The R-group were enriched for BAP1 inactivation, CD8+ T-cell infiltration, T cell co-stimulation, cytolytic activity and mature tertiary lymphoid structures (TLSs). Conversely, the NR group had significantly more aneuploidy (notably uniparental disomy, UPD), and enrichment of epithelial mesenchymal transition, TGF beta signalling, and E2F transcription. Acquired resistance was associated with increased aneuploidy (UPD) and subclonal evolution including a new DNMT3A c2204A>G mutation. **Conclusions:** N met its co-primary endpoint of PFS with responding mesotheliomas harbouring a TLS enriched, inflamed tumour microenvironment and stable genome compared to non-responders. Clinical trial information: NCT03063450. Research Sponsor: Stand Up to Cancer, Cancer Research UK; BMS.

8507

Oral Abstract Session

Association of somatic mutations and histologic subtype/grade on prognosis and PD-L1 expression in mesothelioma. *First Author: Allen Zhu, University of Chicago, Chicago, IL*

Background: Mesothelioma includes epithelioid, sarcomatoid, and biphasic histologic subtypes, and the epithelioid subtype is histologically graded based on mitotic count and nuclear atypia. Correlation between the most common somatic mutations (*BAP1*, *NF2*, *TP53*, *CDKN2A*), and overall survival is poorly understood. High PD-L1 expression is a poor prognostic factor for survival and may be a predictor of response to immunotherapy. Few studies have evaluated the relationships between these factors. **Methods:** We performed a retrospective study in 217 patients with pleural, peritoneal and bicavitary mesothelioma as part of an IRB-approved biobanking protocol. Histologic subtype, grade of epithelioid mesothelioma, tumor stage, and overall survival time were determined. Next-generation DNA sequencing (NGS) was used to identify the prevalence of somatic mutations. PD-L1 immunohistochemistry was obtained on 184 samples and quantified as percentage of tumor cells. Histologic subtype, nuclear grade, clinical stage, PD-L1 expression, survival time, and the prevalence of each mutation were compared using chi-squared, Kruskal-Wallis, or Cox proportional hazard tests. All p-values were determined in R version 4.2.0 using a two-sided alpha error of 0.05 to mark statistical significance. **Results:** The most frequent somatic mutations were found in *BAP1* (99/217, 45.6%), *CDKN2A* (47/217, 21.7%), *TP53* (37/217, 17.1%), and *NF2* (31/217, 14.3%). Patients with *CDKN2A*-mutated mesothelioma experienced shorter survival ($p = 0.032$). *TP53* mutations were associated with higher nuclear grade ($p = 0.015$), higher mitotic count ($p = 0.013$), and greater nuclear atypia ($p = 0.015$). *TP53* mutations were more prevalent in pleural than peritoneal mesothelioma ($p = 0.016$) and in tumors without lymph node metastasis ($p = 0.05$). As expected, patients with epithelioid mesothelioma had superior overall survival ($p = 0.02$) and their tumors had lower PD-L1 expression ($p = 0.007$) than either sarcomatoid or biphasic mesotheliomas. Neither PD-L1 expression nor mutations in *BAP1*, *NF2*, *CDKN2A*, or *TERT* were associated with nuclear grade, atypia, or mitotic count. No association was found between *BAP1* or *NF2* mutations and tumor stage, lymph node metastasis, or PD-L1 expression. **Conclusions:** To our knowledge, this is the first study of this scale to correlate PD-L1 expression, somatic mutation data, histologic features, and survival in mesothelioma patients. The most significant findings were that patients with *CDKN2A* mutations had shorter survival and *TP53* mutations, which were more prevalent in pleural mesotheliomas, were associated with higher nuclear grade, higher mitotic count, and greater nuclear atypia. An ongoing analysis evaluates the contribution of germline mutations, which occurred in a significant proportion (15.7%) of this mesothelioma patient cohort. Research Sponsor: Supported, in part, by John D. Cooney and the firm of Cooney and Conway through the University of Chicago Comprehensive Cancer Center.

8508

Clinical Science Symposium

Phase II trial of neoadjuvant osimertinib for surgically resectable EGFR-mutated non-small cell lung cancer. *First Author: Jacqueline V. Aredo, University of California, San Francisco, San Francisco, CA*

Background: Osimertinib is a third-generation EGFR tyrosine kinase inhibitor (TKI) effective in treating advanced EGFR-mutated non-small cell lung cancer (NSCLC). Adjuvant osimertinib significantly decreases disease recurrence in stage IB-IIIa EGFR-mutated NSCLC. However, the benefit of neoadjuvant osimertinib prior to surgical resection remains unknown. **Methods:** This was a multi-institutional phase II trial of neoadjuvant osimertinib for patients with surgically resectable stage I-IIIa (AJCC V7) EGFR-mutated (L858R or exon 19 deletion) NSCLC (NCT03433469). Patients received osimertinib 80 mg orally daily for up to two 28-day cycles prior to surgical resection. The primary endpoint was major pathological response (mPR) rate ($\leq 10\%$ residual viable tumor). 27 evaluable patients provide 87% power to detect a mPR rate of 50% with $\alpha = 0.05$. Secondary endpoints included pathological response (PR) rate ($\leq 50\%$ residual viable tumor), pathological complete response (pCR) rate, unconfirmed objective response rate (ORR), rate of lymph node downstaging, unanticipated delays to surgery, surgical complication rate, disease-free survival (DFS), overall survival (OS), safety, and tumor mutational profile. **Results:** A total of 27 patients with early-stage (8 stage IA/B, 10 stage IIA/B, 9 stage IIIA) EGFR-mutated (11 exon 19 del, 16 L858R) NSCLC were treated with neoadjuvant osimertinib for a median 56 days prior to surgical resection. 24 (89%) patients underwent subsequent surgery; 3 (11%) patients were converted to definitive chemoradiotherapy. The mPR rate was 15% (4/27 patients) by intention-to-treat analysis. The PR rate was 48% (13/27). No pCRs were observed. Partial responses by radiography were observed in 52% (14/27) of patients and stable disease in 44% (12/27) of patients. Lymph node downstaging was achieved in 44% (4/9) of patients with positive lymph nodes. Median DFS after surgical resection was 32 months (95% CI 26-not reached) with a median follow-up of 11 months. OS data are immature. Significant adverse events occurred in 3 patients with grade 2 (G2) dyspnea, grade 3 (G3) pulmonary embolism, and G3 atrial fibrillation. One patient developed G2 treatment-related pneumonitis that resolved without steroids. Perioperative complications occurred in 38% (9/24) of patients; most involved rapidly reversible postoperative G2 atrial fibrillation (6/9) unrelated to study drug. Tumors were evaluable for genetic alterations from 16 patients. 4/6 patients who did not achieve a PR had tumors that harbored loss of function mutations in *RBM10* as compared to 0/10 patients who achieved a PR ($p < 0.01$). **Conclusions:** Neoadjuvant osimertinib in surgically resectable EGFR-mutated NSCLC achieved a 15% mPR, which did not meet the primary endpoint. Treatment was safe and may induce pathological responses and lymph node-downstaging of disease. Co-mutations in *RBM10* may limit response. Clinical trial information: NCT03433469. Research Sponsor: AstraZeneca.

8510

Rapid Abstract Session

Preliminary results from the Female Asian Nonsmoker Screening Study (FANSS). *First Author: Elaine Shum, NYU Langone Perlmutter Cancer Center, New York, NY*

Background: Lung cancer (LC) is the leading cause of cancer death in Asian Americans and unfortunately the majority are diagnosed at advanced or late stages. In Asia, approximately 60-80% of female LC patients are never smokers. Current screening in the U.S. with low-dose CT (LDCT) Chest scans is offered only to current or former smokers based on the National Lung Screening Trial (NLST). The LC detection rate in NLST was 1.1%. The TALENT study, a LC screening study for high-risk nonsmokers in Taiwan reported a LC detection rate of 2.6% which included invasive adenocarcinoma (adeno), adeno in situ, minimally invasive adeno and adenocarcinoma. Invasive adeno detection rate was 1.52%. We are conducting the ongoing FANSS in the U.S. to screen female Asian nonsmokers with LDCT Chest scans to evaluate the feasibility of a LC screening program in this population. We report preliminary results here. **Methods:** This is an IRB-approved, prospective, multicenter study (NYU, MGH, UCI). Inclusion criteria are women, age between 40-74 years old (yo), never smoked or smoked < 100 cigarettes in one's lifetime and identify as from Asian descent (report ancestry or race from the continent of Asia). Participants (pts) with history of LC or treatment of any cancer < 5 years ago are excluded. Following informed consent, eligible pts undergo a shared-decision making discussion prior to obtaining a baseline LDCT Chest scan, read according to Lung-RADS 1.1 with plan for annual LDCT for two additional years. A plasma-based assay to analyze cell-free DNA (cfDNA) fragments for early detection of cancer by Delfi Diagnostics (Baltimore, MD) is sent at the time of each scan. A questionnaire regarding ethnicity, family history and environmental exposures is collected at baseline. **Results:** From 3/1/21 to 1/15/23, 222 pts signed consent and 201 had a baseline LDCT at NYU. Age range was 40-74 yo and median age of 56.8 yo. 83 (41%) reported a family history of LC. Of 201 pts who completed a baseline LDCT, 87 (43%) were Lung-RADS 1, 101 (50%) were Lung-RADS 2, 6 (3%) were Lung-RADS 3 and 7 (3.5%) were Lung-RADS 4. 5 pts with Lung-RADS 3 and 3 pts with Lung-RADS 4 have solid, subsolid or groundglass nodules > 6 mm that remain in close follow-up. 3 pts were diagnosed with invasive lung adeno for a LC detection rate of 1.5%; 2 are stage IIB and 1 is stage IIIC. All pts were surgically resected, EGFR mutation positive and are receiving adjuvant osimertinib. Analysis of the cfDNA fragmentation profiles is ongoing. **Conclusions:** Our data shows that LC screening in Asian female nonsmokers is feasible. Preliminary results demonstrate an invasive adeno detection rate comparable with TALENT and higher than in NLST. Early detection brings new meaning with the recent FDA approval for adjuvant targeted therapy in early stage LC. The expansion of LC screening guidelines to other high-risk populations warrants further attention. FANSS is continuing to accrue at additional U.S. sites this year. Clinical trial information: NCT05164757. Research Sponsor: NYU Lung Cancer Center; Delfi Diagnostics.

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Rapid Abstract Session

Pembrolizumab and ramucirumab neoadjuvant therapy for PD-L1-positive stage IB-IIIa lung cancer (EAST ENERGY). *First Author: Keiju Aokage, Department of Thoracic surgery, National Cancer Center Hospital East, Kashiwa, Japan*

Background: Neoadjuvant treatments for resectable non-small cell lung cancer (NSCLC) using novel combination therapies are being developed. Angiogenesis inhibitors have been reported to modify tumor immunity, and the efficacy and safety of treatments added to immune checkpoint inhibitors (ICIs) have been investigated in advanced NSCLC. In this multi-institutional phase II study, we evaluated the efficacy and feasibility of neoadjuvant therapy with pembrolizumab and ramucirumab, a direct vascular endothelial growth factor (VEGF) receptor-2 antagonist, followed by surgery, in patients with PD-L1 positive, clinical stage IB-IIIa NSCLC. **Methods:** Patients (aged ≥ 20) with pathologically proven NSCLC harboring PD-L1 expression $\geq 1\%$ (22C3), resectable clinical stage IB-IIIa NSCLC, and performance status of 0 to 1 were eligible. Patients received two cycles of pembrolizumab (200 mg/body) and ramucirumab (10 mg/kg) every three weeks. Surgery was scheduled 4-8 weeks after the last dose. The primary endpoint was to determine the major pathologic response (MPR) rate. The sample size was calculated based on the exact binomial distribution, considering a threshold MPR rate of 20%, an expected MPR rate of 45%, a one-side alpha of 5%, and a desired power of 80%. **Results:** A total of 24 eligible patients, with a median age of 75 years (range 50-78), were enrolled between July 2019 and April 2022; 18 patients were male. The histological subtype was adenocarcinoma in 12 patients, and the clinical stage was IB, IIA, IIB, and IIIA in 1, 4, 9, and 10 patients, respectively. PD-L1 was $\geq 50\%$ in nine patients (37.5%). The MPR rate by the blinded independent central review of three pathologists was 50.0% (90% confidence interval, 31.9-68.1%); therefore, the primary endpoint was met. Six of the 12 patients who achieved MPR showed pathological complete response. One patient developed pneumonia before neoadjuvant treatment and one patient showed progressed disease after neoadjuvant treatment. Grade 3 adverse events (AEs) occurred in nine of 24 patients (37.5%) during the protocol treatment. Postoperative complications of grade 3 AEs, including postoperative hematoma, pulmonary fistula, and intraoperative arterial injury, were observed in three patients. Immune-related AEs related to protocol treatment were thyroid dysfunction, acute tubulointerstitial nephritis, and hepatic dysfunction in three, two, and two patients, respectively; however, no grade 3 or high AEs were observed. Twenty-one patients achieved R0 resection and one patient underwent R1 resection. There were no wound-healing adverse events of concern due to the anti-VEGF action of ramucirumab. **Conclusions:** The results of this study demonstrated that this new neoadjuvant combination of ICI and anti-VEGF agent (pembrolizumab and ramucirumab) is feasible and showed encouraging results. Clinical trial information: NCT04040361. Research Sponsor: MSD and Eli Lilly.

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Rapid Abstract Session

Bemcentinib and pembrolizumab in patients with relapsed mesothelioma: MIST3, a phase IIa trial with cellular and molecular correlates of efficacy. *First Author: Matthew G Krebs, The University of Manchester and The Christie NHS Foundation Trust, Manchester, United Kingdom*

Background: AXL receptor tyrosine kinase is a key facilitator of immune escape and drug resistance, conferring a more aggressive phenotype. Targeting the PD1-PDL1 axis has demonstrated significant efficacy in patients with relapsed malignant mesothelioma (MM), however, responses are only observed in a fraction of patients. Preclinical studies suggest that dual PD1 and AXL inhibition is synergistic. We developed a multi-centre, molecularly stratified phase IIa trial to evaluate the efficacy of AXL/PD-1 inhibition with bemcentinib (Bem)/pembrolizumab (Pem) and to uncover cellular and molecular determinants of efficacy as arm 3 of the Mesothelioma Stratified Therapy umbrella trial (NCT03654833, MIST3). **Methods:** Patients with pleural mesothelioma were enrolled. Key inclusion factors were ECOG performance status (PS) 0-1, prior platinum-based chemotherapy (maximum of 2 prior lines allowed), evidence of disease progression with measurable disease by CT (Modified RECIST 1.1), and adequate haematological/organ function. All patients received 200mg Pem IV q3W in combination with Bem, loading dose 400mg PO for the first 3 days and then 200mg od q3w. Primary endpoint was disease control rate at 12 weeks (DCR12w). Secondary endpoints: DCR at 24 weeks (DCR24w), best objective response rate (ORR) and toxicity (NCI CTCAE 4.03). Pre-treatment fresh biopsy was required to enable multiplex immunofluorescence, whole exome and RNA transcriptome sequencing. Gut microbiome 16s RNA sequencing also was undertaken at baseline (n=21). **Results:** Between September 2020 and March 2022, 26 patients with MM started treatment and received at least one dose of Pem Bem. Median age was 72.5 (range, 55-85) years, 88% were male 12% were female, Histology: 88% epithelioid, 8% Biphaseic, 4% Sarcomatoid, ECOG PS 1 77%, > 1 prior systemic therapy 35%. The median cycles of Pem Bem was 4 (IQR, 2-11). The DCR12w was 46.2% (12/26) (90% confidence limit (CI), 29.2% - 63.4 %); ORR was 15.4% (95%CI, 4.4-34.9%; all PR) with stable disease in 57.7% (36.9 - 76.6%); DCR24w was 38.5% (10/26) (95%CI, 20.2% - 59.4%). Adverse events (any cause): $\geq$ grade 3 toxicities affected 38% of pts and there were no treatment-related deaths. The most frequent adverse events recorded were fatigue in 12/26 (46%) patients and nausea in 11/26 (42%) patients. **Conclusions:** MIST3 met its primary endpoint and warrants further evaluation. Analysis of the cellular and molecular correlates of response are ongoing and will be presented. Clinical trial information: NCT03654833. Research Sponsor: Asthma and Lung UK and Victor Dahdaleh Foundation; Bergen Bio.

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Poster Discussion Session

Final survival data from a randomized phase II trial comparing high-dose with standard-dose twice-daily (BID) thoracic radiotherapy (TRT) in limited stage small-cell lung cancer (LS SCLC). *First Author: Bjorn H. Henning Gronberg, Norwegian University of Science and Technology (NTNU), Trondheim, Norway*

Background: Concurrent chemotherapy and TRT is standard treatment of LS SCLC. BID TRT of 45 Gy/30 fractions is the most recommended schedule. Trials report 5-year survival rates of up to 36%, illustrating that some are cured but also need for better treatment. Many treatment failures are due to relapses within TRT fields, and it has been proposed that higher TRT doses might improve local control and consequently survival. However, high-dose once-daily (QD) TRT of 66-70 Gy do not prolong survival. We investigated whether high-dose BID TRT of 60 Gy/40 fractions was tolerable and improved survival compared with the established 45 Gy schedule (NCT02041845). **Primary analyses** presented at ASCO 2020 showed that the trial was highly positive for the primary endpoint, 2-year survival (60 Gy: 74.2%, 45 Gy: 48.1%, OR 3.09 [95% CI 1.62-5.89]; $p=0.0005$). We now present updated and final survival data. **Methods:** Patients ≥ 18 years with PS 0-2, confirmed SCLC, LS according to the IASLC definition after PET CT staging received 4 courses of platinum/etoposide and were randomized to receive 60 Gy or 45 Gy to PET CT positive lesions. TRT started concurrently with the 2nd chemotherapy course. Responders were offered QD prophylactic cranial irradiation of 25-30 Gy. All patients were followed for 5 years or until death. **Results:** 170 eligible patients were randomized at 22 Scandinavian hospitals from 2014-2018 (60 Gy: $n=89$, 45 Gy: $n=81$). Median age was 65, 31.2% were ≥ 70 years, 57.1% women, 89.4% had PS 0-1, 83.5% stage III disease, 7.6% pleural effusion and 20.0% $\geq 5\%$ weight loss last three months before enrollment. Baseline patient and disease characteristics and TRT planning target volumes were well balanced between treatment arms. Completion rates of chemotherapy (60 Gy: 92.1%, 45 Gy: 87.7%) and TRT (60 Gy: 96.6%, 45 Gy: 91.4%) were similar. Patients on the high-dose arm did not experience more grade 3-4 esophagitis (60 Gy: 21.2%, 45 Gy: 18.2%; $p=0.83$) or pneumonitis (60 Gy: 3.4%, 45 Gy: 0.0%; $p=0.39$), other grade 3-4 toxicity or treatment related deaths. The 60 Gy group had numerically longer PFS (median PFS 60 Gy: 18.6 months [95% CI 11.6-25.6], 45 Gy: 10.9 months [95% CI 8.7-13.2], HR 0.76 [95% CI 0.53-1.08]; $p=0.13$). Results for the primary endpoint remain unchanged. The higher TRT dose significantly prolonged survival (median OS 60 Gy: 43.5 months [95% CI 30.4-56.6], 45 Gy: 22.6 months [95% CI 17.2-28.0], HR 0.69 [0.48-0.99]; $p=0.043$) and provided higher 4.5 year survival rate (60 Gy: 41.6% [95% CI 30.4-56.6], 45 Gy: 28.4% [95% CI 18.9-39.5], OR: 1.79 [95% CI 0.95-3.41]). 5-year survival rates will be presented at the meeting. **Conclusions:** Compared with LS SCLC patients who received standard TRT, patients receiving high-dose BID TRT of 60 Gy did not experience more toxicity, had a substantial prolongation of survival and a much higher long term survival rate. Clinical trial information: NCT02041845. Research Sponsor: The Norwegian Cancer Society; Norwegian University of Science and Technology; The Liaison Committee for Education, Research and Innovation in Central Norway.

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Poster Discussion Session

The prognostic value of patient reported outcomes (PROs) and clinical/demographic variables in the CASPIAN study. *First Author: Apar Kishor Ganti, University of Nebraska Medical Center, Omaha, NE*

Background: PROs have been shown to predict outcomes in non-small cell lung cancer and, using the FACT-G PRO instrument, in extensive stage small cell lung cancer (ES-SCLC). This study explored the relationships between EORTC QLQ-C30 domains and overall survival (OS) and progression free survival (PFS) in the phase III ES-SCLC CASPIAN trial, with and without adjustments for treatment (tx) and baseline clinical and demographic variables. **Methods:** CASPIAN had 3 treatment arms: durvalumab plus platinum-etoposide; durvalumab plus tremelimumab plus platinum-etoposide; and platinum-etoposide alone. It included the EORTC QLQ-C30, a PRO instrument consisting of 5 functioning scales (physical, role, emotional, cognitive, social), a global health status/quality of life (QoL) scale, 3 symptom scales (fatigue, nausea/vomiting, pain), 5 single item symptom assessments (dyspnea, insomnia, appetite loss, constipation, diarrhea) and a single financial difficulties item. Higher functional and QoL scores indicate better health status/function (anticipated positive OS/PFS associations) while higher symptom and financial difficulty scores represent a greater burden (anticipated negative OS/PFS associations). Baseline PRO scores were pooled across the 3 CASPIAN arms to obtain the most PRO information and used in 3 Cox proportional hazard models for OS and PFS: (A) scores only, (B) scores with a tx category for each CASPIAN arm, and (C) scores with tx categories and other baseline covariates (sex, age [< 65 , ≥ 65], ECOG performance status [0, > 1], smoker [Y/N], CNS metastasis [Y/N], race [Asian, non-Asian], stage [III, IV], region [Asia, Europe, North and South America]). Models B and C were stratified by the type of platinum received. Backwards selection found the set of variables most associated with OS and PFS. There was no correction for multiplicity and nominal P-values < 0.05 were used to assess importance. **Results:** The outcomes and models associated with more favorable baseline PRO scale/item scores were: (i) better OS and PFS across all 3 Cox models [physical, role, social, QoL, fatigue, pain]; (ii) better OS [emotional (models A,C), nausea/vomiting (model C), dyspnea (model C)], and (iii) better PFS [emotional (model C), financial difficulties (models A,B,C)]. Among the 90 estimated Cox hazard ratios, 82 had the anticipated directions for OS and PFS with 54/90 of the estimates having $P < 0.05$. In each Cox model, more favorable baseline diarrhea scores were associated with reduced OS. All 15 baseline PRO score domains for OS and 10/15 for PFS were important in the stepwise selection process. **Conclusions:** The results largely indicate that baseline PROs had prognostic value in the CASPIAN trial across different specifications, some including tx and baseline clinical and demographic values. A better understanding of the relationship between tx and PROs may aid tx decisions. Clinical trial information: NCT03043872. Research Sponsor: AstraZeneca.

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Poster Discussion Session

CRES³T: A single-arm confirmatory trial of S-1 plus cisplatin with concurrent radical-dose radiotherapy followed by surgery for superior sulcus tumor. *First Author: Kazuya Takamochi, Department of General Thoracic Surgery, Juntendo University School of Medicine, Tokyo, Japan*

Background: A multicenter, single-arm, confirmatory trial (CRES³T) was conducted to investigate the efficacy and safety of S-1 plus cisplatin and concurrent radical-dose thoracic radiotherapy (TRT) followed by surgery in patients with superior sulcus tumor (SST). To date, no clinical trials on radical-dose TRT in the induction setting for SST have been conducted. **Methods:** SST was defined as a tumor that directly invades the chest wall including the first rib or more cephalad, subclavian artery, or subclavian vein according to CT or MRI scans. Eligible patients were 20 to 75 years old and had pathologically proven non-small cell lung cancer, performance status of 0-1, and no history of prior treatment. The patients received induction therapy consisting of three cycles of S-1 plus cisplatin with concurrent TRT (66 Gy in 33 fractions) followed by surgery. S-1 was administered orally at 40 mg/m² twice per day, on days 1-14 along with an intravenous infusion of cisplatin (60 mg/m²) on day 1. The treatment cycles were repeated every four weeks. The primary endpoint was the 3-year overall survival (OS) rate, and key secondary endpoints included progression-free survival (PFS) rate, objective response rate (ORR), pathological complete remission (pCR) rate, and toxicity. **Results:** Between June 2014 and March 2019, 61 patients registered and received induction therapy. Pathological diagnoses were 30 adenocarcinoma, 20 squamous cell carcinoma, and 11 others. Radiologically diagnosed tumor invasion sites were the chest wall ($n=57$), subclavian artery ($n=18$), and subclavian vein ($n=10$). One patient with distant metastasis that manifested after starting induction therapy was removed from this study. Forty-nine patients underwent lobectomy and resection of the involved sites. The complete resection rate was 98% (48/49). Median follow-up time was 54 months. The 3-year OS and PFS rates were 73% (95% CI: 60-83%) and 53% (95% CI: 40-65%), respectively. The ORR and pCR rate were 42% (25/60, 95% CI: 29-54%) and 33% (16/49, 95% CI: 20-46%), respectively. Grade (G) 3 or 4 toxicities during induction therapy included neutropenia (28%), anemia (13%), thrombocytopenia (5%), and hyponatremia (8%). Two (3%) cases of pneumonia resulted in death. G3 surgical complications such as supraventricular arrhythmia, chylothorax, pleural effusion, pneumonia, mediastinitis, wound infection, and arm neuropathy developed in one (2%) patient each. One (2%) cardiac arrest on postoperative day 3 resulted in death. **Conclusions:** CRES³T demonstrated that induction therapy using S-1 plus cisplatin and concurrent radical-dose TRT followed by surgery was safe and effective in treating SST. Therefore, this strategy is potentially a new standard treatment for SST. (UMIN: 000014386, JRCT: s031180401). Clinical trial information: UMIN000014386. Research Sponsor: None.

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Poster Discussion Session

Phase II study of durvalumab plus olaparib as maintenance therapy in extensive-stage small-cell lung cancer (TRIDENT): Preliminary efficacy and safety results. *First Author: Yan Huang, State Key Laboratory of Oncology in South China, Guangzhou, China*

Background: First-line durvalumab in extensive-stage small-cell lung cancer (ES-SCLC) demonstrated significant improvement of OS in phase III CASPIAN trial. PARP inhibitors have the potential to confer antitumor activity, modify tumor immunogenicity, and sensitize tumors to anti-PD-1/PD-L1 therapy. Durvalumab in combination with Olaparib (a PARPi) had clinical activity in relapsed SCLC in a phase I/II study. This phase II study aimed to assess the efficacy and safety of durvalumab plus olaparib as maintenance therapy in patients with ES-SCLC. **Methods:** TRIDENT is a single arm, multicenter, phase II study. Treatment-naïve ES-SCLC aged ≥ 18 with ECOG PS 0-2 were eligible. Durvalumab (1500 mg) was concurrently administered with platinum-etoposide every 3 weeks for 4 cycles, followed by durvalumab 1500 mg every 4 weeks plus olaparib 300 mg twice daily until disease progression or unacceptable toxicity. The primary endpoint was the rate of progression free survival (PFS) at 12 months, the secondary endpoints included progression free survival, objective response rate (ORR) according to RECIST 1.1, duration of response (DoR), overall survival (OS) and safety profile. All patients should provide tumor sample for biomarker analysis (exploratory endpoint). **Results:** Between August 2021 and August 2022, 60 eligible patients were enrolled from 4 sites in China. At data cut-off (Jan 16th, 2023), 18 (30%) patients were still on treatment. The median age was 63 years (range 57-68). The median cycle of durvalumab was 7 (range 1-17), and durvalumab plus olaparib as maintenance therapy was 3.5 (range 1-13). The PFS rate at 6-, 9-, 12-month were 49.7% [95%CI 37.8%-65.4%], 26.3% [95%CI 13.8%-40.3%] and 18% [95%CI 9.3%-34.7%], respectively. ORR was 75% (45/60), the median DoR was 5.0 months [95%CI 3.8-6.5]. With a median follow-up of 10.5 months, the median PFS was 5.8 months [95%CI 4.9-7.7] as calculated from the first cycle of durvalumab plus chemotherapy. The median OS was not reached [95%CI 10-NA]. Of all, treatment emergent adverse event (AE) occurred in 93.3% (56/60) patients, and AEs $\geq$ grade 3 occurred in 36.7% (22/60) patients. There were no unexpected adverse events identified in this study. There were 5 patients (8.3%) discontinued treatment and 1 death (1.6%) due to AE. Biomarker analysis is still on-going and will be presented in the meeting. **Conclusions:** TRIDENT is the first study to evaluate the efficacy and safety of durvalumab plus olaparib as maintenance therapy in Chinese ES-SCLC patients to date. The preliminary result warrant further investigation of this treatment modality in ES-SCLC. Clinical trial information: NCT05245994. Research Sponsor: This study is sponsored by Sun Yat-sen University Cancer Center; This study is partly supported by AstraZeneca.

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Poster Discussion Session

Associations between patient-reported nutritional status, survival, and toxicity among patients with limited stage small-cell lung cancer (LS SCLC) in a randomized trial of high-dose, twice-daily (BID) thoracic radiotherapy (TRT).
First Author: Evgenia Taranova, University of Bergen, Bergen, Norway

Background: Up to 1/3 of LS SCLC patients are cured by chemoradiotherapy (CRT), but severe toxicity is frequent and population-based studies show that many patients do not receive standard CRT. More knowledge on how to predict who experiences side-effects or achieves long term disease control is needed. Poor nutritional status is strongly associated with inferior survival in many types of cancer including non-small cell lung cancer, but little is known about whether this is the case in LS SCLC. We investigated whether nutritional status reported by patients on the Patient-Generated Subjective Global Assessment Short Form (PG-SGA SF) was associated with toxicity and survival among participants in a trial comparing high dose with standard dose twice-daily TRT in LS-SCLC (NCT02041845, n=170). **Methods:** Patients received four courses of platinum/etoposide chemotherapy and were randomized to TRT of 60 Gy/40 fractions or 45 Gy/30 fractions. Patients completed PG-SGA SF before treatment commenced and were categorized as having low (PG-SGA SF score 0–3.9), intermediate (4.0–8.9) and high (≥9) risk of malnutrition. Toxicity was graded according to CTCAE 4.0. Median follow-up for survival was 49 months. **Results:** 113/170 (66.5%) patients completed PG-SGA SF at baseline. Median age was 65 years, 46.0% were men, 88.5% had PS 0-1, 87.6% stage III disease and 22.1% weight loss of >5% the three months before inclusion. Median PG-SGA SF score was 3.0, 52.2% of patients had low, 29.2% intermediate, and 18.6% high risk of malnutrition. Numerically, there were more patients with stage III, PS 1-2 and pleural fluid among those at high risk. There was no difference in mean no. of chemotherapy courses (low: 3.85, intermediate: 3.88, high: 3.90, p=0.95) or TRT completion (low: 96.6%, intermediate: 97.0%, high: 95.2%, p=1.0). There were no statistically significant differences in proportions who experienced grade 3-4 toxicity (low: 88%, intermediate: 91%, high: 86%, p=0.86), median PFS (low: 15.1 months, intermediate: 11.8 months, high: NR, p=0.23), 2-year survival (low: 68%, intermediate: 52%, high: 67%, p=0.28) or median OS (low: 38.1 months, intermediate: 25.8 months, high: NR, p=0.15). Patients with weight loss >5% did not experience more grade 3-4 toxicity (92% vs. 87%, p=0.73), had similar median PFS (24.0 vs. 15.9 months, p=0.69), 2-year survival (64.0% vs. 66.2%, p=0.84) and median OS (30.6 vs. 35.1 months, p=0.93) as those without. **Conclusions:** Our study suggest that LS SCLC patients tolerate and should receive concurrent chemotherapy and twice-daily TRT regardless of nutritional status and weight loss. Research Sponsor: University of Bergen; Norwegian Cancer Society; The Liaison Committee for education, research and innovation in Central Norway; Norwegian University of Science and Technology; the Nordic Cancer Union.

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Poster Discussion Session

Clinical outcomes with neoadjuvant nivolumab (N) + chemotherapy (C) vs C by definitive surgery in patients (pts) with resectable NSCLC: 3-y results from the phase 3 CheckMate 816 trial. *First Author: Jonathan Spicer, McGill University Health Center, Montreal, QC, Canada*

Background: In CheckMate 816, neoadjuvant N + C demonstrated statistically significant and clinically meaningful improvements in event-free survival (EFS) and pathologic complete response (pCR) vs C in pts with resectable NSCLC. Here, we report clinical outcomes in pts with or without definitive surgery following neoadjuvant treatment (tx). **Methods:** Adults with stage IB (tumors ≥ 4 cm) to IIIA (per AJCC 7th ed) resectable NSCLC, ECOG PS ≤ 1, and no known EGFR/ALK mutations were randomized 1:1 to 3 cycles of N 360 mg + C Q3W or C Q3W, followed by definitive surgery within 6 wk of tx. Primary endpoints were EFS and pCR, both per blinded independent review. Exploratory analyses included EFS (secondary definition; no censoring for subsequent tx), time to death or distant metastasis (TTDM), and DFS2 (EFS on next-line tx) in pts with or without surgery. **Results:** Among 358 randomized pts, 149 (83%; N + C) and 135 (75%; C) had definitive surgery. Baseline characteristics were similar in pts with or without surgery (N + C, 30; C, 44) and between tx arms, except that a higher proportion of pts who did not have surgery had ECOG PS 1 (both arms) or were from Europe (N + C arm). Surgery was canceled due to progressive disease (PD) in 11 (N + C) and 17 (C) pts; PD was locoregional in 4 and 15 pts and distant in 3 and 2 pts, while 4 pts in the N + C arm had both locoregional and distant PD. At database lock (October 14, 2022; median f/u: 41.4 mo), EFS, TTDM, and DFS2 were numerically improved in pts with vs without surgery, regardless of tx arm. In pts with surgery, median TTDM was not reached (NR) vs 46.8 mo (HR, 0.55) with N + C vs C, respectively; 3-y TTDM rates were 77% vs 59%. In pts without surgery, median TTDM was 24.8 vs 15.6 mo (HR, 0.63) with N + C vs C; 3-y rates were 36% vs 13%. Among pts without surgery, 17 (57%) vs 28 (64%) pts in the N + C vs C arms, respectively, received subsequent tx: radiotherapy 37% vs 41%; surgery 3% vs 2%; systemic tx 50% vs 52%. Grade 3/4 tx-related AEs occurred in 38% (N + C) and 36% (C) in pts with surgery, and 26% and 46% in pts without surgery. **Conclusions:** In CheckMate 816, neoadjuvant N + C demonstrated long-term clinical benefit vs C in pts with resectable NSCLC who received definitive surgery. In pts who did not receive definitive surgery, these exploratory analyses showed that neoadjuvant N + C was associated with numerically improved TTDM. Clinical trial information: NCT02998528. Research Sponsor: Bristol Myers Squibb.

	With surgery			Without surgery		
	N + C (n = 149)	C (n = 135)	HR (95% CI) N + C vs C	N + C (n = 30)	C (n = 44)	HR (95% CI) N + C vs C
mEFS,* mo (95% CI)	NR (44.4–NR)	31.8 (18.0–NR)	0.67 (0.47–0.95)	6.7 (2.7–24.9)	4.1 (2.5–11.2)	0.75 (0.44–1.28)
3-y EFS rate, %	62	49	–	8	10	–
mTTDM, mo (95% CI)	NR (34.3–NR)	46.8 (34.3–NR)	0.55 (0.36–0.84)	24.8 (6.7–37.8)	15.6 (11.2–18.6)	0.63 (0.34–1.13)
3-y TTDM rate, %	77	59	–	36	13	–
mEFS2, mo (95% CI)	NR	NR	0.60 (0.39–0.95)	12.3 (8.4–37.8)	15.5 (10.2–18.6)	0.94 (0.53–1.66)
3-y EFS2 rate, %	80	69	–	33	24	–

*Secondary definition. m, median.

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Poster Discussion Session

Pembrolizumab vs placebo for early-stage non–small-cell lung cancer after resection and adjuvant therapy: Subgroup analysis of patients who received adjuvant chemotherapy in the phase 3 PEARLS/KEYNOTE-091 study. *First Author: Kersti Oselin, North Estonia Medical Centre, Tallinn, Estonia*

Background: In the randomized, triple-blind, phase 3 PEARLS/KEYNOTE-091 study (NCT02504372), at the second interim analysis, pembrolizumab (pembro) significantly prolonged DFS vs placebo (pbo) in the overall population of patients (pts) with completely resected stage IB–IIIA NSCLC per AJCC v7 who may or may not have received adjuvant chemotherapy (chemo; up to 4 cycles) as recommended per local guidelines (n = 1177; HR, 0.76 [95% CI, 0.63–0.91]; P = 0.0014). Here we present outcomes for those pts who received 1–4 cycles of prior adjuvant chemo, per protocol. **Methods:** Eligible adults had pathologically confirmed, completely resected stage IB (T ≥ 4 cm), II, or IIIA NSCLC (AJCC v7) of any PD-L1 expression, ECOG performance status of 0 or 1, and had not received neoadjuvant radiotherapy or chemo. Pts were randomized 1:1 to pembro 200 mg or pbo Q3W for 18 doses (~1 year); receipt of adjuvant chemo (yes vs no) was one of the stratification factors. Dual primary endpoints were DFS in the ITT and PD-L1 TPS ≥50% populations. No alpha was assigned to this subgroup analysis of pts who received adjuvant chemo for 1–4 cycles per local guidelines. **Results:** Of 1177 pts in the ITT population, 1010 (85.8%) received adjuvant chemo and were included in this analysis (pembro, n = 506; pbo, n = 504). Pts received a median of 17 and 18 study doses, respectively. As of data cutoff (Sep 20, 2021), 52.6% in the pembro arm vs 64.9% in the pbo arm had completed treatment. Median time from randomization to data cutoff was 37.4 mo. Median (95% CI) DFS was 58.7 mo (39.2 mo–not reached [NR]) in the pembro arm vs 34.9 mo (28.6 mo–NR) in the pbo arm (HR, 0.73 [95% CI, 0.60–0.89]). Estimated 18-mo DFS rates were 73.8% and 63.1%, respectively. In pts with PD-L1 TPS ≥50% (pembro, n = 143; pbo, n = 141), median DFS was NR in both treatment arms (HR, 0.80 [95% CI, 0.54–1.20]). Grade 3–5 adverse events (AEs) occurred in 170 pts (34.3%) in the pembro arm and 128 (25.7%) in the pbo arm (grade 5, 2.2% vs 1.0%). Immune-mediated AEs and infusion reactions occurred in 195 pts (39.3%) in the pembro arm and 69 (13.8%) in the pbo arm. **Conclusions:** Consistent with the ITT population, pembro substantially improved DFS vs pbo in the subgroup of pts with stage IB (T2a ≥ 4 cm), II, or IIIA NSCLC who received adjuvant platinum-based chemo following complete resection. Based on these results, pembro was approved for adjuvant treatment in this pt population by the US FDA. Clinical trial information: NCT02504372. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

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Poster Discussion Session

IMpower010: Exploratory analysis of disease-free survival by KRAS status in patients with stage II-IIIA NSCLC treated with adjuvant atezolizumab vs best supportive care. *First Author: Martin Reck, Lung Clinic Grosshansdorf, Airway Research Center North, German Center of Lung Research, Grosshansdorf, Germany*

Background: The Phase III IMpower010 trial (NCT02486718) met its primary disease-free survival (DFS) endpoint leading to approval of atezolizumab after adjuvant platinum-based chemotherapy for completely resected PD-L1 TC ≥1% or ≥50% stage II-IIIA NSCLC in the US, EU and other regions. Mutant KRAS (mKRAS) is the most prevalent oncogenic driver in metastatic NSCLC (27% mKRAS [KRAS G12C, 11%]; Osta et al, J Thorac Oncol 2019). Here, we report exploratory DFS outcomes by KRAS mutational status in patients from IMpower010. **Methods:** The study design and primary results of IMpower010 have been reported (Felip et al, Lancet 2021). After complete resection, patients received cisplatin-based doublet chemotherapy (1-4 21-day cycles) and were subsequently randomized to receive atezolizumab 1200 mg q3w (16 cycles) or best supportive care (BSC). This post hoc analysis evaluated DFS in subgroups of patients by KRAS mutational status. KRAS mutational status was assessed retrospectively using whole-exome sequencing (WES) on resected tumor tissue. Analyses were conducted in patients whose tumors harbored any mKRAS type, including G12C. A separate analysis of the KRAS G12C subgroup was not conducted due to limited patient numbers. **Results:** Of the 1005 patients in the intention-to-treat population (all randomized patients with stage IB-IIIA NSCLC), 603 comprised the WES biomarker-evaluable population (WES-BEP), and of these, 536 had stage II-IIIA NSCLC. Within the stage II-IIIA WES-BEP, the prevalence of mKRAS and KRAS G12C was 22% (n=118) and 10% (n=52), respectively. mKRAS was enriched in White, non-squamous and smoker populations. Atezolizumab showed DFS improvement vs BSC regardless of KRAS status in the stage II-IIIA WES-BEP (Table). In the mKRAS stage II-IIIA WES-BEP, atezolizumab showed DFS improvement vs BSC regardless of PD-L1 status. **Conclusions:** In IMpower010, the prevalence of mKRAS and KRAS G12C was similar to that seen in metastatic NSCLC. Despite limited patient numbers in this exploratory analysis, DFS appeared to be consistent and in favor of atezolizumab across subgroups regardless of KRAS status. Clinical trial information: NCT02486718. Research Sponsor: F. Hoffman-La Roche, Ltd.

	Atezolizumab median DFS, mo	BSC median DFS, mo	DFS HR (vs BSC) 95% CI
Stage II-IIIA WES-BEP	NR n=270	31.4 n=266	0.70 0.54, 0.91
KRAS WT stage II-IIIA WES-BEP	42.3 n=208	31.4 n=210	0.74 0.55, 1.00
mKRAS stage II-IIIA WES-BEP	NR n=62	25.2 n=56	0.56 0.32, 0.99
mKRAS SP263-evaluable stage II-IIIA WES-BEP	NR n=61	25.2 n=56	0.57 0.32, 1.02
mKRAS SP263-evaluable PD-L1 TC ≥1% stage II-IIIA WES-BEP	NR n=39	21.7 n=32	0.52 0.25, 1.08
mKRAS SP263-evaluable PD-L1 TC <1% stage II-IIIA WES-BEP	NR n=22	31.6 n=24	0.67 0.26, 1.73

NR, not reached; WT, wild type.

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Poster Discussion Session

Response to neoadjuvant immune checkpoint inhibitor (ICI)-based therapy in oncogene-driven resectable non-small cell lung cancer (NSCLC). *First Author: Samuel Rosner, Johns Hopkins University, Baltimore, MD*

Background: Neoadjuvant (NEO) chemotherapy (chemo) plus nivolumab (nivo) has received FDA approval for treatment of resectable NSCLC, demonstrating superior event-free survival compared to chemo alone. However, outcomes of NEO ICI-based therapies in patients (pts) with oncogene-driven (OD)-NSCLC remains an unanswered question. **Methods:** We conducted a retrospective secondary analysis of pts enrolled in the clinical trial NCT02259621 with clinical stage I-IIIa NSCLC, treated with NEO ICI-based therapies: nivo alone, nivo+ipilimumab (ipi), or nivo+chemo followed by surgery. Pts underwent baseline genomic profiling using NGS. Pts with *KRAS*, *EGFR*, *MET*, *BRAF*, *ALK*, *HER2*, *ROS1*, *RET* or *NTRK* alterations were identified as OD-NSCLC. *STK11* and *KEAP1* mutations (mut) were also recorded. For pts who underwent definitive resection (DR) and baseline NGS testing, association of OD-status and clinical outcomes, including major pathologic response (MPR) and recurrence-free survival (RFS) are reported. Proportions are reported with exact 95% binomial confidence intervals (CI). Binomial probabilities are compared with Chi-square or Fisher's exact tests. RFS and median follow-up (f/u) are reported using the Kaplan-Meier (KM) and reverse KM methods, respectively. **Results:** 61 pts received NEO ICI-based therapy: 60% treated with nivo alone, 15% with ipi+nivo and 25% with chemo+nivo. 92% of pts underwent DR. Pathologic complete response (pCR) and MPR rates were, 12.5% and 37.5%, respectively. Baseline NGS testing was available for 47 pts, of whom, 49% had OD-NSCLC, with the majority (78%) harboring a *KRAS* mut. Additional OD alterations included non-classical *EGFR* (9%), *MET* skipping (9%) and *ROS1* fusion (4%), of whom, 3/5 pts had a MPR after NEO-ICI. *STK11* muts were noted in 16% pts, and co-altered with *KRAS* in 9%. Median f/u for OD-NSCLC was 42.58 months. Pts with OD-NSCLC had comparable RFS after NEO-ICI compared to those with non-OD-NSCLC (HR 0.64, CI 0.19-2.13, $p=0.5$), including those with *KRAS*+ disease (HR 0.73, CI 0.2-2.73, $p=0.6$). Pts with co-mut *KRAS*+*STK11*+ trended toward shorter RFS compared to *KRAS*+*STK11*- (HR 6.36, CI 0.56-72.82, $p=0.1$). *STK11*+ also trended toward shorter RFS without reaching statistical significance (HR 2.51, CI 0.67-9.35, $p=0.17$). No significant associations between OD-status and MPR rates were seen, however *KRAS*+ (4/18) vs. *KRAS*- (13/29) trended toward lower MPR rate ($p=0.1$). Four of 5 pts with disease progression preventing DR harbored an *STK11* or *KEAP1* mut. **Conclusions:** Findings from this cohort treated with various NEO ICI-based therapies, suggests comparable RFS, regardless of OD status with the majority harboring *KRAS* muts. Lower MPR rates were observed for pts with *KRAS*+ tumors. *STK11* mut and *KRAS*+*STK11*+ co-mut status both trended toward shorter RFS, though definitive conclusions are limited by cohort size and treatment heterogeneity. Research Sponsor: BMS; Stand Up 2 Cancer (SU2C).

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Poster Session

Safety and efficacy of QL1706 plus carboplatin/etoposide (EC) as first-line (1L) treatment for extensive-stage small-cell lung cancer (ES-SCLC): The results from a phase II single-arm study. *First Author: Yun Fan, Zhejiang Cancer Hospital, Hangzhou, China*

Background: Although the combination of PD-L1 inhibitor and platinum-etoposide chemotherapy has been the preferred 1L treatment for patients (pts) with ES-SCLC, the clinical benefit of the addition of PD-L1 inhibitor was still modest. QL1706 is a novel bifunctional antibody, containing a mixture of anti-PD-1 IgG4 and anti-CTLA-4 IgG1 antibodies produced by MabPair. In phase I trials, QL1706 monotherapy has shown promising antitumor efficacy in nasopharynx cancer and cervical cancer, as well as other advanced solid tumors including SCLC (to be published). This study aims to assess the safety and efficacy of QL1706 plus EC in treatment-naïve ES-SCLC. **Methods:** In this phase II, open-label, single-arm, multi-center study, eligible pts (18-75 years, ECOG 0-1) received 4-6 cycles of QL1706 (5mg/kg, IV, Q3W) plus EC (etoposide, 100 mg/m², D1-3, Q3W; carboplatin, AUC = 5, D1, Q3W), followed by the maintenance therapy of QL1706 until disease progression, intolerable toxicity or other discontinuation events defined in the study protocol. Tumor imaging was performed every 6 weeks for the first year and every 9 weeks thereafter. The primary endpoint is safety. **Results:** From Apr 18, 2022 to Jul 27, 2022, a total of 40 pts were enrolled with a median age of 58.5 years (range, 38–73). 87.5% pts were men, 80% were smokers and 90% had ECOG PS of 1. As of data cutoff (Jan 16, 2023), the median QL1706-treatment duration was 5.9 (range, 0.7–8.9) mo. Twenty pts remained on treatment and 20 pts discontinued due to progressive disease (16, 40.0%) or patient decision (4, 10.0%). Thirty-two (80.0%) pts had at least one TRAE (QL1706-related). Fifteen (37.5%) pts experienced grade 3-4 TRAEs, including neutropenia (8, 20%), thrombocytopenia (4, 10%), anemia (3, 7.5%), WBC count decreased (2, 5.0%), AST increased (2, 5.0%), ALT increased (1, 2.5%), gamma-GT increased (1, 2.5%), rash (1, 2.5%), and diarrhea (1, 2.5%). No grade 5 TRAE occurred. No AE led to discontinuation of any treatment. Of the 39 pts who had at least 1 post-baseline tumor assessment, 37 achieved PR (35 confirmed and 2 unconfirmed) and 1 achieved SD. Thus, the confirmed ORR was 89.7% (95% CI, 75.8%–97.1%), and the DCR was 97.4% (95% CI, 86.5%–99.9%) (per RECIST v1.1). The mDoR was 4.5 (95% CI, 4.2–not evaluable) mo, with the longest response duration more than 7.2 mo and ongoing. The mPFS was 5.7 (95% CI, 5.4–7.1) mo, together with 3 mo- and 6 mo-PFS rates of 94.8 (95% CI, 80.8–98.7%) and 44.7% (95% CI, 27.3–60.6%), respectively. With a median follow-up time for OS of 6.2 mo, the mOS has not been reached. **Conclusions:** QL1706 plus EC chemotherapy showed tolerable safety profile and promising efficacy as first-line treatment for pts with ES-SCLC. These data support further clinical development of QL1706 in ES-SCLC. Clinical trial information: NCT05309629. Research Sponsor: Qilu Pharmaceutical Co., Ltd.

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Poster Session

Predictive value of co-existing genetic alterations and tumor mutation burden for patients with completely resected non-small cell lung cancer harboring EGFR mutation: Biomarker analysis of phase III IMPACT study. *First Author: Satoshi Ikeda, Kanagawa Cardiovascular and Respiratory Center, Yokohama, Japan*

Background: Although osimertinib has recently become an option for adjuvant therapy in many countries, biomarkers predicting the efficacy of adjuvant EGFR-TKI and the risk of postoperative recurrence in completely resected NSCLC harboring EGFR mutations have not been fully investigated. **Methods:** This IMPACT-TR study is an exploratory biomarker study for completely resected, EGFR-mutated NSCLC patients who received gefitinib or cisplatin plus vinorelbine (cis/vin) in a phase III IMPACT study (Trial registration number: UMIN000044738. Funding: AstraZeneca K.K.). Surgically resected lung cancer tissue specimens were analyzed for co-existing somatic mutations and tumor mutation burden (TMB) determined by OncoPrint Tumor Mutation Load, and these data were matched with disease free survival (DFS) and overall survival (OS) data. **Results:** Of the 234 patients in the IMPACT study, 211 patients were enrolled, and 202 patients in the Per Protocol Set were analyzed. The most frequent co-existing somatic mutation was *TP53* (58.4%), followed by *CSMD3* (11.8%), *NOTCH1* (9.9%) and *SYNE1* (9.9%). The median TMB was 6.67 mutations/Mb, and only 15.2% had ≥ 10 mutations/Mb. EGFR mutation subtypes, *TP53* co-mutation and TMB were not associated with DFS or OS in either the gefitinib or cis/vin groups. In the gefitinib group, patients with *NOTCH1* mutation had significantly shorter OS (hazard ratio [HR] 4.18, 95%CI 1.65-10.61, $p=0.003$) and tended to have shorter DFS (HR 1.44, 95%CI 0.62-3.37, $p=0.399$) than those without *NOTCH1* mutation. In the cis/vin group, patients with *CREBBP* mutation had significantly shorter DFS (HR 2.70, 95%CI 1.05-6.97, $p=0.040$) and tended to have shorter OS (HR 3.05, 95%CI 0.90-10.37, $p=0.074$) than those without *CREBBP* mutation. **Conclusions:** This study suggested that *NOTCH1* mutation may be a biomarker to predict poor response to adjuvant gefitinib and *CREBBP* mutation to predict poor response to cis/vin in patients with completely resected, EGFR-mutated NSCLC. Clinical trial information: UMIN000044738. Research Sponsor: AstraZeneca K.K.

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Poster Session

Clinical and financial implications of ADURA trial on a real-world population. *First Author: Bharathi Muthusamy, Cleveland Clinic, Cleveland, OH*

Background: In the ADAURA trial, adjuvant (adj) osimertinib improved disease free survival (DFS) in resected, EGFR-mutant (*EGFRm*) Stage IB-IIIa NSCLC compared to placebo. Based on these results, the FDA approved osimertinib in the adj setting. In this study, we have evaluated the hypothetical clinical and financial effects of adj osimertinib on the early-stage, *EGFRm* NSCLC patients at Cleveland Clinic who were treated prior to the FDA approval. **Methods:** Starting in 2010, Cleveland Clinic has been performing targeted molecular testing in all resected NSCLCs. With this information, we created a database of patients from 01/2010 to 01/2021 with resected, non-squamous NSCLC. The standard of care (SOC) arm of this study consisted of patients with stage IB-IIIa, *EGFRm* disease from our internal database. Data for the adj osimertinib arm were obtained through a microsimulation study by first generating the per-stage DFS distribution in the SOC arm, and then applying the per-stage hazard ratios from ADAURA to obtain the parameters of the exponential DFS distribution with osimertinib treatment. Outcomes and costs, such as treatment and imaging, were directly calculated for the SOC arm based on the amount of time each patient spent in a recurrence-free or recurrent state, and whether there was CNS involvement at recurrence. Costs and outcomes were averaged across 1000 simulated datasets for the osimertinib arm. Based on ADAURA we assumed that 78.4%, 16.2%, and 5.4% of DFS events were CNS- recurrence, CNS+ recurrence, or death. **Results:** 1,487 patients were included in the database. 724 of these patients had stage IB-IIIa disease and *EGFR* testing. 82 patients were *EGFRm*+ (exon 19 deletion or the L858R mutation), and their survival outcomes were used in the SOC arm. At 5 years, 32 (39%) of the patients were alive and disease free. With the addition of adj osimertinib, an estimated average of 61 (71.4%) of patients would have been disease free and alive. This corresponds to an average improvement in 5-year DFS of 35.4%. The cost of testing all 724 patients would have been \$2,865.80 per patient eligible for osimertinib with single-gene *EGFR* testing or \$5,279.11 per eligible patient with targeted NGS testing. The total treatment and healthcare costs with adj osimertinib in the 82 patients would have been \$49,057,952.75 or \$598,267.72 per patient. With SOC (surveillance +/- adj chemotherapy + osimertinib only upon recurrence), total and per patients costs were \$12,297,374.11 and \$149,967.98 respectively. This corresponds to an average increase in total costs of \$448,299.74 per person with the use of adj osimertinib. **Conclusions:** Over a decade at Cleveland Clinic, about 5.5% (1,487) patients with early stage NSCLC would have been affected by the adj osimertinib approval. In our simulation, we estimated adj osimertinib would have improved 5-year DFS by 35.4% (29 more patients) but with a significant financial cost of about \$450,000 per eligible patient. Research Sponsor: None.

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Poster Session

A study of tumor neoantigen burden and HLA-LOH by whole-exome sequencing to characterize immune biomarkers of lung cancer. *First Author: Wei Wang, Department of Thoracic Surgery, Renmin Hospital of Wuhan University, Wuhan, China*

Background: Lung cancer is a leading cause of cancer-related death worldwide. Precision immunotherapy, such as the use of immune checkpoint inhibitors (ICIs), has been shown to improve the survival of lung cancer patients. Cancer cells with high amount of neoantigens are more likely to be captured by immune cells and thus patients with high Tumor Mutation Burden (TMB) and high Tumor Neoantigen Burden (TNB) are estimated to be prone to ICIs treatment. HLA class I is one of the main factors affecting the prognosis of ICI in treatment. Studies have indicated that patients with highly heterozygous HLA-I are more likely to have better responses to ICI treatment. Some specific HLA-I genotypes and somatic mutations can affect the prognosis of ICIs treatment. **Methods:** In this study, we performed whole-exome sequencing (WES) of 200 pairs of tumor and gDNA samples from lung cancer patients. Tumor sample comes from tumor tissue or paraffin-embedded tissue and gDNA is extracted from white blood cells from *peripheral blood*. We analyze the WES data to obtain the TMB and HLA types of each sample. Then the peptide affinity of MHC-I genes were quantified based on IC50(nM) by netMHCpan software, and the level of neoantigen affinity were classified as strong ($IC50 \leq 50nM$), weak ($50nM < IC50 \leq 500nM$), and negative ($IC50 > 500nM$). TNB is defined as the number of high-affinity neoantigens per megabase of interrogated genomic sequence. Then we conducted linear regression analysis to study the statistical relationship between TMB and TNB. Finally, we analyzed the LOH status at the major region of HLA (HLA-A, HLA-B, and HLA-C) and classified the individuals who have LOH at all three types of HLA as HLA-LOH strong positive, samples with one or two LOH among the three HLA types as weak positive, and samples have no LOH are classified as HLA-LOH negative. **Results:** Among the 200 samples, the median value of TMB and TNB is 3.25 Muts/Mb and 1.09 Neos/Mb, respectively. 8.5% of the sample have high TMB ($TMB \geq 10$). TMB and TNB are also significantly positively correlated (p -value < 0.0001). For HLA typing, 82.0% HLA-A, 96.0% HLA-B, and 92.5% HLA-C are heterozygous. The dominant HLA types are: (A*11:01), (A*02:01), (B*46:01), (B*40:01), (C*01:02), and (C*07:02). As for LOH status among the three HLA types, 14.57% of the individuals are HLA-LOH strong positive, 31.66% are HLA-LOH weak positive, and 53.77% of the samples are HLA-LOH negative. Lastly, the average numbers of detected high-affinity neoantigens are statistically significantly related to the occurrence of HLA-LOH (Analysis of Variance p -value < 0.01). **Conclusions:** HLA-LOH occurs in nearly half of our lung cancer samples, and it is associated with TMB-High and TNB-High. The analysis of HLA-LOH refines the prediction of neoantigen and gain understanding of drug resistance and immunotherapy. Research Sponsor: None.

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Poster Session

Differential expression analysis of circRUNX1 in patients with early resected EGFR-mutant NSCLC. *First Author: Carlos Pedraz, Pangaea Oncology, Laboratory of Molecular Biology, Barcelona, Spain*

Background: In the ADAURA study, patients with stage IB-IIIA of resected EGFR mutated lung adenocarcinoma receiving adjuvant osimertinib had a 2-year survival of 89% versus 52% in the placebo group ($p < 0.001$), however, predictive markers of response and recurrence are still needed. Circular RNA (circRNA) is a type of RNA which forms a covalently closed continuous loop. Some circRNAs have been reported as essential for tumor cell proliferation through functions distinct from the canonical linear RNA. In this project, we studied circRNA expression levels in formalin-fixed paraffin-embedded (FFPE) lung tumor samples in order to explore potential biomarkers that could predict the benefit of adjuvant EGFR TKIs in EGFR-mutant NSCLC patients. **Methods:** FFPE tumor samples from patients with EGFR-mutant, stage I-IIIB NSCLC ($n=79$) were collected. RNA was purified using the High Pure FFPE RNA Isolation Kit (Qiagen) and quantified by Nanodrop 2000 (Thermo Scientific). A total of 250 ng of RNA were subjected to overnight hybridization and downstream nCounter processing (NanoString) following manufacturer's instructions for our circRNA custom panel. Differential expression analysis was performed using Excel (Microsoft) and Prism GraphPad (Dotmatics) software. **Results:** Analysis of the 79 samples included in the study shown a cluster of 3 circRNAs significantly upregulated ($p < 0.05$ and > 2 fold-change) in EGFR mutation-positive NSCLC relapsing within the 36 months after resection, including circRUNX1, circFUT8 and circAASDH. Disease-free survival (DFS) was significantly shorter for the subgroup of patients with high versus low circRUNX1 expression. Additional multivariate analysis identified circRUNX1 expression and tumor stage as the only statically significant prognostic factors (circRUNX1 hazard ratio = 4.480, confidence interval = 2.172-9.239, $P < 0.001$; pathological stage hazard ratio = 2.237, confidence interval = 1.183- 4.231, $P = 0.008$). **Conclusions:** CircRUNX1 could be a novel biomarker to predict the benefit of adjuvant EGFR TKIs with regards to DFS in EGFR-mutant resected NSCLC patients. Research Sponsor: None.

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Poster Session

Dynamic ctDNA to inform the precise management of resected NSCLC: LUNGCA-2 study. *First Author: Liang Xia, Institute of Thoracic Oncology and Department of Thoracic Surgery, West China Hospital, Sichuan University, Chengdu, China*

Background: Circulating tumor DNA (ctDNA) has been reported to be valuable for minimal residual disease (MRD) detection, but there is a lack of studies comprehensively assessing whether dynamic ctDNA monitoring can inform whole-course precise postoperative cancer management. In the present study (LUNGCA-2), we analyzed data obtained from longitudinal ctDNA monitoring of stage I-III NSCLC patients in the LUNGCA cohort, and sought to assess the use of dynamic ctDNA monitoring for precise whole-course postoperative management of NSCLC patients. **Methods:** All eligible NSCLC patients underwent curative-intent surgery and subsequently received adjuvant therapies when indicated by clinical practice guidelines for NSCLC. The clinical follow-up was scheduled to be every 3-6 months mainly involving CT and/or MRI. Fresh frozen or paraffin-embedded tissues of primary tumors were collected intraoperatively for baseline somatic mutation profiling. Blood samples were collected before surgery, at 3 days and 1 month after surgery, and then every 3-6 months at clinical visits up to 3 years postoperatively. 233 patients with a total of 2123 plasma samples were ultimately included in the longitudinal ctDNA analysis in the current study. NGS assays were performed with a custom-designed panel that covered 769 cancer-related genes via the MinerVA platform (Genecast Biotechnology Co., Ltd). **Results:** Among the cohort, 166 patients harboring targetable mutations in the primary tumor tissue, 15 were preadjuvant ctDNA positive, and among them, only 25% patients treated with adjuvant TKI therapy experienced relapse during follow-up, and patients received ACT or no adjuvant therapy had a relapse rate of 100%. TKI treatment tended to improve RFS compared with no treatment ($HR 0.1$, $P = 0.025$), but ACT failed to improve RFS ($HR 1.1$, $P = 0.834$). Among all 82 patients receiving adjuvant therapy, the pre- and post-adjuvant therapy postoperative ctDNA status with a negative-negative or positive-negative pattern had similar and favorable RFS ($P = 0.545$) but that patients with a positive-positive or negative-positive pattern had significantly inferior RFS than those with a negative-negative pattern (both $P < 0.001$). For recurrence monitoring, posttreatment ctDNA MRD status had a positive predictive value of 100% and a negative predictive value of 91.8%, and the sensitivity of MRD detection was affected by the organ of relapse. Among positive ctDNA MRD patients, faster increase of ctDNA concentration correlated with more imminent clinical relapse. The median lead time from ctDNA detection to radiological relapse was 273 days. Moreover, ctDNA negativity after relapse was associated with favorable survival. **Conclusions:** These findings highlight the clinical significance of ctDNA dynamics for the precise whole-course postsurgical management of NSCLC patients. Research Sponsor: the National Natural Science Foundation of China; the Major Research Project of Sichuan Province.

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Poster Session

Elucidating the genomic and transcriptomic landscape of L858R vs ex19del EGFR-mutated NSCLC. *First Author: Stephanie Pei Li Saw, National Cancer Centre Singapore, Singapore, Singapore*

Background: Epidermal growth factor receptor (EGFR)-mutated non-small cell lung cancer (NSCLC) is heterogeneous and L858R derive less benefit from osimertinib than ex19del in both the metastatic and adjuvant setting, which remains poorly understood. We sought to examine the genomic and transcriptomic features of L858R vs ex19del. **Methods:** Consecutive patients with AJCC7 Stage IA-IIIA EGFR-mutated NSCLC diagnosed 1/1/2010 – 31/12/2019 who underwent surgery at National Cancer Centre Singapore were included. Patients who received neoadjuvant therapy were excluded. Fresh frozen tumour and normal samples were subject to whole exome sequencing (WES) at 400X and 100X coverage respectively, with approximately 50 million paired-end reads for RNA-seq per sample. Wilcoxon and Fisher's exact test were used for association analysis. **Results:** A total of 203 patients were included. Median age at diagnosis was 66, 66.0% (134/203) were females and 84.2% (171/203) never-smokers. Stage IA comprised 44.3% (90/203), IB 28.6% (58/203), II 15.8% (32/203) and IIIA 11.3% (23/203). Median tumour mutational burden (TMB) was 1.3 mutations/megabase (range 0.3 – 44.3). Ex19del represented 46.3% (94/203) and L858R 41.9% (85/203). Whole genome doubling (WGD) was found in 70.0% (142/203) and was more common in TP53-mutated compared to TP53-wildtype (81.1% vs. 63.6%, $p=0.01$). TP53 mutations were more common in stage II/IIIA tumours compared with stage IB and IA (50.9% vs 32.8% vs 30.0%, $p=0.035$). Comparing ex19del and L858R, there was no difference in stage distribution ($p=0.337$), proportion of TMB ≥ 10 (1.1% vs 5.9%, $p=0.103$), number of cancer co-driver mutations ($p=0.174$), TP53 mutations (39.4% vs 32.9%, $p=0.437$) and WGD (69.1% vs 76.5%, $p=0.316$). L858R had a higher incidence of smoking mutational signature (median 0.35 vs 0.28, $p=0.018$) compared to ex19del despite similar smoking history (15.3% vs 12.8%, $p=0.67$), whereas APOBEC mutational signature was higher in ex19del (median 0.06 vs 0.04, $p=0.015$). L858R tumors were associated with a higher incidence of co-mutations in *RBM10* (21.2% vs 6.38%, $p=0.004$), *RNF213* (10.6% vs 1.06%, $p=0.007$) and amplification of *NTHL1* (15.3% vs 2.13%, $p=0.001$) and *AXIN1* (17.6% vs 3.19%, $p=0.002$) compared to ex19del. Transcriptomic subtype differed significantly by EGFR mutation with a higher representation of TRU subtype among L858R than ex19del (51.0% vs 35.3%, $p=0.010$), while GEP score was similar (median 0.189 vs 0.325, $p=0.122$). **Conclusions:** L858R have distinct co-mutations and copy number alterations compared to ex19del, in addition to a higher representation of smoking mutational signature and TRU subtype. TP53 co-mutations are more frequently observed in higher stage tumours and are associated with WGD. Our findings highlight the molecular heterogeneity of resected EGFR-mutated NSCLC, which could contribute to the differential outcomes to adjuvant osimertinib between ex19del and L858R. Research Sponsor: National Medical Research Council Singapore; Duke-National University of Singapore Oncology Academic Clinical Programme.

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Poster Session

Prevalence of *EGFR* mutations in patients with resected stage I-III non-squamous NSCLC: Results from the EARLY-EGFR study. *First Author: Ross A. Soo, National University Cancer Institute, National University Hospital, Singapore, Singapore*

Background: The prevalence of *EGFR* mutations (*EGFRm*) in resected stage I-III NSCLC remains controversial as prior research studies were retrospective in nature. EARLY-EGFR is the first prospective, international study to determine the prevalence of *EGFRm* and treatment patterns in patients (pts) with early-stage NSCLC. **Methods:** EARLY-EGFR (NCT04742192), a non-interventional real-world study, captured data on *EGFRm* status, treatment patterns, demographic, clinical and pathological characteristics in consecutively enrolled pts with surgically resected stage IA-IIIB (AJCC 8th) non-squamous NSCLC (Mar 2021 – Oct 2022). The primary endpoint was prevalence of *EGFRm* and secondary endpoints included prevalence of *EGFRm* subtypes and treatment patterns. **Results:** Of 601 pts (median [range] age: 62 [30-86] yrs) enrolled at 33 centers across Middle East and Africa (n=16), Latin America (n=80), and Asia (n=505), 317 (52.7%) were females, 354 (58.9%) were never smokers. The majority had stage IA-IB NSCLC (64.1%) involving right lung (62.9%), no nodal involvement (81.5%), T1a-T2b tumor (82.7%), adenocarcinoma histology (98.7%), and 105/420 (25.0%) tumors were poorly differentiated. About 23.3% (130/559) were diagnosed through a screening program; 60/539 (11.1%) reported family history of lung cancer. The overall prevalence of *EGFRm* was 50.7% (300/592). *Exon-19* deletions accounted for 50.3%, *L858R* mutations for 35.7%, and compound mutations for 2.3% of mutations. *EGFRm* tumors were found to be PD-L1 positive in 38.5% of cases (15/39). Women had higher *EGFRm* rate than men (63.6% vs 36.2%). Compared with *EGFR* wild type (*wt*), pts with *EGFRm* were more likely to be never smokers (39.5% vs 60.5%) and have stage I/II NSCLC (46.5% vs 53.5%) (Table). Of 216 stage I/II/III NSCLC pts, only 51.4% received systemic adjuvant therapy. Significantly higher *EGFRm* rates in stages I and II than in stage III NSCLC (p<0.001 and p=0.050) were found, while no significant difference was found between stages I and II NSCLC (p=0.158). **Conclusions:** In this first prospective, real-world study of *EGFRm* prevalence in resected NSCLC, stage III and smoking were independent predictors associated with decreased odds of *EGFRm*. The results highlight the need to adhere to ASCO adjuvant chemotherapy guidelines, as only half of stage II/III NSCLC pts received adjuvant systemic therapy. Clinical trial information: NCT04742192. Research Sponsor: AstraZeneca.

Proportion of <i>EGFRm</i> by smoking status, histology, and stage.					
Variables	Overall (N=601), n (%)	Comparison of mutation rate			
<i>EGFRm</i> (N=300), n	<i>EGFRm</i> (N=292), n	Mutation rate (%)	p-value		
Smoking status					
Current	37 (6.2)	9	25	26.5	<0.001*
Ex	150 (26.6)	58	101	36.5	
Never	354 (58.9)	211	138	60.5	
Histology					
Adenocarcinoma	592 (98.7)	296	288	50.7	0.502
Others	6 (1.3)	4	2	66.7	
Stage					
IA-B	385 (64.0)	210	170	55.3	0.002*
IIA-B	129 (21.5)	60	65	48.0	
IIIA-B	87 (14.5)	30	57	34.5	

Unknown/missing data not included *current and ex-smoker vs never smoker; †stage I and II vs stage III.

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Poster Session

Clinical validation of an activity-based enzyme assay for early stage lung cancer. *First Author: Paul W. Dempsey, Hawkeye Bio, Inc., Torrance, CA*

Background: The USPSTF guidelines recommend annual LDCT scans for 15.5 million adults with a heavy smoking history. While LDCT can reduce deaths by 20%, screening compliance remains low. A blood test with clinically useful, cost effective performance could improve compliance and access when integrated with the standard of care. We describe here a lyophilized nanosensor system for detecting protease enzyme activity in sera with clinically useful diagnostic activity in early stage lung cancer. We evaluated the performance of the assay by examination of prospectively collected sera for detection of cancer in high risk patients. **Methods:** Sera were obtained in multiple independent studies to include pathologically confirmed, treatment naive lung cancer patients and LDCT confirmed negative individuals. Protease activity was measured on 18 different nanosensors built with protease targets mainly selective for members of the Matrix Metalloproteinase and Cathepsin families. Lyophilized plates were incubated with serum and enzyme activity was measured indirectly as a continuous variable by a fluorescent plate reader. A machine learning modeling tool (Emerge) was used to detect signal associated with a cancer "fingerprint" of protease activity. The analysis stratified allocation into training and testing sets of 250 samples each and reserved a third out of sample validation set (250 samples) for reporting. **Results:** 750 clinical samples included 30% lung cancers, 63% males, 91% smokers, and an average age of 63 years (SD=9). Cancer cases were distributed across stages I (41%), II (17%), III (20%) and IV (20%) with 5% unknown. Histological classification included 59% adenocarcinoma, 31% squamous cell and 11% other subtypes. Using an EmERGE model with only nanosensor activity and gender as inputs, we evolved a balanced algorithm. The algorithm can be further modified to favor sensitivity or specificity depending on the application by applying model weighting factors. We report the performance observed in the 250 out of sample validation set at three points on this spectrum (Table). Among Stage I cancer samples, the balanced algorithm had an accuracy of 90% (26/29). **Conclusions:** Current LDCT tools show low compliance. We demonstrate clinical validity of a cost effective tool to detect lung cancer in support of LDCT screening. Based on a simple blood sample, the current test may predict early stage lung cancer with an accuracy of 90%. The performance suggests applications in LDCT compliance, post LDCT management, and eventually screening. A clinically validated version of this technology is being evaluated as a triage tool for LDCT screening. Research Sponsor: Hawkeye Bio, Inc.

	Specificity Max	Balanced	Sensitivity Max
Sensitivity:	62%	90%	97%
(95% CI)*	(49-73%)	(80-96%)	(90-100%)
Specificity:	86%	82%	54%
(95% CI)*	(80-91%)	(76-88%)	(47-62%)

* Clopper Pearson Exact Method.

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Poster Session

Examining ultrafine particle pollution and lung cancer risk in a large, diverse cohort. *First Author: Arthur Bookstein, Keck School of Medicine of University of Southern California, Los Angeles, CA*

Background: Health effects associated with particles less than 2.5 μm in diameter ($\text{PM}_{2.5}$) have been well studied, leading to the establishment of air quality standards and routine monitoring. Additionally, there is growing experimental evidence that ultrafine particles (UFPs), defined as particles less than 0.1 μm in diameter, may adversely affect lung health, eliciting greater injury than larger particles due to deeper penetration into airways and longer retention in the lung parenchyma. Only two epidemiological studies have investigated this topic, finding no associations between ambient UFPs and respiratory mortality or overall lung cancer incidence respectively. Given the limited epidemiologic investigation of UFPs and lung cancer, we examined the association between airport-related UFPs and lung cancer incidence in a large, racially and ethnically diverse cohort. **Methods:** We estimated airport-related UFP exposure for 71,387 participants of the Multiethnic Cohort, who lived within a 53 km $\times$ 43 km grid area around the Los Angeles International Airport (LAX) from date of cohort entry (1993-1996) through December 31, 2013. Cox proportional hazards regression was used, with calendar month/year as the time variable, to examine associations between UFP exposure and lung cancer risk adjusting for demographics, lifetime smoking, neighborhood socioeconomic status, occupation and lifestyle factors. Subgroup analyses were conducted by racial and ethnic groups, lung cancer histology, and smoking status. Copollutant models were run to mutually adjust for other traffic-related air pollutants. **Results:** A per unit increase in the interquartile range (IQR) of airport-related UFP exposure was not associated with lung cancer risk overall [HR = 1.01, 95% CI: 0.97-1.05] or by race and ethnicity. UFP exposure was suggestive of a positive association with risk of lung squamous cell carcinoma (SCC) [HR per IQR = 1.08, 95% CI: 1.00-1.17]. No associations were observed for other histologies [P_{het} for histology = .05]. UFP exposure was associated with an increased SCC risk among current smokers [HR = 1.11, 95% CI: 1.01-1.22] but not among never or past smokers [P_{het} for smoking = 0.51]. **Conclusions:** This study suggests a possible association between airport-related UFP exposure and risk of SCC. These results may be explained by previous studies finding that UFPs activate genes involved in oxidative damage, TNF- α signaling via NF- κ B, and secretion of inflammatory and cardiopulmonary disease biomarkers. These findings warrant further investigation in large epidemiologic cohorts. Research Sponsor: U.S. National Institutes of Health.

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Poster Session

Multi-genomic analysis of compound and uncommon EGFR mutations in patients with non-small cell lung cancer. *First Author: Jayoung Park, Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, South Korea*

Background: There are similar and different properties between the epidermal growth factor receptor mutations (mEGFR), which are classified into common, uncommon, and compound mutation subtypes depending on their location and pattern on the EGFR gene. We investigated the RWD and RNA expression profile of uncommon and compound mutations in the mEGFR+ NSCLC patients. **Methods:** We collected the medical information for stage I-III mEGFR+ NSCLC patients receiving curative surgical resection in Seoul St. Mary's Hospital. We explored the RNA expression profile using multiplex IF and High-Plex Digital Spatial Profiling. A total of 18,676 DEG libraries were constructed, and 151 significance genes with > 2-fold changes, 4-log 2 normalized read counts, and p-value = 0.05 (up and down) were identified. **Results:** In hospital cohort, 941 mEGFR+ cases of total 6,609 cases consist of common, 860 (91.4%), uncommon, 60 (7.4%), and compound, 21 (2.2%). Median relapse-free survival in uncommon and compound mEGFRs (31.4M and 33.7M) was shorter than common mEGFRs (40.1M, p = 0.877), but median overall survival did not differ between the groups. CNS recurrence rates in the uncommon and compound mEGFRs (40.0% and 35.3%) tended to be higher than that of common mEGFRs (27.4%, p = 0.361). Spatial RNA-seq data of the ratio of deconvolution individual cells showed that genes involved in inflammatory and immune response were relatively lower in mEGFR+ groups. According to the difference in DEG library through clustering heat map, uncommon or compound mEGFR in the immune, inflammatory response category, extracellular matrix, RNA splicing gene category, JAK-STAT, p53, PI3K-AKT, and notch signaling pathway related genes were down regulated compared to common mEGFR+ group. Gene ontology string analysis revealed RNA expression of genes in compound mEGFR was functionally associated with chemokine production (23.4%), electron transfer activity (14.9%) and T cell selection (8.5%), and, in uncommon mEGFRs, was associated with regulation of oligopeptide transport (26.1%), hypermethylation of CpG island (21.7%), and CD4+ CD25+ $\alpha\beta$ regulatory T cell lineage commitment (13.0%), compared to common mEGFR+ groups. Based on the GSEA, relatively highly clustered genes in compound mEGFR were the protein modification process, G-protein coupled receptor, regulation of cytosolic calcium ion concentration, and IL-5 production pathways, and lower ES levels in oxidative phosphorylation and RNA processing pathways, when compared to common mEGFR+ groups. **Conclusions:** In conclusion, our results suggest that uncommon and compound mEGFR+ subtypes exhibiting distinguished RNA expression profile of functional signaling pathways and protein network be not same disease entity as common mEGFR+ subtype. Research Sponsor: Bucheon St. Mary's Hospital Clinical Research Laboratory Foundation made in the program year of 2021.

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Poster Session

Validation of recurrence prediction using circulating tumor DNA in patients with curatively treated early stage non-small cell lung cancer. *First Author: Milou Schuurbijs, Department of pulmonary diseases, Radboud university medical center, Nijmegen, Netherlands*

Background: Stage II-III non-small cell lung cancer (NSCLC) patients receive adjuvant chemotherapy after surgery as standard-of-care treatment, despite an absolute 5-year disease free survival benefit of only 5.8%. Stage I patients do not receive adjuvant treatment but may benefit. Identification of residual disease by circulating tumor DNA (ctDNA) after curative intent therapy may allow more accurate decisions. **Methods:** Tumor tissue and serial plasma samples were collected from stage I-III NSCLC patients enrolled in the LEMA trial (NCT02894853). Somatic mutations identified by tumor exome sequencing were used to design patient-specific RaDaR assays, targeting up to 48 variants per patient, to analyze ctDNA in serial plasma samples. Results were compared and combined with an independent dataset (LUCID; Gale et al, Annals Oncol 2022). **Results:** In LEMA, 129 patients (53% stage I, 18% stage II and 29% stage III) were treated with curative intent by surgery (n=117), chemotherapy (n=8) or stereotactic radiotherapy (n=4) and followed for a median of 3.4 years. The LUCID dataset included 88 patients (49%/28%/23% in stage I/II/III). Results in the two cohorts were highly concordant (Table) and were assessed in the combined dataset of 808 serial plasma samples. Before treatment, ctDNA was detected in 22%, 72% and 90% of patients with stage I, II and III disease. ctDNA was detected post-treatment (at least one positive samples $\geq$ 14 days after the end of therapy) in 41/65 (63%) of patients who developed radiographic recurrence of their primary cancer, and preceded recurrence by a median of 204 days. For recurrence prediction by ctDNA detection post-treatment, the sensitivity, specificity, positive and negative predictive value (PPV and NPV) in stage I patients were 53%, 99%, 91% and 90%. In stage II-III patients, sensitivity was higher but specificity and NPV were lower (67%, 93%, 91% and 74%, respectively). ctDNA detection after treatment was associated with shorter recurrence-free survival (hazard ratio (HR) 11.5, P=1.8x10⁻³²) and overall survival (HR 8.1, P=1.2x10⁻¹⁷). **Conclusions:** ctDNA detection by RaDaR assays predicted recurrence in two independent cohorts, confirming the potential to identify patients for adjuvant treatment. In stage I patients with positive ctDNA, adjuvant treatment could be offered with confidence due to high specificity of 99% and PPV of 91%. In stage II-III patients, the primary cancer recurred in a quarter of patients with no ctDNA detected post-treatment (NPV 74%). Our results help identify the potential role for ctDNA analysis as a decision support tool for adjuvant therapy in NSCLC. Research Sponsor: None.

Recurrence prediction by ctDNA detection post-treatment.				
	Sensitivity %	Specificity %	PPV %	NPV %
Combined (n=193)	63	97	91	84
Stage I	53	99	91	90
II-III	67	93	91	74
- LEMA	62	97	92	85
Stage I	50	100	100	89
II-III	68	93	89	77
- LUCID	64	96	90	82
Stage I	57	97	80	91
II-III	65	94	93	68

8537

Poster Session

Phase 1 trial of gavocabtagene autoleucel (gavo-cel, TC-210) in patients (pts) with treatment refractory mesothelioma and other mesothelin-expressing solid tumors. *First Author: Raffit Hassan, Thoracic and GI Malignancies Branch, Center for Cancer Research, National Cancer Institute, Bethesda, MD*

Background: We have conducted a Phase 1 trial of gavo-cel, an autologous genetically engineered anti-mesothelin T cell receptor fusion construct (TRuCTM) cell therapy in pts with refractory mesothelin-expressing mesothelioma (MPM), ovarian cancer (OvC), cholangiocarcinoma (CHO), or non-small cell lung cancer (NCT03907852). **Methods:** T cells were engineered with a lentiviral vector to express an anti-mesothelin single domain antibody fused to the CD3 ϵ subunit, which upon translation, integrated into and reprogrammed native T cell receptors to target mesothelin-expressing cancer cells in an HLA-independent manner. Eligibility required central laboratory confirmation of 2+ or 3+ mesothelin expression by IHC in $\geq$ 50% of tumor cells. Dose escalation followed a modified 3+3 design. **Results:** At data cut-off date (January 17th, 2023), 32 pts (23 MPM, 8 OvC, 1 CHO) received a gavo-cel infusion at one of 7 dose levels (DL): DL0 (n = 1, no lymphodepletion [LD]) and DL1 (n = 8), 5x10⁷ transduced cells/m²; DL2 (n = 1, no LD) and DL3 (n = 13), 1x10⁸ transduced cells/m²; DL3.5 (n = 5), 3x10⁸ transduced cells/m²; DL4 (n = 1, no LD) and DL5 (n = 3), 5x10⁸ transduced cells/m². Median number of prior therapies was 5 (range, 1-13), including immune checkpoint inhibitors (ICI) in 87% of MPM pts. Bridging therapy was required in 24 (75%) pts. Two DLTs were reported: grade (gr) 3 pneumonitis at DL1 and gr5 bronchoalveolar hemorrhage at DL5. At the RP2D (1x10⁸/m² after LD) 2/13 (15%) pts had reversible gr $\geq$ 3 CRS. The ORR and disease control rate was 20% and 77%, respectively. The 6-month OS rate was 70.2%. The ORR of pts with MPM or OvC receiving gavo-cel after LD was 21% and 29%, respectively. The median PFS and OS in MPM was 5.6 and 11.1 mos and in OvC was 5.8 and 9.4 mos. Responses correlated with declines in soluble mesothelin related peptides. Peak expansion and persistence correlated with dose and LD administration. At the RP2D, the median C_{max} was 14,385 copies/ug gDNA (range, 64.4–100,782) and the median peripheral blood (PB) persistence was 84 days (range: 0-170). Consistent elevation in IL-6 and IFN- γ levels but minimal IL-8 and TNF- α were observed. Gavo-cel expanded preferentially in cancerous tissues, where it was detected long after becoming undetectable in PB. Gavo-cel therapy led to increased CD3⁺CD8⁺ T cell tumor infiltration. Non-responders exhibited upregulation of immunoinhibitory ligands (CD155, PDL1), indicating potential resistance mechanisms. **Conclusions:** A single IV gavo-cel infusion at the RP2D was associated with a manageable toxicity profile and high rates of disease control, including objective responses in pts with refractory MPM and OvC. A phase 2 study is underway testing the safety and efficacy of gavo-cel in combination with checkpoint inhibitors in pts with mesothelin-expressing solid tumors. Clinical trial information: NCT03907852. Research Sponsor: TCR2 Therapeutics.

8536

Poster Session

Real-life efficacy of nivolumab plus ipilimumab combination in untreated, unresectable malignant pleural mesotheliomas: Result of French early access program—MESOIMMUNE – GFPC 04-2021. *First Author: Olivier Bylicki, HIA SAINT ANNE, Toulon, France*

Background: The SOC for unresectable malignant pleural mesothelioma (MPM) has changed in 2020 with the combination nivolumab plus ipilimumab (NIVO+IPI) results of CheckMate 743 study. As CheckMate 743 was therapeutic trial in selected MPM patients (pts), additional data would be of interest to confirm the results in real-life setting. **Methods:** The present multicenter, retrospective study assessed the outcomes of NIVO+IPI, via an early access program (EAP) in France, in pts with treatment naïve unresectable MPM. The primary objective was investigator-assessed real world progression-free survival (rwPFS) from initiation of NIVO+IPI, defined as time from first dose of NIVO+IPI to first documentation of objective disease progression or death from any cause. The secondary objectives were real world OS (rwOS), objective response rate (ORR), and safety of NIVO+IPI combination. **Results:** From April 1, 2021 to Feb 15, 2022 (last day of EAP) there were 143 pts included out of 350 pts treated by EAP for unresectable MPM in 44 centers. Population characteristics are described in the table. With a median follow-up of 14.1 months, median rwPFS was 7.8 months (95%CI 6.2-9.5), rwPFS rates no differ according to histological subtypes: rwPFS for epithelioid MPM was 8.1 months (95%CI 6.0-12.6) and 7.4 months (95% CI 5.3-11.2) for other histological subtypes. The median rwOS was not reached (NR), 1-year survival rate was 65% (95% CI 57-75%). Median rwOS was NR and 13.1 (95% CI 7.8- NA) in epithelioid and non-epithelioid MPM, respectively. At 1 year, 71.2% of pts with epithelioid MPM are still alive versus 51.2% in pts with other histological subtypes. ORR was 23.9% (95% CI 16.9-32.0%) with median time to response of 3.68 months (2.33-5.09) after introduction of NIVO+IPI. Disease control rate was 80.4%. Grade 3-4 adverse events (AE) occurred in 37.8%. Severe immune-related AE occurred in 13.9% of patients. Five deaths were associated with treatment-related AEs according to investigators judgment. **Conclusions:** While pt's characteristics differed from the pivotal trial, notably with older and unselected patients, efficacy outcomes that we observed here compares favorably with CheckMate 743 results. Tolerance looks acceptable in real-life setting despite 5 toxic deaths reported. Extended follow-up of our cohort will allow consolidation of the results. Clinical trial information: NCT05308966. Research Sponsor: BMS.

	Nivolumab + Ipilimumab (n=143)
Age, years (SD)	74.7 (9.42)
< 65	20 (14.0%)
$\geq$ 65 to $\leq$ 75	45 (31.5%)
$\geq$ 75	78 (54.5%)
Sex	
Male	120 (83.9%)
Female	23 (16.1%)
Eastern Cooperative Oncology Group Performance status	
0	51 (39.8%)
1	66 (51.6%)
2	9 (7.0%)
$\geq$ 2	2 (1.6%)
Smoking Status	
Current or former	71 (49.7%)
Never	64 (44.8%)
Unknown	13 (5.6%)
Histology	
Epithelioid	99 (69.7%)
Non-Epithelioid	43 (30.3%)
Sarcomatoid	13 (9.2%)
Mixed or other	30 (21.2%)
Stage	n=98
1	9 (9.2%)
2	10 (10.2%)
3	49 (50.0%)
4	30 (30.6%)

8538

Poster Session

Long-term outcomes of single and five fraction schedules of stereotactic body radiation therapy for early-stage central or peripheral NSCLC: Neither fractionation nor location matter? *First Author: Karen Huang, Department of Radiation Medicine, Roswell Park Comprehensive Cancer Center, Buffalo, NY*

Background: Due to concerns with toxicity, treatment of early-stage non-small cell lung cancer (NSCLC) with stereotactic body radiation therapy (SBRT) often involves different fractionation schemes for peripheral and centrally located tumors. There is a paucity of long-term SBRT survival outcomes comparing peripheral versus central NSCLC. **Methods:** This is a single-institution observational cohort study of patients diagnosed with early-stage NSCLC (T1-2NOMO) who underwent 27 Gy in 1 fraction or 50 Gy in 5 fractions with heterogeneity correction at Roswell Park Comprehensive Cancer Center between September 2008 to December 2018. All patients treated with single-fraction SBRT had peripheral NSCLC and those treated with five-fraction SBRT had central NSCLC. Clinically relevant variables including age, gender, race, Karnofsky Performance Status (KPS), histology (adenocarcinoma, squamous cell carcinoma, NSCLC not otherwise specified), T stage, smoking status, tumor location, and the year of SBRT delivery were obtained retrospectively. Cox multivariable analysis (MVA), Kaplan-Meier plot, and log-rank test were performed to evaluate progression-free survival (PFS) and overall survival (OS). Fine-Gray competing risk MVA was performed to evaluate local failure (LF), nodal failure (NF), and distant failure (DF) with death as a competing event. To reduce selection bias, propensity score matching was performed between single- versus five-fraction SBRT cohorts. **Results:** A total of 265 patients (142 female [53.6%]; median age 77 years) met our criteria. There were 74 (27.9%) and 191 (72.1%) patients with central tumors treated with five-fraction SBRT and peripheral tumors treated with single-fraction SBRT, respectively. On Cox MVA, there was no statistically significant difference in OS (peripheral vs central tumors: adjusted hazards ratio [aHR] 1.04, 95% confidence interval [CI] 0.74-1.46, p=0.81) and PFS (peripheral vs central tumors: aHR 1.05, 95% CI 0.76-1.45, p=0.77). On Fine-Gray competing risk MVA comparing peripheral vs. central tumors, there was no statistically significant difference in LF, NF, and DF. After propensity score matching, 68 matched pairs were identified for peripheral vs. central tumors with similar results. **Conclusions:** Among patients with early-stage NSCLC treated with SBRT central versus peripheral location was associated with similar long-term survival and tumor recurrence outcomes. Research Sponsor: None.

8539

Poster Session

EGFR assessment using next generation sequencing as a reflex testing on surgically resected non-squamous non-small cell lung carcinoma. *First Author: Samantha Goffinet, Laboratory of Clinical and Experimental Pathology, Pasteur Hospital, FHU OncoAge, Université Côte d'Azur, CHU Nice, Nice, France*

Background: EGFR status assessment is mandatory in early stage (IB-IIIA) non-squamous non-small cell lung carcinoma (NS-NSCLC), but whether NGS methods should be used as reflex testing for this evaluation in daily practice is controversial. However, co-occurring mutations, notably TP53 mutations, may have an impact on tumor behavior and prognosis, and so, on future adjuvant therapeutic strategies. **Methods:** EGFR mutations were assessed prospectively using NGS (OncoPrint Precision Assay panel) in 720 NS-NSCLC surgically resected between January 2021 and September 2022 in a single institution (LPCE, Nice, France). PD-L1 expression was evaluated in all tumors. Disease free survival (DFS) analysis was available in 675/720 (94%) patients. **Results:** EGFR mutations were detected in 83/720 (11.5%) cases. A common non-compound EGFR mutation (L858R or del19) was observed in 62/83 (75%) cases. 12/83 (14%) and 9/83 (11%) tumors had a rare non-compound and compound EGFR mutations, respectively. 40/83 (48%) has a co-occurring mutation, including a TP53 (30/40; 75%) mutation, mainly in exon 5, 7 or 8. EGFR/TP53 mutated tumors were significantly associated with higher PD-L1 expression compared to EGFR mutated tumors. A significant correlation was noted between worse DFS and the detection of a mutation in EGFR exon 18 mutation, as well as the detection of a co-mutation in TP53 exon 7 and in MET exon 14. **Conclusions:** Genomic alteration should be systematically evaluated using an NGS reflex testing in surgically resected NS-NSCLC, since future adjuvant therapeutic decision making may consider the presence of compound EGFR mutations as well as co-occurring mutations in other genes, especially in TP53. Research Sponsor: Centre Hospitalier Universitaire de Nice.

8541

Poster Session

The RESECT study: Factors associated with overall survival (OS) and relapse-free survival (RFS) among patients with stages I–III resected NSCLC without known EGFR mutations. *First Author: Jhanelle Elaine Gray, Moffitt Cancer Center, Tampa, FL*

Background: Approximately one-third of patients with Stages I–III resected non-small-cell lung cancer (NSCLC) do not survive 5 years from diagnosis. This retrospective observational study analyzed factors associated with OS and real-world (rw) RFS among Stage I–III NSCLC patients before the introduction of immuno-oncology (IO) treatment. **Methods:** We analyzed data from the US CancerLinQ database for adult patients with no known EGFR mutations and no other cancers, who were diagnosed with Stage I–III NSCLC from 2014–2019 and had surgical resection within 140 days after initial diagnosis. 3081 patients met the study criteria of whom 1677 were Stage I, 853 were Stage II, and 551 were Stage III; 4 Stage I patients who received neoadjuvant or perioperative treatment were excluded (too few for analysis). Most patients received surgery only (71.5%); the rest also received adjuvant (24.7%), neoadjuvant (2.4%) or perioperative (1.5%) treatment, most often chemotherapy ± radiotherapy. Key demographics, clinical characteristics, treatment patterns, and relevant 2-way interactions were considered for inclusion in the model, based on Cox regression analyses and medical insights. Multivariable Cox regression analysis (backwards selection, $p < 0.05$) was used to model OS and rwRFS. **Results:** In the multivariable analyses (in which no Stage I patients with neoadjuvant or perioperative treatment were included), factors associated with both OS and rwRFS ($p < 0.05$) were disease stage, race, ethnicity, year of diagnosis, ECOG performance status, and neoadjuvant treatment. Factors associated with OS ($p < 0.05$), but not rwRFS, were age, sex, time from diagnosis to surgery, and type of surgery. Factors associated with rwRFS ($p < 0.05$), but not OS, were geographic region, nodal status, and adjuvant treatment in Stage II and III patients but not Stage I patients. **Conclusions:** This study identified several risk factors associated with OS and rwRFS, many of which are known. Notably, in this analysis, neoadjuvant treatment was associated with both improved OS and rwRFS in Stage II–III patients and was not evaluable in Stage I patients. However, adjuvant treatment was only associated with improved rwRFS, and only in Stage II–III patients. Based on these findings, there remains an unmet need for Stage I–III NSCLC patients. The recent introduction of IO treatment in this setting may help improve patient outcomes. Research Sponsor: AstraZeneca.

8540

Poster Session

Stereotactic body radiation therapy with sequential immunochemotherapy as neoadjuvant therapy in resectable non-small cell lung cancer (SACTION-01 study). *First Author: Ze-Rui Zhao, Sun Yat-Sen University Cancer Center, Guangzhou, VA, China*

Background: Neoadjuvant PD-1 inhibitor plus chemotherapy increases pathological response for resectable non-small cell lung cancer (NSCLC) compared with chemotherapy alone. Previous phase II trial indicated that stereotactic body radiation therapy (SBRT) served as an immunomodulator and enhanced the effect of preoperative immunochemotherapy. However, whether SBRT would further increase the efficacy of immunochemotherapy for NSCLC remains unknown. **Methods:** In this phase II trial, patients with resectable EGFR wild-type stage IIA to IIIB NSCLC were recruited to receive SBRT (24 Gy in 3 daily fractions) to the primary tumor followed by two cycles of PD-1 inhibitor tislelizumab (200 mg) plus platinum-based doublet chemotherapy (Q3W) before surgical resection. The primary endpoint was major pathological response (MPR) defined as no more than 10% of viable tumor cells in the specimen. Simon's optimal two-stage design was used for conducting the trial. The null hypothesis was that the MPR rate is 0.30, and the alternative hypothesis was that the true MPR rate was 0.50. More than 4 MPRs were needed in stage 1 ($n=15$) to continue, and if there were 19 or more MPRs in 46 patients by the end of stage 2, the null hypothesis can be rejected. The design controls the type I error rate at 0.05 and yields the power of 0.80. (NCT05319574). **Results:** Between May 2022 and Jan 2023, 32 patients were enrolled with 31 (96.9%) male and 19 (59.4%) having squamous cell lung cancer. Twenty-six (81.3%) patients had stage IIIA/B disease. All patients received at least one cycle of immunochemotherapy; 23 of the 25 patients (92.0%) who completed treatment had undergone R0 resections, except for one patient who had disease progression and the other one that unable to tolerate surgery because of grade 4 neutropenia. Twenty-two patients underwent minimally invasive approaches and 3 of them (13.6%) converted to thoracotomy. The median percentage of the viable tumor was 0 (interquartile range: 0–4.0%). Twenty patients achieved MPR, which surpassed the prespecified required number to reject the null hypothesis, resulting in the MPR rate of 80.0% (20/25) in the intention-to-treat population, and 87.0% (20/23) in the per-protocol population. Pathological complete response (pCR) was found in 14 patients (56.0% in the intention-to-treat population and 60.9% in the per-protocol population). Nodal clearance status (pNO) was found in 20 of 23 cN1/2 cases (87.0%). Grade 3–4 adverse events related to neoadjuvant treatment included neutropenia (13.0%), anemia (4.3%), and pneumonia (4.3%). No 30-day or 90-day mortality was observed. **Conclusions:** Neoadjuvant SBRT followed by immunochemotherapy yields unprecedentedly high MPR and pCR rates in NSCLC without EGFR mutation. The trial will continue to recruit 14 more patients to reach a final sample size of 46 participants. Clinical trial information: NCT05319574. Research Sponsor: None.

8542

Poster Session

Two-year lung cancer survival between 2000 to 2020: Results from 3 French nationwide cohorts. *First Author: Didier Debieuvre, Service de Pneumologie, Groupe Hospitalier de la Région Mulhouse Sud-Alsace, hôpital Emile-Muller, Mulhouse, France*

Background: Each decade since 2000, the French College of General Hospital Pulmonologists (CPHG) conducts the KBP study, a real-life nationwide prospective multicenter study on LC in non-academic public hospital (NPH). Here, we report the two-year survival (2-y) rate among the 2020 cohort and the comparisons with the 2000 and 2010 cohorts. **Methods:** Collection of all consecutive diagnosed LC, all stage and all histology, between 01/01 and 12/31 in NPH pulmonology or oncology units in 2000, 2010 and 2020 with the same methodology. A Scientific Committee controlled inclusion exhaustivity and quality in each center. Survival rates were calculated using the Kaplan-Meier method and risk factors were assessed using Cox models. **Results:** 8,999 patients were included in 82 centers in 2020. The 2-y survival rate was 40.3%, the median overall survival was 15.3 months. Compared to 2000, mortality rates at 2 years decreased significantly (–19.1%), while early (1 month and 3 months) mortality remains similar. Survival improved in 20 years whatever histologic types (Table). Factors associated with 2-y survival were sex (36.1% vs 48.1% respectively for male and female respectively, significantly increased over 20 years: +15.3% for M and +24.5% for F), high age (>80 y-o), poor ECOG status (3 or 4) and advanced disease. As expected in 2020, TNM stage was still determining for 2-year mortality, 15.2 [12.6–17.7] stage I vs 75.6 [74.4–76.8] stage IV. In 2020 the Covid-19 infection ($n=283$) impacted the survival (HR = 4.02 95%CI [3.33–4.86]) on multivariate analysis adjusted to age, sex, tobacco consumption, histology, ECOG status, TNM stage. **Conclusions:** These results confirmed the major improvement in the last two decades for LC. 5-years survival will provide us more enlightenment. Research Sponsor: AstraZeneca, BMS, MSD, Janssen, Bayer, Boehringer Ingelheim, Lilly, Takeda, Sanofi, Roche, Chugai, Pfizer; Fondation du Souffle, Le Nouveau Souffle, Couleur Espoir, the labeling of InCa and FHF-CNCR.

Mortality rates* - % [95% IC].

	Months	2000	2010	2020
Overall mortality				
1		10.4 [9.6 - 11.2]	9.8 [9.1 - 10.4]	8.2 [7.7 - 8.8]
3		24.6 [23.4 - 25.7]	23.3 [22.3 - 24.3]	20.2 [19.4 - 21.0]
12		60.1 [58.8 - 61.4]	56.9 [55.7 - 58.0]	44.5 [43.4 - 45.5]
24		78.8 [77.7 - 79.8]	74.2 [73.2 - 75.3]	59.7 [58.7 - 60.8]
Median survival time (months)				
		8.8 [8.4 - 9.1]	9.7 [9.4 - 10.1]	15.3 [14.6 - 16.1]
Mortality / histology				
SCLC	Months	2000	2010	2020
24		88.3 [86.0 - 90.3]	86.4 [84.0 - 88.4]	80.6 [78.0 - 82.9]
Squamous	24	75.6 [73.7 - 77.4]	70.9 [68.8 - 73.0]	61.5 [59.1 - 63.6]
Non-SCLC, non-squamous	24	76.5 [74.3 - 78.5]	72.3 [70.7 - 73.9]	54.4 [52.9 - 55.9]

*Preliminary results with 1291 missing data at Month 24 - Update will be available for the congress.

8543

Poster Session

Association of nuclear shape in the tumor epithelium with response to atezolizumab in NSCLC. *First Author: Patrick Leo, Genentech, South San Francisco, CA*

Background: Anti-PD-(L)1 treatment is the standard of care for advanced non-small cell lung cancer (NSCLC). However, additional biomarkers are needed to identify patients who will benefit from these therapies. In this study, we demonstrate the atezolizumab response score (ARS), which uses digital pathology features of the shape and size of nuclei in the tumor epithelium to predict response to the anti-PD-L1 antibody atezolizumab in NSCLC. **Methods:** Patients were drawn from two trials comparing atezolizumab to docetaxel in second-line advanced NSCLC. A single digitized slide stained for the epithelial cell marker pan-cytokeratin (CK) and CD8 was selected for each patient. OAK, a phase III trial, had 819 patients with images available and was used for training the ARS model. POPLAR, the phase II trial preceding OAK, had 168 evaluable patient images for validating ARS. Color deconvolution was used to identify the CK-positive regions in each image. Nuclei were segmented using the hematoxylin channel. The area, perimeter, eccentricity, solidity, and minor/major axis lengths were extracted from each nucleus in the CK-positive compartment of the pathologist-annotated tumor lesion, excluding necrosis and artifacts. Each measure's mean, median, standard deviation, skewness, and kurtosis across the slide was calculated, for a total of 30 features. Features with an interaction $p < 0.35$ with trial arm in a Cox model were used to fit an elastic-net regularized Cox model on the atezolizumab-treated training set patients, producing ARS. The ARS threshold maximizing atezolizumab overall survival (OS) benefit in the ARS-high group was identified in OAK and applied to POPLAR (the validation set). ARS performance was assessed in the validation set by OS concordance index (c-index) and by atezolizumab benefit in the high- vs. low-ARS groups by hazard ratio (HR) [95% confidence interval]. **Results:** ARS employs five features. Lower nuclear median and standard deviation of major axis length, higher perimeter mean and standard deviation, and higher area were associated with better atezolizumab response. In the validation set, high-ARS (prevalence = 42%) patients had longer OS on atezolizumab vs. docetaxel (HR = 0.42 [0.24-0.72]) while low-ARS patients did not (HR = 0.95 [0.62-1.47]). ARS was positively associated with OS in the validation set atezolizumab arm (c-index = 0.60 [0.54-0.66]), but not the docetaxel arm (c-index = 0.47 [0.41-0.54]). **Conclusions:** We validated a nuclear morphology-based biomarker for atezolizumab response in advanced NSCLC. This demonstrates the utility of digital pathology for biomarker development and motivates study into the identified responder phenotype. Combination of ARS with additional markers, such as PD-L1 expression, might further improve stratification. Research Sponsor: Roche.

8545

Poster Session

Phase I Beamion Lung 1 trial of BI 1810631, a HER2 tyrosine kinase inhibitor (TKI), as monotherapy in patients (pts) with advanced/metastatic solid tumors with HER2 aberrations: Updated data. *First Author: John Heymach, Department of Thoracic/Head and Neck Medical Oncology, Division of Cancer Medicine, MD Anderson Cancer Center, University of Texas, Houston, TX*

Background: There is an unmet need for effective TKIs against HER2 mutations in solid tumors, especially NSCLC. BI 1810631 is a highly potent and selective HER2 TKI that covalently binds to both wild-type and mutated HER2 receptors, including exon 20 insertions (ex20ins), while sparing EGFR. Beamion Lung 1 is an ongoing Phase Ia/Ib study to determine the safety, MTD, PK, PD, and preliminary efficacy of BI 1810631 in pts with HER2 aberration-positive solid tumors (NCT04886804). Preliminary results from Phase Ia are presented. **Methods:** In Phase Ia, pts with advanced/unresectable/metastatic solid tumors who were refractory or unsuitable for standard treatment (Tx) and had HER2 aberrations (e.g. overexpression, gene amplification, somatic mutation, or gene rearrangements) were enrolled. Pts received escalating doses of BI 1810631 BID starting from 15 mg or BI 1810631 QD starting from 60 mg via a Bayesian model. Phase Ib will initially include 30 pts with advanced HER2 tyrosine kinase domain mutation-positive, pre-treated NSCLC. Additional cohorts may be included. Primary endpoints: MTD based on DLTs; pts with DLTs (Phase Ia); ORR (Phase Ib). Secondary endpoints: number of pts with DLTs throughout entire Tx period and PK parameters (Phase Ia/Ib); DoR, DCR, duration of disease control, and PFS (Phase Ib). **Results:** As of 23 January 2023, 36 pts had been treated in the US, The Netherlands, Japan, and China. Pts had NSCLC (n = 22), colorectal cancer (n = 3), or other tumors (n = 11). Most pts (n = 26; ex20ins: n = 23) had a pathological HER2 mutation. Median (range) lines of prior systemic Tx: 2.5 (1–8). Prior HER2-targeted Tx: 12 (33%). Pts received BI 1810631 at 15, 30, 60, 100, 150 mg BID (n = 3/3/4/4/3) or 60, 120, 180, 240, 300 mg QD (n = 5/4/5/4/1). Median number of cycles was 4 (range 1–14). Tx is ongoing in 20 pts. To date, 3 DLTs have been observed (grade 2 edema [60 mg BID], grade 3 anemia [60 mg QD], grade 3 elevated ALT [180 mg QD]). The MTD has not been reached with either schedule. Tx-related adverse events (TRAEs) were reported in 25 pts (69%). The most common TRAEs were diarrhea (n = 10), anemia (n = 5), increased alkaline phosphatase, increased creatinine, increased ALT, hypalbuminemia (all n = 4), hypocalcemia, increased AST, dry skin, increased GGT (all n = 3). Three pts had grade 3 TRAEs (anemia/increased GGT [n = 1], increased ALT [n = 2]). Strong preliminary efficacy signals were observed across all dose levels. Of 22 evaluable NSCLC patients, 10 responded (all PRs; all ex20ins) and 11 had SD. Two patients with other tumors (esophagus; cholangiocarcinoma) also achieved PR. **Conclusions:** These preliminary data indicate that BI 1810631 is well tolerated and shows encouraging anti-tumor activity in pts with HER2 aberration-positive solid tumors. Recruitment into Phase Ia is ongoing. Updated data, including durability endpoints, will be presented. Clinical trial information: NCT04886804. Research Sponsor: Boehringer Ingelheim.

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Poster Session

Radiation therapy (RT)-free pembrolizumab plus chemotherapy (P+C) for PD-L1 TPS $\geq 50\%$ locally advanced non-small cell lung cancer (LA-NSCLC): An early report analyzing depth of response from multicenter single arm phase II study (Evolution trial: WJOG11819L). *First Author: Akito Hata, Kobe Minimally Invasive Cancer Center, Kobe, Japan*

Background: Standard of care for unresectable LA-NSCLC is chemoradiation therapy (CRT) followed by durvalumab (D). Survival curves of P monotherapy/P+C for PD-L1 TPS $\geq 50\%$ stage IV NSCLC suggested possible comparable survival to CRT for stage III patients (pts). Moreover, some studies of neoadjuvant C+immunotherapy (I) for stage III pts have demonstrated high pCR and MPR rates, implying potentially outstanding efficacy of C+I for earlier stage. We thus hypothesized P+C without RT in PD-L1 $\geq 50\%$ LA-NSCLC pts provides a comparable efficacy to CRT followed by D while avoiding CRT-induced severe toxicities. **Methods:** This early report focuses on depth of response in a phase II study by WJOG. P with platinum plus pemetrexed (PEM) (non-squamous) or P with carboplatin plus nab-paclitaxel (squamous) was administered every 3 weeks without RT. After four cycles of induction P+C, P with PEM (non-squamous) or P alone (squamous) was continued until progression or 2 years. The primary endpoint was PFS rate at 2 years. **Results:** Between May 2020 and February 2022, 21 pts were enrolled. Median age was 74 (range, 53–89). Stage IIIA/B/C included 12 (57%)/6 (29%)/3 (14%), respectively. Histologic subtypes were 13 (62%) adenocarcinoma, 5 (24%) squamous, and 3 (14%) others. Investigator-assessed best response: 8 (38%) CR; 10 (48%) PR; 2 (10%) SD; and 1 (5%) NE were confirmed, resulting in response rate (RR) of 86% and disease control rate of 95%. RR of TPS 50–79% and 80–100% were 78% and 92%, respectively. Deep response (DR): defined as tumor shrinkage $\geq 80\%$ was obtained in 12 (57%) of 21 pts. DR was accomplished in 4 (44%) of 9 TPS 50–79% and 8 (67%) of 12 TPS 80–100%. Median time to response was 43 (range, 41–92) days. Early tumor shrinkage (ETS): PR-in at the time of first CT evaluation (6 weeks) was achieved in 16 (89%) of 18 CR+PR pts. At the time of data cut-off, median follow-up period was 18.5 (range, 0.3–29.0) months, and 14 (67%) of 21 pts were progression-free. All 12 pts achieving DR, including all 8 CR were progression-free, also in 14 (88%) of 16 ETS pts. Three pts after local progression received salvage definitive-CRT. Median number of P administrations was 20 (range, 1–35). AEs $\geq$ grade 3 were observed in 11 (52%) pts, including: 2 (10%) pneumonitis; 2 (10%) pneumonia; 1 (5%) diarrhea; 1 (5%) ALT elevation; and 1 (5%) acute heart failure, excluding hematological AEs. There was one (5%) possible grade 5 AE (pneumonia). **Conclusions:** RT-free P+C exerted a notably high RR, including some CRs. The deeper/earlier response and higher PD-L1 TPS could be associated with the higher progression-free incidence at the data cut-off. To investigate our hypothesis: RT-free P+C can be a less toxic curative option in selected LA-NSCLC pts with PD-L1 TPS $\geq 50\%$, further matured data is warranted. Clinical trial information: NCT04153734. Research Sponsor: MSD.

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Poster Session

A systematic comparison of whole genome sequencing and targeted panel sequencing for precision oncology. *First Author: Ji-Hyung Park, Graduate School of Medical Science and Engineering, Korea Advanced Institute of Science and Technology, Daejeon, South Korea*

Background: The analysis of the cancer genome provides clinically meaningful information such as actionable cancer driver mutations. Whole genome sequencing (WGS) provides a complete mutational landscape at an affordable cost thereby having increase clinical utility compared to the usual approach of targeted panel sequencing (TPS). To understand the capabilities of WGS in oncology, we conducted a study in lung adenocarcinomas. **Methods:** We produced WGS (surgically resected tumor tissues and matched blood; mean coverage 42x) and TPS (tumor only; SNUH panel encompassing 75 cancer genes; mean coverage 904x) through the Illumina sequencing platform and conducted comprehensive bioinformatic analyses. Oncogenic driver events, including single base substitution (SBS), insertion or deletion (INDEL), complex deletion-insertion, and fusion oncogene, were investigated in both datasets. Lastly, we compared the pattern-based mutational features, such as tumor mutational burden (TMB), mutational signatures, and copy number changes which is associated with genomic instability. **Results:** In 60 lung adenocarcinomas, the TPS method identified 120 driver mutations from the 75 targeted genes. Of these, 114 mutations were also detected by the WGS method, showing 95.0% sensitivity of WGS in detection of core driver mutations. In uncovered genomic regions by TPS, WGS captured 9 additional driver mutations (such as loss-of-function mutations in PIK3R2, ARID2, and APC) and 37 copy number variations (such as amplification of LMO and SMO, deletion of PIK3R1 and APC) in the cancer genes. TMB calculation is straightforward in WGS however, sophisticated considerations were necessary in TPS for TMB, to remove false positives and germline mutations. TPS showed a good capability for identifying hypermutator tumor samples, but a quantitative estimation was not always feasible due to the substantial background fluctuation, particularly for INDELs. Mutational signatures are unique combinations of mutation types in a given sample, which can give important clues to the mechanism underlying mutations. TPS showed adequate mutational signatures (cosine similarity > 0.7), but was not constantly satisfactory in tumors with high TMB ($> 20,000$ genome wide SBS and INDELs). In TPS, approximately 30% of high TMB tumors represented marginal cosine similarity (0.5–0.7), and tobacco smoking related signature (SBS 4) found in WGS was captured only in 50% of the associated cases (9 out of 18). For DNA copy number changes and loss-of-heterozygosity analyses, WGS showed a much higher resolution. **Conclusions:** Our study demonstrates that WGS has comparable capabilities for the detection of driver mutations in core oncogenes and tumor suppressor genes. WGS was superior for pattern-based features, such as TMB, mutational signatures, and copy number changes. WGS is a medically necessary more comprehensive approach to precision oncology. Research Sponsor: None.

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Poster Session

SAKK 16/18: Immune-modulatory radiotherapy to enhance the effects of neoadjuvant PD-L1 blockade after neoadjuvant chemotherapy in patients with resectable stage III (N2) non-small cell lung cancer (NSCLC)—A multicenter phase II trial. *First Author: Laetitia A Mauti, Department of Oncology, Kantonsspital Winterthur, Winterthur, Switzerland*

Background: Neoadjuvant chemo-immunotherapy has become a new standard of care in locally advanced, resectable NSCLC. The SAKK 16/14 trial demonstrated a major improvement in pathological response (pCR), major pathological remission (MPR) and event-free survival (EFS) with the addition of perioperative durvalumab after standard induction chemotherapy (ChT) with cisplatin and docetaxel. Based on data suggesting a potential enhancement of immunotherapy efficacy, the ongoing SAKK 16/18 trial investigates the addition of immune-modulatory radiotherapy (RT) given concurrently with neoadjuvant durvalumab. **Methods:** In this non-comparative randomized phase II trial patients (pts) with resectable stage IIIA-B(N2) (cT1-3 or T4 due to size N2 MO) NSCLC receive 3 cycles of cisplatin 100mg/m² and docetaxel 85mg/m² followed by durvalumab (1500mg) and one of three randomized RT regimens before tumor resection and adjuvant durvalumab for 1 year. RT is delivered to the primary tumor only, using either 20x2 Gy, 5x5 Gy, or 3x8 Gy (delivered inhomogeneously). RT planning is optimized for strict organ at risk and mediastinal lymph node sparing. The primary endpoint is 1-year EFS. We report a preplanned interim analysis of the secondary endpoints safety, surgical outcomes and pathological response after surgery in 25 pts. **Results:** At data cut-off on Oct 8, 2022, 25 pts had reached post-operative day 30 and a total of 31 pts were included in the safety analysis. Thirty pts (97%) had at least one treatment related adverse events (TRAE). Eighty-eight % were attributed to neoadjuvant ChT (16% G3-4), 4% each to neoadjuvant durvalumab (1% G3) and RT (1% G4), and 8% to surgery (35% G3-4). One fatal TRAE occurred in a pt with COVID-pneumonia during neoadjuvant ChT. No difference in safety was seen between the three RT arms. There was no treatment-related cancellation or delay in surgery and 0% 30-day postoperative mortality. Eighty-one % of pts underwent tumor resection (96% RO). Non-resection was due to death (n = 1), progressive disease (n = 3), or unresectable tumor (n = 2). The pCR-rate was 28%, and MPR (≤10% viable tumor cells) was detected in 76% of all specimens. Details of pathological responses with regard to immune-modulatory RT regimen will be presented at the meeting. **Conclusions:** The preplanned interim safety analysis of the SAKK 16/18 trial did not show a relevant increase in TRAE due to immune-modulatory RT. Surgical feasibility and safety are confirmed and the trial continues enrolment to a planned total of 90 pts (30 per RT arm). Preliminary pathological responses are promising, and exploratory analyses will study potential differences between the RT regimens, in order to better understand the potential role of immune-modulatory RT in the multimodal treatment of resectable stage III(N2) NSCLC. Clinical trial information: NCT04245514. Research Sponsor: AstraZeneca.

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Poster Session

Prospective dynamic sampling and molecular residual disease monitoring to predict clinical outcomes for patients with unresectable, locally advanced non-small cell lung cancer undergoing radical radiotherapy. *First Author: Jia-Tao Zhang, Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, Guangzhou, China*

Background: The role of molecular residual disease (MRD) detection in non-small cell lung cancer (NSCLC) patients after definitive resection has been progressively elaborated. However, the dynamic patterns of circulating tumor DNA (ctDNA) during and after radical radiotherapy (RT) remain unclear but are critical for detecting MRD in this context. **Methods:** We enrolled 139 patients with locally advanced NSCLC treated with radical RT in this prospective study. And 761 blood samples were successfully detected by ctDNA-MRD assay at different preset timepoints before, during and after RT. **Results:** There was a declining trend in ctDNA concentrations of “during RT” time point (RT reached 40 Gy) relative to those after RT. Patients with negative ctDNA of “during RT” and “after RT” time points may indicate an early response to RT, and had better progression-free survival (PFS) than those with late response to RT(ctDNA clearance only at “after RT” time point, HR = 0.30, 95%CI: 0.12-0.75, p = 0.004). Moreover, patients with both negative ctDNA of “during RT” and “after RT” time points could not benefit from consolidation therapy (HR = 0.72, 95%CI: 0.29-1.78, p = 0.478), while patients with any positive ctDNA of them could (HR = 0.59, 95%CI: 0.38-0.93, p = 0.023).The sensitivity of longitudinal MRD was 97.8% and only two patients with local progression were overlooked. The 2-year cancer-specific PFS of patients with longitudinal undetectable MRD was 88.4%, which corresponds to the potentially cured population. For patients with only blood-informed MRD detection, the sensitivity and median lead time of longitudinal MRD were 97.7% and 3.9 months, respectively, which indicating the feasibility and efficacy of blood-informed MRD detection strategy. **Conclusions:** These data shed new light on the ctDNA-MRD detection for localized NSCLC patients who received radical RT. Research Sponsor: Key Lab System Project of Guangdong Science and Technology Department, Guangdong Provincial Key Lab of Translational Medicine in Lung Cancer (Grant No. 2017B030314120).

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Poster Session

Sequential intravenous chemotherapy with drug-eluting bead bronchial arterial chemoembolization for the treatment of stages III and IV lung squamous cell carcinoma: A retrospective controlled clinical study. *First Author: Jianfei Tu, The Fifth Affiliated Hospital of Wenzhou Medical College, Lishui, China*

Background: To determine the differences in efficacy and safety between drug-eluting bead bronchial arterial chemoembolization (DEB-BACE) combined with intravenous chemotherapy and systemic chemotherapy alone for the treatment of stages III and IV lung squamous cell carcinoma (LSCC). **Methods:** 136 patients with stages III and IV LSCC were retrospectively recruited between January 2018 and August 2021 and divided into group A (chemotherapy-only, N = 95) and group B (DEB-BACE combined with intravenous chemotherapy, N = 41). The short-term efficacy, hemoptysis and dyspnea remission rates, and incidence of adverse reactions were compared between the two groups. Survival estimation was performed by Kaplan-Meier, and the Log-rank test was performed to compare survival differences between groups. **Results:** The One-month DCR (90.2% vs. 49.5%) and ORR (75.6% vs. 38.9%) were better in group B than in group A (both P < 0.05). Progression-free survival (PFS) was 8.0 months in Group B and 6.0 months in Group A, a statistically significant difference (P < 0.05). The PFS rates at 6, 12, and 24 months were 63.4%, 24.4%, 0.0%, 43.2%, 13.7%, and 0.0% in groups B and A, respectively, this difference was significant (P < 0.05). The median overall survival was better in group B than in group A (19.0 vs 14.0 months, P < 0.05). The OS rates at 6, 12, and 24 months were 100%, 85.4%, 26.8%, 78.9%, 56.8%, and 22.1% in groups B and A, respectively, with statistically significant differences (P < 0.05). The hemoptysis and dyspnea remission rates were better in group B than in group A within one month after treatment (P < 0.05), however, in terms of the incidence of adverse reactions, incidences, such as post-treatment fatigue and bone marrow suppression, were significantly lower in Group B than in Group A during the follow-up period (P < 0.05). **Conclusions:** DEB-BACE combined with intravenous chemotherapy is effective for the treatment of advanced LSCC, with lower adverse reactions, and significant improvement in patients' hemoptysis and dyspnea symptoms, which is worthy of clinical application. Research Sponsor: Lishui Science & Technology Bureau; Zhejiang Medical Association.

8550

Poster Session

Association of circulating CD103⁺ T cells with major pathological response in a randomized phase 2 trial of neoadjuvant durvalumab with or without stereotactic body radiotherapy in patients with early-stage non-small cell lung cancer. *First Author: Zachary Walsh, Columbia University Medical Center, New York, NY*

Background: We previously reported results of a randomized phase 2 study, demonstrating a higher rate of major pathological response to durvalumab in combination with stereotactic body radiotherapy (SBRT) compared to durvalumab alone in patients with localized (stage I-IIIa) non-small cell lung cancer (NSCLC). Biomarkers of response in NSCLC are poorly understood. To address this, we evaluated sequentially collected peripheral blood mononuclear cells (PBMCs) from study participants to identify easily accessible biomarkers associated with major pathological responses. **Methods:** PBMCs were obtained from study participants at defined pre-treatment, peri-operative, and post-operative timepoints. We performed 25-marker spectral flow cytometric analysis of the T cell compartment in these samples and used dimensionality reduction and clustering programs to identify populations of interest. **Results:** Our analysis of these samples revealed populations of both CD4⁺ and CD8⁺ T cells with hallmarks of prior antigen exposure and tissue residency (CD103⁺, CCR7⁺, CD45RA⁺), suggesting tumor-experienced T cells circulating into the blood. Greater pre-treatment frequency of these T cell populations was associated with major pathological responses to neoadjuvant therapy. This observation was consistent when evaluating patients with major pathological responses across both treatment arms, and within the durvalumab plus SBRT group, where we had enough patients with major pathological responses. Maturation of disease-free survival data from this trial will enable us to evaluate the association of these biomarkers with long-term survival. **Conclusions:** Together, these data reveal an unexpected population of T cells in the peripheral blood with features of tissue-residency, which are associated with major pathological responses, and suggest that re-circulation of tumor-experienced T cells may represent a predictive biomarker for neoadjuvant treatment of NSCLC. Research Sponsor: Columbia University Herbert Irving Comprehensive Cancer Center.

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Poster Session

Association of peripheral memory B cell population maintenance and long term survival after perioperative chemoimmunotherapy in NSCLC (NADIM trial). *First Author: Belen Sierra-Rodero, Instituto de Investigación Sanitaria Puerta de Hierro-Segovia de Arana, Hospital Universitario Puerta de Hierro-Majadahonda, Madrid, Spain*

Background: In the context of perioperative immunotherapy, it is crucial to personalize adjuvant treatment, identifying which patients should or should not receive post-surgical immunotherapy. Here we describe the changes in B cell peripheral blood immunophenotype during perioperative immunotherapy and its potential to predict disease progression in patients from NADIM I clinical trial (NCT03081689). **Methods:** Blood samples from 42 patients were obtained at pre-, post-neoadjuvant chemoimmunotherapy (pre-surgery) and at 6 and 12 months of adjuvant IO. Peripheral mononuclear cells were stained with CD19, CD20, CD38, CD24, CD27, CD25, CD10 antibody panel and analyzed by flow cytometry using FlowJo. Statistical analysis in paired samples was performed with Wilcoxon test and differences in parameters' fold changes between disease status groups (Progression-free at 34.2 months) were determined by Mann-Whitney U tests. Variables cutoffs were established using ROC curve analysis. Progression-free survival (PFS) was evaluated using Kaplan-Meier curves and long-rank test. The median follow-up was 38.0 months. **Results:** Regarding the impact of NADIM complete treatment scheme in patient's B cells, there was a reduction of memory B cells (CD19+CD20+CD38-CD24+CD27+; $p < 0.001$) and CD20 levels in total B cells (CD19+CD20+; $p = 0.001$) ($n = 17$). Importantly, this decrease occurs in all patients regardless their pathological response or disease progression. However, the magnitude of the memory B cell percentage and CD20 levels reduction was significantly more pronounced in patients whose disease progress thereafter ($p = 0.023$, $p = 0.052$ at 6 and 12 months for memory B cells; and $p = 0.002$, $p = 0.009$ at 6 and 12 months for CD20 expression). Patients with a relative drop of memory B cells greater than 90% at 6 or 12 months, showed a shorter PFS ($p = 0.028$, $p = 0.007$). Likewise, patients with a relative decrease of CD20 expression on B cells higher than 60% at 6 or 12 months had shorter PFS ($p = 0.016$, $p < 0.001$). The AUC ROCs to identify patients with disease progression, were 0.824 and 0.885 at 6 and 12 months for memory B cells; and 0.912 and 0.981 at 6 and 12 months for CD20 levels. Moreover, memory B cells percentage and CD20 levels decrease occur between surgery and the first 6 months of adjuvant therapy ($n = 21$, $p < 0.001$, $p = 0.025$). After that, these levels are maintained from 6 to 12 months of adjuvant treatment ($n = 20$, $p = 0.290$, $p = 0.682$), thus the overall reduction is also observed between surgery and 12 months samples ($n = 17$, $p < 0.001$, $p = 0.001$). **Conclusions:** Perioperative IO produces a significant reduction in memory B cells and CD20 levels. Importantly, stronger decreases might be helpful to predict progression since they are associated to shorter PFS, indicating that the maintenance of the memory B cell peripheral compartment is relevant for long-term survival of these patients. Research Sponsor: Spanish Health Ministry, ISCIII (PI19/O1652, PI22/O1223); Bristol Meyers Squibb; Horizon 2020 European Union Funding for Research and Innovation (CLARIFY); Spanish Ministry of Science and Innovation (RTC2017-6502-1, RTC2019-007359-1).

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Poster Session

Genomic comparison of MET exon 14 skipping and MET amplified non-small cell lung cancer. *First Author: Rachel Minne, Department of Human Oncology, School of Medicine and Public Health, University of Wisconsin, Madison, WI*

Background: In non-small cell lung cancer (NSCLC), the MET tyrosine kinase receptor can be dysregulated by mutations and/or gene amplification. The most common MET mutation is in exon 14 (METex14), leading to impaired receptor degradation and increased MET-mediated signaling causing sustained tumor proliferation. MET amplification also leads to continued MET signaling and oncogenesis and can be a mechanism of resistance to targeted therapy. We sought to compare the genomic landscape of METex14 and high-level MET amplified tumors, both of which can be targeted with tyrosine kinase inhibitors. **Methods:** We analyzed 18,047 NSCLC tumors (any stage/subtype) sequenced with Tempus xT assay (DNA-seq of 648 genes at 500x coverage, full transcriptome RNA-seq). Tumors were queried for METex14 mutations, high MET amplification (METamp), defined as copy number gain (CNG) ≥ 10 , and other MET mutations (METother). Immuno-oncology (IO) biomarkers were compared across MET-altered and MET wild-type (METwt) groups. The prevalence of somatic gene alterations was compared similarly with the false-discovery rate (FDR) adjustment. **Results:** A total of 276 (1.53%) METex14, 138 (0.76%) METamp, 27 (0.15%) METother, and 17,606 (97.56%) METwt tumors were identified. Across groups, patients with METex14 were older, more likely to be female, and nonsmokers. METex14 exhibited the lowest tumor mutational burden (TMB) and lowest neoantigen tumor burden (NTB). PD-L1 positivity rates were higher in METex14 tumors compared to METamp and METwt tumors. MET log10 gene expression was highest in METamp. METamp exhibited the lowest proportion of CD4 T cells and the highest proportion of NK cells. Compared to METex14, METamp exhibited increased prevalence of TP53 (83% vs 37%), TFCE (46% vs 1.1%), CFTR (37% vs 1.4%), EGFR (31% vs. 7.6%), WNT2 (11% vs 0.4%), KEAP1 (14% vs 0.7%), and STK11 (8% vs 1.4%), and decreased prevalence of MDM2 (4.3% vs. 14%), and FRS2 (2.9% vs. 12%). **Conclusions:** In this large population-based analysis of MET-altered NSCLC, METex14 tumors exhibited differences in IO biomarkers and the somatic landscape compared to non-METex14 NSCLC tumors. Variations in immune profiles may affect immunotherapy selection in MET-altered NSCLC and require further exploration. Research Sponsor: Tempus Labs; U.S. National Institutes of Health.

Characteristic	METex14 (N = 276)	METamp (N = 138)	METother (N = 27)	METwt (N = 17,606)	p-value
TMB ¹	2.6 (1.3, 4.2)	5.4 (3.0, 9.7)	5.0 (3.2, 6.7)	4.6 (2.7, 7.3)	<0.001
NTB ¹	1.22 (0.71, 1.95)	2.93 (1.50, 5.12)	2.44 (1.34, 3.78)	2.20 (1.22, 3.66)	<0.001
PD-L1 positivity (IHC) ²	128 (83%)	64 (75%)	12 (86%)	6,180 (57%)	<0.001
MET log10 gene expression ¹	3.70 (3.45, 3.98)	4.43 (4.26, 4.53)	3.80 (3.69, 4.02)	3.32 (3.07, 3.57)	<0.001
%CD4 T cells of all immune cells ¹	23% (17%, 31%)	17% (11%, 25%)	23% (19%, 30%)	23% (16%, 30%)	<0.001
% NK cells of all immune cells ¹	11% (7%, 17%)	15% (9%, 24%)	14% (11%, 17%)	12% (7%, 18%)	0.013

¹Median (Interquartile range) ²N (%).

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Poster Session

Phase II trial of consolidation pembrolizumab (pembro) after proton reirradiation (re-RT) for thoracic recurrences of non-small cell lung cancer (NSCLC). *First Author: Nikhil Yegya-Raman, University of Pennsylvania, Philadelphia, PA*

Background: Isolated thoracic recurrences of NSCLC in/near previously irradiated fields present a therapeutic challenge. One treatment option is re-RT with proton beam therapy (PBT) to minimize normal tissue exposure; however, distant failure is common. Herein, we report the first prospective trial of PBT re-RT followed by pembro. **Methods:** This phase II, single-arm trial (NCT03087760) enrolled patients (pts) with isolated locoregional recurrences of NSCLC in/near previously irradiated fields. Key inclusion were definitive thoracic RT > 6 months (mo) prior, ECOG 0-1, and clinical target volume (CTV) < 250 cc. Key exclusion were extrathoracic metastases, prior grade ≥ 3 pneumonitis, and prior immunotherapy < 30 days from re-RT start. 4-12 weeks after completion of 60-70 Gy PBT re-RT, pts without progressive disease started pembro 200 mg IV q21 days for up to 12 mo. Primary endpoint was progression-free survival (PFS). Secondary endpoints were overall survival (OS) and CTCAE v5.0 toxicity. PFS and OS were measured from re-RT start and estimated using Kaplan-Meier method. **Results:** Between November 2017 and April 2021, 32 pts were consented; 10 were excluded most commonly due to CTV ≥ 250 cc ($N = 3$) or separate primary ($N = 3$). 22 were eligible and initiated PBT re-RT. Trial closed early due to slow accrual. Median age was 68 years. All recurrences were biopsy-proven; 8 (36%) were squamous. Recurrences were primary tumor ($N = 4$), nodal ($N = 8$), and both ($N = 10$). 8 pts (36%) received prior durvalumab. Median interval from prior RT end to re-RT start was 20 mo (range 10.2-74.8). Median delivered re-RT dose and dose/fraction were 60 Gy (range 18-70) and 2 Gy (range 1.8-4), respectively; 21 pts (95%) received concurrent chemotherapy. 15 pts (68%) initiated consolidation pembro on trial and received a median of 3 cycles (range 2-17). Pembro was discontinued due to completion of 1 year ($N = 3$), disease progression ($N = 4$), toxicity ($N = 5$; 2 pembro-related [grade 2 pneumonitis after cycle 3 and grade 3 mucositis after cycle 13], the former also re-RT-related), death without progression ($N = 2$; NSTEMI and unknown), and pt decision ($N = 1$). Median follow-up was 38.7 mo. Median PFS and OS were 8.8 mo (95% CI 4.2-23.7) and 22.8 mo (95% CI 6.9-not reached) for all pts, respectively, and 13.5 mo (95% CI 4.2-25.3) and 22.8 mo (95% CI 6.5-not reached) for pts who started pembro. Receipt of > 3 cycles pembro ($N = 7$) associated with better OS (median 46.7 vs 13.8 mo, log-rank $p = 0.007$). 10 pts (46%) had grade ≥ 3 toxicity; 2 were pembro-related (grade 3 lymphopenia and mucositis). 1 pt had grade 5 toxicity (aortic fistula), from re-RT. **Conclusions:** In the first prospective trial of PBT re-RT + consolidation pembro, treatment proved feasible and PFS was acceptable though the capacity to administer pembro was limited. This approach may be considered in selected patients with isolated thoracic recurrences of NSCLC. Clinical trial information: NCT03087760. Research Sponsor: Merck & Co.

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Poster Session

Stereotactic ablative radiotherapy with nivolumab for early-stage operable non-small cell lung cancer: A phase 2 study. *First Author: Gustavo Schvartsman, Hospital Israelita Albert Einstein, São Paulo, Brazil*

Background: Surgery is standard of care for patients with stage I non-small cell lung cancer (NSCLC). However, 5-year mortality can reach up to 30%. For patients with contraindication to surgery, treatment with stereotactic ablative radiotherapy (SABR) leads to adequate local tumor control, but has a high rate of regional and distant failure. SABR as neoadjuvant therapy for stage I NSCLC produced a pathologic complete response (pCR) rate of only 60% when surgery was performed after 10 weeks of treatment, demanding improvement in the management of both operable and inoperable early-stage NSCLC. Immune checkpoint inhibitors (ICI) are routinely used in stages III-IV NSCLC, with recent approvals in the peri-operative setting, and may be synergistic with radiotherapy. We hypothesized that neoadjuvant nivolumab plus SABR may improve pCR rate and provide insight to its changes in the tumor micro-environment. **Methods:** This is a phase 2, single arm, open label study evaluating neoadjuvant treatment for patients with NSCLC of up to 4 cm, with no lymph node involvement (AJCC 8th edition: up to cT2aN0), and adequate surgical conditions. Treatment consisted of nivolumab 360 mg every 3 weeks for 3 doses or unacceptable toxicity. SABR started on D1 of nivolumab, with a duration of 2 to 3 weeks, depending on the lesion size and location (3 x 18 Gy; or 5 x 10 Gy; or 8 x 7.5 Gy). Standard-of-care surgery was performed at 10 (+/- 2) weeks after the last radiotherapy dose. The primary endpoint of the study is pCR rate at surgery. Tissue, blood, and stool samples were collected during treatment. **Results:** We included 25 patients. All but one were cared for in the Brazilian public system. Mean age was 68 years. Mean tumor size was 2.45 cm. Only 3 patients were never-smokers. Surgery was performed as scheduled in all but one patient. pCR rate was 80% (19/24) and MPR rate was 83% (20/24) of patients who underwent surgery. Twenty-nine treatment-emergent adverse events occurred in 13 patients (23 grade 1-2 events, two grade 3 and two grade 5 events, being only one grade 3 diarrhea related to experimental treatment). The single patient who was not operated died during study treatment from relapsed acute alcoholic hepatitis. The other grade 5 event was due to a respiratory infection, both unrelated to treatment. Two patients died from surgical complications 185 and 72 days after surgery, respectively (one with pulmonary artery lesion with subsequent clinical complications and other with thromboembolic events), deemed unrelated to experimental treatment. During follow-up, two additional patients died due to comorbidities, and none relapsed to date. **Conclusions:** In this trial with patients with significant comorbidities and smoking history from the public system in Brazil, we demonstrated a pCR rate of 80% with SABR + nivolumab. Further studies are warranted to evaluate this strategy versus surgery in operable patients with stage I disease. Clinical trial information: NCT04271384. Research Sponsor: Bristol-Myers Squibb.

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Poster Session

Assessing the efficacy and safety of DEB-BACE combined with intravenous chemotherapy for the treatment of intermediate to advanced lung adenocarcinoma after progression of targeted drug resistance. *First Author: Lingqiang Lai, The Fifth Affiliated Hospital of Wenzhou Medical College, Lishui, China*

Background: To compare the efficacy and safety of drug-eluting bead bronchial arterial chemoembolization (DEB-BACE) combined with intravenous chemotherapy versus systemic intravenous chemotherapy for intermediate to advanced lung adenocarcinoma with positive driver genes after progression of targeted therapy. **Methods:** A total of 131 patients with intermediate to advanced lung adenocarcinoma were retrospectively recruited from 2018-2022 and divided into Group A (standard chemotherapy regimen, N=62) and Group B (DEB-BACE and intravenous chemotherapy, N=69). The short-term efficacy, hemoptysis remission rate, dyspnea remission rate, and incidence of adverse effects were compared between the two groups using the χ^2 test. Survival estimates were performed by Kaplan-Meier, and a Log-rank test was performed to examine survival differences between groups. **Results:** The three-month disease control rate (DCR): 82.6% vs 58.1% and objective remission rate (ORR: 60.9% vs 38.7%) were better in group B than in group A (both $P < 0.05$). Median progression-free survival (PFS, 10.0 vs 7.9 months) and median overall survival (OS, 33.0 vs 18.0 months) were better in group B than in group A (both $P < 0.05$). The PFS rates at 6, 12, and 24 months were 67.3%, 40.8%, and 0.0% and 54.1%, 23.2%, and 0.0% in groups B and A, respectively; and the OS rates at 6, 12, and 24 months were 100%, 95.7%, 72%, 88.6%, 66.1%, and 21.8% in group B and group A, respectively, with statistically significant differences ($P < 0.05$). Within one month after treatment, group B had better hemoptysis relief (83.3% vs. 20.0%) and dyspnea relief (57.5% vs. 30.0%) than group A (both $P < 0.05$). During the follow-up period, the incidence of adverse reactions was significantly lower in group B than in group A ($P < 0.05$). **Conclusions:** For patients with intermediate to advanced lung adenocarcinoma who have failed to progress on targeted therapy, DEB-BACE combined with intravenous chemotherapy has shown superior efficacy and survival benefit and lower adverse effects, while significantly improving patients' symptoms of hemoptysis and dyspnea, with important application prospects. Research Sponsor: Lishui Science & Technology Bureau; Zhejiang Medical Association.

8557

Poster Session

Development of a novel blood-based RNA gene expression platform for early-stage lung cancer diagnosis. *First Author: Martin J Keiser, IV BioHoldings (IVBH), Newport Beach, CA*

Background: Blood-based methods using circulating tumor DNA (ctDNA) and cell-free DNA (cfDNA) are under development for early and less invasive detection of lung cancer, although detection of the earliest stage cancers (stages 0-II) using these modalities is suboptimal. We hypothesized that a machine learning approach using RNA gene expression may offer important information on the biology of the patient, allowing for gene expression profiles to be used as a surrogate measurement of cancer disease phenotype and as a promising direction for early detection of lung cancer. In a previous study, 23 miRNA biomarkers were successfully discovered and validated for the non-invasive diagnostic classification of lung adenocarcinoma, achieving 97.7% sensitivity, 98.7% specificity in blood obtained from 383 clinical subjects. The aim of this study was to train a machine learning algorithm, from the 23 miRNA features, to test the signature for early lung cancer detection. **Methods:** A large and diverse clinical cohort was obtained from the NIH Gene Expression Omnibus database, GEO Accession Number GSE137140 ($n=3,744$), comprised of miRNA extracted from serum samples consisting of subjects with pre-operative lung cancer ($n=1,566$) and non-cancer controls ($n=2,178$). Our analytic plan leveraged machine learning methods derived from XGBoost classification, a popular supervised-learning algorithm that uses sequentially built shallow decision trees to provide accurate results and avoidance of overfitting. The algorithm was trained using XGBoost 1.4.1.1 R library programmed with R v3.6.3. **Results:** The lung cancer cohort was heavily weighted towards early-stage lung cancer (87.7% stage I/II), including representation across prevalent histologic types (adenocarcinoma 77.8%, non-adenocarcinoma 22.2%) and those who self-reported as never smokers (37.9%). The 23-miRNA signature achieved 98% sensitivity, 89% specificity in the held-out test set (Table). When incorporating age and gender, the 23-miRNA signature achieved 95.5% sensitivity, 90.3% specificity. **Conclusions:** A machine learning approach using RNA gene expression in patient serum achieved high sensitivity and specificity in a large, predominantly early-stage, lung cancer cohort. A multi-analyte, multimodal approach that leverages machine learning algorithms with RNA gene expression profiles and available demographics and clinical risk-factors, represents the possibility to accurately detect lung cancer in the earliest stages. This approach has successfully been translated from microarray to PCR instrumentation, with further validation of this machine learning method and approach currently underway. Research Sponsor: LiquidLung, Inc.; IV BioHoldings, LLC.

Results for miRNA-only XGBoost algorithm in held-out test set.

Predicted Class	Actual Class		
	Total $n=748$ Control Lung Cancer	Control True Negative (388) False Positive (47)	Lung Cancer False Negative (6) True Positive (307)

8556

Poster Session

Phase Ib study of neoadjuvant concurrent chemoradiation plus durvalumab followed by surgery and adjuvant durvalumab for resectable stage III NSCLC. *First Author: Jiyun Lee, Lung Cancer Center, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea*

Background: The use of neoadjuvant and adjuvant immunotherapy in resectable non-small cell lung cancer (NSCLC) has become a standard of care. However, the integration of immunotherapy into a trimodality treatment regimen has not been widely explored. We hypothesized that adding durvalumab to neoadjuvant concurrent chemoradiation and surgery would not increase treatment-related adverse events (TRAE) during neoadjuvant period. **Methods:** This was a prospective, single center, single-arm, open-label phase Ib study. Patients with resectable, stage III N2 NSCLC received concurrent chemoradiation [weekly paclitaxel (45mg/m²)/carboplatin (AUC 2.0) for 5 weeks with radiotherapy 45Gy] and durvalumab 1,500mg Q4W for 2 cycles followed by surgical resection and adjuvant durvalumab for 1 year. The primary endpoint was the frequency of patients who experience grade 3 or more TRAE during neoadjuvant therapy based on CTCAE 4.03. **Results:** Of 30 patients (median age 65.5 years; 67% male), 56.7% had squamous histology and 60.0% had stage IIIA. Any grade AEs and TRAEs (neoadjuvant/adjuvant) were reported in 83.3%/76.7% and 70.0%/63.3% of patients, respectively. Grade 3 or more AEs and TRAEs (neoadjuvant/adjuvant) were reported in 10.0%/3.3% and 10.0%/0.0%, respectively. Grade 3 or more TRAE reported during neoadjuvant treatment were neutropenia, anemia, and nausea, one each; no Grade 5 AEs occurred. Surgical resection was not performed in three patients: two due to treatment-related adverse events (AEs) and one due to patient refusal. Among 27 patients who received complete resection, the pathologic complete response (pCR) rate and major pathologic response (MPR) rate were 40.7% (95% CI, 22.4–61.2) and 74.1% (95% CI, 53.7–88.9), respectively. Excluding four patients with EGFR, ALK, KRAS G12C, or MET ex14skipping mutations, the pCR rate was 47.8% (95% CI, 26.8–69.4) and MPR rate was 87.0% (95% CI, 66.4–97.2). Overall, pathologic downstaging was achieved in 70.4% (95% CI, 49.8–86.2). Objective response rate according to RECIST v1.1 was 50.0% (95% CI, 31.3–68.7). One patient delayed the schedule for surgical resection due to radiation pneumonitis (G2), unrelated to the drug administered. Otherwise, there were no peri-operative mortality or morbidity. All patients who underwent surgery, except one whose disease progressed immediately after resection, received at least one dose of adjuvant durvalumab; 61.5% completed 1-year treatment, 11.5% were continuing treatment, 11.5% discontinued due to AE, and 11.5% discontinued due to disease progression at the time of data cutoff. Grade 3 or more TRAE reported during adjuvant treatment were radiation pneumonitis and proteinuria, one each. **Conclusions:** This study confirms the manageable safety profile of adding durvalumab to neoadjuvant concurrent chemoradiation for treatment of resectable stage III NSCLC. Clinical trial information: NCT03694236. Research Sponsor: AstraZeneca.

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Poster Session

Benefit of post-operative radiation therapy for incompletely resected stage I-IIIa non-small cell lung cancer: An analysis of the National Cancer Database. *First Author: Sindu Iska, Maroon Cancer Center, Cleveland Clinic Florida, Weston, FL*

Background: The presence of micro-residual (R1) or macro-residual (R2) disease in non-small cell lung cancer (NSCLC) is associated with a higher risk of recurrence. The benefits of post-operative radiation therapy (PORT) in incompletely resected NSCLC is not clear. The purpose of this study is to compare median overall survival (mOS) of treatment modalities in the post-operative setting for resected stage I-IIIa NSCLC with residual disease (R1/R2) and to determine if PORT provides benefit in this patient population using the National Cancer Database (NCDB). **Methods:** From the NCDB dataset for the years of 2006-2016, we extracted patients diagnosed with stage I-IIIa NSCLC and who had incomplete resection with residual disease (R1/R2). Kaplan-Meier analysis was performed to differentiate the effect of different post-operative treatment modalities, concurrent chemoradiotherapy (CCRT), sequential chemo-radiotherapy (SCRT) and chemotherapy (CT) alone on mOS. Subsequently, univariate Cox regression was used to identify statistically significant variables, then multivariate Cox regression was performed to establish variables that contributed to the survival. Lastly, multinomial logistic regression was utilized to establish association of the independent factors. SAS version 9.4 was used to analyze the data. **Results:** Among the 2701 patients who met inclusion criteria, the average age was 64.1, 64.8 and 65.9 year old for CCRT, SCRT and CT, respectively. Male's constituted 53.6% and white's were 88.1%, and patient's were distributed equally across clinical stages. The majority of patients received SCRT (51.7%) followed by CT alone (39%), and CCRT (9.2%). There were no statistically significant differences in mOS between the different treatment modalities ($p=0.220$). Patients with R2 were 177% more likely to receive CCRT than CT compared to R1 (OR 2.77, CI 1.86-4.13 and $p<0.001$). Male's were 28% more likely to receive SCRT than CT compared to females (OR 1.28, CI 1.08-1.52 and $p=0.0041$). Nodal involvement was associated with decreased mOS with N2/N3 having 37% lower mOS compared to N0 (HR=1.37, CI 1.19-1.57 and $p<0.0001$). Patients who had R2 disease had a 38% lower mOS compared to those R1 (HR 1.38%, CI 1.19-1.62, $p<0.0001$). **Conclusions:** Despite the risk of unfavorable outcomes for patients with residual disease after surgery for NSCLC, the addition of radiotherapy, either concurrently or sequentially, to CT did not offer statistically significant mOS benefit compared to CT alone. Given the known toxicities of radiation, and the lack of impact on survival, the benefit of post-operative radiation is questionable among patients with residual disease after resection. Research Sponsor: Maroon Cancer Center, Cleveland Clinic Florida.

8559

Poster Session

Large scale evaluation of pulmonary nodule workup: A real-world study of over 150,000 patients in New York State. *First Author: Vamsidhar Velcheti, NYU Langone-Laura and Isaac Perlmutter Cancer Center, New York, NY*

Background: Around 1.6 million patients in the US annually have a pulmonary nodule (PN) found on imaging. Previous studies suggest 1-12% of PNs represent an underlying malignancy at a potentially curative stage. PNs ≥ 6 mm are considered higher risk. Despite guideline availability, only about one-third of commercially insured patients with a PN receive recommended workup, which may include further investigation via imaging or surgery. In addition, patients and providers may delay workup of PNs identified during COVID-19. We aimed to describe variations in PN workup for different patient demographic and clinical characteristics at 7 healthcare institutions in New York (NY) state. **Methods:** We used a retrospective cross-sectional design in which structured demographic and unstructured clinical data were used to analyze patient documents from a NY state health information exchange from January 2018 to February 2022. Clinical features were abstracted using a clinical natural language processing platform, CLIX unlock. **Results:** 58 million documents from 5.5 million unique patients were analyzed. Of the overall 151,436 patients with PNs, workup was found in 47% (71,071). Across institutions, workup ranged between 24% and 52%; 40% (60,749) had evidence of a PN in the upper lung location. We found 52,789 patients (35%) had a maximum PN ≥ 6 mm and of those, 55% (28,958) had a workup (Table). For patients with a PN ≥ 6 mm, workup for non-English speaking patients was 9% lower than for English speaking patients (47% vs 56%), 17% lower for patients 18-44 years than patients 45-90 years (39% vs 56%), 47% lower for patients presenting with a chest injury rather than cancer screening (28% vs 75%), and 9% higher for patients with initial imaging via chest computed tomography (CT) rather than other CT (58% vs 49%). After the start of the COVID-19 pandemic (January 2020), overall workup decreased 3.8% and prevalence of symptoms such as dyspnea and chest pain increased. **Conclusions:** The descriptive findings of this analysis demonstrate gaps and variations in workup for patients with PNs across different demographics and clinical scenarios. A subsequent project is underway to explore strategies for improvement in adherence to guideline-recommended care to benefit patients by diagnosing lung cancer at an earlier, potentially curative stage. Research Sponsor: AstraZeneca LLC.

Workup Across Select Population Characteristics.

Characteristic	Group	Total Patients w/ PNs	Patients w/ Workup n (%)	Total Patients w/ PNs ≥ 6 mm	Patients w/ Workup PNs ≥ 6 mm n (%)
Age	18-44	14,296	4,213 (30)	4,059	1,571 (39)
	44-65	53,032	23,337 (44)	15,925	8,343 (52)
	65+	84,108	43,521 (52)	32,805	19,044 (58)
Language	English	112,409	54,033 (48)	39,647	22,279 (56)
	Spanish	8,990	3,389 (38)	3,045	1,360 (45)
	Chinese	1,258	571 (45)	546	269 (49)
	Other	4,227	1,995 (47)	1,623	848 (52)
Index Imaging Type	CT chest	105,037	52,503 (50)	35,504	20,517 (58)
	CT, other	37,899	14,925 (39)	12,565	6,212 (49)

8561

Poster Session

Incidence, outcomes, and risk factors of acute immune checkpoint inhibitor (ICI) pneumonitis post-chemoradiation with durvalumab for patients with locally advanced non-small cell lung cancer (LA-NSCLC): A population-based multicenter study. *First Author: Chloe Lim, University of Calgary, Calgary, AB, Canada*

Background: The PACIFIC trial has drastically changed the LA-NSCLC treatment paradigm and improved survival outcomes with consolidation durvalumab post-chemoradiotherapy. Despite these promising results, real-world practice has demonstrated that ICI pneumonitis can have significant clinical complications and terminate consolidation therapy prematurely. This study aimed to identify clinical predictors, outcomes, and healthcare utilization in ICI pneumonitis in LA-NSCLC patients who received consolidation durvalumab in real-world practice. **Methods:** Using the Alberta Immunotherapy Database, we retrospectively evaluated all NSCLC patients who received durvalumab in Alberta, Canada from January 2018 to December 2021. Pneumonitis cases were identified based on radiographic changes and oncologists' clinical assessments. We examined incidence and predictive values of severe pneumonitis ($\geq$ grade 3), with secondary outcomes of overall survival (OS) and time-to-treatment failure (TTF). Exploratory multivariate analyses were performed to identify predictive values to developing severe pneumonitis and worse OS/TTF. **Results:** Of 189 total patients, most were ECOG 0-1 (91%) and had partial response from chemoradiation (85%) prior to durvalumab. 49% received full year of therapy (n = 93). Median TTF was 11.2 months, and median OS of 19.7 months with 1-year OS 64% (n = 121). 26% (n = 49) developed any grade of pneumonitis. 9% (n = 17) had severe pneumonitis. Corticosteroids were administered to 86% of the pneumonitis patients (n = 42); 53% (n = 26) required admission. 13% (n = 9) of deaths were attributed to pneumonitis. Male gender and pre-existing autoimmune condition were associated with severe pneumonitis whereas V_{20} (percentage of irradiated lung volume ≥ 20 Gy) was associated with developing any grade pneumonitis. In multivariable analysis, male gender and V_{20} was significantly associated with worse OS whereas older age, smoking status, pneumonitis, and male gender with lower TTF. Pneumonitis development was found to be an independent risk factor for worse OS (p = 0.038) and TTF (p = 0.007). **Conclusions:** We report a pneumonitis incidence comparable to prior retrospective studies and higher rate of severe pneumonitis compared to PACIFIC trial. Our results corroborate that V_{20} , a previously established risk factor for durvalumab associated pneumonitis, is a significant predictor for developing pneumonitis and worse OS. In contrast to smaller retrospective studies, we observed male gender and pre-existing autoimmune conditions appear to predict severe durvalumab associated ICI pneumonitis. These results affirm the importance of careful patient selection for safe completion of consolidation durvalumab in real-world LA-NSCLC population. Research Sponsor: None.

8560

Poster Session

Mortality benefit of a blood-based biomarker panel for lung cancer and the PLCO cohort. *First Author: Johannes Fahrman, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: A 4-protein biomarker panel (4MP) combined with the validated PLCO_{m2012} clinical risk model has been shown to improve lung cancer risk estimation over either metric alone. We investigated whether these panels in combination could also identify individuals at high risk of harboring a lethal lung cancer. **Methods:** We used data from an established logistic regression combining the 4MP and the PLCO_{m2012} risk model, which were assessed in pre-diagnostic sera from 552 lung cancer cases and 2,193 non-cases from the Prostate Lung Colorectal and Ovarian (PLCO) cohort. Of the 552 lung cancer cases, 387 (70%) died from lung cancer. Cumulative incidence of lung cancer death as well as sub-distributional and cause-specific hazard ratios were calculated based on 4MP+PLCO_{m2012} risk scores at a pre-defined 1.0% and 1.7% 6-year risk thresholds, which correspond to the 2013 and 2021 US Preventive Services Task Force lung cancer screening criteria, respectively. **Results:** When considering cases diagnosed within 1 year of blood draw and all non-cases, the AUC estimate of the 4MP+PLCO_{m2012} model for risk prediction of lung cancer death was 0.88 (95% CI: 0.86-0.90). Among cases, the cumulative incidence of lung cancer death was statistically significantly higher in individuals with 4MP+PLCO_{m2012} scores above the 1.0% 6-year risk threshold (modified χ^2 : 5.42, P: 0.02). Corresponding sub-distributional and lung cancer death-specific hazard ratios for test-positive cases were 1.69 (95% CI: 1.07-2.66) and 1.80 (95% CI: 1.15-2.82), respectively. **Conclusions:** The blood-based biomarker panel in combination with PLCO_{m2012} identifies individuals at high risk of a lethal lung cancer. Research Sponsor: U.S. National Institutes of Health; Cancer Prevention & Research Institute of Texas (CPRIT); MD Anderson Moon Shots Program.

8562

Poster Session

Impact of SARS-COV2 infection on the clinical outcomes in patients with lung cancer compared to all other cancers. *First Author: Vaishali Deenadayalan, John H. Stroger, Jr. Hospital of Cook County, Chicago, IL*

Background: The outbreak of 2019 Novel coronavirus disease (COVID) has led to various deleterious outcomes in cancer patients. Those with lung cancer were noted to have increased morbidity and mortality when infected with COVID. We aimed to study the outcomes of COVID infection in patients with lung cancer compared to those with all other types of cancer. **Methods:** Healthcare Cost and Utilization Project-Nationwide Inpatient Sample database-2020 was queried to identify all COVID patients with lung cancer and those with all other types of cancer excluding lung cancer. The groups were compared for socio-demographic differences, medical comorbidities, inpatient mortality, length of stay (LOS), and total hospital charges (THC). Secondary outcomes included a diagnosis of thrombocytopenia (TCP), Acute Respiratory Failure (ARF), sepsis, anemia, pancytopenia and shock. Statistics were performed using t-test, univariate and multinomial logistic regression. **Results:** A total 1,050,045 COVID-19 admissions in cancer patients were identified, of which 4,625 (8.7%) had lung cancer whereas 48,840 (91.3%) had other types of cancer other than lung cancer. Lung cancer patients were older (Mean age 72 vs 69 years, p < 0.01). There was a higher prevalence of lung cancer compared to other cancers in whites (71 vs 58%, p < 0.01), hispanics had a lesser prevalence of lung cancer (7 vs 17%, p < 0.01). Lung cancer patients has a higher Charlson Comorbidity burden (> 2) compared to other cancers (91 vs 62%, p < 0.01). Lung cancer patients were less likely to have private insurance (14 vs 22%, p < 0.01). Among the comorbidity burden, lung cancer patients had a higher rate of dyslipidemia, COPD, Coronary artery disease, Smoking, venous thromboembolism (p < 0.05). A total of 8,135 cancer patients who were admitted with COVID died, among them 970 (11.9%) had lung cancer and 7,165 (88.1%) had other types of cancer making up 21% of all lung cancer admissions that died compared to 14.7% other cancer admissions (p < 0.05). On multivariate regression analysis, after adjusting for confounders those with lung cancer had a higher odds of all-cause mortality (aOR 1.37; 95% CI: 1.13-1.67, p = 0.002). Among lung cancer patients, adjusted LOS was reduced by 0.6 days (95% CI: -1.2 to -0.1, p = 0.017) and adjusted THC was decreased by \$11,977 (95% CI: -19,010 to -4,943, p = 0.001). Among the secondary outcomes, lung cancer patients had lower rates of thrombocytopenia (6.5 vs 8.8%, p = 0.01) and anaemia (34.4 vs 38.5%, p = 0.02) compared to other cancer types. **Conclusions:** COVID-19 infection led to increased mortality in lung cancer patients compared to those with other types of cancer. The lower healthcare utilization was likely due to early mortality in the lung cancer cohort. This study calls attention to the increased vulnerability of lung cancer patients to the SARS COV2 infection than other cancer types. Research Sponsor: None.

8563

Poster Session

Development and validation of a prediction model for the recurrence of stage 1 EGFR mutation positive NSCLC in patients using machine learning with WES-based gene sets. *First Author: Akiko Tateishi, Department of Thoracic Oncology, National Cancer Center Hospital, Tokyo, Japan*

Background: Predicting the risk of postoperative recurrence is becoming increasingly important in EGFR mutation positive (EGFR-m) non-small cell lung cancer (NSCLC). Only a few reports conducted whole exome sequencing (WES) for genomic profiling in large scale EGFR-m NSCLC cases. **Methods:** We conducted WES and analyzed the clinical course of patients (pts) with NSCLC who underwent surgery between 1985 and 2019 in the PRISM project of our institute. We evaluated the EGFR-m patients' characteristics, recurrence-free survival (RFS), and developed a prediction model using machine learning, Overlapping Group LASSO to predict whether the EGFR-m patients will recur within 5 years or not as "high-risk" and "low-risk". To develop and validate the prediction model, we divided the data from 2006 as the training cohort data set and the data before 2006 as the validation cohort data set. After the development of the prediction model, we performed a stratified Cox proportional hazards model to compare the RFS between the predicted groups. **Results:** A total of 585/1351 (43.3%) pts were EGFR-m included in the PRISM project. Of all pts, stage I, EGFR-m were 205 pts. The median RFS of the stage I, EGFR-m 123.1 months (m). In the training cohort, the model detected 43 pts for high-risk and 88 pts for low-risk. In the validation cohort, the model predicted 29 pts for high-risk and 45 pts for low-risk. Median RFS of high-risk vs. low-risk were 52.2 m vs. 105 m (HR 2.43, $p=0.01$). The 1-year RFS rate, 2-year RFS rate, and 5-year RFS rates for high-risk and low-risk pts were 100% vs. 98.5%, 66.7% vs. 89.2%, and 41.7% vs. 66.1%, respectively. Twenty-eight gene set coefficients were non-zero in the prediction model. The gene sets with large positive coefficients that were considered important for prediction as "high risk" were the gene sets affected by KRAS gene overexpression and p53 gene knockdown. In contrast, gene sets repressed by mTOR inhibition and genes repressed by TBK1 gene knockdown and KRAS gene overexpression had large negative coefficients. **Conclusions:** We developed and validated the prediction model whether the EGFR-m patients will recur within 5 years or not. EGFR-m NSCLC recurrence appears to be high risk with pathways associated with KRAS and p53 genes, and low risk with mutations in the gene sets suppressed by the mTOR pathway and TBK1 gene. Research Sponsor: None.

	Training cohort (n=131)		Validation cohort (n=74)	
	High risk (n=43)	Low risk (n=88)	High risk (n=29)	Low risk (n=45)
median RFS (m), 95%CI	32.8 [23.5-44.8]	-	52.2 [23.7-NR]	105 [73.1-NR]
HR, p-value			2.43, $p=0.01$	
1-year RFS rate (%)	89 [81-98]	100 [100-100]	100 [100-100]	98.5 [95.5-100]
2-year RFS rate (%)	60 [49-75]	100 [100-100]	66.7 [44.7-99.5]	89.2 [82.0-97.1]
5-year RFS rate (%)	0	100 [100-100]	41.7 [21.3-81.4]	66.1 [55.5-78.7]

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Poster Session

Association of immune-related adverse events and efficacy outcomes in phase II trial of consolidation nivolumab plus ipilimumab or nivolumab alone after chemoradiation in patients with unresectable stage III non-small-cell lung cancer (NSCLC). *First Author: Cynthia Wei, Indiana University School of Medicine, Indianapolis, IN*

Background: Immunotherapy has been widely incorporated into the treatment of patients with non-small-cell lung cancer. Many of these patients will experience immune-related adverse events (irAEs) that may lead to early discontinuation of therapy. Previous studies have reported that patients with Stage III and metastatic NSCLC who experienced irAEs receive fewer cycles of immunotherapy without decreased efficacy. Here we report a retrospective analysis of the association between irAEs and efficacy outcomes from the BTRC LUN 16-081 randomized phase 2 trial of consolidation immunotherapy with nivolumab (N) plus ipilimumab (IPI) vs N alone following concurrent chemoradiotherapy in patients with unresectable Stage IIIA/IIIB NSCLC. **Methods:** A total of 105 eligible patients were enrolled from 9/2017 to 4/2021. Demographics, disease characteristics, and number of immunotherapy cycles received were reported in patients with and without irAEs in the two arms. Chi-square test was used for comparisons for categorical variables and Wilcoxon test for continuous variables. The Kaplan-Meier method was used to analyze progression-free survival (PFS) and overall survival (OS). A log-rank test was used to compare groups. **Results:** In treatment arm A (N alone), any grade irAEs occurred in 64.8% of patients. At a follow up of 48 months, there was no significant difference in number of N cycles started (6 vs 6, $p=0.238$), progression free survival (29.4 vs 31.9 mo, $p=0.897$), or overall survival (NE vs. 31.9 mo, $p=0.798$) in patients with and without irAEs. Patients who discontinued N because of irAEs ($n=8$ or 14.8% of patients) received significantly fewer cycles of N (2 vs 6, $p<.0001$) and had a shorter PFS (8.2 vs. 31.9 months, $p<.0001$) and OS (12.3 months vs. NE, $p<.0001$). In treatment arm B (IPI+N), any grade irAEs occurred in 84.3% of patients. At follow up of 48 months, there was no significant difference in number of IPI+N started (4 vs. 4, $p=0.260$) or overall survival (NE vs. NE, $p=0.576$), but there was a significantly longer PFS in those who experienced irAEs (30.9 months vs. 6.8 months, $p=0.0083$). Patients who discontinued IPI+N because of irAEs ($n=18$ or 35.3% of patients) received significantly fewer cycles of IPI+N (2 vs 4, $p<.0001$) without a significant difference in PFS (28.1 vs. 25.3 mo, $p=0.830$) or OS (NE vs NE, $p=0.755$). **Conclusions:** The occurrence of irAEs alone in both arms, regardless of number, was not associated with decreased efficacy outcomes in this exploratory analysis. However, if irAEs resulted in the discontinuation of therapy, these patients did have a shorter PFS and OS in the N alone arm. This difference was not observed in the IPI+N arm and those who experienced any irAEs in the IPI+N arm had an improved PFS. Research Sponsor: Bristol Myers Squibb.

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Poster Session

Phase II trial of safety and efficacy of tislelizumab plus chemotherapy in stage II-IV non small cell lung cancer (LungMark). *First Author: Yaobin Lin, Department of Thoracic Surgery, Sun Yat-Sen University Cancer Center, Guangzhou, China*

Background: The current study aimed to investigate the safety and efficacy of chemotherapy with PD-1 inhibitor, tislelizumab, for stage II-IV NSCLC. Meanwhile to explore the potential biomarkers for safety and efficacy of tislelizumab plus chemotherapy in NSCLC. **Methods:** This was an open-label, multicenter, phase 2 trial conducted at 3 hospitals in China. Patients with treatment-naïve, stage II-IV NSCLC without EGFR/ALK driver mutations were enrolled. This study consisted of two cohorts, one cohort is potentially resectable disease (PRD) and the other is unresectable disease (URD). The PRD patients received 3-4 cycles of tislelizumab (200 mg Q3w) plus carboplatin-based chemotherapy. Candidates eligible for surgery underwent surgery, followed by adjuvant tislelizumab monotherapy for 1 year. The URD patients received platinum-based doublet chemotherapy plus tislelizumab for 4-6 cycles, followed by tislelizumab for squamous and tislelizumab in combination with pemetrexed for non-squamous, until disease progression or intolerable toxicity. Primary endpoint was safety. Secondary endpoints were efficacy, such as MPR/pCR (PRD cohort), ORR, PFS and OS, etc. Multi-omics analysis of baseline and post-treatment samples were conducted to explore the safety and efficacy for chemoimmunotherapy. (NCT05244837). **Results:** Between December 2020 and November 2022, a total of 100 eligible patients were enrolled and received at least one cycle of immunotherapy. 58 patients were with PRD, of whom 40 (68.9%) were squamous cell lung cancer. 50 (86.2%) patients were stage III disease. During neoadjuvant treatment period, 52 patients (91.2%) experienced neoadjuvant TRAEs. Most of the TRAEs were grade 1 or 2. No grade 4 or 5 TRAEs was observed. The most common grade 1 or 2 TRAEs were alopecia ($n=29$; 50.9%), anemia ($n=25$; 43.9%), rash ($n=29$; 50.9%). Four patients (7.0%) experienced severe TRAE of grade 3 increased ALT/AST. 39 patients received surgical resection, R0 resection was performed for 38 (97.4%) patients. 29 (74.4%) achieved MPR (major pathological response), including 19 (48.7%) with a complete pathological response (pCR). 42 patients with URD were enrolled, 26 (61.9%) patients were stage IV disease. 37 patients (88.1%) experienced TRAEs. The most common grade 1 or 2 TRAEs were anemia ($n=27$; 64.3%), rash ($n=12$; 57.0%). Severe TRAEs occurred in 8 (2.0%) cases, including increased ALT/AST, decreased white blood cell count etc. 29 genes were identified as differentially expressed in pre-treatment tumors from patients with pCR compared to non-pCR. **Conclusions:** Neoadjuvant tislelizumab plus chemotherapy was safe and effective with high MPR and manageable TRAEs in patients with PRD. For patients with URD, tislelizumab plus chemotherapy was generally well tolerated. We have identified a differential immune landscape between pCR and non-pCR tumors. Clinical trial information: NCT05244837. Research Sponsor: None.

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Poster Session

EGFR tyrosine kinase inhibitors (TKIs) versus durvalumab (durva) following concurrent chemoradiation (CRT) in unresectable EGFR-mutant non-small-cell lung cancer (NSCLC). *First Author: Amin Nassar, Yale Cancer Center, New Haven, CT*

Background: Adjuvant osimertinib (osi) improves disease-free survival (DFS) in patients (pts) with resected, early-stage, EGFR-mutant (EGFRmut) NSCLC, yet the benefit of osi after CRT in pts with unresectable locally advanced NSCLC is unknown. Post-hoc analysis of the PACIFIC trial showed a lack of survival benefit with consolidation durva versus placebo in pts with EGFRmut NSCLC. Comparisons between consolidation durva and EGFR TKIs in unresectable EGFRmut NSCLC following CRT are lacking. **Methods:** We conducted a multi-institutional retrospective analysis of pts with stage III unresectable EGFRmut NSCLC (exon19 deletion, exon21 L858R), who received EGFR TKI or durva after ≥ 2 cycles of platinum-based chemotherapy plus definitive radiation therapy between 2015-2022. Baseline characteristics including age, sex, smoking history, PD-L1 status, and outcomes on DFS, overall survival (OS), and safety were collected. Multivariable (MVA) cox regression analysis was used for statistical analysis. Treatment-related adverse events (trAE) were defined using CTCAE 5.0. **Results:** Seventeen pts from 12 institutions received an EGFR TKI (osi, $n=15$; erlotinib, $n=2$), and 13 pts received consolidation durva. Median follow-up was 23 months. Median age of all pts was 61 years (IQR:52-72) and 76.7% were female. Most pts in both groups had never-smoked and had adenocarcinoma. All pts received ≥ 60 Gy of radiation with concurrent chemotherapy. PD-L1 expression was $\geq 50\%$ in 1/10 (10%) pts treated with durva vs 6/13 (46.2%) treated with TKI, $p=0.09$. Median duration on treatment for EGFR TKI and durva was 12.2 months and 4.8 months, respectively. Pts treated with EGFR TKI had significantly longer 24-month DFS versus pts treated with durva after adjusting for stage (3A vs 3B vs 3C) (Table). Any grade trAE occurred in 58.8% (10/17) of pts treated with EGFR TKI vs 38.5% (5/13) with durva. Grade > 3 trAE occurred in 15.4% (1 pneumonitis and 1 AST/ALT elevation) of pts treated with durva but in none of pts treated with EGFR TKI. Three pts within each arm came off treatment due to toxicity (EGFR TKI: 1 pneumonitis and 2 dermatitis; durva: 1 of each pneumonitis, Type 1 diabetes, AST/ALT elevation). **Conclusions:** EGFR TKI therapy after definitive CRT was associated with significantly longer DFS compared to durva in this retrospective study of pts with stage III unresectable EGFRmut NSCLC, without unanticipated safety signals. Follow-up is ongoing and OS outcomes will be evaluated subsequently. Further investigation is warranted to define the optimal therapy for locally advanced EGFRmut NSCLC. Research Sponsor: None.

Treatment	Median DFS, months (95% CI)	24-month DFS, % (95% CI)	DFS Hazard ratio (95% CI), p-value
EGFR TKI, N=17	28 (15.4-49)	88 (67-100)	0.09, 95% CI (0.01-0.58), $p<0.01$
Durva, N=13	8.5 (3.6-NR*)	31 (14-70)	

NR=Not reached.

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Poster Session

A combinatorial model of plasma proteins and LDCT imaging and the diagnosis of pulmonary nodules. *First Author: Meng Yang, Department of Pulmonary and Critical Care Medicine, Center of Respiratory Medicine, China-Japan Friendship Hospital, Beijing, China*

Background: Low dosage computer tomography (LDCT) has been widely adopted as a sensitive method to detect early-stage lung cancer; however, debate regarding its accuracy and overdiagnosis is still ongoing. An accurate non-invasive test is needed to identify malignant nodules and reduce unnecessary invasive procedures. Studies show that plasma proteins and LDCT imaging features may be used to discriminate malignant pulmonary nodules from benign ones. We aimed to develop a combinatorial approach integrating serum protein markers and imaging features to improve the classification of pulmonary nodules. **Methods:** This study established a prospective research cohort, which enrolled 608 patients of pulmonary nodules. Plasma samples were collected to measure protein levels using Proximity Extension Assay (PEA) technology. The imaging features of the pulmonary nodules were extracted using the python 'radiomics' package. Following feature extraction, a deep learning networks model was built using training cases. The model was then tested in the testing set to evaluate its accuracy and robustness. **Results:** From the study cohort, 184 benign (BN) and 184 malignant (MT) samples matched for sex and age were chosen to have a representative training set. The rest 240 samples (81 BN and 159 MT) were used as a testing set. Image features were extracted from 448 patients (119 BN and 153 MT in training; 57 BN and 119 MT in testing) with raw LDCT image available. In the testing set, the model trained using only protein levels had an AUC of 0.83 [0.782-0.877] (sensitivity = 71.1% [95% CI 63.6-77.6]; specificity = 82.7% [73.1-89.4]) when classifying plasma samples of lung cancers from those of benign nodules. In comparison, the imaging features-only model had an AUC of 0.874 [0.821-0.916] (sensitivity = 81.5 [73.6-87.5]; specificity = 73.7 [61.0-83.4]). The combinatorial model integrating both protein and imaging features had an AUC of 0.878 [0.830-0.921] (sensitivity = 83.2% [75.5-88.8]; specificity = 77.2% [64.8-86.2]). Notably, the combinatorial model was highly sensitive for early-stage lung cancer, achieving a sensitivity of 93.1% [78.0-98.1] when classifying stage-0 lung cancer cases (n = 29) and 94.8% [85.9-98.2] for stage-I cases (N = 58). Its sensitivity for stage II-IV (n = 7) and clinically diagnosed lung cancers cases (n = 25) were 100% [64.6-100] and 40.0% [23.4-59.3], respectively. **Conclusions:** This study aimed to construct a model to distinguish malignant pulmonary nodules from benign lung diseases using protein levels and LDCT imaging features. The resulted combinatorial model showed by utilizing both types of features, it was able to accurately differentiate benign and malignant pulmonary nodules, suggesting it may provide guidance for the clinical management of these nodules. Research Sponsor: National Key Research and Development Program of China (2019YFC1315800).

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Poster Session

Optimal number of lymph node stations associated with improved survival among patients with non-small cell lung cancer (NSCLC). *First Author: Meredith Ray, University of Memphis, School of Public Health, Memphis, TN*

Background: Good quality pathologic nodal evaluation is associated with improved long-term survival in NSCLC after surgical resection. However, there is no universal definition of quality. We examined the association between number of lymph node stations (NLNS) sampled and overall survival. **Methods:** We examined the population-based Mid-South Quality of Surgical Resection (MS-QSR) cohort, excluding patients with neoadjuvant therapy, positive margins, and secondary resections. We summarized demographic and clinical characteristics with appropriate statistics. We employed four Cox regression models: 1) including NLNS as the only predictor; 2) model 1, adjusting for age, sex, histology, clinical stage, extent of resection, and surgical technique; 3) examined the impact of pathologic staging (pStage in 3 groups: IA/IB [<4 cm tumor size]; IB[>4 cm]/II/IIIA[pN2-]; pN2]) by modeling interaction with pStage and NLNS; 4) model 3 plus adjustments (no clinical stage). In a cut point analysis to identify the optimal NLNS for improved survival, we dichotomized the NLNS for cut points 0 to 12. Hazard ratios (HR) were calculated (as above) and plotted for each dichotomization. **Results:** The 3916 eligible patients were 21% Black, 54% male, 15% on Medicaid and 49% Medicare; 84% and 85% had clinical and pathologic stage I/II, respectively; 84% had no invasive staging; 84% had a PET-CT scan. For every additional lymph node station sampled, the HR decreased by 0.94 (95% confidence interval: 0.92, 0.96). After adjustments, the HR remained significant (Table). Our pStage cohorts comprised of 2474 (64%) IA/IB[<4 cm]; 1080 (28%) IB[>4 cm]/II/IIIA[pN2-]; and 290 (8%) pN2+. Once stratified, HRs remained significant among those with early stage but not for pN2+ (Table). When further adjusted, only pStage IA/IB[<4 cm] patients had a significant HR, 0.94 (0.91, 0.97). The cut point analysis indicated sequential survival improvement up to ≥ 7 total stations sampled, consistently across all models/adjustments. **Conclusions:** The number of lymph node stations examined is directly associated with survival after lung cancer resection. Examination of a total of 7 intrapulmonary, hilar and mediastinal stations seems optimal. Hazard ratios (95% confidence intervals) for modeling hazards as a function of lymph node stations sampled (model 1), further adjusted for age, sex, histology, clinical stage, extent of resection, and surgical technique (model 2), including interaction with pathologic stage with no adjustments (model 3), and interaction with pathologic stage with adjustments (no clinical stage) (model 4). Research Sponsor: U.S. National Institutes of Health.

	All LN Stations
Model 1:	0.94 (0.92, 0.96)
Model 2:	0.97 (0.95, 1)
Model 3: IA/IB[<4 cm] IB-4cm/II/IIIA[pN2-] pN2+	0.9 (0.88, 0.93) 0.94 (0.9, 0.98) 1.03 (0.94, 1.12)
Model 4: IA/IB[<4 cm] IB-4cm/II/IIIA[pN2-] pN2+	0.94 (0.91, 0.97) 0.97 (0.93, 1.01) 1.07 (0.98, 1.17)

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Poster Session

Cancer risk assessment in patients with persistent pulmonary nodules and its correlation with cancer-free survival. *First Author: Hui Li, Department of Thoracic/Head and Neck Medical Oncology, Department of Imaging Physics, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: With the wide use of CT for lung cancer screening and diagnosis, detection of pulmonary nodules increases drastically. Brock malignancy risk scoring is a validated risk prediction model for distinguishing malignant nodules, but it only provides a snapshot without incorporating the dynamic changes of lung nodules. Our study tested the performance of Brock malignancy risk scoring system in patients with persistent lung nodules. **Methods:** We prospectively studied a cohort of 304 patients with persistent lung nodules (at least 2 CT scans, 3 months apart with no evidence of shrinkage) who were under management at MD Anderson Cancer Center from 11/28/2018 to 12/14/2022. These lung nodules were assessed by radiologists with Brock full model. These patients were followed up routinely and subjected to biopsy as determined by treating physicians. The area under the receiver operating characteristic curve (AUC) and the optimal cut-off of Brock model was studied. Additionally, we studied another cohort with 130 patients with histologically confirmed lung cancer. We retrospectively reviewed the CT or PET/CT scans and assessed the corresponding persistent lung nodules as defined above prior to the cancer diagnosis. We explored the correlations among nodule characteristics, demographic factors and Brock cancer risk scores. Cox proportional hazards model was built for multivariate analysis. **Results:** The median follow-up time for the prospective cohort was 337 days and 40 of the 304 patients (13.16%) were diagnosed with lung cancer with a median lung cancer-free survival of 228 days. The mean risk score was 24.20% (0.12%-62.86%) for histologically confirmed malignant vs 11.01% (0.07%-61.84%) for the remaining lung nodules (P < 0.001). Of note, 4 of 46 (8.70%) patients with persistent lung nodules of risk scores between 5%-10% and 8 of 134 (5.97%) patients with risk score < 5% were diagnosed with lung cancer. The AUC for Brock model was 0.72 and the optimal cut-off value is 10.64% (sensitivity: 0.702, specificity: 0.677). Among the retrospective cohort of 130 lung cancer patients (82.3% adenocarcinoma, 13.1% squamous cell carcinoma and 4.6% others), the predicted risk score ranged from 0.09% to 85.82%, including 33.85% of patients with risk score < 10% and 26.15% of patients with predicted risk score < 5%. The risk score was not correlated with age, sex, race, ethnicity, smoking history, family history of lung cancer, emphysema, nodule types or locations. The low-risk patients had a longer median cancer-free time (P = 0.001). **Conclusions:** Persistency is an important risk factor for malignant lung nodules. Using Brock criteria, a substantial proportion of lung nodules with true malignant potential can be overlooked because of predicted "low risk". Improved prediction models incorporating the dynamic changes of lung nodules are warranted to guide early diagnosis of lung cancer. Research Sponsor: The University of Texas MD Anderson Lung Cancer Moon Shot Program.

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Poster Session

Reevaluating the role of adjuvant chemotherapy in early-stage, resectable NSCLC with high-risk clinical and pathologic features. *First Author: Brendan Heiden, Washington University School of Medicine, St. Louis, MO*

Background: The preferred treatment for early-stage non-small cell lung cancer remains surgical resection with the consideration of adjuvant chemotherapy for tumors with certain high-risk features. It is commonly cited that such treatments confer a meager 5% 5-year survival benefit compared to observation alone. We sought to reassess the benefit of adjuvant chemotherapy using modern, real-world datasets. **Methods:** We performed a retrospective cohort study using a dataset from the National Cancer Database. All patients with early-stage stage NSCLC (3-5cm, node-negative) who would be eligible for adjuvant chemotherapy based on National Comprehensive Cancer Network guidelines were included (i.e., presence of at least 1 high-risk feature). High-risk clinical and pathologic features were defined as poor differentiation, tumor size (≥ 4 cm), non-anatomic wedge resection, inadequate lymph node evaluation, vascular invasion, and visceral pleural involvement. We employed average treatment effect on the treated (ATT) weighting to match patients with similar demographic, tumor, and treatment-related variables to compare outcomes between chemotherapy versus observation groups. The primary outcome was overall survival. These findings were further validated in an independent cohort from the US Veteran Health Administration (VHA). **Results:** The study included 10,812 patients with early-stage NSCLC who had at least 1 high-risk feature. The frequencies of high-risk features were as follows: tumor size ≥ 4 cm (n = 3,271, 30.3%), poor differentiation (n = 9,454, 87.4%), visceral-pleural invasion (n = 2,542, 23.5%), vascular invasion (n = 1,742, 16.11%), non-anatomic wedge resection (n = 781, 7.2%), and inadequate nodal sampling (n = 6,306, 58.3%). Despite the presence of high-risk features, only 1,427 (13.2%) patients received adjuvant chemotherapy. In the ATT weighted analysis, 1,261 (49.7%) patients received adjuvant chemotherapy and 1,278 (50.3%) patients received observation. The 5-year overall survival was 70.0% (95% CI 67.1-72.7) in the chemotherapy group versus 62.0% (95% CI 60.2-63.7%) in the observation group (absolute 5-year survival difference 8.0%). In the VHA cohort, 11.3% of patients received adjuvant chemotherapy. Similarly, the 5-year overall survival was 64.0% (95% CI 51.4-74.2) in the chemotherapy group versus 56.2% (95% CI 48.3-63.4) in the observation group (absolute 5-year survival difference 7.8%). **Conclusions:** These data suggest a notably larger benefit of adjuvant chemotherapy in eligible patients with high-risk clinical pathologic features compared to commonly cited statistics. With the addition of more robust treatment options in early-stage disease, adherence to adjuvant and neoadjuvant treatment guidelines may disproportionately improve early-stage NSCLC outcomes following curative-intent resection. Research Sponsor: Department of Veterans Affairs.

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Poster Session

Acute hospitalizations after proton beam therapy (PBT) versus intensity-modulated radiotherapy (IMRT) for locally advanced non-small-cell lung cancer (LA-NSCLC) in the era of immune checkpoint inhibitor (ICI) consolidation: A retrospective propensity score weighted study. *First Author: Michelle Iocolano, University of Pennsylvania, Philadelphia, PA*

Background: Prior work found that PBT is associated with fewer acute hospitalizations compared to photons for a variety of cancers. Patients (pts) with LA-NSCLC treated with concurrent chemoradiation (cCRT) and ICI consolidation are at high risk for treatment-related toxicity and acute hospitalizations. We hypothesized that PBT is associated with fewer acute unplanned hospitalizations as compared to IMRT in the era of ICI consolidation. **Methods:** This single institution, multi-site retrospective study included consecutive pts with LA-NSCLC treated with definitive cCRT with either PBT or IMRT from October 2017 to December 2021. Pts were evaluated for consolidative ICI. Primary endpoint was unplanned hospitalization within 90 days of first radiation (RT) treatment. Secondary endpoints included grade 3+ pneumonitis, grade 3+ esophagitis, PFS, and OS. Logistic regression was used to assess associations with 90-day hospitalization. Competing risk regression was used for grade 3+ pneumonitis and esophagitis and Cox regression for PFS and OS. Inverse probability treatment weighting (IPTW) was applied to adjust for differences in PBT and IMRT groups. **Results:** 316 pts were included: 117 (37%) received PBT and 199 (63%) IMRT. Median age was 68.5 yrs; median RT dose 66.6 Gy (IQR 65.9-70.0). PBT group was older (median 71.1 vs 67.2 yrs, $p < 0.005$) and had a higher Charlson comorbidity index (CCI) (median 4 vs 3, $p = 0.02$). There was no difference in receipt of ICI consolidation (66.7% vs 68.3%, $p = 0.76$). PBT group had lower mean heart dose (5.9 vs 10.8 Gy, $p < 0.001$), LAD V15 (0 vs 6%, $p = 0.001$), mean lung dose (14.7 vs 15.7 Gy, $p < 0.008$) and effective dose to immune circulating cells (median 3.7 vs 4.9 Gy, $p < 0.001$) but not mean esophagus dose. PBT was associated with fewer unplanned 90-day hospitalizations (23.9% vs 34.7%; aOR 0.52, 95% CI 0.30-0.90, $p = 0.02$). This difference persisted on IPTW analysis (OR 0.48, 95% CI 0.33-0.70, $p = 0.0002$) after adjusting for CCI, ECOG, smoking pack yrs, T stage, N stage, target volume, concurrent chemotherapy agent and histology. Reasons for hospitalization in PBT and IMRT groups included progression (1.4% vs 1.6%), definite/probable toxicity from cCRT (11.4% vs 18.2%), possible toxicity from cCRT (7.3% vs 12.8%) or unrelated to cCRT (2.5% vs 2.3%). There was no significant difference between PBT and IMRT groups in G3+ pneumonitis (1-year 6.0% vs 9.1%, $p = 0.49$), G3+ esophagitis (1-year 6.0% vs 6.5%, $p = 0.71$), PFS (median 14.4 vs 15.1 months, $p = 0.69$), or OS (median 34.2 vs 29.4 months, $p = 0.41$); results remained unchanged in IPTW analysis. **Conclusions:** Among pts with LA-NSCLC treated with cCRT in the era of ICI consolidation, PBT was associated with fewer acute unplanned hospitalizations compared to IMRT. Research Sponsor: None.

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Poster Session

A theranostic approach: Imaging and therapy of delta-like ligand 3-expressing small cell lung cancers. *First Author: Salomon Tendler, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Small cell lung cancer (SCLC) is a highly radiosensitive tumor, with selective cell surface expression of the inhibitory Notch ligand Delta-like ligand 3 (DLL3). This facilitates targeted radionuclide therapy accompanied by complementary imaging agents to evaluate and monitor disease progression. The project aims to identify the next generation of DLL3-targeting radioimmunoconjugates to improve the clinical outcome for SCLC patients. **Methods:** In collaboration with the Tri-Institutional Therapeutics Discovery Institute, we screened and assessed >100 humanized antibodies for their binding affinities, internalization rates, and other pharmacodynamic properties. Here, we present data on two leading candidates (mAb1 and mAb2) holding highest promise in both imaging and therapy studies conducted in DLL3-expressing SCLC tumors. For in vivo imaging, antibodies were radiolabeled with Zirconium-89 (^{89}Zr), which allows for immuno-positron emission tomography (immunoPET). Therapeutic studies were performed with the same antibodies conjugated with Lutetium-177 (^{177}Lu). Human SCLC NCI-H82 xenografts were implanted in nude athymic female mice. ImmunoPET scans were acquired during multiple time points post-injection of the imaging agent, and terminal biodistribution analysis was performed. Treatment studies included administration of 400 and 600 Ci ^{177}Lu -conjugated antibodies in cohorts of mice, with appropriate positive and negative controls. **Results:** Both lead antibodies demonstrated efficient radioconjugation with either isotope. ImmunoPET imaging utilizing ^{89}Zr showed specific high-level tumor uptake for both clones with low background in non-tumor organs. *Ex vivo* gamma counting biodistribution analysis, performed 120 hours post-injection, confirmed these findings. Dosimetry estimates suggested a similar therapeutic index between the two clones, with the bone marrow being the dose-limiting organ. Preliminary results from therapy studies demonstrate a statistically significant ($p < 0.05$) prolonged overall survival for the experimental arms compared to controls, and include durable tumor responses. As expected for radionuclide therapy, transient hematologic suppression was observed within 7-10 days after the beginning of the treatment, with normalization of blood cell counts for all groups within three weeks. **Conclusions:** This study highlights the promise held by novel DLL3-direct radioimmunoconjugates as a diagnostic tracer, prognostic biomarker, and therapeutic agent. Both lead candidates appear promising for translation as both imaging and therapeutic agents for patients with SCLC. Research Sponsor: NIH grants; Druckenmiller Lung Cancer Foundation.

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Poster Session

Association of single-click radiomic classifier with response and prognosis in non-small cell lung cancers (NSCLC) treated with immune checkpoint inhibitors. *First Author: Amogh Hiremath, Picture Health, Cleveland, OH*

Background: Radiomics has shown promise to non-invasively phenotype disease and address the limitations of extant biomarkers (e.g. PD for immune checkpoint inhibitors (ICI) in cancers, such as NSCLC. However, considerable barriers to the clinical adoption of these tools remain, such as their dependence on precise annotation of tumor extent by experienced clinical users. Here, we demonstrate a radiomic solution that requires only a single user mouse click within one or more target lesions on a baseline CT scan, to contour tumors in 3D and generate a patient-level radiomic prediction of response and outcome in ICI treated NSCLC patients. **Methods:** 1778 CT scans from 1261 patients were used to develop and validate an interactive, semi-automated tool for predicting ICI outcomes in NSCLC patients prior to therapy. A user click based deep learning contouring model was trained and validated on 1146 patients, then used to create annotations for radiomic analysis. A least absolute shrinkage and selection operator (LASSO) Cox proportional hazards model was utilized to select features associated with post-ICI overall survival (OS) and derive a radiomic risk score within a training cohort ($n=74$) that can separate patients into high and low risk groups. The model was tested on held out pre-treatment CTs of 41 ICI recipients from 2 institutions for association with OS, progression-free survival (PFS), and objective response (OR). **Results:** A total of 77 lesions were identified and segmented within the testing set. Average volume per lesion was 54.10 mL and per patient was 101.60 mL. OR was observed in 48.70% of patients. A threshold of -0.31 defining high and low radiomic risk groups was chosen based on optimal separation within the training set (HR=2.59 [95% 1.48-4.50], $p=0.0009$). Radiomic risk groups significantly stratified patients by OS (C-index=0.64, HR=3.03 [95% 1.15-8.02], $p=0.03$) and PFS (C-index=0.59, HR=3.20 [95% 1.13-9.10], $p=0.03$). Radiomic IO risk group was independently prognostic of clinical variables (Table 1) and further predicted ICI response with AUC=0.74 [95% 0.71-0.78]. **Conclusions:** From a single click in target lesions, our model was able to predict response and prognosis of ICI recipients from a baseline radiology scan. Additional multi-site validation and prospective evaluation will assess the value of the radiomics classifier as a decision support tool in the clinic. Research Sponsor: Industrial funding.

Variables	HR [95% CI]	p
Radiomic high risk	4.82 [1.41-16.53]	0.01
Gender (F vs. M)	0.81 [0.27-2.45]	0.71
Stage (per stage increase)	2.62 [0.60-11.44]	0.20
Smoking history	0.68 [0.28-1.64]	0.39
Histology	0.88 [0.54-1.45]	0.62

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Poster Session

Reconsidering the cutoff between sensitive and refractory relapses in extensive-stage small cell lung cancer in the era of immunotherapy. *First Author: Masahiro Torasawa, Department of Thoracic Oncology, National Cancer Center Hospital, Tokyo, Japan*

Background: The use of platinum-based doublet chemotherapy combined with immune checkpoint inhibitors (ICIs) has demonstrated promising outcomes in the first-line treatment of extensive-stage small cell lung cancer (ES-SCLC). Relapsed SCLC has been classified into "sensitive" or "refractory" relapse types according to cutoff values (60 or 90 days) of duration from the last chemotherapy administration to disease progression. However, it is unclear whether these cutoff values can be applied to ICI combination therapy. **Methods:** We retrospectively analyzed a multicenter database of ES-SCLC patients who received second-line therapy after the platinum-etoposide plus ICI (atezolizumab or durvalumab). An optimal cutoff value for the platinum-free interval (PFI) was selected, which minimized the two-sided p-value and maximized hazard ratio (HR) regarding relapse type (sensitive or refractory according to a cutoff value) calculated from a multivariable Cox regression model for overall survival (OS) including performance status (PS) and sex as covariates. The internal validity of the selected cutoff value was assessed via two-fold cross-validation (CV) manner. **Results:** A total of 101 patients (61 deaths) from 10 hospitals were included in the study. The median follow-up period was 21.1 months. The optimal cutoff value was 75 days ($p=0.0002$), and when applying this cutoff value, median OS was 15.9 and 5.0 months of sensitive- ($n=51$) and refractory- ($n=50$) relapsed patients, and the HR calculated from a two-fold CV was 3.13 (95% confidence interval [CI], 1.66 to 5.90). Additionally, traditional cutoff values of 60 and 90 days also predicted prognosis better, but cutoff values of 110 days or longer did not (Table). **Conclusions:** Even in the era of combined immunotherapy in ES-SCLC patients, the threshold days for classifying as sensitive- or refractory- relapse did not exhibit a significant change compared to the pre-immunotherapy era. Although further validation studies with a larger sample size would be needed, relapse type classification using the selected cutoff value of 75 days is worth considering as a new prognostic factor for relapsed ES-SCLC patients. Research Sponsor: None.

PFI cutoffs related to OS in relapsed SCLC.

Cutoff (days)	p-value	significance level	Cutoff (days)	p-value	significance level	Cutoff (days)	p-value	significance level	Cutoff (days)	p-value	significance level
25	0.0443	*	65	0.0054	**	105	0.0351	*	145	0.6057	n.s.
30	0.0443	*	70	0.0009	***	110	0.1251	n.s.	150	0.4389	n.s.
35	0.0268	*	75	0.0002	***	115	0.2073	n.s.	155	0.1944	n.s.
40	0.0268	*	80	0.0026	**	120	0.2968	n.s.	160	0.1182	n.s.
45	0.0128	**	85	0.0026	**	125	0.3107	n.s.	165	0.1182	n.s.
50	0.0063	**	90	0.0049	**	130	0.5647	n.s.	170	0.1182	n.s.
55	0.0002	***	95	0.0098	**	135	0.5647	n.s.	175	0.1182	n.s.
60	0.0023	**	100	0.0200	*	140	0.6057	n.s.	180	0.1300	n.s.

*: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$, n.s.: not significant.

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Poster Session

Analysis of tumor- and circulating-free DNA methylation to identify clinically relevant small cell lung cancer subtypes. *First Author: Simon Heeke, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Small-cell lung cancer (SCLC) is an aggressive malignancy composed of distinct transcriptional subtypes, defined by the predominant expression of one of the three transcription factors ASCL1 (SCLC-A), NEUROD1 (SCLC-N) and POU2F3 (SCLC-P) as well as an inflamed subtype (SCLC-I; see Gay et al. Cancer Cell. 2021), each with potential therapeutic vulnerabilities. Implementing subtyping in the clinic has remained challenging due to limited tissue availability, particularly for longitudinal monitoring. Given the known epigenetic regulation of critical SCLC transcriptional programs, we hypothesized that there would be subtype-specific patterns of DNA methylation that could be detected in tumor or blood from SCLC patients. **Methods:** We included 179 patients with SCLC and performed RNA sequencing and genomic-wide reduced-representation bisulfite sequencing (RRBS). We further analyzed DNA methylation in 68 plasma samples including longitudinal samples to track SCLC subtype evolution over time. **Results:** Using machine learning approaches, we developed a highly accurate DNA methylation-based classifier (SCLC-DMC) that could distinguish SCLC subtypes using clinical tumor samples with 95.8% accuracy in the testing set compared to mRNA-based profiling. We further adjusted the classifier for circulating-free DNA (cfDNA) to subtype SCLC from plasma. Using the cfDNA classifier (cfDMC), we could demonstrate that SCLC subtypes evolve frequently during disease progression, highlighting the need for longitudinal tracking of SCLC during clinical treatment. Furthermore, methylation-based subtyping predicted response to a wide variety of drugs in preclinical models like CDK and AURK inhibitors, and clinical outcomes were indistinguishable in cohorts of patients subtyped using mRNA or SCLC-DMC ($p = 0.95$). **Conclusions:** These data establish that tumor and cfDNA methylation can be used to identify SCLC subtypes and guide precision SCLC therapy. Research Sponsor: U.S. National Institutes of Health.

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Poster Session

Phase I/II combination study of tificemalimab with toripalimab in patients with refractory extensive stage small cell lung cancer (ES-SCLC). *First Author: Ying Cheng, Department of Medical Thoracic Oncology, Jilin Cancer Hospital, Changchun, China*

Background: The B- and T-lymphocyte attenuator (BTLA) is a novel inhibitory co-signaling receptor expressed on B cell, T cells and NK cells. Co-blockade of the BTLA and PD-1 pathways improved antigen specific anti-tumor T cell response. Tificemalimab (JS004 or TAB004) is a humanized IgG4 monoclonal antibody with a hinge mutation (S228P) that binds BTLA and blocks its interaction with its ligand HVEM. In previous phase I studies, tificemalimab has shown preliminary anti-tumor activities as monotherapy or in combination with toripalimab (anti-PD-1) with a manageable safety profile in patients with advanced malignancies. **Methods:** Eligible ES-SCLC patients refractory to prior therapies were enrolled in this I/II study (NCT05000684). Patients received 200mg tificemalimab and 240mg toripalimab intravenously once every three weeks until disease progression, intolerable toxicity or 2 years of treatment. Study objectives included safety, anti-tumor activity and correlative biomarkers. **Results:** As of Jan 31, 2023, a total of 43 ES-SCLC patients refractory to prior therapy were enrolled. The median age was 60.0 (range 38-75) years. The median prior line of therapy was 1 and 14 (32.6%) patients received prior anti-PD-1/L1 treatment. By the cut-off date, the median follow-up duration was 12.1 weeks. Thirty-two (74.4%) patients experienced treatment-emergent adverse events (TEAEs); 12 (27.9%) patients experienced grade ≥ 3 TEAEs. The most common TEAEs were hyponatremia (16.3%), alanine aminotransferase increased (14%), aspartate aminotransferase increased (14%), and blood creatine phosphokinase increased (14%). Three (7.0%) patients experienced treatment-related adverse events (TRAEs) led to interruption of study drugs and no TRAEs led to discontinuation of study drugs were reported. Fifteen (34.9%) patients experienced immune related AE (irAEs), and 2 (4.7%) patients experienced grade ≥ 3 irAEs. Among 38 efficacy evaluable patients, the ORR was 26.3% and the DCR was 57.9%. The ORR was 8.3% in immunotherapy treated patients and 40.0% in immunotherapy naïve patients. By the cut-off date, 70.0% of the responses were ongoing and the median duration of response was not reached. Tumor expression of HVEM and PD-L1 was evaluated to explore the correlation with clinical response. **Conclusions:** Tificemalimab in combination with toripalimab were well tolerated in patients with refractory ES-SCLC. Further clinical evaluation of this combination treatment in SCLC is warranted. Clinical trial information: NCT05000684. Research Sponsor: Shanghai Junshi Biosciences.

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Poster Session

Pathological images machine learning and prediction of long-term efficacy for immunotherapy in small cell lung cancer. *First Author: Yuki Sato, Kobe City Medical Center General Hospital, Kobe, Japan*

Background: In development of effective treatment such as immune checkpoint inhibitors (ICIs) among patients with small-cell lung cancer (SCLC), the absence of biomarkers is critical. Tumor-infiltrating lymphocytes are the main activator of anti-tumor immunity and could be a promising biomarker if TIL can be objectively assessed throughout the whole tumor immune microenvironment (TIME). To evaluate TIME, pathological assessment is one of the easiest ways. Recently, several studies showed that machine learning analysis can assess type of lymphocytes and their localization in pathological images. Here, we aimed to develop a novel biomarker to predict efficacy of ICI in SCLC using machine learning of pathological images. **Methods:** This study was a biomarker analysis of the APOLLO study which was 32-centered, prospective cohort study of patients with extensive-stage SCLC who received chemo-immunotherapy as the first-line treatment between September 2019 and September 2020. The patient who can provide sufficient tumor tissue sample from the primary tumor were enrolled. We trained a classifier which predicts 365-day progression-free survival (PFS) by all three types of pathological images (hematoxylin and eosin, programmed death-ligand 1, and CD8_FoxP3) and patient information, and developed the patient information model, pathological image model, and combination model. We used the area under the curves (AUC) to evaluate the machine learning models. **Results:** Of 78 patients, the median age was 78 (interquartile range, 48-87), 65 patients (83%) were male, 67 patients (86%) had a performance status of 0 or 1, and three patients (3.8%) treated with steroid therapy. Among all patients, the median PFS and the 365-day PFS rates were 145 days and 10.3%. The mean AUC of these models was 0.789 (range, 0.571-0.982) in the patient information model, 0.782 (range, 0.750-0.911) in the pathological image model, and 0.868 (range, 0.786-0.929) in the combination model, respectively. According to the median precision model, the median PFS was longer for the high efficacy group than the low efficacy group (the patient information model; hazard ratio (HR) 0.468, 95% confidence intervals (CI) 0.287-0.762. the pathological image model; HR 0.334, 95%CI 0.117-0.628. the combination model; HR 0.353, 95%CI 0.195-0.637). **Conclusions:** Using machine learning by pathological images, we could predict the efficacy of immunotherapy in SCLC. This study demonstrated the potential of machine learning to help the biomarker development in SCLC by assessing TIME. Clinical trial information: UMIN000038064. Research Sponsor: Chugai Pharmaceutical Co. Ltd.

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Poster Session

Updated safety and efficacy results of SHR-1316 combined with chemotherapy and sequential chest radiotherapy as first-line therapy for extensive-stage small cell lung cancer (ES-SCLC) from a phase II trial. *First Author: Dawei Chen, Shandong Cancer Hospital, Shandong University, Jinan, China*

Background: CAPSTONE-1 study showed that SHR-1316 (PD-L1 antibody) combined with first-line chemotherapy could prolong overall survival in patients (pts) with ES-SCLC. Previous studies have shown that radiotherapy could potentially promote tumor antigen presentation and reverse immunosuppressive microenvironment in tumor. The purpose of this study was to explore the efficacy and safety of SHR-1316 combined with chemotherapy and sequential chest radiotherapy as first-line therapy for ES-SCLC. **Methods:** Key inclusion factors were 18-75 years old, histologically or cytologically confirmed ES-SCLC, ECOG performance status 0-1, no previous systematic treatment. Pts included in this study received 4-6 cycles of SHR-1316 (20mg/kg, D1, q3w) combined with EP/EC (cisplatin, 75mg/m², D1-3, q3w or carboplatin, AUC = 5, D1, q3w and etoposide, 100mg/m², D1-5, q3w), sequentially SHR-1316 combined with chest radiotherapy ($\geq 3\text{Gy} \times 10\text{f}$ or $\geq 2\text{Gy} \times 25\text{f}$, involved-field irradiation), and then entered the maintenance treatment stage until disease progression or intolerable side effects. The main endpoints included objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS) and safety. **Results:** From October 2020 to January 2023, 63 pts with ES-SCLC were enrolled and received at least one dose of SHR-1316, 33 of them have received chest radiotherapy. The median age was 63 (range: 38-75), and most pts were male (53, 84.1%), former smokers (42, 66.7%) with an ECOG performance status 1 (60, 95.2%). At baseline, 24 (38.1%) pts were diagnosed with brain metastasis and 19 (30.2%) pts had liver metastasis. At the data cutoff date, the average number of treatment cycles was 6.9, 17 pts remained on treatment. 55 pts had at least one post-treatment tumor assessment. 41 pts achieved a confirmed partial response, and 12 pts had stable disease. The confirmed ORR and DCR were 74.5% and 96.4%, respectively. The median PFS was 7(CI: 4.3-9.7) months. Adverse events (AEs) occurred in 47 (74.6%) pts. Grade 3 or 4 AEs occurred in 35 (55.6%) pts. The most common grade 3 or 4 AEs included neutropenia (27, 42.9%), leukopenia (13, 20.6%), lymphocytopenia (5, 7.9%), pneumonia (4, 6.3%), anemia (3, 4.8%), and thrombocytopenia (2, 3.2%). **Conclusions:** SHR-1316 combined with chemotherapy and sequential chest radiotherapy as first-line therapy for ES-SCLC showed promising efficacy and acceptable safety. It is worthy of further clinical exploration. Clinical trial information: NCT04562337. Research Sponsor: None.

8581

Poster Session

Characteristics and outcomes of patients with small cell lung cancer (SCLC) detected with CT screening at a single health system. *First Author: Manasi Manoj Godbole, Henry Ford Cancer Institute, Henry Ford Health, Detroit, MI*

Background: At diagnosis, the majority of SCLC patients have extensive-stage disease, and their median survival is only 13 months, even with the addition of checkpoint inhibitors. Previous CT screening trials did not reveal reduction in mortality for SCLC patients. The aim of our study was to analyze the baseline characteristics and clinical outcomes of SCLC patients diagnosed with low-dose CT scan as a part of lung cancer screening program. **Methods:** A retrospective chart review-based study of SCLC patients diagnosed clinically or by lung cancer screening between January 2018 and June 2022 at the Henry Ford Health System was conducted. Baseline characteristics, details of SCLC diagnosis and treatment, and outcome were recorded. Statistical analysis was performed using Chi-squared test, T-test and log-rank test. **Results:** Of the 258 patients who met eligibility criteria, 34 were diagnosed by lung cancer screening. Patients diagnosed with screening tended to be older (mean age- 70.5 years vs. 67.3 years, $p=0.010$). There were no differences in gender distribution, race and smoking status. Mean smoking history was 43 pack-years in both groups. Among screen-detected patients, 73.5% had limited-stage disease compared to 36.6% among clinically detected patients ($p<0.001$). No significant difference in the presence of brain metastases at diagnosis was observed. Among screen-detected patients, 97.1% received any therapy compared to 85.3% among the clinically detected patients ($p=0.105$). Overall survival (OS) was significantly better in screen-detected patients, with a 3-year survival rate of 45.5% vs. 17% ($p=0.00027$). By multivariable analysis, OS was better in screen-detected patients (HR=0.37, 95% CI 0.20-0.68; $p=0.001$) (Table). There was no significant difference in progression-free survival between the groups. **Conclusions:** Our results demonstrate that SCLC patients diagnosed through the lung cancer screening program have better overall survival rates than those diagnosed clinically. These results suggest that developing appropriate screening measures may impact SCLC-related mortality. Research Sponsor: None.

Impact on overall survival.

Variable	N (%)	Hazard Ratio (Univariable)	Hazard Ratio (Multivariable)
Screening	34 (13.2)	0.37 (0.22-0.65, $p<0.001$)	0.45 (0.25-0.79, $p=0.005$)
Age (Mean [SD])	67.7 (9.3)	1.01 (0.99-1.03, $p=0.172$)	1.02 (1.00-1.04, $p=0.024$)
Female	146 (56.6)	1.09 (0.80-1.47, $p=0.589$)	1.38 (0.99-1.90, $p=0.054$)
Active smoker	77 (29.8)	Ref	Ref
Former smoker	172 (66.7)	0.90 (0.65-1.24, $p=0.508$)	1.08 (0.76-1.52, $p=0.670$)
Never smoker	9 (3.5)	1.08 (0.47-2.52, $p=0.851$)	1.31 (0.51-3.35, $p=0.576$)
Extensive stage	151 (58.5)	Ref	Ref
Limited stage	107 (41.5)	0.44 (0.32-0.61, $p<0.001$)	0.42 (0.29-0.61, $p<0.001$)
Treatment received	224 (86.8)	0.13 (0.08-0.20, $p<0.001$)	0.11 (0.07-0.19, $p<0.001$)

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Poster Session

Tarlatamab in small cell lung cancer (SCLC): Safety and efficacy analyzed by baseline brain metastasis. *First Author: Stephane Champiat, Gustave Roussy, Département d'Innovation Thérapeutique et d'Essais Précoces (DITEP), Villejuif, France*

Background: Tarlatamab, a BiTE molecule targeting DLL3 and CD3, is being studied in patients (pts) with extensive stage small cell lung cancer (ES-SCLC).¹ Up to 25% of pts diagnosed with SCLC have brain metastases (BM) and 50% or more will develop BM during the course of the disease. Pts with ES-SCLC and BM have poor prognosis and quality of life. We analyzed the characteristics and outcomes of pts included in the tarlatamab phase 1 study (NCT03319940) who had baseline BM vs those who did not. **Methods:** Pts included in the phase 1 trial had SCLC that progressed after ≥ 1 platinum-based regimen and received tarlatamab (0.003–100 mg IV). Pts with treated BM were eligible if local therapy was delivered ≥ 2 weeks prior to first tarlatamab dose. **Results:** As of 03 January 2023, 192 pts had received tarlatamab as monotherapy. Median age was 62 (range, 32–80) y; 188 pts (98%) had ECOG PS 0–1 and median prior therapy lines was 2 (range, 1–6), with 107 pts (56%) receiving prior anti-PD1/PD-L1. 48 pts (25%) had BM at screening and 142 (74%) did not (No BM); data was missing for 2 pts (1%). Pts with BM were more likely to have received > 3 prior lines of therapy (BM, 29%; No BM, 9%) and have a record of prior brain radiation (BM, 85%; No BM, 40%); otherwise, characteristics of pts with BM were generally similar to those without. Tarlatamab delivered comparable activity in pts with BM vs. those without in terms of objective response rate (ORR; 20%, 25%) and disease control rate (DCR; 59%, 50%) (Table). Median duration of response (DoR) was 14.9 months (BM) vs. 13.0 months (No BM). Median overall survival (OS) was 13.2 months in the BM group vs 15.5 months in the no BM group. Safety outcomes were similar in terms of treatment-related AEs (TRAEs; BM, 90%; No BM, 94%) and grade (≥ 3 (BM, 38%; No BM, 39%). Groups were also comparable with respect to immune effecter cell-associated neurotoxicity syndrome (ICANS) and associated neurologic events (any-grade, 6% vs 9%; $gr \geq 3$, 4% vs 4%) and neutropenia (any-grade, 10% vs 15%; $gr \geq 3$, 8% vs 8%). AEs numerically different in the BM vs No BM group included $gr \geq 4$ TRAEs (17%, 7%) and any-grade CRS (67%, 54%). The only grade 5 TRAE (pneumonitis) occurred in the BM group. **Conclusions:** Tarlatamab continues to show promising efficacy and is generally safe in pts with ES SCLC irrespective of the presence of BM. Rates of ICANS and associated neurologic AEs were comparable between those with and without BM at baseline. Reference: 1. Paz-Ares L, et al. J Clin Oncol. DOI:10.1200/JCO.22.02823. Clinical trial information: NCT03319940. Research Sponsor: Amgen.

Efficacy in pts with and w/o BM, Interim efficacy analysis set.

	BM (n = 46)	No BM (n = 136)
ORR, n (%)	9 (19.6%)	34 (25.0%)
DCR, n (%)	27 (58.7%)	68 (50.0%)
DoR, median (95% CI)*	14.9 (3.8, NR)	13.0 (7.4, NR)
PFS, median (95% CI)	3.7 (1.9, 4.8)	3.7 (1.9, 5.3)
OS, median (95% CI)	13.2 (6.6, NR)	15.5 (10.6, NR)

*BM, n=9; No BM, n=34 CI, confidence interval; DCR, disease control rate; NR, not reached; PFS, progression-free survival.

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Poster Session

Long-term effectiveness and treatment sequences in patients with extensive stage small cell lung cancer receiving atezolizumab plus chemotherapy: Results of the IFCT-1905-CLINATEZO real-world study. *First Author: Lionel Falchero, Hôpitaux Nord-Ouest, Service de Pneumologie et Cancérologie Thoracique, Villefranche-Sur-Saône, France*

Background: Small cell lung cancer (SCLC) is a highly aggressive type of lung cancer with a tendency towards early recurrence and limited survival. Standard-of-care in 1st-line treatment is platinum-etoposide chemotherapy plus anti-PD-L1 immune checkpoint inhibitor atezolizumab or durvalumab, based on landmark, randomized, phase 3 clinical trials. **Methods:** IFCT 1905-CLINATEZO is a nationwide, non-interventional, retrospective chart review study of patients (pts) with extensive-stage SCLC who received atezolizumab + chemotherapy as part of the French early access program between May 2019 and January 2020 (1402 pts). Inclusions were exhaustive per participating centers (65/307). Data collection run from February to November 2021. Key objectives were to assess effectiveness and safety of atezolizumab + chemotherapy and analyze subsequent treatment sequences. **Results:** The population analyzed included 518 out of the 1402 pts. There were 66% male and mean age was 65.7 years (range: 36.7-88.0); 89% had a performance status (PS) 0/1 and 27% brain metastases. Almost all the pts (96%) were smokers, with a median number of pack-years of 40. Fifty-five pts (10.6%) received at least 1 previous treatment. Median number of atezolizumab injections was 7 (range: [1-48]) for a median duration of 4.9 months (95% CI 4.5-5.1). Twenty-seven pts (5%) were under ongoing treatment at date of last news. Atezolizumab was continued beyond disease progression in 122 pts (24%) for a median duration of 1.9 months (95% CI 1.4-2.3). Best objective response was complete and partial response in 19 (3.9%) and 378 pts (77.1%) respectively; stable disease was observed in 50 pts (10.2%). After a median follow-up of 30.8 months (95% CI: [29.9-31.5]), median overall survival (OS), 12- and 24-months OS rates were 11.3 months (95% CI: [10.1-12.4]), 46.7% (95% CI 42.3-50.9) and 21.2% (95% CI 17.7-24.8) respectively. Median real world-progression free survival (based on date of the first source evidence for progression referenced by the treating physician), 6- and 12-months rates were 5.2 months (95% CI 5.0-5.4), 37.5% (95% CI 33.3-41.7) and 15.2% (95% CI 12.2-18.6) respectively. For the pts with PS 0/1, median OS was 12.2 months (95% CI 11.0-13.5). For the 55 pts with previous treatment, median OS was 14.9 months (95% CI 10.1-21.5). A total of 326 (66.4%) pts received subsequent treatment. **Conclusions:** IFCT 1905-CLINATEZO study shows the reproducibility, in a real-life setting, of the key survival outcomes of IMpower-133, that may be attributed to the selection of pts fit for this regimen, the adoption of pragmatic approaches for the management of pts receiving atezolizumab, that includes concurrent radiotherapy and treatment beyond progression, and the high proportion of pts treated with 2nd-line therapies, mostly based on chemotherapy. Research Sponsor: ROCHE.

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Poster Session

IFCT-2105 lurbinectin real-world effectiveness and treatment sequences in patients (pts) with extensive-stage small cell lung cancer (ES-SCLC) who received lurbinectin as part of the French Early Access Program (EAP-ATU). *First Author: Nicolas Girard, Institut du Thorax Curie Montsouris, Institut Curie, Paris, France*

Background: Novel options are needed for pts with ES-SCLC after the failure of first-line chemotherapy. Lurbinectin demonstrated efficacy in a landmark phase II study [Trigo et al. Lancet Oncol. 2020 May;21(5):645], and was granted EAP-ATU in France in June 2020. **Methods:** Multicenter, retrospective cohort of consecutive pts with histologically or cytologically confirmed ES-SCLC, who received at least one dose of treatment with lurbinectin as part of the French EAP-ATU from June 2020 until March 2021, and gave consent for the data collection, were enrolled in 47 sites. Primary and secondary endpoints were description of clinical characteristics, and exposure to treatment, response, PFS, OS, safety. **Results:** 312 pts – 64% male, median age 65 years, 72% PS0-1, 47% with brain metastasis, 58% with previous immunotherapy – were enrolled. Lurbinectin was administered as second-line in 44% of pts; 58% were chemotherapy-refractory. Pts received a median number of 3 cycles of lurbinectin. Concurrent radiotherapy on metastases was delivered to 38% of pts. Lurbinectin was discontinued because of progression/death/toxicity/other reasons in 83%/8%/5%/4% of pts. Grade3/4 events were observed in 9%/5% of pts. Response rate was 22% [95%CI 17-27%], disease control rate was 38% [95%CI 32-44%]. After a median follow-up of 20.8 months, median PFS and OS were 1.9 [95%CI 1.8-2] and 4.7 [95%CI 4-5.4] months; 6-month PFS and OS were 7% [4-10%] and 42% [95%CI 37-48%]. PS ≤ 2 and chemotherapy-free interval ≥ 90 days were associated with significantly longer OS (HR = 0.71 [95%CI 0.53-0.95] and HR = 0.58 [95%CI 0.44-0.76] respectively). Main sites of progression were the lung (39% of pts), the brain (39% of pts), the liver (30% of pts), and the mediastinum (30% of pts). Subsequent treatment was administered to 154 pts after discontinuation of lurbinectin, mostly consisting of topotecan (26% of pts); response/disease control rates, and median PFS of first subsequent treatment were 11% [95%CI 6-17%], 35% [95%CI 27-44%], and 1.9 [95%CI 1.7-2.3] months. **Conclusions:** Lurbinectin provides an additional option from second-line for ES-SCLC, with efficacy outcomes comparable to that of historical treatments. Research Sponsor: PharmaMar.

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Poster Session

Phase Ib/IIa study assessing the safety and efficacy of AL8326 monotherapy in patients with ≥ 3 rd line small cell lung cancer (SCLC) treatment. *First Author: Xiaochun Zhang, The Affiliated Hospital of Qingdao University, Qingdao, China*

Background: AL8326 is a novel, orally administered, small molecule tyrosine kinase inhibitor (TKI). The primary objective of this Phase Ib/IIa study is to evaluate the safety and efficacy of AL8326 monotherapy in patients with ≥ 3 rd line small cell lung cancer (SCLC) treatment. **Methods:** Patients with a diagnosis of small cell lung cancer either limited or extended stage requiring third or further line treatment were eligible for enrollment. The regimen was a 28-day cycle with oral AL8326 administered at 60 mg once per day via RECIST1.1 evaluation until disease progression (PD), or intolerable toxicity or any other reason discontinuations. **Results:** At the cut-off date Nov 30, 2022, total n = 30 patients were enrolled. The objective response rate (ORR) was 20% (6/30) (4 confirmed). The disease control rate (DCR) was 56.7% (17/30). Median progression-free survival (PFS) was 3.65 months (95% CI: 1.9 – 5.5) and median overall survival (OS) was 10.42 months (95% CI: 5.4, NE). The median duration of response (DOR) was 5.6 months. All 30 subjects had reported AE at least once. Common treatment emergent adverse events (TEAE) were similar to other TKI drug and included (incidence $\geq 20\%$): thyroid stimulating hormone (TSH) increase (46.67%), proteinuria (43.33%), weight loss (40.00%), hypertension (36.67%), thrombocytopenia (33.33%), diarrhea (33.33%), positive fecal occult blood (30.00%), hypercholesterolemia (26.67%), hypertriglyceridemia (26.67%), hand- foot syndrome (HFS) (20.00%), loss of appetite (20.00%). Most of these AEs were grade 1-2 (CTCAE V5.0). **Conclusions:** AL8326 has demonstrated acceptable tolerability and positive efficacy on small cell lung cancer treatment. A US Phase 2 (NCT05363280) study is ongoing and a phase 3 study is in preparation. Clinical trial information: NCT04890795. Research Sponsor: AL8326.

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Poster Session

Efficacy and safety of high dose twice-daily thoracic radiotherapy versus standard dose for limited stage small-cell lung cancer: A multicentre, open-label randomised, phase 3 trial. *First Author: Jiayi Yu, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Radiation Oncology, Peking University Cancer Hospital & Institute, Beijing, China*

Background: We aimed to assess the efficacy and safety of high-dose, hyperfractionated thoracic radiotherapy of 54 Gy in 30 fractions compared with standard dose (45 Gy in 30 fractions) as a first-line treatment for LS-SCLC. **Methods:** The study was an open-label, randomised, phase 3 trial, done at 16 public hospitals in China. Key inclusion criteria were patients aged 18-70 years, with previously histologically or cytologically confirmed LS-SCLC, previously untreated or received 1-2 courses of intravenous cisplatin (75 mg/m² of body-surface area, on day 1 or divided into two days of each cycle) or carboplatin (area under the curve of 5 mg/mL per min, day 1 of each cycle) and intravenous etoposide (100 mg/m² of body-surface area, on days 1-3 of each cycle), and an Eastern Cooperative Oncology Group (ECOG) performance status of 0-1. Eligible patients were randomly assigned (1:1) to receive receive volumetric-modulated arc radiotherapy (VMAT) of 45 Gy in 30 fractions or the simultaneous integrated boost VMAT (SIB-VMAT) of 54 Gy in 30 fractions to the primary lung tumour and lymph node metastases starting 0-42 days after the first chemotherapy course. Both groups of patients received thoracic radiotherapy twice per day and 10 fractions per week. Prophylactic cranial radiation (PCI, 25Gy in 10 fractions) was implemented to patients with responsive disease. The primary endpoint was overall survival. Safety was analysed in the as-treated population. This study is complete and registered with ClinicalTrials.gov, NCT03214003. **Results:** Between June 30, 2017, and April 6, 2021, 224 eligible patients were enrolled and randomly assigned to 54 Gy (n = 108) or 45 Gy (n = 116). Median follow-up for the primary analysis was 45 months (IQR 41-48). Median overall survival was significantly improved in the 54 Gy group (62.4 months) compared with the 45 Gy group (43.1 months; p = 0.001). Median progression-free survival was significantly improved in the 54 Gy group (30.5 months) compared with the 45 Gy group (16.7 months; p = 0.044). The most common grade 3-4 adverse events were neutropenia (30 [28%] of 108 patients in the 54 Gy group vs 27 [23%] of 116 patients in the 45 Gy group), neutropenic infections (6 [6%] vs 2 [2%]), thrombocytopenia (13 [12%] vs 12 [10%]), anaemia (6 [6%] vs 4 [3%]), and oesophagitis (1 [1%] vs 3 [3%]). There were one treatment-related deaths in 54 Gy group (myocardial infarction). **Conclusions:** Compared with standard thoracic radiotherapy dose of 45 Gy, the high dose of 54 Gy improved overall survival and progression-free survival without increasing toxicities in patients with LS-SCLC, supporting twice-daily hyperfractionated thoracic radiotherapy of 54 Gy with concurrent chemotherapy is an alternative treatment option for LS-SCLC. Clinical trial information: NCT03214003. Research Sponsor: Beijing Health and Health Science Technology Achievements and Appropriate Technology Promotion Project (No. BHTPP202026); Chinese Society of Clinical Oncology (CSCO) – Linghang cancer research (No. Y-2019AZMS-0519).

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Poster Session

Tumor microenvironment-mediated immune profiles and efficacy of platinum doublet chemotherapy plus ICIs stratified by DLL3 expression in small cell lung cancer. *First Author: Masayuki Shirasawa, Department of Thoracic Oncology, National Cancer Center Hospital, Tokyo, Japan*

Background: Delta-like ligand 3 (DLL3) frequently expressed in small cell lung cancer (SCLC) and has been emerged as a therapeutic target. However, it remains unclear how DLL3 expression status affects tumor microenvironment (TME)-mediated immune profiles and clinical outcomes of platinum doublet chemotherapy plus ICIs in SCLC patients. **Methods:** We retrospectively reviewed post-surgical limited-stage (LS)-SCLC, and extensive-stage (ES)-SCLC patients treated with platinum and etoposide (PE) plus anti-PD-L1 antibody. In LS-SCLC cohort, the transcriptome and whole-exome sequencing (WES) analysis were performed to assess the immune profiles, mutation status and neoantigen status. In ES-SCLC cohort, the association between the efficacy of immunochemotherapy and DLL3 expression by transcriptome analysis were evaluated. **Results:** Fifty-nine and 17 patients were included in the LS- and ES-SCLC cohort, respectively. In LS-SCLC cohort (n = 59), WES analysis revealed that SCLC with DLL3^{High} had a significantly higher number of neoantigens (77 [95% confidence interval (CI) 65-113] vs. 48 [95% CI 17-58], p = 0.004), and a significantly higher rate of signature SBS4 associated with smoking (43% [95% CI 28-53] vs. 28% [95% CI 15-36], p = 0.02), although TMB did not differ according to DLL expression (6.6 mut/Mb [95% CI 5.3-9.6] vs. 6.5 mut/Mb [95% CI 5.2-9.9], p = 0.26). The transcriptome analysis in LS-SCLC cohort revealed that SCLC with DLL3^{High} tumors had significantly suppressed immune-related pathways (IFN- γ response, inflammatory response, and TNF α signaling via nfkb), and dendritic cells (DC) function (DC Differentiation, DC Antigen Processing and Presentation, DC Migration). Profiling tumor infiltrating immune cells with CIBERSORT showed that SCLC with DLL3^{High} had significantly lower proportions of T-cells, macrophages, and DCs compared with those with DLL3^{Low}. These results suggested that DLL3^{High} tumors suppressed tumor immunity by inhibiting antigen-presenting function. In ES-SCLC cohort (n = 17), the PFS of PE plus anti-PD-L1 antibody in patients with DLL3^{High} was significantly worse than those in patients with DLL3^{Low} (4.1 months [95% CI, 2.0-6.3] vs. 7.4 months [95% CI, 2.5-12.3]; HR 3.78 [95% CI, 1.1-12.5], p = 0.03). **Conclusions:** SCLC with high DLL3 expression was characterized by resistance to immunochemotherapy due to suppressed tumor immunity, although those tumors had higher neoantigen loads. Research Sponsor: JST AIP-PRISM, Grant Number JPMJCR18Y4; MHLW ICT infrastructure establishment and implementation of artificial intelligence for clinical and medical research program, Grant Number JP21AC5001.

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Poster Session

The effect of various social determinants of health on overall survival in the SCLC population. *First Author: Matthew M Mirsky, University Hospitals Seidman Cancer Center and Case Western Reserve University, Cleveland, OH*

Background: Small cell lung cancer (SCLC) comprises 10-15% of all lung cancers yet little is known about the impact of social determinants of health (SDOH) on outcomes in patients with SCLC. This study aims to assess the impact of various SDOH on overall survival (OS) in patients diagnosed with SCLC at a single institution. **Methods:** We have established a large clinical/pathologic/genomic database of all patients diagnosed and treated for SCLC between 1998-2022 at our institution for retrospective study. Demographic data including sex, race, age, stage, address, and smoking status were collected. Poverty index was assessed by percent of school-aged children in poverty at the school district level based off 2021 census using the SAIPE tool and stratified as low (poverty index ≤ 15.1) and high (poverty index > 15.1). Water/Air carcinogens were obtained by zip code through EPA TRI Explorer database at year of SCLC diagnosis. Food desert designation was acquired through USDA low income and low access atlas at 0.5 miles for urban residences and 10 miles for rural residences respectively. Violent crime rates were obtained from the FBI Crime Data Explorer by year of diagnosis and police department jurisdiction. OS was computed from date of diagnosis to death or last known follow up date, and univariate Cox proportional hazards (PH) regression analysis was performed. Factors that were significant at significance level of 0.25 in univariate analysis were further evaluated using multivariable Cox PH model. **Results:** A total of 982 patients with SCLC were included. Univariate PH analysis demonstrated statistically significant improvement in OS with younger age (HR = 1.03, 95% CI 1.02-1.03, p < 0.0001), female sex (HR = 0.8, 95% CI 0.7-0.92, p 0.001), low poverty index (HR = 1.12, 95% CI 0.98-1.12, p = 0.097), limited stage disease (HR = 3.12, 95% CI 2.66-3.66, p < 0.0001), and lack of air pollution exposure (HR = 1.09, 95% CI 0.95-1.24, p = 0.227). Multivariable PH analysis showed statistically significant OS improvement for those from lower poverty areas (HR = 1.22, 95% CI: 1.07- 1.4, p = 0.004) as well as in those without air pollution exposure (HR = 1.21, 95% CI: 1.05- 1.39, p = 0.008), controlling for age, sex, stage and smoking. Exposure to water pollution, violent crime rate, food desert designation and pack years smoked were not found to be independent predictors of OS. **Conclusions:** In this large detailed cohort of 982 patients with SCLC, there was a significantly lower OS for patients living in high poverty areas and for patients exposed to air pollutants. This effect was durable even after for controlling for age, sex, stage, and smoking status, demonstrating that these are independent risk factors associated with poorer OS. Our next research steps will be to examine the biologic basis for these disparities through genomic and transcriptomic analysis. Research Sponsor: None.

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Poster Session

Assessing inpatient outcomes for patients with small cell lung cancer presenting with superior vena cava thrombosis. *First Author: Jay Vakil, John H. Stroger, Jr. Hospital of Cook County, Chicago, IL*

Background: Superior Vena Cava Syndrome (SVCS) is a condition characterized by obstruction of the SVC that can commonly be caused by thrombus formation in the SVC. Small cell lung cancer (SCLC) frequently results in obstruction of the SVC. When severe enough, SVCS can present as a life-threatening oncological emergency. In this study we aim to explore baseline characteristics of SVC thrombosis (SVCT) in patients with SCLC, the prevalence of US hospitalizations, and disparities with regards to race and socioeconomic status. **Methods:** National Inpatient Sample was utilized to obtain pertinent data. Total hospitalizations with coexistent comorbidities of SCLC were extracted from the 2016 to 2019 database. Adult patients with a secondary diagnosis of SVC thrombosis were determined by using ICD-10 codes. We studied the racial and socioeconomic differences as well as length of stay (LOS), total hospital charges (THC), and all-cause mortality outcomes in cancer patients with and without SVC thrombosis. Statistical analysis was performed on STATA, with logistic regression analyses and chi-square tests. **Results:** A total of 480,750 patients were hospitalized for SCLC. 720 of these patients had SVC thrombosis (0.15% of SCLC patients). The mean age of those with thrombi was significantly lower compared to those without thrombi (64 vs. 69, $p < 0.001$). The SCLC with SVCT cohort had statistically higher proportion of black patients than the other cohort. Charlson index was significantly higher in SCLC with SVCT cohort (5.8 vs. 5, $p < 0.001$). Average income between the two cohort groups were similar. Medicaid and private insurance utilization were more common in SCLC with SVCT admissions compared to without SVCT. Patients presenting with SVC thrombosis had an increased hospital LOS (10 vs. 6 days, $p < 0.001$) and cost compared to other cohorts (\$117,320 vs. \$80,806, $p < 0.005$). All-cause mortality in patients with SCLC was 7.7% and the presence of SVC thrombosis significantly increased the odds of inpatient mortality (18.0%). Non-White races were associated with higher odds of mortality in SCLC admissions. In addition, patients with SVC thrombus also had greater odds of having a concomitant pulmonary embolism during hospitalization. **Conclusions:** In this study we found that race, insurance type, and comorbidities impacted the likelihood of developing thrombosis in the superior vena cava in patients with SCLC. Though the incidence is rare, SVC thrombosis indicates a poor prognostic factor for patients with SCLC. Further studies to evaluate these disparities in race and socioeconomic factors are warranted. The development of thrombosis and subsequent SVC syndrome is a potentially life-threatening condition; addressing potential reversible risk factors could improve mortality in a large subgroup of hospitalizations related to SCLC. Research Sponsor: None.

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Poster Session

Efficacy and safety of lurbinectedin in elderly patients with relapsed SCLC. *First Author: Sophie Cousin, Medical Oncology Department, Institut Bergonié, Bordeaux, France*

Background: Relapsed SCLC is a difficult-to-treat disease. A considerable number of SCLC patients are elderly with associated fragility and numerous comorbidities. Accelerated approval from the US FDA of lurbinectedin (Zepzelca) 3.2 mg/m² q3wk as second-line therapy in metastatic small cell lung cancer (SCLC) was based on results from a phase 2 basket trial (NCT02454972) showing overall response rate of 35.2% and duration of response of 5.3 months. The ATLANTIS trial (NCT02566993) assessed the combination of lurbinectedin 2mg/m²/doxorubicin (DOX) 40 mg/m² as second-line treatment for SCLC vs. a control arm of topotecan/CAV. **Methods:** This *post hoc* analysis explores the efficacy and safety of lurbinectedin in relapsed SCLC patients ≥65 years included in both phase 2 basket (26 patients treated with lurbinectedin) and ATLANTIS (121 patients treated with lurbinectedin/DOX and 118 patients treated in the control arm) trials. This analysis did not include patients from the phase 2 basket trial with chemotherapy-free interval (CTFI) < 30 days, as these patients were excluded in the ATLANTIS trial. **Results:** Median age was similar (72.5 in lurbinectedin basket vs. 69 in ATLANTIS lurbinectedin/DOX vs. 69 in ATLANTIS control arm), most were males (65.4% vs. 57.9% vs. 60.2%), with ECOG PS 1 (65.4% vs. 68.6% vs. 68.6%) and CNS involvement (7.7% vs. 10.7% vs. 15.3%). Median CTFI (days) was also similar (105.5 vs. 123 vs. 120). Median number of cycles was 4 vs. 6 vs. 4. Main efficacy and safety results are shown in the table. Treatment-related adverse events (AEs) were reported in 92.3%, 92.6% and 94.1% of patients, respectively (grade ≥3 in 50.0%, 59.5% and 81.4%). **Conclusions:** In elderly patients, lurbinectedin seems to be superior to the standard of care in terms of both efficacy (higher response rate and longer duration of response and overall survival) and safety (less associated hematological AEs), which reinforces its role as a treatment option in relapsed SCLC patients ≥65 years. Clinical trial information: NCT02454972, NCT02566993. Research Sponsor: PharmaMar.

	Basket (n=26)	ATLANTIS*		
		Lurbi/DOX (n=121)	Control (CAV/topotecan) (n=118)	OR/HR (95%CI)**
ORR confirmed by IRC (%) (95% CI)	34.6 (17.2-55.7)	24.8 (17.4-33.5)	26.3 (18.6-35.2)	0.93 (0.50, 1.73)
Median DoR by IRC (mo) (95% CI)	5.1 (2.4-5.9)	6.9 (4.1-10.1)	4.2 (3.6-5.7)	0.482 (0.260-0.892)
Median PFS by IRC (mo) (95% CI)	3.4 (2.6-5.1)	4.2 (3.5-4.0)	3.0 (2.8-4.0)	0.645 (0.495-0.859)
Median OS (mo) (95% CI)	9.7 (6.2-14.9)	9.0 (7.8-10.8)	5.9 (5.3-7.6)	0.755 (0.576-0.991)
Most frequent AEs, regardless of relationship (%)		Grade ≥3	Grade ≥3	p-value***
Anemia	19.2	23.1	36.4	0.0333
Febrile neutropenia	3.8	5.0	9.3	0.2161
Fatigue	15.4	13.2	15.3	0.7130
Neutropenia	65.4	43.8	73.7	<0.0001
Thrombocytopenia	7.7	16.5	33.9	0.0027

* Growth colony-stimulating factors were mandatory for both ATLANTIS treatment arms. ** Nominal comparisons in ATLANTIS (small number of patients in basket trial)/AEs, adverse events; CI, confidence interval; mo, months; OS, overall survival.

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Poster Session

A multicenter phase I/II trial of induction chemotherapy followed by camrelizumab, apatinib, plus chemotherapy as first-line treatment for extensive-stage small-cell lung cancer. *First Author: Chengzhi Zhou, Pulmonary and Critical Care Medicine, Guangzhou Institute of Respiratory Health, National Center for Respiratory Medicine, State Key Laboratory of Respiratory Diseases, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China*

Background: Extensive-stage small-cell lung cancer (ES-SCLC) is a highly aggressive tumor with poor prognosis and limited treatment options. It is necessary to explore new first-line therapeutic strategies to improve patients' outcomes. This study aimed to assess the safety and efficacy of induction chemotherapy followed by camrelizumab, apatinib plus chemotherapy as first-line treatment in patients with ES-SCLC. **Methods:** Patients (pts) aged 18-75 years with histopathologically confirmed ES-SCLC and ECOG performance score of 0-1 who did not receive systemic treatment were prospectively enrolled to this study. After two 21-day cycles of induction chemotherapy (etoposide 100 mg/m² on days 1-3 and carboplatin AUC 5 mg/mL/min on day 1 [ECI], pts received camrelizumab (200 mg, q3w) plus apatinib (250 mg, qd) and EC for 2-4 cycles, then followed by camrelizumab and apatinib as maintenance treatment until disease progression/unacceptable toxicity/up to two years. The primary endpoint was safety. Secondary endpoints were objective response rate (ORR), PFS and OS. Targeted sequencing and whole transcriptome sequencing (WTS) were performed for pts who had sufficient tissue samples. **Results:** From Jan 28, 2021 to Aug 20, 2022, 40 eligible pts were enrolled. At the data cut-off (Jan 21, 2023), the median follow-up time was 13.6 months. Grade 3/4 treatment-related adverse events (TRAEs) were reported in 72.5% (29/40) of pts. The most common grade 3/4 TRAEs were decreased neutrophil count (35.0%, 14/40), anemia (15.0%, 6/40), decreased platelet count (12.5%, 5/40), increased serum alanine aminotransferase (12.5%, 5/40), and hyponatremia (12.5%, 5/40). Hemoptysis was observed in 15.0% of (6/40) pts, all of whom were grade 1-2. No treatment-related deaths occurred. Efficacy was evaluated in 36 pts who received two cycles of induction therapy and had at least one post-treatment efficacy evaluation. The ORR after two cycles of induction chemotherapy was 66.7% (24/36). The overall ORR and disease control rate reached 88.9% (32/36) and 97.2% (35/36), respectively. The median PFS was 7.4 months (95% CI: 6.5-8.3). The 1-year OS rate was 63.4%. Thirty and 20 pts underwent targeted sequencing and WTS, respectively. Pts with high tumor mutational burden level (TMB ≥ 7.0, $p < 0.001$), high homologous recombination deficiency score (HRD ≥ 34.0, $p = 0.012$), and altered *RB1* ($p < 0.001$) presented a longer PFS, respectively. WTS suggested that high expression of cancer-associated fibroblast signature was associated with a shorter PFS ($p = 0.001$). **Conclusions:** Induction chemotherapy followed by camrelizumab, apatinib plus EC and then maintenance therapy showed acceptable safety and encouraging efficacy, and might be a promising regimen as first-line treatment in ES-SCLC. TMB, HRD and *RB1* might be predictive biomarkers of response to the regimen. Clinical trial information: NCT05001412. Research Sponsor: 1. Beijing Xisike Clinical Oncology Research Foundation (Grant No.Y-HS202102-0118); 2. Guangzhou Science and Technology Program (Grant No.202102010371); 3. Zhijiang Laboratory-The open project (Grant No.2021PEOAC06).

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Poster Session

Dissecting small cell lung cancer subtypes with cell-free DNA fragmentomes. *First Author: Lorenzo Rinaldi, Delfi Diagnostics, Inc., Baltimore, MD*

Background: Although small cell lung cancer (SCLC) is managed as a single cancer type, new evidence supports that subtypes (high vs low neuroendocrine) of SCLC acquire diverse transcriptional and epigenetic states. Furthermore, distinct SCLC subtypes acquire unique therapeutic vulnerabilities, such as the low-neuroendocrine highly inflamed SCLC subtype that has been linked to immunotherapy sensitivity. We have previously shown that DELFI (DNA evaluation of fragments for early interception) can be used to non-invasively distinguish SCLC from non-small cell lung cancer (NSCLC). Here, we report a preliminary analysis of using the DELFI approach for distinguishing among SCLC subtypes. **Methods:** Circulating cell-free DNA (cfDNA) was isolated from plasma samples of patients diagnosed with relapsed SCLC and treated with durvalumab plus olaparib in a phase II trial (NCT02484404). Over 200 cfDNA libraries were prepared for whole genome sequencing in batches with internal controls. To infer tumor gene expression profiles in cfDNA, we investigated genome-wide signals of tissue-specific transcription factors differentially regulated in SCLC, and applied a novel DELFI-based approach to inform SCLC molecular subtypes. Clinical information, patient-matched tissue transcriptome (RNA-seq), and chromatin accessibility data (ATAC-seq) were examined in orthogonal analyses. **Results:** The DELFI classifier detected SCLC cases ($N = 47$) with a median DELFI score of 1.0 (95% CI 0.99-1), significantly higher than previously reported scores for other lung cancer subtypes. Comparison of DELFI fragmentome signals to publicly available tumor transcriptomes shows subtype-level concordance ($r = 0.78$, $p < 0.001$, Pearson), particularly in pre-treatment SCLC cases separating high- vs low-neuroendocrine subtypes. High-neuroendocrine SCLCs exhibited a decrease in aggregate cfDNA fragment coverage at *ASCL1* transcription factor binding sites relative to low-neuroendocrine SCLCs ($r = 0.90$, $p < 0.001$, Pearson). Additionally, low-neuroendocrine SCLCs revealed a significant decrease in aggregate cfDNA fragment coverage at genomic binding sites regulated by hematopoietic transcription factors, reflecting the inflamed phenotype of this SCLC subtype. Integration of these approaches provided a cfDNA fragmentation-based machine learning model that distinguished SCLC subtypes with high performance. **Conclusions:** Genome-wide cfDNA fragmentome analyses can differentiate high- and low-neuroendocrine SCLC subtypes. Given the challenges for performing SCLC biopsies in a clinical setting, we believe this approach could be a viable method of subtyping SCLC in a non-invasive manner. Research Sponsor: Delfi Diagnostics; U.S. National Institutes of Health.

8593

Poster Session

Phase 2 small cell lung cancer (SCLC) cohort of a phase 1b/2 trial of a liposomal formulation of eribulin in combination with nivolumab. *First Author: Koichi Azuma, Kurume University Hospital, Kurume, Japan*

Background: E7389-LF is a liposomal formulation of the microtubule dynamics inhibitor eribulin. Combining E7389-LF with an immune checkpoint inhibitor (ICI; eg, nivolumab) may improve antitumor response via vascular remodeling. The phase 1b part of the open-label Study 120 evaluated the dosing and safety of E7389-LF in combination with nivolumab in patients (pts) with solid tumors. The phase 2 part assessed efficacy and safety in disease cohorts; herein, we report results from the SCLC cohort. **Methods:** Pts with unresectable and measurable SCLC who had progression during or after 1st-line (1L) platinum-based chemotherapy with/without an ICI were enrolled to the SCLC cohort of the phase 2 part of Study 120. Pts received E7389-LF 2.1 mg/m² in combination with nivolumab 360 mg IV Q3W. The primary objective of the phase 2 part was to assess the objective response rate (ORR). Secondary objectives included assessments of safety and progression-free survival (PFS); exploratory objectives included the disease control rate (DCR), overall survival (OS), and biomarker analysis. Tumor response was assessed by investigators per RECIST v1.1 Q6W. All adverse events (AEs) were monitored and recorded. **Results:** In the SCLC cohort, 34 pts were enrolled; the median age was 66.0 years (range 46–81). At data cutoff (May 31, 2022), 5 pts (14.7%) were undergoing treatment. Discontinuations occurred in 29 pts (85.3%)—26 (76.5%) primarily due to disease progression, 3 (8.8%) due to an AE. Efficacy analyses included 33 pts, as 1 pt had their diagnosis of SCLC changed to a different cancer type after being enrolled. Of the 33 evaluable pts, 27 (81.8%) had an ICI as part of their prior 1L therapy. The ORR of E7389-LF in combination with nivolumab was 24.2% (95% CI 11.1–42.3) in the evaluable population; the DCR was 75.8% (95% CI 57.7–88.9). Median PFS was 3.98 mos (95% CI 2.63–4.40); the 6-mo PFS rate was 27.7% (95% CI 13.0–44.6). At a median follow-up period of 10.6 mos, median OS was not reached (95% CI not estimable); the 6-mo OS rate was 90.9% (95% CI 74.4–97.0). Treatment-related, treatment-emergent (TE) AEs of any grade and of grade ≥3 severity occurred in 97.1% (n = 33) and 82.4% (n = 28) of the 34 enrolled pts, respectively; the most common treatment-related TEAE was neutropenia (any grade: 58.8% [n = 20]; grade ≥3: 52.9% [n = 18]). The neutrophil count nadir occurred around cycle 1 day 8. TEAEs led to dose reduction of E7389-LF in 19 pts (55.9%). Withdrawal of E7389-LF or nivolumab occurred in 5 pts (14.7%): acute kidney injury, cough, myocarditis, pneumonitis, and radiation pneumonitis (n = 1 each). Changes in vascular and immune-related plasma markers were observed. **Conclusions:** E7389-LF in combination with nivolumab showed notable antitumor activity as 2L therapy in pts with SCLC, as evidenced by the notable ORR of 24.2%. No new safety signals were observed for this combination. Clinical trial information: NCT04078295. Research Sponsor: This trial was sponsored by Eisai Co., Ltd., Tokyo, Japan. Nivolumab was provided by Ono Pharmaceutical Co., Ltd., Osaka, Japan.

8595

Poster Session

Role of consolidative thoracic and prophylactic cranial radiation in extensive stage small cell lung cancer in chemo-immunotherapy era. *First Author: Jai Kumar Khatri, Marshall University School of Medicine, Edwards Cancer Center, Huntington, WV*

Background: The role of consolidative thoracic and prophylactic brain radiation in extensive stage small cell lung cancer patients is controversial. We investigated the factors associated with the use of any radiation therapy (RT) and whether Radiation has a benefit to overall survival (OS) in the total patient group and whether this benefit is the same if Chemotherapy (CT) only is used, or chemo-immunotherapy (CT-IO) is used. **Methods:** The NCDB database was queried from years 2017-2019. Patients receiving systemic therapy-STX (CT or CT-IO) had to have at least 6 months of follow-up and have no brain metastases at diagnosis. All RT patients had to receive upfront systemic therapy, were treated 2 to 6 months from diagnosis, and if treated to the brain received 25Gy in 10 fractions only. Multi-variate analyses (MVA) were used to determine factors associated with OS and selection for any radiation. Propensity matching for factors affecting OS were used to generate Kaplan-Meier OS curves. Log-rank tests were used to determine differences in Kaplan Meier survival curves for the effects of RT on OS. **Results:** The total number of patients receiving RT or systemic therapy alone as well as their median follow-ups(months(mn)) were (981, 33.02mn) and (8909, 30.59mn). The median time to the start of STX and RT were 22days and 135 days respectively. MVA noted that RT had a greater effect on OS (Thoracic, Brain, Both – HRs = 0.78, 0.75, and 0.68) than other interventions including IO (HR 0.87) and palliative care without RT (HR 1.07). Selection for radiation depended significantly upon factors affecting OS(HR) including liver metastases (0.59), females (1.21), age/10yr(0.78) and Charlson co-morbidity index of > 3(0.66), but did not depend upon insurance status, race, or county income/high school graduation rates. Propensity score matched OS curves noted the same effects of RT on OS whether CT or CT-IO was given. The lowest HRs were noted when both thoracic and brain RT were given (see table). **Conclusions:** The patient with extensive stage small cell lung cancer who reach candidacy and receive RT may have a significant improvement in OS compared to the patients treated only with CT or CT-IO. Combined thoracic and prophylactic brain RT seems to be better than either one alone. The impact of radiation whether given to one or two sites may be more beneficial than immunotherapy added to chemotherapy. Research Sponsor: None.

Regimen	HR	p-value	N	18Month OS-KM
CT only	REF	REF	5783	15%
CT + Thoracic RT vs CT with no RT (Ref)	0.68(0.59,0.77)	< 0.0001	256	28%
CT + Brain RT vs Ref	0.67(0.60,0.76)	< 0.0001	305	33%
CT + Both Brain and Thoracic RT vs Ref	0.59(0.49,0.70)	< 0.0001	112	39%
CT-IO	REF	REF	3126	19%
CT-IO with thoracic RT vs CT-IO (Ref)	0.68 (0.56,0.83)	< 0.0001	119	38%
CT-IO with brain RT vs REF	0.73(0.60,0.88)	< 0.0001	132	38%
CT-IO with Thoracic + brain RT vs Ref	0.62(0.46,0.82)	< 0.0001	57	44%

8594

Poster Session

Spatially resolved multi-region transcriptomic subtyping and assessment of gene expression profiles associated with long-term benefit from chemo-immunotherapy in patients with extensive-stage small cell lung cancer (ES-SCLC). *First Author: Melina Peressini, Hospital Universitario 12 de Octubre, Madrid, Spain*

Background: Transcriptomic subtyping holds promise for personalized therapy in SCLC, but intratumoral transcriptomic heterogeneity and its clinical significance remain poorly defined. In this study, we aimed to assess transcription factor defined subtypes within multiple regions of intact tissues and identify gene sets associated with long-term chemo-immunotherapy benefit. **Methods:** We assessed baseline FFPE tumors from 32 ES-SCLC patients enrolled in the IMfirst clinical trial (EudraCT: 2019-002784-10). We used GeoMx DSP to perform transcriptomic analysis from multiple intratumoral regions of interest (ROIs). We used an assay with +1800 genes (GeoMx CTA) plus custom-designed mRNA probes targeting subtype-defining transcription factors not included in the CTA assay (POU2F3, NEUROD1, and YAP1). Custom probes were quantitatively validated using FFPE cell lines. **Results:** We profiled 175 ROIs from 32 tumors. Cluster analysis based on the expression of ASCL1, NEUROD1, POU2F3, and YAP1 showed that all samples clustered within 4 groups: SCLC-A (76 ROIs [43%]), SCLC-N (31 ROIs [18%]), SCLC-P (18 ROIs [10%]), and SCLC-Y (50 ROIs [29%]). ASCL1 was the most abundantly expressed transcription factor, prevalent in the SCLC-A subtype, and showed inverse correlation with POU2F3 (r=−0.55, p<0.0001) and YAP1(r=−0.70, p<0.0001). YAP1 was expressed at low levels and was more broadly distributed across all 4 subtypes. Differential expression and gene set enrichment analysis (GSEA) using linear mixed models revealed that SCLC-A subtype was enriched in cell cycle and DNA damage repair genes, and showed repression of multiple gene sets associated with anti-tumor immune response. In contrast, SCLC-Y subtype showed the opposite pattern. The SCLC-P subtype was also enriched in genes related to cancer antigens and T-cell checkpoints. Most patients (n=18, 56%) had tumors with coexistence of more than one subtype, not evident through morphological inspection. Combined SCLC-A and SCLC-Y subtypes was the most common mixed phenotype (n=8, 25%). Four patients (13%) had tumors with coexistence of three subtypes. Transcriptional subtypes, subtype-defining transcription factors as single genes, or the presence of subtype heterogeneity, were not associated with outcomes. Gene sets involved in mitochondrial metabolism and MHC class I antigen presentation were the highest enriched pathways in tumors from patients with sustained benefit (time to progression³ 12 months). **Conclusions:** This study reveals substantial intratumoral transcriptomic subtype heterogeneity in human SCLC. In this limited sample set, we did not observe outcome association for transcriptional subtypes. Our findings related to long-term chemo-immunotherapy benefit require validation in independent cohorts. Research Sponsor: Roche Pharma SA.

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Poster Session

Brain metastasis burden and management in small cell lung cancer: An analysis of 8705 patients. *First Author: Karolina Gaebe, University of Toronto, Toronto, ON, Canada*

Background: Patients with small cell lung cancer (SCLC) have historically been characterised by poor overall survival (OS) and high risk for intracranial metastatic disease (IMD), but large-scale real-world evidence on clinical presentation and treatment in this population is lacking. These patients traditionally receive whole brain radiation therapy (WBRT) for IMD, however, a recent systematic review has indicated that OS following stereotactic radiosurgery (SRS) may be non-inferior compared with WBRT. We aim to describe the clinical characteristics and outcomes of patients with SCLC and IMD in Ontario, Canada. **Methods:** We included all patients diagnosed with SCLC between April 2007 and March 2018 identified through a provincial health administrative database. Information on patient and treatment characteristics, incidence and time to IMD, and OS from time of SCLC diagnosis were collected and analyzed using R. **Results:** A total of 8705 patients were included. Median age was 68 years (range 18-103). Most patients presented with extensive disease (n = 5625) and were diagnosed after 2011 (n = 5768). Patients who received chemotherapy (n = 5563) had significantly longer OS than those who did not (median 10.64 vs 1.58 months (mo), hazard ratio (HR) 0.36, 95% confidence interval (CI) 0.34-0.37). 6662 patients received brain imaging at the time of primary diagnosis (CT: 5126, MRI: 1536), and 88% of patients surviving longer than 6 mo received more than one follow-up brain scan. 31% developed IMD (synchronous: 1175, asynchronous: 1511) with median intracranial progression-free survival of 5.65 mo. Median OS of patients with IMD was 9.76 mo, 29 and 1300 received SRS and WBRT as first treatment for their IMD, respectively. OS was in favour of SRS over WBRT (median 20.47 vs 8.74 mo, HR 0.57, 95% CI 0.39-0.84), which remained significant in multivariate analysis (p < 0.001). **Conclusions:** OS for patients with SCLC remains poor, and many patients present with IMD. With careful selection, patients with SCLC may benefit from SRS treatment. Research Sponsor: None.

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Poster Session

Molecular predictors and immunomodulatory role of dual checkpoint inhibitor blockade using ipilimumab/nivolumab in patients with extensive stage small cell lung cancer. *First Author: Anne C. Chiang, Yale University School of Medicine, New Haven, CT*

Background: Small cell lung cancer (SCLC) is an aggressive neuroendocrine carcinoma with poor prognosis. In extensive stage patients, frontline treatment with chemoimmunotherapy shows modest clinical benefit. However, the biological impact of immunotherapy in SCLC is poorly understood with no clear predictive biomarkers to guide patient selection in this setting. **Methods:** We collected paired baseline (pre-treatment), on-treatment (week 4), and progression biopsies from patients with relapsed advanced-stage SCLC treated with combination nivolumab (nivo) and ipilimumab (ipi) in a single-arm, phase 2 clinical trial (NCT03670056). Nivo 1 mg/kg and ipi 3 mg/kg were administered every 3 weeks for 4 cycles, followed by nivo maintenance until progressive disease (PD) by RECIST 1.1 or treatment-limiting toxicity. Paired pre/on-treatment samples were available from 16/22 patients, as well as 3 biopsies at progression. The tumor samples were studied using whole exome DNA sequencing (including germline DNA) and RNA-sequencing coupled to Ocean Genomics TxomeAI data analysis pipeline. **Results:** 6/11 evaluable patients had PD; 5 patients showed clinical activity of treatment (3 with stable disease, 2 with partial response). The frequency of deleterious mutations in *TP53* and *RB1* was 91% and 64%, respectively. Mutations in *HLA-A* were more common in baseline samples from patients with PD than those with clinical activity. New *TP53* and *PLEC* mutations were found 4 of 6 patients with PD in week 4 samples vs baseline. The baseline tumor mutational burden was not associated with treatment sensitivity and prominently increased in week 4 biopsies of PD patients. All four molecular SCLC transcriptomic subtypes based on the expression of *ASCL1*, *NEUROD1*, and *POU2F3* were present in the trial with SCLC-A being the most common (9/16 cases). All patients with clinical activity to ipi/nivo were of SCLC-A subtype. 2/16 of cases showed a different molecular subtype after 4 weeks of treatment: one case with SCLC-N switched to SCLC-A and another case converted from SCLC-A to SCLC-N. Comparison of baseline and on-treatment samples showed upregulation of transcripts associated with T-cell activation and PD-1 signaling. In the 3 biopsies at progression, transcriptomic changes included reduction of neutrophil degranulation, type 1/2 interferon and signatures, as well as down-regulation of β -2 microglobulin, while cell cycle and mitotic prophase pathways were overexpressed. **Conclusions:** Dual checkpoint blockade using nivo/ipi has a prominent immunomodulatory role in extensive stage SCLC characterized by increased local adaptive immune responses, reduced HLA class-I antigen presentation and change in the molecular subtype in a subset of cases. We identified genomic features associated with treatment sensitivity/resistance. Clinical trial information: NCT03670056. Research Sponsor: Bristol-Myers Squibb.

TPS8599

Poster Session

Durvalumab with chemotherapy as first line treatment in advanced pleural mesothelioma: A phase 3, randomised trial (DREAM3R). *First Author: Patrick M. Forde, Bloomberg–Kimmel Institute for Cancer Immunotherapy, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, Baltimore, MD*

Background: Two phase 2 trials of durvalumab plus chemotherapy in advanced pleural mesothelioma exceeded pre-specified efficacy criteria. The recent CM 743 trial showed overall survival (OS) was longer in those assigned ipilimumab and nivolumab (ipi nivo) than standard chemotherapy, however the benefits were primarily in the subgroup with non-epithelioid histology. DREAM3R will determine the effectiveness of durvalumab plus chemotherapy as first line treatment for advanced pleural mesothelioma. The DREAM3R protocol was recently amended to allow treatment with ipi nivo as per CM 743 in the control group, and to confine further accrual to epithelioid subtype. **Methods:** Treatment-naïve patients with advanced, epithelioid pleural mesothelioma will be randomized (1:1) to either experimental group treatment: durvalumab 1500 mg every 3 weeks plus chemotherapy (pemetrexed 500 mg/m² plus either cisplatin 75 mg/m² or carboplatin AUC 5) every 3 weeks for 4-6 cycles, followed by durvalumab 1500 mg every 4 weeks until disease progression, unacceptable toxicity or patient withdrawal, or control group treatment: physician's choice of either chemotherapy or ipi nivo (up to 2 years). The target sample size of 480 recruited over 33 months, with follow up for another 18 months provides over 85% power if the true hazard ratio for OS is 0.70, with 2-sided alpha of 0.05, assuming a median OS of 18 months in the control group. Key eligibility criteria: Epithelioid pleural mesothelioma; measurable disease per RECIST 1.1 modified for mesothelioma; ECOG PS 0-1; and adequate hematologic, renal, and liver function. Exclusions: Prior systemic anticancer treatment for pleural mesothelioma, diagnosis based solely on cytology or fine needle aspiration biopsy, contraindication to immunotherapy or conditions requiring immunosuppressive agents or corticosteroids. Participants are stratified at randomization for: age (18-70 years vs. > 70), sex, planned control regimen (chemotherapy or ipi nivo), platinum (cisplatin vs. carboplatin) and geographic region (USA vs. ANZ). The primary endpoint is OS. Secondary endpoints include progression-free survival; objective tumor response; adverse events; health-related quality of life; and use of healthcare resources in ANZ. Tertiary objectives are to identify potential prognostic and/or predictive biomarkers (including those identified in prior phase 2 studies, PD-L1 expression, tumor mutation burden, genomic characteristics, and HLA subtypes), validation of radiological measures of response, and studies of possible radiomic biomarkers in mesothelioma. The study is active and enrolling in both ANZ and in the US. Clinical trial information: NCT04334759 and ACTRN12620001199909. Research Sponsor: AstraZeneca.

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Poster Session

Utilization of circulating tumor DNA (ctDNA) analysis to detect minimal residual disease post-surgery and disease progression in metastatic thymic tumors. *First Author: Fatemeh Ardeshtir-Larijani, Indiana University, Melvin and Bren Simon Cancer Center, Indianapolis, IN*

Background: Thymic epithelial tumors (TETs) are rare and tend to have an indolent disease course. Follow-up consists of physical examinations and routine imaging (CT scans) with no currently available biomarkers to complement surveillance. This study aimed to assess the utility of ctDNA in MRD detection and disease monitoring in TETs. **Methods:** From Nov 2020 till Feb 2022, ctDNA analysis using a tumor-informed mPCR-NGS (Signatera) assay was performed on 29 patients (pts) with primary (pTETs) or metastatic TETs (mTETs). For pts with early-stage disease, the baseline ctDNA was measured 4-8 w post-surgery and repeated q3m. For mTETs, ctDNA was measured at the first visit, and then q3m with interval CT scan q3-4 m. ctDNA was quantified as mean tumor molecules (MTM)/mL of plasma. All pts had at least one measurement (up to 4). GraphPad was used for statistical analysis. **Results:** Of 29 pts overall, 9 pts were excluded at the time of analysis for various reasons; a) insufficient specimen (n=5), b) presence of concurrent active cancer (n=2), and c) final report delay (n=2). Of 20 evaluable pts, 7 pts had pTETs and 13 mTETs. The median age was 50 yrs (range, 17-72), and WHO histology distribution of AB=3, B1=5, B2=9, B3=12, TC=3. History of autoimmune disease and second malignancy (not active at the time of obtaining ctDNA) was reported in 33% (n=9) and 40% (n=8) of evaluable pts, respectively. Of 13 metastatic pts, 6 had stage IVA with pleural-only metastasis, 7 pts had Stage IVB with 2 extra-thoracic (liver, adrenal), and 5 with intrathoracic (lung, chest wall, and LNs) involvement. From 7 pTETs, 6 pts had R0 resection with undetectable post-operative ctDNA, while R1 resection with detectable ctDNA was reported (0.47 MTM/mL) in one pt. In mTETs, the mean level of ctDNA in pts with the stable disease was 0.18 MTM/mL (0.1-0.2), pleural-only progression 1.26 MTM/mL (0.1-1.9), and progressive disease (primary and/or pleural) 7.67 MTM/mL (5.04-9.5). Comparing the mean level of ctDNA in clinically stable metastatic pts with those who had progression, pts with pleural-only progression did not have a significantly higher level of ctDNA (p=0.51). In contrast, pts with primary and/or pleural progression had significantly higher levels of ctDNA (p=0.02). The level of ctDNA correlated with tumor size. An increase of 4-6mm in tumor size was associated with an approximate 0.2 MTM/mL increase in ctDNA or making the undetectable status detectable. **Conclusions:** The ctDNA level correlates well with the tumor volume in mTETs. In pTETs, ctDNA was negative following R0 resection but not in the R1, supporting its potential use as a surrogate biomarker for MRD. This is a pilot study, and the expansion of these data is ongoing to validate the utility of ctDNA testing in these settings. If validated, ctDNA may augment or minimize the routine use of CT scans for disease monitoring in resected and mTETs. Research Sponsor: Alumni award hematology/oncology fellowship/ Indiana University.

TPS8600

Poster Session

A randomised phase II trial of niraparib versus active symptom control in patients with previously treated mesothelioma: NERO. *First Author: Gareth Owen Griffiths, Cancer Research UK Clinical Trials Unit, University of Southampton, Southampton, United Kingdom*

Background: Malignant mesothelioma is a universally lethal cancer that has been increasing over the last three decades. No treatment has been licenced for patients with relapsed mesothelioma after receipt of licenced systemic anti-cancer therapy in the UK. A previous single-arm phase IIa trial (MiST1) evaluated the efficacy of Poly (ADP-ribose) polymerase (PARP) inhibition in mesothelioma, which met its primary endpoint with 15% of patients having durable responses exceeding 1 year. Therefore, there is a need to evaluate PARP inhibitors in a randomised trial in relapsed mesothelioma patients. NERO is currently in progress in this setting. **Methods:** Co-ordinated by the CRUK Southampton Clinical Trials Unit, NERO is a multicentre, two arm, open-label UK randomised phase II trial comparing niraparib + Active Symptom Control (ASC) versus ASC alone in mesothelioma patients who have relapsed after previously receiving platinum-based systemic therapy. NERO is not restricted by line of therapy and treatment allocation ratio is 2:1 (niraparib + ASC:ASC), stratified by histology and response to prior platinum-based therapy. Participants will receive either niraparib + ASC or ASC alone for a period of 24 weeks. Participants will be treated until disease progression, withdrawal, death or development of significant treatment limiting toxicity. Participants randomised to niraparib will receive 200/300 mg every day in a 21-day cycle. The primary endpoint is progression-free survival, where progression is determined by modified RECIST or RECIST 1.1; investigator reported progression; or death from any cause, whichever comes first. Time to event data will be analysed and presented using Kaplan-Meier curves according to the intention to treat principle, with treatment-related intercurrent events handled using the treatment strategy policy, and study withdrawal following the "while on study" strategy. A Cox proportional hazards model will be used to calculate the Hazard Ratio, 95% CIs and p-value adjusted for stratification factors. Median PFS and 6 and 12 month PFS will also be reported. Secondary endpoints include overall survival, best overall response, 12 and 24 week disease control, duration of response, treatment compliance and safety/tolerability. Patients consent to provide mandatory diagnostic tissue blocks, blood samples and an optional stool sample for translational research. These will be used to interrogate homologous recombination deficiency and its association with response in NERO, translational research comprising multi-omic analysis with multiplex immune landscape phenotyping will be analysed and correlated with clinical outcome using machine learning. NERO opened in July 2022 and will be run in approximately 10 UK secondary care hospitals with the aim of recruiting 84 evaluable patients (recruitment is currently 24 on 11-Jan-2023). Clinical trial information: NCT05455424. Research Sponsor: Asthma and Lung UK; GSK.

TPS8601

Poster Session

Nivolumab with chemotherapy in pleural mesothelioma after surgery: The NICITA trial. *First Author: Rajiv Shah, Department of Thoracic Oncology/ Internal Medicine, Thoraxklinik, Heidelberg University Hospital and Translational Lung Research Center Heidelberg (TLRC), German Center for Lung Research (DZL), Heidelberg, Germany*

Background: Pleural mesothelioma (PM) is a highly aggressive cancer of the pleura, predominantly caused by prior asbestos exposure. Currently, there is no approved standard therapy for the treatment of early-stage PM. In most cases a multimodal therapy is recommended consisting of locoregional treatment by surgical cytoreduction via extended pleurectomy/decortication (eP/D), which, if feasible, can be combined with hyperthermic intrathoracic chemoperfusion (HITOC), together with inductive or adjuvant chemotherapy. Considering the immunogenic effects of chemotherapy on the tumor microenvironment, synergistic effects are expected when such a treatment is combined with immune checkpoint inhibitor therapy. In addition, interactions between immune infiltrates and mesothelioma cells play a role in the advent of PM, also implying a beneficial role for immunotherapy in this entity. This is also supported by recent clinical data that demonstrated beneficial effects of immune checkpoint inhibitors in patients with advanced PM. The NICITA trial is an investigator-initiated trial, investigating the combination of adjuvant chemotherapy with immune checkpoint inhibitor compared to chemotherapy alone in radically resected patients with early stage PM. **Methods:** The NICITA trial is a randomized, open-label, phase II clinical trial that is conducted in 14 centers across Germany. Eligible patients have been diagnosed with PM in tumor stages I-III (UICC 8th edition) and epithelioid subtype, and must have undergone cytoreductive surgery by eP/D with or without HITOC. Patients will be randomized 1:1 to receive either a combination of 4 cycles of pemetrexed/platinum-based adjuvant chemotherapy and nivolumab (480 mg q4w) followed by nivolumab maintenance therapy (12 cycles, 480 mg q4w) or 4 cycles of adjuvant chemotherapy only. Stratification will take place according to previous HITOC treatment (yes vs. no), ECOG status (0, 1 vs. 2), and achievement of macroscopic complete resection (yes vs. no). The primary endpoint of this trial is time-to-next-treatment. Secondary endpoints include additional measures of efficacy (progression-free survival, overall survival, measures of treatment-beyond-progression) and quality of life, as well as the assessment of safety. Furthermore, a comprehensive longitudinal collection of biomarker samples, including tumor tissue, blood, and stool samples, for an accompanying translational research project is implemented in this clinical trial. Sample size justification: the recruitment of 46 patients to each arm with a low drop-out rate of 13% appears feasible resulting in 40 patients to be analyzed per arm. This sample size will permit a descriptive comparison and adequately describe the tested treatment options as deduced from the precision of the median TNT confidence interval estimate. As of February 2nd 2023, 85 of planned 92 patients have been enrolled into the NICITA trial. Clinical trial information: NCT04177953. Research Sponsor: Bristol Myers Squibb GmbH & Co. KGaA (BMS).

TPS8603

Poster Session

Phase 2 randomized trial of neoadjuvant or palliative chemotherapy with or without immunotherapy for peritoneal mesothelioma (Alliance A092001). *First Author: Aaron Scott Mansfield, Mayo Clinic, Rochester, MN*

Background: Peritoneal mesothelioma is a rare and poorly studied disease with few treatment options. For patients (pts) who are not surgical candidates, treatment recommendations for systemic therapy have been extrapolated from clinical trials for pleural mesothelioma that commonly exclude pts with peritoneal mesothelioma. Recently, the combination of the PD-1 inhibitor nivolumab and the CTLA-4 inhibitor ipilimumab received FDA-approval for the frontline treatment of non-resectable pleural mesothelioma. Additionally, a prospective, non-randomized phase 2 trial demonstrated activity with combined PD-L1 (atezolizumab) and VEGF (bevacizumab) blockade in peritoneal mesothelioma. In parallel, encouraging activity with combined chemo-immunotherapy has been reported in pleural mesothelioma. Given the benefits observed with immunotherapy, and the potential to improve upon those with chemotherapy and VEGF inhibition, we seek to determine whether the addition of the PD-L1 inhibitor atezolizumab improves outcomes with chemotherapy and bevacizumab in pts with newly diagnosed peritoneal mesothelioma. **Methods:** Alliance for Clinical Trials in Oncology A092001 is a prospective, randomized phase 2 clinical trial. All pts with newly diagnosed peritoneal mesothelioma will be randomized 1:1 using a dynamic allocation Pocock-Simon procedure to receive carboplatin, pemetrexed and bevacizumab, with or without atezolizumab, every 21 days for four cycles. Patients who are eligible to proceed with surgery after four cycles of therapy will then do so. Pts who are not eligible to proceed with surgery may receive maintenance bevacizumab and atezolizumab, or second-line atezolizumab with bevacizumab until progression of disease or toxicity. The primary objective is to determine if frontline treatment with carboplatin, pemetrexed, bevacizumab and atezolizumab results in a superior best response rate (RR) to carboplatin, pemetrexed and bevacizumab as determined by RECIST. With 31 eligible pts per arm (62 eligible total), this randomized design has 80% power to detect an improvement in the RR from 20% to 45%, with a 1-sided significance level of 0.10 where an interim futility analysis will be conducted after 32 pts are enrolled. Stratification factors include eligibility for cytoreductive surgery at diagnosis and histologic subtype. Secondary endpoints include progression-free survival, overall survival and adverse events. As integrated biomarkers, we will determine if soluble mesothelin-related peptides and megakaryocyte potentiating factor correlate with responses. This trial was recently approved by the National Cancer Institute Central IRB and is activating at sites across the country. Clinical trial information: NCT05001880. Research Sponsor: U.S. National Institutes of Health; Alliance.

TPS8602

Poster Session

Neoadjuvant immunotherapy in sarcomatoid mesothelioma (Alliance A082101). *First Author: Aaron Scott Mansfield, Mayo Clinic, Rochester, MN*

Background: Sarcomatoid mesothelioma is the most aggressive form of pleural mesothelioma and is associated with the worst prognosis of the histologic variants of this disease. In the Checkmate 743 clinical trial the patients with sarcomatoid mesothelioma who received ipilimumab and nivolumab had survival outcomes that were similar to those of patients with epithelioid mesothelioma. In comparison, the patients with sarcomatoid mesothelioma who received chemotherapy had the worst outcomes in this trial, highlighting the known limited efficacy of chemotherapy against this histologic variant. Checkmate 743 demonstrated that ipilimumab and nivolumab is a new standard of care for non-epithelioid mesothelioma. Surgery typically has not been offered to this group of patients given their historically poor outcomes. With the significant survival gains seen in patients with sarcomatoid mesothelioma treated with immunotherapy, we hypothesized that surgery may extend the benefits seen with immunotherapy. **Methods:** Alliance for Clinical Trials in Oncology A082101 is a prospective, phase 2 nonrandomized clinical trial for patients with sarcomatoid mesothelioma. The co-primary objectives are to determine the percentage of patients with potentially resectable sarcomatoid mesothelioma able to proceed with surgery after neoadjuvant ipilimumab and nivolumab, and the progression-free survival (PFS) at 12 months (12-month PFS). For sample size determination, we assumed that if the true rate of surgery is 75% or greater, it would indicate that neoadjuvant immunotherapy is feasible to be given prior to surgery. On the other hand, if the true rate of surgery is 50% or less it would indicate that neoadjuvant immunotherapy is not worthy of further investigation. Twenty-six (26) eligible patients will be needed to receive neoadjuvant immunotherapy. If 16 or fewer of the 26 eligible patients proceed to surgery, it will be concluded that the experimental therapy is not worthy of further investigation. Otherwise, it will be concluded that the experimental therapy is worthy of further investigation. Safety monitoring will be done through a 6-week run-in for the first 10 patients to assess for pre-operative and post-operative toxicities and complications. Sequential boundaries will be used to monitor severe toxicity and complication rates. Accrual will be halted if excessive numbers of severe toxicity and complications in pre-operative and post-operative phases are seen. Tumor and blood-based biomarkers will be included as exploratory biomarkers. Clinical trial information: NCT05647265. Research Sponsor: U.S. National Institutes of Health; Alliance.

TPS8604

Poster Session

NeoCOAST-2: A phase 2 study of neoadjuvant durvalumab plus novel immunotherapies (IO) and chemotherapy (CT) or MEDI5752 (volrustomig) plus CT, followed by surgery and adjuvant durvalumab plus novel IO or volrustomig alone in patients with resectable non-small-cell lung cancer (NSCLC). *First Author: Florian Guisier, Department of Pneumology, Rouen University Hospital, Rouen, France*

Background: Neoadjuvant platinum-based CT plus IO prolongs event-free survival (EFS) and increases pathological complete response (pCR) rate in patients with resectable NSCLC vs CT alone (Forte et al. N Engl J Med 2022). IO+IO+CT combinations have the potential to further improve pCR and survival outcomes. The phase 2 NeoCOAST-2 study (NCT05061550) is evaluating multiple neoadjuvant IO+IO+CT combinations in patients with resectable, early stage NSCLC. Novel IO molecules being evaluated include the anti-CD73 monoclonal antibody (mAb), oleclumab; the anti-NKG2A mAb, monalizumab; and the PD-1/CTLA-4 bispecific mAb, volrustomig. The latter recently demonstrated durable responses vs a PD-1 inhibitor plus CT as first-line treatment for patients with metastatic NSCLC (ESMO 2022; LBA56). Here we describe the NeoCOAST-2 study design. **Methods:** This randomized, open-label, multicenter study will enroll approximately 210 patients with previously untreated, histologically/cytologically confirmed, resectable Stage IIA–IIIB (AJCC 8th edition) NSCLC. Patients will be stratified by PD-L1 expression (< 1% vs ≥ 1%) and receive treatment with durvalumab + oleclumab + CT, durvalumab + monalizumab + CT, or volrustomig + CT every 3 weeks for 4 cycles prior to surgery, followed by adjuvant durvalumab + oleclumab, durvalumab + monalizumab, or volrustomig for up to 1 year or until disease progression per RECIST v1.1. Surgery should occur within 40 days after the last dose of neoadjuvant therapy and adjuvant therapy should commence within 10 weeks after surgery. The primary endpoints are pCR rate (per blinded independent pathologist review) and safety and tolerability. Secondary endpoints include investigator-assessed EFS, disease-free survival and overall survival, feasibility to surgery, major pathological response rate, objective response rate following neoadjuvant therapy, pharmacokinetics, immunogenicity, and changes in circulating tumor DNA. The study is currently recruiting patients across the US, Europe, Canada, and Asia. Clinical trial information: NCT05061550. Research Sponsor: AstraZeneca.

TPS8605

Poster Session

A phase I-III platform study evaluating the safety and efficacy of multiple therapies in patients with biomarker-defined locally advanced, unresectable stage III non-small-cell lung cancer (NSCLC). *First Author: Luis G. Paz-Ares, Hospital Universitario, 12 de Octubre, Universidad Complutense de Madrid, Madrid, Spain*

Background: Durvalumab following chemoradiation (CRT) is a standard of care for unresectable stage III NSCLC, but there remains an unmet need for improved therapeutic options among patients with driver-mutated tumors that are unresponsive to immunotherapy. As targeting of specific driver mutations (e.g. *ALK*, *RET*, *ROS1*) has proven effective in the metastatic setting, it is hypothesized that outcomes could also be improved for patients with driver-mutated stage III NSCLC. **Methods:** B042777 (NCT05170204) is a phase I-III platform study evaluating the safety and efficacy of multiple targeted therapies versus durvalumab following CRT in patients with locally advanced, unresectable stage III NSCLC. Biomarker eligibility is determined via local tissue testing or central testing within the BX43361 master screening study (NCT05419375). Biomarker-eligible patients are enrolled into the relevant cohort and randomized 1:1 to receive durvalumab or targeted therapy (alectinib [*ALK*], entrectinib [*ROS1*], or pralsetinib [*RET* fusion+]). New cohorts may be added in the future. Key inclusion criteria: locally advanced, unresectable stage III NSCLC, age ≥ 18 years, ≥ 2 prior cycles of concurrent or sequential CRT (cCRT or sCRT), and ECOG PS 0–2. Patients are stratified based on staging (IIIA vs IIIB or IIIC), CRT type (cCRT vs sCRT), and PD-L1 status (tumor cell score $< 1\%$ vs $\geq 1\%$ vs unknown) and will receive investigational treatment for three years or durvalumab for one year, until progression or maximum duration of treatment, unacceptable toxicity, consent withdrawal, or death. Primary endpoint: progression-free survival (RECIST v1.1) by blinded independent central review. Key secondary endpoints: distant metastasis-free survival, time to CNS progression, objective response rate, duration of response, overall survival, and safety (adverse events). Time to confirmed deterioration and patient-reported outcomes will be assessed through questionnaires. Tumor response will be assessed by CT/MRI imaging at regular intervals. Enrollment is ongoing (target of 320 patients) across 200 sites in 11 countries. As of 7 February 2023, five patients have been randomized. This trial in progress was previously presented at ELCC, Luis Paz-Ares *et al.* (#744), and reused with permission. Clinical trial information: NCT05170204. Research Sponsor: These trials are sponsored by F. Hoffmann-La Roche Ltd.

TPS8607

Poster Session

Phase 3 study of durvalumab with SBRT for unresected stage I/II, lymph-node negative NSCLC (PACIFIC-4/RTOG3515). *First Author: Clifford Grant Robinson, Department of Radiation Oncology, Washington University in St. Louis/Siteman Cancer Center, St. Louis, MO*

Background: Stereotactic body radiation therapy (SBRT) is a standard treatment for patients with unresectable (UR) stage I/II, lymph-node negative NSCLC, with excellent safety and high rates of primary tumor control. Despite predominant regional and distant failure that increases with tumor size, no adjuvant therapy is approved for these patients. Durvalumab is a selective, high-affinity, human IgG1 monoclonal antibody that blocks PD-L1 binding to PD-1/CD80. In the placebo-controlled, phase 3 PACIFIC trial of patients with stage III UR-NSCLC without disease progression on/after concurrent chemoradiotherapy, durvalumab improved progression-free survival (PFS) and overall survival (OS) with manageable safety (Antonia, *et al.* 2017; 2018), leading to its approval in stage III UR-NSCLC. Osimertinib is a 3rd-generation, irreversible CNS-active EGFR tyrosine kinase inhibitor that selectively inhibits NSCLC tumors with EGFR-sensitizing mutations (EGFRm). In the recent placebo-controlled, phase 3 ADAURA trial, osimertinib demonstrated statistically significant and clinically meaningful improvement in disease-free survival (DFS) (HR, 0.20 [99.12% CI, 0.14–0.30], $P < 0.001$) in patients with resected stage IB-IIIa EGFRm NSCLC (Wu, *et al.* 2020), leading to its approval in an adjuvant setting. Based on data for durvalumab and osimertinib in the early-stage setting, PACIFIC-4 is designed to assess the efficacy and safety of durvalumab combined with SBRT in patients with stage I/II UR-NSCLC and osimertinib after SBRT in patients with stage I/II EGFRm UR-NSCLC. **Methods:** PACIFIC-4 (NCT03833154) is an international, phase 3 study with two independent cohorts. Eligible patients are ≥ 18 years of age with stage T1-T3, N0, M0 unresected NSCLC and ECOG PS 0–2. The main cohort of approximately 630 patients will be randomized (1:1) in a double-blind manner, stratified by tumor size and location, to receive durvalumab (1500 mg IV) or placebo every 4 weeks for up to 26 cycles with concurrent standard of care (SoC) SBRT. The primary endpoint in this cohort is PFS (RECIST v1.1) by blinded independent central review; other endpoints include OS, health-related quality of life, and safety. The protocol was amended (v4) to exclude patients with an identified EGFRm from the main cohort and add a separate cohort of approximately 60 patients with EGFRm (L858R or Ex19del) who will receive osimertinib 80 mg PO QD, following SoC SBRT, for up to 36 months. The primary endpoint in this cohort is 4-year PFS (RECIST v1.1) by independent central review; secondary endpoints include PFS, OS, and safety. Trial recruitment is ongoing. Previously presented at the European Lung Cancer Congress (ELCC) 2022, FPN (Final Publication Number): 122TiP, Clifford Robinson *et al.* – Reused with permission. Clinical trial information: NCT03833154. Research Sponsor: AstraZeneca.

TPS8606

Poster Session

A randomized, double blinded, multicenter phase 3 study of platinum-based chemotherapy with or without QL1706 as adjuvant therapy in completely resected stage II-IIIB NSCLC. *First Author: Yuming Zhu, Department of Medical Oncology, Shanghai Pulmonary Hospital, Shanghai, China*

Background: Adjuvant atezolizumab is approved for PD-L1 positive stage II-IIIA NSCLC in USA and China. To date, there are few clinical studies on dual immune checkpoint inhibitors in adjuvant settings of NSCLC. QL1706, a MabPair product, is a novel bifunctional antibody containing a mixture of anti-PD-1 IgG4 and anti-CTLA-4 IgG1 antibodies. QL1706 monotherapy has demonstrated good safety and promising antitumor activity in advanced solid tumors in a phase Ia/Ib study with 518 patients, including 146 NSCLC patients. Meanwhile, in NSCLC patients with negative oncogene drivers, QL1706 plus 2 cycles of chemotherapy as first line treatment resulted in an ORR of 58.6% (17/29) and the mPFS was 6.97 months. Furthermore, in the EGFR mutant NSCLC patients who previously were treated with EGFR-TKI, QL1706 plus platinum-based chemotherapy and bevacizumab showed promising efficacy with an ORR of 64.5% (20/31). This study is designed to investigate the efficacy and safety of QL1706 or placebo plus platinum doublet chemotherapy as adjuvant treatment in stage II-IIIB NSCLC. **Methods:** In this phase III, randomized, double-blind, placebo-controlled, multicenter study, 632 eligible pts, who is completely resected stage II-IIIB NSCLC (AJCC 8th) with negative EGFR, ALK etc, will be enrolled. Pts will be randomized 1:1 to receive QL1706 (5 mg/kg) or placebo plus chemotherapy, administered every 3 weeks (Q3W). The regimen of vinorelbine/paclitaxel plus cisplatin/carboplatin is chosen for squamous NSCLC, while pemetrexed/vinorelbine plus cisplatin/carboplatin for non-squamous NSCLC. Randomization will be stratified by PD-L1 TPS (ie, $< 1\%$, $\geq 1\%$), disease stage (stage II, III) and predominant tumor histology (ie, squamous vs non-squamous). The primary endpoint is disease-free survival (DFS) per investigators in PD-L1 TPS $\geq 1\%$ pts and in all randomized pts, which will be tested hierarchically. An interim analysis is to occur when about 70% DFS events achieved in pts with PD-L1 $\geq 1\%$. Enrollment began in Nov, 2022. ClinicalTrials.gov NCT05487391. Clinical trial information: NCT05487391. Research Sponsor: Qilu Pharmaceutical Co., Ltd.

TPS8608

Poster Session

A master screening study to determine biomarker status and trial eligibility for patients with malignant tumors. *First Author: Benjamin J. Solomon, Peter MacCallum Cancer Centre, Melbourne, Australia*

Background: Targeting of oncogenic driver alterations has proven to be an effective clinical approach across many tumor types. As a result of the approval of targeted therapies against oncogenic driver alterations, molecular biomarker testing is commonly recommended for patients with advanced/metastatic non-small cell lung cancer (NSCLC) before initiation of first-line treatment. Although there are emerging clinical trial data using targeted therapies in patients with early-stage NSCLC, currently molecular biomarker testing is not universally performed as part of routine clinical practice in the early-stage setting. Screening platforms can be utilized to provide comprehensive, validated biomarker testing to facilitate access to clinical trials for appropriate investigational therapies, based on biomarker status. This type of approach aims to be more efficient and to streamline patient recruitment and improve patient access to clinical trials where biomarker testing is not currently performed as part of routine care, especially when the biomarkers of interest are at low prevalence. **Methods:** This global, non-Investigational Medicinal Product (non-IMP), multicenter master screening study (NCT05419375) provides centralized tissue-based testing to determine patients' biomarker eligibility for linked Roche clinical trials. Currently this study is only open to screening patients for a linked platform study in unresectable stage III NSCLC (NCT05170204). However, it is envisaged that this screening study will be expanded to support additional clinical trials and indications in the future. Eligible patients must be aged ≥ 18 years with locally advanced, unresectable stage III NSCLC (according to AJCC 8th edition), an ECOG PS of 0–2, confirmed availability of a formalin-fixed paraffin-embedded tumor specimen obtained prior to chemoradiation, and adequate hematologic and end-organ function. If a patient is found to have an oncogenic driver mutation and is considered a good candidate for a linked clinical trial, the investigator may propose that they be screened into the respective study. Tumor tissue samples will be centrally tested by validated molecular tests for the presence of specific genetic alterations: *EGFR*, *ALK*, *ROS1*, *KRAS*, *BRAF*, *HER2*, *RET*, *MET*, and *NTRK1/2/3*. Immunohistochemistry may also be performed to determine PD-L1 expression as required by the linked trial eligibility criteria. The primary objective of this screening trial is to determine the biomarker status of patients and their eligibility to participate in a linked clinical trial. Exploratory objectives include characterization of biomarker profiles and patients' subsequent treatment. No therapeutic intervention will be administered in this study. Enrollment is ongoing across 51 sites in ten countries, with a target enrolment of 15,000 patients. As of 9 February 2023, 27 patients have been enrolled. Clinical trial information: NCT05419375. Research Sponsor: This study is sponsored by F. Hoffmann-La Roche Ltd. Third-party medical writing assistance, under the direction of the authors, was provided by Vanessa Poon, BSc of Ashfield MedComms, an Inizio company, and was funded by F. Hoffmann-La Roche Ltd.

TPS8609

Poster Session

Phase 3 trial of durvalumab combined with domvanalimab following concurrent chemoradiotherapy (cCRT) in patients with unresectable stage III NSCLC (PACIFIC-8). *First Author: Mustafa Özgüroğlu, Istanbul University—Cerrahpaşa, Cerrahpaşa School of Medicine, Istanbul, Turkey*

Background: The PACIFIC trial (NCT02125461) established up to 12 months of consolidation therapy with durvalumab as standard of care (SoC) for patients with unresectable stage III non-small-cell lung cancer (NSCLC) and no disease progression after platinum-based cCRT. To improve outcomes further in this population, novel immunotherapy combinations that build on the backbone of PD-L1 inhibition with durvalumab are being explored. Domvanalimab (AB154) is a Fc-silent humanized IgG1 monoclonal antibody that blocks interaction of the T cell immunoreceptor with Ig and ITIM domains (TIGIT; upregulated by immune cells) with CD112 and CD155 (expressed by tumor and antigen-presenting cells), reducing inhibition of T cells and natural killer cells and, thereby, promoting antitumor activity. The combination of TIGIT inhibition with PD-(L)1 inhibition has shown encouraging activity in phase 1 and 2 trials in metastatic NSCLC, with enriched benefit observed among patients with PD-L1 positive tumors (Rodriguez-Abreu, et al. 2020; Niu, et al. 2020). In ARC-7 (NCT04262856), a randomized, phase 2 trial, the combination of domvanalimab and PD-1 inhibition was associated with improvement in progression-free survival (PFS) versus PD-1 inhibition alone (HR, 0.55; 95% CI, 0.31–1.0) in treatment-naïve patients with metastatic NSCLC and high PD-L1 expression (tumor proportion score $\geq 50\%$) (Johnson, et al. 2022). PACIFIC-8 (NCT05211895) is assessing the efficacy and safety of durvalumab combined with domvanalimab as consolidation therapy in patients with PD-L1 positive, unresectable stage III NSCLC and no disease progression after platinum-based cCRT. **Methods:** PACIFIC-8 is a phase 3, double-blind, placebo-controlled, randomized, global trial. Eligible patients (aged ≥ 18 years) must have PD-L1 positive, unresectable stage III NSCLC (tumor cell [TC] expression $\geq 1\%$ by central lab; VENTANA SP263 IHC assay), WHO performance status 0/1, documented EGFR/ALK wild-type tumor status, and not have progressed following definitive, platinum-based cCRT (≥ 2 cycles). Approximately 860 patients will be randomized (1:1) to receive SoC durvalumab (1500 mg IV) combined with either domvanalimab (20 mg/kg IV) or placebo, every 4 weeks for up to 12 months. The primary endpoint is PFS (RECIST v1.1) by blinded independent central review (BICR) in patients with PD-L1 TC $\geq 50\%$. Secondary endpoints include PFS (RECIST v1.1; BICR) in patients with PD-L1 TC $\geq 1\%$, overall survival, objective response rate and duration of response (RECIST v1.1; BICR), safety/tolerability, and patient-reported outcomes. Trial enrollment is ongoing. *Previously presented at the European Society for Medical Oncology (ESMO) Congress 2022, FPN (Final Publication Number): 971TiP, Mustafa Özgüroğlu et al. – Reused with permission.* Clinical trial information: NCT05211895. Research Sponsor: AstraZeneca.

TPS8611

Poster Session

Randomized phase 3 study of tarlatamab, a DLL3-targeting bispecific T-cell engager (BiTE), compared to standard of care in patients with relapsed small cell lung cancer (DeLLphi-304). *First Author: Luis G. Paz-Ares, Hospital Universitario 12 de Octubre, CNIO-H120 Lung Cancer Unit, Ciberonc and Universidad Complutense, Madrid, Spain*

Background: Small cell lung cancer (SCLC) is an aggressive malignancy for which very few patients achieve long term disease control; response to most treatments is transient and second line treatment options are limited. Delta-like ligand 3 (DLL3) is a Notch ligand aberrantly expressed on the surface of up to 85% of SCLC cells and minimally expressed in normal tissues, making it an attractive therapeutic target. Tarlatamab is a bispecific T cell engager (BiTE) molecule designed to bind DLL3 on target cancer cells and CD3 on T cells, thereby driving T cell-dependent killing of tumor cells. Results from the first-in-human study in patients with relapsed/refractory SCLC (DeLLphi-300; NCT03319940) demonstrate tarlatamab efficacy in pretreated patients with confirmed responses in 23% of patients and median duration of response > 12 months.¹ Median overall survival (OS) was 13.2 months. Grade ≥ 3 treatment-related AEs (TRAEs) occurred in 31% of patients and TRAEs resulted in discontinuation in 4% of patients. This promising efficacy/safety profile is being evaluated further in a phase 2, open-label study in patients with relapsed/refractory SCLC after ≥ 2 lines of prior treatment (DeLLphi-301; NCT05060016). **Methods:** NCT05740566 is a randomized, open-label, phase 3 study of tarlatamab compared with standard of care (SOC) in ~ 700 patients with relapsed SCLC after platinum-based first-line chemotherapy. Patients will be randomized 1:1 to receive tarlatamab or SOC therapy (lurbinectedin or topotecan in US, Canada, Australia, Singapore, Korea; amrubicin in Japan; topotecan in all countries except Japan), stratified by prior anti-programmed cell death 1 (PD-1) or anti-programmed cell death ligand 1 (PD-L1) exposure, chemotherapy-free interval, presence of brain metastases, and SOC (topotecan/amrubicin vs lurbinectedin). The primary objective is to compare the efficacy of tarlatamab with SOC on prolonging OS. Key secondary endpoints include comparison of progression free survival (PFS) based on investigator assessment per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) and patient-reported outcomes (PRO) including disease-related symptoms, physical function, and global health status of quality of life. Key eligibility criteria include adults with histologically or cytologically confirmed relapsed SCLC who progressed following 1 platinum-based regimen. Patients must have measurable lesions as defined per RECIST 1.1 within the 21-day screening period and must have adequate organ function. Exclusions include untreated or symptomatic central nervous system metastases, history of immune checkpoint inhibitor use resulting in severe immune-mediated adverse event, and previous history of NSCLC. Enrollment is ongoing. References 1. Paz-Ares L, et al. *J Clin Oncol*. DOI:1200/JCO.22.02823. Clinical trial information: NCT05740566. Research Sponsor: Amgen.

TPS8610

Poster Session

Phase 3 study of durvalumab combined with oleclumab or monalizumab in patients with unresectable stage III NSCLC (PACIFIC-9). *First Author: Fabrice Barlesi, Gustave Roussy and Paris Saclay University, Faculty of Medicine, Villejuif / Kremlin-Bicêtre, France*

Background: Based on the findings of the phase 3 PACIFIC trial, durvalumab as consolidation therapy is the standard of care for patients with unresectable Stage III NSCLC and no disease progression following chemoradiotherapy (CRT; the PACIFIC regimen). However, further improvements in outcomes are needed for this population and, to build upon the backbone of PD-L1 inhibition with durvalumab, immunotherapy combinations including anti-TIGIT, anti-CD73, and anti-NKG2a monoclonal antibodies (mAbs) are now being explored. Two potential candidates, oleclumab and monalizumab, have demonstrated encouraging clinical activity in a randomized, phase 2 trial when combined with durvalumab in this setting. Oleclumab (MEDI9447) is a human IgG1 λ mAb that inhibits the function of CD73, to reduce extracellular adenosine production and thus promote antitumor immunity. Monalizumab (IPH2201) is a first-in-class, humanized, IgG4 mAb that prevents NKG2A from binding to HLA-E, which reduces inhibition of natural killer and CD8+ T cells. The combination of each of these molecules with durvalumab consolidation therapy was evaluated in the phase 2 COAST study (NCT03822351). In COAST (n = 189), patients receiving combination therapy reported numerically higher objective response rates (durvalumab plus oleclumab: 30.0%; durvalumab plus monalizumab: 35.5%; durvalumab monotherapy: 17.9%) and prolonged progression-free survival versus durvalumab alone, with no new/significant safety signals (Herbst, et al. 2022). Thus, the combination of oleclumab or monalizumab with consolidative durvalumab warrants further evaluation in a phase 3 trial. **Methods:** PACIFIC-9 (NCT05221840) is a phase 3, double-blind, placebo-controlled, randomized, international trial. Eligible patients (age ≥ 18 years) must have EGFR/ALK wild-type unresectable Stage III NSCLC, a WHO performance status of 0/1, documented PD-L1 status, and must not have progressed following ≥ 2 cycles of definitive, platinum-based concurrent CRT. Approximately 999 patients will be randomized (1:1:1) to receive up to 12 months of treatment (in 28-day cycles) with durvalumab plus either oleclumab (Arm A); monalizumab (Arm B); or placebo (Arm C). The primary endpoint is progression-free survival (RECIST v1.1) by blinded independent central review (BICR). Overall survival is a key secondary endpoint. Other secondary endpoints include objective response rate and duration of response (RECIST v1.1; BICR), patient-reported outcomes, PD-L1 expression on tumor cells relative to efficacy outcomes, and safety/tolerability (CTCAE v5.0). Trial enrollment is ongoing. *Previously presented at the World Conference on Lung Cancer (WCLC) 2022, FPN (Final Publication Number): P1.10-01, Fabrice Barlesi et al.* Clinical trial information: NCT05221840. Research Sponsor: AstraZeneca.

TPS8612

Poster Session

A phase II study to evaluate the efficacy and safety of combination therapy of durvalumab (MEDI4736) and amrubicin in patients with recurrent small cell lung cancer (SCLC): Aphrodite trial, in progress. *First Author: Yuka Kato, Department of Thoracic oncology and Medicine, National Hospital Organization Shikoku Cancer Center, Matsuyama-City, Ehime, Japan*

Background: Immunochemotherapy (ICT) is the standard first-line treatment for extensive stage (ES)-SCLC. However, progression-free survival for patients (pts) treated with ICT as first-line therapy is approximately 5 months, and half of the pts will relapse within 6 months. Several drugs have been approved for the treatment after relapse, and amrubicin has been used as a second-line treatment in Japan for 20 years. However, the efficacy of pts treated with amrubicin is unsatisfactory, the median survival was 9.2 months (pts with sensitive relapse (SR-pts)) and 2.6 months (pts with refractory relapse (RR-pts)), indicating an urgent need for new therapeutic strategies in the treatment of post-relapse SCLC pts. A retrospective study showed significant improvement in survival for patients who progress on immunochemotherapy, treated with same ICI plus chemotherapy as second-line therapy (Trans Lung Cancer Rec. 2020). Cytotoxic chemotherapy introduced immunogenic cell death and the addition of chemotherapy to ICI might have a synergistic effect. Based on these assumptions, the combination of amrubicin with ICI may provide additional benefit for post-progression pts and we are therefore initiating this study. **Methods:** This is an open-label, single-arm, multicenter, physician-initiated Phase 2 study of amrubicin plus durvalumab in Japanese pts with relapsed SCLC. The study is divided into a lead-in cohort (LIC) and a Phase 2 part; the LIC will use a 3+3 design to ensure safety and will proceed to the Phase 2 part if the first 3 pts have no dose limiting toxicity (DLT) or the first 6 pts have only 1 DLT. Eligibility criteria include pts with ES-SCLC who relapse after platinum-containing chemotherapy with durvalumab as first-line therapy, age ≥ 20 , ECOG 0-1. The primary endpoint is 1-year survival. Patients were treated with intravenous amrubicin 40 mg/m² on day 1-3 and durvalumab 1500 mg/body on day 1 every 3 weeks until PD or unacceptable toxicity. The planned number of pts was 18 each with sensitive relapse (SR-pts) and refractory relapse (RR-pts) which was calculated based on the results of a previous randomized controlled trial (J Clin Oncol. 2008). In this trial, the point estimates and two-sided 90% confidence intervals (Clopper Pearson method) for 1-year survival corresponding to the expected 1-year survival were: SR-pts (11/18 patients): 0.611 (90% CI: 0.392-0.801), RR-pts (8/18 0.444 (90% CI: 0.244-0.659). Enrollment began in October 2022, and will be completed by March 2025. Clinical trial information: jRCT2061220036. Research Sponsor: AstraZeneca.

TPS8613

Poster Session

A phase III study of lurbinectedin alone or in combination with irinotecan vs investigator's choice (topotecan or irinotecan) in patients with relapsed small cell lung cancer (SCLC; LAGOON trial). *First Author: Benjamin Besse, Institut Gustave Roussy, Villejuif, France*

Background: Lurbinectedin is a novel synthetic chemical entity that acts as an inhibitor of oncogenic transcription and is active in tumors addicted to transcription. A phase II Basket trial (NCT02454972) in patients with small cell lung cancer (SCLC) treated with lurbinectedin in the second-line setting showed overall response rate (ORR) of 35.2% and median duration of response (DoR) of 5.3 months, with durable responses (43.0% $\geq$ 6 months). Based on these results, lurbinectedin was granted accelerated approval by the US FDA. An ongoing phase I/II trial (NCT02611024) is evaluating the lurbinectedin/irinotecan combination. Preliminary results showed ORR of 62% and median DoR of 5.7 months (2020 World Conference on Lung Cancer) warranting expansion to 100 patients. These results have supported the conduction of a phase III trial (LAGOON - NCT05153239). **Methods:** LAGOON is a randomized phase III clinical trial evaluating two experimental arms (lurbinectedin alone, 3.2 mg/m² D1 q3wk, or lurbinectedin 2 mg/m² D1 plus irinotecan D1, D8 q3wk) versus Investigator's Choice (topotecan D1-5 q3wk or irinotecan D1 q3wk according to label) as control arm in relapsed SCLC patients. Approximately 705 patients will be enrolled. Central randomization will be implemented (1:1:1 ratio). Stratification will be done according to chemotherapy-free interval (CTFI) after first line (sensitive vs. resistant); prior anti-PD-(L)1; baseline central nervous system (CNS) involvement; lactate dehydrogenase value, and Investigator's preference for the Control Arm. Main inclusion criteria include age $\geq$ 18 years, confirmed SCLC diagnosis, one prior line of platinum-containing chemotherapy with/without anti-PD-(L)1, and CTFI $\geq$ 30 days. Patients with CNS metastases can participate if pretreated and radiologically stable for at least 4 weeks. Main exclusion criteria include platinum-naïve patients, patients pretreated with more than one prior chemotherapy regimen (including platinum re-challenge), and prior treatment with lurbinectedin, trabectedin, PM14, or topoisomerase I inhibitors. An Independent Data Monitoring Committee will oversee the conduct of the study. An Independent Review Committee will provide the patient's response at each tumor assessment endpoint to determine the best patient's response and the date of objective response or progression/censoring according to RECIST v.1.1. Clinical trial information: NCT05153239. Research Sponsor: PharmaMar.

TPS8615

Poster Session

Dares: A phase II trial of durvalumab and ablative radiation in extensive stage small cell lung cancer. *First Author: Aditya Juloori, University of Chicago Medical Center, Chicago, IL*

Background: Most patients diagnosed with small cell lung cancer have extensive stage disease (ES-SCLC) at presentation, portending a poor prognosis with median survival rate of 9 - 11 months and a 2-year overall survival (OS) of less than 5%. Checkpoint inhibitors have recently transformed the landscape for first-line treatment for ES-SCLC patients with the CASPIAN and IMpower133 trials demonstrating an OS benefit with the addition of Durvalumab and Atezolizumab to chemotherapy, respectively. Hypofractionated ablative radiation therapy (RT) provides effective local metastasis control. Increasing evidence suggests that apart from its direct effects, ablative RT can trigger the innate and adaptive immune system. Beyond synergistic mechanisms of modulating the immune response, direct tumor debulking by radiation may also be particularly well suited as an adjunct to immunotherapy. Such upfront cytoreduction can relieve tumor-related immunosuppression and prevent early treatment failure at sites of initial involvement. Prior studies have demonstrated OS and PFS benefits to the addition of local therapy in metastatic non-small cell lung cancer. Multi-site ablative RT has also been shown to be safe in the setting of immunotherapy in multiple published prospective trials. We hypothesize that the addition of RT to chemotherapy and Durvalumab for newly diagnosed ES-SCLC patients will improve PFS. **Methods:** 49 patients will be enrolled across four institutions in this phase II clinical trial. Treatment naïve ES-SCLC patients with PS 0-2 who have at least one RECIST measurable lesion meeting criteria for ablative radiation will be eligible for enrollment. Patients with symptomatic brain metastasis will undergo cranial radiotherapy prior to starting on trial. Patients will be treated with four cycles of platinum/etoposide and Durvalumab. During cycle 2, patients will undergo ablative radiation therapy to 1 - 4 sites of extracranial disease. Radiation dose and organ at risk (OAR) constraints are consistent with NRG BR001. During planning, OAR constraints will be prioritized over tumor coverage. Following four cycles of chemotherapy and Durvalumab, patients will continue with maintenance Durvalumab 1500 mg q28 days until progression, toxicity, or study withdrawal. The primary endpoint is PFS. Using a historic control of 5 month median PFS with chemo/immunotherapy from CASPIAN and IMpower133, we hypothesized that the addition of ablative RT would improve the PFS from 5 months to 8 months. Sample size of 49 patients was calculated for 80% power with alpha of 0.1. Secondary endpoints include overall survival, time to second line therapy, response rate, and rate of grade 3+ adverse events. Peripheral blood, stool, nasal, and buccal samples will be obtained at baseline, after RT, and at the time of progression and/or immune-related toxicity and will be used for exploratory analysis. NCT05068232. Clinical trial information: NCT05068232. Research Sponsor: AstraZeneca.

TPS8614

Poster Session

Prophylactic cerebral irradiation or active brain magnetic resonance imaging surveillance in small-cell lung cancer patients (EORTC-1901: PRIMaLung). *First Author: Antonin Levy, Gustave Roussy, Villejuif, France*

Background: PRIMaLung is an EORTC-sponsored study. Primary objective is to show that overall survival with brain MRI surveillance alone is non-inferior to brain MRI surveillance combined with PCI in patients with SCLC. PCI is currently SOC in most institutions, but can be associated with neurocognitive toxicity and impact quality of life. 600 patients will be recruited from 50 EORTC centres in 10 countries. This study is currently recruiting and will play an important role in clarifying whether MRI surveillance is a viable strategy in SCLC. Furthermore, it will answer important questions about the role of PCI in the era of immunotherapy, particularly in ES-SCLC. **Methods:** Key eligibility: ECOG performance status $\leq$ 2 patients with SCLC (Limited or Extensive-Stage, stage I-IV) who did not progress after ($\leq$ 16 weeks from day 1 of last cycle of chemotherapy to randomisation) completed standard therapy. Absence of progression, brain metastases or leptomeningeal disease after completing therapy. Trial Interventions: Patients will be randomised 1:1 to receive brain MRI surveillance with or without PCI (25Gy in 10 fractions). Primary objective - to show that overall survival with brain MRI surveillance alone is non-inferior to brain MRI surveillance combined with PCI. Secondary objectives - cognitive failure-free survival, quality of life and acute/late toxicities according to CTCAE v5.0. The trial was open to recruitment on 27/10/2022. Three countries open to date (Belgium, Switzerland, UK). Further sites in France, Poland and Austria will be open to recruitment Q1 2023. The first patient has been randomized on the 4th of January 2023. Further information: <https://clinicaltrials.gov/ct2/show/NCT04790253> contact: 1901@EORTC.org. Clinical trial information: NCT04790253. Research Sponsor: Astra Zeneca; EORTC LCG, PHRC-K (France), Ligue contre le Cancer (France), CE (Belgium), Swiss Cancer League (Switzerland).

TPS8616

Poster Session

Phase II study of hemithoracic intensity-modulated pleural radiation therapy (IMPRINT) for patients with pleural metastases from thymic malignancies. *First Author: Andreas Rimner, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Pleural metastases are common sites for recurrence and progression in patients with thymic malignancies. The management of pleural metastases typically involves surgical resection with or without neoadjuvant or adjuvant systemic therapy. After surgical resection of pleural metastases, the 5-year progression-free survival (PFS) rate is about 29-45%. While radiation therapy (RT) is standardly used in the management of locally-advanced thymic malignancies, the role of RT in patients with pleural metastases is unclear. Intensity-modulated pleural radiation therapy (IMPRINT) is a RT technique currently being used to treat malignant pleural mesothelioma (MPM) patients with 2 intact lungs at centers that specialize in MPM treatment. This IMPRINT technique can potentially be extrapolated to thymic patients with pleural metastases. Because the risk of toxicity is of greater concern for thymic patients given their overall relatively favorable prognosis, the rate of toxicity, particularly radiation pneumonitis, needs to be established in the thymic patient population. **Methods:** This is a single-arm, single institution Phase II study of hemithoracic IMPRINT for patients with pleural metastases from thymic malignancies. The primary endpoint of this study is grade 3 or higher radiation pneumonitis within 4 months of completing RT. Secondary endpoints include any toxicity, progression-free survival, patterns of failure and overall survival. Patients must have a pathologically confirmed diagnosis of a thymic malignancy with radiologic or pathologic evidence of pleural metastases. Thymoma or thymic carcinoma are allowed. Patients may have de novo stage IVA disease or recurrent disease in the pleura. There must be no evidence of extra-thoracic metastatic disease or contralateral pleural/pericardial disease. Surgical resection of the pleural nodules (ex: pleurectomy/decortication, debulking/metastectomy) are allowed. Extrapleural pneumonectomy is not allowed. Patients are excluded if they have undergone prior thoracic radiation therapy preventing hemithoracic pleural IMRT, whereas prior thymic bed radiation and/or prior pleural SBRT are allowed. RT will be administered to the ipsilateral pleura to 50.4 Gy in 28 fractions. An optional dose-painting boost to gross disease up to 60 Gy while respecting normal tissue constraints is allowed. Patients can be treated with photon or proton therapy. Simulation, contouring and RT planning guidelines have been developed. Patients will be followed per protocol at regular intervals for at least 12 months following RT. The expected accrual is 36 patients over 4 years. Further information can be found on clinicaltrials.gov (NCT05354570). Clinical trial information: NCT05354570. Research Sponsor: Memorial Sloan Kettering Cancer Center.

LBA9000

Oral Abstract Session

Pemetrexed and platinum with or without pembrolizumab for tyrosine kinase inhibitor (TKI)-resistant, EGFR-mutant, metastatic nonsquamous NSCLC: Phase 3 KEYNOTE-789 study. *First Author: James Chih-Hsin Yang, National Taiwan University Hospital and National Taiwan University Cancer Center, Taipei, Taiwan*

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2023, issue of the *Journal of Clinical Oncology*.

9002

Oral Abstract Session

Sunvazertinib for the treatment of NSCLC with EGFR Exon20 insertion mutations: The first pivotal study results. *First Author: Mengzhao Wang, Department of Respiratory and Critical Care Medicine, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China*

Background: Sunvazertinib (DZD9008) is a rationally designed selective, irreversible EGFR exon20 insertion (exon20ins) inhibitor with wild-type EGFR selectivity. Here we reported the results of WU-KONG6, the first pivotal study of sunvazertinib in previously treated NSCLC patients with EGFR exon20ins. **Methods:** WU-KONG6 (NCT05712902 and CTR20211009) is a phase II, multi-center pivotal study in NSCLC patients with EGFR exon20ins, whose diseases had progressed on or were after platinum-based chemotherapy. Tumor tissue EGFR exon20ins status was tested by local or central laboratory. The primary and key secondary endpoint were objective response rate (ORR) and duration of response (DoR), respectively, assessed by Blinded Independent Central Review (BICR). Patients received 300 mg sunvazertinib once daily until discontinuation criteria were met. **Results:** Between July 19, 2021, and May 6, 2022, a total of 104 Chinese patients were enrolled into WU-KONG6 study. The efficacy analysis set included 97 patients, whose EGFR exon20ins status was retrospectively confirmed by a central laboratory. A total of 30 different exon20ins subtypes were enrolled. The median age was 58 years; 59.8% (58/97) were female; 95.9% (93/97) were adenocarcinoma; 95.9% (93/97) had metastatic diseases at study entry; 32% (31/97) had baseline brain metastasis; the median prior lines of therapy were 2. By the data cutoff date (October 17, 2022), the BICR assessed confirmed ORR (cORR) was 60.8% (59/97). In patients with baseline brain metastasis, the cORR was 48.5% (15/31). Anti-tumor efficacy was observed irrespective of age, gender, smoking status, prior lines of therapies, prior onco-immunotherapies, mutation subtypes, and baseline brain metastasis. By the data cut-off date, median follow-up time for responders was 7.1 months, and 64.4% (38/59) of responders were still responding. The longest DoR was > 11 months, and the median DoR has not been reached. The safety analysis set included all enrolled 104 patients. The most common treatment emergent adverse events (TEAEs) were similar as what have been previously reported for sunvazertinib, and also similar as that of other EGFR inhibitors. Majority of the TEAEs were grade 1 or 2, and clinically manageable. **Conclusions:** The first pivotal study results confirmed sunvazertinib's superior anti-tumor efficacy than the current available therapy for NSCLC with EGFR exon20ins. The safety profile from WU-KONG6 study was consistent with previously reported findings. The updated data will be presented at the meeting. A multinational phase II pivotal study (WU-KONG1, NCT03974022) with the same study design is ongoing in the USA, Australia, and countries/regions in Asia, Europe and South America. Clinical trial information: NCT05712902. Research Sponsor: Dizal Pharmaceutical.

9001

Oral Abstract Session

Randomized phase 3 study of first-line AZD3759 (zorifertinib) versus gefitinib or erlotinib in EGFR-mutant (EGFRm+) non-small-cell lung cancer (NSCLC) with central nervous system (CNS) metastasis. *First Author: Yi-Long Wu, Guangdong Lung Cancer Institute, Guangzhou, China*

Background: Patients (pts) with EGFRm+ NSCLC have high rates of CNS metastasis, few treatment options, and a poor prognosis. So far there are no solid evidence from head to head phase 3 trials in this setting. The potent EGFR TKI AZD3759 has high blood-brain barrier penetration, preliminary data has shown promising intracranial (IC) and systemic antitumor activity, and a tolerable safety profile. **Methods:** This was the first phase 3, open-label, multicenter, randomized controlled trial to compare the efficacy and safety of first-line AZD3759 with first generation EGFR TKIs specifically in pts with EGFRm+ (L858R and/or exon 19Del) NSCLC and CNS metastasis. Adult pts were randomized 1:1 to receive AZD3759 (200 mg twice daily) or first generation EGFR TKIs (the control group, gefitinib 250 mg or erlotinib 150 mg once daily). The primary endpoint was progression-free survival (PFS) by blinded independent central review (BICR) per RECIST 1.1. **Results:** Between Feb 1, 2019, and Jan 12, 2021, 439 pts were randomized: 220 to AZD3759 and 219 to the control group. As of July 12, 2022, median follow-up was 20.4 months (mo) for both. Median PFS (95% CI) was significantly superior with AZD3759 vs the control group (9.6 [8.2–9.7] vs 6.9 [6.3–8.0] mo; HR 0.719, 95% CI 0.580–0.893; p=0.0024). The objective response rate (ORR; BICR/RECIST 1.1) was 68.6% for AZD3759 vs 58.4% for the control group (p=0.027), with a trend toward longer median duration of response (DoR) with AZD3759 (8.2 vs 6.8 mo; p=0.0997). IC PFS, ORR, and DoR with AZD3759 were all superior vs the control group regardless of the assessor or evaluation criteria. The overall survival was immature. The incidence of any-grade treatment-related adverse events (TRAEs) was similar between the two groups (97.7% vs 94.0%). Grade ≥3 TRAEs occurred in 65.9% (AZD3759) and 18.3% (the control group) of pts. The main TRAEs were skin and subcutaneous tissue events, gastrointestinal system events and abnormal liver function. No new safety signals arose. **Conclusions:** First-line AZD3759 demonstrated superior systemic and IC antitumor efficacy compared with first generation EGFR TKIs in pts with EGFRm+ NSCLC and CNS metastasis. Adverse events were as expected and manageable. IC antitumor activity. Clinical trial information: NCT03653546. Research Sponsor: Alpha Biopharma (Jiangsu) Co., Ltd.

IC variable	Assessor	AZD3759	The control group	HR/OR (95% CI)	p
median PFS (mo)	BICR ^a	15.2	8.3	HR 0.467 (0.352–0.619)	<0.0001
	INV ^b	17.9	11.1	HR 0.627 (0.466–0.844)	0.0018
ORR (%) ^c	BICR ^a	75.0	64.2	OR 1.658 (0.993–2.768)	0.0534
	INV ^b	75.6	62.3	OR 1.904 (1.098–3.302)	0.0218
median DoR (mo) ^c	BICR ^a	12.4	7.0	HR 0.521 (0.352–0.773)	0.0009
	INV ^b	13.8	11.1	HR 0.789 (0.501–1.244)	0.3037

^aIC lesions were evaluated separately per RECIST 1.1. ^bEvaluated per Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM). ^cConfirmed responses. INV, investigator; OR, odds ratio.

9003

Oral Abstract Session

Final overall survival and biomarker analyses of CHOICE-01: A double-blind randomized phase 3 study of toripalimab versus placebo in combination chemotherapy for advanced NSCLC without EGFR/ALK mutations. *First Author: Jie Wang, State Key Laboratory of Molecular Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China*

Background: Toripalimab in combination with chemotherapy showed significant improvement over chemotherapy alone in progression-free survival (PFS) and overall survival (OS) as first-line treatment of advanced NSCLC at the final PFS analysis of the CHOICE-01 study (NCT03856411). Here we report the final OS analysis. **Methods:** Patients (n=465) with treatment-naïve, advanced NSCLC without EGFR/ALK mutations were randomized 2:1 to receive toripalimab 240 mg (n=309) or placebo (n=156) in combination with chemotherapy for 4–6 cycles, followed by maintenance toripalimab or placebo plus standard care until disease progression, intolerable toxicity, or completion of 2 years of treatment. Patients from the placebo arm were actively crossed-over to receive toripalimab upon disease progression. The primary endpoint was PFS. The secondary endpoints included OS and safety. **Results:** By the cutoff date of August 31, 2022, when 283 events triggered the final OS analysis, the median survival follow up was 19.4 months. A significant improvement in OS was observed for the toripalimab arm over the placebo arm: HR=0.73 (95% CI: 0.57–0.93), two-sided p=0.0108, median OS 23.8 vs 17.0 months. A consistent effect on OS, favoring the toripalimab arm, was observed all PD-L1 expression subgroups. The OS benefit is greater in non-squamous NSCLC, HR=0.50 (95% CI: 0.36–0.70), median OS 27.8 vs 15.9 months, whereas no significant difference was found in the squamous subgroup (mOS 19.6 vs 18.1 months) despite a significant PFS improvement. The squamous subgroup had a high 70% crossover rate. No new safety signal was identified since the interim report. The incidence of Grade ≥3 adverse events (AEs) (78.9% vs 82.1%) was similar between the two arms. AEs leading to discontinuation of toripalimab/placebo (14.3% vs 3.2%), fatal AEs (5.5% vs 2.6%), and immune-related (irAEs) (50.6% vs. 21.2%) were more frequent in the toripalimab arm. Whole exome sequencing results indicated patients with mutations in the FAK-PI3K-Akt pathway achieved significantly better OS from the toripalimab arm. **Conclusions:** The addition of toripalimab to chemotherapy in patients with advanced NSCLC provided significant OS benefit than chemotherapy alone with a manageable safety profile. These results support the use of toripalimab with chemotherapy as 1st line therapy for advanced NSCLC patients without EGFR/ALK mutations. Clinical trial information: NCT03856411. Research Sponsor: Shanghai Junshi Biosciences.

9004

Oral Abstract Session

TROPION-Lung02: Datopotamab deruxitecan (Dato-DXd) plus pembrolizumab (pembro) with or without platinum chemotherapy (Pt-CT) in advanced non-small cell lung cancer (aNSCLC). *First Author: Yasushi Goto, National Cancer Center Hospital, Tokyo, Japan*

Background: Despite advances in first-line (1L) immunotherapy ± CT, most patients (pts) with aNSCLC experience disease progression, necessitating novel strategies. Dato-DXd is an antibody drug conjugate (ADC) composed of a humanized anti-TROP2 IgG1 monoclonal antibody covalently linked to a topoisomerase I inhibitor payload via a plasma-stable tetrapeptide-based cleavable linker. Dato-DXd had encouraging efficacy and manageable safety in heavily pretreated aNSCLC. Dato-DXd + immunotherapy yielded greater preclinical activity than either agent alone. **Methods:** TROPION-Lung02 (NCT04526691) is a phase 1b, global, dose-escalation and -expansion study evaluating Dato-DXd (4 or 6 mg/kg) + pembro 200 mg ± Pt-CT (cisplatin 75 mg/m² or carboplatin AUC 5) every 21 days across 6 cohorts. Pts in escalation may have received ≤2 prior lines of therapy for aNSCLC. Pts in expansion were primarily treatment (tx) naïve (pts receiving Dato-DXd + pembro may have ≤1 prior Pt-based tx). The primary objective is to assess safety and tolerability, including dose-limiting toxicities (DLTs). Secondary objectives include evaluation of efficacy, pharmacokinetics, and immunogenicity. **Results:** As of the Oct 31, 2022, data cutoff (DCO), 120 pts were treated. All cohorts met DLT criteria to move to escalation. Median age was 65 years. PD-L1 expression was <1%, 1%-49%, and ≥50% in 40%, 33%, and 26% of pts, respectively. Median tx duration was 4.6 mo, with 55% receiving tx at DCO. The most frequent any-grade (gr) tx-emergent adverse events (TEAEs) were nausea (45%) and stomatitis (45%). Gr ≥3 TEAEs occurred in 61% of pts; most frequent were neutrophil count decreased (8%) and amylase increased (8%). TEAEs that were serious, associated with discontinuation, or associated with death occurred in 31%, 24% (16% associated with Dato-DXd), and 6% of pts, respectively. Dose reductions due to TEAEs associated with Dato-DXd occurred in 17%. Drug-related interstitial lung disease occurred in 12 pts (10%; 9 gr 1/2; 3 gr 3). The objective response rate (ORR) with 1L Dato-DXd + pembro doublet and Dato-DXd + pembro + Pt-CT triplet tx was 60% (95% CI, 36%-81%; 12 [2 unconfirmed]/20) and 55% (95% CI, 39%-70%; 23 [5 unconfirmed]/42), respectively. The ORR for any line of therapy was 38% (95% CI, 25%-54%; 18 [2 unconfirmed]/47) with doublet and 47% (95% CI, 34%-60%; 28 [5 unconfirmed]/60) with triplet tx. In both subsets, the disease control rate was 85% and median duration of response was not reached. Responses were observed in all 3 PD-L1 expression level subgroups. Although immature, median progression-free survival (95% CI) was 10.8 (8.3-15.2) and 7.8 mo (5.5-NE) with doublet and triplet tx, respectively. **Conclusions:** Dato-DXd + pembro ± Pt-CT demonstrated tolerable safety with notable 1L activity in this first and largest dataset with an ADC + immunotherapy ± Pt-CT in aNSCLC pts. Clinical trial information: NCT04526691. Research Sponsor: Daiichi Sankyo, Inc.

9006

Oral Abstract Session

The primary endpoint analysis of SCARLET study: A single-arm, phase II study of sotorasib plus carboplatin-pemetrexed in patients with advanced non-squamous, non-small cell lung cancer with KRAS G12C mutation (WJOG14821L). *First Author: Shinya Sakata, Department of Respiratory Medicine, Kumamoto University Hospital, Kumamoto, NA, Japan*

Background: Efficacy and safety of sotorasib in combination with platinum-doublet chemotherapy in KRAS G12C-mutated non-squamous, non-small cell lung cancer (non-Sq, NSCLC) has not been investigated. **Methods:** In this single-arm, phase 2 study, chemotherapy-naïve, advanced non-Sq, NSCLC patients with KRAS G12C mutation were enrolled. Participants were treated with sotorasib 960mg, QD plus carboplatin (AUC 5)/pemetrexed 500mg/m² for four cycles, followed by sotorasib plus pemetrexed until disease progression. The primary endpoint was overall response rate (ORR) by independent review. The secondary endpoints were progression-free survival (PFS), overall survival (OS) and safety. Using plasma samples, next-generation sequencing analysis was done at baseline, 3 weeks and disease progression. Regarding statistical consideration, the threshold and the expected ORR were set as 40% and 65%, respectively with one-sided $\alpha = 0.1$, and $\beta = 0.1$, the required sample size was 28 cases (Simon's two-stage design). A total of 30 cases was planned to take into account the possibility of a few dropped or ineligible cases. This study was funded by AMGEN Inc. and Trial identification no. is jRCT2051210086. **Results:** Between Oct 2021 and Jul 2022, 30 patients were enrolled. Twenty-nine and 27 were analyzed for safety and efficacy, respectively. Of those, median age was 70, male/female: 25/5, never-/smoker: 1/29, ECOG performance status: 0/1 11/19 and PD-L1 expression level: ≥50%/1-49%/<1% 15/10/5. The primary endpoint, ORR by independent review was 88.9% (80%CI 78.5-94.8%). Median PFS was not reached mainly due to shorter follow-up period (median 4.2 months) and PFS rate at 6 months was 61.2%. OS rate at 6 months was 87.0%. Subgroup analysis revealed that ORR did not differ by PD-L1 expression level (≥50%/1-49%/<1%: 76.9%/77.8%/80.0%, respectively). Common adverse events were anemia, neutrophil count decreased, nausea and platelet count decreased. Grade ≥3 AEs were mostly hematological toxicities, but one treatment-related death (pneumonia) occurred. At baseline, 70% of plasma samples were positive for KRAS G12C and most common co-occurring mutation was TP53 (50%). At 3 weeks, plasma KRAS G12C disappeared among 60% of patients. **Conclusions:** Sotorasib in combination with CBDCA/PEM demonstrated favorable ORR and tolerability in advanced non-Sq, NSCLC patients with KRAS G12C mutation. Clinical trial information: jRCT2051210086. Research Sponsor: AMGEN Inc.

LBA9005

Oral Abstract Session

Tumor treating field (TTFields) therapy with standard of care (SOC) in metastatic non-small cell lung cancer (mNSCLC) following platinum failure: Randomized, phase 3 LUNAR study. *First Author: Tician Leal, Winship Cancer Institute of Emory University, Atlanta, GA*

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2023, issue of the *Journal of Clinical Oncology*.

9007

Oral Abstract Session

KontRast-01 update: Safety and efficacy of JDQ443 in KRAS G12C-mutated solid tumors including non-small cell lung cancer (NSCLC). *First Author: Philippe Alexandre Cassier, Centre Léon Bérard, Lyon, France*

Background: KRAS G12C oncogenic mutations occur in ~13% of NSCLCs and up to 4% of other solid tumors. JDQ443 is a selective, covalent, orally bioavailable KRAS^{G12C} inhibitor that irreversibly traps KRAS^{G12C} in the inactive, GDP-bound state. Clinical activity was seen in initial cohorts of patients (pts) treated with JDQ443 monotherapy, and 200 mg twice daily (BID) was selected as the recommended dose (RD) for expansion (Tan DS, *et al.* AACR 2022; Abstract CT033). **Methods:** KontRast-01 (NCT04699188) is a Phase Ib/II, open-label, multicenter, dose-escalation (DEs), and dose-expansion (DEX) trial of JDQ443 as a monotherapy or in combination with TNO155 (SHP2 inhibitor) and/or tislelizumab (anti-PD-1 monoclonal antibody). Primary objectives of DEs are to assess safety/tolerability and identify the RD and regimens for future studies. The primary objective of DEX is to assess efficacy. Key inclusion criteria: advanced, KRAS G12C-mutated solid tumors; previous standard-of-care treatment; age ≥18 years; and ECOG PS 0-1. Prior KRAS^{G12C} inhibitor treatment is not permitted for the JDQ443 monotherapy arm and is allowed for the JDQ443 + TNO155 and JDQ443 + tislelizumab DEs arms. **Results:** As of Oct 28, 2022, 84 pts were treated with JDQ443 monotherapy, orally, continuously, in DEs, DEX, and food effect (FE) cohorts at 200 mg once daily (QD; n=10), 400 mg QD (n=11), 200 mg BID (n=56), and 300 mg BID (n=7). Median age was 61 years (range 26-83); median prior lines of therapy was 3 (range 1-7); and indications included NSCLC (n=38), colorectal cancer (n=42), and others (n=4). Median duration of exposure was 14.6 weeks (range 0.1-68.4) for all pts and 15.1 weeks (0.1-68.1) for pts treated at 200 mg BID. Among pts treated at 200 mg BID, 40 (71.4%) and 4 (7.1%) experienced treatment-related adverse events (TRAEs) of any grade (Gr) and of Gr 3, respectively. There were no Gr 4-5 TRAEs at any dose level. The most common TRAEs (any Gr, occurring in ≥10% of pts) at 200 mg BID were fatigue (17.9%), edema (14.3%), diarrhea (16.1%), nausea (16.1%), vomiting (10.7%), and peripheral neuropathy (10.7%). Gr 3 TRAEs were neutropenia in 2 pts, ALT and AST increase in 1 pt, and myalgia in 1 pt. One pt receiving 200 mg BID required a dose reduction due to a TRAE of Gr 2 peripheral neuropathy. Among response evaluable pts with NSCLC treated in DEs and FE cohorts, the confirmed overall response rate was 41.7% (10/24 pts) across dose levels and 54.5% (6/11 pts) at the RD of 200 mg BID. Combination JDQ443 + TNO155 and JDQ443 + tislelizumab arms are enrolling. Additional data will be available at the time of presentation. **Conclusions:** JDQ443 demonstrates an acceptable safety and tolerability profile at 200 mg BID, with clinical activity in pts with NSCLC. Enrollment is ongoing to the JDQ443 monotherapy DEX and the JDQ443 + TNO155 and JDQ443 + tislelizumab combination arms. Clinical trial information: NCT04699188. Research Sponsor: Novartis Pharmaceuticals Corporation.

9008

Oral Abstract Session

Biomarker subgroup analyses of CodeBreak 200, a phase 3 trial of sotorasib versus (vs) docetaxel in patients (pts) with pretreated *KRAS* G12C-mutated advanced non-small cell lung cancer (NSCLC). *First Author: Ferdinando Skoulidis, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Sotorasib is a first-in-class oral, irreversible *KRAS*^{G12C} inhibitor approved for adults with pretreated *KRAS* G12C-mutated advanced NSCLC. In CodeBreak 200, the first *KRAS*^{G12C} inhibitor randomized phase 3 trial, sotorasib demonstrated superior progression-free survival (PFS) and overall response rate (ORR) vs docetaxel and a more favorable safety profile. We report prespecified exploratory biomarker analyses comparing sotorasib vs docetaxel efficacy in molecularly-defined *KRAS* G12C-mutated advanced NSCLC subsets. **Methods:** In CodeBreak 200, 345 pts with *KRAS* G12C-mutated advanced NSCLC who progressed after platinum-based chemotherapy and a checkpoint inhibitor were randomized 1:1 to oral sotorasib 960 mg daily or IV docetaxel 75 mg/m² Q3W. Primary endpoint was PFS by blinded independent central review (RECIST 1.1; key secondary endpoint: ORR). In prespecified exploratory analyses, baseline tissue and plasma samples were analyzed for key genomic alterations (eg, *STK11*, *KEAP1*, *EGFR*, *MET*, *TP53*), by central targeted next-generation sequencing (Skoulidis *N Engl J Med* 2021), and PD-L1 protein level by local standard of care testing in biomarker-evaluable cases; biomarker status was correlated with PFS and ORR. Inferred tumor mutation burden by plasma circulating tumor DNA (sum of mutant molecular variant reads) was assessed. Association of baseline genomic alterations with long-term benefit (PFS ≥ 6 m) vs early progression (PFS < 3 m; no complete/partial response) was evaluated. **Results:** Most prevalent *KRAS* G12C co-alterations in biomarker-evaluable cases with available tumor and/or plasma samples (n=317) were *TP53* (181 [57.1%]), *STK11* (119 [37.5%]), and *KEAP1* (82 [25.9%]) in CodeBreak 200, consistent with CodeBreak 100; 55 (17.4%) pts had *STK11* and *KEAP1* co-alterations. Sotorasib showed superior clinical benefit vs docetaxel independently of PD-L1 expression and across all prespecified subgroups (eg, *STK11*, *KEAP1*, *TP53*). No clinical response occurred with either treatment in 26 (8.2%) pts with additional *KRAS* alterations, including amplifications. High baseline plasma tumor burden was associated with greater odds of early progression vs long-term benefit in both arms (odds ratio, 3.54 [95%CI 1.83-6.85] per tertile increase; p<0.0001). Correlation of *KRAS* G12C co-alterations with response detected a signal toward shorter median PFS (sotorasib, 2.8 m [95%CI 1.6-3.4]; docetaxel, 7.5 m [95%CI 3.0-NE]) with sotorasib vs docetaxel in pts with *KRAS* G12C and *NOTCH1* co-altered tumors. **Conclusions:** Sotorasib demonstrated consistent clinical benefit vs docetaxel in all prespecified molecularly-defined subgroups (eg, *STK11*, *KEAP1*, *TP53*) in this exploratory analysis of CodeBreak 200. No predictive biomarkers were confirmed, but novel hypothesis-generating signals were observed. Clinical trial information: NCT04303780. Research Sponsor: Amgen Inc.

9011

Rapid Abstract Session

BLU-945 monotherapy and in combination with osimertinib (OSI) in previously treated patients with advanced *EGFR*-mutant (*EGFRm*) NSCLC in the phase 1/2 SYMPHONY study. *First Author: Yasir Y Elamin, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Despite improved frontline OSI treatment outcomes, patients (pts) with advanced *EGFRm* NSCLC inevitably progress, with worse outcomes in the *EGFR* L858R subgroup (median PFS of 14.4 vs 21.4 mo in pts with exon 19 deletions). BLU-945 is an investigational, next-generation, oral tyrosine kinase inhibitor (TKI) that targets common *EGFR*-activating and T790M and C797X resistance mutations, while being selective against *EGFR* wild type (WT). Preclinically, BLU-945 in combination (combo) with OSI had enhanced potency on L858R and extended antitumor response durability versus OSI alone. SYMPHONY (NCT04862780) is an ongoing first-in-human phase 1/2 study of BLU-945 monotherapy (mono) or combo with OSI. **Methods:** In the phase 1 dose escalation, pts (aged ≥18 y; metastatic *EGFRm* NSCLC; ECOG PS 0-1; treated with ≥1 *EGFR* TKI) received BLU-945 mono starting at 25 mg QD. Pts progressing on OSI could receive BLU-945 with 80 mg OSI starting at 50% of the highest safe BLU-945 mono dose. Each dose escalation followed a Bayesian Optimal Interval design. Safety, including dose-limiting toxicities (DLT), PK, and circulating tumor DNA (ctDNA) mutational status were assessed. **Results:** As of Jan 6, 2023, 108 pts received BLU-945 mono (25-600 mg QD; 100-300 mg BID). Pts had a median of 3 lines of prior therapy and were genomically complex with ctDNA detectable *EGFR* on-target and/or off-target resistance alterations (46%) at baseline. DLTs included alanine transaminase (ALT) and aspartate transaminase (AST) elevation, hepatic cytolysis, fatigue, nausea, vomiting, and hyponatremia, occurring at doses of ≥400 mg/d. The maximum tolerated dose was 500 mg/d. The most common AEs were nausea (42%), headache (40%), increased ALT (38%), increased AST (37%), and vomiting (32%). Robust on-target *EGFR* activity was observed with ctDNA reduction on day 15 in 90%, 85% and 70% of *EGFR* T790M, C797S, and L858R alleles at ≥400 mg/d doses, respectively. At ≥400 mg/d, 48% had tumor shrinkage, including partial responses (PRs). Twenty-five pts received BLU-945 (200-400 mg QD; 100-200 mg BID) combo with OSI. Pts had a median of 2 lines of prior therapy. The most common combo AEs were fatigue (36%), diarrhea (32%), headache (32%), and nausea (28%). Other *EGFR* WT AEs were dry skin (20%) and rash (8%). One DLT (Grade 4 pneumonitis) was reported in the BLU-945 300 mg QD with OSI group. Tumor reductions, including PRs in 2 pts progressing on OSI, were observed at ≥300 mg/d. Dose escalation is ongoing. **Conclusions:** BLU-945 mono and combo with OSI were generally well tolerated and showed robust on-target *EGFR* ctDNA reduction, with tumor shrinkage in genomically heterogeneous, heavily pretreated pts. Combo showed responses at BLU-945 doses lower than in mono, consistent with additive benefit. The combo safety profile and on-target activity provide rationale for further development in front line. Clinical trial information: NCT04862780. Research Sponsor: Blueprint Medicines.

LBA9009

Clinical Science Symposium

A phase III study comparing *EGFR* tyrosine kinase inhibitor (*EGFR*-TKI) monotherapy and *EGFR*-TKI with inserted cisplatin (CDDP) plus pemetrexed (PEM) as a first-line treatment in patients (pts) with advanced non-squamous non-small-cell lung cancer (NSqNSCLC) harboring *EGFR* activating mutation (*EGFR*-NSqNSCLC): JCOG1404/WJOG8214L, AGAIN study. *First Author: Shintaro Kanda, Department of Hematology and Clinical Oncology, Shinshu University School of Medicine, Matsumoto-Shi, Japan*

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2023, issue of the *Journal of Clinical Oncology*.

9012

Rapid Abstract Session

First-line immune checkpoint inhibitors alone or in combination with chemotherapy in real-life elderly patients with advanced non-small cell lung cancer (NEJ057). *First Author: Mao Uematsu, Department of Thoracic Oncology and Respiratory Medicine, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tokyo, Japan*

Background: Immune checkpoint inhibitor (ICI) plus chemotherapy is now a standard treatment for non-small cell lung cancer (NSCLC) without targetable oncogene alterations. However, the efficacy and safety of ICI plus chemotherapy (ICI-chemo) in 75 years or older patients have not been elucidated. The aim of this study is to reveal the real-world choice of first-line drugs in elderly patients (pts) and evaluate the efficacy and safety of ICI-chemo. **Methods:** We conducted a multicenter (58 centers in Japan), retrospective cohort study of consecutive 75 years or older pts with clinical stage IIIB, IIIC, IV, postoperative or radiotherapy recurrent NSCLC who started first-line systemic therapy between December 2018 and March 2021. Pts with epidermal growth factor receptor mutations, anaplastic lymphoma kinase rearrangements, or whose first-line systemic therapy was molecular targeted therapy were excluded. **Results:** A total of 1245 pts were enrolled: median (range) age 78 (75-95) years; 278 (22%) female; 367 (29%) ECOG PS 0, 680 (55%) PS 1 and 171 (14%) PS 2; 678 (54%) adenocarcinoma; PD-L1 tumor proportion score ≥50%: 268 (22%) <1%, 387 (31%) 1-49% and 410 (34%) ≥50%; 354 (28%) ICI-chemo, 425 (34%) ICI alone, 311 (25%) platinum-doublet chemotherapy and 155 (12%) single agent chemotherapy. The median overall survival (OS) was 20.0 months (95% CI, 17.1-23.6) in the ICI-chemo group, 19.8 months (95%CI, 16.5-23.8) in the ICI alone group, 12.8 months (95%CI, 10.7-15.6) in the platinum-doublet chemotherapy group and 9.5 months (95%CI, 7.4-13.4) in the single agent chemotherapy group, respectively. After propensity score matching, there was no difference in OS and progression-free survival (PFS) between ICI-chemo group (n=96) and ICI alone group (n=95) in PD-L1 ≥1% (OS: HR, 0.98; 95% CI, 0.67-1.42; PFS: HR, 0.92; 95% CI, 0.67-1.25). Regardless of PD-L1 subgroups (1-49% or ≥50%), no significant differences in OS and PFS were observed. Concerning safety, Grade 3 or higher immune-related adverse events (irAEs) occurred in 86 pts (24.3%) in the ICI-chemo group and 76 pts (17.9%) in the ICI alone group (p=0.03). The number of pts who required steroids for irAEs was 115 (32.5%) in the ICI-chemo group and 105 (24.7%) in the ICI alone group (p=0.02). Pneumonitis was reported in 83 pts (23.4%) in the ICI-chemo group and 66 pts (15.6%) in the ICI alone group (p=0.006). **Conclusions:** In real-world data for pts aged 75 years or older, ICI-chemo did not improve survival and increased the incidence of grade 3 or higher irAEs compared to ICI alone. Based on our results, ICI alone is recommended for elderly pts with PD-L1 positive NSCLC. Clinical trial information: UMIN000046700. Research Sponsor: None.

9013

Clinical Science Symposium

Predictive biomarkers for treatment with amivantamab plus lazertinib among EGFR-mutated NSCLC in the post-osimertinib setting: Analysis of tissue IHC and ctDNA NGS. First Author: Benjamin Besse, Gustave Roussy, Villejuif, France

Background: Amivantamab (ami) is a bispecific antibody targeting EGFR and MET with immune cell-directing activity, and lazertinib (laz) is a brain-penetrant, third-generation EGFR tyrosine kinase inhibitor. In a previous report, the overall response rate (ORR) of ami+laz in the post-osimertinib (osi) setting was 36%, with median duration of response of 9.6 months (Bauml JCO 2021; 39:15_suppl, 9006). Exploratory analyses suggested certain immunohistochemistry (IHC) and ctDNA-based next-generation sequencing (NGS) biomarkers may enrich for response. A prospective study was conducted to further evaluate these potential biomarkers. **Methods:** CHRYSALIS-2 (NCT04077463), an ongoing phase 1/1b study, examines the efficacy (ORR per RECIST v1.1) of ami+laz in patients (pts) with EGFR-mutated NSCLC. Cohort D enrolled osi-relapsed, chemotherapy-naïve pts with EGFR exon 19 deletion or L858R mutated advanced NSCLC who had tumor tissue for IHC staining and plasma for ctDNA NGS collected after their most recent therapy. Training and validation subsets identified biomarker criteria and predictive validity, respectively. A Bayesian posterior probability (biomarker positive group ORR is $\geq 35\%$ and negative group ORR is $\leq 20\%$) was predefined to be $\geq 85\%$ for acceptance. **Results:** There were 101 response-evaluable pts enrolled in Cohort D. A total of 87 pts had detectable baseline ctDNA and 77 pts had evaluable MET IHC. The training set (n = 50) identified IHC-based MET expression of 3+ staining on $\geq 25\%$ of tumor cells (MET+) as a potential predictive biomarker, and the validation set (n = 27) confirmed these results. Of those with MET IHC data, 28/77 (36%) were MET+. The overall ORR for MET+ was 61% (95% CI, 41–78) and 12% (95% CI, 5–25) for MET-, with median PFS for MET+ not reached (95% CI, 4.3–NE) vs 4.1 months (95% CI, 2.8–5.7) for MET-. NGS evaluation of ctDNA did not identify predictive biomarkers meeting predetermined criteria. Of note, only 1 pt was identified by ctDNA as having MET amplification (the pt was also MET+ by IHC). Further details will be provided at the time of presentation. **Conclusions:** MET+ by IHC may be a predictive biomarker for response to ami+laz in the post-osi, chemotherapy-naïve setting. In contrast, molecular profiling with ctDNA failed to identify a subgroup of pts more likely to benefit. Ami+laz represents a potential chemotherapy-free option for pts with EGFR-mutated advanced NSCLC who have progressed on osi and are also MET+ by IHC. Clinical trial information: NCT04077463. Research Sponsor: Janssen.

9015

Poster Discussion Session

FAK inhibition with novel FAK/ALK inhibitor APG-2449 could overcome resistance in NSCLC patients who are resistant to second-generation ALK inhibitors. First Author: Yuxiang Ma, Sun Yat-sen University Cancer Center, Guangzhou, China

Background: APG-2449 is a novel, orally active FAK inhibitor and an ALK/ROS1 tyrosine kinase inhibitor (TKI) that has shown potent activity in preclinical models. It had been demonstrated that APG-2449 was well tolerated, and preliminary efficacy was observed in pts who were resistant to second-generation ALK/ROS1⁺ inhibitors (Zhao H et al. *J Clin Oncol* 2022; 40:9071). We provide updated safety and efficacy results and potential mechanisms of action(s) of this therapy. **Methods:** After the RP2D was determined as 1,200 mg daily (QD), NSCLC pts were enrolled into 2 dose expansion cohorts. Cohort 1 included pts who were resistant to second-generation ALK/ROS1⁺ TKIs. Cohort 2 included those who were ALK or ROS1⁺ TKI naïve. **Results:** As of December 9, 2022, 130 pts enrolled (median [range] age 53 [21–78] years; 53.8% female) with NSCLC, mesothelioma, or ovarian cancer were treated with APG-2449 at doses ranging from 900 to 1,500 mg. A total of 117 (90%) pts experienced treatment-related adverse events (TRAEs). The most frequent TRAEs included elevated blood creatinine (43.8%), ALT (40.8%), and AST (33.1%) levels, as well as gastrointestinal disorders: nausea (25.4%), vomiting (21.5%), and diarrhea (21.5%). A total of 17 (13.1%) TRAEs were grade ≥ 3 . In a subgroup of pts with TKI-naïve NSCLC (n = 33; 31 with efficacy evaluable), the overall response rate (ORR) and the disease control rate (DCR = CR + PR + SD) were 70.6% (12/17) and 88.2% (15/17), respectively, in ROS1⁺ treatment naïve pts; the ORR and DCR were 78.6% (11/14) and 100% (14/14) in ALK⁺ treatment naïve pts. Of 27 NSCLC pts resistant to second-generation ALK inhibitors, 7 were observed with PR (7/27; 25.9%) during APG-2449 treatment at RP2D. In this subgroup, compared to baseline, pts who experienced PR showed lower phosphorylated FAK (pFAK) levels in peripheral blood mononuclear cells (PBMCs) by Day 28 (24 hours after dosing on D28) than pts who experienced SD. Furthermore, pts with progressive disease showed an increase of PBMC pFAK levels on D28 compared to baseline, indicating that APG-2449 could inhibit FAK phosphorylation. Pts with higher pFAK expression in tumor tissues at baseline tended to achieve better clinical responses than those with lower pFAK expression post APG-2449 treatment. **Conclusions:** APG-2449 showed a favorable preliminary safety profile and antitumor efficacy in pts with NSCLC. Preliminary efficacy was observed in those whose disease was TKI naïve and resistant to second-generation ALK inhibitors. FAK inhibition could be a novel approach to overcome ALK resistance in pts with NSCLC who are resistant to second-generation ALK inhibitors. Internal study identifier: APG2449XC101. Clinical trial information: NCT03917043. Research Sponsor: Ascentage Pharma Group Corp Ltd.

9014

Poster Discussion Session

Safety and preliminary efficacy of YK-029A, a novel EGFR TKI, in patients with advanced NSCLC harboring ex20ins, T790M or rare mutations. First Author: Jianchun Duan, State Key Laboratory of Molecular Oncology, Department of Medical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Background: This study aimed to evaluate the safety and preliminary efficacy of YK-029A, a novel third-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, in treated or untreated patients with advanced NSCLC. **Methods:** This dose-escalation and dose-expansion phase 1 trial recruited previously untreated or treated patients with EGFR ex20ins mutant locally advanced or metastatic NSCLC and previously treated patients with EGFR T790M or rare mutations. In dose-escalation phase, patients with EGFR T790M mutation were enrolled. YK-029A was given at doses of 50, 100, 150, 200 to 250 mg/day (3+3 design). In dose-expansion phase, patients with EGFR T790M, EGFR ex20ins, or rare mutations were enrolled. The primary objective was safety. Dose-limiting toxicity (DLT) and maximum tolerated dose (MTD) were explored. In the treatment-naïve cohort of EGFR ex20ins mutant NSCLC, patients were administered oral YK-029A 200 mg once daily in a 28-day cycle, and efficacy was assessed by the independent review committee. The study was registered (chinadrugtrials.org.cn, CTR20180350). **Results:** A total of 108 were included in the safety analysis set. DLT did not occur in dose-escalation phase. MTD was not reached. Treatment-emergent adverse events (TEAEs) of any grade and grade ≥ 3 occurred in 106 (98.1%) and 41 (38.0%) patients, respectively. Treatment-related adverse events (TRAEs) of any grade and grade ≥ 3 occurred in 102 (94.4%) and 30 (27.8%) patients, respectively. One patient had liver abscess related to YK-029A and died. Three patients terminated the treatment because of TEAEs. The most common TRAEs were diarrhea (46.3%), anemia (38.0%), and rash (32.4%). For the treatment-naïve EGFR ex20ins mutant cohort, 26 patients were included in the efficacy analysis set. Most patients were adenocarcinoma (96.4%) and at stage IV (85.7%). At the cut-off date on October 30, 2022, 19 patients (73.1%) had partial remission, five patients (19.2%) had stable disease, and two patients (7.7%) developed disease progression. The confirmed objective response rate achieved 73.1% (95% confidence interval [CI], 52.21% to 88.43%). The median progression-free survival was 9.3 months (95% CI, 5.85 to not evaluated). **Conclusions:** YK-029A was well tolerated and showed preliminary efficacy in treatment-naïve EGFR ex20ins mutant patients with locally advanced or metastatic NSCLC. Research Sponsor: Puhe Biopharma Co., Ltd.

	Treatment-naïve ex20ins cohort (200 mg) (N=26)
Objective response rate	73.1% (95% CI, 52.21% to 88.43%)
Disease control rate	92.3% (95% CI, 74.87% to 99.05%)
Median progression-free survival, months	9.3 (95% CI, 5.85 to NE)
Median duration of response, months	7.5 (95% CI, 3.75 to NE)
12-month overall survival rate	83.1% (95% CI, 47.17% to 95.53%)

LBA9016

Poster Discussion Session

Intracranial efficacy of sotorasib versus docetaxel in pretreated KRAS G12C-mutated advanced non-small cell lung cancer (NSCLC): Practice-informing data from a global, phase 3, randomized, controlled trial (RCT). First Author: Anne-Marie C. Dingemans, Erasmus MC Cancer Institute, University Medical Center, Rotterdam, Netherlands

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2023, issue of the *Journal of Clinical Oncology*.

9017

Poster Discussion Session

Intracranial and systemic efficacy of repotrectinib in advanced *ROS1* fusion-positive (*ROS1*+) non-small cell lung cancer (NSCLC) and central nervous system metastases (CNS mets) in the phase 1/2 TRIDENT-1. *First Author: Jessica Jiyeong Lin, Massachusetts General Hospital Cancer Center, Boston, MA*

Background: Repotrectinib is a next-generation ROS1 and TRK tyrosine kinase inhibitor (TKI) that has demonstrated durable activity with a manageable safety profile in TKI-naïve and TKI-pretreated patients (pts) with advanced *ROS1*+ NSCLC. We report the first analysis of outcomes on repotrectinib in pts with *ROS1*+ NSCLC by baseline (BL) CNS met status in the global pivotal phase 1/2 TRIDENT-1 trial (NCT03093116). **Methods:** Pts with *ROS1*+ NSCLC were assigned to 4 cohorts by treatment history: ROS1 TKI-naïve, 1 ROS1 TKI and no chemotherapy (chemo), 1 ROS1 TKI and 1 platinum-based chemo, and 2 ROS1 TKIs and no chemo. Treated or untreated asymptomatic CNS mets were permitted. Brain scans were mandated for all pts in phase 2 at screening and at protocol-specified intervals until progression. Endpoints included confirmed objective response rate (cORR) and duration of response (DOR) by blinded independent central review (BICR; RECIST v1.1); intracranial ORR (icORR) in pts with measurable brain mets at BL by BICR per mRECIST v1.1; and safety. **Results:** In pts with BL measurable CNS mets who were TKI-naïve (n = 8) and in those with 1 TKI and no chemo (n = 12), icORR (95% CI) was 88% (47-100) and 42% (15-72), respectively. At data cutoff (June 20, 2022), 0 of 7 responders in the TKI-naïve cohort and 2 of 5 in the cohort with 1 prior TKI and no chemo had intracranial progression or death; intracranial DOR range was 1.9-14.8+ mo (TKI-naïve) and 3.0-11.1+ mo (1 TKI and no chemo), with 86% and 80% of pts with an intracranial response remaining on treatment, respectively. Median follow-up and systemic response by CNS met status are shown in the Table. In pts with *ROS1*+ NSCLC with (n = 118) or without (n = 178) CNS mets, most common any-grade neurologic treatment-emergent adverse events were dizziness (57% / 63%), dysgeusia (42% / 53%), paresthesia (32% / 34%), headache (27% / 12%), ataxia (17% / 22%), and memory impairment (14% / 10%). **Conclusions:** In TRIDENT-1, repotrectinib showed durable clinical activity in ROS1 TKI-naïve and -pretreated pts with or without BL CNS mets, including intracranial responses. Repotrectinib safety profile was similar in pts with *ROS1*+ NSCLC with or without CNS mets. Clinical trial information: NCT03093116. Research Sponsor: Turning Point Therapeutics Inc, a wholly owned subsidiary of Bristol Myers Squibb Company.

Systemic response to repotrectinib in pts with <i>ROS1</i> + NSCLC with/without BL CNS mets per BICR.				
	ROS1 TKI naïve n = 71	1 TKI and no chemo n = 56	1 TKI and 1 chemo n = 26	2 TKIs and no chemo n = 18
Median follow-up, mo	18.1	15.5	21.3	14.1
Pts with CNS mets, n (%)	18 (25)	24 (43)	10 (38)	8 (44)
cORR, %	89	33	40	13
95% CI	65-99	16-55	12-74	0.3-53
6-mo DOR 95% CI	100	63	50	100-100
	100-100	29-96	1-99	-
12-mo DOR	93	-	-	-
95% CI*	79-100	-	-	-
Pts without CNS mets, n (%)	53 (75)	32 (57)	16 (62)	10 (56)
cORR, %	76	41	44	40
95% CI	62-86	24-59	20-70	12-74
6-mo DOR	87	92	71	50
95% CI	77-98	76-100	38-100	1-99
12-mo DOR	84	-	-	-
95% CI*	72-96	-	-	-

*Not reported for TKI-pretreated cohorts due to small n's at risk.

9019

Poster Discussion Session

LIBELULE: A randomized phase III study to evaluate the clinical relevance of early liquid biopsy (LB) in patients with suspicious metastatic lung cancer. *First Author: Aurélie Swalduz, Department of Medical Oncology, Centre Léon Bérard, Lyon, France*

Background: Timeliness of molecular testing is essential to minimize the time to appropriate 1st line treatment initiation (TTI) in advanced NSCLC pts. We hypothesized that LB-based molecular testing performed at the patient's 1st visit could reduce this TTI. **Methods:** LIBELULE is a multicenter, randomized, comparative, open-label study, enrolling pts with radiological suspicion of stage IV lung cancer, no prior biopsy or cytology for advanced NSCLC diagnosis. In Arm A, a LB was performed at the 1st visit using the InVisionFirst-Lung assay, an amplicon-based NGS panel covering 37-NSCLC associated genes. When LB results were informative, treatment was initiated on the basis of: InVisionFirst-Lung alone for pts with *EGFR*, *BRAF V600E* mutation (mut), *ALK* or *ROS1* rearrangement (category 1 alterations); InVisionFirst-Lung and pathological results for pts with *ERBB2*, *MET* exon 14, *KRAS*, *BRAF* non V600 and/or *LKB1* mut, *RET* or *NTRK* rearrangement (category 2 alterations). In control Arm B, histological sampling was planned with genomic analysis when indicated (local LB allowed) and treatment was initiated according to ESMO guidelines. The primary endpoint was the time from randomization to initiation of appropriate treatment based on informative genomic and pathological results. 286 pts were needed to detect a 21% shortening in TTI ($\alpha = 0.05$, $1-\beta = 90\%$). **Results:** 319 pts were randomized between Arm A (n = 161) and B (n = 158): median age 68 y (39-97), 56.1% male, 28.5% non-smokers, PS0-1 82%, PS $\geq$ 2 18.1%; adenocarcinoma: 56.7%, squamous cell carcinoma: 11%, SCLC: 10%, other tumor types: 5%. 5.3% of pts had no cancer. In Arm A, 81% of pts had ctDNA findings; category 1 and category 2 alterations were identified on tissue and/or LB in 29.2% (*EGFR* mut: 21.7%) and 24%, respectively, whereas in Arm B, 23.2% of pts had category 1 (*EGFR* mut: 20.3%) and 20% had category 2 alterations detected. Systemic treatment was initiated in 74.5% and 65.8% of pts in Arm A and B, respectively. Main reasons for not initiating treatment were diagnosis other than cancer, local treatment and palliative care. The mean TTI was 29.0 days (d) (95%CI 25.9-32.1) in Arm A vs 33.9 d (95%CI 28.4-39.5) in Arm B in the intention-to-treat population (p = 0.28), but significantly shorter in Arm A 29.1 d vs 38.8 d in Arm B for pts receiving systemic treatment (p = 0.01). The mean TTI was significantly shorter (21 d vs 37.4 d) in pts with category 1 alterations (p = 0.004) as well as the time to contributive genomic analysis (17.9 d vs 25.6 d; p < 0.001) in Arm A and B, respectively. In Arm A, 7.4% of pts vs 13.3% in Arm B initiated a treatment without genomic analysis available. **Conclusions:** Early LB significantly reduces the time to contributive molecular analysis and the time to initiation of appropriate 1st line therapy in pts eligible for systemic treatment, especially for pts with actionable alterations indicating targeted 1st line therapy. Clinical trial information: NCT03721120. Research Sponsor: Grant from French Ministry of Health PHRC-K 2017.

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Poster Discussion Session

Efficacy and safety of encorafenib (enco) plus binimetinib (bini) in patients with *BRAF* V600E-mutant (*BRAF*^{V600E}) metastatic non-small cell lung cancer (NSCLC) from the phase 2 PHAROS study. *First Author: Gregory J. Riely, Thoracic Oncology Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: The combination of dabrafenib, a BRAF inhibitor, and trametinib, a MEK inhibitor, is a current standard of care for patients (pts) with *BRAF*^{V600E} NSCLC. We report efficacy and safety of enco+bini in pts with *BRAF*^{V600E} metastatic NSCLC. **Methods:** PHAROS is an ongoing, open-label, single-arm, phase 2 study that enrolled pts with *BRAF*^{V600E} metastatic NSCLC who had measurable disease by RECIST 1.1 and Eastern Cooperative Oncology Group performance status of 0 or 1, and who were either treatment-naïve or had received 1 prior therapy (chemotherapy, monotherapy, or combination immunotherapy) for metastatic disease. Exclusion criteria included prior treatment with a BRAF or MEK inhibitor. Pts received enco 450 mg QD + bini 45 mg BID administered orally in 28-day cycles. The primary endpoint was confirmed objective response rate (ORR) by independent radiology review (IRR). Secondary endpoints included duration of response (DOR), disease control rate (DCR), progression-free survival (PFS), and time to response (TTR), all by IRR, and safety. Exploratory endpoints included biomarker assessments. **Results:** At the data cutoff (Sep 22, 2022), 98 pts (59 treatment-naïve, 39 previously treated) received enco+bini. The median duration of treatment was 9.2 months with enco and 8.4 months with bini. Treatment is ongoing in 34% of the pts; 38% permanently discontinued due to disease progression and 18% due to adverse events (AEs). The ORR (95% CI) by IRR was 75% (62, 85) in treatment-naïve and 46% (30, 63) in previously treated pts. Secondary endpoints are shown in the table. The most frequent ($\geq$ 30%) treatment-related AEs (TRAEs) were nausea (50%), diarrhea (43%), and fatigue (32%). AEs led to permanent discontinuation of enco+bini in 15% of pts and dose reductions in 24% of pts. One grade 5 TRAE of intracranial hemorrhage was reported. Next-generation sequencing analysis was conducted with archival tumor biopsies from 48 treatment-naïve and 32 previously treated pts. The most frequent genomic alterations, in addition to *BRAF*^{V600E}, were *SETD2* and *TP53* (43% each), *SMAD4* (21%), *ATM*, *MLL2*, *CSF1R*, and *SMARCA4* (14% each), and *CDKN2A* (11%). **Conclusions:** The combination of enco+bini showed meaningful clinical benefit in treatment-naïve and previously treated pts with *BRAF*^{V600E} metastatic NSCLC. The safety profile of enco+bini was generally consistent with that established for pts with *BRAF*^{V600E} melanoma. ClinicalTrials.gov: NCT03915951. Clinical trial information: NCT03915951. Research Sponsor: Pfizer.

Secondary endpoints by IRR.		
	Treatment-naïve	Previously treated
n	44	18
Median DOR (95% CI), months	NE (23.1-NE)	16.7 (7.4-NE)
DOR $\geq$ 12 months, n (%)	26 (59)	6 (33)
Median TTR (range), months	1.9 (1.1-19.1)	1.7 (1.2-7.3)
n	59	39
DCR after 24 weeks, % (95% CI)	64 (51-76)	41 (26-58)
Median PFS (95% CI), months	NE (15.7-NE)	9.3 (6.2-NE)
NE, not estimable.		

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Poster Discussion Session

Large-scale transcriptomic profiling of the tumor immune microenvironment in *ALK*+ lung cancer. *First Author: Vincent K. Lam, The Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, Baltimore, MD*

Background: Patients (pts) with *ALK*+ Non-Small Cell Lung Cancer (NSCLC) do not derive significant clinical benefit from immune checkpoint inhibitors. To better understand this lack of immunotherapy sensitivity, we aimed to characterize major immune components of the tumor microenvironment (TME) by comprehensive transcriptomic and immunohistochemistry (IHC) analyses. **Methods:** We analyzed NGS data from 5490 NSCLC pts that underwent DNA (592 Gene Panel, NextSeq, or WES, NovaSeq) and RNA (NovaSeq, WTS) sequencing at Caris Life Sciences (Phoenix, AZ). 374 *ALK*-rearranged cases were evaluated, along with 3169 *KRAS*-mut (*STK11/KEAP1*-wt) and 1947 *EGFR*-mut cases serving as comparators with known heterogeneous and inert immune TMEs, respectively. PD-L1 (22C3) was evaluated by IHC. Immune cell fractions were inferred using quanTiseq. Gene expression profiles were analyzed for a T cell-inflamed signature (TIS) predictive of response to immunotherapy and for other immune modulatory genes such as *IFNG*, *GZMB*, *TGFB1*, and those of the adenosine pathway (*CD73/NT5E*, *CD39/ENTPD1*, *ADORA1*, *ADORA2A/B*). A significant difference between genomic subgroups was defined as fold-change > 1.2 . In an independent cohort of 14 *ALK*+ NSCLC pts, density and spatial organization of CD4+ and CD8+ T cells, Tregs, major myeloid lineage cells, PD-L1, and CD73 were assessed by quantitative IHC. **Results:** *ALK*+ tumors were associated with high PD-L1 ($\geq$ 50%) expression (40% vs 47% for *KRAS*-mut vs 18% for *EGFR*-mut, p < 0.001) and low TMB (median 3 mut/MB vs 9 for *KRAS*-mut vs 4 for *EGFR*-mut, p < 0.001). The abundance of CD8+ T cells (fold-change -1.3, p < 0.001), Tregs (fold-change -1.2, p < 0.001), M2 macrophages (fold-change 1.2, p < 0.001), and CD4+ T cells (fold-change 1.9, p < 0.001) differed from *KRAS*-mut; notably, similar to *EGFR*-mut. In *ALK*+ tumors, *IFNG* (fold-change -1.5, p < 0.001), *GZMB* (fold-change -1.6, p < 0.001), *TGFB* (fold-change -1.3, p < 0.001), *LAG-3* (fold-change -1.4 p < 0.001), *CD73/NT53* (fold-change -1.7 p < 0.001), and *ADORA2A* (fold-change -1.4, p < 0.001) were decreased while *ADORA1* (fold-change 1.3, p < 0.001) was increased compared to *KRAS*-mut. *EML4-ALK* comprised 94.7% of the *ALK*+ tumors and distribution of *EML4-ALK* variants was consistent with prior reports (e.g. v1 35.6%, v3 35.1%). Immune cell fractions and immune-related gene expression did not vary significantly between major variant subgroups (v1 vs non-v1, and v3 vs non-v3, p > 0.05). **Conclusions:** To our knowledge this is the largest transcriptomic analysis of the *ALK*+ NSCLC TME. Despite high levels of PD-L1, *ALK*+ tumors exhibit multiple features of an inert immune TME, primarily characterized by low TMB and decreased CD8+ T cells and immune activation markers. Our findings suggest that, while immunosuppressive factors such as M2 macrophages and adenosine signaling may also be targeted, strategies to enhance immunogenicity are critical for an effective immune response in *ALK*+ NSCLC. Research Sponsor: Lung Cancer Foundation of America and International Lung Cancer Foundation.

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Poster Discussion Session

Tepotinib + osimertinib for *EGFR* mutant (*EGFRm*) NSCLC with *MET* amplification (*METamp*) after first-line (1L) osimertinib. *First Author: Daniel Shao-Weng Tan, Division of Medical Oncology, National Cancer Centre, Singapore, Singapore*

Background: *METamp* is a common resistance mechanism developed in patients (pts) with *EGFRm* NSCLC treated with osimertinib. *MET* tyrosine kinase inhibitors (TKIs) such as tepotinib may be effective in treating these pts after osimertinib. Here we report interim data from the INSIGHT 2 study evaluating tepotinib + osimertinib in *EGFRm* NSCLC with *METamp* previously treated with osimertinib. **Methods:** In this open-label Phase II study (INSIGHT 2, NCT03940703), pts with advanced *EGFRm* NSCLC with *METamp* after progression on 1L osimertinib received tepotinib 500 mg (450 mg active moiety) + osimertinib 80 mg once daily. *METamp* was centrally detected in tissue biopsy (TBx) by FISH (*MET* gene copy number [GCN] ≥ 5 and/or *MET/CEP7* ≥ 2) and/or in liquid biopsy (LBx) by NGS (*MET* plasma GCN ≥ 2.3 ; Archer). The primary endpoint was objective response by Independent Review Committee in tepotinib + osimertinib treated pts with centrally detected *METamp* by FISH (FISH+). Efficacy data are reported for pts with ≥ 3 months' follow-up, and safety for all pts who received one dose of tepotinib + osimertinib by Sep 26, 2022 (data cut-off). **Results:** Among 472 pts prescreened, 451 pts had *METamp* results by either TBx FISH and/or LBx NGS, of which 175 (38.8%) were positive for *METamp*. 122 pts received tepotinib + osimertinib (median age 61 years [range 20–84], 59.8% female, 59.8% Asian, 68.0% never smoker, 72.1% ECOG PS 1). In 98 pts with FISH *METamp* (29.6% had < 12 months on 1L osimertinib; median GCN 11 [range 5.0–50.6]; mean $\pm$ SD sum of target lesion diameters [SOLD] 73.2 ± 47.1 mm), objective response rate (ORR) was 43.9% (95% CI 33.9, 54.3), median (m) DOR was 9.7 months (95% CI 5.6, ne), mPFS was 5.4 months (95% CI 4.2, 7.1), and mOS was not reached (95% CI 11.1, ne). Of the 98 pts, treatment is ongoing in 42 pts. In 31 pts with *METamp* detected by LBx NGS, of which 24 were also FISH+ (mean $\pm$ SD SOLD 93.9 ± 51.4 mm), ORR was 51.6% (95% CI 33.1, 69.8), mDOR was 5.6 months (95% CI 2.9, ne), mPFS was 4.6 months (95% CI 2.7, 6.9), and mOS was not reached (95% CI 6.8, ne). Of 122 pts treated with tepotinib + osimertinib, any grade treatment-related AEs were reported by 99 (81.1%) pts including 34 (27.9%) Grade ≥ 3 . Most common ($> 15\%$ pts) treatment-related AEs included diarrhea 46.7% (0% Grade ≥ 3), peripheral edema 34.4% (4.1% Grade ≥ 3), paronychia 20.5% (0.8% Grade ≥ 3), decreased appetite 18.0% (3.3% Grade ≥ 3), and nausea 16.4% (1.6% Grade ≥ 3). Treatment-related AEs led to a dose reduction in 21 (17.2%) pts, following either or both treatments and led to treatment discontinuation in 7 pts (5.7%). **Conclusions:** In this interim analysis of INSIGHT 2, tepotinib + osimertinib was highly active with durable responses, and was well tolerated in pts with *EGFRm* NSCLC with *METamp* after progression on 1L osimertinib. Tepotinib + osimertinib provides a potential chemotherapy-sparing oral targeted therapy option in this population with a high unmet need. Clinical trial information: NCT03940703. Research Sponsor: the healthcare business of Merck KGaA, Darmstadt, Germany.

LBA9023

Poster Discussion Session

First-line (1L) nivolumab (N) + ipilimumab (I) + chemotherapy (C) vs C alone in patients (pts) with metastatic NSCLC (mNSCLC) from CheckMate 9LA: 4-y clinical update and outcomes by tumor histologic subtype (THS). *First Author: David Paul Carbone, The Ohio State University Comprehensive Cancer Center, Columbus, OH*

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2023, issue of the *Journal of Clinical Oncology*.

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Poster Discussion Session

Circulating tumor DNA (ctDNA) dynamics and survival outcomes in patients (pts) with advanced non-small cell lung cancer (aNSCLC) and high ($> 50\%$) programmed cell death-ligand 1 (PD-L1) expression, randomized to cemiplimab (cemi) vs chemotherapy (chemo). *First Author: Natalie I Vokes, Thoracic Head & Neck Medical Oncology, MD Anderson Cancer Center, Houston, TX*

Background: While ctDNA has emerged as a promising tool for monitoring response on therapy, there is a paucity of data from prospective, randomised Phase 3 studies to establish clear criteria for the clinical application of ctDNA. In the EMPower-Lung 1 study, first line (1L) cemi monotherapy improved overall survival (OS) vs platinum chemo in pts with aNSCLC, PD-L1 $\geq 50\%$, and no EGFR, ALK, or ROS1 aberrations and an acceptable risk/benefit profile. We performed personalized tumor-specific analysis of ctDNA from pts treated in the EMPower-Lung 1 study to determine the optimal time point and magnitude of ctDNA variation that are associated with OS and progression-free survival (PFS). **Methods:** Tumor tissue next-generation sequencing was performed to identify tumor-specific DNA variants. ctDNA levels were monitored using personalized pt specific probe sets (Natera, Foundation Medicine) in the plasma at baseline, end of week 3 (W3) and W9. Endpoints included overall response rate (ORR) complete or partial response (CR/PR), stable disease (SD) and progressive disease (PD) per RECIST 1.1, OS and PFS. Association between ctDNA decrease and clinical endpoints was tested in 3 groups of pts defined by sensitivity analysis: no-decrease, any decrease (molecular response, MR), and complete clearance (complete MR, cMR) of ctDNA. **Results:** ctDNA analysis was performed on samples from 175 pts (chemo n = 89; cemi n = 86). Baseline characteristics, ORR, OS, and PFS were comparable to those of the intention to treat population. At W9, cMR/MR was associated with clinical response to cemi (CR/PR: 97%, SD:58%, PD:17%), but not with clinical response to chemo, as it was detected in the majority of chemo pts across all RECIST categories (CR/PR: 100%, SD:90%, PD:80%). In the cemi arm, ctDNA cMR was associated with the longest survival, with median OS (mOS) not-reached compared to pts with MR (mOS of 29 months) and pts with no-decrease (mOS of 8 months), as well as statistically significant hazard ratios (cMR vs MR: W9 HR = 8, 95% CI 1.8-35, p = 0.0056; cMR vs no-decrease: W9 HR = 25, 5.7–110, p = 0.000021 and W3 HR = 5.9, 1.4-25, p = 0.017). Delayed MR/cMR (i.e., MR/cMR at W9 but not at W3) was observed in 8/66 pts (12%), and transient MR (i.e., MR at W3 but not W9) in 9/66 pts (14%), with available ctDNA data at both timepoints. **Conclusions:** This is the largest data set to date correlating ctDNA levels with efficacy outcomes from a randomized clinical trial comparing chemo with immunotherapy in 1L aNSCLC. The results indicate that lack of treatment-induced decrease in ctDNA may identify pts with inferior OS benefit from cemi monotherapy as early as 3 weeks following initiation of therapy and can inform future use of early ctDNA response assessment in prospective interventional studies. Clinical trial information: NCT03088540. Research Sponsor: Regeneron Pharmaceuticals, Inc. and Sanofi.

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Poster Discussion Session

Safety and clinical activity of target-preserving anti-CTLA-4 antibody ONC-392 as monotherapy in NSCLC patients who progressed on PD(L)1-targeted immunotherapy. *First Author: Kai He, James Thoracic Oncology Center, The Ohio State University Comprehensive Cancer Center, Columbus, OH*

Background: PD-1 or PD-L1 inhibitors have transformed clinical care of NSCLC patients. However, many patients may develop primary or secondary resistant to PD-(L)1 inhibitors. The marketed anti-CTLA-4 mAbs are ineffective as monotherapy for NSCLC. ONC-392 is a novel target-preserving anti-CTLA-4 antibodies that confers immunotherapeutic effect by selective depletion of regulatory T cells (Treg) in the tumor microenvironment. Preclinical studies show that ONC-392 is more effective and less toxic for immunotherapy than other clinically used anti-CTLA-4 antibodies. In first-in-human study in patients with advanced solid cancer, the recommended Phase 2 dose (RP2D) for ONC-392 monotherapy was established as 10 mg/kg. In this study, we tested safety and clinical activities of ONC-392 in NSCLC patients who progressed on PD(L)1-targeted therapy. **Methods:** Anti-PD-(L)1 resistant NSCLC patients were enrolled as parts of PRESERVE-001 studies (NCT04140526) expansion cohort Part C Arm I and treated with 2 cycles of 10 mg/kg, followed by 6 mg/kg, q3w, ONC-392 by IV infusion. Safety was evaluated based on treatment emergent and treatment-related adverse events, while efficacy was evaluated by investigators using RECIST1.1 criteria. **Results:** As of December 18, 2022, 33 NSCLC patients have received at least one dose of ONC-392 at 10 mg/kg. The median age is 66 yrs (range 43 – 89 yr), 61% male. 61% were non-squamous cell carcinoma and 39% were squamous cell carcinoma. 27% are ECOG score 0 and 73% were ECOG score 1. The median prior treatment was 2 cycles (range 1 to 4). The average ONC-392 treatment period was 3.5 cycles (range 1 to 13 cycles). Overall, the patients with TRAE in grade 3 or above is 33% (11/33), including diarrhea/colitis (3, 9%), AST/ALT increase or hepatitis (3, 9%), muscular weakness (2, 6%), nephritis (1, 3%), adrenal insufficiency (1, 3%). Due to pace of enrollment, efficacy data are available in 22 patients. 6 of 22 evaluable patients have partial response and 12 patients have stable disease per RECIST 1.1, resulting in a response rate of 27% and disease control rate of 82% among evaluable patients. The median follow-up period for all patients is 5.8 months and 8.6 months for 20 alive patients (range 2.9 to 14.1 months). The estimated 6- and 12-month overall survival (OS) rates were 65% and 55%. Median OS has not reached. **Conclusions:** Overall, ONC-392 monotherapy with 10 mg/kg is safe and tolerable. Onc-392 monotherapy has showed encouraging anti-tumor activity in IO-resistant NSCLC when compared with historical data. Based on these encouraging data, we have initiated a Phase 3 study testing ONC-392 monotherapy among NSCLC who progressed on PD(L)1-targeting immunotherapy (NCT05671510). Clinical trial information: NCT04140526. Research Sponsor: OncoC4, Inc.; U.S. National Institutes of Health.

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Poster Discussion Session

SI-B001 plus chemotherapy in patients with locally advanced or metastatic EGFR/ALK wild-type non-small cell lung cancer: A phase II, multicenter, open-label study. *First Author: Yuanyuan Zhao, Department of Medical Oncology, Sun Yat-sen University Cancer Center & State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangzhou, China*

Background: SI-B001 is a first-in-class novel EGFR×HER3 bispecific antibody. The objective of this phase II study was to investigate the efficacy and safety of SI-B001 in combination with chemotherapy in pts with locally advanced or metastatic EGFR/ALK wild-type NSCLC. **Methods:** This phase II study enrolled patients with locally advanced or metastatic EGFR/ALK wild-type NSCLC who had failed first-line anti-PD-1/L1 therapy, with or without platinum-based chemotherapy (PBC). This study consisted of three cohorts: In Cohort A pts received SI-B001 plus PBC as second-line treatment after failure to first-line anti-PD-1/L1 antibody monotherapy; Cohort B pts received SI-B001 plus docetaxel as second-line treatment after failure to first-line anti-PD-1/L1 therapy plus PBC; Cohort C pts received SI-B001 plus docetaxel as third-line or higher treatment after failure to first-line anti-PD-1/L1 therapy and PBC. This study evaluated SI-B001 in three distinct dosing schedules: Schedule 1 (16+9mg/kg once weekly), Schedule 2 (14mg/kg on Days 1 and 8 every 3 weeks), and Schedule 3 (21+12mg/kg once weekly). The primary endpoints of the study were to determine the objective response rate (ORR) in evaluable patients and to identify the optimal dose. The secondary endpoints included assessment of progression-free survival (PFS), disease control rate (DCR), duration of response (DOR), and safety. **Results:** As of November 11, 2022, 55 pts have been enrolled in the study, including 1 pt in Cohort A, 45 pts in Cohort B, 8 pts in Cohort C, and one pt enrolled based on the investigator's discretion. Of the 55 pts, 48 were evaluable for efficacy; ORR (n/N, [95%CI]) of 31.3% (15/48, [18.7, 46.3]), DCR of 77.1% (37/48, [62.7, 88.0]). In Cohort B, 23 pts were enrolled in schedule 1, 21 pts were enrolled in schedule 2, and 1 pt was enrolled in schedule 3. Of the 45 pts enrolled in Cohort B, 38 were evaluable for efficacy. Among 22 evaluable pts in schedule 1 the ORR was 45.5% (10/22, [24.5, 67.8]) and the DCR was 68.2% (15/22, [45.1, 86.1]). 18 out of the 22 had no actionable genomic alterations (AGA), the ORR was 50.0% (9/18, [26.0, 74.0]), the DCR was 72.2% (13/18, [46.5, 90.3]), and the mPFS has not been reached. The most common grade ≥3 treatment-related adverse events (TRAEs) were myelosuppression (17%), decreased neutrophil count (15%), and decreased white blood cell count (12%). There was no drug-related death. **Conclusions:** SI-B001 plus docetaxel demonstrated antitumor activity in locally advanced or metastatic NSCLC EGFR/ALK wild-type pts who failed on prior first-line anti-PD-1/L1 antibody plus PBC, especially without AGA. The toxicity of SI-B001 + docetaxel was manageable. These findings support the continued investigation of SI-B001 and docetaxel as a treatment option in NSCLC. Clinical trial information: NCT05020457. Research Sponsor: Sichuan Baili Pharmaceutical Co., Ltd.

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Poster Session

The genomic, transcriptomic, and immunological landscape of SGLT2 in lung cancer. *First Author: Heng Tan, University of Miami/Jackson Memorial Hospital, Miami, FL*

Background: Retrospective data suggest that SGLT2 inhibitors, commonly used in diabetes, are associated with a lower incidence of cancer development and *in vivo* data indicate SGLT2 plays a role in the development of NSCLC. We investigated the genomic and immunological landscape of NSCLC [adenocarcinoma (AC) or squamous cell carcinoma (SCC) histology] with high and low expression of the SGLT2-coding gene *SGLT2* and the relationship with clinical outcomes. **Methods:** NSCLC tumors of AC (N = 11,725) or SCC (N = 4,158) histology were tested at Caris Life Sciences (Phoenix, AZ) with NextGen Sequencing on DNA (592 genes or whole exome) and RNA (whole transcriptome). PD-L1 expression (22C3; Positive (+): TPS ≥1%) was assessed by IHC. High tumor mutational burden (TMB-H) was defined as ≥10 mutations/MB. Mutations were defined as pathogenic SNVs/indels. *SGLT2*-H and -L expression (transcripts per million) was defined as top and bottom quartile, respectively. A transcriptomic signature predictive of response to immunotherapy was applied (T cell-inflamed). The Mann-Whitney U test was applied as appropriate, with P-values adjusted for multiple comparisons (p < .05). Real-world overall survival (OS) data was obtained from insurance claims and Kaplan-Meier estimates were calculated for molecularly defined subpopulations of patients (N = 13,505). **Results:** In AC tumors, *SGLT2*-H was associated with higher rates of *EGFR* (20.8 vs 13.5%, p < .05) and *STK11* mutations (20.1 vs 12.9%, p < .05), but lower rates of *TP53* (50.8 vs 69.5%, p < .05) and *ARID1A* (8.7 vs 4.6%, p < .05) mutations. There was no significant difference in the *KRAS* mutation rate (35.6 vs 37.1%, p = 1). AC and SCC *SGLT2*-H tumors had a lower prevalence of PD-L1+ (AC: 47 vs 68%, SCC: 50 vs 67%, p < .05). AC *SGLT2*-H tumors had a lower prevalence of TMB-H (30 vs 39%, p < .05), but not in SCC (40 vs 41%, p = .6). *SGLT2*-H tumors were associated with a higher prevalence of T cell-inflamed tumors (AC: 40 vs 19%, SCC: 33 vs 11%, p < .05). *SGLT2*-H AC had longer OS as compared to *SGLT2*-L AC tumors (HR = 0.787 [1.73-.85], p < .001) but no significant difference in time on treatment (TOT) with pembrolizumab was observed (HR .90 [1.78-1.03], p = .13). *SGLT2*-H SCC tumors had significantly longer OS (HR .88, [1.78-1.00], p = .045) and they had significantly longer TOT with pembrolizumab (HR .72 [1.56-.94], p = .01). Finally, *SGLT2*-H, *KRAS* mutant AC tumors had significantly longer OS (HR .64 [1.57-.73], p < .001) whereas *SGLT2*-H *KRAS* mutant SCC tumors (HR 1.46 [1.83-2.57], p = .19) trended towards shorter OS. **Conclusions:** *SGLT2* expression was associated with a highly altered genomic landscape in AC. In specific mutational and histological subgroups, differences in *SGLT2* expression were associated with OS and responsiveness to immunotherapy. These mutational and histological subtypes should be further investigated as research on SGLT2 inhibitors progresses. Research Sponsor: None.

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Poster Session

Large-scale comparative analysis of clinico-genomic characteristics, treatment outcomes and resistant mechanisms of *ALK/ROS1/RET*-rearranged non-small cell lung cancer (NSCLC) in a nationwide genomic screening project (LC-SCRUM-Asia/TRY). *First Author: Yosuke Kagawa, National Cancer Center Hospital East, Chiba, Japan*

Background: There is limited understanding of the clinico-genomic differences among *ALK/ROS1/RET*-rearranged NSCLC due to their low frequency. We aimed to characterize these fusions using a large-scale LC-SCRUM-Asia/TRY database. **Methods:** We conducted a prospective screening of treatment-naïve and refractory lung cancer to identify genomic alterations using RT-PCR and/or targeted next-generation sequencing (NGS) assays in LC-SCRUM-Asia/TRY. We compared clinico-genomic characteristics, treatment outcomes and resistant mechanisms among *ALK/ROS1/RET*-rearranged NSCLC. **Results:** Between February 2013 and December 2022, 18,616 lung cancer patients (pts) were enrolled in LC-SCRUM-Asia/TRY and 16,583 were NSCLC pts. *ALK/ROS1/RET* fusions were identified in 430 (2.6%)/240 (1.4%)/202 (1.2%) pts in NSCLC. The patient characteristics were as follows (*ALK/ROS1/RET*): median age, 58/60/63 years; females, 53/54/54%; never-smokers, 57/55/59%; adenocarcinoma, 93/95/96%. The frequencies of brain metastasis at diagnosis were 26/20/19% (p = 0.15). Among pts tested by NGS, the frequencies of *TP53*, *TET2* and *NOTCH1* mutations were lower in *ALK* than in *ROS1* and *RET* (*TP53*; 23/34/27%, *NOTCH1*; 17/34/35%, *TET2*; 17/30/32%). Overall survival (OS) was significantly longer in *ALK* than in *ROS1* (mOS [*ALK/ROS1/RET*] 108.8 vs. 43.6 vs. not reached [NR] months, *ALK* vs. *ROS1*; p < 0.01, *ALK* vs. *RET*; p = 0.04) among stage IV pts underwent TKI therapy. *TP53* mutation was associated with shorter OS in all three fusions (mOS [*TP53* mt+/mt-] *ALK*; 35.7 vs. 108.8, p < 0.01, *ROS1*; 26.4 vs. 47.4, p = 0.06, *RET*; 28.9 vs. 76.1 months, p = 0.05), shorter PFS with first line alectinib in *ALK* (mPFS [*TP53* mt+/mt-] 11.0 vs. 38.4 months, hazard ratio [HR] 2.5 [95% CI, 1.5-4.2], p < 0.01) and shorter PFS with initial crizotinib in *ROS1* (mPFS [*TP53* mt+/mt-] 5.8 vs. 25.2 months, HR 2.6 [95% CI, 1.3-4.8], p < 0.01). There was no significant difference in PFS with first-line platinum plus pemetrexed among fusions (mPFS 12.6 vs. 10.7 vs. 9.2 months) and PFS with initial immune checkpoint inhibitors among fusions (mPFS 3.9 vs. 5.1 vs. 3.0 months). Among 60/13/10 re-biopsy samples refractory to TKI, on-target resistant mutations were identified in 14 (23%) /3 (23%) /1 (10%) samples. **Conclusions:** Pts with *ALK/ROS1/RET*-rearranged NSCLC shared similar characteristics, but the occurrence of concomitant mutations was lower in *ALK* than in *ROS1* and *RET*. *TP53* mutation was associated with worse prognosis in pts with *ALK/ROS1/RET*-rearranged NSCLC. Among those received TKI, pts with *ALK*-rearranged NSCLC had better prognosis than those with *ROS1* and *RET*-rearranged NSCLC. The development of highly effective molecular targeted therapies for *ROS1*- and *RET*-rearranged NSCLC is warranted. Research Sponsor: None.

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Poster Session

Peripheral myeloid cells as prognostic markers in patients (pts) with non-small cell lung cancer (NSCLC) treated with cemiplimab: Pooled analysis of EMPOWER-Lung 1 and EMPOWER-Lung 3 phase 3 trials. *First Author: Joseph Christopher Murray, Johns Hopkins Kimmel Cancer Center, Baltimore, MD*

Background: Circulating innate and adaptive immune cells can modulate clinical responses to immune checkpoint inhibition in pts with cancer; however, there are no clear validated baseline clinical tests to guide clinicians, outside of programmed cell death-ligand 1 (PD-L1) IHC tests on limited biopsy specimens. High neutrophil/lymphocyte ratio (NLR) is associated with poor prognosis in NSCLC, but data are limited on the potential contribution of other immune cells such as monocytes and eosinophils in modulating systemic immune response. Further, previous correlative studies have not established clinically actionable immune cell cut-off values. **Methods:** We used multiple quantitative analytic methods including multivariable Cox regression and conditional decision trees to assess the prognostic importance of NLR and peripheral myeloid cells, including monocytes and eosinophils, in pts with NSCLC treated with cemiplimab in Phase 3 trials EMPOWER-Lung 1 (NCT03088540) and EMPOWER-Lung 3 (NCT03409614). In EMPOWER-Lung 1, pts with PD-L1 ≥50% were randomized 1:1 to cemiplimab 350 mg every 3 weeks (Q3W) or platinum-based chemotherapy (chemo). EMPOWER-Lung 3 was a 2-part study. In Part 1, pts with PD-L1 < 50% were randomized 1:1 to chemo, cemiplimab 350 mg Q3W + chemo, or cemiplimab 350 mg Q3W + ipilimumab 50 mg Q6W + chemo. In Part 2, pts were randomized 2:1 to receive cemiplimab 350 mg or placebo Q3W + chemo. **Results:** Overall, 691 pts in EMPOWER-Lung 1 and 769 pts in EMPOWER-Lung 3 were included in this analysis. The results showed significant association between multiple factors including NLR and overall survival (OS) and progression-free survival (PFS). For pts with NLR > 3.98 vs ≤3.98, median OS (95% CI) was 10 (9-13) vs 20 (17-24) months (HR: 2.04; 95% CI: 1.60-2.61; P < 0.001) and median PFS (95% CI) was 4 (4-6) vs 6 (6-7) months (HR: 1.80; 95% CI: 1.50-2.18; P < 0.001), respectively, accounting for known prognostic factors. In multivariable analyses, monocytes (OS HR: 1.72; 95% CI: 1.29-2.30; P < 0.001; PFS HR: 1.37; 95% CI: 1.08-1.75; P = 0.010) and log eosinophils (OS HR: 0.90; 95% CI: 0.85-0.97; P = 0.003; PFS HR: 0.93; 95% CI: 0.88-0.98; P = 0.004) were significantly associated with OS and PFS in both studies. (Neutrophil + monocyte)/lymphocyte ratio was the top predictor of both OS and PFS in decision tree analysis. Peripheral blood cell count correlations were not affected by tumor PD-L1 levels (p < 0.15 for all markers). **Conclusions:** This is a large and comprehensive prognostic analysis of data from two prospective Phase 3 clinical trials in advanced NSCLC. Clinically actionable peripheral blood cell count parameters, incorporating putative immunosuppressive myeloid cells (neutrophils and monocytes) and protective lymphocytes and eosinophils, may help predict response to anti-PD-1 therapy in advanced NSCLC. Clinical trial information: NCT03088540, NCT03409614. Research Sponsor: Regeneron Pharmaceuticals, Inc., and Sanofi.

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Poster Session

Impact of *EML4-ALK* fusion variant and co-occurring *TP53* mutation on treatment duration of first-line next-generation ALK TKIs in ALK fusion+ NSCLC. *First Author: Kaushal Parikh, Mayo Clinic, Rochester, MN*

Background: Molecular biomarkers such as *EML4-ALK* fusion variant 3 (V3) and *TP53* mutation are associated with poor prognosis in patients (pts) with anaplastic lymphoma kinase fusion positive (*ALK*+) non-small cell lung cancer (NSCLC). We evaluated the effect of *EML4-ALK* fusion variants and *TP53* mutation status on time to treatment discontinuation (TTD) of first-line (1L) treatment with a next-generation ALK tyrosine kinase inhibitor (TKI) in pts with *ALK*+ NSCLC in the real-world setting. **Methods:** Pts with advanced/metastatic NSCLC who were *ALK*+ in circulating tumor DNA by Guardant360 (G360) liquid biopsy test from Jan 1, 2018, to Dec 31, 2021, and received 1L monotherapy with a next-generation ALK TKI (alectinib, brigatinib, ceritinib, lorlatinib) were identified in the Guardant INFORM clinical-genomics database. Median TTD of 1L ALK TKI treatment was determined by Kaplan-Meier (KM) methods. The impact of *EML4-ALK* fusion variant and *TP53* mutation status on TTD was evaluated. **Results:** Database search identified 495 pts with advanced/metastatic NSCLC who had *ALK* fusion by G360; of these, 214 pts received 1L treatment with a next-generation ALK TKI; 164 had G360 testing before treatment (alectinib, n=147; brigatinib, n=7; ceritinib, n=2; lorlatinib, n=8). Among these 164 pts, median age was 58.6 y, 53% were female, and 29% had baseline brain metastases. Median follow-up from start of 1L treatment was 14.8 mo. Median TTD was 19.6 mo (95% CI: 13.6–not reached [NR]). *TP53* mutations were detected in 66 pts (40%). Median (95% CI) TTD in pts with *TP53* mutation vs WT was 17.1 (9.5–28.5) vs 21.9 mo (14.3–NR; log-rank $P=0.1712$). Of 130 pts with *EML4-ALK* fusion variant type detected, 63 (48%) had V1, 54 (42%) V3, 8 (6%) V2, 4 (3%) V5, and 1 (1%) V8. In pts with *EML4-ALK* fusion V1 vs V3, median (95% CI) TTD was 19.0 (13.6–NR) vs 21.8 mo (8.7–NR; HR: 0.73; log-rank $P=0.3039$), with the KM plot showing numerically longer TTD in pts with V1 vs V3 during the first 18 mo and lines crossing at the tail end. Of 117 pts with both an *EML4-ALK* fusion variant (V1/V3) and *TP53* data, 21 (18%) had both V3 and a *TP53* mutation. Pts with co-occurring *EML4-ALK* V3 and *TP53* mutation had the shortest TTD (median TTD 8.7 [3.9–NR; HR: 2.59; $P=0.0219$]; Table). **Conclusions:** Among pts with NSCLC and *ALK* fusion, co-occurrence of *EML4-ALK* V3 and *TP53* mutation is common and associated with poor prognosis and high risk of early discontinuation of 1L treatment with a next-generation ALK TKI, most likely due to disease progression. Additional novel or combination therapies are warranted for this subpopulation. Research Sponsor: Takeda Development Center Americas, Inc., Lexington, MA, USA.

	n ^a	Median TTD (95% CI), mo	HR (95% CI)	P value
<i>EML4-ALK</i> V1 and <i>TP53</i> WT	38	19.5 (11.4–NR)	Reference	
<i>EML4-ALK</i> V1 and <i>TP53</i> +	25	19.0 (9.5–NR)	1.01 (0.42–2.44)	0.9849
<i>EML4-ALK</i> V3 and <i>TP53</i> WT	33	NE (9.4–NR)	0.89 (0.38–2.09)	0.7873
<i>EML4-ALK</i> V3 and <i>TP53</i> +	21	8.7 (3.9–NR)	2.59 (1.15–5.84)	0.0219

^a 117 pts had data for both *TP53* and *EML4-ALK* V1 or V3.

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Poster Session

MSH3 and MSH6 gene polymorphisms: Association with lung cancer susceptibility and prognostic value in patients with NSCLC undergoing platinum-based chemotherapy. *First Author: Navneet Singh, Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, India*

Background: DNA mismatch repair (MMR) pathway is responsible for recognizing and repairing errors (insertion, deletion and misincorporation of bases) occurring during DNA replication and recombination. Single nucleotide polymorphisms (SNPs) in *MSH3* and *MSH6* genes are related to development of various cancers. SNPs of particular interest include rs26279 G > A polymorphism for *MSH3* and rs3136228 557G > T polymorphism for *MSH6*. In this cohort study, we evaluated the association of *MSH3* (rs26279) and *MSH6* (rs3136228) SNPs with occurrence of lung cancer (LC), baseline demographic and clinical characteristics and with overall survival (OS) amongst LC patients undergoing platinum-based doublet chemotherapy. **Methods:** 500 LC patients and 500 healthy controls were enrolled. Genomic DNA was isolated from 4ml of peripheral blood using a phenol-chloroform extraction procedure and genotyping of patients and controls was performed using PCR-RFLP. All enrolled patients had pathologically confirmed LC. Written informed consent was obtained from all enrolled subjects and the study was approved by institutional ethics committee. Odds ratio (OR) and 95% confidence intervals (CIs) were calculated using logistic regression analysis. Kaplan-Meier method was used for OS analysis and (multivariate) Cox regression models to obtain (adjusted) hazards ratios (HRs). **Results:** Mean age (61 years) was similar for cases and controls. Compared to controls, LC cohort had higher prevalence of non-smokers (20% vs. 10%), female sex (20% vs. 9%) and smoking pack-years (mean 20.8 vs. 13.8). Majority of LC patients had metastatic disease (54%) and ECOG performance status of 0-1 (45%) or 2 (40%). Adenocarcinoma and squamous were equi-prevalent (41% each). Mutant genotype (TT) for *MSH6* polymorphism was more frequent in LC patients (OR = 1.43; 95% CI = 1.01 – 2.03; $p = 0.03$) with the association more marked in adenocarcinoma histology (OR = 1.74; 95% CI = 1.05 – 2.93; $p = 0.03$). For non-smokers, mutant genotype (TT) for *MSH6* polymorphism was associated with a 3-fold increased risk of LC (OR = 3.22; 95% CI = 1.26 – 8.18; $p = 0.01$). Amongst females, heterozygous genotype (GA) for *MSH3* polymorphism was more frequent amongst LC cases (24%) than controls (16%) (OR = 2.35, 95% CI = 0.85 – 6.52, $p = 0.04$). Patients treated with docetaxel-platinum chemotherapy and carrying heterozygous (GT) genotype for *MSH6* polymorphism had worse OS (median 4.9 vs 9.1 months; adjusted HR = 2.3; $p = 0.03$). No association was observed between *MSH3* (rs26279) and *MSH6* (rs3136228) polymorphisms and other baseline clinical/demographic characteristics. **Conclusions:** The results of this cohort study suggest that *MSH3* and *MSH6* polymorphisms are involved in modulating the risk towards LC occurrence. *MSH6* polymorphism is also associated with higher mortality amongst patients treated with docetaxel-platinum chemotherapy. Research Sponsor: None.

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Poster Session

Real-world testing and treatment patterns among patients with stage IV non-small cell lung cancer: A retrospective observational study. *First Author: Jeffrey A. Scott, Integra Connect PrecisionQ, West Palm Beach, FL*

Background: Guidelines (NCCN, CAP/IASLC/AMP) recommend clinical molecular testing of patients with advanced NSCLC to inform therapy decisions. We investigated the testing and treatment patterns of patients with stage 4 NSCLC treated in the real-world setting. **Methods:** This retrospective observational study included de-identified stage 4 NSCLC patients from the Integra Connect PrecisionQ database (ICD) enriched with information obtained by curation. Patients with a positive mutation for EGFR, ALK, ROS1, BRAF, MET, RET, HER2, or NTRK and who initiated treatment for stage 4 NSCLC between 01/01/2018 and 12/31/2021 were included with follow-up through 05/31/2022. Also included were demographics, ECOG score, time of ordering test, and date of death. Genomic test data were classified by method and type of test. Overall survival (OS) was calculated using Kaplan-Meier curves and data are presented using descriptive statistics. **Results:** Of 5195 patients in the ICD with stage 4 NSCLC, 3532 patients initiated first line of therapy (LOT1), and 2899 had somatic molecular testing ordered, specifically via tissue-based next-generation sequencing (NGS, 30%), plasma-based NGS (26%), or non-NGS methods (44%). A total of 934 patients tested positive for a driver mutation at any time during the study observation period, and 671 patients (72%) had test results available before initiating treatment. Of those treated after receiving biomarker results, 407 (61%) initiated treatment with a tyrosine kinase inhibitor (TKI), 43 (6%) with chemotherapy (chemo), 156 (23%) with chemo + immuno-oncology (IO), and 65 (10%) with IO. The median OS (95% confidence interval [CI]) was 24.46 (21.90–29.18) months for patients treated with TKI and 14.2 (11.6–16.5) months for patients treated without TKI (unadjusted hazard ratio [95% CI], 1.56 [1.26, 1.92]; $P < 0.001$). **Conclusions:** Among patients with stage 4 NSCLC treated in the real-world setting, patients treated with TKI after receiving test results had better overall survival than patients treated without TKI. While subject to the limitations of a retrospective observational real-world data study, this study suggests that, with regard to utilizing genomic testing and appropriate selection of targeted treatment, adherence to treatment guidelines may improve patient outcomes. As new targeted agents continue to emerge in NSCLC, these data encourage utilization of genomic testing data to guide treatment selection. We acknowledge the significant contributions of our dear friend, Dr. Robert E. Smith, whose cheerful enthusiasm and deep expertise were a driving force of this work. Research Sponsor: Thermo Fisher.

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Poster Session

Impact of genomic alterations measured in circulating tumor DNA (ctDNA) on clinical response to telisotuzumab vedotin treatment in patients with non-small cell lung cancer (NSCLC). *First Author: D. Ross Camidge, University of Colorado Cancer Center, Aurora, CO*

Background: The antibody-drug conjugate telisotuzumab vedotin (Teliso-V) is composed of the c-Met-targeting antibody telisotuzumab (ABT-700) linked to the microtubule inhibitor monomethyl auristatin E. In the LUMINOSITY study (NCT03539536), efficacy of Teliso-V was seen in patients (pts) with *EGFR* wildtype nonsquamous NSCLC and c-Met overexpression ($\geq 25\%$ tumor cells at 4+ intensity by IHC); overall response rate: 36.5%. Data are limited on whether specific driver oncogene states affect responses. We investigated genomic alterations in relation to response to Teliso-V in this population. **Methods:** Pts received 1.9 mg/kg Teliso-V monotherapy once every 2 weeks in LUMINOSITY. ctDNA was isolated from plasma collected at different timepoints. The PGDx elio plasma complete assay was used to identify genomic alterations in ctDNA samples. This assay included 521 genes for single nucleotide variants and insertion-deletion mutations, 38 for amplifications (amp), and 21 for translocations. **Results:** In total, 52 pts were included in the study; ctDNA from 48 pts was analyzed. The overall response rate among pts with ctDNA results was 37.5% (18 pts with partial response) compared with 36.5% for the ITT population of 52 pts. Genomic alterations are listed in the Table. Three out of 4 pts with *MET* amp at baseline responded, accounting for 17% of total responses. The observed *MET* amp frequency in this *MET* IHC pre-selected cohort was 8%, which is similar to the prevalence observed in tissue analysis by FISH. Of note, 1 nonresponder harbored a *MET* ex14del mutation at baseline, and a responder had a low-frequency mutation detected at the final visit. Mutations in *KRAS* were the most common genomic alteration and were detected in 13 (27%) pts at baseline. Three pts with a *KRAS* mutation were responders; among these, 2 out of 3 had a *KRAS* G12C mutation (seen in 3 pts total). Response rates were higher in pts with *MET* amp (75%; 95% CI: 0.30, 0.95) vs those without *MET* amp (34%; 0.22, 0.49), and higher in pts without *KRAS* mutations (43%; 0.28, 0.59) vs those with *KRAS* mutations (23%; 0.08, 0.50); however, confidence intervals were wide and larger sample sizes are needed. **Conclusions:** *MET* amp occurred more frequently in responders; however, Teliso-V activity was not restricted to these pts, as most responders were not *MET* amplified. Specific genomic alterations beyond *MET* may influence clinical response. The current analysis demonstrated numeric differences between pts with identified drivers who did or did not respond to Teliso-V. Additional research on this topic is needed in larger pt cohorts and/or with tissue-based NGS analyses. Research Sponsor: AbbVie Inc.

Genomic alterations at baseline.			
n (%)	Responders n = 18	Nonresponders n = 30	
Amplification			
<i>MET</i>	3 (17)	1 (3)	
Translocations			
<i>RET</i>	2 (11)	0	
<i>ALK</i>	0	1 (3)	
<i>FGFR1</i>	0	1 (3)	
<i>ROS1</i>	0	1 (3)	
Mutations			
<i>KRAS</i>	3 (17)	10 (33)	
<i>MET</i> ex14del	0	1 (3)	
<i>BRAF</i>	0	1 (3)	

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Poster Session

Analytical and clinical validation of oncomine Dx target (ODxT) test and local testing for identifying patients with HER2 (*ERBB2*)-mutant (HER2m) non-small-cell lung cancer (NSCLC) for treatment with trastuzumab deruxtecan (T-DXd) in DESTINY-Lung01/02 (DL-01/02). *First Author: Bob T. Li, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Based on the international DL-01 trial, the US Food and Drug Administration (FDA) approved the ODxT Test as a companion diagnostic (CDx) to identify patients (pts) with NSCLC harboring activating HER2 mutations who may benefit from T-DXd. The ODxT Test uses next-generation sequencing (NGS) to detect genomic alterations in formalin-fixed, paraffin-embedded tumor tissue. The accuracy of the ODxT Test by central testing and its agreement with clinical trial assays (CTAs; NGS, polymerase chain reaction, etc.) by local testing was evaluated using analytical and clinical validation data from DL-01 cohort 2 and DL-02 arm 1. **Methods:** ODxT Test and Illumina TruSight Tumor170 NGS assay results were compared for analytical accuracy in NSCLC samples from DL-01 and commercial vendors. Diagnostic agreement was assessed for DL-01/02 by concordance between the ODxT Test and CTAs. Clinical accuracy per objective response rate (ORR) and duration of response (DoR) to T-DXd were evaluated in all pts with HER2m NSCLC identified by ODxT Test vs CTA. Activating HER2 mutations included single nucleotide variants and exon 20 insertions. Pts received T-DXd 6.4 mg/kg in DL-01 or 5.4 mg/kg (FDA-approved dose) in DL-02 every 3 weeks. **Results:** NSCLC samples from DL-01 (n = 91), DL-02 (n = 102), and commercial vendors (n = 129) were individually assessed. The ODxT Test met requirements for analytical accuracy (≥90% agreement when excluding unknown results), with a positive percent agreement (PPA) of 100% and negative percent agreement (NPA) of 99.1% for detecting HER2 mutations. Clinical accuracy of the ODxT Test also met FDA requirements (excluding unknowns) for NPA (≥98%) and PPA (95% CI lower bound ≥85%). DL-01 PPA (95% CI) was 98.0% (89.2%-100%) and NPA was 100.0% (96.6%-100%); for DL-02, PPA was 96.7% (88.7%-99.6%) and NPA was 100% (96.6%-100%). In DL-01, confirmed ORR (95% CI) for pts with HER2m NSCLC identified by central ODxT Test was 58.3% (43.2%-72.4%) vs 54.9% (44.2%-65.4%) of pts identified by local CTA; median DoR (95% CI) was 12.0 mo (5.5 mo-18.2 mo) per the ODxT Test vs 9.3 mo (5.7 mo-14.7 mo) per CTA. In DL-02 (prespecified interim analysis early cohort), ORR (95% CI) was 53.6% (33.9%-72.5%) per ODxT Test vs 53.8% (39.5%-67.8%) per CTA; median DoR (95% CI) was not estimable (NE [NE-NE]) per the ODxT Test and NE (4.2 mo-NE) per CTA. **Conclusions:** This study demonstrates the analytical and clinical accuracy of the ODxT Test as a CDx for detecting activating HER2 mutations in NSCLC to identify pts who may benefit from T-DXd. A high level of agreement was also shown between the ODxT Test and CTAs. Clinical trials for HER2m NSCLC may successfully use a central testing assay as a CDx while allowing adequately validated local testing assays to expedite patient enrollment. Clinical trial information: NCT03505710, NCT04644237. Research Sponsor: Daiichi Sankyo, Inc and AstraZeneca.

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Poster Session

The effect of ctDNA tumor fraction (TF) on overall survival and concordance between tissue genomics and ctDNA in Lung-MAP. *First Author: Philip C. Mack, Mount Sinai Health System, New York, NY*

Background: Discordance in genomic profiling between tumor tissue and ctDNA can occur due to *inter-patient* variability in shed tumor DNA, and *intra-patient* variability in sources of cell-free DNA (tumor heterogeneity, metastatic variants, CHIP). TF is an aneuploidy-based estimation of tumor-specific DNA in circulation. We evaluated the impact of TF levels on overall survival (OS), mutation concordance and tumor mutation burden in tissue (tTMB) and ctDNA (bTMB) in the LUNGMAP screening study. **Methods:** Eligible advanced NSCLC pts had blood drawn ≤30 days of fresh tissue biopsy with no intervening therapies. Genomic profiling was done by FoundationOne CDx and FoundationOne Liquid CDx. ctDNA TF was quantified via aneuploidy using deviations in genome-wide SNP coverage or somatic allele frequencies if under aneuploidy LoD. High TF was defined as ≥10%. Concordance among driver genes, cancer genes of interest (CGol: *TP53*, *PIK3CA*, *STK11*, *KEAP1*, *RB1*, *PTEN*, *ATM*, *BRCA1/2*), and variant subtype were assessed by the percentage positive agreement (PPA) and positive predictive value (PPV) with 95% confidence intervals (CI). OS by TF used a Cox model and log-rank test. PPA and TF among CGols was compared with a Wilcoxon test. Correlation between tTMB and bTMB used Lin's coefficient (LC). **Results:** 167 pts met inclusion criteria; 161 had TF data with 51 (32%) ≥10% (high TF). High TF was associated with worse OS (HR: 2.06 [1.43-2.95], p<0.001). The PPA and PPV ranged from 50%-100% and 60%-100%, respectively for driver genes. The PPA was numerically larger for high versus low TF for most drivers (p=0.18) and significantly larger for all mutations and SNVs combined (Table). For CGol, the distribution of PPA differed between high and low TF (p=0.03). The median PPA for CGol (25thtile, 75thtile) was 56% (50,87) for low TF and 100% (100,100) for high TF. PPV for CGol did not differ by TF (p=0.20). High TF was associated with higher levels of TMB and bTMB (p<0.01 for both). TMB LC (CI) for low and high TF were 0.46 (0.27,0.61) and 0.69 (0.53,0.81). **Conclusions:** High TF was associated with worse OS, better PPA among CGol, and better LC for t/bTMB. TF may improve the clinical utility of mutations detected by liquid biopsies and should be reported and considered in interpreting these results. Research Sponsor: U.S. National Institutes of Health; National Institutes of Health; Friends of Cancer Research.

	All Samples: PPA (CI)	High TF: PPA (CI)	Low TF: PPA (CI)	All Samples: PPV (CI)	High TF: PPV (CI)	Low TF: PPV (CI)
KRAS	83 (70,92)	100 (75,100)	76 (60,89)	100 (92,100)	100 (75,100)	100 (88,100)
EGFR	80 (44,97)	100 (40,100)	67 (22,96)	89 (52,100)	100 (40,100)	100 (40,100)
MET	50 (12,88)	67 (9,99)	33 (1,91)	60 (15,95)	67 (9,99)	50 (1,99)
ERBB2	100 (16,100)	100 (2,100)	100 (16,100)	67 (9,99)	50 (1,99)	100 (16,100)
RET	100 (16,100)	NA	100 (2,100)	100 (16,100)	NA	100 (2,100)
All mutations	57 (52,62)	57 (52,62)	69 (61,78)	49 (43,56)	72 (68,77)	78 (70,86)
67 (62,73) Short-variants	80 (75,86)	96 (93,100)	71 (63,79)	72 (68,77)	78 (72,85)	68 (62,73)

9034

Poster Session

Molecular characterization of resistance to immune checkpoint inhibitor and chemotherapy treatment in advanced non-small cell lung cancer. *First Author: Jordan Kardos, Gilead Sciences, Inc., Foster City, CA*

Background: Non-small cell lung cancer (NSCLC) is the most common type of lung cancer and a leading cause of cancer death. Standard of care (SOC) treatment for advanced NSCLC patients include immune checkpoint inhibitors (ICI) and/or chemotherapy (CT). However, the majority of patients do not respond to SOC therapy. Mechanisms of resistance and how they differ across treatments are not fully understood. We characterized molecular markers of resistance for advanced NSCLC patients with ICI monotherapy, CT, or combination ICI-CT. **Methods:** Advanced stage III or IV NSCLC patients with adenocarcinoma histology who received at least 21 days of ICI monotherapy, CT, or combination ICI-CT were identified from a de-identified, multimodal real-world database from Tempus Labs, Inc. All patients had a tissue biopsy taken within 100 days prior to the specified therapy start and all samples underwent next generation sequencing with the Tempus xT assays (DNA-seq of 596-648 genes at 500x coverage and whole transcriptome RNA-seq). Resistance to therapy was defined as having time to next treatment < 90 days, or disease progression or death within 120 days of therapy initiation. We characterized the clinical and molecular characteristics of patients and compared differential expression of genes by resistance status for each cohort. **Results:** A total of 365 patients were included in the study (ICI = 121, CT = 122, ICI-CT = 122). Across cohorts, 30% of patients were identified as having resistance to treatment (ICI = 35%, CT = 23%, ICI-CT = 32%). 53% of patients were > 65 years (median [range] = 67 [25- 88]), and 53% were males. Most patients were white (63%) and had a history of tobacco use (85% current or former smoker). At the time of biopsy, most patients were diagnosed with metastatic NSCLC (Stage IV = 73%) and had received no previous lines of therapy (92%). The alteration frequencies of known NSCLC oncogenic driver mutations including TP53 (65%), KRAS (42%), STK11 (14%), KEAP1 (11%), and EGFR (9%) were broadly consistent with previous characterizations of NSCLC. Validated biomarkers of response to ICI treatment such as Tumor Mutation Burden, IFN-γ signaling, PD-1, and PD-L1 expression were negatively associated with resistance to ICI treatment. Across the ICI, ICI-CT, and CT cohorts, 253, 153, and 178 genes, respectively, were significantly upregulated (FDR < 0.05, LogFC > 1) in patients with resistance to treatment. Of the 550 distinct genes correlated to resistance across treatments, 95% were unique to each cohort, and only 32 genes (5%) were shared across more than one treatment cohort. **Conclusions:** Distinct molecular characteristics were associated with resistance to ICI and/or CT treatment. This suggests that mechanisms of resistance to ICI monotherapy, ICI-CT, or CT could be separate and unique. Further research can provide valuable insights for novel therapies or combinations. Research Sponsor: Gilead Sciences.

9036

Poster Session

Efficacy and safety of polymeric micelle paclitaxel (pm-Pac) plus tislelizumab and carboplatin for first-line treatment of patients with advanced squamous non-small-cell lung cancer. *First Author: Meiqi Shi, Department of Medical Oncology, Jiangsu Cancer Hospital & Jiangsu Institute of Cancer Research & The Affiliated Cancer Hospital of Nanjing Medical University, Nanjing, Jiangsu, China*

Background: The pm-paclitaxel formulation for injection (pm-Pac), a novel drug delivery system composed of nanoparticle-encapsulated paclitaxel micelles, combined with cisplatin has been proven to improve clinical outcomes in patients with advanced non-small-cell lung cancer (NSCLC). But the efficacy and safety of pm-Pac in addition to PD-1/PD-L1 inhibitors had never been reported before. **Methods:** Treatment-naïve, stage IIIB/IV Sq-NSCLC patients with ECOG PS 0-2(≤1, 91.1%) were eligible. Participants were given intravenous Tislelizumab (200mg, d1) plus pm-Pac (230 mg/m², d1) and carboplatin (AUC 5, d1), every 3 weeks until progression or unacceptable toxicity, with local radiotherapy or surgery allowed if treatment needed. The primary endpoints were ORR and safety. The secondary endpoints include DCR, PFS, and OS. AEs were graded according to CTCAE v5.0. **Results:** From Nov 2021 to Dec 2022, 45 patients were enrolled. The median age was 68 years (range 41-84), and most were male (93%) and former/current smokers (87%). 3 patients had baseline brain metastases and 31 patients had baseline PD-L1 evaluated. Twenty-two patients (48.9%) received subsequent local treatment because of the stable efficacy, including 18 radiotherapy and 4 surgery. Among all, 2 achieved confirmed CR, 36 achieved PR, 7 achieved SD, ORR was 84.4% and DCR was 100%. PFS and OS were immature. Kaplan-Meier survival analysis indicated that the 6m-PFS rate was 94.8% (95%CI:89.8% , 97.6%), and a total of 41 (91.1%) patients are still alive on 1L treatment at the last follow-up on Feb 2023.The most common TRAE were alopecia (91.1%), leukopenia (80%), peripheral neurosensory numbness (55.6%) and extremity pain (24.4%). The most common grade 3 or higher AE was neutropenia (33.3%), which is commonly associated with chemotherapy. **Conclusions:** This is the first report about the new chemo-drug pm-Pac plus PD-1 inhibitor regimen that significantly improved ORR for advanced Sq-NSCLC with a tolerable safety profile, supporting further development of this new combination in the first-line treatment. Response rates. Research Sponsor: None.

Characteristic	Total (n)	CR(n)	PR(n)	SD (n)	PD (n)	ORR (%)	DCR (%)
Male	42	1	34	7	0	83.3	100
Female	3	1	2	0	0	100	100
Stage III	17	2	13	2	0	88.2	100
Stage IV	28	0	23	5	0	82.1	100
PD-L1 expression							
< 1%	15	2	10	3	0	80	100
1%-49%	10	0	9	1	0	90	100
≥50%	6	0	5	1	0	83.3	100
Unknown	14	0	12	2	0	85.7	100

Keywords: Pm-paclitaxel, PD-1 inhibitor, Advanced Sq-NSCLC.

9037

Poster Session

Exploring the potential of combination immune checkpoint strategies in non-small cell lung cancer (NSCLC). *First Author: Aakash Desai, Mayo Clinic, Rochester, MN*

Background: The clinical outcomes for patients with NSCLC remain suboptimal despite recent advancements in anti-PD-1/PD-L1 immunotherapies. Thus, identification of rational combinations of novel immune checkpoint (IC) strategies is imperative. This study aimed to comprehensively characterize the expression of IC targets to inform drug development and design effective combinatorial strategies, to advance the search for optimized therapies for NSCLC. **Methods:** We analyzed the differential gene expression of IC targets in 537 primary lung adenocarcinoma (LUAD) samples and 59 normal lung tissue samples pre-immunotherapy receipt using RNA-sequencing data from The Cancer Genome Atlas. Gene expression of IC-targets including *PDCD1* (PD-1), *CD274* (PD-L1), *CTLA4*, *TIGIT*, *LAG3*, *HAVCR2* (TIM-3), *VSIR* (VISTA), *ICOS*, *CD276* (B7-H3), *BTLA*, *IDO1*, *KLRD1* (CD94/NKG2A), *NT5E* (CD39), *TNFRSF4* (OX-40), *TNFRSF18* (GITR), and *TNFRSF9* (4-1BB) were obtained. Differential gene expression was determined intra-tumorally by comparison of transcripts per million and inter-tumorally using the DESeq2 algorithm. Log2 fold change >0.5 and false discovery rate adjusted $P < 0.05$ were used as criteria for significant differential expression. Hierarchical clustering was used to identify subsets of tumors with similar profiles of IC-targetable gene expression. **Results:** Tumors showed significantly increased expression of *TNFRSF18* (GITR), *NT5E* (CD39), *TNFRSF9* (4-1BB), *LAG3*, *TIGIT*, *CTLA4*, *PD-1*, *BTLA*, *B7-H3*, and *OX-40* (Table 1). On the other hand, tumors exhibited significant downregulation of *CD274* (PD-L1), *HAVCR2* (TIM-3), *ICOS*, *KLRD1* (CD94/NKG2A), and *VSIR* (VISTA). Hierarchical clustering revealed recurrent patterns of IC gene overexpression which were characterized by: 1) *IDO1*-hi, 2) *CD276*-mid + *TNFRSF18*-mid, 3) *VSIR*-hi, 4) *CD276*-hi, 5) *NT5E*-hi, and 6) *CD276*-mid + *NT5E*-mid. Interestingly, patterns of IC gene expression distinguish tumors from controls. Of note, high *VSIR* expression was specific to normal tissue rather than tumors. **Conclusions:** Our study identified many IC targetable genes that were significantly overexpressed in tumors. However, subsets of tumors showed distinct and segregable combinations of overexpressed IC genes. These results suggest heterogeneous mechanisms of immune evasion in NSCLC, which may explain suboptimal outcomes with anti-PD-1/PD-L1 based strategies in this patient population. Our findings emphasize the importance of biomarker-guided approaches for the optimal selection of ICs and the development of rational combinatorial immunotherapies in NSCLC. Research Sponsor: None.

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Poster Session

Effects of mutations in SWI/SNF subunits on context-specific prognosis in driver positive and driver negative NSCLC. *First Author: Benjamin Herzberg, Columbia University Irving Medical Center, New York, NY*

Background: Mutations (mt) in the Switch/Sucrose-Nonfermentable chromatin remodeling complex (SWI/SNF) are commonly found in NSCLC and have been associated with worse prognosis. However, the overall prognostic role of the individual SWI/SNF subunits in all NSCLCs and in oncogenic driver-positive (D+) and driver-negative (D-) groups remains unclear. Our study attempts to clarify the prognostic role of SWI/SNF subunit alterations in these populations. **Methods:** 42,379 NSCLC tumor specimens were tested at Caris Life Sciences (Phoenix, AZ) with NextGen Sequencing (NGS) of DNA (592-gene panel or whole-exome sequencing). Based on the observed frequency of likely pathogenic/pathogenic (LP/P) mts, the four most commonly-altered SWI/SNF subunits – ARID1A (8.29%), SMARCA4 (6.29%), ARID2 (3.05%) and PBRM1 (1.98%) – were further analyzed. We divided the cohort by driver mts. D+ tumors possessed at least one of the following alterations: LP/P mts in KRAS, EGFR, BRAF, ERBB2 or MET; METex14 skipping; ERBB2 amplification, LP/P fusions in ALK (including IHC overexpression), RET, ROS1, NTRK (1-3) & NRG1. D- tumors were devoid of mts/amplifications/fusions in all genes mentioned above. Kaplan-Meier analysis was performed on real world survival data ($n = 24685$) obtained from insurance claims. Statistical significance was determined using chi-square and Mann-Whitney U test adjusted for multiple comparisons ($q < 0.05$). **Results:** Of the SWI/SNF genes, only SMARCA4mts were associated with worse survival in the overall (HR = 1.46), D+ (HR = 1.984) and D- (HR = 1.224) cohorts (all $p < 0.01$). While SMARCA4mt was associated in the D- cohort with KEAP1 and STK11 mts, the worse prognosis persisted even in their absence (HR = 1.41, $p < 0.001$). To understand the role of SWI/SNF mts in the context of driver co-mts, we compared the survival of D+ vs D- tumors for each SWI/SNF subunit. As expected, D+ tumors were associated with better survival in SWI/SNF wild-type (wt) tumors (HRs 0.76-0.78, $p < 0.00001$). There was no survival effect of ARID1A, ARID2 or PBRM1 mts (HRs = 0.9-1, $p = ns$). In contrast, in SMARCA4mts, D+ tumors had much worse survival than D- (HR = 1.295, $p = 0.003$). This effect is driven by the KRASmt cohort, as KRASmt/SMARCA4mt tumors had significantly worse survival compared with D- tumors (HR = 1.882, $p < 0.001$). Of note, KRASmts are enriched in the D+/SMARCA4mt subgroup (78% of all oncogenic drivers). When KRASmts were removed from the D+ group, no survival difference was observed between D+ and D- SMARCA4mt tumors (HR = 0.938, $p = ns$). **Conclusions:** In this largest-ever retrospective cohort of NSCLC patients with SWI/SNF mutations, SMARCA4mt is the only SWI/SNF alteration broadly associated with worse survival. SMARCA4mt is associated with particularly short survival in KRASmt tumors. These data suggest underlying biology which may inform further investigation and therapeutic development. Research Sponsor: None.

9038

Poster Session

Co-mutational status and PD-L1 expression in KRAS mutant non-small cell lung cancer (NSCLC): Role in treatment selection and association with clinical outcomes. *First Author: Hina Khan, The Warren Alpert Medical School of Brown University, Providence, RI*

Background: In NSCLC, different *KRAS* mutations (mt) define unique subgroups and certain co-mutations (co-mt) could have prognostic and therapeutic implications. Retrospective studies associate poor prognosis with co-mts in *STK11* and *KEAP1* with *KRAS*. It is unclear if PD-L1 expression and co-mt in *KRAS* mt NSCLC impacts outcomes. **Methods:** Molecular profiles of 27748 NSCLC tumors were tested with next-generation sequencing (Caris Life Sciences, Phoenix, AZ) and classified by *KRAS* mt. PD-L1 IHC (22C3) was reported as TPS. Real-world post-immunotherapy (IO) overall survival (OS) was obtained from insurance claims and calculated from start of an immune check-point inhibitor (with or without chemotherapy) to the last day of follow-up. **Results:** In all, 7634 (28%) samples had a *KRAS* mt; most common being G12C (11%), G12V (5.3%), G12D (3.9%) and G13X (2.0%). The most frequent co-mt was *KRAS*-TP53 (KP) (46%), similar in all *KRAS* subtypes. *KRAS*-STK11 (KL) was in 23% of *KRAS* mt, enriched in G13X (33%) and lowest in G12D (16%). *KRAS*-KEAP1 (KK) was co-mt in 10% of *KRAS* mt, highest in G13X (16%) and lowest in G12D (8%). *KRAS*mt/STK11wt/KEAP1wt/TP53wt (K only) was 27% of *KRAS* mt, highest in G12D (36%) and lowest in G13X (16%). A small subgroup, 5.6% was *KRAS*-STK11-KEAP1 co-mt (KKL). The majority of pts in the KL (61%), KK (52%) and KKL (62%) cohorts had TPS <1%. In 1723 *KRAS* mt NSCLC pts treated with IO, KL, KK and KKL had significantly worse post-IO OS than KP and K only (table); KKL had the lowest OS. In the TPS ≥ 1% *KRAS* mt group, KL, KK and KKL had worse post-IO OS than KP and K-only. In TPS <1% group, KL and KK had poor post-IO OS and K-only had favorable outcomes. However, KP had worse post-IO OS compared to K-only in TPS <1%. In G12C and G12V, similar trend with worse post-IO OS in KL, KK and KKL, compared to KP and K only was noted. **Conclusions:** We report a large real-world dataset evaluating outcomes with check-point inhibitors in NSCLCs with *KRAS* and specific co-mts. KL, KK and KKL subgroups demonstrate universally poor outcomes in all *KRAS* subtypes irrespective of PD-L1. Pts with KP co-mts have adverse post-IO outcomes in TPS <1% but favorable in TPS ≥ 1%. TPS score remains a predictive marker of IO outcomes in KP, but not in KL, KK and KKL. These observations emphasize that both PD-L1 and co-mts have a clear association with clinical outcomes in *KRAS*-mt NSCLC, and must be used in predictive models for individualized therapy. Research Sponsor: None.

	N	Post-IO OS (months) (95% CI)		
		All	TPS <1%	TPS ≥ 1%
All <i>KRAS</i>	1723	16.8 (15-18.6)	13.3 (11.6-15.6)	15.4 (13.1-18.3)
KP	826	17.9 (15.3-20.7)	10.4 (8.8-13.5)*	17.5 (13.2-21)
KL	350	10.7 (9.4-12.3)*	11.8 (10-14.4)*	9.1 (6.1-12.3)*
KK	163	8.9 (6.7-10.7)*	8.9 (6.1-11)*	7.5 (2.3-11.6)*
KKL	83	8 (5.3-9.9)*	8.9 (6.1-11)*	3.7 (1.3-9.8)*
K-only	465	21 (17.6-25.7)	23.2 (14.9-31.1)‡	18.4 (13.5-24.5)

Some with overlaps: *: significantly different from K-only &: significantly different from KP.

9040

Poster Session

TROP2 expression and response to immune checkpoint inhibition in patients with advanced non-small cell lung cancer. *First Author: Antoine Italiano, Early Phase Trials Unit, Institut Bergonié and University of Bordeaux, Bordeaux, France*

Background: Despite anti-monoclonal antibodies targeting programmed cell death-1 (PD-1) or its ligand PD-L1 revolution, most patients (pts) with advanced NSCLC displayed primary resistance to PD1/PD-L1 blockade. Identifying targetable alterations involved in resistance represent a promising approach to improve immunotherapy efficacy. TROP2 expression is associated with a poor prognosis in NSCLC, and offers a promising target for treatment with the development of new antibody drug conjugate. TROP2 has been suggested to play a role in innate immunity response, but, it's unclear whether TROP2 expression by tumor cells is detrimental specifically in the context of PD1/PD-L1 blockade. The aim of our study was to investigate the role of TROP2 expression in outcome of NSCLC pts treated with ICI. **Methods:** We analyzed the largest NSCLC gene expression data set worldwide including the whole-transcriptome profile of 891 pre-treatment tumors from POP-LAR and OAK trials, two randomized studies assessing the efficacy of atezolizumab versus docetaxel in NSCLC. We complemented this transcriptional approach with multiplex IF and digital pathology analysis to confirm our findings at the protein level. We investigated whether a non-invasive approach focusing on the level of plasma levels of circulating TROP2 may be relevant to predict efficacy of ICI. **Results:** The PFS of pts with high expression of TROP2 was significantly lower than in pts with low expression 2.5 vs 4.1 months, $p < 0.001$. Strikingly, high TROP2 expression was also associated with lower clinical benefit rate 15% vs 28%, $p = 0.009$ and worse overall survival (OS) 12.6 vs 16.3 months, $p = 0.007$. When adjusting for covariates such as histological subtype, TMS signature, PD-L1 expression, TROP2 remained independently associated with PFS and OS. None of these correlations were observed in the docetaxel arm, suggesting a predictive value of TROP2 gene expression specifically for response to ICI. By using a deconvolution approach, we also observed that TROP2-high tumors were characterized by a significant lowest expression of genes specific to immune populations (T effector memory cells, Th17 cells). Multiplex IF on an independent cohort 53 NSCLC tumors confirmed the correlation between high TROP2, microenvironment features and poor response to PD1 inhibition. Analysis of circulating plasma levels of TROP2 in 97 NSCLC patients revealed a strong correlation with expression in tumor tissue. High plasma levels of circulating TROP2 was also significantly associated with worse ORR, PFS and OS on treatment with PD1/PDL1 antagonist. **Conclusions:** Our study revealed that TROP2 expression by tumor cells in NSCLC is associated with worse outcome in patients with NSCLC independently of PDL1 expression. Targeting TROP2 in combination with ICI may represent a promising strategy to improve ICI efficacy in pts with TROP2-high NSCLC. Research Sponsor: None.

9041

Poster Session

Pre-treatment plasma-informed circulating tumor DNA detection as an early identification of therapeutic benefit for patients with untreated advanced lung squamous cell carcinoma. *First Author: Tao Jiang, Department of Medical Oncology, Shanghai Pulmonary Hospital and Thoracic Cancer Institute, Tongji University School of Medicine, Shanghai, China*

Background: Circulating tumor DNA (ctDNA) detection as a promising prognostic factor to assess treatment response has been widely studied with customized tumor-informed strategies, the application of which was limited by the inaccessibility for tumor biopsies in a substantial proportion of patients. To overcome this challenge, we presented a proof-of-concept study for the development of a novel personalized pre-treatment plasma-informed next generation sequencing (NGS) panel and investigated its prognostic value for first line treatment in patients with advanced lung squamous cell carcinoma (LUSC). **Methods:** Paired plasma and white blood cell (WBC) samples were collected from 227 of stage IIIB-IV LUSC patients who were treated with first line either chemotherapy or chemotherapy plus PD-1 blockade at pre- and post-treatment. Somatic mutations in pre-treatment plasma were identified with a 769-gene based NGS panel (Genecast, Wuxi, China) followed with germline or clonal hematopoietic variants filtering by referring to the WBC samples. Positive variants detected in the pre-treatment plasma served as a basis for personalized variants tracking in post-treatment plasma. ctDNA kinetics was measured by plasmaDelta ($\Delta\text{geneaf} = (\text{post-treatment geneaf} - \text{pre-treatment geneaf}) / \text{pre-treatment geneaf}$; geneaf was defined by variant allele frequency for each individual gene). Progression-free survival (PFS) as the primary endpoint and overall survival (OS) as the secondary endpoint were assessed. **Results:** ctDNA positivity was observed in 80% (182/227) of pre-treatment samples and subsequently 54% (99/182) of post-treatment samples. ctDNA positivity at post-treatment was shown to be a significant predictor for both PFS and OS in the whole group as well in the sub-treatment groups (Table). After adjusting for clinicopathologic variables, ctDNA positivity remained significantly associated with both worse PFS and OS (PFS: HR = 2.3, $P < 0.001$ and OS: HR = 2.56, $P < 0.001$). ctDNA kinetics further identified a worse treatment response group. Patients with high plasma-Delta had remarkably worse outcomes than patients with low plasma-Delta (PFS: HR = 4.8; 95%CI=2.8-8.3; $P < 0.001$ and OS: HR=2.8; 95%CI=1.7-4.6; $P < 0.001$). **Conclusions:** These results demonstrated the feasibility of pre-treatment plasma-informed ctDNA detection and kinetics for monitoring treatment response in LUSC patients whose tumor biopsies were unavailable. Research Sponsor: None.

Prognostic value of ctDNA positivity.						
Groups	No. of ctDNA positive patients	No. Of ctDNA negative patients	PFS		OS	
			HR (95% CI)	P value	HR (95% CI)	P value
All	99	83	3.2 (2.3-4.4)	<0.001	3.4 (2.3-5.0)	<0.001
Chemotherapy plus PD-1 blockade	39	49	2.7 (1.7-4.4)	<0.001	3.8 (2.1-6.8)	<0.001
Chemotherapy only	60	34	3.5 (2.1-5.7)	<0.001	2.9 (1.6-5.0)	<0.001

9043

Poster Session

Factors impacting outcomes in individuals ≥ 80 years with non-small cell lung cancer (NSCLC): A national cancer database (NCDB) analysis. *First Author: Ethan Burns, Houston Methodist Neal Cancer Center, Houston, TX*

Background: Older individuals with advanced/metastatic NSCLC have inferior outcomes compared to younger patients. Aside from baseline comorbidities and treatment-limiting toxicities, identifying factors that impact overall survival (OS) in this population is needed. The aim of this study is to assess characteristics impacting outcomes in patients ≥ 80 years with NSCLC using the NCDB. **Methods:** Adults ≥ 80 years with NSCLC, stage III/IV disease, diagnosed between 2015-2018, and available demographic data were included. Age, sex, race, insurance status, hospital subtype, Charelsion-Deyvo comorbidity (CDCC) index, cancer stage (III/IV), geographic region in the United States (US), and histologic NSCLC subtypes were compared. Kaplan-Meier methodology assessed differences in median OS, and differences were compared using hazard ratios (HR) with 95% confidence intervals (CI). Pearson Chi-Squared test assessed the significance of covariates, and a p value < 0.05 was considered statistically significant. **Results:** There were 42,356 patients included. Median age was 83 (80-90) years, 20,422 were (48.2%) female, 35,653 (84.2%) were white, 37,738 (89.1%) had medicare coverage, 11,055 (26.1%) received treatment at an academic hospital, and 14,383 (33.9%) received care in the southern United States. Treatment at an academic hospital (HR: 0.91 [95% CI: 0.87, 0.95], $p < 0.001$), females (HR: 0.82 [95% CI 0.81, 0.84], $p < 0.001$), Medicaid (HR: 0.77 [95% CI: 0.65, 0.93], $p = 0.005$) vs no insurance, and adenocarcinoma (HR: 0.79 [95% CI: 0.74, 0.84], $p < 0.001$) or squamous cell carcinoma (HR: 0.84 [95% CI: 0.80, 0.90], $p < 0.001$) had better outcomes. Patients in the Northeastern (HR: 0.90 [95% CI: 0.87, 0.93], $p < 0.001$), Southern (HR: 0.92 [95% CI: 0.89, 0.94], $p < 0.001$), and Western (HR: 0.89 [95% CI: 0.88, 0.93], $p < 0.001$) US had better OS compared to the Midwest. Compared to whites, patients who were black (HR: 0.92 [95% CI: 0.88, 0.85], $p < 0.001$), Asian (HR: 0.77 [95% CI: 0.72, 0.82], $p < 0.001$), Hispanic (HR: 0.83 [95% CI: 0.78, 0.88], $p < 0.001$), or other (HR: 0.88 [95% CI: 0.79, 0.97] had better outcomes. Per year increase in age (HR 1.009 [95% CI: 1.006, 1.013], $p < 0.001$), patients with CDCC score of 1 (HR: 1.16 [95% CI: 1.14, 1.19], $p < 0.001$), 2 (HR: 1.22 [95% CI: 1.18, 1.27], $p < 0.001$), and ≥ 3 (HR: 1.33 [95% CI: 1.284, 1.380], $p < 0.001$) vs 0, and stage IV NSCLC (HR: 1.83 [95% CI: 1.79, 1.88], $p = 0.000$) had poorer survival. **Conclusions:** White race, males, uninsured status, receipt of treatment in the Midwest, community hospital treatment, large cell histology, advancing age, stage IV disease, and increasing CDCC score all had poorer outcomes in adults ≥ 80 years with advanced NSCLC. These factors should be taken into consideration when discussing the diagnosis, management, and expectations of the disease course with patients in the geriatric age group. Research Sponsor: None.

9042

Poster Session

Treatment at twilight: Is less more in the management of octogenarians with non-small cell lung cancer (NSCLC)? *First Author: Ethan Burns, Houston Methodist Cancer Center, Houston, TX*

Background: Treatment of advanced/metastatic NSCLC in older patients is hindered by performance status, comorbidities, and treatment toxicities. Moreover, whether multiagent chemotherapy in combination with immune checkpoint inhibitor (ICI) therapy outweighs a conservative approach is controversial. This study aims to assess treatment patterns and outcomes in patients ≥ 80 years with NSCLC through data provided by the national cancer database (NCDB). **Methods:** Adults ≥ 80 years with stage III/IV NSCLC, available treatment data, and diagnosis between 2015-2018 were included. Patients were stratified by therapy including none, ICI alone, chemotherapy alone, and chemotherapy+ICI; radiation and surgical management was also assessed. Median overall survival (OS) was evaluated by Kaplan-Meier survival methods, and differences were assessed by hazard ratios (HR) and 95% confidence intervals (CI). The mean difference in OS was compared between systemic therapy arms. Pearson Chi-Squared tests assessed the significance of treatment differences, with a p-value of < 0.05 considered statistically significant. **Results:** There were 42,356 patients included; 29,698 (70.1%) had stage IV disease and 26,314 (62.1%) had adenocarcinoma. A total of 3,248 (7.7%) received ICI, 11,505 (27.2%) received chemotherapy, 2,393 (5.6%) received chemotherapy+ICI, and 25,210 (59.5%) received no therapy. Median OS for no therapy, ICI, chemotherapy, and chemotherapy+ICI was 2.63 (95% CI: 2.57, 2.69), 10.68 (95% CI: 9.96, 11.39), 12.35 (95% CI: 11.98, 12.72), and 14.03 (95% CI: 13.87, 14.88) months, respectively. Compared to no therapy, ICI alone (HR: 0.377 [95% CI: 0.361, 0.393], $p = 0.000$), chemotherapy alone (HR: 0.439 [95% CI: 0.426, 0.452], $p = 0.000$), and chemotherapy+ICI (HR: 0.345 [95% CI 0.328, 0.363], $p = 0.000$) improved OS. Compared to ICI, chemotherapy and chemotherapy+ICI had a longer mean OS difference of 2.48 (95% CI 1.82, 3.13) ($p < 0.001$) and 1.9 (95% CI 1.01, 2.78 ($p < 0.001$)) months, respectively. In chemotherapy alone, the median OS was 1.12 months (95% CI: 0.55, 1.70) ($p < 0.001$) longer with multiagent vs single agent. There was no difference between chemotherapy vs chemotherapy+ICI (0.57 months [95% CI: 0.16, 1.31], $p = 0.234$), or for ICI+single agent vs ICI+multiagent (0.67 months [95% CI -1.18, 2.54], $p = 1.00$). Treatment with radiation (HR: 0.664 [95% CI: 0.649, 0.679], $p < 0.001$), primary-sit(HR: 0.495 [95% CI: 0.465, 0.527], $p < 0.001$) and non-primary surgery (HR: 0.867 [95% CI: 0.811, 0.927], $p < 0.001$), and receipt of ICI vs no ICI (HR: 0.912 [95% CI 0.873, 0.954], $p < 0.001$) improved OS. **Conclusions:** Patients ≥ 80 years with NSCLC derived most benefit from multiagent chemotherapy or chemotherapy+ICI, with no OS difference between ICI+single or ICI+multiagent therapy. ICI alone and no therapy had inferior OS. Future trials to corroborate this finding would benefit the elderly population. Research Sponsor: None.

9044

Poster Session

A phase II study of afatinib in combination with pemetrexed and carboplatin in patients with EGFR mutation positive non-squamous, advanced non-small-cell lung cancer (NSCLC) refractory to first-line osimertinib treatment: NEJ025B. *First Author: Tatsuro Fukuhara, Department of Respiratory Medicine, Miyagi Cancer Center, Natori, Japan*

Background: To date, osimertinib has been commonly used as a first-line treatment for EGFR mutated advanced NSCLC. However, the issue of what constitutes effective treatment after osimertinib failure remains. We evaluated treatment with afatinib plus chemotherapy for EGFR mutated NSCLC resistant to osimertinib. **Methods:** Patients (pts) with EGFRm (Del19 or L858R) after failure of osimertinib treatment were assigned to a regimen of afatinib 20mg daily combined with carboplatin AUC5 mg/ml/min and pemetrexed 500mg/m² every 3 weeks followed by maintenance treatment with afatinib plus pemetrexed until disease progression or unacceptable toxicity was noted. The primary endpoint was rate of PFS at 6 months after initiation of treatment (6M-PFSR). The threshold was set at 35% and the expected value at 60% (two-sided P-value of 5% and power of 80%). Thirty-one patients were required, and the target number of patients was set at 35 after accounting for ineligible cases. Secondary endpoints were PFS, OS, ORR, DOR, and Safety. In this study, blood samples were collected before and after study treatment and at the time of PD to examine biomarkers using CAPP-SEQ. This biomarker study is ongoing. **Results:** Between June 7, 2020 and January 19, 2022, 36 pts were enrolled. One patient was found to meet the exclusion criteria, and the efficacy was analyzed in the other 35 patients. The mean age was 70 years, 60% were women, and 54.3% were nonsmokers. The 6M-PFSR, the primary endpoint, was 57.1%. The confidence interval of 39.3%-71.5% exceeded the threshold of 35%, and the study met its primary endpoint. Notably, 24.1% of pts had a long-term PFS of 1 year or longer. ORR was 48.6%, DCR was 88.6%, median PFS was 8.2M, median DOR was 5.6 M, and median OS was not reached. By mutation type, ORR were similar for Del19 and L858R (46.7% and 50.0%, respectively), but median PFS tended to be longer for Del19 compared to L858R (9.6M and 5.2M, respectively). Pts who responded to previous osimertinib therapy (CR and PR: n = 29) tended to have longer mPFS compared to non-responders (SD, PD, and NE: n = 6) (8.5M and 5.8M, respectively). Adverse events due to TKI and chemotherapy were observed. Diarrhea (52.8%), anorexia (44.4%), fatigue (33.3%), and paronychia (36.1%) were the most frequent adverse events, and these adverse events were predictable and manageable. Interstitial pneumonia developed in three patients (8%), one of whom was the only death in the study. **Conclusions:** The combination of afatinib and the platinum doublet showed satisfactory efficacy with manageable adverse events in tumors refractory to osimertinib, and met its primary endpoint. OS follow-up and biomarker analyses are still ongoing. This regimen is expected to be a candidate for second-line therapy after osimertinib. Clinical trial information: jRCTs021200005. Research Sponsor: supported by Boehringer.

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Poster Session

Uncommon *EGFR* mutations conducted with osimertinib in patients with NSCLC (UNICORN): A phase 2 study. *First Author: Yusuke Okuma, Department of Thoracic Oncology, National Cancer Center Hospital, Tokyo, Japan*

Background: Non-small cell lung cancer (NSCLC) harboring uncommon *EGFR* mutation (u-*EGFR*m), excluding exon 20 insertion, is a heterogeneous rare fraction consisting of 10% of all *EGFR* mutations. Key drugs for metastatic NSCLC (mNSCLC) u-*EGFR*m are limited, with only afatinib being FDA approved. Data on the efficacy of osimertinib for previously untreated metastatic patients (pts) harboring u-*EGFR*m NSCLC is limited. **Methods:** UNICORN study for previously untreated mNSCLC pts harboring u-*EGFR*m, excluding exon 20 insertion mutation, evaluating osimertinib with a dose of 80 mg QD orally is a multicenter, open-label, single-arm phase 2 study. The primary endpoint was the overall response rate (ORR) evaluated by central review according to the Response Evaluation Criteria in Solid Tumors (version 1.1), and key secondary endpoints were disease control rate (DCR), progression-free survival (PFS), overall survival (OS), duration of response (DoR), and safety. **Results:** Between March 2020 to May 2022, a total of 42 pts were registered. Among the eligible 40 pts, 45.0% were female; the median age was 72 years (range 39-88); 42.5% were never smokers or light smokers; 92.5% were adenocarcinomas, solitary u-*EGFR*m/compound mutation ratio was 57.5%/42.5%. The most common mutations were G719X (50.0%), followed by S768I (25.0%), L861Q (20.0%), and others, including compound mutation data. The ORR was 55.0% (90% confidence interval [CI]; 40.9-68.5), the DCR was 90.0% (95% CI; 76.3-97.2), the mPFS was 9.4 months (95% CI; 3.7-15.2) after a median follow-up of 27.0 months, the mOS was not reached (NR) (95% CI, 19.23-NR), and the mDoR 22.7 months (95% CI; 9.43-NR). In solitary and compound mutations with u-*EGFR* m NSCLC, ORR was 52.2%/58.8%, mPFS was 5.4 months/11.4 months, mOS 23.0 months/NR, and mDoR was 22.7 months/NR, respectively. Safety was similar to previous reports and Grade 3/4 AEs were reported in 8 of 36 pts (27.5%) and 12.5% of pts developed pneumonitis. All of the AEs were manageable and there were no treatment-related deaths. **Conclusions:** Osimertinib in mNSCLC pts harboring u-*EGFR*m other than exon 20 insertions showed clinical activity with manageable toxicities. These results suggest that osimertinib can be considered as a treatment option for this specific population. Clinical trial registration: jRCT071200002. The study was funded by AstraZeneca. Clinical trial information: jRCT071200002. Research Sponsor: AstraZeneca.

9047

Poster Session

Updated efficacy and safety of entrectinib in patients (pts) with locally advanced/metastatic *NTRK* fusion-positive (fp) non-small cell lung cancer (NSCLC). *First Author: Byoung Chul Cho, Yonsei University College of Medicine, Seoul, Korea, Republic of (South)*

Background: *NTRK* fusions, encoding for constitutively active oncogenic tropomyosin receptor kinase proteins, are present in many solid tumors, including NSCLC. As central nervous system (CNS) metastases are common in pts with advanced NSCLC, treatments with intracranial efficacy are needed. Entrectinib, a potent CNS-active tyrosine kinase inhibitor, has previously demonstrated efficacy in pts with *NTRK*-fp NSCLC in an integrated analysis of three phase I/II trials (ALKA-372-001 [EudraCT, 2012-000148-88], STARTRK-1 [NCT02097810], STARTRK-2 [NCT02568267]); objective response rate (ORR) was 63.6% (14/22; data cutoff: August 31 2020). We present updated data for this cohort. **Methods:** Pts $\geq$ 18 years old with locally advanced/metastatic *NTRK*-fp tumors were enrolled and received 600 mg oral entrectinib until disease progression, toxicity, or death. At Week 4 and then every 8 weeks, tumour response was assessed by blinded independent central review (BICR) per RECIST v1.1. Co-primary endpoints were ORR and duration of response (DoR). Secondary endpoints included progression-free survival (PFS), overall survival (OS), intracranial efficacy, and safety. Enrollment cutoff: July 2 2020; data cutoff: August 2 2021. **Results:** The efficacy-evaluable population included 31 pts with *NTRK*-fp NSCLC. Median age was 60.0 years (range 22-88); 26 pts (83.9%) had adenocarcinoma; 11 pts (35.5%) had $\geq$ 2 prior lines of systemic therapy; 18 pts (58.1%) were current or former smokers; 15 pts (48.4%) had investigator-assessed baseline CNS metastases. Median survival follow up was 21.8 months (95% CI 19.5-30.2). Entrectinib treatment showed efficacy in pts with *NTRK*-fp NSCLC, including those with baseline CNS metastases by investigator (Table). In pts with BICR-assessed CNS metastases, intracranial ORR was 60.0% (6/10; 95% CI 26.2-87.8), median intracranial DoR was not estimable (NE), and median intracranial PFS was 8.9 months (95% CI 5.6-NE). In the safety-evaluable population (N=35), most treatment-related adverse events (TRAEs) were Grade 1-2 and non-serious. TRAEs led to dose reduction, interruption and discontinuation in 31.4%, 28.6%, and 5.7% of pts, respectively, and no treatment-related deaths occurred. **Conclusions:** In line with previously reported data, treatment with entrectinib was associated with deep and durable systemic and intracranial responses in pts with advanced *NTRK*-fp NSCLC. Clinical trial information: EUCR 2012-000148-88, NCT02097810, NCT02568267. Research Sponsor: This study is sponsored by F. Hoffmann-La Roche Ltd, Third-party medical writing assistance, under the direction of authors, was provided by Vanessa Poon, BSc, of Ashfield MedComms, an Inizio company, and was funded by F. Hoffmann-La Roche Ltd.

	All pts (N=31)	Baseline CNS metastases* (n=15)	No baseline CNS metastases* (n=16)
ORR, n (%)	20 (64.5)	9 (60.0)	11 (68.8)
95% CI	45.4-80.8	32.3-83.7	41.3-89.0
Complete response	5 (16.1)	1 (6.7)	4 (25.0)
Partial response	15 (48.4)	8 (53.3)	7 (43.8)
Median time to event, months (95% CI)			
DoR	27.1 (14.8-29.4)	29.4 (13.0-NE)	19.9 (10.4-NE)
PFS	20.8 (13.8-30.4)	30.3 (4.7-30.4)	20.8 (14.9-NE)
OS	NE	NE (8.9-NE)	NE
* Per investigator			
CI, confidence interval			

9046

Poster Session

Role of immunotherapy in stage IV non-small cell lung cancer with liver metastasis: A NCDB analysis. *First Author: Takefumi Komiya, Penn State Cancer Institute, Hershey, PA*

Background: Despite approvals of immune checkpoint inhibitors in stage IV non-small cell lung cancer (NSCLC), survival benefit of immunotherapy (IO) in those with liver metastasis is controversial. Randomized controlled trials demonstrated conflicting results. **Methods:** Using National Cancer Database (NCDB), Stage IV NSCLC cases diagnosed in 2016-2017 with at least 30-day follow up were analyzed. Clinical demographics included age (20-69 vs. 70+), sex (male vs. female), race (whites vs. others), institution (academic vs. others), Charlson-Deyo score (0-1 vs. 2-3), year of diagnosis (2016 vs. 2017), Histology (adenocarcinoma NOS vs. other), brain metastasis (Yes vs. No), bone metastasis (Yes vs. No), liver metastasis (Yes vs. No). They were divided into liver-metastasis positive (LM+) vs. negative (LM-). Information regarding cancer treatment was limited to the first course of therapy, including surgery for primary lesion (Yes vs. No), radiation (Yes vs. No), multi-agent chemotherapy (Yes vs. No), and IO (Yes vs. No). Overall Survival (OS) analysis was performed using Kaplan-Meier curves and Log-rank tests. Cox proportional hazard model was used for multivariate analyses. A two-sided p-value < 0.05 was considered as significant. **Results:** A total of 13,594 LM+ and 69,885 LM- cases met eligibility and further analyzed. 2,944 and 15,553 patients were treated with IO, respectively. No significant association between use of IO and status of liver metastasis was observed (p = 0.124). The median OS in LM+ cases was significantly shorter than that in LM- cases (5.0 vs 8.8 months, respectively, p < 0.0001). Use of IO was associated with improved OS in both LM+ and LM- cohorts with similar HRs/p-values (0.62/ < 0.0001 and 0.64/ < 0.0001, respectively). Multivariate analysis demonstrated that use of IO had a significantly improved OS in both LM+ (HR = 0.69, p < 0.0001) and LM- (HR = 0.64, p < 0.0001) cohorts. The OS benefit of IO in LM+ cohort remained with propensity score matching analysis (mOS 9.0 vs. 4.4 months, HR = 0.62, p < 0.0001). Further exploratory analysis focusing on those treated with multiagent chemotherapy showed that the addition of IO improved OS in both LM+ (HR = 0.77, p < 0.0001) and LM- (HR = 0.79, p < 0.0001) cohorts. **Conclusions:** This retrospective study using one of the largest cancer databases suggests that use of IO improves OS of NSCLC patients with LM regardless of chemotherapy status, and its magnitude of OS benefit is similar to that in LM-patients. Research Sponsor: None.

	LM+ with IO	LM+ without IO	LM- with IO	LM- without IO
Median OS (month)	9.0	4.1	15.6	7.2
12-month OS (%)	41.7	24.1	57.8	37.9
24-month OS (%)	24.8	13.1	37.6	23.7

9048

Poster Session

Initial chemotherapy for locally advanced and metastatic NUT carcinoma: A report from the NUT carcinoma registry. *First Author: Jia Luo, Dana-Farber Cancer Institute, Boston, MA*

Background: NUT carcinoma (NC) is an uncommon squamous cell cancer. This disease is driven by a *NUTM1* gene fusion, most commonly encoding a BRD4-NUT fusion oncoprotein, that enhances transcription of numerous genes including *MYC*. BET bromodomain inhibitors (BBDi), which block oncoprotein binding, are being studied in clinical trials. A subset of NC is sensitive to chemotherapy, but the optimal regimen is unknown; experts have recommended platinum- (PLAT) and ifosfamide-based (IFOS) therapy based on case reports. **Methods:** Patients with NC with known chemotherapy treatment and survival outcomes who consented to participate in a worldwide registry were included. Cohorts of patients with non-metastatic and metastatic disease were of interest. Medical records were manually reviewed. Results were summarized using 95% confidence intervals (95CI) and Kaplan Meier survival estimates, when appropriate. **Results:** A total of 60 patients with NC were included and received either PLAT (83%) or IFOS (17%); 38% were female and the median age was 37 (range 10-82); 55% of tumors were thoracic primaries, 48% had squamous differentiation, and 70% were driven by BRD4-NUTM1 (n = 43 with known fusion status). Of 31 patients with non-metastatic disease, 32% had a thoracic primary; 23% received peri-operative chemotherapy and 77% received concurrent chemoradiation (cRT). The most common chemotherapies used for cRT were cisplatin (n = 12), platinum-taxane (n = 6), and platinum-etoposide (n = 5). Of 4 non-metastatic patients who received IFOS, 4 (100%) had a disease-free survival (DFS) > 3 months and 1 (25%) had a DFS > 1 year. By comparison, of the 27 patients who received PLAT, the estimated 3-month and 1-year DFS was 70% (95CI 48-84%) and 53% (95CI 30-71%) respectively. Of the 29 patients with metastatic disease, 79% had a thoracic primary; 6 received IFOS and 23 received PLAT. The most common chemotherapies were platinum-taxane (52%), platinum-etoposide (17%), and ifosfamide-etoposide (14%). ORR of IFOS vs PLAT was 50% (95CI 12-88%) vs 23% (95CI 7-44%). Compared to IFOS, PLAT had similar 3-month and 6-month PFS (3; 6mo: PLAT est: 36% [95CI 18-56%]; 9% [95CI 2-25%] vs IFOS 50%; 17%). The estimated 1-year OS and 1-year OS were 18% (95CI 6-35%) vs 33% for PLAT vs IFOS respectively. Of the 5 patients (8%) with a known OS > 3 years, all had a non-thoracic primary, non-metastatic disease, and had received PLAT. **Conclusions:** NUT carcinoma is a highly aggressive disease. There may be a numerically higher ORR for ifosfamide-based therapy as compared to platinum-based therapy, with limited durability. Development of effective combination targeted therapies, eg. combinations with BBDi, is an urgent unmet need for this patient population. Research Sponsor: U.S. National Institutes of Health; Lowe Center for Thoracic Oncology, Friends of Jay Dion, Ryan Richards Foundation, McDevitt Strong, Max Vincze Foundation; U.S. National Institutes of Health; R01CA124633-16.

9049

Poster Session

Thoracic SMARCA4-deficient cancer descriptors and clinicopathologic determinants of survival: Analysis of a pooled database. *First Author: Frankie Lee Powell, Feist-Weiller Cancer Center at LSUHSC-Shreveport, Shreveport, LA*

Background: Inactivation of SMARCA4, a catalytic subunit of the SWI/SNF complex, has been linked to high-grade aggressive cancers with poor prognoses. SMARCA4-deficient thoracic tumors (SDTT) can involve any part of the chest cavity, including the lungs, mediastinum, pleura, and chest wall. SDTT's detailed clinical features and optimal treatment still need to be clarified. Therefore, we conducted this pooled database analysis to delineate key clinicopathological characteristics, prognostic indicators, and treatment modalities that affect survival in this unique group of thoracic cancers. **Methods:** To study the demographic characteristics, molecular and immunohistochemical signatures, therapeutic interventions, survival, and prognostic factors, we compiled a pooled database of 120 cases of SDTT. Kaplan-Meier survival curves were constructed. Cox proportional hazards model and Log-rank tests were used to assess the influence of demographic and clinicopathologic factors on overall survival (OS). **Results:** A total of 120 patients with confirmed SDTT were identified. The median age was 54, with a peak incidence between 56 and 68. There was a male preponderance with M:F of 3. The median duration of symptoms before diagnosis was 3.5 months. Patients presented with local disease in 11%, locally advanced in 21%, and metastases in 61%. The primary sites were the lungs (45%), mediastinum (42%), and pleura (13%). Common metastatic sites were bone (32%), adrenals (30%), liver (20%), Brain (20%), and lungs (18%). The median OS of the whole group was 6 months. Ninety percent of patients had a smoking history with a median of 26 pack-years. Histology comprised epithelioid/rhabdoid (79%) and carcinoma (adenocarcinoma, mucinous, and undifferentiated, 21%). Carcinomas had a better median OS than sarcomatous histology (11 vs. 6 months, $p=0.03$). Furthermore, early stages (NO/N1) had a superior median OS compared to advanced stages ($N\geq 2$, M+) (16 vs. 5 months, $p=0.02$). Compared to no treatment, local therapies (surgery (S) or radiation (RT)), combination chemotherapy (CT), and combined modalities (CT $\pm$ S/RT) were statistically superior with a median OS of 1, 4, 6, and 11 months, respectively ($p<0.0001$). Further analysis revealed CT+S had superior median OS to CT+RT (16 vs. 9.5 months). Moreover, those with immune checkpoint inhibitors incorporated into their therapies had the best median OS outcomes ($p<0.0001$). Age, sex, primary site, and size did not impact OS. **Conclusions:** This study presents updated clinicopathologic data from a pooled cohort of patients with SDTT cancers. It identifies the histologic type, stage, and treatment approach as critical determinants of OS. Research Sponsor: None.

9051

Poster Session

Clinical outcomes among patients with advanced non-small cell lung cancer who received targeted therapy in a real-world setting. *First Author: Mo Yang, EMD Serono, Rockland, MA*

Background: In the past decade, therapies targeting *EGFR*, *KRAS*, *ALK*, *ROS1*, *BRAF*, *NTRK*, *MET*, *RET*, *HER2* and PD-L1 were approved and recommended by National Comprehensive Cancer Network (NCCN) for use in advanced non-small cell lung cancer (aNSCLC). This study compared real-world clinical outcomes in biomarker positive patients with aNSCLC who received treatments based on the NCCN NSCLC Guidelines (v5.2021) versus other therapies in the US. **Methods:** This is a retrospective cohort study of patients with aNSCLC using the TEMPUS oncology dataset. Patients were included if they were diagnosed with stage IIIB-IV NSCLC (index date) between 1/1/2012 and 12/31/2020, ≥ 18 years of age at index, were biomarker (i.e., *EGFR*, *KRAS*, *ALK*, *ROS1*, *BRAF*, *NTRK*, *MET*, *RET*, or PD-L1) positive, and received at least one line of treatment. Patients were stratified by NCCN recommended treatment (v5.2021) receipt anytime following aNSCLC diagnosis. Median overall survival (mOS), progression free survival (mPFS), and time to next treatment (mTTNT) were evaluated by treatment group using Kaplan Meier analysis. Patient demographic and clinical characteristics were evaluated as potential predictors of receipt of NCCN recommended therapy. **Results:** Of the 2,158 biomarker positive patients who met study criteria, 55.7% ($N=1,201$) received NCCN recommended treatment. PDL1 (38.0%), *EGFR* (32.2%), and/or *KRAS* (30.3%) were the most common over-expressions/mutations. Biomarker positive patients with aNSCLC treated with NCCN recommended treatment ($N=1,201$) in any line had significantly longer mOS (24.7mo, 95% CI: 22.5–27.6) than those treated with non-recommended treatment ($N=957$, 19.8mo, 95% CI: 17.5–22.6) ($p<0.001$). Biomarker positive patients with aNSCLC treated with NCCN recommended treatment also had significantly longer mPFS (8.5mo, 95% CI: 7.9–9.0) and mTTNT (20.6mo, 95% CI: 19.3–23.7) than those treated with non-recommended treatment (4.9mo, 95% CI: 4.5–5.4) and (11.0mo, 95% CI: 10.0–12.7), respectively (both $p<0.001$). Never smokers (vs current smokers), patients of unknown or other race (vs whites), and patients who received 2 or more lines of treatment (vs 1) were more likely to receive NCCN recommended treatment and those with squamous or other/unknown histology (vs non-squamous) or missing ECOG scores (vs ECOG 0) were less likely to receive NCCN recommended treatment. **Conclusions:** In this study, biomarker positive patients with aNSCLC who received NCCN recommended treatment had significantly longer mOS, mPFS, and mTTNT than those who were treated with non-recommended regimens. Following the recommendations of the NCCN NSCLC Panel improves real-world clinical outcomes among biomarker positive patients with aNSCLC. Meanwhile, some biomarker positive patients—including current smokers and those with squamous cell histology—were less likely to receive targeted treatments. Research Sponsor: The healthcare business of Merck KGaA, Darmstadt, Germany.

9050

Poster Session

Safety, pharmacokinetics (PK), pharmacodynamics (PD) and preliminary efficacy of AZD2936, a bispecific antibody targeting PD-1 and TIGIT, in checkpoint inhibitor (CPI)-experienced advanced/metastatic non-small-cell lung cancer (NSCLC): First report of ARTEMIDE-01. *First Author: Kristoffer Staal Rohrberg, University Hospital of Copenhagen, Copenhagen, Denmark*

Background: PD-1 and TIGIT are implicated in cancer-related T cell immunosuppression. AZD2936 is a bispecific, humanized IgG1 (triple-mutated to minimize Fc effector function) targeting PD-1 and TIGIT. It has demonstrated encouraging activity compared to both anti-PD-1 and anti-PD-1/TIGIT combinations in murine models. We report data from dose escalation (Part A) and an expansion cohort (Part B) of the first-in-human study ARTEMIDE-01 (NCT04995523). **Methods:** This open-label, multicenter study enrolled pts with advanced NSCLC who had prior CPI treatment and a PD-L1 tumor proportion score $\geq 1\%$. Part A evaluated doses of 70–1500 mg IV Q3W; Part B evaluated the recommended phase 2 dose (RP2D). Primary endpoints included safety, tolerability, dose-limiting toxicities (DLTs) and preliminary efficacy. Secondary endpoints included PK and PD, defined as percentage PD-1 and TIGIT receptor occupancy (RO). **Results:** As of Dec 5, 2022, 80 pts were enrolled (Part A, $n=48$; Part B, $n=32$). Pts were 62.5% male, median age 63.5 years; 72.5% had adenocarcinoma, 23.8% had squamous cell carcinoma; 96.3% had metastatic disease; and 22.5% had brain metastases. They had a median of 2 prior regimens. Median duration of therapy was 11 wks. AZD2936 was well tolerated with no DLTs. In total, 46.3% of pts had treatment-related adverse events (TRAEs), all grade 1–3; the most common were pruritus, rash and lipase increased (6.3% each). Serious TRAEs occurred in 3 pts (3.8%): immune system disorder, acute hepatitis and fatigue ($n=1$ each). AZD2936 systemic exposure increased in a near dose-proportional manner. Doses of ≥ 210 mg achieved $\sim 90\%$ PD-1 and TIGIT RO in peripheral T cells. The RP2D was determined to be 750 mg Q3W based on safety, preliminary efficacy, PK/PD and modeling analysis predicting intratumoral RO. Among 76 evaluable pts, 3 had a partial response and 30 had stable disease (Table). Time to response was 1.9–4.0 mos and duration of response was 2.1–6.4 mos. **Conclusions:** In this interim analysis, AZD2936 showed an acceptable safety profile and preliminary antitumor activity in pts with advanced/metastatic NSCLC previously treated with standard therapy including CPIs. Further exploration of AZD2936 in CPI-naïve NSCLC pts, including a randomized dose optimization cohort is ongoing. Clinical trial information: NCT04995523. Research Sponsor: AstraZeneca.

Safety and preliminary antitumor efficacy of AZD2936.	
Safety, n (%)	N=80
Treatment-emergent AEs, any grade / grade ≥ 3	70 (87.5) / 22 (27.5)
AEs related to AZD2936, any grade / grade ≥ 3	37 (46.3) / 4 (5.0)
AEs leading to discontinuation	3 (3.8)
Response and disease control	Evaluable pts (n=76)
Overall response rate, % (95% CI)	3.9 (0.8, 11.1)
Partial response, n (%)	3 (3.9)
Stable disease, n (%)	30 (39.5)
Disease control at 9 weeks, n (%)	33 (43.4)
Disease control at 27 weeks, n (%)	11 (14.5)

9052

Poster Session

Prognostic and predictive implications of plasma ctDNA in guiding first-line targeted therapy for metastatic HER2-mutant non-small cell lung cancer (NSCLC). *First Author: Si-Yang Liu, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Trastuzumab deruxtecan (T-DXd) is the first HER2-targeted drug approved for NSCLC with human epidermal growth factor receptor 2 (*HER2*, *ERBB2*) mutation in the second or later line settings. However, the optimal first-line treatment for these patients remains unclear. Access to rapid tissue sequencing is not always available, thus presenting challenges to first-line drug development. Circulating tumor DNA (ctDNA) analysis has the potential to overcome these obstacles to guide optimal first-line targeted therapy for patients with *HER2*-mutant NSCLC. **Methods:** We retrospectively analyzed patients with metastatic *HER2*-mutant NSCLC who underwent prospective clinical ctDNA sequencing at Memorial Sloan Kettering Cancer Center (MSK) from January 2016 to September 2022. *HER2* mutations were identified by next-generation sequencing through MSK-IMPACT, MSK-ACCESS or Resolution ctDx Lung. **Results:** We identified 64 patients with metastatic *HER2*-mutant NSCLC who had received at least one line of systematic therapy. The median age was 63 years (range: 23–90), and there were more women ($n = 38$, 60%), and never-smokers ($n = 38$, 60%). The activating *HER2* mutations included exon 20 insertions (73%), exon 8 (11%), 19 (11%), and 20 SNVs (5%). Plasma ctDNA was tested before initial therapy in 40 patients with a median overall survival (OS) of 28 months (95% CI 21–34), in whom 31 patients (78%) had at least one detectable ctDNA alteration by MSK-ACCESS and ctDx Lung. 55% (17/31) received chemoimmunotherapy with pembrolizumab as the first-line treatment. The median time to treatment discontinuation (TTD) was 6 months (95%CI 5.5–6.9). Additionally, 19% of patients (6/31) received a *HER2*-targeted antibody-drug conjugates (ADC) as first-line treatment with a median TTD of 6 months (95% CI 2–10), including 5 with T-DM1 and one who received first-line T-DXd treatment with a TTD of 9 months. Patients with baseline ctDNA alterations had significantly shorter OS (hazard ratio (HR), 5.25; 95% CI, 1–24; $p = 0.019$). **Conclusions:** Baseline plasma ctDNA has the potential to guide first-line targeted therapy for patients with *HER2*-mutant NSCLC. As an independent negative prognostic biomarker, detectable ctDNA at baseline would need to be taken into account for patient selection in future studies to avoid underestimating the effects of therapy. Research Sponsor: TBD.

9053

Poster Session

Safety and efficacy of immune checkpoint inhibitors in patients with cancer and pre-existing autoimmune disease: A systematic review and meta-analysis in non-small cell lung cancer. *First Author: Wint Yan Aung, Northwell Health, Manhasset, NY*

Background: Cancer patients with pre-existing autoimmune diseases (AID) have been traditionally excluded from clinical trials of immune checkpoint inhibitors (ICI) due to concerns for immune activation leading to toxicity. As indications for ICI expand, there is a need for robust data on safety and efficacy of ICI in cancer patients with AID. Existing studies examined a heterogeneous group of cancers and do not include a comparison to cancer patients without pre-existing AID. Therefore, data are lacking concerning how safety and efficacy of ICI in this group of patients may differ from the general population and whether the results are generalizable to non-small cell lung cancer (NSCLC). **Methods:** We searched for studies consisting of NSCLC, AID, ICI, treatment response, and adverse events using database-controlled vocabulary terms. We systematically searched Medline (PubMed), EMBASE, Scopus, CINAHL, and Web of Science. We selected studies that included NSCLC and excluded abstracts, case reports, review articles, and articles lacking outcomes or populations of interest. Three authors (WA, CL, NS) independently reviewed all abstracts to determine study eligibility and quality. Study quality was assessed using the Newcastle-Ottawa Scale. Study data were pooled using random-effects meta-analysis. **Results:** Data were extracted from 24 cohort studies, consisting of 10,924 cancer patients, of which 4353 were NSCLC patients. Studies examined a broad spectrum of AID consisting of 1157 patients, of which 291 were NSCLC patients. Pooled analysis revealed an AID flare incidence of 36% (95%CI 27%-46%) in all cancers and 23% (95%CI 9%-40%) in NSCLC. Tests of subgroup difference revealed no significant difference in AID flares by organ system in all cancers and NSCLC ($p = 0.602$ and $p = 0.19$, respectively). Pre-existing AID was associated with a higher risk of de novo iRAE in all cancer patients (RR 1.38, 95%CI 1.16-1.65) and in NSCLC patients (RR 1.51, 95%CI 1.12-2.03). There was no difference in de novo grade 3-4 iRAE and tumor response between cancer patients with and without AID. However, in NSCLC patients, pre-existing AID was associated with a 2-fold increased risk of de novo grade 3-4 iRAE (RR 1.95, 95%CI 1.01-3.75) but also better tumor response in achieving a complete or partial response (RR 1.56, 95%CI 1.19-2.04). **Conclusions:** Pre-existing AID confers an increased risk of toxicity during ICI therapy. NSCLC patients with AID are at a higher risk of de novo grade 3-4 iRAE but are also more likely to achieve treatment response than those without AID. Multidisciplinary collaboration is paramount when considering ICI therapy in this patient population with careful calculation of risk and benefit as well as close monitoring for toxicity. Research Sponsor: None.

9055

Poster Session

Assessment of sociodemographic disparities in outcomes among pts with metastatic NSCLC (mNSCLC) receiving select immuno-oncology (IO) regimens: CORRELATE. *First Author: Stephen V. Liu, Georgetown University, Washington, DC*

Background: IO treatment (tx) has transformed the care of pts with mNSCLC, persistently demonstrating significant survival benefits over chemotherapy. Prior analyses have shown OS and PFS are shorter in the real-world (rw) setting compared with randomized clinical trials (RCTs). A contributing factor may be the more diverse sociodemographic characteristics of pts in the rw. Race and socio-economic status (SES), in particular, have been associated with disparities in cancer outcomes, which may be related to inequalities in healthcare access. One aim of CORRELATE was to assess whether outcomes differ based on sociodemographic characteristics in pts receiving IO in the rw setting. **Methods:** Eligible pts from the US Flatiron Enhanced Datamart database had mNSCLC (progressed or *de novo*), started 1L IO tx between Nov 1 2016 and May 31 2021, and met eligibility criteria based on 6 RCTs (KEYNOTE [KN]-024, KN-189, KN-407, IMpower150, CheckMate [CM] 9LA and CM 227) for IO regimens approved in the US for mNSCLC. Flatiron's area-level measure of SES, available for pts treated at community oncology centers, was based on a validated composite index and has 5 levels (highest [5] to lowest [1]). Multivariate Cox regression models were used to determine the association of sociodemographic variables (age, sex, race, US region and SES) with OS and rPFS separately; smoking history, ECOG performance status (PS) and PD-L1 expression were also included in the models, as were any pairwise interactions that were statistically significant ($P < 0.05$). **Results:** 2070 pts with non-missing data on the variables of interest were included in the dataset: 60% were aged ≥ 65 y, 86% white, 55% male and 53% were from the US Southern region. SES was relatively evenly distributed (SES 1-5: 18%, 22%, 21%, 24% and 15%, respectively); 41% of pts had PD-L1 $\geq 50\%$ (17% unknown PD-L1 expression), 61% had ECOG PS 1 and 92% were former/current smokers. Median OS was 13.3 mos (95% CI 12.3-14.7); median rPFS was 5.9 mos (5.6-6.2). In the multivariate analyses, race, region and SES did not have a statistically significant association with either OS or rPFS. Older age (≥ 65 y; $P = 0.0091$) and male sex ($P < 0.0001$) were associated with a higher risk of death (HR [95% CI] 1.16 [1.04-1.29] and 1.28 [1.15-1.43], respectively). For rPFS, the interaction between sex and smoking status was statistically significant ($P = 0.0312$); specifically, female non-smokers had a higher risk of progression or death vs female smokers (HR 1.45 [95% CI 1.15-1.82]). **Conclusions:** Our results from a nationally representative dataset of pts with mNSCLC treated at non-academic facilities show that, in pts who had equivalent access to IO tx, the OS and rPFS benefits derived from IO were similar, irrespective of race, region or SES. More efforts are required to identify and address barriers of access to care to ensure that all pts receive appropriate cancer tx. Research Sponsor: AstraZeneca.

9054

Poster Session

Phase II trial of lazertinib in patients with epidermal growth factor receptor (EGFR) mutation-positive (M+), metastatic non-small cell lung cancer (NSCLC) with asymptomatic or mild symptomatic brain metastases after failure of EGFR tyrosine kinase inhibitor (TKI) (KCSG LU20-15). *First Author: Min Hee Hong, Yonsei Cancer Center, Seoul, South Korea*

Background: Central nervous system (CNS) metastases occur not infrequently, ultimately devastating consequences in advanced EGFR M+ NSCLC. Lazertinib, a 3rd-generation (G) EGFR-TKI, has shown potent antitumor activity in EGFR-mutant NSCLC. We conducted a phase II single-arm study of lazertinib in EGFR M+ NSCLC patients (pts) having CNS metastases to evaluate its CNS activity. **Methods:** The patients exhibiting CNS progression upon 1st or 2nd-G EGFR-TKIs with least one measurable CNS lesion were enrolled. The primary endpoint was intracranial objective response rate (iORR) in evaluable for response set (ERS). Secondary endpoints included iORR without T790M mutation, overall ORR (oORR), disease control rate (DCR), intracranial progression-free survival (iPFS) in ERS. Overall survival (OS) and safety analyses were performed in pts who received at least one dose of lazertinib. Cerebrospinal fluid (CSF) penetration was measured as exploratory biomarker study. **Results:** Of 40 pts enrolled, 38 were evaluable for tumor response. Nineteen pts harbored exon 19 deletion and 21 pts for exon 21 L858R and 30% of pts had radiologic evidence of leptomeningeal carcinomatosis (LM) with 2 cytological confirmed cases. Forty-five percent of pts received afatinib as first line treatment, followed by 42.5% of gefitinib and 12.5% of erlotinib. Baseline plasma samples of all the 40 patients obtained for liquid-based next-generation sequencing (Guardant360) and T790M was found in 5 pts prior to lazertinib treatment. iORR was 57.9% (22/38). iORR with T790M-negative, oORR, and DCR were 54.5%, 39.5%, and 97.4%, respectively. With median follow-up of 13.6 months, median iPFS and OS were not reached. Treatment-related adverse events (TRAEs) emerged in 85.0% of pts with most common TRAEs being skin rash (50.0%) and paresthesia (42.5%). Grade 3 or 4 TRAEs were reported in 10.0%. The CSF penetration rates of lazertinib and its metabolite (YH26334) were 46.2% and 33.1%, respectively in paired CSF and plasma samples, suggesting high CNS penetration efficacy. **Conclusions:** Lazertinib has substantial CNS activity regardless of T790M status against the progression of intracranial metastases $\pm$ LM during the treatment of 1st or 2nd-G EGFR-TKIs in metastatic EGFR M+ NSCLC pts. These results suggest that using lazertinib instead of brain local treatment would be a potential strategy in EGFR M+ NSCLC, who progressed on CNS metastases after prior EGFR-TKI. Clinical trial information: NCT05326425. Research Sponsor: Yuhan.

Efficacy outcome.

Intracranial response, % (95% CI)	
iORR	57.9 (40.8 – 73.7)
iORR in T790M-negative patients	54.5 (36.4 – 71.9)
Best intracranial response, No. (%)	
Complete response	2 (5)
Partial response	20 (52.6)
Stable disease	15 (37.5)
Progressive disease	1 (2.5)
Not evaluable	2 (5)

9056

Poster Session

Long-term efficacy and safety of larotrectinib in patients with tropomyosin receptor kinase (TRK) fusion lung cancer. *First Author: Jessica Jiyeong Lin, Department of Medicine, Massachusetts General Hospital, Boston, MA*

Background: Neurotrophic tyrosine receptor kinase (*NTRK*) gene fusions are oncogenic drivers in a variety of tumor types, including lung cancer. Larotrectinib is a highly selective, central nervous system (CNS)-active TRK inhibitor that demonstrated rapid, deep, and durable responses in patients (pts) with TRK fusion lung cancer (Drilon et al. ASCO 2022) and is considered a preferred first-line therapy option for these pts (Owen et al. J Clin Oncol 2022). We report updated data from a larger cohort with longer follow-up. **Methods:** Pts with TRK fusion lung cancer enrolled in 2 larotrectinib clinical trials (NCT02576431 and NCT02122913) were included in this analysis. Larotrectinib was administered at 100 mg twice daily, and response was assessed by independent review committee (IRC) per RECIST v1.1. **Results:** As of July 20, 2022, 30 pts with a median age of 55.5 years (range 25–81) with TRK fusion lung cancer enrolled, including 12 pts with CNS metastases at baseline. The gene fusions involved *NTRK1* ($n = 24$; 80%) or *NTRK3* ($n = 6$; 20%). Pts received a median of 2 prior lines of systemic therapies, with 20 pts (67%) receiving ≥ 2 . Among 27 pts eligible for IRC assessment, the objective response rate (ORR) was 74% (95% CI 54–89): 3 complete responses, 17 partial responses (PR), 4 stable disease (SD), 2 progressive disease (PD), and 1 not evaluable. Among the 12 pts with baseline CNS metastases, the ORR was 67% (95% CI 35–90): 8 PR, 2 SD, and 2 PD. The median time to response for all responders was 1.8 months. Median duration of response (DoR) was 33.9 months (95% CI 9.5–not estimable [NE]); median follow-up was 22.9 months. Median progression-free survival (PFS) was 33.0 months (95% CI 11.3–NE); median follow-up was 24.7 months. Median overall survival (OS) was 39.3 months (95% CI 17.2–NE); median follow-up was 23.1 months. For the 12 pts with CNS metastases, the medians for DoR, PFS, and OS were 9.5, 9.9, and 19.4 months, with median follow-ups of 17.4, 19.3, and 22.2 months, respectively. Duration of treatment for all pts evaluable per IRC ranged from 0.3+ to 75.2+ months. At data cut-off, 10 pts had progressed, with 6 continuing treatment post-progression for ≥ 4 weeks due to continued clinical benefit. Treatment-related adverse events (TRAEs) were predominantly Grade 1–2. Grade 3–4 TRAEs were reported in 5 pts (2 each increased aspartate aminotransferase, increased weight; 1 each increased alanine aminotransferase, myalgia, hypersensitivity). There were no treatment discontinuations due to TRAEs. **Conclusions:** In this larger dataset with longer follow-up, larotrectinib continued to demonstrate rapid and durable responses, extended survival, and favorable long-term safety in pts with advanced TRK fusion lung cancer, including those with CNS metastases. These results support the wider adoption of next-generation sequencing testing for *NTRK1–3* gene fusions in pts with lung cancer. Clinical trial information: NCT02576431, NCT02122913. Research Sponsor: These studies were funded by Bayer HealthCare Pharmaceuticals, Inc. and Loxo Oncology, Inc., a wholly owned subsidiary of Eli Lilly and Company.

9057

Poster Session

The safety and efficacy of SNK01 (autologous natural killer cells) in combination with cytotoxic chemotherapy after failure of prior tyrosine kinase inhibitor in non-small cell lung cancer: Preclinical mouse model and phase I/IIa clinical study. *First Author: Myeong Geun Choi, Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Mokdong Hospital, College of Medicine, Ewha Womans University, Seoul, Seoul, South Korea*

Background: It is challenging to choose subsequent treatment option in patients with Osimertinib resistance in epidermal growth factor receptor (EGFR)-mutated non-small cell lung cancer (NSCLC). Meanwhile, antitumor effect of the antibody-dependent cellular cytotoxicity of natural killer (NK) cells mediated by cetuximab –anti-EGFR monoclonal antibody– has been reported. Therefore, we aimed to evaluate the safety and efficacy of SNK01 (non-genetically modified autologous NK cell) in combination with cytotoxic chemotherapy including cetuximab in NSCLC after failure to prior tyrosine kinase inhibitor (TKI) in a preclinical humanized cell line-derived xenograft (CDX) mouse model and phase I/IIa clinical study. **Methods:** We established a humanized CDX mouse model using Osimertinib-resistant lung cancer cell line. Re- construction of the humanized mouse, CDX-related skills, and analytic data were made according to C&SR Inc. manufacturing technique & SOP protocol. The mice were divided into 4 groups based on treatment (no treatment [n = 2]; Cetuximab only [n = 3]; SNK01 only [n = 4]; SNK01 plus Cetuximab [n = 4]) and treated weekly for 5 weeks (SNK01, 1x10⁷ cells/dose; Cetuximab, 20 ug/dose). In the clinical study, 12 patients with EGFR-mutated NSCLC who failed prior TKI treatment were finally enrolled. They received weekly SNK01 in combination with Gemcitabine/Carboplatin (n = 6) or Gemcitabine/Carboplatin/Cetuximab (n = 6), and dose escalation of SNK01 following “3+3” design (4x10⁹ cells/dose or 6x10⁹ cells/dose). The primary endpoint was safety, and secondary endpoint was efficacy. **Results:** In the preclinical study, flow cytometry analysis showed that NK cells (CD45+/CD56+/CD3-) were significantly increased in the groups administrated SNK01. The volume of tumor extracted after completion of treatment was the smallest in SNK01 plus cetuximab group. In the clinical study, the median age of patients was 61 years, 33.3% were male, and all patients had adenocarcinoma. The enrolled patients received weekly infusions of SNK01 for 7 to 8 weeks (4x10⁹ cells/dose [n = 6]; 6x10⁹ cells/dose [n = 6]). Since dose limiting toxicity was not observed, maximum tolerated dose of SNK01 was determined to be 6x10⁹ cells/dose. SNK01-related adverse event ≥grade 3 was also not observed. In the efficacy analysis, objective response rate was 25%, disease control rate was 100% (partial response, n = 3/12; stable disease, n = 9/12), and median progression free survival (PFS) was 143 days. PFS will be updated as some patients are still being followed. **Conclusions:** SNK01 in combination with cytotoxic chemotherapy, including cetuximab in EGFR-mutated NSCLC with resistance to TKI was safe and showed a potential antitumor effect in this preclinical study and early phase I/IIa clinical trial. Clinical trial information: NCT04872634. Research Sponsor: NKMAX.

9059

Poster Session

Phase 2 clinical trial of the proautophagic drug ABTL0812 combined with paclitaxel and carboplatin in first-line patients with advanced squamous non-small cell lung carcinoma. *First Author: Joaquim Bosch-Barrera, Catalan Institute of Oncology, Hospital Josep Trueta, IDIBGi. Medical Oncology, Girona, Spain*

Background: ABTL0812 induces the inhibition of Akt/mTOR pathway by upregulation of TRIB3 protein, an endogenous Akt inhibitor, and promotes endoplasmic reticulum (ER) stress. As a result, ABTL0812 induces cytotoxic autophagy that leads to specific death of cancer cells, without affecting non-tumor cell viability. A Phase II clinical trial was designed where ABTL0812 was evaluated in combination with paclitaxel and carboplatin in first-line patients with advanced squamous non-small cell lung cancer (NSCLC). **Methods:** ABTL0812 was administered 1300 mg TID orally with 175 mg/m² paclitaxel and AUC5 carboplatin every 3 weeks, for up to 8 cycles, followed by ABTL0812 as a maintenance until disease progression or unacceptable toxicity. The study enrolled patients with non-irradiable IIIB stage or stage IV squamous NSCLC. Primary endpoint was overall response rate (ORR) by RECIST criteria v.1.1. Secondary endpoints were progression free survival (PFS), overall survival (OS), duration of response (DOR), safety and tolerability according to CTCAE v4.03, pharmacokinetics (PK) of ABTL0812 enantiomers ((-)-ABTL and (+)-ABTL) and pharmacodynamics assessed by two surrogate blood biomarkers: TRIB3 and CHOP. **Results:** Forty patients were included; median age was 66.1 years old; 90% men/10% women; 100% ECOG 0-1; 30% current smokers/67.5% former smokers and 37.5% had received prior chemotherapy > 12 months before inclusion. 39 patients had at least 1 adverse event (AE), anemia appeared in 32.5% of the patients (5.0% grade 3), neutropenia in 27.5% (25% grades 3-4) and thrombocytopenia in 17.5% of the patients (2.5% grade 3). For non-hematological AEs, asthenia was reported in 62.5% of the patients (2.5% grade 3); diarrhea in 45% (no grade 3-4) and nausea in 37.5% (5% grades 3-4). Twenty-five patients reach the primary endpoint for efficacy evaluation. ORR was 52.0% (95% CI 34.2-65.9) and 32.0% of the patients had stable disease. Median OS was 22.5 months (10.4-NC), median progression free survival 6.2 months (4.4-8.8), and DOR 5.1 months (3.9-7.4). Area under the curve (µg·h/ml) for (-)-ABTL and (+)-ABTL were 39.0±12.3 and 17.1±6.3 respectively, maximal concentrations (µg/ml) were 6.4±2.6 and 5.1±2.2 and minimum concentrations (µg/ml) 2.2±1.5 and 0.8±1.3. TRIB3 and CHOP PD biomarkers were induced by the treatment. **Conclusions:** The combination of ABTL0812 with paclitaxel and carboplatin shows survival outcomes that compare favorably with historical controls in squamous-NSCLC with an acceptable safety profile. PK analysis is compatible with drug activity, and pharmacodynamic analysis shows drug engagement. Clinical trial information: NCT03366480. Research Sponsor: Ability Pharmaceuticals SA; Government of Spain.

9058

Poster Session

Impact of first-line immunotherapy on survival and intracranial outcomes from a real-world cohort of patients with non-small cell lung cancer with brain metastases at diagnosis. *First Author: Benoît Nigen, Nantes University Hospital, Nantes, France*

Background: Although brain metastases (BM) at diagnosis are common in non-squamous NSCLC patients (ns-NSCLC), they have been mostly excluded from randomized trials. The aim of this retrospective study was to evaluate real-world outcomes of frontline immune checkpoint inhibitor (ICI) in these patients. **Methods:** We conducted a retrospective study to assess the intracranial and overall efficacy of first-line ICI-based therapy compared to chemotherapy (CT) in ns-NSCLC patients diagnosed with BM, showing no targetable alterations. Patients were divided according to systemic therapy: CT, ICI, or CT-ICI respectively. Primary endpoint was overall survival (OS), compared using Kaplan-Meier and Cox methodology. Secondary endpoint was intracranial progression free survival (icPFS). **Results:** Between 01-2018 and 05-2021, 118 newly diagnosed ns-NSCLC patients with BM were included (52 CT, 38 ICI and 28 CT-ICI). Median follow-up was 30.0 months [95% CI: 25.9-36.0]. Intracranial radiotherapy was delivered for 75.0%, 68.4% and 67.9% of patients for CT, ICI and CT-ICI groups (p = 0.805) respectively. OS rates at 24 months were respectively 25.3% (95% CI: 15.7-40.9), 44.6% (95% CI: 30.8-64.7) and 50.5% (95% CI: 34.3-74.4) in CT, ICI and CT-ICI groups (p = 0.048). Twelve-month icPFS was respectively 17.0% (95% CI: 9-32), 47% (95% CI: 33-66) and 45% (95% CI: 30-69) in CT, ICI and CT-ICI groups. After adjustment, ICI and CT-ICI were associated with a better OS compared to CT (HR = 0.46, 95%CI: 0.23-0.89, p = 0.021 and HR = 0.52, 95%CI: 0.27-1.01, p = 0.054 respectively). ICI and CT-ICI were associated with a significant reduction in the risk of intracranial progression by 54% (HR = 0.46, 95%CI: 0.25-0.84, p = 0.0123) and 59% (HR = 0.41, 95%CI: 0.23-0.77, p = 0.0050) compared to CT. Stereotactic radiosurgery was associated with an increased icPFS compared to systemic therapy alone (HR = 0.51, 95% CI: 0.29 – 0.92, p = 0.0247), whereas whole-brain was not (p = 0.096). **Conclusions:** Real-life ns-NSCLC patients with BM at diagnosis treated frontline with ICI presented OS and icPFS benefit compared to CT alone. A prospective assessment of the ideal type and sequence of systemic and local therapy should be conducted. Research Sponsor: None.

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Poster Session

Long-term outcomes of tepotinib in patients with MET exon 14 skipping NSCLC from the VISION study. *First Author: Paul K. Paik, Thoracic Oncology Service, Memorial Sloan-Kettering Cancer Center, New York, NY*

Background: Tepotinib is a highly selective MET inhibitor with clinical activity in patients (pts) with MET exon 14 (METex14) skipping NSCLC. We previously reported robust and durable activity of tepotinib from the Phase II VISION study (NCT02864992; data cut: Feb 20, 2022; median follow-up: 26.1 months [mos]; Thomas, et al. WCLC 2022). Here, we report long-term outcomes from VISION, fulfilling an FDA post-market requirement (data cut: Nov 20, 2022; follow-up: Cohort A [primary cohort] ≥35 mos, Cohort C [confirmatory cohort] ≥18 mos). **Methods:** Pts with advanced METex14 skipping NSCLC detected by liquid and/or tissue (T+) biopsy received tepotinib 500 mg (450 mg active moiety) once daily. The primary endpoint was objective response by independent review using RECIST v1.1. Secondary endpoints included duration of response (DOR), progression-free survival (PFS), overall survival (OS), and safety. **Results:** Of 313 pts enrolled, median age was 72 years (range 41–94) and pts received tepotinib for a mean (standard deviation [SD]) of 11.5 mos (11.6); median follow-up was 32.6 mos (range 0.3–71.9). First line (1L) pts (n=164; median age: 74 years [range 47–94]; male: 50.6%; ECOG PS 1: 72.0%; smoking history: 53.7%) received tepotinib for a mean (SD) of 12.4 mos (12.2), with 27 pts still receiving treatment. ORR was 57.3% (95% CI: 49.4, 65.0), mDOR was 46.4 mos (13.8, not estimable [ne]), mPFS was 12.6 mos (9.7, 17.7), and mOS was 21.3 mos (14.2, 25.9). Among 111 1L T+ pts, ORR was 58.6% (48.8, 67.8), mDOR was 46.4 mos (15.2, ne), mPFS was 15.9 mos (11.0, 49.7), and mOS was 29.7 mos (18.8, ne) (Table). Second-or-later line (2L+) pts (n=149; median age: 71 years [range 41–89]; male: 47.7%; ECOG PS 1: 75.8%; smoking history: 40.9%) received tepotinib for a mean (SD) of 10.5 mos (11.0), with 10 pts still receiving treatment. ORR was 45.0% (36.8, 53.3) and mDOR was 12.6 mos (9.5, 18.5). Across all 313 pts, ORR was 51.4% (45.8, 57.1), mDOR was 18.0 mos (12.4, 46.4), mPFS was 11.2 mos (9.5, 13.8), and mOS was 19.6 mos (16.2, 22.9). No new safety concerns were observed. Grade ≥3 treatment-related adverse events (TRAEs) occurred in 34.8% of pts; 14.7% of pts discontinued treatment due to TRAEs. Any grade related peripheral edema occurred in 67.1% of pts (Grade ≥3: 11.2%). **Conclusions:** The long-term outcomes of VISION demonstrate the robust and durable clinical activity of tepotinib, particularly in 1L T+ pts, and manageable safety profile, further defining its use in clinical practice. Clinical trial information: NCT02864992. Research Sponsor: The healthcare business of Merck KGaA, Darmstadt, Germany.

Efficacy	Overall N=313	1L n=164	2L+ n=149	1L T+ n=111	2L+ T+ n=97
ORR, %	51.4	57.3	45.0	46.4	49.5
(95% CI)	(45.8, 57.1)	(49.4, 65.0)	(36.8, 53.3)	(48.8, 67.8)	(39.2, 59.8)
mDOR, mos	18.0	46.4	12.6	46.4	12.4
(95% CI)	(12.4, 46.4)	(13.8, ne)	(9.5, 18.5)	(15.2, ne)	(8.3, 18.0)
mPFS, mos	11.2	12.6	11.0	15.9	11.5
(95% CI)	(9.5, 13.8)	(9.7, 17.7)	(8.2, 13.7)	(11.0, 49.7)	(8.2, 14.7)
mOS, mos	19.6	21.3	19.3	29.7	20.4
(95% CI)	(16.2, 22.9)	(14.2, 25.9)	(15.6, 22.3)	(18.8, ne)	(17.0, 25.5)

9061

Poster Session

Long-term follow-up of “adjuvant” pembrolizumab following locally ablative therapy for oligometastatic non-small cell lung cancer. *First Author: David John Cantor, University of Pennsylvania, Philadelphia, PA*

Background: Patients with oligometastatic (OM) non-small cell lung cancer (NSCLC) benefit from local ablative therapies (LAT); however, the role of adjuvant systemic therapies post LAT remains less clear. In a single-arm Phase II clinical trial (NCT02316002), we demonstrated that patients with OM NSCLC treated with adjuvant pembrolizumab following LAT had superior progression free survival (PFS) compared to historical controls. Here, we present long term follow-up on PFS and overall survival (OS). **Methods:** Patients with OM (≤ 4 metastatic sites) NSCLC treated with LAT to all sites received pembrolizumab every 21 days for up to 16 cycles from February 1, 2015 through September 30, 2017. Other key inclusion criteria included ECOG PS 0-1 and the absence of autoimmune diseases. Patients were eligible regardless of the number of prior therapies or PD-L1 status. Our study design was an intention to treat analysis with a null hypothesis that PFS would be equivalent to historical controls (6.6 months) compared with the alternative that PFS would be greater than 10 months. Assuming 42 patients enrolled over 2 years, we calculated 80% power to detect improvement in PFS with a 1-sided 5% significance level. Primary efficacy endpoint was PFS from the start of pembrolizumab and was defined as evidence of progressive disease (PD) via RECIST v1.1 criteria, death, or last contact. Secondary endpoints included OS, determined by date of death or last contact, and safety. Cox proportional hazard models were performed to assess associations between clinicopathologic features and PFS or OS. **Results:** 51 patients enrolled in the study; 45 patients (median age, 64 years [range, 46-82]; 21 [47%] women; 31 [69%] with solitary OM site) received pembrolizumab following LAT. Patients received a median of 11 cycles of pembrolizumab; 18 (40%) patients completed 16 cycles. At the data cutoff (December 1, 2022; median f/u, 65.8 months), 32 patients had PD, 19 patients died, and 13 patients had no evidence of relapse. Median PFS was 19.7 months (95% CI, 7.6-31.7 months); median OS was not reached (95% CI, NR-NR). OS rate at 5 years was 60.0% (SE, 7.4%). Upon PD, 94% of patients received salvage therapies. Median OS from the time of PD was 39.7 months (95% CI, 13.8-65.6 months). Metachronous OM disease was significantly associated with improved OS (HR, 3.2 [95% CI, 1.5-6.7] and PFS (HR, 2.9 [95% CI, 1.2-7.5]) via multivariate Cox proportional-hazard models. The number of OM sites, CNS disease, nodal stage at diagnosis, or tumor PD-L1 status was not significantly associated with PFS or OS. We did not observe new safety signals for pembrolizumab following LAT aside from those previously reported. **Conclusions:** Pembrolizumab following LAT for OM NSCLC results in promising PFS and OS compared to historical experience with a tolerable safety profile. Further investigation of this approach with a randomized trial is warranted. Clinical trial information: NCT02316002. Research Sponsor: Merck & Co.; U.S. National Institutes of Health.

9063

Poster Session

Management of patients with ALK-positive advanced non-small cell lung cancer who received brain radiotherapy on study in the phase 3 CROWN trial. *First Author: Todd Michael Bauer, Sarah Cannon Research Institute, Tennessee Oncology, Nashville, TN*

Background: Approximately 30% of patients with ALK-positive non-small cell lung cancer (NSCLC) present with brain metastases at diagnosis. Lorlatinib is a potent brain-penetrant ALK tyrosine kinase inhibitor (TKI) that showed improved time to intracranial (IC) progression compared with crizotinib in patients with and without brain metastases at baseline. This post hoc analysis from the phase 3 CROWN study summarizes the management of patients who received brain radiotherapy (RT) during the study. **Methods:** In the CROWN study, 296 patients with previously untreated ALK-positive advanced NSCLC were randomized 1:1 to receive oral lorlatinib 100 mg once daily ($n = 149$) or crizotinib 250 mg twice daily ($n = 147$). Patients who received brain RT while on study treatment or after the initiation of subsequent systemic anticancer therapy were included in this post hoc analysis. **Results:** As of September 20, 2021, at approximately 3 years of follow-up, median time to IC progression was not reached (NR; 95% CI, NR-NR) in the lorlatinib arm and was 16.6 (95% CI, 11.1-NR) months in the crizotinib arm. At the time of this analysis, 4 of 149 patients (2.7%) in the lorlatinib arm and 20 of 147 patients (13.6%) in the crizotinib arm received brain RT; study treatment was ongoing in 2 of 4 patients (50.0%) in the lorlatinib arm and discontinued in all 20 patients in the crizotinib arm. Median time from randomization to first brain RT was 18.2 (range, 6.4-31.3) months in the lorlatinib arm and 11.1 (range, 2.5-37.5) months in the crizotinib arm. In patients who had brain RT, median duration of treatment was 20.0 (IQR, 6.3-37.1) months with lorlatinib and 7.8 (IQR, 4.0-11.1) months with crizotinib. In the lorlatinib arm, 2 of 4 patients (50.0%) received concomitant brain RT and continued lorlatinib beyond progression. In the crizotinib arm, patients received brain RT while on study treatment or on subsequent systemic anticancer therapies with ALK TKIs or chemotherapy. Follow-up analysis is ongoing. **Conclusions:** At approximately 3 years of follow-up in the CROWN study, fewer patients in the lorlatinib arm received brain RT than those in the crizotinib arm. At the time of this analysis, study treatment was ongoing in 2 of 4 patients (50.0%) in the lorlatinib arm but was discontinued in all patients in the crizotinib arm. Patients were mostly managed with other ALK TKIs and/or chemotherapy following brain RT in the crizotinib arm. ClinicalTrials.gov: NCT03052608. Clinical trial information: NCT03052608. Research Sponsor: Pfizer.

9062

Poster Session

Mechanisms of resistance to tyrosine kinase inhibitor treatments in patients with ROS1 fusion-positive non-small cell lung cancer. *First Author: Jialei Wang, Department of Thoracic Medical Oncology, Fudan University Shanghai Cancer Center, Shanghai, China*

Background: ROS1 rearrangement was found in about 1% non-small cell lung cancer (NSCLC), and the fusion proteins created during this process will result in the successive activation of the ROS1 kinase domain. NSCLC patients with ROS1 gene fusions were considered a unique subtype highly sensitive to related tyrosine kinase inhibitor (TKI) treatments. However, the acquired TKI resistance was the major hurdle preventing patients from getting prolonged treatment benefits. **Methods:** 107 patients diagnosed with advanced or metastatic NSCLC harboring ROS1 fusion were retrospectively recruited. All patients were treated with crizotinib as first-line treatment, and 21 patients received lorlatinib after crizotinib progression. Samples were collected at baseline, after crizotinib progression, and after lorlatinib progression, which all underwent targeted DNA sequencing. TKIs binding to mutated ROS1 fusion proteins was simulated using molecular dynamics simulations. **Results:** The most witnessed fusion partner of ROS1 was CD74 (58%), followed by SDC4 (14%), EZR (11%), and SLC34A2 (9%). The median progression-free survival was 12.9 months for crizotinib and 6.4 months for lorlatinib. Patients with CD74-ROS1 and SLC34A2-ROS1 had significantly longer PFS than those with other ROS1 fusion types when treated with crizotinib. Patients with baseline TP53 mutations showed worse PFS compared to TP53 wild-type (WT) patients ($P < 0.001$, HR: 0.19, 95%CI: 0.09-0.39) under crizotinib treatment. An accumulation of both on-target (baseline vs. post-crizotinib vs. post-lorlatinib: 0% vs. 43% vs. 62%) and off-target resistant mutations (baseline vs. post-crizotinib vs. post-lorlatinib: 22% vs. 26% vs. 43%) after multiple TKI treatments was observed. A total of ten on-target resistance mutations were detected after TKI therapies, with 4 first-reported mutations (ROS1 L2010M, G1957A, D1988N, L1982V). According to the molecular dynamics simulation results, ROS1 L2010M mutations (happening in the ROS1 kinase ATP binding cassette) maybe resistant to lorlatinib, entrectinib, cabozantinib, and crizotinib. ROS1 G1957A may lead to resistance to cabozantinib. Moreover, all four novel on-target mutations may lead to resistance to crizotinib. **Conclusions:** In summary, CD74- and SLC34A2-ROS1 patients showed better crizotinib efficacy with different resistance mutation patterns. Patients of these subtypes are potential beneficiaries of molecular testing after crizotinib progression, directing future treatment strategies. Multiple TKI treatments may lead to the accumulation of both on-target and off-target resistance mutations. In addition, 4 novel ROS1 on-target mutations identified underwent molecular dynamics simulations, unveiling potential resistance to different TKIs, which can provide vital information for future ROS1 fusion-positive NSCLC patient treatment selections. Research Sponsor: None.

9064

Poster Session

Emerging phase 1 data of BLU-451 in advanced NSCLC with EGFR exon 20 insertions. *First Author: Danny Nguyen, City of Hope- Long Beach Elm, Long Beach, CA*

Background: In patients (pts) with NSCLC harboring *EGFR* exon 20 insertions (ex20ins), treatment options are limited, with platinum-based chemotherapy with/without programmed death-ligand 1 inhibitors being the standard of care in first line, and recent accelerated approvals of mobocertinib and amivantamab in the USA for second-line treatment. These second-line therapies have overall response rates of 28% and 40%, respectively, limited CNS activity, and are associated with AEs such as severe gastrointestinal AEs and edema. BLU-451 is an investigational, CNS-penetrant, potent, selective, and wild-type sparing *EGFR* tyrosine kinase inhibitor that is under investigation in the ongoing phase 1/2 CONCERTO trial (NCT05241873), including in pts with ex20ins. **Methods:** In phase 1 dose escalation using a 3+3 design, BLU-451 monotherapy was administered orally QD or BID and given in continuous 21-day cycles. The primary objectives include maximum tolerated dose (MTD) and/or recommended phase 2 dose (RP2D) determinations and safety. Key secondary objectives include antitumor activity, PK, and pharmacodynamics. Pts with *EGFR* ex20ins-positive NSCLC after prior platinum-based chemotherapy were enrolled. Prior ex20ins-targeted therapy and asymptomatic CNS disease were permitted. Tumor response was assessed per RECIST v1.1. Serial blood samples for analysis of BLU-451 PK and circulating tumor DNA (ctDNA) were collected. **Results:** As of Jan 20, 2023, 28 pts have been enrolled and dosed in 5 cohorts (100 mg–400 mg QD and 200 mg BID), including 19 (68%) pts with exon 20 insertions. The median number of prior systemic lines of therapy was 2.5 (range, 1–10), and 19/28 (68%) pts had prior ex20ins-targeted agents. The most common AEs were diarrhea (21%), cough (18%), fatigue (14%), pruritis (14%) and rash (14%); all were Grade 1 or 2. There were no dose-limiting toxicities. Partial responses, including a disappearance of a CNS target lesion, were seen, and early evidence of on-target activity with ctDNA reductions was observed. **Conclusions:** As of the data cutoff, BLU-451 monotherapy was generally well tolerated, with early evidence of clinical activity in heavily pretreated pts with *EGFR* ex20ins-positive NSCLC. Early data at initial dose levels consisted of tumor reduction including responses, CNS activity, and ctDNA responses. The dose escalation is ongoing to determine the MTD and/or RP2D. Clinical trial information: NCT05241873. Research Sponsor: Blueprint Medicines.

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Poster Session

First results from the RETgistry: A global consortium for the study of resistance to RET inhibition in *RET*-altered solid tumors. *First Author: Alissa Jamie Cooper, Massachusetts General Hospital, Boston, MA*

Background: Rearranged during transfection (*RET*) gene alterations are the oncogenic driver in diverse tumor types, including *RET* fusions identified in 1-2% of non-small cell lung cancers (NSCLC). While *RET*-selective tyrosine kinase inhibitors (TKIs) selpercatinib and pralsetinib are effective, acquired drug resistance remains a challenge. Here, we report the initial results from the RETgistry, an international consortium aimed at elucidating mechanisms of resistance to *RET* TKIs across *RET*-altered solid tumors. **Methods:** This was a retrospective analysis performed across 16 institutions. Patients (pts) were eligible if they had advanced solid tumor harboring an oncogenic *RET* alteration, received ≥ 1 *RET* TKI with disease progression, and underwent resistant tumor or liquid biopsy for next-generation sequencing (NGS). **Results:** A total of 103 time-distinct biopsies (62 tissue, 30 plasma, 11 paired tissue/plasma) were included in analysis, obtained from 88 pts with progression on a *RET*-selective TKI [selpercatinib (n = 70), pralsetinib (n = 14), selpercatinib and pralsetinib sequentially (n = 4)]. Pts had the following tumor types: 72 NSCLC (69% *KIF5B-RET*, 21% *CCDC6-RET*, 10% other *RET* fusion), 13 medullary thyroid cancer (TC) (54% *RET* M918T, 46% other *RET* mutation), and 2 papillary and 1 anaplastic TC (all, *RET* fusion). Median age was 58 (range, 21-86); 48% were male with 89% never/light smokers. Median duration of *RET* TKI preceding biopsies [first-line, n = 32 (31%); second-line, n = 42 (41%); third-/greater-line, n = 29 (28%)] was 16.5 months (mos) (95% CI, 14.0-19.6); median PFS was 14.1 mos (95% CI, 9.3-17.0). Resistant biopsies were obtained at median 15.0 mos from TKI initiation (range, 1.8-58.8). Acquired *RET* mutations were detected in 14 (14%), most common being G810 substitutions in 12 (12%). Potential off-target resistance gene alterations identified in 43 cases (42%) included *MET* amplification (14%), *BRAF* V600E or fusion (2%), *KRAS* gain or mutation (5%), *ERBB2* amplification (2%), *EGFR* amplification (3%), *ROS1* fusion (1%), and activating *PIK3CA* mutation or *PTEN* loss (4%). No resistant lung cancer biopsy demonstrated small cell transformation. The duration of TKI therapy (HR 0.64, p = 0.11) or PFS (HR 0.75, p = 0.33) did not differ according to the presence of on-target vs off-target resistance. NGS analyses of pre-*RET*-selective TKI tumors (n = 92) revealed frequent co-occurring alterations in *TP53* (29%) and *CDKN2A/B* (12%). **Conclusions:** On-target resistance to *RET* inhibition due to acquired *RET* mutations was less common than off-target resistance, identified in 14%. The majority of *RET* TKI resistance is mediated by off-target mechanisms such as bypass receptor tyrosine kinase activation. Further studies are warranted to enable the development of therapeutic strategies to address resistance in pts with *RET*-altered tumors. The RETgistry accrual and data analyses continue. Research Sponsor: Happy Lungs.

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Poster Session

Sex differences in prognostic utility of peripheral eosinophil count in first-line immune checkpoint therapy against metastatic NSCLC. *First Author: Hyunwoo Kwon, Ohio State University Comprehensive Cancer Center, Columbus, OH*

Background: To date, few studies have associated elevated Absolute Eosinophil Count (AEC) with improved outcome to a single agent immune checkpoint inhibitor (ICI) as first or subsequent line of therapy in patients with NSCLC. Here, we investigated prognostic utility of AEC and the sex difference in patients undergoing standard-of-care first-line ICI with or without chemotherapy for metastatic NSCLC. **Methods:** This was a retrospective cohort study of 310 patients with Stage IV NSCLC treated with first-line ICI-based therapies (alone or in combination with chemotherapy) under IRB approved protocol 2021C0069. Demographic data are summarized in the table. Peripheral AEC measured by cells/microL was collected within 1 week before the start of therapy. Eosinophil count was evaluated in males and females by both descriptive statistics and Chi-squared test as a continuous and categorical variable, respectively. High level of baseline AEC was defined as 75th percentile (270 cells/microL). Overall Survival (OS) was plotted using the Kaplan-Meier method and p-values from log-rank test were reported. PD-L1 was assessed by tumor proportion score (TPS) and classified into < 1%, 1 to 49% and $\geq 50\%$. **Results:** 14% male vs 6% female patients were found to have peripheral eosinophilia (AEC ≥ 500) at the start of immunotherapy, p = 0.02. Patients with lower AEC had a median OS of 18.6 months vs 29.3 months in those with higher AEC (p = 0.02, HR: 1.465, 95% CI: 1.073-2.001). Patients with higher baseline AEC showed a sex difference, with median OS of 23.9 months in males vs 19.4 months in females with over 60% survival at the time of last follow up (p = 0.04, HR: 1.934, 95% CI: 1.040-3.597). This difference was seen with ICI monotherapy (p = 0.02, HR: 2.630, 95% CI: 1.192-5.805), but not ICI with chemotherapy (p = 0.83, HR: 1.116, 95% CI: 0.4054-3.070). Higher AEC was associated with TPS $\geq 50\%$ in both males and females (p = 0.004 and 0.001, respectively), though no significant sex difference was observed. **Conclusions:** Our data highlight critical sex differences in interpretation of baseline AEC in patients on ICI therapy for metastatic NSCLC. While males have a higher frequency of peripheral eosinophilia, higher AEC correlates to improved OS predominantly in females. Further, this female-biased outcome is seen only with ICI monotherapy, even though higher AEC is associated with high PD-L1 expression in both sexes. Future studies are indicated to assess the longitudinal trend in eosinophil count as well as their active versus passive role in anti-tumor immunity and toxicity in the presence or absence of chemotherapy. Research Sponsor: REDCap project (National Center for Advancing Translational Sciences, Grant UL1TR001070); Corresponding author Dr. Owen is supported by a LUNGevity Career Development Award.

Demographic summary.		
	Male	Female
Sex	55%	45%
Age		
Median (range), in years	66 (39-89)	64 (31-95)
ECOG		
0	20%	22%
1	53%	50%
≥ 2	27%	28%
Histology		
Squamous	25%	12%
Non-squamous	75%	88%
PD-L1 TPS		
< 1%	29%	41%
1-49%	26%	21%
$\geq 50\%$	45%	38%
Treatment		
ICI monotherapy	47%	37%
ICI with chemotherapy	53%	63%

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Poster Session

Efficacy and safety of PD-1/PD-L1 inhibitor plus platinum-based chemotherapy vs. platinum-based chemotherapy alone in patients with previously untreated advanced large-cell neuroendocrine cancer of the lung. *First Author: Fengchun Mu, Department of Radiation Oncology, Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, Jinan, China*

Background: Large-cell neuroendocrine carcinoma (LCNEC) is a rare tumor with a poor prognosis and limited treatment options. The efficacy of first-line therapies for LCNEC has not yet been established. This study evaluated the efficacy and safety of the combination of PD-1/PD-L1 inhibitor and platinum-based chemotherapy in treatment-naïve patients with advanced LCNEC. **Methods:** We retrospectively analyzed patients with advanced LCNEC who were treated with a PD-1/PD-L1 inhibitor plus platinum-based chemotherapy (PD-1/PD-L1 inhibitor group) or with platinum-based chemotherapy alone (chemotherapy group) based on data obtained from electronic databases of three participating cancer centers from January 2015 to August 2022. Progression-free survival (PFS), overall survival (OS), objective response rate (ORR), and disease control rate (DCR) were evaluated for each group. Safety was assessed in all patients who received at least one dose of their assigned treatment. **Results:** Among the 75 enrolled patients, 25 were allocated to receive PD-1/PD-L1 inhibitor plus platinum-based chemotherapy and 50 were allocated to receive platinum-based chemotherapy alone (patients were matched 1:2 on baseline characteristics). The median PFS was 15.1 months (95% confidence interval [CI], 7.1–23.2) in the PD-1/PD-L1 inhibitor group and 5.3 months (95% CI, 4.4–6.2) in the chemotherapy group (hazard ratio [HR], 0.26; 95% CI, 0.113–0.428; p < 0.0001). The 12-month OS was 88.0% (95% CI, 67.7–96.9) in the PD-1/PD-L1 inhibitor group and 56.0% (95% CI, 41.4–69.7) in the chemotherapy group (p = 0.0056). The ORRs in the two groups were 40% and 16%, respectively (p = 0.022), and the DCRs were 96% and 70%, respectively (p = 0.010). Regarding safety, the most common incidences of grade ≥ 3 adverse events involved neutropenia, leukopenia, anemia, and fatigue. There were no significant differences between the two groups. Immune-related adverse events (irAEs) in the PD-1/PD-L1 inhibitor group included cutaneous hemangiomas, hypothyroidism, anaphylaxis, and pneumonitis. Grade 3 or 4 irAEs were not observed. No new safety signals were noted. **Conclusions:** First-line PD-1/PD-L1 inhibitor plus platinum-based chemotherapy significantly improved PFS in patients with advanced LCNEC compared with platinum-based chemotherapy alone. Research Sponsor: None.

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Poster Session

Nivolumab (Nivo) plus ipilimumab (Ipi) 6-month treatment versus continuation in patients with advanced non-small-cell-lung cancer (aNSCLC): 3-year results of the IFCT-1701 DICIPLE phase 3 trial. *First Author: Gerard Zalcman, Université Paris Cité, Thoracic Oncology Department & CIC Inserm 1425, Hôpital Bichat Claude Bernard, AP-HP, Nord, Paris, France*

Background: 1st-line immunotherapy (io) is a standard treatment for patients (pts) with advanced NSCLC devoid of targetable mutation. Classical 2-year io duration does not rely on indubitable evidence. We aimed to assess whether 6-month nivo/ipi was equivalent to continuation until progression or unacceptable toxicity in pts with disease control (DC). **Methods:** In this multicenter non-inferiority randomized phase 3 trial, eligible treatment-naïve pts, age > 18 , PS 0-1, had stage IV NSCLC and measurable disease. They received Nivo 3 mg/kg q2w plus Ipi 1 mg/kg q6w, until progression or unacceptable toxicity for a maximum of 6-month induction treatment. At 6 months, pts with DC and no severe TRAEs were randomized (1:1) into io continuation (arm A), and observation (arm B). At progression, arm A pts received an investigator's choice 2nd line platinum-based chemo, while arm B pts resumed double io. Primary endpoint was progression-free survival (PFS). 450 pts x 2 were to be randomized, to achieve 80% power, with 0.025 one-sided α error. Observing that European filing for the io combo was not submitted, the trial's steering committee recommended to stop the accrual on Jan. 2021. **Results:** From May. 2018 to Jan. 2021, 265 pts (70.6% male, 62.7yr median age, 59% stage IVB, 22.3% SCC, 9.9% PDL1 $\geq 50\%$, 12.2% PDL1 $< 1\%$) were accrued. 138 (72.6%) pts had disease progression before 6 months, 11 died (5.8%), 30 (15.8%) experienced TRAEs contra-indicating continuation, 11 (5.8%) were deemed ineligible for randomization. 71 pts with DC were randomized. With a median follow-up from randomization of 29.9 months, median PFS was 20.5 (7.4-36.7) months in arm A, 35.2 (21.4-NR) in arm B. 12-month PFS was 55.6% (38.0-69.9) and 81.2% (62.9-91.1), respectively (p=0.08). Adj.HR (arm B vs. arm A) was 0.66, 95%CI (0.28-1.31), p=0.23. OS data, yet immature, did not show any significant difference between both arms (adj.HR arm B vs. A: 0.54 95%CI (0.20-1.49), p=0.23). From randomization, 28.6% G3-5 TRAEs in arm A were observed vs. 2.9% in arm B (p=0.005). **Conclusions:** The 6-month i.o. interruption for NSCLC patients with DC did not yield significant PFS or OS differences in this prematurely halted trial. Updated OS with a 3-year follow-up, quality of life and biomarker data, will be presented at the meeting. Clinical trial information: NCT03469960. Research Sponsor: BMS; IFCT.

Spectrum of acquired *KRAS* mutations in driver mutation-positive non-small cell lung cancer. *First Author: Joshua E. Reuss, Lombardi Comprehensive Cancer Center, Georgetown University, Washington, DC*

Background: With the emergence of effective targeted-therapies for *KRAS* G12C, and the development of promising agents for *KRAS* G12V and G12D among others, the identity of unique *KRAS* mutations in non-small cell lung cancer (NSCLC) has become increasingly relevant. Acquired *KRAS* mutations are a known mechanism of resistance observed across driver mutation-positive (DM+) NSCLC. The incidence and diversity of these acquired alterations, and whether they differ from those observed in *de novo* *KRAS*-mutated NSCLC, is unknown. **Methods:** NSCLC molecular profiles were obtained using next-generation sequencing (Caris Life Sciences) with paired whole-transcriptomic sequencing (Illumina NovaSeq) and immunohistochemistry (Caris Life Sciences). Demographic data were abstracted from medical records. *KRAS* mutation diversity was defined for *de novo* *KRAS*-mutated (*KRASmt*) NSCLC (*KRAS* as only identified driver – *KRASmt_dn*) and DM+ NSCLC with acquired *KRAS* mutations (concurrent *KRASmt* with other known driver – *KRASmt_acq*). Fisher's exact test was used to compare the distribution of unique *KRAS* mutations between the groups. Due to the unique biology of NSCLC with class II/III *BRAF* mutations, this subset was removed from the *KRASmt_acq* subgroup for the final analysis. **Results:** A total of 5932 *KRASmt* NSCLC samples were identified, among which 5879 were *KRASmt_dn* and 53 were *KRASmt_acq* (see table). The distribution of unique *KRAS* mutations was not significantly different between groups ($p = 0.14$). Within the *KRASmt_dn* group, *KRAS* G12C was most common (40%), followed by G12V (19%), G12D (14%), G12A (7%) and Q61H/G13C (4% each). In the *KRASmt_acq* group, *KRAS* G12C was most common (30%), followed by G12D (19%), G12V (17%), Q61H (11%), G12A (7%), and G13C (6%). The most common observed driver mutations in the *KRASmt_acq* group were *EGFR* (38%) and *MET* (30%). In the *EGFR* group, *KRAS* G12D (25%), Q61H/G12C (20% each), G12V/G13C (10% each), and G12F/A/R (5% each) were observed. In the *MET* group, *KRAS* G12C (25%), G12D/N/A (19% each), Q61H (12%) and G12S (6%) were seen. Among 7 patients with a documented history of smoking in the *KRASmt_acq* group, *KRAS* G12D and Q61H were most common (29% each), followed by G12V/F and G13C (14% each). **Conclusions:** While the distribution of unique *KRAS* mutations did not differ significantly between *KRASmt_dn* and *KRASmt_acq* groups, acquired *KRAS* mutations were seen across DM+ NSCLC subsets, among which the frequency of observed mutations appeared to vary. The functional and immunological significance of these mutations, and their impact on clinical outcomes, warrants further investigation. Research Sponsor: None.

	<i>KRASmt</i> _dn	<i>KRASmt</i> _acq	<i>EGFR</i>	<i>MET</i>	<i>ALK</i>	<i>HER2</i>	<i>ROS1</i>	<i>BRAF</i> Class 1
# of pts	5879	53	20	16	7	6	1	3
G12C	40%	30%	20%	25%	57%	50%	100%	-
G12D	14%	19%	25%	19%	-	33%	-	-
G12V	19%	17%	10%	19%	29%	-	-	67%
G12A	7%	7%	5%	19%	-	-	-	-
Q61H	4%	11%	20%	12%	-	-	-	-
G13C	4%	6%	10%	-	-	-	-	33%
G12F	2%	2%	5%	-	-	-	-	-
G12R	1%	2%	5%	-	-	-	-	-
G12S	2%	4%	-	6%	-	17%	-	-
Other	7%	2%	-	-	14%	-	-	-

Sexual dysfunction in women with lung cancer: Updates from the SHAWL study. *First Author: Narjst Florez, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA*

Background: Despite its direct correlation with quality of life, sexual dysfunction is under-discussed and underreported in patients with lung cancer (LC). Sexual dysfunction is highly prevalent in patients with LC, with issues persisting over time; however, most data precede the approval of targeted therapies and immune checkpoint inhibitors. We report updated data from the SHAWL study, focusing on women's sex life satisfaction. **Methods:** This cross-sectional, international survey study was administered via the G02 Foundation Lung Cancer Registry. We utilized the Patient-Reported Outcomes Measurement Information System (PROMIS) Sexual Function and Satisfaction Measures for data collection. Participants were recruited from June 2020 to June 2021. Eligibility criteria included age > 18 years, self-identification as a woman, and an LC diagnosis within ten years. Participants were asked about sexual health pertaining to 30 days before survey completion, now referred to as "recent." **Results:** The survey was administered to 249 women (median age: 61 years). Most (67%) had stage IV LC and 47% were receiving targeted therapy; 66% were undergoing active treatment. Before LC diagnosis, 49% (117) of participants reported having no sexual health issues. Most women (54%, 128) indicated having had recent sexual activity, though 77% (183) reported moderate to severe sexual dysfunction. Indeed, only 7.5% (18) reported being quite or very interested in sexual activity, and only 6.7% (16) felt as if they always or often wanted to be involved in it. Out of the 128 women indicating recent sexual activity, the vast majority (72%, 91) also reported minimal to no satisfaction with their sex life, with 17% (22), 31% (39), and 24% (30) reporting none, a little bit, and some satisfaction, respectively. The most common reasons for lack of recent sexual activity were lack of interest (68%, 76) or vaginal dryness or pain (30%, 33). Most women (69%, 88) also reported rarely becoming sufficiently lubricated during sexual activity, with 54% (68) indicating that it was difficult to impossible to do so. Patients with stage IV diagnosis had a lower interest in and desire for sexual activity than those with non-metastatic LC. Patients not receiving active treatment reported similar rates of lack of interest and desire for sexual activity as those in active cancer therapy. Patients on targeted therapy had similar rates of sexual dysfunction as those receiving other LC treatments. **Conclusions:** The SHAWL study is the largest study evaluating sexual dysfunction and satisfaction in women with lung cancer in our current clinical environment. Sexual dysfunction, dissatisfaction, and lack of interest in sexual activity were highly prevalent in women with LC regardless of treatment status and type of therapy, suggesting that even after treatment completion, sexual issues persist. Sexual health should be integrated into thoracic oncology care for all patients with lung cancer. Research Sponsor: G02 Foundation for Lung Cancer and University of Wisconsin Carbone Cancer Center.

Patients with *EGFR* mutant (m) MET-altered NSCLC receiving tepotinib with an *EGFR* tyrosine kinase inhibitor (TKI): A case series. *First Author: Xiuning Le, Department of Thoracic Head and Neck Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Oncogenic activation of MET is a common mechanism of acquired resistance to *EGFR* TKIs in patients (pts) with *EGFRm* NSCLC, with *MET* amplification (amp) constituting the most frequent cause of bypass pathway activation. Currently, there are no approved targeted treatment options for these pts. Data from the Phase II INSIGHT (NCT01982955) and INSIGHT 2 (NCT03940703) studies indicate the combination of the selective MET TKI tepotinib plus an *EGFR* TKI has encouraging activity. We present a case series of pts with *EGFRm* MET-altered NSCLC receiving tepotinib plus an *EGFR* TKI outside of clinical trials. **Methods:** Access to tepotinib was provided to pts with *EGFRm* MET-altered NSCLC and resistance to *EGFR* TKIs through unsolicited compassionate use requests. All pts received tepotinib (500 mg [450 mg active moiety] once daily; first dose by Oct 2022) plus an *EGFR* TKI. Participating physicians provided case information up to January 2023. **Results:** 28 cases of pts with *EGFRm* NSCLC and MET alterations who received tepotinib plus an *EGFR* TKI were collated. 21 pts had *METamp* after *EGFR* TKI treatment, 5 had MET overexpression, and 2 had *MET* exon 14 skipping. Pts were aged 41–86 years, 15 were Asian, 13 were white, 19 were female, 8 had smoking history, and all had adenocarcinoma histology. *METamp* was detected by tissue biopsy in 17 pts, and liquid biopsy in 4 pts. Of 12 pts with *METamp* detected by FISH, gene copy number ranged from 5.3–33.4, and *MET:CEP7* ratio from 0.7–15.1. *EGFR* TKIs received in combination with tepotinib were osimertinib ($n = 21$, 19 of whom received prior osimertinib), gefitinib ($n = 6$), dacomitinib ($n = 1$), afatinib ($n = 1$), with 1 pt received gefitinib followed by osimertinib. Tepotinib plus *EGFR* TKI was received by 9 pts as second-line, 9 as third-line, and 10 as fourth-or-later line. Median treatment duration was 8.8 months (range 1.3–20.6), with treatment ongoing in 13 pts (10 with current duration ≥ 10 months). Per the physician's assessment, 25/28 pts (89%) had clinical benefit, 16 of whom (57%) were considered to have a partial response (PR). Clinical benefit was reported in 18/21 (86%) pts with *METamp* (12 PR, 57%), in 5/5 with MET overexpression (2 PR), and 2/2 with *MET* exon 14 skipping (2 PR). The most reported adverse event (AE) considered related to tepotinib was edema in 15 pts (most commonly peripheral edema). Grade 3 AEs related to tepotinib were reported in 5 pts (including Grade 3 edema in 2 pts), 1 of whom discontinued the combination due to Grade 3 pneumonitis. **Conclusions:** Tepotinib plus an *EGFR* TKI showed promising clinical activity in pts with MET-altered NSCLC who have progressed on a previous *EGFR* TKI, including those with several lines of prior treatment. Clinical benefit was observed irrespective of MET alteration type in this case series of pts treated outside of clinical trials, with a large proportion of patients continuing to benefit from ongoing treatment. Research Sponsor: The healthcare business of Merck KGaA, Darmstadt, Germany.

Outcomes of patients with advanced *EGFR* mutant lung cancer treated with first line (1L) osimertinib (osi) who would not have met eligibility criteria for the FLAURA trial. *First Author: Connor Wells, BC Cancer Agency, Vancouver, BC, Canada*

Background: Osi is a 1L therapy for *EGFR* mutant lung cancer based on the results of the FLAURA clinical trial. Patients on clinical trial are typically highly selected and the overall effectiveness of therapies may be lower in the real-world setting. We report the real-world outcomes of patients treated with first line osi and compare the outcomes of trial eligible and ineligible patients. **Methods:** Pharmacy records from January 2020 to October 2022 were used to retrospectively identify patients who received 1L osi for advanced *EGFR* mutant (exon 19 del. or exon 21 L858R) lung cancer in British Columbia, Canada. Patients were deemed ineligible for the FLAURA trial if they met one of five criteria: ECOG ≥ 2 , unstable brain metastases (symptomatic or on steroids), hemoglobin < 90 , platelet < 100 , or creatinine clearance < 50 . Comparisons of overall survival (OS) and time to treatment discontinuation (TTD) were made between using Kaplan-Meier survival curves and log-rank testing. Hazard ratios (HR) are reported using Cox regression adjusting for baseline factors (Table). **Results:** Of 312 patients included, 133 (43%) were considered FLAURA-ineligible. Reasons for ineligibility were poor ECOG ($n = 120$ [including ECOG 2=69, ECOG 3=48, and ECOG 4=4]), unstable brain metastases ($n = 21$), anemia ($n = 7$), thrombocytopenia ($n = 5$), and low creatinine clearance ($n = 9$). Median follow up was 22.7 months. At the time of analysis, 103/133 (77%) of ineligible patients had discontinued osi and 87/133 (65%) had died. 82/179 (45%) of eligible patients had discontinued osi and 53/179 (30%) were deceased. The median TTD in the ineligible group was 11.9 months (95% CI 10.5–15.5) vs 26.9 months (95% CI 21.9–34.6) in the eligible group ($p < 0.001$), HR 2.1 (95% CI 1.5–2.9, $p < 0.001$). The median OS in the ineligible group was 15.8 months (95% CI 12.4 to 21.1) vs NR [not reached] (95% CI 28.5 to NR) in the eligible group ($p < 0.001$), HR 2.6 (95% CI 1.8–3.7, $p < 0.001$). Rates of dose reduction for toxicity were similar between ineligible (25%) and eligible (19%) patients ($p = 0.25$). Second-line therapy was received by 28/102 (27%) of trial ineligible patients and 46/82 (56%) of trial eligible patients. **Conclusions:** Over 40% of the real-world population receiving 1L osi would have been ineligible for the FLAURA clinical trial. These patients had significantly inferior outcomes. This study provides benchmark data to better inform patient prognosis using real-world data. Research Sponsor: None.

	Trial Ineligible (n= 133)	Trial Eligible (n= 179)
Age (mean, years; range)	69 (37-92)	68 (33-95)
Male	52/133 (39%)	57/179 (31%)
Asian Ethnicity	61/133 (46%)	86/179 (48%)
Exon 19 mutation	65/133 (49%)	105/179 (59%)
Smoking History	50/133 (38%)	53/177 (30%)
De novo stage IV	113/133 (85%)	123/179 (69%)
Asymptomatic Brain Metastases	34/133 (26%)	34/179 (19%)
Lactate dehydrogenase elevated	46/132 (35%)	35/177 (20%)

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Poster Session

Efficacy and safety of sunvozertinib in treatment naïve NSCLC patients with EGFR exon20 insertion mutations. *First Author: Yan Xu, Department of Respiratory and Critical Care Medicine, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China*

Background: Sunvozertinib (DZD9008) is a rationally designed, irreversible EGFR inhibitor targeting *EGFR* mutations with wild-type EGFR selectivity. Two pivotal second line studies (WU-KONG1 [NCT03974022] and WU-KONG6 [NCT05712902 and CTR20211009]) are ongoing in NSCLC patients with *EGFR* exon20 insertion mutations (exon20ins). Primary analysis of WU-KONG6 study demonstrated promising efficacy and safety of sunvozertinib in ≥ second line setting. Herein, we reported preliminary results of sunvozertinib in the first line setting. **Methods:** Two ongoing studies WU-KONG1 and WU-KONG15 (NCT05559645) enrolled treatment naïve advanced NSCLC patients with *EGFR* exon20ins. WU-KONG1 is a multinational phase I/II study, and WU-KONG15 is an investigator-initiated phase II study in China. *EGFR* mutation status was confirmed by local or central testing using tissue or cytological samples. Sunvozertinib was administered orally until disease progression or other discontinuation criteria were met. Patients who had at least one post-treatment RECIST assessment by investigators were evaluable for efficacy analysis, and all patients who received at least one dose of sunvozertinib were included in the safety analysis. **Results:** As of January 15, 2023, a total of 36 treatment naïve advanced NSCLC patients with *EGFR* exon20ins received sunvozertinib daily dosing at RP2Ds. Median age was 66.5 years, and 63.9% (23/36) were female. The baseline ECOG PS was 0 or 1. Majority of patients (33/36, 91.7%) had metastatic diseases at study entry, with 22.2% (8/36) having > 3 metastatic sites and 22.2% (8/36) having baseline brain metastasis (BM). The most frequent mutation subtypes included 769_ASV (13/36, 36.1%), 770_SVD (2/36, 5.6%) and others (21/36, 58.3%). In 26 efficacy-evaluable patients, 19 patients showed tumor response, with a best objective response rate of 73.1%, among them 14 patients had confirmed response, and another 3 patients were still on treatment and pending confirmation. In patients with BM, tumor response was also observed intracranially. Median duration of response had not been reached by the data cut-off date. Safety findings were consistent with what was observed in previous studies of sunvozertinib. The most common treatment emergent adverse events (TEAEs) included diarrhea, CPK increase, and skin rash. The majority of adverse events were CTCAE grade 1 or 2 and manageable with supportive measures. **Conclusions:** Consistent with second line results, sunvozertinib demonstrated promising efficacy and safety profile as monotherapy in the first line setting for patients with advanced *EGFR* exon20ins NSCLC. The updated data will be presented at the conference. A phase III, multinational, randomized study (WU-KONG28, NCT05668988) is ongoing to compare sunvozertinib to chemotherapy as first line treatment for *EGFR* exon20ins NSCLC. Clinical trial information: NCT03974022, NCT05559645. Research Sponsor: Dical Pharmaceutical.

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Poster Session

Circulating tumor DNA (ctDNA) monitoring to inform maintenance outcomes in patients (pts) with advanced NSCLC treated with induction atezolizumab+carboplatin+nab-paclitaxel (A+CnP). *First Author: Bruna Pellini, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL*

Background: Chemoimmunotherapy (ChemoIO) is a prevalent first-line treatment for advanced NSCLC without driver mutations, with maintenance therapy recommended after induction. However, real-world data suggests variability in maintenance therapy's timing, intensity, and duration. Motivated by evidence that ctDNA monitoring can predict outcomes in pts receiving IO for advanced cancers, we hypothesized ctDNA monitoring could inform outcomes in advanced NSCLC prior to the start of maintenance therapy. **Methods:** This retrospective study included 98 pts from a completed phase III trial of A+CnP in squamous NSCLC (IMPower131; G029437). Pts were treated with 4 or 6 cycles of induction A+CnP followed by maintenance atezolizumab. ctDNA monitoring utilized FoundationOneTracker, involving 1) comprehensive genomic profiling of pretreatment tumor tissue, 2) variant selection using an algorithm to filter out non-tumor variants, and 3) multiplex PCR of up to 16 variants to detect ctDNA and quantify plasma mean tumor molecules per mL (MTM/mL). Progression free-survival (PFS) and overall survival (OS) were estimated with Kaplan-Meier analysis and hazard ratios (HR) were calculated using multivariate Cox proportional hazard models adjusting for age, smoking history, PD-L1, and performance status. PFS and OS analyses were landmarked from C4D1 unless otherwise stated; pts with progression/death before the landmark date were excluded. **Results:** TP53 (91%), CDKN2A (41%) and PIK3CA (32%) were frequently altered in baseline tissue; 51% had TMB ≥10 mut/Mb. A median of 10 variants (range 2-16) were tracked per pt. ctDNA was detected (ctDNA+) in 43% of C4D1 samples (median 15.2 MTM/mL, range 0.3-787.3). ctDNA+ at C4D1 was associated with a lower objective response rate (41%) compared to undetectable ctDNA (ctDNA-, 77%, p < 0.001). Pts with ctDNA- at C4D1 (56/96) had better PFS than their ctDNA+ counterparts (median PFS from C4D1 7.7 vs 2.8 months; HR: 3.07 [1.88-5.02]). Median OS from C4D1 was not reached for ctDNA- pts and was 8.3 months for ctDNA+ pts (HR: 4.31 [2.31-8.06]). In a C6D1 landmark analysis of 34 pts who were ctDNA+ at C4D1, prolonged induction (6 cycles vs 4 cycles) was not associated with any improvement in PFS (1.6 vs 2.2 months, HR 1.41 [0.58-3.39]) or OS (4.7 vs 9.8 months, HR 1.84 [0.71-4.76]). Additional analysis of plasma samples at baseline and on-treatment time points is ongoing. **Conclusions:** On-treatment ctDNA monitoring during induction chemoIO can inform outcome on subsequent maintenance therapy in pts with advanced NSCLC. For pts with ctDNA+, prolonged induction chemoIO was not associated with improved outcomes. ctDNA testing during induction chemoIO may offer an opportunity to identify pts at higher risk for disease progression and inform selection for novel personalized maintenance treatment strategies. Research Sponsor: Foundation Medicine Inc.; Genentech; Natera.

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Poster Session

Detection of MET amplification (METamp) in patients with EGFR mutant (m) NSCLC after first-line (1L) osimertinib. *First Author: Helena Alexandra Yu, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: METamp is a common resistance mechanism to osimertinib in patients with EGFRm NSCLC and is associated with sensitivity to MET TKIs. Reported METamp rates vary considerably depending on the type of biopsy and assay used. Here, we report a large comprehensive analysis of METamp detected by TBx FISH (FISH+) and/or LBx NGS (L+) after 1L osimertinib. **Methods:** During prescreening of the INSIGHT 2 study (NCT03940703) of tepotinib + osimertinib in post 1L osimertinib patients (pts) with EGFRm NSCLC, METamp was centrally assessed by TBx FISH (METGCN ≥5 and/or MET/CEP7 ≥2) and/or by LBx NGS (MET plasma GCN ≥2.3; Archer). **Results:** Of 472 pre-screened pts (64% female, 57% Asian, 97% adenocarcinoma), 350 provided TBx and 443 provided LBx. After excluding 36 TBx and 7 LBx 'not analyzed/not evaluable' samples, there were 314 TBx (163 from primary tumors, 151 from metastases) and 436 LBx samples with METamp results (positive or negative). Overall, FISH+ METamp was detected in 159/314 pts (50.6%), with similar FISH+ rates in the primary tumor (77/163, 47.2%) and metastases (82/151, 54.3%). FISH+ METamp detection by region was: 43.6% (82/188) in Asia, 61.5% (72/117) in Europe, and 55.6% (5/9) in the US. When limiting analysis to sites without reported local prescreening, the overall FISH+ METamp rate was 46.5% (93/200) and by region was: 43.5% (60/138) in Asia, 52.7% (29/55) in Europe, and 57.1% (4/7) in the US. In 159 FISH+ pts, median GCN was 11.8 (range 5.0-50.6) and median MET/CEP7 ratio was 2.3 (range 0.8-12.7). Mean TBx turn-around time (TAT) from shipment to results was 6.8 days. Overall, L+ METamp was detected in 51/436 pts (11.7%). In 35 L+ pts who were also FISH+, the median GCN was 16.6 (range 5.3-45.3) and median MET/CEP7 ratio was 4.5 (range 1.0-12.7). 299 pts had both central TBx FISH and LBx NGS results (Table), of whom 152 (50.8%) were FISH+ and 38 (12.7%) were L+. LBx NGS identified METamp with high specificity (negative percentage agreement [NPA] 98.0%) but low sensitivity (positive percentage agreement [PPA] 23.0%) compared with TBx FISH: only 3/38 L+ samples were FISH+ but 117/152 FISH+ samples (77.0%) were L-. Clinical activity of tepotinib + osimertinib was comparable in FISH+ and L+ pts. **Conclusions:** In this large comprehensive analysis, FISH+ METamp was detected in ~50% of pts progressing on 1L osimertinib, while L+ METamp was detected in only 11.7% of pts. METamp, which is the most common mechanism of resistance post 1L osimertinib, can frequently be undetected by using LBx NGS only. Given high specificity but low sensitivity of LBx, L+ pts can receive a MET TKI while a negative METamp result by LBx should be confirmed by FISH. FISH allows optimal identification of METamp post 1L osimertinib, can be delivered in a clinically meaningful timeframe, and may allow more pts to benefit from an oral MET TKI. Clinical trial information: NCT03940703. Research Sponsor: the healthcare business of Merck KGaA, Darmstadt, Germany.

		TBx FISH	
Pts with central TBx and LBx results		FISH+	FISH-
LBx NGS	L+	35	3
	L-	117	144
	Total	152	147
		Total	
		38	261
		299	299

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Poster Session

Utility of ctDNA tumor fraction to inform negative liquid biopsy (LBx) results and need for tissue reflex in advanced non-small cell lung cancer (aNSCLC). *First Author: Christian Diego Rolfo, Icahn School of Medicine at Mount Sinai, New York, NY*

Background: Negative LBx results can be challenging to interpret. Absence of a targetable alteration may accurately reflect the tumor genotype (true negative) or may represent a false negative due to insufficient ctDNA shed, concealing a targetable oncogenic driver. Reflex to tissue biopsy (TBx) profiling is thus advised, per FDA label, for negative LBx results. Here we investigate whether algorithmic quantification of ctDNA in a LBx sample can increase confidence in negative LBx results, reducing need for confirmatory TBx testing. **Methods:** This study used the nationwide (US-based) de-identified Flatiron Health-Foundation Medicine NSCLC clinico-genomic database (CGDB) from approximately 280 US cancer clinics (~800 sites of care), limited to patients (pts) with aNSCLC receiving any multi-gene LBx followed by TBx CGP. In parallel, we queried an institutional database of pts with both LBx (FoundationOneLiquid CDx, F1LCDx) and TBx (FoundationOneCDx, F1CDx) to calculate positive predictive agreement (PPA) and negative predictive value (NPV) of LBx compared to TBx for detection of 7 targetable NSCLC driver alterations: KRAS G12X, EGFR, MET exon 14, BRAF V600E mutations or ALK, ROS1, and RET rearrangements. Foundation Medicine's ctDNA tumor fraction (TF) on F1LCDx is a composite algorithm prioritizing aneuploidy at higher levels to avoid germline signal and prioritizing variant allele frequency of canonical alterations at lower levels to maximize dynamic range. **Results:** Of 1,734 LBx sent prior to 1st-line therapy in pts with aNSCLC, 59% (1,024) were negative for an NCCN biomarker. For 465 pts with TBx after negative LBx (median 2.4 weeks from LBx to TBx result), 179 (38%) had a driver detected on reflex to TBx. In 45 receiving matched targeted therapy, median real-world PFS was 25 months. For pts starting therapy after reflex to TBx (n = 233), median time from LBx result to start of therapy was 4.7 weeks. To understand whether reflex to tissue may be avoided in some cases, LBx (F1LCDx) sensitivity was studied across 2,138 pairs in the institutional database. PPA for the 7 driver alterations was 59% overall (679/1,157) and improved to 96% (433/453) when limited to cases with TF ≥1%. Similarly, NPV was modest overall (67%) but improved when limited to LBx specimens with TF ≥1% (96%). Studying TF in the CGDB cohort, 33 of 85 pts (39%) with reflex TBx after negative LBx had a LBx TF ≥1% and, given high NPV for driver alterations, might have avoided reflex to confirmatory TBx. **Conclusions:** Elevated TF (≥1%) on F1LCDx informs assay sensitivity and identifies a subset of LBx results with high NPV where reflex to TBx, and the associated treatment delay, may be less valuable. Conversely, for pts with a negative LBx with low TF (< 1%) on F1LCDx, reflex to TBx is an important follow-on step to identify potentially missed driver alterations with potential for durable benefit on targeted therapy. Research Sponsor: Foundation Medicine Inc.

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Poster Session

Treatment patterns and unmet need for patients with advanced non-small cell lung cancer and poor performance status: A real-world evidence study. *First Author: Stephen V. Liu, Georgetown University, Washington, DC*

Background: Performance Status (PS) is prognostic for poorer survival in oncology. Poor PS (pPS) may lead to inferior outcomes both as an independent factor and by limiting the range of available treatment options and the ability of patients to tolerate those regimens. Despite high real-world prevalence, patients with pPS are consistently underrepresented in clinical trials. Limited information is available regarding current treatment patterns for patients with pPS and advanced or metastatic non-small cell lung cancer (mNSCLC). **Methods:** We conducted a retrospective analysis using the nationwide de-identified Flatiron Health electronic health record (EHR)-derived database, selecting patients with mNSCLC diagnosed between 2017-2022 without *EGFR* or *ALK* genomic tumor aberrations. We estimated the prevalence of pPS (ECOG 2-3) within this cohort, and described common systemic treatment patterns by year and by PD-L1 status. For the subset of patients treated with pemetrexed/pembrolizumab/carboplatin (PPC), we estimated the association between pPS versus good PS (gPS - 0/1) and early discontinuation (< 4 cycles) or dose reduction (AUC < 4) of carboplatin using logistic regression controlling for observable confounders. **Results:** One quarter (24%) of the 22,575 patients in our sample had pPS. Relative to patients with gPS, patients with pPS were more likely to be older (mean age 72 vs. 69y, $p < 0.001$), to have stage IV cancer (62% vs 56%, $p < 0.001$) and less likely to have known PD-L1 status (60% vs. 63%, $p = 0.002$). The fraction of patients with no documented treatment was substantially higher among pPS versus gPS (37% vs. 21%). In the subset of patients with PS3, 53% of patients had no documented treatment. The most common treatment regimens among pPS patients were mono-immunotherapy (mono-IO - 19%) and PPC (15%). Use of mono-IO was positively correlated with higher PD-L1 expression (44% vs. 14% vs. 5.9% in PD-L1 high/low/negative, respectively). No documented treatment was negatively correlated with PD-L1 status (26% vs. 35% vs. 42%). Among patients with PS3, higher rates of no documented treatment were observed (39% vs. 50% vs 58% for PD-L1 high/low/negative, respectively). Anti-CTLA-4 combination use was low regardless of PS. pPS was associated with greater likelihood of early carboplatin discontinuation, (adjusted odds ratio, aOR 2.06), and dose reduction (aOR 1.75), both $p < 0.001$. **Conclusions:** One quarter of patients with mNSCLC have pPS. These patients are almost twice as likely to receive no treatment as those with gPS, and within the subset treated with the most common platinum containing regimen (PPC), pPS patients are also more likely to both initiate carboplatin at a reduced dose, and to discontinue it prior to completion. This suggests a substantial unmet need for this important subset of patients with mNSCLC. Research Sponsor: Genentech, Inc.

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Poster Session

A biomarker study of atezolizumab (atezo) + bevacizumab (bev) + carboplatin (carbo) + paclitaxel (pac) (ABCP) for patients with NSCLC harboring *EGFR* mutations (EGFRm) after failure of TKI therapy: NEJ043. *First Author: Satoshi Watanabe, Department of Respiratory Medicine and Infectious Diseases, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan*

Background: EGFRm NSCLC patients (pts) have limited treatment options after EGFR-TKI failure. We previously showed that the NEJ043 study investigating ABCP in EGFRm NSCLC pts after EGFR-TKI failure had a clinically meaningful efficacy (Furuya et al, ASCO 2022). Here we report the results of the biomarker study of NEJ043. **Methods:** NEJ043 study is a phase II study to evaluate the efficacy of ABCP in sensitizing EGFRm nonsquamous NSCLC pts after TKI failure. Pts received atezo (1200 mg), bev (15 mg/kg), carbo (AUC 6 mg/mL/min), and pac (175 mg/m²) every 3 weeks up to 4 cycles followed by atezo plus bev until loss of clinical benefit. Before treatment initiation and three cycles of ABCP, peripheral blood mononuclear cells (PBMCs) were collected, and immunophenotypic data at each time point was obtained by flow cytometry. **Results:** 60 pts were included in the NEJ043 study and PBMCs were obtained from 31 pts. Pts with a higher percentage of CD11b^{DR}CD3^{CD14}⁺ myeloid-derived suppressor cells (MDSCs) before ABCP had significantly longer PFS (median, 9.7 months (95% CI, 5.3-17.7) vs 5.6 months (95% CI, 3.9-8.1); HR 0.38; $P = 0.0313$). Further analysis of the immune cell phenotypes that changed between pre-treatment and the third cycle showed that pts with increased CD62L^{low}CD8⁺ cells (median, 12.8 months (95% CI, 5.6-20.3) vs 5.7 months (95% CI, 4.4-8.1); HR 0.25; $P = 0.003$) and PD-1⁺CCR7⁺CD45RA^{CD8}⁺ cells (median, 8.5 months (95% CI, 5.6-13.8) vs 5.7 months (95% CI, 2.6-8.1); HR 0.37; $P = 0.0324$) had significantly longer PFS. **Conclusions:** Inhibition of MDSCs by ABCP, especially bev, may be important for EGFRm pts whose antitumor immunity is suppressed by MDSCs before treatment. Better PFS may be expected in pts in whom ABCP therapy induced CD62L^{low}CD8⁺ effector T cells and PD-1⁺CCR7⁺CD45RA^{CD8}⁺ effector memory T cells. Clinical trial information: jRCTs031190066. Research Sponsor: Chugai Pharmaceutical Co., Ltd.

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Poster Session

Integrated efficacy and safety of brigatinib in patients with ALK TKI-naïve advanced *ALK*⁺ NSCLC in the ALTA-1L and J-ALTA studies. *First Author: D. Ross Camidge, University of Colorado Cancer Center, Aurora, CO*

Background: Brigatinib demonstrated efficacy and manageable safety in patients (pts) with anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitor (TKI)-naïve *ALK*⁺ non-small cell lung cancer (NSCLC) in phase 3 (ALTA-1L) and phase 2 (J-ALTA) trials. We present results of integrated efficacy and safety analyses of ALTA-1L and J-ALTA. **Methods:** ALTA-1L (NCT02737501) and J-ALTA (NCT03410108; conducted in Japan) were open-label, multicenter studies in pts with advanced or metastatic *ALK*⁺ NSCLC. Pts in ALTA-1L and in part 3 of J-ALTA were *ALK* TKI-naïve. Stable or asymptomatic brain metastases were allowed in both studies. Pts received brigatinib 180 mg qd (7-day lead-in at 90 mg). Primary endpoints were blinded independent review committee (IRC)-assessed progression-free survival (PFS) in ALTA-1L and IRC-assessed 12-month PFS in the J-ALTA *ALK* TKI-naïve cohort (both per RECIST v 1.1). Secondary endpoints included IRC-assessed objective response rate (ORR), duration of response, intracranial ORR, intracranial PFS, overall survival, and safety. Pooled efficacy and safety data from both studies are presented. **Results:** The pooled analysis population included 169 pts (ALTA-1L, N = 137; J-ALTA *ALK* TKI-naïve cohort, N = 32). Median follow-up overall was 35.8 months (last pt last contact: ALTA-1L, January 2021; J-ALTA, July 2021). Most (66%) pts were aged < 65 years, 24% had baseline brain metastases, 95% had stage IV disease at study entry, and 21% had received prior chemotherapy for locally advanced or metastatic disease. With brigatinib treatment, median PFS by IRC was 29.3 months (95% CI, 23.9–44.7). The confirmed ORR was 79% (95% CI, 72–85%), with 36 complete responses and 97 partial responses. Median duration of response was 38.1 months (95% CI, 22.9–not reached). Median overall survival was not reached; the 3-year survival rate was 74% (95% CI: 66–80%; 84 pts at risk). Intracranial ORR and intracranial PFS will be presented. Grade 3/4 treatment-emergent adverse events were reported in 74% of pts; the most common were increased blood creatine phosphokinase (31%), hypertension (18%), and increased lipase (16%). Any grade interstitial lung disease/pneumonitis was reported in 12 (7%) of pts. Adverse events led to treatment discontinuation in 11% of pts. **Conclusions:** Brigatinib treatment demonstrated clinically meaningful systemic and intracranial efficacy in this integrated analysis of pts with *ALK* TKI-naïve advanced or metastatic *ALK*⁺ NSCLC in the ALTA-1L or J-ALTA trials. Safety results were consistent with the known profile for brigatinib, with no new safety findings. Clinical trial information: NCT02737501; NCT03410108. Research Sponsor: Takeda Pharmaceutical Company Limited, Inc., Lexington, MA, USA.

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Poster Session

Tislelizumab plus chemotherapy in patients with advanced brain metastases of non-squamous non-small cell lung cancer: A multicenter, prospective, open-label phase 2 study. *First Author: Yan Huang, Sun Yat-Sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center of Cancer Medicine, Guangdong Key Laboratory of Nasopharyngeal Carcinoma Diagnosis and Therapy, Sun Yat-sen University, Guangzhou, China*

Background: Patients (pts) with brain metastases (BM) were usually unrepresented in clinical trials assessing the efficacy of PD-(L) 1 inhibitors. Here, we investigated the efficacy and safety of tislelizumab (TIS) plus chemotherapy in NSCLC pts with asymptomatic untreated BM or with stable BM after local radiotherapy. **Methods:** This multicenter, prospective, open-label phase 2 study enrolled systemic treatment-naïve pts with stage IV non-squamous (nsq) NSCLC without EGFR or ALK mutations who had BM. Pts received TIS combined with pemetrexed and carboplatin for 4 cycles, followed by maintenance TIS and pemetrexed. RECIST v1.1 and RANO-BM were applied for assessment for systematic and brain disease, respectively. The primary endpoint was the investigator-assessed 1-year PFS rate per RECIST v1.1. **Results:** 36 pts were enrolled with 77.8% having stage IVB disease, 25.0% liver metastases and 41.7% bone metastases. 29 (80.6%) pts were with untreated, asymptomatic brain metastases, and the other 7 (19.4%) received radiotherapy for BM previously. As of 30 Nov 2022, the median follow-up was 12.3 months. 1-year systematic PFS rate was 36.8% (95% CI, 18.0-55.7), with median PFS of 7.5 months (95% CI, 5.1-NE). Systematic ORR was 50.0% (95% CI, 31.9-68.1%). Median OS was not reached, with 1-year OS rate of 70.5% (95% CI, 51.7-83.1). For intracranial efficacy assessment per RANO-BM, 1-year intracranial PFS (iPFS) rate was 56.6% (95% CI, 31.7-75.5), with 45.5% (95% CI, 19.4, 68.5) and 100% in pts with untreated and pretreated BM, respectively. Intracranial ORR was 56.7% (95% CI, 37.4-74.5%), with 53.8% (95% CI, 33.4-73.4%) in pts with untreated BM and 75% (95% CI, 19.4-99.4%) in pretreated BM. No grade 5 toxicities were observed. Grade 3-4 TRAEs occurred in 33.3% (12/36) of pts. 13.9% of pts experienced iRAEs; grade 3-4 iRAEs occurred in 2 (5.6%) pts. **Conclusions:** TIS plus chemotherapy yielded promising systematic and intracranial PFS, and was generally well tolerated in nsq-NSCLC pts with untreated or pretreated BM. Clinical trial information: NCT04507217. Research Sponsor: None.

	Efficacy analysis set* (EAS)	
	EAS per RECIST v1.1 (n=32)	EAS per RANO-BM (n=30)
1-year PFS rate, % (95% CI)	36.8 (18.0, 55.7)	56.7 (31.7, 75.5)
Median PFS, months (95% CI)	7.5 (5.1, NE)	NR (8.2, NE)
ORR, % (95% CI)	50.0 (31.9, 68.1)	56.7 (37.4, 74.5)
DCR, % (95% CI)	90.6 (75.0, 98.0)	96.7 (82.8, 99.9)
1-year OS rate, % (95% CI)	70.5 (51.7, 83.1)	

*Efficacy analysis set included pts receiving ≥ 1 dose of TIS or chemotherapy, and having completed ≥ 1 post-treatment tumor assessment unless treatment was discontinued before the first tumor assessment due to disease progression or death; NR, not reached; NE, not estimable.

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Poster Session

Patient-reported outcomes of furmonertinib versus gefitinib in patients with locally advanced or metastatic, EGFR mutation-positive non-small cell lung cancer (FURLONG): A multicenter, double-blind, randomized phase 3 study. *First Author: Yuankai Shi, Department of Medical Oncology, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing Key Laboratory of Clinical Study On Anticancer Molecular Targeted Drugs, Beijing, China*

Background: Furmonertinib showed superior efficacy compared with gefitinib as first-line therapy in Chinese patients with EGFR mutation-positive non-small cell lung cancer (NSCLC), along with an acceptable safety profile without new signals in the FURLONG study. Here we present patient-reported outcomes (PROs). **Methods:** FURLONG is a multicenter, double-blind, double dummy, randomized phase 3 study done in 55 hospitals across mainland China. Eligible patients were randomly assigned (1:1) to receive either furmonertinib or gefitinib. The primary endpoint of IRC-assessed progression-free survival has been reported previously. PROs as prespecified secondary outcomes by the European Organization for Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire Core 30 (QLQ-C30) and Quality-of-Life Questionnaire Lung Cancer 13 (QLQ-LC13), were analyzed in randomly assigned patients who had received at least one dose of study drug and completed at least one PRO assessment. Changes from baseline to randomized treatment discontinuation were analyzed with mixed model for repeated measures and time-to-event analyses. This study is ongoing for survival follow-up. **Results:** 357 patients received at least one dose of study drug, all of them completed at least one PRO assessment. Questionnaire completion rates were ≥95% at most time points. Baseline mean scores were similar in the furmonertinib and gefitinib groups. From baseline to randomized treatment discontinuation, statistically significant differences favoring furmonertinib for physical function, nausea/vomiting, appetite loss, diarrhea, alopecia, and other pain (any pain other than chest, arm, or shoulder pain) were observed. Time to deterioration in physical function, cognitive function, nausea/vomiting, appetite loss, diarrhea, cough, dyspnea, dysphagia, and alopecia were significantly longer with furmonertinib versus gefitinib (Table). **Conclusions:** Furmonertinib demonstrated favorable PROs as measured by the EORTC QLQ-C30 and QLQ-L13 versus gefitinib. These data presented the positive benefit risk profile of first-line furmonertinib and further support this novel third generation EGFR-TKI as a new standard of first line treatment in EGFR mutation-positive NSCLC. Clinical trial information: NCT03787992. Research Sponsor: Shanghai Allist Pharmaceuticals Co., Ltd.; China National Major Project for New Drug Innovation (2017ZX09304015).

	HR (95%CI)	P value
Physical function	0.63 (0.42, 0.94)	0.021
Cognitive function	0.73 (0.54, 0.98)	0.034
Nausea/vomiting	0.64 (0.41, 0.99)	0.042
Appetite loss	0.63 (0.43, 0.92)	0.016
Diarrhea	0.63 (0.46, 0.85)	0.002
Dyspnea	0.72 (0.53, 0.98)	0.034
Cough	0.67 (0.44, 1.00)	0.049
Dysphagia	0.54 (0.35, 0.83)	0.004
Alopecia	0.62 (0.42, 0.90)	0.011

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Poster Session

Clinical and genomic predictors of response and toxicity to sotorasib in a real-world cohort of patients with advanced KRAS G12C-mutant non-small cell lung cancer. *First Author: Kathryn C. Arbour, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: With the accelerated approval of the KRAS G12C inhibitor sotorasib for patients with advanced KRAS G12C-mutant non-small cell lung cancer (NSCLC), there is a new need to explore efficacy and identify clinical and genomic factors associated with activity and toxicity among patients treated in routine clinical practice. **Methods:** Patients(pts) treated with sotorasib outside of the clinical trial setting at three institutions (MSK, Columbia, NYU) were examined to identify factors associated with real-world PFS (rwPFS), overall survival (OS), real-world (rw) response, and clinically significant toxicity (CTCAE v5.0 grade 3 or higher treatment-related adverse events [G3+ TRAE]). *TP53*, *STK11*, and *KEAP1* status were assessed by targeted NGS. Response and rwPFS were determined by investigator assessment of radiology reports. rwPFS and OS were estimated by Kaplan-Meier methods; log-rank tests were used for univariate group comparisons and Mantel-Haenszel method was used to determine hazard ratios (HRs). Fisher's exact test was used to determine associations between categorical variables. **Results:** 105 pts with advanced KRAS G12C-mutant NSCLC treated with sotorasib were identified. The response rate for patients treated was 28%, with median rwPFS of 5.3 months, and median OS of 12.6 months. *KEAP1* co-mutations were associated with shorter rwPFS and OS (rwPFS HR 3.19, *P* = 0.004; OS HR 4.10, *P* = 0.003); no significant differences in rwPFS or OS were observed among pts with or without *TP53* co-mutations (rwPFS HR 1.10, *P* = 0.731; OS HR 1.19, *P* = 0.631) or *STK11* co-mutations (rwPFS HR 1.66, *P* = 0.098; OS HR 1.73, *P* = 0.168). Dual *STK11/KEAP1* co-mutation status was associated with shorter OS compared to *STK11* wild-type (WT)/*KEAP1* mutant (MUT) status (OS HR 4.04, *P* = 0.033) and *STK11* MUT/*KEAP1* WT status (OS HR 5.41, *P* = 0.012). 16/105 (15%) pts experienced G3+ TRAEs. 15/16 (94%) patients with G3+ TRAE had previously been treated with immune checkpoint inhibitor (ICI). Among pts with prior ICI exposure (*n* = 86), last exposure within 12 weeks of sotorasib initiation was associated with G3+ sotorasib TRAEs (*P* < 0.001) and TRAE-related sotorasib discontinuation (*P* = 0.014); there was no association between prior irAE during ICI therapy and G3+ sotorasib TRAEs (*P* = 0.757). In total, 15/53 (28%) pts with last ICI exposure within 12 weeks of sotorasib initiation experienced G3+ TRAEs, most commonly hepatotoxicity. No cases of G3+ TRAEs were observed in 33 pts with last ICI exposure > 12 weeks prior to sotorasib treatment. **Conclusions:** Among patients treated with sotorasib in routine clinical practice, *KEAP1* co-mutations were associated with poor outcomes. Severe toxicity was almost exclusively associated with recent ICI exposure. These observations may help further guide sequencing of sotorasib and may help inform the next generation of KRAS G12C clinical trials. Research Sponsor: LUNGEVITY Foundation.

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Poster Session

Mobocertinib efficacy in patients with NSCLC and EGFR exon 20 insertion mutations (ex20ins) identified by next-generation sequencing (NGS) of circulating tumor DNA (ctDNA). *First Author: Joel W. Neal, Stanford University Medical Center, Stanford, CA*

Background: EGFR ex20ins are distinct targetable driver mutations present in ~2% of all NSCLC. While most EGFR TKIs have limited effectiveness, mobocertinib is the first oral therapy approved for this unmet need. EGFR ex20ins are heterogeneous (> 60 variants), and PCR testing detects a limited number of variants, leading to undetected disease in ~50% of cases, whereas NGS can identify all such mutations. Testing plasma ctDNA is a noninvasive approach for detection of genomic variants, such as EGFR ex20ins. **Methods:** In the mobocertinib phase 1/2 study (NCT02716116), patients were enrolled based on EGFR ex20ins detected by various local tissue or liquid clinical trial assays (CTAs). Baseline plasma samples were collected and processed to extract cell-free DNA and were evaluated for EGFR ex20ins status using FoundationOne Liquid CDx (F1LCDX), an NGS-based plasma ctDNA test. Concordance between F1LCDX and the CTAs was demonstrated by testing patient samples from the phase 1/2 trial and paired tissue and plasma samples from commercially acquired and stage-matched patients with NSCLC (*N* = 305). Efficacy analyses by assay method were performed in EGFR ex20ins-positive platinum-pretreated patients (PPP; *n* = 114 [FDA approved population]; data cutoff: 1 Nov 2021) in the phase 1/2 trial. **Results:** Concordance between F1LCDX and CTAs was demonstrated with samples from the CTA-positive (*n* = 159) and CTA-negative populations (*n* = 87) tested by F1LCDX where tissue and plasma were assessable; the point estimate of positive percentage agreement (95% CI) was 68.6% (61.0–75.3), and the point estimate of negative percentage agreement was 100% (95.8–100). F1LCDX detected 34 individual EGFR ex20ins variant types. In the response evaluable population, patients who tested EGFR ex20ins positive by F1LCDX (*n* = 55) demonstrated confirmed ORR (34.5%) and disease control rate (74.5%), which was comparable to those observed among all PPP in the phase 1/2 trial (confirmed ORR: 28%; confirmed disease control rate: 78%). **Conclusions:** Mobocertinib has shown efficacy in PPP with EGFR ex20ins NSCLC. F1LCDX effectively identified patients with EGFR ex20ins who may benefit from mobocertinib, providing an additional noninvasive diagnostic option to guide treatment. Clinical trial information: NCT02716116. Research Sponsor: Takeda Development Center Americas, Inc., Lexington, MA, USA.

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Poster Session

Survival associations and driver oncogene overlap for copy-number amplifications of ERBB2, KRAS and MET in non-small cell lung cancer. *First Author: Alexander Watson, Tom Baker Cancer Center, Calgary, AB, Canada*

Background: Next-generation sequencing (NGS) to detect targetable oncogenic driver mutations is standard of care in non-small cell lung cancer (NSCLC). However, the interpretation and clinical impact of copy number amplifications (CNA) of driver genes is less clear. *ERBB2*, *KRAS* and *MET* are oncogenic drivers with intersecting resistance mechanisms and evolving therapeutic landscapes. We examined the overlap between other oncogenic drivers and CNA of these genes, and the association of CNA with overall survival (OS), in a cohort of patients with NSCLC. **Methods:** NGS of DNA (592 genes or WES)/RNA (WTS) was performed for 5870 consecutive lung adenocarcinoma tumors submitted to Caris Life Sciences (Phoenix, AZ). The copy number of each exon was determined by calculating the average depth of the sample along with the sequencing depth of each exon. Driver oncogenes (Driver+/-) were defined as pathogenic fusions in *ALK*, *NTRK* (1.2 and 3), *RET* and *ROS1* or pathogenic SNVs/indels in *ALK*, *BRAF*, *EGFR*, *ERBB2*, *KRAS*, *MET*. Tumor mutational burden high (TMB-H) was defined as 10 mutations per MB. The χ^2 test was applied as appropriate (*p* < .05). **Results:** The cohort was 55% female; median age was 69 years (range 24-89) and similar across all cohorts. Incidence of CNA at different amplification thresholds was correlated with oncogene drivers. At CNA ≥6 for *ERBB2* and *KRAS*, but CNA ≥4 for *MET*, a significant tendency for mutual exclusivity with driver mutations was observed (log2 odds ratio *ERBB2*: -3.1, *KRAS*: -1.1, *MET*: -2.2, all *p* < .001). Tumors meeting these thresholds were designated CNA-High (Gene-H), versus CNA-Low (Gene-L). Only one tumor harboured two CNA-H genes (*KRAS* and *MET*). Independent of CNA status, the TMB-H frequency was decreased in Driver+ tumors (27% vs 52% in Driver-, *p* < .001). CNA-H tumors were associated with decreased OS (compared to CNA-L); for *ERBB2*-H, hazard ratio (HR) 1.74 (95% CI 1.44-2.10, *p* < .001), for *KRAS*-H HR 1.29 (1.16-1.65, *p* < .001), and for *MET*-H HR 1.46 (1.28-1.68, *p* < .001). Similar results were observed when stratified by driver mutation status (Table), with the exception of *KRAS*/Driver- tumors. **Conclusions:** These data suggest tumors with high CNA of *ERBB2*, *KRAS* and *MET* represent clinically distinct entities and are significantly less likely to harbour concurrent driver oncogenes. The association between increased copy number and worse OS suggests amplified tumors are an important area for therapeutic development. Overall survival (collection to last contact) for *ERBB2*, *KRAS* and *MET* CNA-High versus CNA-Low tumors, by Driver mutation status. Research Sponsor: Caris Life Sciences.

	HR for death (CNA-High vs -Low)	Low CI	Upper CI	p-value
<i>ERBB2</i>				
Driver +	1.30	0.90	1.89	.16
Driver -	1.71	2.00	2.43	.003
<i>KRAS</i>				
Driver +	1.50	1.17	1.91	.001
Driver -	0.92	0.60	1.42	.669
<i>MET</i>				
Driver +	1.62	1.29	2.02	<0.001
Driver -	1.47	1.14	1.90	.003

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Poster Session

Impact on turnaround times (TAT) among non-squamous non-small cell lung cancer (NSCLC) patients across three time periods with varying biomarker testing techniques. *First Author: Zhen (Jason) Fan, University of Toronto, Toronto, ON, Canada*

Background: Biomarker testing and identification of actionable genomic alterations (AGAs) in NSCLC patients have led to targeted therapy use and improved outcomes, particularly in advanced stages. We sought to evaluate the impact of different testing paradigms on TAT, particularly with respect to treatment decision and time to initiation of treatment, across three time periods. **Methods:** A retrospective review of stage III or IV non-squamous NSCLC patients at the Princess Margaret Cancer Centre (Toronto, Canada) was conducted. Both *de novo* advanced and patients with metastatic progressions are included. Cohort 1 (C1; 01/2015 – 01/2017) underwent reflex EGFR (EntroGen) and ALK (5A4 immunohistochemistry, IHC) single gene testing. Cohort 2 (C2; 02/2017 – 09/2020) underwent reflex next generation sequencing (NGS; TruSight Tumor 15), ALK and ROS1 testing. Cohort 3 (C3; 10/2020 – 01/2022) underwent reflex comprehensive NGS (161 genes, OncoPrint OCA v3). Descriptive statistics are presented, including AGAs found and TAT from biopsy to result sign-out, and treatment related TAT. **Results:** Three cohorts of stage III and IV patients were identified, with C1 having proportionally more females (60%), never smokers (42%) with adenocarcinomas (98%). More patients with AGA were identified using NGS with larger panels (42%, 41%, 57%, respectively across C1 – C3). However, there is a longer median time from first oncology visit to treatment (14, 22, 27 days, respectively across C1-C3), and longer biopsy to treatment TAT trended towards more comprehensive testing (34, 38, 40 days, respectively across C1 – C3) in stage IV patients. **Conclusions:** As more comprehensive biomarker testing became available, more AGAs are identified with an increase in TAT from biopsy to sign-out and treatment start. Despite our institutional policy of reflex testing, future endeavours will be focus on ways to reduce TAT. Research Sponsor: Princess Margaret Cancer Center; Pfizer; PM Lung Cancer Molecular Diagnostics Program.

Cohort	C1	C2	C3
Patients with successful testing (n)	177	657	205
Median age (range)	70 years (46-93)	69 years (19-97)	70 years (33-91)
Female	106 (60%)	313 (48%)	102 (50%)
Never smoker	71 (42%)	193 (30%)	68 (34%)
Adenocarcinoma	173 (98%)	558 (85%)	184 (90%)
Stage IV patients with AGAs identified	52/123 (42%)	191/463 (41%)	*84/148 (57%)
Median time from biopsy to result sign-out	14 days (IQR: 10-19)	28 days (IQR: 22-33)	31 days (IQR: 27-38)
Median time from first oncology visit to treatment (stage IV only)	14 days (IQR: 2-28)	22 days (IQR: 14-36)	27 days (IQR: 15-38)
Median time from biopsy to treatment (stage IV only)	34 days (IQR: 22-52)	38 days (IQR: 26-52)	40 days (IQR: 22-60)

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Poster Session

Phase II results of ivonescimab (AK112/ SMT112), a novel PD-1/VEGF bispecific, in combination with chemotherapy for first line treatment of advanced or metastatic non-small cell lung cancer (NSCLC) without actionable genomic alterations (AGA) in EGFR/ALK. *First Author: Li Zhang, Sun Yat-Sen University Cancer Center, Guangzhou, China*

Background: Since the initial approval of bevacizumab (bev) with chemo in NSCLC, the subsequent focus of bev use in combination with PD1 therapy for first line metastatic disease has largely focused on non-squamous (non-SCC) histology. Ivonescimab is a novel anti-PD-1/VEGF bispecific antibody. The bispecific approach to these targets has the potential to recalibrate the malignant immuno-architecture in favor of a more immune-responsive and anti-tumor microenvironment. Cooperative VEGF binding with the bispecific has been shown to elevate affinity of ivonescimab to PD-1 by more than 10-fold. Ivonescimab has a mean $T_{1/2}$ of 6-7 days while bev $T_{1/2}$ is 20 days. Therefore, we aimed to assess the efficacy and safety of ivonescimab combined with chemotherapy for first line advanced or metastatic NSCLC in patients (pts) with squamous (SCC) or non-SCC NSCLC. **Methods:** An open-label, multicenter phase II study evaluating the efficacy and safety of ivonescimab combined with chemotherapy in pts with advanced or metastatic NSCLC. Pts were enrolled into 3 cohorts based on prior therapy and presence of AGA. Data from pts with prior therapy for advanced or metastatic disease were presented in ASCO 2022 and here we report additional pts and longer-term data from pts with NSCLC without AGA receiving first line therapy for advanced/metastatic disease. Pts were treated with 10 or 20 mg/kg ivonescimab once every 3wks combined with carboplatin and pemetrexed (non-SCC) or carboplatin and paclitaxel (SCC). The primary endpoint was ORR per RECIST by investigator. **Results:** 135 pts with advanced or metastatic NSCLC received ivonescimab plus chemotherapy including 63 with SCC and 72 with non-SCC. Median age was 61 yrs (. 78% male, 3% and 97% pts had ECOG PS 0 and 1, respectively, and 20% pts had baseline brain metastasis. Median follow-up was 11.5 mo. Pts with SCC experienced a 75% ORR with median DOR 15.4 mo, 95% DCR, the 9-mo PFS and OS rate was 67% and 93%, respectively. Pts with non-SCC experienced a 55% ORR, DOR was not reached, 100% DCR, the 9-mo PFS rate and OS rate was 61% and 81%, respectively. The most common treatment related adverse events (TRAEs) $\geq 10\%$ were epistaxis, proteinuria, rash, amylase increased, anemia, ALT increased, infusion related reaction, AST increased, pruritus, decreased appetite, and WBC decreased. Grade ≥ 3 TRAEs occurred in 28.1% TRAE leading to discontinuation occurred in 6.7% of pts. **Conclusions:** Ivonescimab, plus chemotherapy has shown promising anti-tumor activity in pts with advanced/metastatic NSCLC without AGA and can be administered safely in combination with platinum doublet chemotherapy to patients with SCC and non-SCC histology. Clinical trial information: NCT04736823. Research Sponsor: Akeso Biopharma, Inc.

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Poster Session

Immune checkpoint inhibitors use and the incidence of hepatitis B virus reactivation or immune-related hepatitis in non-small cell lung cancer patients with chronic hepatitis B. *First Author: Joohyun Hong, Yongin Severance Hospital, Gyeonggi-Do, Korea, Republic of (South)*

Background: The safety and efficacy of immune-checkpoint inhibitors (ICIs) has not been thoroughly investigated in non-small cell lung cancer (NSCLC) patients with chronic hepatitis B (CHB) or occult hepatitis B infection (OBI). We analyzed incidence of hepatitis B virus (HBV) reactivation, immune-related hepatitis and jaundice in NSCLC patients treated with ICIs according to HBV DNA and hepatitis B serologic markers in real-world setting. **Methods:** A total of 1,277, consecutive NSCLC patients treated with ICIs from January 2015 to December 2020 at the Samsung Medical Center, Seoul, Korea were analyzed. Among them, 52 patients were hepatitis B surface antigen (+) (Group A, CHB), 759 patients were HBsAg (-)/anti-HBc IgG (+) (Group B, OBI), and 466 patients were HBsAg (-)/anti-HBc IgG (-) (Group C). Among 52 patients with CHB, 38 patients (73.1%) were receiving antiviral therapy. Primary endpoint was HBV reactivation, immune-related hepatitis and jaundice. Secondary endpoints include other immune-related adverse events, objective response rate, progression free survival (PFS) and overall survival (OS). **Results:** HBV reactivation was observed in two patients (0.2%) which was exclusively observed in Group A (CHB). Among CHB patients who were not receiving antiviral therapy, HBV reactivation was observed for 14.3% (2/14 patients). Incidence of immune-related hepatitis were 21.2%, 30.3% and 30.5% for Group A, Group B and Group C ($p > 0.05$), respectively, and incidence of immune-related of jaundice was 3.8%, 4.0% and 2.8% for Group A, Group B and Group C ($p > 0.05$), respectively. Incidence of $\geq$ grade 3 other immune-related adverse events, objective response rate, PFS, and OS were comparable among three group ($p > 0.05$ for all comparison). **Conclusions:** In this large, real-world cohort study, safety and efficacy of ICIs were comparable in patients with CHB or OBI, suggesting similar outcomes can be expected with ICIs in patients with CHB or OBI. HBV reactivation was observed in patients with CHB without antiviral therapy indicating antiviral prophylaxis might be required for them. For patients with OBI, risk of HBV reactivation was null. Research Sponsor: None.

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Poster Session

First line (1L) durvalumab in patients with PD-L1 positive, advanced non-small cell lung cancer (NSCLC) with a performance status of 2 (PS2): Primary analysis of the multicenter, single-arm phase II trial SAKK 19/17. *First Author: Michael Thomas Mark, Division of Oncology/Hematology, Cantonal Hospital Graubünden, Chur, Switzerland*

Background: The safety and efficacy of 1L durvalumab in PS2 patients (pts) with advanced NSCLC is unknown. Important safety data leading to exclusion of pts with relevant respiratory symptoms have been published as an interim report. Here we present the primary analysis of 1L durvalumab in PS2 pts, unsuitable for combination chemotherapy and PD-L1 expression in $\geq 25\%$ of tumor cells. **Methods:** In this single-arm, multicenter, phase II trial pts with PD-L1 positive (tumor proportional score, TPS $\geq 25\%$), advanced NSCLC with PS2, unsuitable for combination chemotherapy determined by the investigators, in the absence of known contraindications for immunotherapy and sufficient organ function, received a fixed dose of 1500 mg durvalumab every four weeks. The primary endpoint was overall survival (OS) at 6 months. The statistical hypothesis was to improve OS at 6 months from $\leq 35\%$ to $\geq 53\%$. Adverse events (AEs) were assessed according to National Cancer Institute Common Terminology Criteria for AEs (NCI CTCAE) version 5.0. **Results:** Forty-eight pts were included (29 males, 19 females). Median age was 76 years (range, 37-87). OS at 6 months was 60% (95% CI: 45-74%). OS at 6 months after the exclusion of pts with initially relevant respiratory symptoms was 67% (95% CI: 46-84%, $n = 27$) compared to the subgroup of pts without this exclusion criteria who were recruited before the amendment (52%, 95% CI: 30-74%, $n = 21$). Median OS was 8.5 months (95% CI: 4.4-16.7). Objective response rate and median PFS were 17% (95% CI: 8-30%) and 2.5 months (95% CI: 1.8-7.1). Thirty-three deaths (69%) were observed to date. Ten early fatal events considered not treatment-related occurred during the first 5 weeks of treatment. Four out of the first 7 early fatal events (4/7; 57%) were respiratory failures in pts with advanced symptomatic primary lung tumors. Only 3 more early fatal events occurred after the protocol amendment excluding pts with severe respiratory symptoms. Thirty-nine patients (81%) had an AE grade ≥ 3 (G3). The most frequent AEs ≥ 3 were lung infection (19%), dyspnea (15%) and hypertension (10%), respectively. Treatment-related AEs ≥ 3 were reported in 9 pts (19%) and included colonic perforation in one patient (grade 5), colitis in 5 pts (10%), hepatitis and increased lipase in 3 pts each (6%). **Conclusions:** 1L durvalumab in PS2 pts with advanced PD-L1 positive (TPS $\geq 25\%$) NSCLC is effective and led to a promising 6-month OS of 60%. Four-weekly durvalumab can be safely offered to pts presenting without severe pulmonary symptoms who are not candidates for chemotherapy. Clinical trial information: NCT03620669. Research Sponsor: AstraZeneca.

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Poster Session

Safety, efficacy and biomarker data in patients with non-small cell lung cancer treated with the anti-IL1RAP antibody nadunolimab in combination with platinum doublet. *First Author: Luis G. Paz-Ares, Hospital Universitario 12 de Octubre, Madrid, Spain*

Background: Interleukin-1 Receptor Accessory Protein (IL1RAP), expressed in various tumors, is essential for IL-1 α and IL-1 β signaling. IL-1 α /IL-1 β are implicated in tumor progression and therapy resistance, and chemotherapy can upregulate IL-1 α in e.g. non-small cell lung cancer (NSCLC). Nadunolimab (CAN04), a fully humanized ADCC-enhanced IgG1 antibody, targets IL1RAP and blocks IL-1 α /IL-1 β signaling. Here, data are reported from clinical phase 1/2 trials in NSCLC pts given nadunolimab and platinum doublet. **Methods:** Pts with advanced NSCLC, 1st line or progressed on pembrolizumab, received nadunolimab at 1 (n=16), 2.5 (n=3) or 5 mg/kg (n=11) with cisplatin/gemcitabine (NCG), or at 2.5 mg/kg with carboplatin/pemetrexed (NCP) (n=5). Four additional pts, 3rd line or beyond, received NCG at 1 or 1.75 mg/kg nadunolimab. Primary objective was safety; efficacy was evaluated as a secondary objective and effects on serum and tumor tissue biomarkers explored. **Results:** The 30 1st or 2nd line pts given NCG had a median PFS of 7.2 months (95% CI 5.5-8.2), ORR of 53% (34-72) and DoR of 5.8 months (3.7-7.5). A dose-response trend was observed for PFS and DoR (Table). Twenty non-progressing pts continued nadunolimab as monotherapy post chemo; 8 of these remained in disease control for a further 12-131 wks. Nadunolimab monotherapy was well tolerated with $\geq$ grade 3 adverse events reported less frequently. Two pts (non-squamous, 2nd line post pembrolizumab) showed complete responses, one observed after >40 wks of nadunolimab monotherapy. Furthermore, confirmed partial responses were observed in 3 of 5 pts given NCP, and 2 of 4 3rd line or beyond pts given NCG. NCG reduced several serum markers, e.g. CRP and tumor-promoting HGF, effects which were maintained by nadunolimab monotherapy. Additionally, a decrease of MCP-3 and 4 was observed during monotherapy. NCG also reduced IL-1- and tumor microenvironment (TME)-related markers in serum (angiopoietin 1, CXCL5, IL-8, TWEAK and VEGFA). Spatial analyses of protein and RNA markers in tumor biopsies are ongoing to verify potential effects in the TME. **Conclusions:** NCG shows promising efficacy in NSCLC with a trend for dose response, and long-term disease control by nadunolimab monotherapy post chemo with good safety. These observations are supported by changes in TME-related serum biomarkers. Preliminary data suggest similar efficacy with NCP, and in more heavily pretreated pts. Clinical trial information: NCT03267316, NCT05116891. Research Sponsor: Cantargia AB.

Dose (mg/kg)	n	PFS (mos)	95% CI	ORR (%)	95% CI	DoR (mos)	95% CI
1	16	5.6	3.9-7.4	50	24.7-75.3	4.7	3.6-7.5
2.5	3	7.6	NE	66.7	9.4-99.2	NE	NE
5	11	8.2	5.6-11.1	54.5	23.4-83.3	6.6	NE

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Poster Session

RET testing and treatment patterns among patients with aNSCLC in US clinical practice. *First Author: Eunice Kim, Genentech, Inc., South San Francisco, CA*

Background: Biomarker testing, including for rearrangement during transfection (RET), is recommended and important in selecting efficacious targeted therapy for patients with advanced non-small cell lung cancer (aNSCLC). This retrospective cohort study characterized RET testing and treatment patterns among aNSCLC patients in clinical practice. **Methods:** We used the nationwide Flatiron Health electronic health record-derived de-identified database to select patients diagnosed with aNSCLC (stage $\geq$ IIIB) from 2017-2022. We measured rates of RET testing (test result $\leq$ 90 days after advanced diagnosis). We used logistic regression to identify baseline characteristics predictive of timely testing. Finally, we described treatment patterns for patients with RET+ aNSCLC before and after the US approval of RET inhibitors. **Results:** Among 26,329 aNSCLC patients, rates of RET testing $\leq$ 90 days after advanced diagnosis increased from 25% (2017 Q1) to 73% (2022 Q1). Patients were less likely to receive RET testing within 90 days if they were Black (multivariate odds ratio [OR] 0.8) or Hispanic (OR 0.8) compared to White, or had Medicare (OR 0.9; all p<0.001) compared to commercial insurance. Patients were more likely to receive RET testing within 90 days if they were in the highest socioeconomic quintile (OR 1.4), had *de novo* disease (OR 2.1), or no history of smoking (OR 1.3; all p<0.001). Between 2017 and 2022, there were increases in the use of next-generation sequencing (66% to 89%) and blood samples for biomarker testing (25% to 49%) and a decrease in mean days from diagnosis to test result (33 to 28) for the first RET test among those who had testing within 90 days. Among all patients with aNSCLC tested within 90 days (n=12,275), 73 were RET+ and received 1L treatment $\leq$ 90 days after advanced diagnosis. The most common 1L treatments before (n=35) and after (n=38) RET inhibitor approval were chemotherapy (40%) and RET inhibitor (42%), respectively (Table). **Conclusions:** RET testing has increased over time, but certain patient subgroups are less likely to receive timely RET testing and therefore may not be optimally treated. Among patients with RET+ aNSCLC identified after RET inhibitor approval, only 42% were treated with a RET inhibitor in the 1L setting. These results suggest both disparities in access to RET testing and unmet medical need among patients with RET+ aNSCLC. Research Sponsor: This study is sponsored by Genentech, Inc.

Treatment patterns of RET+ patients.			
Treatment type	Patients who initiated 1L before approval of 1st RET inhibitor (n=35 of 73)		Patients who initiated 1L after approval of 1st RET inhibitor (n=38 of 73)
Chemotherapy only	14 (40%)		4 (11%)
Chemotherapy + Checkpoint inhibitor	10 (29%)		7 (18%)
Checkpoint inhibitor only	5 (14%)		4 (11%)
RET inhibitor	-		16 (42%)
Other targeted therapy	2 (6%)		3 (8%)
Clinical trial drug	4 (11%)		1 (3%)
Other	0 (0%)		3 (8%)

9090

Poster Session

The impact of PD-L1 expression and co-mutations on outcome of KRAS-driven non-small-cell lung cancer. *First Author: Petros Christopoulos, Department of Thoracic Oncology, Thoraxklinik and National Center for Tumor Diseases at Heidelberg University Hospital, Heidelberg, Germany; Translational Lung Research Center Heidelberg (TLRC-H), Member of the German Center for Lung Research (DZL), Heidelberg, Germany*

Background: Interest has surged for KRAS mutated ($KRAS^{mut}$) non-small-cell lung cancer (NSCLC) after approval of the covalent $KRAS^{G12C}$ inhibitors sotorasib and adagrasib. It remains unclear, how prognosis of these tumors is influenced by co-mutations and which cases could benefit most from novel drugs alongside immunotherapy (IO) or chemo-immunotherapy (CHT-IO). **Methods:** This retrospective study included all NSCLC patients with $KRAS^{mut}$ NSCLC treated in the Thoraxklinik Heidelberg from 01/2014 until 01/2021. For molecular profiling, PCR-based next-generation sequencing (NGS) was performed with a 40-gene panel, including *TP53*, *KEAP1* and *STK11*. Date of progression was verified through reevaluation of radiologic images by the investigators according to RECIST v1.1. Stratification was performed according to the type of KRAS mutation ($G12C$ vs. other), presence of *TP53*, *STK11* and *KEAP1* co-mutations (vs. wild-type [WT] status), and the PD-L1 tumor proportion score (TPS < 1 *aka* PD-L1^{neg}, vs. TPS 1-49, vs. TPS 50+ *aka* PD-L1^{high}). **Results:** Among 370 identified patients, no differences (all p-values > 0.08) were observed between $KRAS^{G12C}$ (n = 163) and $KRAS^{non-G12C}$ (n = 207) regarding clinicopathological features, like age (median 65 years), sex, smoking status, initial ECOG performance status, PD-L1 TPS, type of treatment in any line, number of treatment lines, and overall survival (OS, 19.4 months in median; details in the poster). In contrast, there was a strong association of PD-L1 TPS with OS (20.2 vs. 9.7 months for PD-L1^{high} vs. PD-L1^{neg}, p = 0.011) and progression-free survival (PFS, 5.7 vs. 1.9 months, p = 0.004) under IO. In addition, specifically within the PD-L1^{neg} subset, OS was longer for $KRAS^{G12C}$ compared to $KRAS^{other}$ patients (22.6 months vs. 12.1 months, p = 0.032). This was driven by the longer PFS under CHT-IO (9.7 vs. 4.5 months for $KRAS^{G12C}$ vs. $KRAS^{other}$, p = 0.005), particularly in the absence of *TP53* mutations (8.5 vs. 4.0 months with p = 0.004 for $TP53^{wt}$ patients; p > 0.50 for $TP53^{mut}$) and *KEAP1* mutations (11.3 vs. 5.1 months with p = 0.01 for $KEAP1^{wt}$ patients; p > 0.70 for $KEAP1^{mut}$). Also, across all patients, *KEAP1*^{mut} cases showed a trend for shorter PFS under CHT-IO (2.7 vs. 8.0 months, p = 0.07) and IO (1.9 vs. 3.9 months, p = 0.081), as well as shorter OS (15.9 vs. 19.5 months, p = 0.068) compared to *KEAP1*^{wt}, in contrast to *STK11*^{mut} cases (p = 0.42-0.92 for the same comparisons). Overall, $KRAS^{mut}$ NSCLC after chemotherapy and immunotherapy showed poor prognosis under standard therapies with a median PFS of 3 months, and a median OS of 6.8 months. **Conclusions:** In PD-L1^{neg} NSCLC, $KRAS^{G12C}$ is associated with better outcome under CHT-IO and longer OS compared to $KRAS^{other}$, especially in the absence of *TP53* and *KEAP1* co-mutations. *KEAP1*, but not *STK11* mutations are associated with impaired benefit from (CHT-)IO in $KRAS^{mut}$ NSCLC. Treatment of $KRAS^{mut}$ NSCLC after chemo-immunotherapy represents an unmet medical need. Research Sponsor: Amgen GmbH; Thoraxklinik Heidelberg.

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Poster Session

Explore ALK: Alectinib activity in patients with ALK+ metastatic non-small cell lung cancer—A national real world analysis (GFPC 03-2019). *First Author: Aurélie Swalduz, Department of Medical Oncology, Centre Léon Bérard, Lyon, France*

Background: Alectinib is a standard of care option in advanced ALK-rearranged (ALK+) non-small cell lung cancer (NSCLC) patients (pts), with efficacy established by phase 3 trials, in first-line and beyond. There are few efficacy data in unselected populations. **Methods:** The objective of this study was to evaluate the efficacy of alectinib in real-world setting. All ALK+ advanced NSCLC pts initiating alectinib, between December 13, 2017 (date of access in France) and June 27, 2020, whatever the line, were included in explore ALK study. Patient characteristics, alectinib duration of treatment (DOT), progression-free survival assessed locally (rwPFS), overall survival (OS) according to the prescription line of alectinib, the presence of brain metastases at alectinib initiation, response rate and tolerance were collected from the medical files. **Results:** The analysis included 223 pts: 46.2% were men, 84.7% had no smoking history or were former smokers, median age was 59 (22-101) years and 95% were adenocarcinomas. Alectinib was initiated as first-line treatment in 119 pts, with a PS of 0/1/>1 in 42%/31%/27% of cases, a median number of metastatic sites of 2 (cerebral, hepatic, bone in 33%, 24% and 32% of cases). In first-line setting, after a median follow-up of 33.7 months (95%CI, 32.2-37.5), the median of rwPFS and DOT were 28.1 (95%CI, 20.7-40.4) and 26.9 (95%CI, 20.2-31.3) months, respectively. The median OS was not reach (NR), the 3-year OS rate was 72.1%. The rwPFS was not significantly different depending on whether or not the patient has brain metastases, 28.1 (95%CI, 14.5-NR) and 30.5 (85%CI, 18.9-40.4) months, respectively. The best response was complete (CR), partial (PR) and stable (SD) in 21%, 58% and 17%. The cerebral response, evaluable in 30/39 of the pts, was CR, PR and SD in 26%, 46% and 23% respectively; 33% of pts had a grade 3 adverse event, resulting in a temporary interruption of treatment in 7.6% of cases and a permanent discontinuation in 5.9% of cases. At the time of progression, 48.1% of pts had a new biopsy (66% of tissue biopsy). Efficacy data for alectinib prescribed as second line and above are summarized in the table. **Conclusions:** In this large real-world, cohort of unselected advanced ALK+ NSCLC pts, alectinib initiated in 1st-line or beyond provides similar efficacy and safety results as obtained in phase III clinical trials. Research Sponsor: Roche.

Line of alectinib initiation	Median (95% CI)
2 nd (n = 49)	
Duration of treatment	28.9 (17.7-40.6)
rw PFS	28.5 (16.5-49)
pts with cerebral metastasis (n= 23)	30.9 (17.49)
pts without cerebral metastasis (n = 26)	16.8 (9.9-NR)
OS	NR (NR-NR)
3-year OS rate	70.1%
3 rd (n = 25)	
Duration of treatment	20.6 (17.7-31.2)
rw PFS	19.6 (13.9-31)
OS	NR (36-NR)
3-year OS rate	70.6%
4 th (n = 12)	
Duration of treatment	18.7 (1.7-32.7)
rwPFS	17.4 (2.2-22.5)
OS	35.1 (7.8-NR)
>5 th (n = 18)	
Duration of treatment	14.7 (3.1-29.4)
rwPFS	11.7 (3.1-21)
OS	40.1 (7.9-NR)

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Poster Session

A phase I trial of sequential dosing of sonidegib and pembrolizumab in advanced solid tumors (aST) and non-small-cell lung cancer (NSCLC). *First Author: Mohamed Shanshal, Mayo Clinic, Rochester, MN*

Background: Pembrolizumab interrupts PD-1/L1 interaction and is efficacious in many cancers. However, resistance invariably emerges in the majority of patients. Potential mechanisms include activation of compensatory pathways. The inhibition of sonic hedgehog signaling (SHH) was previously shown to induce intratumoral (IT) infiltration by CD4+, CD8+ and HLA-DR class II cells. Our preclinical data showed SHH inhibitor enhanced IT penetration by monoclonal antibodies and induced PD-L1 expression. We conducted a phase I study using a novel sequential pulse dosing of sonidegib followed by pembrolizumab in aST with an expansion cohort to determine the maximum tolerated dose (MTD), tolerability and preliminary efficacy. **Methods:** The dose escalation utilized a 3+3 design to determine the MTD and proceeded to expansion cohort upon determination of the MTD. Patients enrolled to each dose level were observed for dose limiting toxicities (DLTs) during the 1st cycle. The expansion cohort consisted of NSCLC and head/neck squamous cell carcinoma (HNSCC) previously treated by anti-PD1/L1. The recommended phase 2 dose (RP2D) was determined following the review of the toxicity profile of the combination from all cycles. The study treatment consisted of sonidegib oral daily from day 1 to 8 and pembrolizumab I.V. 200 mg on day 8 on an every 3-week cycle. The sonidegib dose levels explored were 400, 600 and 800 mg. Archival tumor and blood specimens were collected for correlative studies. Adverse events (AEs) were categorized and graded per CTCAE v5.0, and tumor response by RECIST v1.1. **Results:** The study enrolled a total of 33 patients and 29 received treatment (13 in escalation and 16 in expansion), including patients with NSCLC, HNSCC, skin cancer, gastric cancer and melanoma. The enrollment to the NSCLC cohort is complete and HNSCC continues. No DLT was encountered during dose escalation and the MTD was not reached. The highest planned dose level was selected to proceed to expansion (sonidegib 800mg days 1-8 in combination with pembrolizumab I.V. 200 mg on day 8 on an every 3-week cycle). The expansion cohort proceeded to enroll 15 patients evaluable for AEs (10 NSCLC and 5 HNSCC). Grade 3 and above treatment-related AEs across all patients were hyperglycemia, fatigue, dyspepsia, abdominal pain. The mature efficacy data will be reported at the meeting. **Conclusions:** The study successfully determined the RP2D of sonidegib when dosed sequentially with pembrolizumab in advanced solid tumors. The AE profile of the combination is similar to that for respective agents given individually. The efficacy data among anti-PD1/PDL1-treated NSCLC will be reported at the meeting. Clinical trial information: NCT04007744. Research Sponsor: Sun Pharma.

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Poster Session

Updated molecular analysis of MET exon 14 skipping mutations (METex14) in non-small cell lung cancer (NSCLC). *First Author: Jennifer Aline Marks, Lombardi Comprehensive Cancer Center, Georgetown University, Washington, DC*

Background: METex14 is a heterogeneous family of mutations (mt) in NSCLC that can be effectively treated with approved targeted agents. Unlike some other drivers in NSCLC, METex14 occurs in both squamous and adenocarcinoma histology and in both smokers and non-smokers. Here, we present updated results from analysis of a large dataset to characterize the mutational landscape within METex14 NSCLC. **Methods:** NSCLC tissue samples were analyzed with DNA-based next-generation sequencing (NGS; 592 genes, NextSeq) or whole-exome sequencing (NovaSeq). RNA-based whole transcriptome sequencing (WTS, NovaSeq), and PD-L1 immunohistochemistry (Dako 22C3) at Caris Life Sciences (Phoenix, AZ). METex14 was detected by WTS. TMB-high was defined as ≥ 10 mt/Mb. Chi-square, Fisher's exact or Mann-Whitney U tests were used to determine statistical significance and corrected for multiple hypothesis testing ($q < 0.05$). Immune cell estimates (quanTiseq) and pathway analysis (ssGSEA) were informed by WTS analysis. **Results:** A total of 711 METex14 cases were detected with 288 distinct METex14 mt. By histology, 79 (11.1%) were squamous (Sq), 478 (67.23%) were nonsquamous (nSq), and 24 (3.23%) were adenocarcinomas. The most common METex14 mt were D1028H (8.1%), D1028N (7.8%), c.3082+2T>C (5.0%), D1028Y (4.6%), and c.3082+1G>T (4.4%). Co-mutated TP53 was common (43.4%) but varied by specific METex14 mt, observed in 60.0% of MET c.3082+3A>G vs 16.7% of MET G344R. Co-amplified CDK4 was found in 9.3%, with 42.9% in MET c.2924-1G>A vs 6.7% in MET c.3082+1G>T ($p < 0.05$). High TMB was seen in 9%; median TMB ranged from 2 mt/Mb in MET c.3082+2T>A to 6.5 mt/Mb in MET c.3082+2T>G ($p < 0.05$). PD-L1 $\geq 1\%$ was seen in 80.8% compared to 56.2% in METex14-WT ($p < 0.05$), and median PD-L1 tumor proportion score (TPS) ranged from 0% in MET G344R to 75% in MET c.3082+2T>A ($p < 0.05$). Co-mutations varied by histology: in Sq-NSCLC, 18.18% had TP53 mt ($q < 0.05$), 8.97% had POT1 mt ($p < 0.05$), 6.06% had TERT mt ($p < 0.05$), 5.13% CASP8 mt ($q < 0.05$), and 2.53% RNF43 mt ($p < 0.05$), while in nSq-NSCLC, 45.51% had TP53 mt, 3.38% had POT1 mt, 0.87% had TERT mt, and 0% in CASP8 and RNF43 mt. Smoking status was available for 120 cases: 88% were smokers and 12% were nonsmokers. Wnt, Hedgehog, and Notch signaling were enriched in nSq ($q < 0.05$) while upregulation of KRAS signaling, Epithelial-Mesenchymal Transition, and angiogenesis pathways were enriched in smokers with METex14 NSCLC ($q < 0.2$). Higher estimates of neutrophils and lower estimates of M2 macrophages, NK cells, and CD8+ T-cells were observed in Sq-NSCLC. PD-L1, PD-1, HAVCR-2, IDO-1 and IFN- γ expression were higher in nSq than Sq-NSCLC ($q < 0.05$). **Conclusions:** METex14 NSCLC is highly heterogeneous, with variations in co-mutation, TMB, and PD-L1 expression. Although Sq- and nSq-NSCLC harbor METex14, the enrichment of oncogenic pathways and infiltrating immune cells differ between histology and smoking history. Research Sponsor: None.

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Poster Session

Characterization of diverse targetable alterations in ERBB2 and ERBB3 in 93,465 non-small cell lung cancers (NSCLC). *First Author: Dazhi Liu, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Recently, fam-trastuzumab deruxtecan-nxki was approved for NSCLC with selected activating ERBB2 (HER2) mutations. Patritumab deruxtecan, a novel HER3 directed antibody drug conjugate, exhibits *in vitro* activity against HER3 mutations. We present a comprehensive landscape of ERBB2/ERBB3 alterations (alt) that may predict sensitivity to HER2/HER3 targeted therapies in development. **Methods:** We queried an institutional database (Foundation Medicine) of tissue or liquid comprehensive genomic profiling (CGP) results from 93,465 patients with NSCLC (85,704 tissue and 7,761 liquid samples). ERBB2 amp was defined as $\geq$ sample ploidy +3. Activating/likely activating alts were called using annotations including presence in COSMIC, functional knowledge of the gene affected, internal insights, and characterization in the literature. ctDNA tumor fraction (TF) on FoundationOneLiquid Cdx was estimated using a composite algorithm. **Results:** Activating/likely activating alt in ERBB2 and ERBB3 were detected in 3.9% ($n = 3337$) and 0.8% ($n = 696$) of NSCLC tissue samples, respectively (ERBB2: 2.0% amp, 1.7% mutations [mut; SNVs or indels], 0.001% rearrangements [RE], and 0.2% multiple; ERBB3: 0.5% amp, 0.3% mut, and 0.004% multiple). Age at diagnosis, sex, and predicted ancestry were similar among patients with ERBB2alt and ERBB2wt tumors. ERBB2alt were more frequently observed in non-squamous NSCLC (4.3% vs 2.3% in SCC), largely driven by differential ERBB2 mut frequencies (2.0% vs 0.4%). ERBB2 mut were most common in the kinase domain (KD; 70%, 56% of which were exon 20 insertions [ex20ins]), followed by the extracellular domain (ECD; 20%) and transmembrane domain (TMD; 6%), while ERBB3 mut were most common in the ECD (88%, most commonly V104L/M and G284R). ERBB2 RE or splice mut affecting exon 16 were detected in 23 cases (0.03%). While ERBB2 alt were mutually exclusive with other oncogenic drivers (KRAS, ALK, BRAF, EGFR, MET, ROS1, RET; each $p < 0.05$), ERBB3 alt were found to co-occur with both ERBB2 (8.5% vs 3.9% ERBB2wt, $p < 0.001$) and MET (8.6% vs 5.2% ERBB2wt, $p < 0.001$) alt. A similar distribution of ERBB2 alt (1.6% amp, 2.4% mut, 0.4% multiple) was detected in liquid samples with elevated TF ($\geq 10\%$; $n = 1458$); across all liquid samples, ERBB2 mut frequency was comparable to tissue (1.5%) but frequency of amp was 0.5%. In our study, 26% of ERBB2 mut tissue samples had activating/likely activating mut not included in the DESTINY-Lung01 trial, most notably 100% of both TMD mut ($n = 99$) and exon 16 alt ($n = 25$), as well as 35% of ECD mut (117/331) and 14% of KD mut (162/1145), including 6% of ex20ins). **Conclusions:** Diverse ERBB2 and ERBB3 alt in NSCLC may predict sensitivity to anti-HER2/3 therapies, but not all classes of alts are detected/ reported by all profiling assays. Utilization of comprehensive testing to guide biomarker definitions, treatment selection, and clinical trial enrollment is imperative. Research Sponsor: Foundation Medicine, Inc.

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Poster Session

Long-term outcome for patients with advanced non-small-cell lung cancer treated by autologous cytokine-induced killer (CIK) cell immunotherapy in combination with sintilimab plus chemotherapy: NSCLC-CCICC-002. *First Author: Liang Liu, Tianjin Medical University Cancer Institute and Hospital, Tianjin, China*

Background: Autologous cytokine-induced killer (CIK) cell immunotherapy in combination with Sintilimab demonstrated robust antitumor activity and safety in the phase Ib CCICC-002 study (NCT03987867) of Non-Small-Cell Lung Cancer. Long-term outcomes in patients are reported herein. **Methods:** Systemic therapy naïve patients received platinum-based doublet chemotherapy, Sintilimab (PD1 inhibitor), and CIK cells every 3 weeks for 4 cycles, then maintenance treatment with Sintilimab in squamous and with Sintilimab plus pemetrexed in non-squamous NSCLC until disease progression or unacceptable toxicity or two years. Kaplan-Meier estimates of overall survival (OS) and progression-free survival (PFS) were calculated. OS and PFS were based on immune-related response criteria by investigator assessment (data cut-off, January 31, 2023). **Results:** From May 2019 to Jan 2021, CCICC-002 enrolled 33 patients (19 squamous, 14 non-squamous NSCLC; 1 patient was excluded because the second biopsy revealed EGFR mutation) aged 46-73 years with median follow-up was 31.4 months (range, 7.6-44.4 months). Estimated 3-year OS was 51.8% in all patients; median OS was not reached (95% CI, 26.6 months-not reached) in all patients. In subgroups, median OS was 27.6 months (95% CI, 13.4 months-not reached) in squamous NSCLC and not reached (95% CI, 29.9 months-not reached) in non-squamous NSCLC, respectively. Median OS was not reached (95% CI, 27.6 months-not reached) in PD-L1 positive patients and 28.3 months (95% CI, 15.6 months-not reached) in PD-L1 negative patients, respectively. Estimated 3-year PFS rate was 27.5% and median PFS was 17.9 months (95% CI, 8.2-26.5 months) in all patients. Median PFS was 17.3 months (95% CI, 5.0-24.0 months) in squamous NSCLC and 22.4 months (95% CI, 5.7 months-not reached) in non-squamous NSCLC, respectively. Median response duration was 18.7 months (95% CI, 10.1-27.6 months). 30.3% of patients were ongoing at data cut-off, and the longest response was ongoing at 41.3 months. 1 of the 5 CMR (complete metabolic response by PET-CT) patients experienced disease progression during observation. Treatment-related AEs (TRAES) occurred in 94.0% of patients and resulted in study discontinuation in 7.8%, and 15.2% experienced grade 3/4 TRAE. **Conclusions:** This long-term analysis of CCICC-002 represents the longest follow-up for CIK to date and confirms the durable antitumor activity and tolerability of CIK cells therapy in combination with Sintilimab plus chemotherapy in advanced NSCLC. Further studies are warranted to confirm these preliminary results. Clinical trial information: NCT03987867. Research Sponsor: Tianjin Medical University Cancer Institute and Hospital.

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Poster Session

A nation-wide genomic screening project for further development of targeted therapies in treatment-refractory non-small-cell lung cancer (LC-SCRUM-TRY). *First Author: Hiroki Izumi, National Cancer Center Hospital East, Kashiwa, Japan*

Background: Targeted therapies based on oncogenic drivers demonstrate dramatic and durable response in patients with non-small cell lung cancer (NSCLC). However, acquired resistance inevitably develop by diverse genomic resistance mechanisms. Genotype-matched targeted therapies to overcome treatment-resistance have not been established, except osimertinib against *EGFR* T790M mutation. **Methods:** We established a nation-wide genomic screening project in treatment-resistant NSCLC (LC-SCRUM-TRY; UMIN000041957) in September 2020 to identify the genetic resistant alterations, and to promote clinical therapeutic development. Enrolled patients have been screened for genetic alterations using a rapid next-generation sequencing (NGS) system, OncoPrint Precision Assay (OPA) for tissue samples, and Guardant 360 (G360) or OPA for plasma samples. *MET* amplification was also evaluated by FISH for NSCLC post EGFR-TKI treatment. **Results:** As of January 2023, 129 institutions in Japan were participating, and 1252 patients had been enrolled. Sample types were tissue (84%), and plasma (16%), respectively. Turn-around-time (median [interquartile range]) of OPA and G360 was 5 (4-6), and 9 (8-10.5) days, respectively. Of these, a total of 711 (57%) were already identified to have oncogenic driver at enrollment (*EGFR*, 556 [43%]; *ALK*, 70 [6%]; *RET*, 22 [2%]; *ROS1*, 21 [2%]; *KRAS*, 15 [1%]; *ERBB2* exon 20 insertion [ex20ins], 8 [0.6%]; *MET* exon 14 skipping [ex14skip], 8 [0.6%]; *BRAF*V600E, 7 [0.6%]; *NTRK3*, 2 [0.2%]; others, 2 [0.2%]). Of 556 *EGFR*-mutated NSCLC, 537 (97%) were enrolled post EGFR-TKIs. *EGFR* mutation subtypes were exon 19 deletion (52%), L858R (41%), ex20ins (1%), others (6%), respectively. Of 537 EGFR-TKI resistant tumors, 326 (40%) had at least one genetic alteration related with drug resistance, including *EGFR* alterations (amplification [13%], C797S [4%], A750P [3%], E709X [2%], L792X [1%], L718Q [1%]), *MET* amp (16%), and other driver mutation/rearrangement (8%). Through this screening, 37 (7%) of patients resistant to EGFR-TKI were enrolled into clinical trials, with 16/102 (16%) patients with targetable alterations (*MET* amp or *EGFR* C797S). In addition, of 541 NSCLC without oncogenic drivers at enrollment, 116 (21%) were identified to have actionable oncogenic drivers with FDA-approved drug (*KRAS* G12C, 23 [4%]; *ERBB2* ex20ins, 23 [4%]; *RET*, 13 [2%]; *MET* ex14skip, 13 [2%]; *EGFR* except ex20ins, [4%]; *EGFR* ex20ins, 10 [2%]; *ALK*, 6 [1%]; *ROS1*, 5 [1%]). **Conclusions:** LC-SCRUM-TRY contributes to the clinical development of precision medicine to overcome drug resistance, especially for *EGFR*-mutated NSCLC resistant to EGFR-TKI. This screening platform also help to practice precision medicine for patients initially diagnosed as driver-negative. Clinical trial information: UMIN000041957. Research Sponsor: Amgen, Nippon Boehringer Ingelheim, Takeda, Haihe Biopharma, AstraZeneca, Eli Lilly Japan, Janssen, Novartis, Turning Point Therapeutics, Spectrum Pharmaceuticals.

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Poster Session

Patient-reported outcomes in patients with metastatic non-squamous non-small cell lung cancer from the PERLA trial comparing first-line chemotherapy plus dostarlimab or pembrolizumab. *First Author: Martin Reck, Lungen Clinic, Grosshansdorf, Germany*

Background: PERLA (NCT04581824) is a global, randomized, Phase II, double-blind study assessing the efficacy and safety of chemotherapy (CT) combined with programmed death 1 (PD-1) inhibitors dostarlimab (dostCT) and pembrolizumab (pembCT) as first-line (1L) treatment (tx) for patients (pts) with metastatic non-oncogene-driven, non-squamous, NSCLC. DostCT had similar efficacy and safety to pembCT [1]. Exploratory analyses of patient-reported outcomes (PROs) from PERLA have been conducted. **Methods:** In PERLA, pts with ECOG status 0-1 were randomized 1:1 to receive ≤ 35 cycles (C) of dostCT or pembCT Q3W (CT was ≤ 35 cycles [C] of 500 mg/m² pemetrexed every 3 weeks [Q3W] and ≤ 4 C of cisplatin or carboplatin). PROs were collected at baseline (BL), Q3W until C4, Q9W until C16, Q12W until end of tx and at 30-day safety follow-up. Change from BL in EORTC QLQ-C30 and QLQ-LC13 were analyzed using a longitudinal mixed model, with a ≥ 10 -point change from BL considered clinically meaningful; scores were categorized as improved, stable, or worsened. Time to deterioration (TTD) in QLQ-C30 and selected QLQ-LC13 symptoms were estimated using Kaplan-Meier methods. **Results:** Analysis populations for dostCT/pembCT included 102/99 pts for QLQ-C30 and 96/90 pts for QLQ-LC13. Completion rates for QLQ-C30 and QLQ-LC13 were $>80\%$ up to C4 in both tx arms, decreasing after C7. At C13, 55.0% [n=33/60] and 54.2% [n=32/59] of dostCT pts, and 37.1% [n=23/62] and 35.7% [n=20/56] of pembCT pts completed QLQ-C30 and QLQ-LC13, respectively. Overall, least squares (LS) mean QLQ-C30 and QLQ-LC13 scores remained stable up to C13. Relative to BL, average pt functioning (e.g., physical, role) and cancer symptoms (e.g., pain, cough, dyspnea) were stable through C13 (~ 1 yr on tx); no clinically meaningful difference in LS mean QLQ-C30 or QLQ-LC13 scores were observed between tx arms. Across most QLQ-C30 and QLQ-LC13 subscales, $>60\%$ pts in both tx arms had stable or improved responses up to C13. At C13, meaningful improvements in chest pain and dyspnea were reported in a higher % of dostCT pts (34.4% [n=11/32] and 40.6% [n=13/32], respectively) than pembCT pts (10.0% [n=2/20] and 25.0% [n=5/20], respectively). TTD for QLQ-C30 and QLQ-LC13 subscales were comparable between tx arms, except for longer median TTD in dyspnea in dostCT pts (N=96) than pembCT pts (N=90) (4.24 vs 1.54 months; HR 0.64 [95% CI: 0.44-0.93]). **Conclusions:** HRQoL was similar and stable through C13 in both tx arms. These results supplement efficacy and safety data reported in PERLA and support further investigation of dostarlimab as an appropriate PD-1 inhibitor for use in combination with standard of care and novel therapies in metastatic NSCLC. References: 1. Peters, S *et al.* *IOTECH* 2022;16(S1):100162 Funding: GSK (213403). Editorial support provided by Fishawack Health, funded by GSK. Clinical trial information: NCT04581824. Research Sponsor: GSK (213403).

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Poster Session

Retrospective clinical analysis of circulating tumor DNA (ctDNA)-based molecular response (MR) and baseline blood-based tumor mutational burden (bTMB) for monitoring response in phase 3 trial of bintrafusp alfa vs. pembrolizumab treatment of non-small cell lung cancer (NSCLC). *First Author: Zheng Feng, Clinical Measurements Sciences, Global Research & Development, EMD Serono, Billerica, MA USA, an affiliate of Merck KGaA, Billerica, MA*

Background: The clinical utility of ctDNA-based approaches, such as bTMB and MR, to monitor and predict response during chemo-immunotherapy was evaluated using longitudinal cohort samples from a Phase 3 study of bintrafusp alfa versus pembrolizumab as a first-line treatment in patients with PD-L1 expressing advanced NSCLC. **Methods:** ctDNA was collected at baseline and day 42 after treatment with bintrafusp alfa (Q2W, 1200mg) or pembrolizumab (Q3W, 200mg). The GuardantOMNI liquid biopsy (LBx) assay was used to detect somatic alterations in 497 genes and generate bTMB from baseline, and MR scores from baseline and day 42 (n = 424 samples). bTMB and somatic alterations influencing response were explored. MR scores were calculated using the validated Guardant Response algorithm. Associations between ctDNA metrics and PFS were assessed. **Results:** 418/424 samples passed sequencing QC; of these, somatic mutations were detected in 236/237 baseline samples and 177/181 day 42 samples. Of 212 NSCLC patients with eligible bTMB results at baseline, 104 (49.1%) patients received bintrafusp alfa and 108 (50.9%) received pembrolizumab. bTMB high (bTMB-H) is defined as >20 mut/MB. In the bintrafusp alfa arm, PFS was significantly longer in patients with bTMB-H (median 8.3 months vs 2.7 months, p = 0.00086). In the pembrolizumab arm, PFS was also longer in patients with bTMB-H (median 5.65 months vs 5.5 months, p = 0.0898). Of 132 NSCLC patients with eligible MR results, 67 (50.8%) patients received bintrafusp alfa and 65 (49.2%) patients received pembrolizumab. In the bintrafusp alfa arm, molecular responders had significantly longer PFS (median 7.9 months vs 4.2 months, p = 0.00042). In the pembrolizumab arm, molecular responders also had significantly longer PFS (median 8.95 months vs 4.1 months, p = 0.00054). **Conclusions:** ctDNA analysis from plasma samples supported MR assessment in patients treated with ICI, indicating its utility as an adjunct to RECIST in monitoring of tumor response. Blood-based TMB-high was associated with immunotherapy treatment benefit. Analysis of b-TMB and MR allowed identification of patients with improved PFS in both treatment arms. Investigation of treatment specific TMB cut off selection and potential clinical utility of defined somatic mutations is ongoing. Clinical trial information: NCT03631706. Research Sponsor: This research was supported by the healthcare business of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945).

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Poster Session

RAMP 202: A phase 2 study of avutometinib (VS-6766) $\pm$ defactinib, in patients with advanced KRAS G12V mutant non-small cell lung cancer (NSCLC). *First Author: Joshua E. Reuss, Lombardi Comprehensive Cancer Center, Georgetown University, Washington, DC*

Background: *KRAS* mutations (mt) occur in $\sim 30\%$ of lung adenocarcinomas, among which G12C is most common (40%), followed by G12V (22%) and G12D (16%). Approved treatments for advanced *KRAS* mt NSCLC (excluding G12C) are limited to chemotherapy and immune checkpoint inhibitors (ICIs). Avutometinib is a novel small molecule RAF/MEK clamp. Focal adhesion kinase (FAK) activation is a resistance mechanism to RAF/MEK inhibition. Defactinib, a small molecule FAK inhibitor, has shown synergistic antitumor activity with avutometinib in preclinical models. In prior studies, avutometinib $\pm$ defactinib has shown responses in patients (pts) with *KRAS* mt NSCLC, including *KRAS* G12V. **Methods:** RAMP 202 is a randomized, phase 2, adaptive, multicenter, open-label study evaluating the efficacy and safety of avutometinib $\pm$ defactinib in previously-treated *KRAS* mt NSCLC (NCT04620330). Key inclusion criteria include histologically confirmed NSCLC with known *KRAS* mt and ≥ 1 prior systemic therapy (platinum-based and immune checkpoint inhibitor or appropriate therapy for activating mutation). Part A evaluated the optimal regimen, either 4.0 mg avutometinib orally (PO), twice weekly, 3 weeks on, 1 week off (mono) or 3.2 mg avutometinib PO twice weekly + 200 mg defactinib PO twice per day, 3 weeks on, 1 week off (combo) in pts with *KRAS* G12V mt NSCLC. Primary endpoint was confirmed objective response rate (ORR) by blinded independent central review. The optimal regimen determined in Part A would subsequently be assessed for efficacy in Part B. Exploratory assessment of ORR is also planned in *KRAS*-other (non-G12V) NSCLC. **Results:** Of 35 pts with *KRAS* G12V enrolled to Part A, 16 pts received mono, and 19 received combo. Patients received up to 5 lines of prior systemic therapy (median 2), including prior platinum-based chemotherapy, ICIs, and bevacizumab. No confirmed responses were seen in the mono group. In the combo group, 2 pts (11%) experienced a confirmed partial response. The duration of each response was 7.9 and 8.5 months, with both ongoing at data cut. The majority of treatment-related adverse events (TRAEs, any grade) (N = 72) were mild to moderate. The most common Grade ≥ 3 TRAEs included blood CPK increase (11.1%), diarrhea (5.6%), anemia (5.6%), and rash (1.4%). Most AEs were manageable/reversible. **Conclusions:** In this heavily pretreated population of patients with *KRAS* G12V mt NSCLC, limited clinical activity was observed with combination therapy. While no new safety signals were identified, criteria to proceed to part B were not met, and further evaluation of avutometinib $\pm$ defactinib in *KRAS* G12V mt NSCLC will not be pursued. Additional trials evaluating rational avutometinib combinations (sotorasib, adagrasib, everolimus) are ongoing in patients with *KRAS* mt NSCLC. Clinical trial information: NCT04620330. Research Sponsor: Verastem Oncology.

9101

Poster Session

Association between duration of immunotherapy and overall survival in advanced non-small-cell lung cancer. *First Author: Lova Sun, University of Pennsylvania, Philadelphia, PA*

Background: For patients (pts) with advanced non-small cell lung cancer (NSCLC) treated with front line immunotherapy-based treatment, the optimal duration of immune checkpoint inhibitor (ICI) treatment is unknown. We aimed to assess practice patterns surrounding ICI treatment discontinuation at two years, and to evaluate association of duration of therapy with overall survival by comparing pts who received fixed duration ICI therapy for 2 years vs those who continued therapy beyond two years. **Methods:** This study used the nationwide Flatiron Health electronic health record (EHR)-derived de-identified database, and included adult pts diagnosed with advanced NSCLC from 2016-2020, who received frontline immunotherapy-based treatment. Pts who were still on treatment without progression at 2 years were classified as “fixed duration” (treatment discontinuation at 2 years, between 700-760 days) vs “indefinite duration” (continued treatment beyond two years, > 760 days). Overall survival from 760 days was analyzed using Kaplan-Meier methodology. Multivariable Cox regression adjusted for patient and cancer-specific factors was used to compare survival between fixed and indefinite-duration groups. **Results:** Our analytic cohort consisted of 113 pts in the fixed duration group and 593 in the indefinite duration group; median age was 69, 49% were female, and 71% were White. Pts in the fixed duration group were more likely to have a history of smoking and be treated at an academic center. There was no significant difference in overall survival between pts in the fixed duration and indefinite duration groups, either on univariable (HR 1.26, 95% CI 0.77-2.08) or multivariable Cox regression (HR 1.33, 95% CI 0.78-2.25). **Conclusions:** In a real world cohort of advanced NSCLC pts treated with front line ICI, only about 1 in 5 stopped treatment at two years rather than continuing treatment beyond two years. The lack of significant overall survival advantage for the indefinite duration cohort on adjusted analysis provides reassurance to pts and providers who wish to stop therapy at 2 years. Research Sponsor: None.

9102

Poster Session

The final analysis of a phase I/II study of nivolumab, ipilimumab combined with nintedanib in advanced non-small cell lung cancer. *First Author: Sonam Puri, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT*

Background: Nintedanib (NT) is an oral triple kinase inhibitor that is active against NSCLC and inhibits the activity of the immunosuppressive cancer associated fibroblasts in the tumor microenvironment (TME). Targeting the TME with NT may represent an important synergistic approach in improving immunotherapy (IO) outcomes for NSCLC. We initiated a phase I/II trial to evaluate the combination of NT, nivolumab (N) and ipilimumab (I) in advanced (a)NSCLC. Based on the phase IB (dose escalation) results, the combination of N (3mg/kg/2w), I (1mg/kg/6w) and NT (150mg once daily) was declared as the recommended phase 2 dose (RP2D). Here we present the final analysis of the regimen in treatment naïve (TN), and IO pretreated (IP) aNSCLC. **Methods:** This is a single institution, non-randomized, parallel assignment phase I/II clinical trial of aNSCLC pts. Eligible pts were TN (Arm A) or with disease progression following IO (Arm B) with planned sample size of 40/arm. Enrollment into phase II was by the Bayesian two-stage design method with the primary objective of determining the overall response rate (ORR) in the intent to treat population. Key secondary objectives were overall survival (OS) and progression-free survival (PFS). Descriptive statistics were used to summarize demographic and safety data. The Kaplan-Meier method with log-rank test (5% level of significance, 95% CI and 2-sided test) was used for survival analysis. **Results:** 22 and 29 pts received the N+I+NT at the RP2D in Arm A and B, respectively. The median age was 67 [42;92] with 53% (27/51) females, 84% (42/51) Caucasian, ECOG 1 in 88% (45/51), and a current/prior history of tobacco use in 88% (45/51) pts. Adenocarcinoma histology was common (64%, 33/51) with PD-L1 ≥1% in 52% (22/42) pts. As of Oct 24, 2022, 18 and 26 pts were evaluable for response in Arm A and B, respectively. Clinical efficacy was observed in the TN and IP cohorts (Table). The most common treatment-related adverse events (TRAEs) were similar in both cohorts. TRAE of any grade in Arm A were nausea (8, 36%), diarrhea (8, 36%), fatigue (7, 32%), and in Arm B were nausea (10, 34%), fatigue (9, 31%), anorexia (8, 27%). **Conclusions:** The combination of nivolumab, ipilimumab and nintedanib had a manageable toxicity profile and demonstrated promising antitumor activity in both TN and IP aNSCLC patients. Clinical trial information: NCT03377023. Research Sponsor: Drug support BI, BMS, Other support: Florida Department of Health James and Esther King Grant.

	TN/Arm A (N=22)	IP/Arm B (N=29)
ORR, n, % (95% CI)	9, 40.9 (21.5, 63.3)	6, 20.7 (8.7, 40.3)
Best overall response, n (%)		
Complete response (CR), cCR*	1 (4.5), 0	1 (3.4), 1
Partial response (PR), cPR**	8 (36.4), 5	5 (17.2), 3
Stable disease (SD)	7 (31.8), 7	11 (37.9)
Progressive disease (PD)	3 (13.6)	9 (31.0)
Not evaluable/Not assessed	3 (13.6)	3 (10.3)
Disease control rate, % (95% CI)	72.7 [49.6, 88.4]	58.6 [39.1, 75.9]
Median PFS, mo (95% CI)	5.5 (2.9, N.E.)	2.7 (1.5, 6.9)
Median OS, mo (95% CI)	17.1 (5.5, N.E.)	8.5 (5.7, 25.3)

*Confirmed CR, ** Confirmed PR.

9103

Poster Session

Anti-tumor activity of sunvozertinib in NSCLC with EGFR sensitizing mutations after failure of EGFR TKI treatment. *First Author: James Chih-Hsin Yang, National Taiwan University Hospital, Taipei City, Taiwan*

Background: Sunvozertinib is a rationally designed, irreversible EGFR inhibitor targeting various EGFR mutations with wild-type EGFR selectivity. Clinical studies have showed its superior efficacy than current available therapies and favorable safety profile for treating NSCLC patients with EGFR exon20 mutations. Here we reported its anti-tumor activity in patients with EGFR sensitizing mutations (EGFRm) who failed from standard EGFR TKI treatment. **Methods:** This is a pooled analysis of three clinical studies in patients with EGFRm or HER2m NSCLC: WU-KONG1 (multinational phase I/II study, NCT03974022), WU-KONG2 (phase I study in China, CTR20192097), and WU-KONG15 (phase II study in China, NCT05559645). Patients were enrolled to receive sunvozertinib once daily at defined doses until discontinuation criteria were met. Patients who had EGFRm NSCLC, at least one measurable lesion at baseline, received at least one dose of sunvozertinib, and underwent at least one post-treatment RECIST assessment were evaluable for efficacy analysis. Patients with EGFRm or HER2m NSCLC who failed from standard systemic therapies and received at least one dose of sunvozertinib were included in the safety analysis. **Results:** As of October 17, 2022, a total of 32 patients who met efficacy evaluable criteria were included in the analysis. The doses of sunvozertinib ranged from 50 mg - 400 mg. Baseline characteristics: median age was 64.5 years old; 68.8% (22/32) were female; 75.0% (24/32) ECOG PS was 1; 34.4% (11/32) had more than three metastatic sites; 43.8% (14/32) had baseline brain metastases. Patients were heavily pretreated, with a median of 5 lines (range 1 - 16) of prior therapies. All patients had been treated with at least one type of EGFR TKI, including 68.8% (22/32) had been treated with a 3rd generation EGFR TKI. The majority of patients (29/32, 90.6%) had also been treated with chemotherapy. Anti-tumor activity was observed starting from 50 mg. Per investigators' assessment, the best objective response rate (BoR) was 21.9% (7/32). Anti-tumor activity was observed regardless of T790M mutation status. At the data cutoff date, the median duration of response and progression-free survival were 4.0 months and 5.9 months, respectively. Sunvozertinib was well-tolerated across all dose levels. The safety profile was similar to what has been previously reported. The longest treatment duration was more than 35 months (still ongoing). **Conclusions:** Sunvozertinib monotherapy demonstrated promising anti-tumor activity in heavily pretreated EGFRm NSCLC patients. Further clinical evaluation of sunvozertinib in this patient population is warranted. The updated data will be presented at the conference. Clinical trial information: NCT05559645 NCT03974022 and CTR20192097. Research Sponsor: Dizal Pharmaceutical.

9104

Poster Session

Association of alterations in multiple tumor suppressor genes with poor outcomes in patients with EGFR-mutant lung cancer. *First Author: Paul Stockhammer, Yale School of Medicine, New Haven, CT*

Background: Co-occurring alterations in tumor suppressor genes (TSG) have been described as determinants of disease heterogeneity in EGFR-mutant non-small cell lung cancer (NSCLC), however, detailed analyses of their impact on patient outcomes are limited. **Methods:** Patients with EGFR-mutant NSCLC treated with EGFR tyrosine kinase inhibitors (TKIs) at the Yale Cancer Center who had tumor genomic profiling either before EGFR-TKI therapy (pre-TKI) or at disease progression (post-TKI) were included. Whole exome sequencing (WES) of paired pre- and post-TKI tumor specimens were performed for a subset of patients. The cohort was divided into three subgroups based on alterations in *TP53* and five additional TSGs (*RB1*, *NF1*, *ARID1A*, *BRCA1* and *PTEN*): patients with tumors harboring a *TP53* mutation plus a mutation in at least 1 additional TSG (*TP53*^{mut}/TSG^{mut}), patients with tumors harboring a *TP53* mutation without an additional TSG mutation (*TP53*^{mut}/TSG^{wt}), and patients with *TP53*^{wt} tumors. Clinical characteristics including progression-free (PFS) and overall survival (OS) were assessed. **Results:** One-hundred-one patients were included in this retrospective study. *TP53* mutations were identified in 65 (64%) tumors, of which 23 (35%) and 42 (65%) were classified as *TP53*^{mut}/TSG^{mut} and *TP53*^{mut}/TSG^{wt}, respectively. Among those cases with paired WES available (n = 34), frequencies of alterations in the six included TSGs did not significantly differ between pre- and post-TKI tumor specimens. In the full study cohort, the presence of a *TP53* mutation was associated with numerically worse PFS (HR 1.46, CI 0.97 – 2.21, p = 0.09) and OS (HR 1.68, CI 1.05 – 2.70, p = 0.04) on first-line EGFR-TKI. Strikingly, after dividing the *TP53*^{mut} cohort into *TP53*^{mut}/TSG^{mut} and *TP53*^{mut}/TSG^{wt} cases, alterations in additional TSG were found to drive the poor outcomes: *TP53*^{mut}/TSG^{mut} cases had significantly worse PFS and OS on first-line EGFR TKI than *TP53*^{mut}/TSG^{wt} (mPFS 8.0 vs 10.6 months, p = 0.006; mOS 30.0 vs 33.3 months, p = 0.12) or *TP53*^{wt} cases (mPFS 8.0 vs 12.6 months, p < 0.0001; mOS 30.0 vs 48.8 months, p = 0.001). There was no significant difference in PFS or OS between patients with *TP53*^{mut}/TSG^{wt} and *TP53*^{wt} tumors. Similar outcome differences between the three groups were found in patients who received osimertinib in the second-line setting. **Conclusions:** The inferior outcomes associated with EGFR/*TP53*-mutant NSCLC tumors may be due to additional TSG alterations rather than *TP53* mutational status alone. Alterations in the investigated TSGs did not appear to emerge under EGFR-TKI therapy, which suggests that they are truncal. Our findings may have implications for understanding the biologic underpinnings of differential outcomes to EGFR TKIs. Research Sponsor: U.S. National Institutes of Health.

9105

Poster Session

Safety and efficacy of inetetamab in combination with pyrotinib in HER2 mutant patients with non-small cell lung cancer (NSCLC): An open-label, phase Ib trial. *First Author: Wenfeng Fang, Department of Medical Oncology, Sun Yat-sen University Cancer Center & State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangzhou, Guangdong, China*

Background: Currently, limited targeted therapies are available for HER2 mutant NSCLC patients. Previous studies have shown the antitumor activity of pyrotinib in advanced NSCLC patients with HER2 mutations. Inetetamab is a recombinant humanized anti-HER2 monoclonal antibody. Whether inetetamab combined with pyrotinib could show manageable safety and more active antitumor activity remains unknown. This study was designed to evaluate the safety and efficacy of inetetamab in combination with pyrotinib in HER2 mutant patients with advanced NSCLC. **Methods:** This study was an open-label, phase Ib study. The HER2 mutant patients with locally advanced or metastatic NSCLC were assigned to receive inetetamab combined with pyrotinib. The study consisted of dose-escalation part and dose-expansion part. During dose-escalation period, the parallel "3+3" dose-escalation design was used to determine the dose-limiting toxicity (DLT). Inetetamab was administered every 3 weeks (8 mg/kg loading dose for cycle 1, followed by 6 mg/kg in subsequent cycles) with pyrotinib (dose-escalation part, 240mg QD, 320mg QD; dose-expansion part, 320mg QD). Primary endpoint of the study was DLT dosage and safety. The DLT was assessed during the 21-day DLT evaluation period after the first dose. Secondary endpoints included objective response rate (ORR), disease control rate (DCR), progression free survival and overall survival. **Results:** Between August 6, 2021, and August 25, 2022, 48 patients were enrolled. No DLT occurred during pyrotinib 240mg and 320mg escalation period. Therefore, pyrotinib 320mg was chosen as expansion dose. The most common treatment-related adverse events (TRAEs) were diarrhea (66.7% [2/3] in pyrotinib 240mg group, 95.6% [43/45] in pyrotinib 320mg group), rash (66.7% [2/3] in pyrotinib 240mg group, 22.2% [10/45] in pyrotinib 320mg group) and vomiting (0 in pyrotinib 240mg group, 24.4% [11/45] in pyrotinib 320mg group). TRAEs were generally Grade (G) 1-2. Only 7 patients reported G3 TRAE (1 in pyrotinib 240mg group, 6 in pyrotinib 320mg group). The preliminary efficacy was shown in the table below. The ORR and DCR of group receiving inetetamab with pyrotinib 240mg were 0% and 66.7%, respectively. The ORR and DCR of inetetamab with pyrotinib 320mg group were 36.6% and 85.4% respectively. The relationship between different mutation subtypes or co-mutations and efficacy will be updated during the conference reports. **Conclusions:** The preliminary data of inetetamab in combination with pyrotinib showed manageable safety and compelling antitumor activity in advanced NSCLC patients harboring HER2 mutations. Clinical trial information: NCT05016544. Research Sponsor: None.

Response	Inetetamab with Pyrotinib 240mg (n = 3)	Inetetamab with Pyrotinib 320mg(n = 41)
Partial response	0	15
Stable disease	2	20
Progressive disease	1	6
ORR	0	36.6%
DCR	66.7%	85.4%

9107

Poster Session

Clinical and molecular features of long-term response to anti-PD-(L)1 therapy in patients with advanced non-small cell lung cancer. *First Author: Rohit Thummalapalli, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: PD-(L)1 blockade can generate long-term responses in subsets of patients (pts) with advanced non-small cell lung cancer (NSCLC), but the clinical and molecular features of long-term responders (LTR) are not well established. Whereas features predictive of initial response have been rigorously explored, long-term follow up in large cohorts is required to identify features distinguishing LTR from short-term responders (STR). **Methods:** We analyzed pts with advanced NSCLC treated with anti-PD-(L)1 therapy at three institutions (MSK, DFCI, MDACC) between 2011 and 2022; responses were assessed by RECIST. LTR was defined as partial response (PR) or complete response (CR) $\geq$ 24 months; STR was defined as PR/CR $<$ 12 months followed by progressive disease (PD). PD-L1 IHC, tumor mutational burden (TMB), next generation sequencing (NGS), and whole exome sequencing (WES) results from subsets of pts were analyzed. High TMB was defined by harmonized TMB z-score $\geq$ 0 ($\geq$ median TMB in each cohort: $\geq$ 7.9 for MSK, $\geq$ 10.5 for DFCI). **Results:** Among 3240 pts overall (MSK = 1536, DFCI = 1238, MDACC = 466), LTR was achieved in 267 (8.2%, 95% CI 7.3 to 9.2%) and STR was achieved in 213 (6.6%, 95% CI 5.7 to 7.5%), with similar rates from each site. 5-year overall survival (OS) was 83% among LTR and 20% among STR. In univariate analyses, non-squamous histology (non-SQ: odds ratio [OR] 2.13, $p = 0.005$), peripheral blood derived neutrophil to lymphocyte ratio (dNLR) $<$ 3.0 (OR 2.15, $p < 0.001$), and high TMB (OR 2.25, $p = 0.001$) were associated with LTR compared to STR; high PD-L1 (PD-L1 $\geq$ 50%: OR 1.19, $p = 0.494$) was not. In multivariate analyses, non-SQ histology (OR 2.56, $p = 0.047$) and high TMB (OR 2.73, $p = 0.001$) remained independently associated with LTR over STR. Among LTR compared to patients with best response of PD, dNLR $<$ 3.0 (OR 1.72, $p = 0.030$), high PD-L1 (OR 5.23, $p < 0.001$), and high TMB (OR 2.55, $p = 0.001$) associated with LTR. LTR showed deeper radiographic responses compared to STR (best response of -50% or greater: OR 3.88, $p < 0.01$). Among 1798 pts with NGS, pathogenic *ARID1A* alterations were numerically higher among LTR compared to STR, but this was not significant when accounting for multiple hypothesis testing (14% vs 2%, $p = 0.022$, $q = 0.196$). Among 73 pts with available WES, both clonal ($p = 0.037$) and subclonal TMB ($p = 0.010$) were significantly higher among LTR compared to STR. **Conclusions:** We report outcomes from $>$ 10 years of advanced NSCLC pts treated with anti-PD(L)1 therapy in a large multicenter cohort, with on-going response at 2 years associated with $>$ 80% 5-year OS. High TMB was a strong independent predictor of LTR over STR. Non-squamous histology, low dNLR, and depth of response also correlate with LTR, while no individual genomic alterations clearly distinguish LTR. These features may assist in identifying pts more likely to derive durable benefit from anti-PD(L)1 therapy without treatment intensification. Research Sponsor: U.S. National Institutes of Health.

9106

Poster Session

Dacomitinib for patients with non-small cell lung cancer harboring uncommon epidermal growth factor receptor mutations: Do mutation patterns matter? *First Author: Hong-Shuai Li, Department of Medical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China*

Background: Previous evidence has revealed the potential efficacy of dacomitinib in patients with advanced non-small cell lung cancer (NSCLC) carrying uncommon epidermal growth factor receptor (EGFR) mutations, but it remains unknown whether there are differences in its efficacy for different combination patterns of these uncommon mutations. **Methods:** The AFANDA cohort, an ambispective cohort including 121 NSCLC patients with uncommon EGFR mutations admitted from two tertiary hospitals in China, was employed for exploration. Meanwhile, a cohort of 63 patients with common mutations was included for comparison. Objective response rate (ORR), progression-free survival (PFS), and adverse events (AEs) were assessed between groups. **Results:** A total of 133 patients with advanced or recurrent NSCLC that received dacomitinib were eligible for analysis. Baseline characteristics were balanced between subgroups. A significant difference was observed between patients with common mutations (C group, $n = 63$), common mutation plus uncommon mutations (C+U group, $n = 24$), and uncommon mutations (U group, $n = 46$) regarding to PFS (mPFS: 7.07, 8.17, and 11.97 months; $p = 0.026$). Moreover, the highest ORR and DCR of the U group were observed among subgroups, although the differences were not statistically significant (ORR, 40.4%, 40.9%, and 61.4%; $p = 0.085$; DCR, 78.9%, 72.7%, 90.9%; $p = 0.134$). Furthermore, the multivariate analysis revealed that the mutation pattern was an independent prognostic indicator of PFS ($p = 0.049$), with the C+U group having the highest risk of progression (HR [hazard ratio]: 1.438, 95% CI [confidence interval]: 0.818-2.528) while the U group having the lowest one (HR: 0.666, 95% CI: 0.409-1.084). For toxicity analysis, no significant difference was observed regarding grade 3-4 AEs among subgroups (12.7%, 8.3%, 13.0%; $p = 0.827$). The drug resistance analysis did not reveal a significant difference concerning the secondary T790M mutation rate (26.3%, 0%, 13.3%; $p = 0.331$). **Conclusions:** Dacomitinib demonstrated different therapeutic efficacy for patients with NSCLC harboring different combination patterns of uncommon EGFR mutation, which should be considered in clinical trials' design and clinical application. Research Sponsor: None.

Multivariate Cox regression analysis.				
Variables	N	Multivariate Analysis		
		HR	95% CI	p value
Number of distant metastatic organs				< 0.001
≤3	104/29	2.741	1.667-4.507	
Stage				0.060
III+IV	106/27	0.551	0.296-1.026	
Recurrence				< 0.001
Application line				
1	71	Reference	/	
2	21	1.629	0.886-2.998	0.116
≥3	41	4.607	2.830-7.498	< 0.001
Application dosage		0.655	0.447-0.960	0.030
15mg	15			
30mg	88			
45mg	28			
Others	2			
Mutation group				0.049
C	63	Reference	/	
C+U	24	1.438	0.818-2.528	0.207
U	46	0.666	0.409-1.084	0.102

9108

Poster Session

Tissue and plasma-based mechanisms of resistance to first-line osimertinib in EGFR-mutant NSCLC: A multi-institutional cohort. *First Author: Zofia Piotrowska, Massachusetts General Hospital, Harvard Medical School, Boston, MA*

Background: Osimertinib (osi) is the preferred 1st line (1L) therapy for patients (pts) with EGFR+ NSCLC, but acquired resistance is universal. Identification of mechanisms of resistance (MoR) to 1L osi can inform subsequent therapies. We report a retrospective, multi-institutional cohort of pts with tissue biopsy (TBx) and/or liquid biopsy (LBx) upon 1L osi progression (PD). **Methods:** Pts with advanced EGFR+ NSCLC who had TBx and/or LBx (for ctDNA analysis) obtained at PD on 1L osi at 8 participating institutions were included. Molecular testing was performed using next-generation sequencing (NGS) and, in a subset, FISH per local standards. We retrospectively collected clinical characteristics, tissue histology, NGS/FISH results and subsequent therapies. **Results:** 193 pts (128 female; median age 64 yrs) had TBx ($n = 129$) and/or LBx ($n = 122$) upon PD on 1L osi, 58/193 had both tissue and ctDNA. Primary EGFR mutations included del19 (102), L858R (76), and other (15). Median time from osi start to first bx was 14 mos (range, 1-55). MoRs are summarized in the table. In all, 86/193 (45%) pts had a known MoR identified on TBx and/or LBx. Among 129 pts with TBx, histologic transformation (trans) and MET amplification (amp) were the most common MoR, each seen in 16% pts. Among 122 pts with LBx, secondary EGFR mutations were the most common MoR, seen in 15%. Among the 58 pts with both TBx + LBx, discordance between major MoRs was seen in 21/58 pts (36%), most commonly due to histologic trans detected on TBx only ($n = 7$) and discordant MET amp status ($n = 8$; 6 TBx+/LBx-, 2 TBx-/LBx+). No MoR was identified in 53% TBx and 75% LBx (including 14% Lbx where the original EGFR mutation was not detected in ctDNA). Results of TBx led to MoR-directed 2L therapy in 41/129 (32%) pts, while LBx results led to MoR-directed 2L therapy in 16/122 (13%). **Conclusions:** In this large, multi-institutional cohort, histologic trans (16%) and MET amp (16%) were the most common MoR to 1L osimertinib on tissue bx. In ctDNA, secondary EGFR mutations (15%) were the most frequent MoR. The results of TBx were more likely to impact second-line therapy than LBx. Our results underscore the importance of tissue biopsy (and limitations of liquid biopsy) after osimertinib PD, where tissue testing remains the gold standard. In addition, with more than half of patients having no identifiable MoR despite comprehensive testing, our results highlight the need for MoR-agnostic treatment strategies. Research Sponsor: None.

Major MoR	Tissue (N = 129) n (%)	ctDNA (N = 122) n (%)
Secondary EGFR Mutations	12 (10)	18 (15)
- C797S	7 (5)	10 (8)
- Other (G724S, L718QV, T790M)	5 (4)	8 (7)
MET Amp	20 (16)	7 (6)
MET Exon 14 Skipping		1 (1)
HER2/HER3 Amp	1 (1)	1 (1)
KRAS Amp/KRAS Mutation	4 (3)	2 (2)
BRAF V600E	3 (2)	3 (3)
Fusion (ALK, RET or BRAF)	2 (2)	3 (3)
PIK3CA	3 (2)	3 (3)
Histologic Trans	20 (16)	N/E
- SCLC	16 (12)	
- Squamous	3 (2)	
- SCLC + Squamous	1 (1)	
Multiple MoR Detected	5 (4)	6 (5)
No identified MoR	69 (53)	91 (75)

9109

Poster Session

Contemporary biomarker testing rates in both early and advanced NSCLC: Results from the MYLUNG pragmatic study. *First Author: Makenzi Colleen Evangelist, US Oncology Research/New York Oncology Hematology, Albany, NY*

Background: The MYLUNG (Molecularly Informed Lung Cancer Treatment in a Community Cancer Network) consortium pragmatic study aims to identify and overcome barriers to timely and appropriate biomarker testing in patients (pts) with NSCLC. We previously reported retrospective real-world testing rates for 5 biomarkers from 2018-2020 in metastatic pts. We now report results from the prospective observational phase, including additional biomarkers in pts with both early and advanced NSCLC. **Methods:** This was a prospective, non-interventional cohort study of newly diagnosed pts with early stage (ES), locally advanced (LA), or metastatic NSCLC (mNSCLC) between 12/2020 and 9/2022 and enrolled from 12 community practices (69 sites) across The US Oncology Network. The proportion of pts with test results for 9 biomarkers at time of protocol initiation were examined: ALK, BRAF, EGFR, ROS1, PD-L1, KRAS, MET, NTRK, and RET. Timing of tests, use of single vs multigene NGS testing, clinical and socioeconomic factors, and reasons for not testing were collected in real time. **Results:** Of 1002 pts screened, 987 were enrolled and analyzed. There were 405 stage IB-IIIC pts (n = 284 stage IB-IIIA (ES cohort); n = 121 stage IIIB-IIIC (LA cohort)) and 582 stage IV pts (mNSCLC cohort). Descriptions for ES and LA vs mNSCLC pts respectively include median age 68 vs 69 yrs, 49% vs 52% female, 83% vs 77% white, 58% vs 79% adenocarcinoma histology, 71% vs 68% ECOG 0-1, and 33% vs 30% high school education level. Testing rates for ES vs mNSCLC cohorts are shown in the table below: prior to treatment initiation, 64% of ES and 83% of mNSCLC pts had at least one biomarker result; and 37% of mNSCLC pts had results for all 9 biomarkers. NGS testing occurred in 37% and 57% of the ES and mNSCLC cohorts respectively. Reasons for not testing included: barriers to ordering (42%, 25%), insufficient tissue (18%, 18%), clinical deterioration/crisis (5%, 12%), and other reasons (37%, 49%), respectively. **Conclusions:** As more genomic alterations are identified in NSCLC, we observed that many pts do not get full genotyping prior to treatment, and biomarker testing remains of utmost importance. Further analyses by distinct stages (e.g. LA), histology, social determinants, utilization of targeted therapies, and other reasons for not testing will be performed. These data will be used to evaluate future prospective interventions for MYLUNG, to help improve comprehensive biomarker testing for NSCLC. Research Sponsor: Amgen, AstraZeneca, Eli Lilly, Genentech, Mirati.

	Early Stage Stage IB-IIIA N = 284	mNSCLC Stage IV N = 582
Pts receiving treatment, n	273	555
Pts with biomarker result prior to treatment, n (%)^a	174 (64)	461 (83)
ALK ^b	114 (66)	356 (77)
BRAF ^b	117 (67)	336 (73)
EGFR ^b	142 (82)	372 (81)
KRAS ^b	108 (62)	295 (64)
MET ^b	106 (61)	330 (72)
NTRK ^b	78 (45)	254 (55)
PD-L1 ^b	151 (87)	390 (85)
RET ^b	106 (61)	306 (66)
ROS1 ^b	114 (66)	345 (75)

^aDenominator: pts receiving treatment ^bDenominator: pts with biomarker result prior to treatment.

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Poster Session

A first-in-human phase I, dose-escalation and dose-expansion study of SY-5007, a highly potent and selective RET inhibitor, in Chinese patients with advanced RET positive solid tumors. *First Author: Caicun Zhou, Department of Medical Oncology, Shanghai Pulmonary Hospital and Thoracic Cancer Institute, Tongji University School of Medicine, Shanghai, China*

Background: RET gene fusions have been identified as oncogenic drivers in 1-2% of non-small-cell lung cancer (NSCLC) and 10-20% of papillary thyroid carcinomas. Activating RET mutations occur in 50-60% of medullary thyroid cancer (MTC). Recently, selective RET TKIs, selpercatinib and pralsetinib, were approved for RET positive solid tumors by FDA. SY-5007 is a highly potent RET inhibitor that selectively targets RET fusions and mutations. This study is to investigate the safety, PK characteristics and preliminary efficacy of SY-5007 in Chinese patients with advanced RET-altered solid tumors. **Methods:** In this first-in-human phase I study, eligible patients previously treated and with positive RET were enrolled. In the dose escalation phase, following 3+3 design, the patients were administered orally with SY-5007 20 mg once daily, or 20, 40, 80, 120, 160, 200 mg twice daily in a 28-day cycle. The expansion doses (160 and 200 mg twice daily) were executed in a dose expansion phase to determine a recommended phase II dose (RP2D). Then three cohorts (RET fusion-positive NSCLC or thyroid cancers and RET mutant MTC) at RP2D were expanded in eligible patients. Primary endpoints included safety, tolerability, MTD, DLTs. Secondary endpoints included PK and preliminary antitumor activity of SY-5007 per RECIST v1.1. **Results:** As of Feb.06, 2023, a total of 60 patients including 55 RET fusion NSCLC and 5 RET mutant solid tumors were enrolled into dose escalation cohorts (n = 17) and dose expansion cohorts (n = 43). Totally, 55 (91.7%) patients experienced treatment-related adverse events (TRAEs) including increased aspartate aminotransferase (50.0%), increased alanine aminotransferase (41.7%), diarrhea (41.7%), etc. Grade ≥3 TRAEs were observed in 22 (36.7%) patients including hypertension (15%), diarrhea (5%), increased alanine aminotransferase (3.3%), etc. PK study showed SY-5007 was absorbed rapidly, exposure of SY-5007 increased in a dose-dependent manner at doses between 20 and 160 mg twice daily, and it was saturated at 160 mg twice daily. In 50 evaluable patients, the overall ORR and DCR was 62.0% (95% CI, 47.2-75.4) and 94.0% (95% CI, 83.5-98.8), respectively. 29 patients (24 NSCLC, 4 MTC) received SY-5007 at 160 mg twice daily, 27 of 28 (96.4%) evaluable patients showed tumor regression, ORR and DCR was 72.4% (95% CI, 52.8-87.3) and 89.7% (95% CI, 72.7-97.8), respectively. For NSCLC patients, the ORR and DCR was 75.0% (95% CI, 53.9-90.2) and 91.7% (95% CI, 73.0-99.0), respectively. **Conclusions:** SY-5007 was well tolerated in patients. Preliminary anti-tumor activity was also observed in patients with advanced RET-fusion positive NSCLC and RET mutant MTC. The pivotal Phase II clinical study of SY-5007 in NSCLC patients is ongoing. Research Sponsor: Shouyao Holdings (Beijing) Co., Ltd. Clinical trial information: NCT05278364. Research Sponsor: Shouyao Holdings (Beijing) Co., Ltd.

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Poster Session

Efficacy and safety of SY-3505, a third-generation ALK TKI, in ALK-positive advanced non-small cell lung cancer: Results from a phase I/II, multi-center study. *First Author: Yuankai Shi, Department of Medical Oncology, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing Key Laboratory of Clinical Study On Anticancer Molecular Targeted Drugs, Beijing, China*

Background: SY-3505 is a potent, brain-penetrant, 3rd-generation (gen) anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitor (TKI) with preclinical activity against both wild-type and most known resistance mutations of ALK occurring in 1st and 2nd-gen ALK TKI-resistant patients. Here we report the efficacy and safety results from the ongoing phase I/II study of SY-3505. **Methods:** Patients aged ≥18 years with histologically/cytologically confirmed, advanced, ALK-positive non-small cell lung cancer (NSCLC) and an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0-2 were recruited from 13 hospitals in China. In phase I study, patients received SY-3505 from 25-800mg once daily in dose-escalation phase, followed by dose-expansion at 500/600mg. Patients received alectinib only or ≥2 prior ALK TKIs were recruited in phase II study and treated with SY-3505 at 600mg once daily. The primary endpoint was investigator (INV)-assessed objective response rate (ORR) per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Secondary endpoints included disease control rate (DCR), duration of response (DoR), progression-free survival (PFS), overall survival (OS) and safety. **Results:** At data cut-off date of Feb.03, 2023, 92 ALK-positive NSCLC patients were enrolled in phase I/II, 82 were evaluable for efficacy, the ORR was 34.2% (95% confidence interval [CI] 24.0-45.5%), DCR was 74.4% (95% CI 63.6-83.4%). Herein the ORR and DCR of 59 patients in phase I for dose-escalation and dose-expansion was 32.3% (95% CI 20.6-45.6%) and 69.5% (95% CI 56.1-80.8%), respectively; median DoR and PFS was 11.1 (95% CI 5.28-not reached [NR]) and 6.20 (95% CI 3.08-10.3) months, respectively. Fifty-six patients received SY-3505 at 600mg once daily (two patients received non-alectinib 2nd-gen ALK TKI only, 22 received alectinib only and 32 received ≥2 prior ALK TKIs). Thirty-two (57.1%) patients experienced treatment-related adverse events (TRAEs) and two (3.6%) had grade ≥3 TRAEs. The most common TRAEs were diarrhea (42.9%), nausea (28.6%) and vomiting (26.8%), consistent with previous reported in phase I. Forty-seven patients were evaluable for efficacy, the ORR and DCR was 38.3% (95% CI 24.5-53.6%) and 83.0% (95% CI 69.2-92.4%), respectively. Median DoR and PFS were NR. Twenty-two patients had baseline central nervous system metastases, the ORR and DCR was 50.0% and 86.4%, respectively. **Conclusions:** SY-3505 was well-tolerated and showed significant and durable clinical activity in ALK-positive NSCLC patients who received at least one prior 2nd-gen ALK TKI, demonstrating a potential new treatment option for these patient population. Pivotal clinical study will be performed in future. Clinical trial information: NCT05257512. Research Sponsor: Shouyao Holdings (Beijing) Co., Ltd.

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Poster Session

Phase 1 study evaluating the safety, tolerability, pharmacokinetics (PK), and efficacy of GEC255, a novel KRAS^{G12C} inhibitor, in advanced solid tumors. *First Author: Yan Zhang, Department of Thoracic Oncology, Cancer Centre, Sichuan University West China Hospital, Chengdu, China*

Background: The KRAS^{G12C} mutation occurs in 12-14% of NSCLC and in 3-5% of CRC patients and is recognized as an oncogenic driver mutation. Recently the discovery of a cryptic binding pocket within the effector region of the KRAS^{G12C} oncoprotein has led to the rapid clinical development of a new series of specific inhibitors. GEC255 is a novel small molecule which showed excellent target engagement ability and a favorable pharmacological profile. **Methods:** This is a phase 1, open-label, multicenter study (CTR20212486) to evaluate the safety, tolerability, pharmacokinetics (PK), and efficacy of GEC255 in patients (pts) with advanced solid tumors bearing KRAS^{G12C} mutation. The primary endpoint is safety and key secondary endpoints include PK and ORR. Key inclusion criteria: KRAS^{G12C} mutation identified through digital PCR, measurable or evaluable disease, ECOG PS ≤1, and life expectancy > 3 months. Key exclusion criteria: previous administration of specific KRAS^{G12C} inhibitors, uncontrollable plasma cavity effusion. Phase 1a is an accelerated titration, dose-escalating study to determine the maximum tolerated dose (MTD) or recommended phase 2 dose (RP2D). Phase 1b is a dose expansion study which will enroll pts with NSCLC, CRC, and other solid tumors harboring the KRAS^{G12C} mutation. GEC255 will be administered PO QD until disease progression, intolerance, or withdrawal of consent. **Results:** 16 NSCLC pts (15 men, 1 woman, median age 58 y) were enrolled in Phase 1 dose escalation for the first 4 dose cohorts followed with dose escalation in chosen doses. No dose-limiting toxicity was observed and MTD has not been identified yet. GEC255 showed the linear increase in AUC exposure and C_{max} with increasing doses. T_{max} was 2-4 hours in all dosing groups and C_{trough} within the 24-hour period was higher than pERK IC₅₀ even in low dose group. The half-life of GEC255 in 24h period is about 8-9h and there is no increase in AUC upon daily dosing for 28 consecutive days. Among the 16 pts, most pts (n = 13) had ≥1 prior lines of treatment (tx). A total of 15 patients had treatment-related adverse events and most AEs are G1 or G2 (93.3%); the most frequent AEs are diarrhea (56.3%), ALT increase (37.5%), rashes (25%), and anemia (25%). Tumor response was evaluated in 13 pts. 10 pts (76.9%) had objective response (complete or partial response) and 12 pts (92.3%) had disease control (objective response or stable disease). In 600mg dose group, the ORR was 83.3% and DCR was 100% (n = 6). 7 pts are continuing to receive GEC255. **Conclusions:** GEC255 has been well tolerated at the doses tested and has shown encouraging anticancer activity to advanced NSCLC patients with KRAS^{G12C} mutation pts. MTD has not been determined, and enrollment into the dose exploration is ongoing. (<http://www.chinadrug-trials.org.cn/index.html>). Clinical trial information: CTR20212486. Research Sponsor: GenEros Biopharma Research Center, Hangzhou, Zhejiang, China.

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Poster Session

First-in-human, multicenter phase I study of TGRX-326 in patients with advanced ALK-positive non-small cell lung cancer. *First Author: Hongyun Zhao, Department of Clinical Research, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangzhou, China*

Background: TGRX-326, a deuterated derivative of lorlatinib (LOR), is a potent 3rd generation ALK and ROS1 dual TKI with high potency against multiple ALK-resistant mutations. Deuteration of the key metabolic site of the molecule allows to achieve a higher exposure than with LOR and this may result in alleviated toxicities and better efficacy. **Methods:** The study comprised 3 phases: dose escalation (D-ESCAL), dose expansion (D-EXP) and cohort expansion (C-EXP). In D-ESCAL and D-EXP, ALK+ pts prior failed on 2nd gen ALK-TKIs or ROS1+ pts resistant to crizotinib (CRZ) were enrolled; in C-EXP, ALK+ pts progression after CRZ (C-EXP-A1), progression after ≥ 1 2nd gen TKIs (C-EXP A2), ROS1+ progression after CRZ (C-EXP-B) and pts with ALK TKI naïve (C-EXP-C) were enrolled. **Results:** Up to Jan 13, 2023, 185 pts (median age 53 years, 45.9% male) were enrolled; Median treatment and follow-up was 5.5 and 6.7 months, respectively. There were no DLT observed and no MTD identified in D-ESCAL (5-125mg QD, n=19). Based on the safety, efficacy and PK exposure data of 42 pts in D-ESCAL and D-EXP, 60 mg QD was selected as the RP2D for C-EXP, the average AUC₀₋₂₄ of 60mg QD reached to 5443ng*hr/mL. Treatment-related adverse events (TRAEs) occurred in 87.5% patients (162/185), the most common TRAEs were hypercholesterolemia (74.1%), hypertriglyceridemia (68.1%), weight gain (36.2%), peripheral edema (15.7%), peripheral neuropathy (14.1%). As for R2PD, 132 of 155 (85.2%) experienced TRAEs, Grade ≥3 TRAEs occurred in 19.7%, most frequent were hypertriglyceridemia (11%) and hypercholesterolemia (8.4%). Dose interruptions and dose reductions associated with TRAEs were reported in 10 (5.4%) and 5 (2.7%) pts respectively. Confirmed response were observed in 142 ALK+ pts enrolled in C-EXP, results are shown in the Table (Efficacy of B-ROS1+ pts will be reported separately). Eleven ALK mutations were detected in 16 pts (either alone or in combination); 50.0% pts achieved PR. Out of 6 pts who were positive for G1202R, 50.0% experienced PR. **Conclusions:** TGRX-326 was well tolerated in pts with advanced ALK+ NSCLC and showed promising clinical antitumor activity irrespectively of ALK+ resistance to CRZ and 2nd gen TKIs, especially among those with brain metastases. Impressive activity was seen in ALK TKI naïve NSCLC. TGRX-326 demonstrated antitumor activity against multiple ALK mutations including G1202R. Clinical trial information: NCT05441956. Research Sponsor: Shenzhen TargetRx, Inc.

	C-EXP A1	C-EXP A2	C-EXP A2	C-EXP A2	C-EXP C
Prior TKI	CRZ	1 ALK TKI ^a	2 ALK TKIs ^a	≥3 ALK TKIs ^a	None
Nr of pts	15	40	37	17	33
ORR, n (%)	9(60.0)	14(35.0)	14(37.8)	5(29.4)	24(72.7)
DCR, n (%)	15(100.0)	29(72.5)	31(83.8)	16(94.1)	30(90.9)
Nr of pts with IC target lesions	5	5	13	8	8
IC-ORR, n (%)	3(60.0)	4(80.0)	7(53.8)	6(75.0)	6(75.0)
IC-DCR, n (%)	5(100.0)	4(80.0)	11(84.6)	8(100.0)	8(100.0)

IC: intracranial;^aLines of therapy.

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Poster Session

Implementation strategies for monitoring adherence in real time (iSMART): A pilot randomized trial. *First Author: Katharine A. Rendle, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA*

Background: Helping patients to manage symptoms and adhere to oral anticancer agents (OACAs) is a major challenge in oncology. OACAs cause side effects that can lead to suboptimal adherence if not optimally managed, contributing to decreased effectiveness. Low-cost, text messaging approaches have shown promise, but have not been robustly studied in oncology. Guided by principles from implementation and behavioral science, we developed and tested the effect of an augmented intelligence chatbot on OACA adherence and symptom burden in patients with advanced lung cancer. **Methods:** We conducted a two-arm pilot randomized trial (NCT04347161) to evaluate the effect of the chatbot on OACA adherence and symptom burden compared to usual care. The chatbot engages patients via text messaging and applies natural language processing and machine learning to learn from interactions. Core functionalities include: 1) motivational daily adherence reminders, 2) longitudinal symptom monitoring with self-management support, and 3) bidirectional communication with clinical teams. Participants included English-speaking patients with advanced lung cancer treated with any of 9 OACAs targeting EGFR, ALK, or ROS-1. The primary outcome was 12-week adherence, measured using the microelectronic monitoring system (MEMS) and defined dichotomously if the patient achieved ≥95% adherent days or not. Secondary outcomes were assessed at baseline and 12 weeks using validated survey instruments, including symptom burden using the Edmonton Symptom Assessment System Total Distress Score (range 0-90), health-related quality of life (HRQOL) using EQ-5D-3L (range 0-100), and usability using Health-ITUES (range 1-5). We used multivariable logistic regression adjusting for stratification variables to test the chatbot's effect on adherence (intent-to-treat analysis) and evaluated mean differences (by arm) in secondary outcomes using Fisher's exact test. **Results:** From February 2021 to August 2022, 75 patients across 4 sites enrolled (median age 65 years, 64% female, 88% White, 21.3% high school education or lower); 50.7% (n=38) were randomized to intervention. Compared to usual care, we observed no significant differences in adherence in the intervention arm (78.8% vs 81.8%; aOR=1.7 95% CI: 0.3-9.4). However, in contrast to those in usual care, participants in the intervention arm had significantly greater decreases in symptom burden (mean difference: -2.7 vs 2.6; p<0.05) and increases in HRQOL (mean difference: 4.1 vs -4.8; p<0.05) from baseline to 12 weeks. Overall chatbot usability was high (mean score=3.9). **Conclusions:** In this pilot randomized trial, an augmented intelligence chatbot successfully reduced symptom burden and improved HRQOL but did not significantly alter OACA adherence. Chatbots are a potentially scalable strategy for improving symptom management that warrant study in larger randomized trials. Clinical trial information: NCT04347161. Research Sponsor: Lung Cancer Research Foundation grant supported by funds from Pfizer.

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Poster Session

SKB264 (TROP2-ADC) for the treatment of patients with advanced NSCLC: Efficacy and safety data from a phase 2 study. *First Author: Wenfeng Fang, Department of Medical Oncology, Sun Yat-sen University Cancer Center & State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangzhou, Guangdong, China*

Background: TROP2 (trophoblast cell surface antigen 2) is commonly overexpressed in non-small cell lung cancer (NSCLC) and associated with poor prognosis. SKB264 is a novel anti-TROP2 ADC developed using sulfonyl pyrimidine-CL2A-carbonate linker to conjugate its payload, a belotecan-derivative topoisomerase I inhibitor, to achieve an average Drug-to-antibody Ratio (DAR) of 7.4. The design was to achieve a more effective balance between stability in circulation and release of the ADC payload in tumor cells. Here we report clinical efficacy and safety results of SKB264 in the treatment of patients (pts) with NSCLC from a Phase 2 expansion cohort. TROP2 expression level by immunohistochemistry was assessed retrospectively. Correlation analyses between response and TROP2 level will be provided. **Methods:** This is a Phase 1/2, multicenter dose-escalation/expansion study in pts with relapsed or refractory locally advanced/metastatic NSCLC and other tumor types (NCT04152499). All NSCLC pts received SKB264 at 5 mg/kg IV Q2W. Tumor assessments based on RECIST 1.1 were performed every 8 weeks by investigators. **Results:** As of February 9th, 2023, 43 pts (63% male, 88% ECOG PS 1, median age 58 yrs [44-74]) were enrolled. Median follow-up was 11.5 months (mo; 95% CI, 10.4-12.2). Median treatment duration was 5.7 mo (range, 0.5-14.1). Among 39 response-evaluable pts, the ORR was 44% (17/39, 15 confirmed and 2 pending confirmation), median DoR was 9.3 mo (range, 1.3+ to 11.2+), 6-month DoR rate was 77%. For EGFR wild type subgroup (previously received median 2 lines of therapy including anti-PD-1/L1), the ORR was 26% (5/19), DCR was 89% (17/19), median PFS was 5.3 mo, and 9-month OS rate was 80.4%. For subgroup with TKI resistant EGFR mutant NSCLC (50% also failed at least one line of chemotherapy), the ORR was 60% (12/20), DCR was 100% (20/20), median PFS was 11.1 mo, and 9-month PFS rate was 66.7%. 67.4% (29/43) of pts had Grade ≥ 3 treatment-related adverse events (TRAEs). The most common Grade ≥3 TRAEs (occurred in ≥5% of pts) were neutrophil count decreased (32.6%), anemia (30.2%), white blood cell count (WBC) decreased (23.3%), stomatitis (9.3%), rash (7.0%), and lymphocyte count decreased (7.0%). Grade 4 TRAEs occurred only for neutropenia and WBC decreased. Most of the hematotoxicity occurred within the first two months of treatment and resolved after treatment with granulocyte colony stimulating factor or erythropoietin without blood transfusions. 23.3% (10/43) of the pts experienced dose reduction due to TRAEs. No neuropathy or drug-related ILD/pneumonitis was reported. No TRAEs led to treatment discontinuation or death. **Conclusions:** SKB264 at 5 mg/kg Q2W demonstrated encouraging anti-tumor activity and manageable safety profile in pts with relapsed or refractory locally advanced/metastatic NSCLC. TRAEs were mainly hematologic. Phase 3 studies of SKB264 in pts with advanced NSCLC have been planned. Clinical trial information: NCT04152499. Research Sponsor: Sichuan Kelun-Biotech Biopharmaceutical Co., Ltd.

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Poster Session

Characteristics of long-term survivors with EGFR mutant (EGFRm) metastatic non-small cell lung cancer (mNSCLC). *First Author: Melina Elpi Marmarelis, University of Pennsylvania, Philadelphia, PA*

Background: Although osimertinib has become standard first-line (1L) therapy for patients (pts) with EGFRm mNSCLC, a subset treated with earlier-generation EGFR-targeted TKIs and chemotherapy have had long-term survival. We sought to characterize clinical features of long-term survival in pts with EGFRm mNSCLC treated prior to the osimertinib era. **Methods:** Data were abstracted from electronic medical records at 12 cancer centers participating in the Academic Thoracic Oncology Medical Investigator's Consortium (ATOMIC). We included patients with mNSCLC with sensitizing mutations in EGFR who started 1L systemic therapy before 2015. Survival distributions and predictors were assessed using Kaplan-Meier estimates and a multivariable Cox proportional hazards model including time-dependent brain metastasis (met) development, age, 1L therapy (targeted vs. chemotherapy), sex, race, and smoking status. Multivariable logistic regression was used to evaluate baseline predictors associated with 5+ year survival vs. not for those with known survival status at 5 years after start of 1L. **Results:** We identified 304 patients (69% female, 56% White, 29% Asian, mean age 61.2). First-line targeted therapy was given in 70% of patients. With a median follow-up of 81.5 months, median overall survival was 63.5 months (95% CI 59.4-71.9). 135 (44%) pts survived 5+ years; among those with baseline next-generation sequencing (NGS), presence of a baseline pathogenic ERBB2 variant was higher in 5+ year survivors (4/51 [8%], 2x amplification, y772_A775dup, S310F) v others (1/65 [2%], amplification). Among 161 pts with baseline brain imaging, both baseline and on-treatment development of brain mets were associated with worse survival (HR 1.29, 95% CI 1.21-1.37; HR 1.59, 95% CI 1.47-1.72; both P < 0.001). Excluding 22 patients lost to follow-up before 5 years, a history of smoking (OR 2.99, 95% CI 1.35-6.90, P = 0.008) and baseline brain metastases (OR 3.57, 95% CI 1.64-8.13, P = 0.002) were associated with death before 5 years. **Conclusions:** Long-term survivors with EGFRm mNSCLC treated before the osimertinib era were more likely to be non-smokers and have no baseline brain metastases. This highlights a subset of EGFRm patients who had excellent outcomes with older treatment strategies and may not benefit as much from intensification approaches. Additional baseline mutational data will be presented at the conference. Research Sponsor: AstraZeneca; LUNGEVITY.

Association between real-world, upfront, next-generation sequencing and overall survival (OS) in advanced non-small-cell lung cancer (aNSCLC) in the United States. *First Author: Benjamin Philip Levy, John Hopkins Sidney Kimmel Cancer Center, Washington, DC*

Background: Multiple biomarker testing strategies exist as the treatments of aNSCLC rapidly evolve. While upfront NGS is considered optimal, this practice has not been universally adopted. Surprisingly, the impact of NGS vs non-NGS approaches on OS is unclear, with the largest study to date demonstrating lack of benefit. We aim to identify the genomic testing strategy associated with the most optimal OS in aNSCLC using data from a large, contemporary electronic health record (EHR) database. **Methods:** This retrospective study used Flatiron EHR data. Patients diagnosed with aNSCLC between 11 Apr 2019 and 31 Dec 2021 who received systemic therapy were identified and followed from the date of diagnosis to 31 May 2022 or death. Testing methods reported within the patient's chart were extracted. Methods assessed included NGS (defined as any test type with 'NGS' as test name) and non-NGS (defined as PCR, FISH, IHC, and other sequencing methods not containing 'NGS'). Upfront testing was defined as tests received on or prior to the date of initiation of first-line (1L) therapy. Kaplan-Meier analyses were used to estimate and compare real-world overall survival (rWOS) by testing strategies. Among those with actionable genetic mutations, we also explored rWOS by timing of targeted therapy (TT) initiation. **Results:** Of a total 13,139 patients, mean age was 69, 49% female, 64% white, 33% Medicare insured, and 88% treated in community setting only. Median follow up time was 9 months. The percentage of patients with upfront NGS increased from 29% in 2019 to 66% in 2022. Median OS (mOS) was longest in patients with upfront NGS compared to those with upfront non-NGS genomic tests ($p < 0.05$), those with NGS after 1L ($p < 0.05$), and those with no NGS test ever ($p < 0.05$) (see table). 19% of patients with upfront NGS vs. 15% of those with upfront non-NGS received TT in 1L; 23% of patients with NGS vs. 19% of those with upfront non-NGS received TT at any line of therapy. In patients with actionable genetic mutations, mOS decreased with later initiation of TT; mOS was not reached (NR) (34.6 – NR) in patients who initiated TT in 1L, 34.7 (29.1 – NR) months in those with 2L TT, and 24.3 (20.3 – 30.1) months in those who initiated TT in 3L. **Conclusions:** This is the first and largest study to demonstrate that upfront NGS testing leads to better OS when compared to upfront non-NGS genomic testing, later NGS, or no-NGS in aNSCLC. In line with these results, we also found an OS benefit associated with earlier TT initiation. These results highlight the significant impact of upfront NGS testing and underscore for the need for both education and wider accessibility of NGS testing. Research Sponsor: Novartis, Inc.

	Upfront NGS testing (n = 6,210)	Upfront non-NGS genomic testing (n = 2,697)	NGS testing after 1L initiation (n = 2,824)	No NGS tested ever (n = 2,152)
Median OS (CI) in months	20.9 (19.8-21.9)	17.5 (16.1-19.2)	18.2 (16.6-19.4)	16.9 (15.3-18.6)

FDA analysis of toxicity profiles of oral TKIs recently approved for non-small cell lung cancer based on receipt of prior immune checkpoint inhibitor therapy. *First Author: Yufan Liu, United States Food and Drug Administration, Silver Spring, MD*

Background: Immune checkpoint inhibitors (ICIs) targeting PD-(L)1 are standard front-line therapy for advanced non-small cell lung cancer (NSCLC). Molecularly targeted tyrosine kinase inhibitors (TKIs) are standard of care for subsets of oncogene-driven NSCLC. Published literature suggests the possibility of increased toxicity in patients who receive ICIs followed by *EGFR* or *ALK* TKI treatment. However, the toxicity profile in patients who receive ICIs followed by TKIs with other genomic targets has not been well described. **Methods:** Marketing applications for TKIs in patients with NSCLC submitted to the Office of Oncologic Diseases between Jan 2019 to Dec 2022 were reviewed. Datasets were analyzed for demographics, treatment-emergent adverse events (TEAE), and prior anti-cancer therapies for TKI-treated patients in the primary efficacy population. Drug classes for which $< 5\%$ of patients received prior ICI were excluded. Grade 3-4 TEAE, serious adverse events (SAE), discontinuation TEAE and TEAE of interest (hepatotoxicity, rash, and interstitial lung disease [ILD]) were summarized. **Results:** 9 applications were identified and 2 were excluded. The remaining applications involved TKIs targeting *EGFR* exon 20 insertion, *KRAS G12C*, *MET* exon 14 skipping, and *RET* fusion alterations. Analyses included 867 patients; 61% received prior ICI therapy. Patient characteristics and results of analyses are presented in the table. In our pooled analysis, the incidence of Grade 3-4 AEs, SAEs, and hepatotoxicity were slightly higher in the prior ICI group, while the incidence of discontinuation TEAE, ILD, and rash were similar between groups. Analysis for hepatotoxicity was limited to reported AEs (did not include analysis of laboratory data). Review of toxicity data across individual drug classes did not show major differences compared to the overall results. **Conclusions:** Our analysis of safety data for newer TKIs with varied genomic targets does not appear to show excessive toxicity in patients with NSCLC who received prior ICI compared to those who did not. In future clinical trials evaluating TKIs in this population, inclusion of patients who have received prior ICI therapy should be considered when appropriate. Research Sponsor: None.

TEAE summary for TKIs in patients with NSCLC based on receipt of prior ICI (N=867).		
	Prior ICI Therapy (N = 528)	No Prior ICI Therapy (N = 339)
Demographics		
Sex	54% F	56% F
Age (years), median (range)	63 (25-89)	65 (23-90)
Race	67% White	48% White
	25% Asian	46% Asian
	4% Black	2% Black
Ethnicity	3% Hispanic or Latino	1% Hispanic or Latino
Region	60% U.S.	29% U.S.
	19% Asia	44% Asia
	19% Europe	25% Europe
Prior Radiotherapy	59%	45%
Drug Class	35% <i>RET</i>	44% <i>RET</i>
	14% <i>MET</i> exon 14 skipping	33% <i>MET</i> exon 14 skipping
	42% <i>KRAS G12C</i>	4% <i>KRAS G12C</i>
	9% <i>EGFR</i> ex20 ins	19% <i>EGFR</i> ex20 ins
Toxicity		
Grade 3 or 4 TEAE, %	71	63
SAEs, %	56	45
Discontinuation AE, %	12	12
Hepatotoxicity, %	4	1
ILD, %	4	6
Rash, %	26	25

Clinical, pathologic, and genomic hallmarks of *KRAS*-amplified non-small cell lung cancer. *First Author: Biagio Ricciuti, Dana-Farber Cancer Institute, Lowe Center for Thoracic Oncology, Boston, MA*

Background: *KRAS*-mutant non-small cell lung cancers (NSCLCs) have unique clinicopathologic and genomic features, and novel therapies are in development to target many *KRAS*-mutant tumor types. Whether *KRAS* amplification also defines a unique, potentially targetable, molecular subset of NSCLC is currently unknown. **Methods:** Clinicopathologic and genomic data were abstracted from multiple independent cohorts of pts whose cancers underwent tumor genomic profiling at the Dana-Farber Cancer Institute (Cohort 1), AACR Project GENIE v.13, The Cancer Genome Atlas (TCGA), and 212 other studies (Cohort 2). Patient (pt) outcomes were examined according to *KRAS* amplification status (*KRAS* amplified vs *KRAS* non-amplified). Whole transcriptome sequencing and quantitative proteomics data from TCGA and the Cancer Cell Line Encyclopedia (CCLE) were used to correlate *KRAS* amplification with *KRAS* RNA levels and protein expression. **Results:** Among 15,341 pts with NSCLC, *KRAS* amplification was identified in 355 (2.3%) cases (median number of copies [range]: 11 [7-87]); the prevalence was similar in adenocarcinomas and squamous cell carcinomas. Compared to *KRAS* non-amplified cases, pts with *KRAS*-amplified NSCLC were more likely to be men (52.4% vs 45.6%, $p = 0.01$), have a history of smoking (82.1% vs 64.2%, $p < 0.01$), and higher median pack-years (35 vs 23.5, $p < 0.01$). However, median age was similar between the two groups (66 vs 66, $p = 0.88$). *KRAS* amplification was also associated with higher aneuploidy (median fraction of genome altered 30.4% vs 14.3%, $p < 0.01$), tumor mutational burden ($p < 0.01$ across different platforms), and increased median PD-L1 expression (20% vs 5%, $p = 0.01$). Of the 355 NSCLC samples with *KRAS* amplification, 152 (43%) had no concurrent oncogene driver mutations. In unbiased mutation enrichment analyses, *KRAS*-amplified tumors were enriched in concurrent mutations in *KRAS*, *PALB2*, *POLE*, and *SLC34A2* ($q < 0.1$), while *KRAS* non-amplified tumors were enriched for oncogenic *EGFR* mutations ($q < 0.1$). Transcriptomic and proteomic profiling from the TCGA and CCLE cohorts demonstrated that *KRAS* amplification was associated with significantly increased *KRAS* mRNA ($p < 0.01$) and protein expression ($p < 0.01$), compared to *KRAS* non-amplified samples. In pts with available clinical outcomes data in the combined cohort ($N = 9,335$), the median overall survival (OS) from the date of diagnosis was significantly shorter in *KRAS*-amplified vs *KRAS* non-amplified cases (adjusted HR: 1.40, $p < 0.01$). *KRAS* amplification was confirmed to confer significantly worse survival outcomes in pts with both *KRAS* wild-type ($N = 6,695$, adjusted HR 1.37, $p = 0.02$) and *KRAS*-mutant ($N = 2,640$, adjusted HR 1.34, $p = 0.02$) NSCLC. These results were independently replicated in Cohort 1 and Cohort 2. **Conclusions:** *KRAS* amplification defines a novel molecular subset of NSCLC characterized by distinct clinicopathologic and genomic features and worse survival. Research Sponsor: None.

Stimulus of interferon gene (*STING*) expression as a biomarker for overall survival in PDL1-negative, TMB-low non-small cell lung cancer (NSCLC) treated with immune checkpoint inhibitors (ICIs). *First Author: Matthew James Hadfield, RI Hosp Brown Univ, Providence, RI*

Background: cGAS-STING (CGS) is an intracellular DNA sensing pathway that when activated, stimulates interferon and other immune-related signaling pathways. While increased expression of CGS-related genes has been associated with better survival in NSCLC, studies investigating this phenomenon in tumors less likely to respond to ICIs such as PDL1-negative, TMB-Low NSCLC are lacking. Here we report the role of CGS pathway in NSCLC tumors that are both PDL1-negative and TMB-Low. **Methods:** DNA (592-gene or whole exome) and RNA sequencing (whole transcriptome) was performed for NSCLC specimens ($n=7264$) submitted to Caris Life Sciences (Phoenix, AZ). PDL1 negativity was defined as $< 1\%$ TPS score (22C3) & TMB-Low as < 10 mutations/Mb. Hierarchical Agglomerative Clustering (HAC) was performed on STING pathway genes (CXCL10, CCL5 and GZB) and tumors were grouped into STING-high ($n=3070$), STING-intermediate ($n=1609$) and STING-low ($n=2585$) groups. Microenvironmental cell populations (MCP)-counter analysis was used to estimate cellular composition of immune cells. Statistical significance was determined using chi-square/Fisher's exact/Mann-Whitney U tests and adjusted for multiple comparisons ($q < 0.05$). Kaplan Meier method was used to estimate the overall survival (OS) derived from insurance claims of IO treated pts with NSCLC ($n=400$). Pts were stratified into groups above or below the median expression of the *STING* gene (*TMEM173*). **Results:** Compared to STING-low, tumors that were STING-high had enrichment in immune cell infiltrates including CD8+ T cells (4.4-fold) and B-cells (5.9-fold); Additionally, STING-high cohort had significantly higher expression of immune checkpoint (IC) genes including *CD274* (2.5-fold), *CD80* (2.7-fold, all $q < 0.05$). STING-high tumors also had a higher prevalence of *TP53* mutations (mts) and a lower prevalence of *STK11* and *KEAP1* mts (Table). Median overall survival (OS) was 21.1 months in the STING-high cohort ($n=200$) vs 11.9 months in the STING-low cohort ($n=199$) in IO treated pts (HR = 0.62, $p < 0.0001$). **Conclusions:** To our knowledge this is the largest real-world dataset indicating that enrichment of both the *STING* gene, and gene signatures associated with the STING pathway represent valuable transcriptomic biomarkers to stratify pts with PDL1-negative and TMB-Low NSCLC who benefit more from IO therapies. Conversely, novel IO combination strategies need to be employed in STING-low tumors to enhance outcomes. Research Sponsor: None.

Alterations	Overall STING- HIGH (n=3070)	Overall STING-LOW (n=2585)
<i>STK11</i> (% Prevalence)	15.4	21.3
<i>KEAP1</i> (% Prevalence)	10.6	15.8
<i>TP53</i> (% Prevalence)	56.5	50

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Poster Session

Nivolumab and ipilimumab in advanced non small cell lung cancer previously treated with PD1 axis inhibition. *First Author: Scott N. Gettinger, Yale Cancer Center, New Haven, CT*

Background: Nivolumab combined with ipilimumab is currently one of many first line treatment options for patients with advanced non-small cell lung cancer (NSCLC). The benefit of this regimen in patients with NSCLC previously treated with a programmed death 1 (PD1) axis inhibitor is unclear. **Methods:** We conducted a phase II study (NCT03262779) of nivolumab and ipilimumab in patients with PD1L1 unselected advanced NSCLC with either primary resistance (cohort 1) or acquired resistance (cohort 2) to prior PD1 axis inhibitor therapy. Nivolumab 3 mg/kg was administered intravenously every 2 weeks, and ipilimumab 1 mg/kg every 6 weeks, and continued until disease progression or treatment limiting toxicity. If > 1 response or prolonged stability (> 24 weeks) using immune related response criteria were observed in the first 10 patients treated on cohort 1, an additional 30 patients would be accrued (simon 2-stage). A total of 10 patients would be accrued to cohort 2 (exploratory cohort). The primary endpoint was objective response rate (ORR) by RECIST v1.1 in cohort 1. Secondary endpoints included, ORR in cohort 2, progression free survival (PFS) and overall survival (OS) in both cohorts. **Results:** Among 10 patients with primary resistance to PD1 axis inhibitor therapy, no objective responses were observed (8 patients had progressive disease (PD) and 2 patients had unconfirmed stable disease (SD) as best response). Among 10 patients with acquired resistance to PD-1 axis inhibitor therapy, ORR was 10% (1 patient with confirmed complete response, 5 patients with confirmed SD including 4 patients with SD lasting more than 9 months, 3 patients with unconfirmed SD, and 1 patient with PD). Durable clinical benefit (DCB, response or SD for at least 6 months) rate was 50%. Median duration of benefit in the 5 patients with DCB was 11.9 months. Nine of the 10 patients in cohort 2 developed initial resistance to PD-1 axis inhibitor monotherapy (rather than combination chemo-immunotherapy), all received immunotherapy as part of their last line of therapy. The remaining patient developed resistance while on maintenance chemoimmunotherapy after initial response to chemoimmunotherapy; best response to trial therapy in this patient was unconfirmed SD. Median PFS/ OS in cohort 1 were 1.8 months/ 6.8 months, and in cohort 2, 6.7 months/ 31.8 months. Grade 3 treatment-related adverse events (TRAEs) occurred in 4 patients across both cohorts, including colitis (2 pts), diabetes (1 pt), pneumonia (1 pt) and elevated lipase (1 pt). There were no grade 4/5 TRAEs. Two patients discontinued trial therapy due to toxicity (colitis), both in cohort 2. **Conclusions:** Combination immunotherapy with nivolumab and ipilimumab does not overcome primary resistance to PD1 axis inhibitor therapy; however, can overcome acquired resistance to PD1 axis inhibitor therapy. Translational studies from tumor and serial peripheral blood collections are ongoing. Clinical trial information: NCT03262779. Research Sponsor: BMS; U.S. National Institutes of Health.

9123

Poster Session

Amplification of wild-type *RET* and clinical response to selpercatinib for non-small-cell lung cancer (NSCLC). *First Author: Malini Marion Gandhi, Dana-Farber Cancer Institute, Lowe Center for Thoracic Oncology, Boston, MA*

Background: *RET* rearrangements and *RET* kinase domain mutations represent targetable genomic alterations in various cancer types. However, the frequency and characteristics of *RET* amplification in cancer and its potential role as a targetable oncogenic driver are not well-characterized. **Methods:** In a pan-cancer cohort of patients at the Dana-Farber Cancer Institute (DFCI) whose tumors underwent next-generation sequencing (NGS), we evaluated the frequency of wild-type (wt) *RET* amplification (defined as ≥ 6 copies) in the absence of *RET* rearrangements or activating mutations. We validated our findings using merged data from the TCGA, GENIE, and China Pan-Cancer datasets. **Results:** The frequency of wt *RET* amplification across all cancers was 0.08% (28/34,463) in the DFCI cohort and 0.16% (145/91,466) in the validation cohort. In NSCLC, the frequency of *RET* amplification was 0.10% (5/4773) in the DFCI cohort and 0.13% (15/11,622) in the validation cohort. Other cancer types with *RET* amplification included hepatobiliary cancer, prostate cancer, and breast cancer, among others. For 22 *RET*-amplified cases with available copy number data, the median *RET* gene copy number was 7 (range 6-36). Among 20 *RET*-amplified NSCLCs, 10 had no other known driver mutations, and 10 had concurrent driver mutations (including *MET* exon 14 skipping, *MET* amplification, *KRAS* G12C/S/D, *EGFR* L858R, *EGFR* exon 20 insertion, and *EGFR* exon 19 deletion). In cases with available smoking status, 5 out of 6 patients with *RET*-amplified NSCLC had a history of tobacco use. A 69-year-old man with unresectable stage III NSCLC had disease recurrence after chemoradiation and durvalumab. Both the initial and recurrent biopsy samples showed focal high-level *RET* amplification (22 and 28 copies, respectively); genomic and RNA sequencing showed no other driver mutations or *RET* rearrangements. He experienced partial response to the selective *RET* inhibitor selpercatinib with decrease of both intracranial and systemic tumor burden. **Conclusions:** Amplification of wt *RET* represents a novel, targetable, rare molecular subset of NSCLC and other cancers. Research Sponsor: None.

9122

Poster Session

A decision-making tool for first-line treatment in advanced non-small-cell lung cancer based on plasma proteomic biomarkers. *First Author: Itamar Sela, OncoHost LTD, Binyamina, Israel*

Background: Initial treatment selection for advanced NSCLC patients without driver mutations is mainly based on evaluating PD-L1 expression levels in the tumor tissue. However, PD-L1 assays are only moderately predictive. In addition, the guidelines for the PD-L1 $\geq 50\%$ subpopulation are not definitive, enabling the usage of immune checkpoint inhibitors (ICI) either as a monotherapy or combined with chemotherapy. Here we aim to provide a decision-making tool for the first-line treatment of advanced NSCLC patients based on plasma derived biomarkers obtained before treatment initiation. **Methods:** Pre-treatment plasma samples were collected from 545 NSCLC patients receiving ICI-based therapy. Clinical benefit was evaluated based on progression-free survival (PFS) at 12 months as a threshold. Deep plasma proteomic profiling was performed using aptamer technology. Based on the proteomic profiles, a computational model, termed PROphet, was developed and evaluated in a blinded manner on the validation subset ($n = 272$). The model output, clinical benefit probability, was used to stratify the patients into two groups, PROphet-positive or -negative. **Results:** The model displayed good performance with a high correlation between the predicted clinical benefit and the observed clinical benefit rate ($R^2 = 0.97$), outperforming a PD-L1-based prediction model ($R^2 = 0.35$). Patients classified as PROphet-positive achieved significantly longer overall survival (OS) than PROphet-negative patients, with a median OS of 25.9 versus 10.8 months (hazard ratio, HR = 0.51; 95% confidence interval, CI = 0.37-0.70; p -value < 0.001). Next, we examined the clinical utility of combining the PROphet output with PD-L1 levels by comparing different treatment modalities. Focusing on PD-L1 $\geq 50\%$, patients with PROphet-positive results displayed similar OS and PFS when receiving ICI monotherapy or ICI-chemotherapy (OS HR = 0.77; CI = 0.42-1.43; p -value = 0.4096), suggesting that these patients may consider monotherapy, thus avoiding chemotherapy-related toxicity. Conversely, PD-L1 $\geq 50\%$ patients with a PROphet-negative result displayed a significantly longer OS and PFS when receiving ICI-chemotherapy in comparison to ICI monotherapy, with a median OS that was not reached versus 11.10 months in the combination therapy and monotherapy groups, respectively (HR = 0.29; CI = 0.14-0.59; p -value < 0.001). These patients should consider combination therapy, avoiding a treatment that is suboptimal for them. Results for PD-L1 1-49% and < 1% provide additional clinical information for each subgroup. **Conclusions:** Plasma proteomic profiling can provide biomarkers that accurately predict the benefit of ICI-based treatment. The model output complements tissue PD-L1 expression levels as a tool to assist therapeutic decisions. Research Sponsor: OncoHost LTD.

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Poster Session

Multi-center real-world data curation and assessment of tumor growth rate and overall survival in advanced NSCLC treated with PD-(L)1 immune checkpoint inhibitor therapy. *First Author: Chiharu Sako, Onc.AI, San Carlos, CA*

Background: While Immune Checkpoint Inhibitors (ICI) have become the standard-of-care for advanced non-small cell lung cancer (NSCLC) for certain patient populations, durable responses only occur in a small subset of patients. Therefore, there is an unmet need to identify patients that will respond before and during treatment to optimize treatment strategies. Multiple studies have shown promise that quantitative imaging biomarkers can predict response to ICI therapy. Studies have also shown that tumor growth parameters derived from time series data can provide early indications of long-term response. However, most studies to date have investigated single institution or clinical trial datasets, which are inadequate to capture the broad spectrum of real-world diversity of ICI treatments. In this study, we aimed to build a generalizable, well-validated imaging biomarker for treatment response. **Methods:** We have curated a retrospective dataset including serial imaging data of 1,215 advanced NSCLC patients who received ICIs from nine institutions across the US and Europe, capturing the diversity of the imaging data, such as CT scanner models, image acquisition parameters, reconstruction algorithms, as well as diversity in patient population, performance status, and treatment settings. Expert lesion annotations and manual volumetric segmentations were performed on all visible lesions (ranging from 1-18 lesions per subject, totaling 6,441 lesions) across the serial imaging data (ranging from 1-18 follow-up scans per subject), which enables lesion and organ-specific tumor burden assessment. We stratified overall survival based on volumetric response and tumor growth rate using a model defined by the sum of exponential growth (g) and decay (d), $vol(t) = vol(0) * (e^{gt} + e^{-dt} - 1)$. **Results:** Survival analysis showed that the 3-month volumetric response ($N = 875$) was significantly associated with overall survival (OS) for the lowest quartile (Q1; log-rank p -value, $P = 2.1 \times 10^{-4}$) and highest quartile (Q4; $P = 9.8 \times 10^{-5}$) compared to the middle quartiles (Q2+Q3). The median overall survival (OS) stratified by the volumetric response was 547.7, 450.9, and 332.0 days in the Q1, Q2+Q3, Q4 quadrants, respectively. Among patients having a minimum of 2 follow-up scans in the first 18 weeks ($N = 264$), we found that patients with the tumor growth parameter (g) in the highest quartile had significantly lower OS compared to the patients in the Q2+Q3 quadrants ($P = 7.2 \times 10^{-5}$). **Conclusions:** Our results demonstrate the potential of large multi-center real-world imaging datasets in investigating novel early response assessment methodologies, such as volumetric tumor burden quantification and tumor growth modeling. In our further work, we will investigate response patterns at individual lesion levels and correlations with overall patient-level response. Research Sponsor: Onc.AI.

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Poster Session

Phase II randomized trial of first-line pembrolizumab and vorinostat in patients with metastatic NSCLC (mNSCLC): Final results. *First Author: Andreas Nicholas Saltos, Moffitt Cancer Center, Tampa, FL*

Background: Histone deacetylase inhibitors enhance tumor immunogenicity through various mechanisms including induced expression of MHC and T cell chemokines. A previous phase I trial demonstrated the combination of pembrolizumab (P) with vorinostat (V) in advanced/metastatic (m)NSCLC was well tolerated with signals of activity in ICI-pretreated pts. To further investigate the combination, we conducted a first-line, phase II trial. **Methods:** Pts with treatment-naïve mNSCLC and tumor PD-L1 expression $\geq 1\%$ were eligible. Pts were randomized, open-label, 1:1 to receive P 200 mg IV q3 wk as monotherapy [Arm A] vs P 200 mg IV q3 wk plus V 400 mg PO daily [Arm B]. The primary endpoint was overall response rate (ORR). Secondary endpoints included DOR, PFS and OS. Tumor biopsies were collected both pre- and on-treatment (day 15-21) for exploratory correlative analysis including gene expression and changes in the tumor microenvironment. **Results:** Between 7/2017–2/2022, 86 pts were enrolled, with 83 pts evaluable for response (40 in Arm A and 43 in Arm B). Median age was 69 (range 44–87), 47% female, and ECOG PS 0/1 in 9%/91%. PD-L1 TPS was $\geq 50\%$ in 20/40 (50%) of pts in Arm A, and in 23/46 (50%) of pts in Arm B. The most common TRAEs in Arm A included diarrhea (15%) and fatigue (10%). 3 pts in Arm A experienced grade ≥ 3 irAEs (including 1 each of grade 3 hepatitis, pneumonitis, and rash). The most common TRAEs in Arm B included fatigue (41%), nausea (44%), diarrhea (35%) and increased creatinine (33%). 3 pts in Arm B experienced grade ≥ 3 irAE (2 grade 3 pneumonitis and 1 grade 4 myopericarditis). In Arm B, 22/45 (49%) of pts had a dose-reduction in vorinostat, most commonly due to grade 2-3 fatigue or nausea. Efficacy results by intention-to-treat are summarized in the Table below. For evaluable patients only, ORR was 44% in Arm B (19/43) and 28% in Arm A (11/40) ($p=0.18$). RNA-sequencing of a subset of patients showed a significant increase in interferon- γ pathway activity in both Arms. However, between the two Arms, interferon- γ pathway activity was enhanced to greater extent in Arm B, which may have contributed the higher overall response rate. **Conclusions:** To our knowledge, this is the first randomized trial investigating the combination of HDAC inhibition and anti-PD1 therapy in NSCLC. Although the combination arm had a numerically higher ORR compared to P monotherapy, the result did not meet the primary endpoint for significance. While there were no new safety signals with the combination therapy, reduction or interruption in V dose occurred frequently, which may have contributed to lack of survival differences between arms. Clinical trial information: NCT02638090. Research Sponsor: Merck Sharp & Dohme LLC; Department of Defense.

Best response:	Arm A N= 40	Arm B N = 46	P value
PR/CR	11 (28%)	19 (41%)	p=0.266
SD	15 (38%)	15 (33%)	
PD	14 (35%)	9 (20%)	
NE		3 (7%)	p=0.508
DCR	26 (65%)	34 (74%)	
Median PFS	4.5 mo	4.3 mo	p = 0.8

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Poster Session

Changes in PD-L1 and tumor mutational burden between paired samples and relationship to immune checkpoint inhibitor outcomes in non-small cell lung cancer. *First Author: Alessandro Di Federico, Dana-Farber Cancer Institute, Lowe Center for Thoracic Oncology, Boston, MA*

Background: Programmed cell death receptor ligand 1 (PD-L1) tumor proportion score (TPS) and tumor mutational burden (TMB) are key biomarkers of response to immune checkpoint inhibitors (ICI) in non-small cell lung cancer (NSCLC). How often PD-L1 and TMB values change across samples within individual patients (pts) and the impact of this variation on ICI outcomes are limited. **Methods:** Pts with NSCLC and multiple PD-L1 or TMB assessments at the Dana-Farber Cancer Institute were included. Clinicopathologic and genomic data were analyzed in association with PD-L1 and TMB changes. In patients with > 2 samples, each sample was paired with the subsequent and each pair was analyzed independently. Minor and major changes in PD-L1 were defined as absolute changes of 10-49% and 50-100%, respectively. **Results:** The PD-L1 cohort included 402 sample pairs (median Δ PD-L1: 0; range: -90,+95%) and the TMB cohort included 413 sample pairs (median Δ TMB: 0 mut/Mb; range: -20.6,+24.5). Concordance between pairs was high for both PD-L1 ($R=0.53$, $P < 0.01$) and TMB ($R=0.80$, $P < 0.01$). Samples taken within < 1 year had higher concordance for PD-L1 than samples taken ≥ 1 year apart ($P < 0.01$), but length of time between biopsies did not impact TMB concordance. Minor or no changes in PD-L1 were observed in 82.3% of pairs; the frequency of major increases was 9.7% and major decreases was 8%. After dividing TMB into tertiles, 72.6% sample pairs showed no tertile change, 16% increased to a higher tertile, and 11.4% decreased to a lower tertile. PD-L1, but not TMB, decreased with intervening ICI ($P = 0.02$), but PD-L1 and TMB did not change significantly with other intervening systemic therapies. Acquired copy number losses of the *CD274* gene (encoding for PD-L1) were enriched in pairs with a major PD-L1 decrease ($Q < 0.05$). Similarly, acquired loss of chromosome 9p (which contains the *CD274* locus) correlated with a reduction in PD-L1, while 9p gains correlated with an increase in PD-L1 ($P = 0.02$). A total of 142 pts had multiple PD-L1 scores assessed before ICI initiation. Among pts with at least one PD-L1-positive sample (TPS $\geq 1\%$), the presence of another sample that was PD-L1 negative ($< 1\%$) correlated with worse outcomes to ICI compared to pts with no PD-L1-negative samples: response rate was 11% vs 39% ($P < 0.01$), median progression-free survival (mPFS) 2.7 vs 8.0 months ($P < 0.01$), and median overall survival 13.6 vs 21.2 months ($P = 0.05$), respectively. Among pts with at least one PD-L1 TPS $\geq 1\%$ and one $< 1\%$, cases where the last PD-L1 TPS before ICI was $\geq 1\%$ achieved longer mPFS than if the pre-ICI sample was PD-L1 negative (3.6 vs 1.8 months, $P = 0.03$). **Conclusions:** Although PD-L1 and TMB generally had high intrapatient concordance across samples, significant changes in values occurred in some patients. Variations in PD-L1 influenced ICI outcomes, warranting an assessment proximal to ICI initiation whenever feasible. Research Sponsor: None.

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Poster Session

Subcutaneous amivantamab (ami) in patients (pts) with advanced solid malignancies: The PALOMA study—Updated safety and identification of the recommended phase 2 dose. *First Author: Anna Rachel Minchom, Drug Development Unit at Royal Marsden Hospital/Institute of Cancer Research, Sutton, United Kingdom*

Background: Ami, an EGFR-MET bispecific antibody, is approved for pts with advanced *EGFR* exon 20 insertion non-small cell lung cancer after progression on platinum-based chemotherapy. Intravenous (IV) delivery is associated with infusion-related reactions (IRRs) in 67% of pts, requiring splitting the first dose over 2 days (Park *Ann Oncol* 2021; 32[suppl_5]:S981). PALOMA (NCT04606381) is an ongoing phase 1b dose escalation study of subcutaneous (SC) ami $\pm$ rHuPH20 (a hyaluronidase that aids SC agent absorption) in pts with advanced solid tumors who may benefit from *EGFR*- or *MET*-directed therapy. Preliminary results showed SC ami was well tolerated, improved time and ease of administration, and meaningfully reduced IRRs (Krebs *Cancer Res* 2022;82: 12_Supplement, CT198). We present updated safety results and identification of the recommended phase 2 dose (RP2D) for ami SC Q2W administration. **Methods:** PALOMA enrolled pts with various advanced solid tumors. Objectives were to evaluate administration feasibility, safety, and PK of low and high concentration formulations of ami SC (50 mg/mL ami $\pm$ rHuPH20 [Part 1; Cohorts 1a/b] and 160 mg/mL ami $\pm$ rHuPH20 [Part 2; Cohorts 2a/b, Cohort 3a, Cohort 5a]). Cohorts 1a/b and 2a/b received 1050 mg (1400 mg, ≥ 80 kg), Cohort 3a received 1600 mg (2240 mg, ≥ 80 kg), and Cohort 5a received 2560 mg (3360 mg, ≥ 80 kg). Cohorts 1-3 were dosed weekly for the first 4 weeks and Q2W thereafter. Cohort 5a was dosed weekly for the first 3 weeks and Q3W thereafter. **Results:** As of Jan 3, 2023, 81 pts were enrolled (16 pts in Part 1, 65 pts in Part 2) and majority had NSCLC (71; 88%). Median age was 64 years, 44 (54%) pts were female, and most pts were White (44; 54%) or Asian (34; 42%). Across all doses, IRRs were reported by 13 (16%) pts; all of grade 1-2. The most frequent manifestations of IRRs were chills (7%), pyrexia (7%), and asymptomatic tachycardia (4%). Treatment-emergent AEs (TEAEs) of rash were reported by 59 (73%) pts, with no grade ≥ 3 . In total, 3 (4%) pts discontinued ami SC due to toxicity (2 pneumonitis, 1 asthenia). Grade ≥ 3 related TEAEs were reported by 3 (4%) pts (hyponatremia, lymphopenia, hypertension). Full ami SC dosing on day 1 was feasible (≤ 7 min), obviating the need for split dosing. PK analysis confirmed that ami SC 1600 mg (2240 mg, ≥ 80 kg) Q2W resulted in similar exposure to the approved IV dose (1050 mg [1400 mg, ≥ 80 kg] Q2W). Compared to IV, ami SC resulted in lower C_{max} and equal or higher C_{trough} and AUC_{0-336h} at Cycles 2 and 4. Based on these data, ami SC 1600 mg (2240 mg, ≥ 80 kg) was selected as the RP2D for ami SC Q2W administration. **Conclusions:** Ami SC was well tolerated with meaningful reductions in administration time and TEAEs. Ami SC provided a quantitative and qualitative improvement in the symptoms of IRRs vs historical IV rates. The identified RP2D for ami SC on the Q2W schedule achieved similar exposure as the approved IV dose. Clinical trial information: NCT04606381. Research Sponsor: Janssen R&D, LLC.

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Poster Session

Results from a first-in-human phase 1B study of a complement factor H inhibitor (GT103) in patients with non-small cell lung cancer (NSCLC). *First Author: Jeffrey Melson Clarke, Duke Cancer Institute, Durham, NC*

Background: GT103 is a first-in-class IgG3 monoclonal antibody that was derived from a single human B cell and inhibits complement factor H (CFH). CFH is implicated in cancer immune evasion and overexpression portends a poor prognosis in multiple malignancies. CFH regulates C3 convertase in the alternative pathway of the complement cascade, limiting downstream opsonization and membrane attack complex formation. Monoclonal antibody inhibition of CFH facilitates complement-dependent tumor cell lysis, modulates the adaptive immune response, and inhibits tumor growth. **Methods:** GT103 is being evaluated in a multi-institutional, first-in-human, phase 1b study in patients with advanced stage, refractory NSCLC. A standard '3+3' dose escalation schema was used across four dose levels, with treatment given until disease progression or unacceptable toxicity. Dose limiting toxicity (DLT) observation period included cycle 1 and radiographic disease assessment was performed every 6 weeks. We have previously reported that no DLT was seen at the highest two dose levels of 3 mg/kg or 10 mg/kg administered IV every 3 weeks. Two expansion cohorts have now been opened at 10 mg/kg IV every 2 week and 15 mg/kg every 3 weeks dose levels allowing up to 6 patients at each dose level. We herein present updated clinical outcomes and analysis of correlative biomarkers. **Results:** As of February 3, 2023, twenty-five patients have been treated, with a median follow up of 230 days. Five of the 21 patients in the dose escalation cohort demonstrated stable disease by RECIST criteria. In the 10 mg/kg dose level, one patient has experienced prolonged disease stabilization and has received 12 cycles to date with tumor reduction on CT. The DLT period is ongoing for two patients enrolled in the 10 mg/kg IV every 2 weeks and two patients in the 15 mg/kg every 3 weeks expansion cohorts. Soluble C5b-9 (sC5b-9) is a candidate pharmacodynamic biomarker for GT103 and was measured at baseline and at day 15 from patients in all four dose escalation levels (0.3, 1, 3, 10 mg/kg). An increase in sC5b-9 was found in 13 of 21 patients at day 15. A marked doubling of the baseline sC5b-9 level was demonstrated in a subset of patients by day 15 indicative of biologic activity. **Conclusions:** GT103 is well tolerated in heavily pretreated advanced NSCLC population. Early clinical activity has been demonstrated to date with stable disease seen in 24% of patients. Updated clinical results and correlative data will be presented. A separate phase 2 study of combination GT103 with pembrolizumab is planned for patients with refractory NSCLC. Trial Registration: The study was approved by Duke University IRB with approval number Pro00104564. Clinical trial information: NCT04314089. Research Sponsor: Grid Therapeutics.

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Poster Session

Clinical and genomic landscape of EGFR-mutant lung cancers (LCs) with squamous and adenosquamous differentiation. *First Author: Arielle Elkrif, Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Outcomes to first-line therapy with osimertinib in patients (pts) with EGFR-mutant (EGFR+) squamous (sq) or adenosquamous (adenosq) LC have not been well described. Pts also undergo adenocarcinoma to squamous transformation (transformed) after treatment with EGFR tyrosine kinase inhibitor (TKI). The clinical and genomic characteristics of pts with EGFR+ sq and adenosq LC are largely unknown. **Methods:** We clinically and genomically characterized all pts with EGFR+ LC with baseline sq or adenosq histology and transformed histology at Memorial Sloan Kettering Cancer Center. Next-generation sequencing was performed with the MSK-IMPACT. We compared clinical outcomes (time to discontinuation (TTD), overall survival (OS), and post-progression survival after osimertinib discontinuation (PPS)) among the different cohorts. **Results:** A total of 51 pts were identified: 14 with baseline sq/adenosq treated with first-line (1L) osimertinib; 8 transformed cases post 1L osimertinib; 13 with baseline sq/adenosq treated with early generation TKI; 3 transformed cases post early generation TKI; the remainder of pts had early-stage EGFR+LC with baseline sq/adenosq. Median age was 63, and 57% were female. Eighteen (35%) were former or current smokers. Among pts with baseline sq/adenosq histology who were treated with 1L osimertinib, median TTD was 11.1 months (95%CI 7.7, not reached (NR)), and median OS was 24.3 months (95%CI 11.1 months, NR). Compared to a non-overlapping time-matched cohort with baseline adenocarcinoma treated with 1L osimertinib (N = 55), TTD was numerically shorter in the sq/adenosq cohort (11 vs. 17 months, HR 1.8, p = 0.076), and median OS was significantly shorter (24 vs. 33 months, HR 2.64, p = 0.03). PPS was shortest in baseline sq/adenosq (5 months, HR 2.94, p = 0.023), but similar in transformed (11 months, HR 0.89, p = 0.8) compared to adeno (11 months). The sq/adenosq cohort had significantly higher proportion of L858R EGFR (48% vs 31% p < 0.001) and atypical EGFR mutations at baseline (17% vs 7.3%, p < 0.001) compared to the adenocarcinoma cohort. PIK3CA mutations were enriched at baseline in the sq/adenosq cohort. In the transformed cases, RB1 alterations were present in 13% at baseline. There was a similar distribution of type of EGFR mutations in the non-overlapping pts in the AACR GENIE EGFR+ LC cohort with sq/adenosq histology (N = 4, 50% L858R, 25% atypical). **Conclusions:** Pts with EGFR+ sq/adenosq LCs exhibit inferior TTD and OS with 1L osimertinib compared to adenocarcinoma controls. Sq/adenosq LCs appear to be molecularly distinct with enrichment in EGFR L858R and atypical EGFR mutations. Transcriptomic profiling of a subset of samples will be presented. Our findings highlight the need for novel therapeutic strategies among pts in this high-risk subgroup. Research Sponsor: U.S. National Institutes of Health.

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Poster Session

A phase 2a study evaluating the efficacy and safety of sunitinib in patients with advanced non-small-cell lung cancer (NSCLC) harboring uncommon EGFR mutations. *First Author: Fengying Wu, Shanghai Pulmonary Hospital, Shanghai, China*

Background: Although non-small cell lung cancer (NSCLC) patients with tumor harboring classical Epidermal Growth Factor Receptor (EGFR) mutations have numerous therapeutic choices, uncommon EGFR mutation NSCLC patients have limited treatment options. Sunitinib is a selective tyrosine kinase inhibitor (TKI) targeting uncommon EGFR mutations. **Methods:** In this multicenter, open-label phase 2a study, treatment-naïve adults with NSCLC harboring uncommon EGFR mutations (G719X, S768I, L861Q) received oral sunitinib monotherapy at 80 or 64 mg/day (Chinese trial register CTR20190681). The primary endpoint was objective response rate (ORR) per RECIST v1.1. Secondary endpoints included duration of response (DoR), overall survival (OS), safety and tolerability. Adverse events (AEs) were graded according to the CTCAE v5.0. **Results:** Sunitinib was administered to 30 NSCLC patients at 80 (n = 15) or 64 (n = 15) mg/day. Median age was 60 years old (range 47-74 years). Twenty patients (66.7%) were females, 10 patients (33.3%) had a history of smoking. Patients had an ECOG PS of 0 (10.0%) or 1 (90.0%). Tumors had a G719X (36.7%), L861Q (30.0%), or S768I (20.0%) EGFR mutation, or a combination of these uncommon EGFR mutations (13.3%). None had EGFR T790M, L858R, exon 19 deletions, or exon 20 insertions. The ORR was 71.4% (20/28), including 92.9% (13/14) and 50.0% (7/14) in the 80 and 64 mg/day cohorts, respectively. The disease control rate (DCR) was 96.4%, including 100.0% (14/14) and 92.8% (13/14) in the 80 and 64 mg/day cohorts, respectively. All responses were partial responses. The median DoR was 12.5 months (20.3 and 9.2 months in the 80 and 64 mg/day cohorts, respectively). One-year OS was 84.7% (92.9% and 75.0% in the 80 and 64 mg/day cohorts, respectively). As of 15 January 2022 (database lock), 11 (36.7%) patients were still receiving sunitinib treatment. Grade ≥3 treatment emerged AEs were similar in the 80 mg/day (80.0%, 12/15) and 64 mg/day (73.3%, 11/15) cohorts. The most frequently reported grade ≥3 treatment-related AEs (TRAEs) were diarrhea (36.7%), abnormal liver function (13.3%), and rash (10.0%). One grade 4 TRAE was observed: hypokalemia in the 64 mg/day cohort. **Conclusions:** Sunitinib demonstrated a high response rate with durable antitumor activity in patients with NSCLC harboring uncommon EGFR mutations. The toxicities are expected and comparable to other EGFR TKIs. A multi-center phase 2b study is ongoing in the United States and China to further evaluate Sunitinib in uncommon EGFR mutation NSCLC. Clinical trial information: CTR20190681. Research Sponsor: Suzhong Pharmaceutical Group Co., LTD.

9130

Poster Session

Evaluating generalizability of practice-changing randomized clinical trials in non-small cell lung cancer using machine learning-based in-silico trials. *First Author: Xavier Orcutt, Chinle Comprehensive Health Care Facility, Chinle, AZ*

Background: Results of randomized clinical trials (RCTs) of anticancer agents are not generalizable to many real-world patients. Advances in machine learning (ML) and increasing availability of curated real-world data offer opportunities to assess generalizability by simulating trials "in-silico". Our objective was to assess the generalizability of survival outcomes reported in 2 practice-changing phase III trials in first-line (1L) advanced non-small cell lung cancer (aNSCLC). **Methods:** Our cohort included patients from the nationwide Flatiron Health EHR-derived de-identified database diagnosed with stage IIIB-IV or recurrent aNSCLC between 2011 and 2020. First, we trained and validated supervised ML models (gradient boosted, random forest, support vector machine and penalized Cox) to predict 1-year survival for patients with aNSCLC; the Lung Cancer Prognostic Index (LCPI), a published disease-specific prognostic index, was used as a comparator model. We used 130 demographic, vital sign, laboratory, and biomarker features at aNSCLC diagnosis to build models. Second, we used the best-performing ML model to create 4 prognostic risk groups. Third, we simulated 2 seminal trials for 1L treatment of aNSCLC, using inverse probability of treatment-weighted survival analyses, coarsely reproducing inclusion/exclusion criteria across ML-derived risk groups. We compared median overall survival (mOS) using Kaplan-Meier curves from the start of 1L treatment to death in in-silico trials (ISTs) vs. RCTs. **Results:** Our cohort included 61,339 patients with aNSCLC. The best-performing gradient boosted model outperformed the LCPI (AUC 0.784 vs 0.688). In ISTs, survival benefits of novel treatments varied across risk groups and were generally lower in ISTs compared to RCTs (Table). IST results in high- and very high-risk patients were inconsistent with RCT survival results. For example, for KEYNOTE-024, mOS in the pembrolizumab arm was 30.0 months, whereas in the IST, mOS among patients receiving pembrolizumab varied from 1.3 months in very high-risk patients to 41.5 months in low-risk patients. RCT results overestimated treatment effects for high-risk aNSCLC patients. **Conclusions:** ML-based ISTs can reveal heterogeneity in real-world survival outcomes associated with novel oncology treatments and elucidate populations for whom RCT results generalize poorly. Research Sponsor: None.

Trial	RCT: mOS (mos) Treatment vs Control (difference in mOS)	IST: mOS (mos) Treatment vs Control (difference in mOS) by Risk Group				
		All (n = 61,069)	Very High (n = 9,630)	High (n = 22,123)	Medium (n = 18,166)	Low (n = 11,420)
KEYNOTE-024 (2016)	30.0 vs 14.2 (15.8)	10.9 vs 5.0 (5.9)	1.3 vs 1.7 (-0.4)	5.6 vs 4.9 (0.7)	21.6 vs 9.4 (12.2)	41.5 vs 17.0 (24.5)
KEYNOTE-189 (2018)	22.0 vs 10.7 (11.3)	14.0 vs 4.9 (9.1)	1.9 vs 1.5 (0.4)	6.6 vs 4.4 (2.2)	19.3 vs 9.2 (10.1)	43.1 vs 25.5 (17.6)

9132

Poster Session

Artificial intelligence algorithm developed to predict immune checkpoint inhibitors efficacy in non-small-cell lung cancer. *First Author: Mehrdad Rakae, University Hospital of North Norway, Tromsø, Norway*

Background: Many non-small cell lung cancer (NSCLC) patients with high PD-L1 IHC expression and/or high TMB level do not respond to immune-check point inhibitors (ICIs). Discovery of novel predictive biomarkers for ICI response in NSCLC continues to be a critical unmet medical need, given the expense, potential toxicity, and therapeutic delay due to ICI treatment without benefit. **Methods:** We developed a supervised deep learning algorithm (Deep-IO) to predict therapeutic response to ICIs in NSCLC patients from standard histology whole slide hematoxylin and eosin (H&E) images, which was trained based on ICI objective response rate. We utilized a convolutional neural network (CNN) implemented in Pytorch. The efficiency of the Deep-IO was evaluated through classification performance metrics and the area under the receiver operating characteristic curve (AUROC). The algorithm was trained and tested on 85218 tiles (size: 512x512 pixels) in 446 advanced stage NSCLC patients from the Dana Farber Cancer Institute (DFCI), all treated with ICI monotherapy. **Results:** The objective response rate, comprising complete and partial response, was 26% (n = 114) in the overall cohort. The DFCI patient cohort was randomly split into a training set (N=379, 85%) and a test set (N=67, 15%). The classifier's predicted class (responder vs non-responder) probabilities at the tiles level were averaged for each patient. Quantitative evaluation of whole section test dataset shows that the developed model achieves the accuracy of 0.72, weighted average (WAVG) precision of 0.77, WAVG recall of 0.72 and WAVG F-score of 0.74 on classifying ICI non-responders from responders. Comparing with PD-L1 expression (TPS%) and TMB (mu/Mb), Deep-IO had superior predictive power for ICI response (AUROC=0.75) in the test set. The combined Deep-IO+PD-L1 scores resulted in a significantly greater AUROC value of 0.82 compared to single tests and a 32% improvement in specificity (0.88 vs. 0.56) compared to PD-L1 evaluation alone (Table). **Conclusions:** This proof-of-concept study shows that an artificial intelligence-powered H&E image classifier can predict ICI effectiveness in NSCLC. Deep-IO outperformed both established predictive biomarkers. We will assess Deep-IO in additional external NSCLC data sets for validation and confirmation. Research Sponsor: None.

Biomarker	AUROC	Specificity	Sensitivity	PPV	NPV
Deep-IO+PD-L1	0.82	0.88	0.70	0.58	0.92
Deep-IO	0.75	0.55	0.93	0.34	0.97
PD-L1	0.67	0.56	0.80	0.31	0.92
TMB	0.61	0.25	0.97	0.25	0.99

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Poster Session

Investigating racial inequities of circulating tumor DNA (ctDNA) use in patients with non-small cell lung cancer: A real world analysis. *First Author: Angelica D'Aiello, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY*

Background: The use of ctDNA has emerged as an invaluable adjunct to tissue-based molecular testing, though it remains unclear if racial inequities associated with ctDNA implementation exist. We sought to assess disparities in frequency of actionable alterations detected and utilization of those results for treatment decisions in a diverse urban population of NSCLC patients. **Methods:** We performed a retrospective study of NSCLC patients who received Guardant ctDNA testing from 11/2015-10/2022. Kaplan Meier curves with log-rank tests were used to assess time-to-treatment initiation or treatment change from date of ctDNA collection among race/ethnicity subgroups (Hispanic, Black, White). Univariate associations between race/ethnicity subgroups, NCCN actionable mutation detection, and variant allele frequency, were assessed using Chi-Square and Kruskal-Wallis tests for categorical and continuous variables, respectively. **Results:** We identified 258 subjects. The race/ethnicity distribution in order of prevalence was Hispanic (33.0%, n = 85), Black (32.6%, n = 84), White (24.8%, n = 64), and Asian/other/unknown (9.7%, n = 25). Median turnaround time for ctDNA result was 8 days (range 2-24 days) from collection date. Median time-to-treatment initiation or change was 25 days for the combined cohort, and 24 days for patients with treatment naïve metastatic disease. Time-to-treatment initiation or change was similar among race/ethnicity subgroups in the combined cohort, as well as those specifically with metastatic disease not yet initiated on treatment at time of ctDNA testing (p = 0.52 and p = 0.43, respectively). Similar proportions of all race/ethnicity subgroups had an NCCN actionable mutation detected (p = 0.92) and similar variant allele frequencies (p = 0.68). An NCCN actionable mutation was detected in 35.3% (n = 91) of patients, the most common being EGFR (n = 53) and KRAS G12C (n = 17). CtDNA results helped avoid the need for repeat tissue biopsy in 25.6% (n = 66) of patients. Of the 68% (n = 175) of patients with paired tissue and liquid biopsies, 24.0% (n = 42) of patients had discordant results, and 8.6% (n = 15) had additional alterations detected on liquid biopsy. **Conclusions:** In our diverse cohort, we observed a similarly high detection rate of actionable mutations and early time-to-treatment based on ctDNA results across all race/ethnicity subgroups. In addition, ctDNA helped avoid need for repeat tissue biopsy in 25% of patients and yielded additional alterations not detected on tissue in nearly 10% of patients with discordant results. Our findings suggest that broad based molecular testing utilizing ctDNA is not only feasible, but also that it enables faster time-to-treatment in a racially diverse urban population. Continued efforts are necessary to ensure timely molecular testing among all patients, and to identify any racial inequities that may exist. Research Sponsor: None.

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Poster Session

Final results from a phase II trial of CIMAvax-EGF and nivolumab as second-line (2L) therapy after platinum-based chemotherapy in advanced non-small cell lung cancer (NSCLC). *First Author: Rachel Frascati, Roswell Park Comprehensive Cancer Center, Buffalo, NY*

Background: CIMAvax-EGF (C-E) is a recombinant anti-human epidermal growth factor (EGF) depleting immunotherapy which has previously shown increased survival as maintenance after platinum-based chemotherapy in patients (pts) with advanced NSCLC. The primary objective of this single-arm phase II trial was to evaluate the 12-month overall survival (OS) in pts receiving C-E in combination with Nivolumab(N) as 2L therapy for advanced NSCLC. **Methods:** Pts with previously treated, immunotherapy-naïve advanced NSCLC received 2.4 mg C-E IM every 2 weeks(w) for 4 doses (loading phase) in combination with N 240mg IV every 2 w, then continued monthly maintenance C-E combined with N 240mg IV every 2 w. Enrollment to this arm was terminated before estimated sample size was met due to poor accrual as immunotherapy became incorporated into 1st line therapy. We present OS and progression-free survival (PFS) data [determined using a Kaplan-Meier test with 90% confidence intervals (CI)] of pts who were able to complete the loading phase per protocol (PP). **Results:** 21 out of 23 enrolled pts were included in the PP analysis. Among the 21 pts, 17 (81.0%) had non-squamous(nsq) histology, 12 (57.1%) were KRAS wildtype (9.5% unknown status), 13 (61.9%) had PD-L1 tumor proportion score 0%. 43% pts (n=3) with known KRAS mutation (n=7) had co-mutated STK11. Disease control rate was 47.6% (n=10) defined as pts who had stable disease or partial response as best response per RECIST v1.1. The 21 PP pts had a 29% 3-year(yr) OS rate (90% CI 14, 45; intention-to-treat [ITT] population in 23 pts with 26% 3-yr OS rate, 90% CI 13, 42). Median(m) OS for PP pts was 11.9 months, 90% CI 8.0 – 23.9 months (ITT mOS 10.4 months, 90% CI 6.8-13.6). Pts with squamous histology had a better 3-yr OS rate compared to those with nsq histology [50% (90% CI 10, 81) vs 24% (90% CI 9, 41), respectively]. Pts with PD-L1 expression $\geq 1\%$ had higher 3-yr OS [38% (90% CI 12, 63)] and 3-year PFS [38% (90% CI 12, 63)] compared to pts with no PD-L1 expression (3-yr OS 23% [90% CI 8, 44] and 3-yr PFS 8% [90% CI 1, 25]). mOS, 1-yr and 3-yr OS for EGFR/ALK/KRAS wildtype pts was higher [31.7 months (90% CI 5.9, NR), 67% (90% CI 4, 84), 50% (90% CI 24, 71), respectively] compared to KRAS mutated NSCLC [10.1 months (90% CI 6.5, 12.1), 29% (90% CI 6, 56), 0% (90% CI 1, 41), respectively]. **Conclusions:** NSCLC pts who were able to complete the PP combination of C-E plus N at the minimum had numerically better OS compared to historical study cohorts with N as 2L monotherapy. Among pts who completed PP treatment, pts with KRAS wildtype NSCLC had the longest mOS observed. C-E is currently being investigated in combination with pembrolizumab as maintenance therapy after completing 1L chemoimmunotherapy for NSCLC with PD-L1 $< 50\%$ and as 1L therapy in combination with pembrolizumab for EGFR/ALK wildtype NSCLC and PD-L1 $\geq 50\%$. Clinical trial information: NCT02955290. Research Sponsor: Roswell Park Alliance Foundation.

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Poster Session

Amivantamab and lazertinib in treatment-naïve EGFR-mutated advanced non-small-cell lung cancer (NSCLC): Long-term follow-up and ctDNA results from CHRYSALIS. *First Author: Se-Hoon Lee, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea*

Background: CHRYSALIS (NCT02609776) evaluated the combination of amivantamab (ami) and lazertinib (laz) in treatment-naïve patients (pts) with epidermal growth factor receptor (EGFR)-mutated NSCLC. As previously reported, all 20 pts achieved a partial response (overall response rate of 100%) but interpretation of long-term outcomes was limited by the length of follow up (Cho *Ann Oncol* 2020;31: suppl.4, 12580; Cho *J Thorac Oncol* 2022;17:S126, P1.16-01). Herein, we present long-term results from this treatment-naïve cohort. **Methods:** The treatment-naïve cohort enrolled pts with EGFR exon 19 deletion (ex19del) or L858R mutated advanced NSCLC. All pts received 1050 mg IV ami (1400 mg if ≥ 80 kg) and 240 mg oral laz. Response was assessed by the investigator per RECIST v1.1. Circulating tumor DNA (ctDNA) was analyzed from plasma samples prior to initiation of treatment, at Cycle 3 Day 1, and at end of treatment (EOT). **Results:** Of the 20 pts enrolled in the treatment-naïve cohort (median 62.5 years, 55% women, all Asian), 11 had EGFR ex19del and 9 had L858R NSCLC. As of Nov 15, 2022, the median follow-up and duration of treatment were 33.6 and 33.5 months, respectively. Ten (50%) pts were progression-free and remained on treatment, including 7 of 11 (64%) with ex19del and 3 of 9 (33%) with L858R. The median duration of response (DOR), median progression-free survival (PFS), and median overall survival (OS) were not estimable. The estimated landmark PFS rate was 85% at 12 months, 65% at 24 months, and 51% at 36 months. Of note, 2 (10%) pts were treated beyond progression. The longest ongoing pt has a duration of treatment of 37.2 months and DOR of 35.7 months. Treatment-related dose interruptions, reductions, and discontinuations of either ami and laz occurred in 7 (35%) pts, 8 (40%) pts, and 1 (5%) pt, respectively. The safety profile was consistent with prior reports, with predominantly on-target EGFR- or MET-related adverse events. Among the 10 pts who discontinued treatment, 4 submitted samples for ctDNA analysis at both baseline and EOT. There was 1 pt with new PIK3CA mutations, 1 with low-level HER2 amplification, 1 pt with a new CCNE1 and EGFR amplification, and 1 pt with no new mutations detected. Updated data on ctDNA at EOT may be available at the time of congress presentation. **Conclusions:** At a median duration of treatment of 33.5 months, median DOR, PFS, and OS have not been reached in treatment-naïve pts receiving ami+laz, with 50% remaining progression-free and on treatment. No new safety signals were identified. The ongoing phase 3 MARIPOSA study (NCT04487080) is further investigating ami+laz vs osimertinib vs laz in previously untreated, EGFR-mutated, advanced NSCLC. Clinical trial information: NCT02609776. Research Sponsor: Janssen R&D, LLC.

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Poster Session

Real-world outcomes of first-line immune checkpoint inhibitors with or without chemotherapy in KRAS G12C altered NSCLC according to PD-L1 status. *First Author: Charu Aggarwal, University of Pennsylvania, Philadelphia, PA*

Background: There is a considerable debate whether treatment approaches should be tailored in advanced KRAS G12C-mutated NSCLC. Increasing evidence suggests that KRAS G12C-mutated NSCLC is associated with genomic heterogeneity that may impact clinical outcomes. Herein, we report a multimodal, real world outcomes analysis of 1L patients with advanced KRAS G12C-mutated NSCLC stratified by treatment type and PD-L1 status. **Methods:** Deidentified multimodal real-world data (RWD) of 1576 advanced, 1L NSCLC patients across the US were retrospectively analyzed from the Tempus database. Selection criteria included: Tempus xT targeted NGS, known PD-L1 status, absence of EGFR, ALK and ROS1 mutations, and treatment with chemotherapy (CT) + pembrolizumab (P), or P only. Patients were stratified by the presence or absence (wt) of KRAS G12C alterations. Median OS (mOS) was estimated using Kaplan-Meier methods. Subgroup analyses were performed using Cox model stratified by KRAS G12C status, PD-L1 status, and pathogenic alterations of STK11 and KEAP1. **Results:** In this study, two cohorts were assessed, KRAS G12C (n = 201) and KRAS G12C wt (n = 1375). Characteristics and demographics were balanced between both cohorts. Among TPS < 50 patients treated with CT + P, KRAS G12C (n = 109, 54%) had a mOS of 11.64 months (m) versus 16.81m (HR = 1.32, p = 0.06) for KRAS G12C wt (n = 864, 62.8%). Among TPS < 1 patients treated with CT + P, KRAS G12C (n = 46, 22%) had a mOS of 11.18 m versus 16.44 m (HR = 1.67, p = 0.01) for KRAS G12C wt (n = 489, 35%). Among TPS ≥ 50 patients treated with P only, KRAS G12C (n = 45, 22.3%) had a mOS of 30.03m compared to 25.03m (HR = 0.94, p = 0.83) in KRAS G12Cwt (n = 236, 17.1%). TPS < 50 subgroup was enriched for select co-mutations with KRAS G12C (STK11, 24.5%; KEAP1, 10.7%) vs. TPS ≥ 50 (STK11, 3.8%; KEAP1, 5.1%). When evaluating the impact of co-mutations in the KRAS G12C with TPS < 50 , STK11 (n = 30) mOS was 10.59m (HR = 1.01, p = 0.81) and KEAP1 (n = 13) mOS was 7.63m (HR = 2.14, p = 0.03). **Conclusions:** This largest RWD analysis to date demonstrates that 1L KRAS G12C NSCLC patients with TPS $< 1\%$ and $< 50\%$ receiving standard CT + P have the shortest survival among all evaluated sub-groups. Novel KRAS G12C targeted combination therapies in development for this patient population may offer the promise of better outcomes. Research Sponsor: Tempus Labs and Mirati Therapeutics.

		CT + P		P	
PD-L1 Status	mOS (m)	KRAS G12C	KRAS G12Cwt	KRAS G12C	KRAS G12Cwt
		11.18 (n = 46)	16.44 (n = 489)	16.31 (n = 3)	15.71 (n = 38)
TPS < 1	HR [95% CI] p-value	1.67 [1.12 - 2.50] p = 0.01		1.57 [0.34 - 7.06] p = 0.56	
TPS 1-49	mOS (m)	16.91 (n = 63)	19.58 (n = 375)	NA (n = 10)	23.70 (n = 66)
	HR [95% CI] p-value	1.12 [0.73 - 1.73] p = 0.59		0.35 [0.05 - 2.69] p = 0.32	
TPS < 50	mOS (m)	11.64 (n = 109)	16.81 (n = 864)	16.31 (n = 13)	15.72 (n = 104)
	HR [95% CI] p-value	1.32 [0.99 - 1.77] p = 0.06		0.72 [0.22 - 2.35] p = 0.58	
TPS ≥ 50	mOS (m)	NA (n = 34)	18.02 (n = 171)	30.03 (n = 45)	25.03 (n = 236)
	HR [95% CI] p-value	0.60 [0.29 - 1.22] p = 0.16		0.94 [0.54 - 1.64] p = 0.83	

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Poster Session

Risk factors for venous thromboembolism (VTE) among patients with EGFR-mutated advanced non-small cell lung cancer (NSCLC) receiving amivantamab plus lazertinib versus either agent alone. *First Author: Nicolas Girard, Institut Curie, Institut du Thorax Curie-Montsouris, Paris, France*

Background: Amivantamab (ami), an EGFR and cMET bispecific antibody with immune cell-directing activity, and lazertinib (laz), a CNS-penetrant 3rd-generation EGFR tyrosine kinase inhibitor have shown clinical activity in biomarker-selected patients (pts) with advanced NSCLC. Antitumor activity has been suggested to be improved when the agents are given in combination (Leighl *Ann Oncol* 2021;32:suppl_5, 1192MO). We examined the incidence of VTE, a common adverse event (AE) among pts with lung cancer, for those receiving ami monotherapy, laz monotherapy, and ami+laz to investigate if there is elevated risk and understand potential predisposing risk factors. **Methods:** CHRYSLIS (NCT02609776; ami monotherapy and ami+laz), CHRYSLIS-2 (NCT04077463; ami+laz), and LASER201 (NCT04075396; laz monotherapy) are ongoing open-label studies of locally advanced/metastatic NSCLC. Two descriptive, univariate risk analyses were performed, with the primary analysis including all treatment-emergent VTE events (grouped term) and a secondary analysis that excluded VTE events occurring after progression of disease (PD) or within 30 days prior to PD. **Results:** This analysis included 560 pts who received ami monotherapy, 536 ami+laz, and 252 laz monotherapy, predominantly in the TKI-relapsed setting. The incidence of VTE events of any grade was numerically higher in pts who received ami+laz (21%) than those who received ami (11%) or laz (11%) monotherapy. The median time to onset of the first VTE event was 84.5 days for ami, 79 days for ami+laz, and 170 days for laz. The majority (64%) of ami+laz pts had VTE events in the first 4 months. The most common VTE events by preferred term were pulmonary embolism and deep vein thrombosis. The incidence of grade ≥ 3 VTE events was comparable among pts receiving ami (5%), ami+laz (6%), and laz (6%), and there were no grade 5 VTE events for ami+laz. The overall incidence of serious VTE AEs was low (ami, 3%; ami+laz, 5%; laz, 4%). There were 6 discontinuations due to VTE, 1 (0.2%) ami, 2 (0.4%) for ami+laz, and 3 (1.2%) laz. In the primary analysis, age ≥ 60 years was a significant risk factor ($P < 0.05$). In the secondary analysis, age ≥ 60 years, ECOG performance status of 1 (vs 0), and response to therapy (partial response or better) were significant risk factors ($P < 0.05$). **Conclusions:** Lung cancer diagnosis is a known risk factor for VTE. In a review across clinical trials, single-arm cohort data suggest there is a numerically higher incidence of VTE for ami+laz compared with each monotherapy. Age ≥ 60 years, ECOG performance status, and response to treatment are potential risk factors. The relationship between response and VTE is emerging and may reflect possible immune or inflammatory-mediated mechanisms. Further efforts to understand VTE-associated risk factors in randomized clinical trials are ongoing. Clinical trial information: NCT02609776, NCT04077463, NCT04075396. Research Sponsor: Janssen R&D, LLC.

TPS9140

Poster Session

A phase 1a/1b study of aurora kinase A inhibitor VIC-1911 as monotherapy and in combination with sotorasib for the treatment of KRAS G12C-mutant non-small-cell lung cancer. *First Author: Sarah B. Goldberg, Yale Cancer Center, Yale School of Medicine, New Haven, CT*

Background: Activity of direct covalent KRAS^{G12C} inhibitors in NSCLC is limited by mutational and adaptive resistance. AURKA has roles in centrosome maturation and cytokinesis. AURKA amplification/overexpression is reported in multiple tumors, including NSCLC, and AURKA signaling may mediate adaptive resistance to KRAS inhibition. VIC-1911 is a highly selective, orally active small molecule inhibitor of AURKA. VIC-1911 demonstrated monotherapy activity *in vitro* in KRAS^{G12C}-mutant human NSCLC cells with intrinsic and acquired resistance to the KRAS^{G12C} inhibitor sotorasib, and combination VIC-1911 and sotorasib showed synergy in the same cell lines. Combination VIC-1911 and sotorasib delayed the emergence of adaptive resistance *in vitro*. These findings suggest that 1) AURKA activation is present in both intrinsic and acquired resistance to sotorasib in KRAS^{G12C}-mutant NSCLC and 2) the combination of VIC-1911 and sotorasib is a potential therapeutic approach for KRAS^{G12C}-mutant NSCLC with intrinsic or acquired resistance to sotorasib monotherapy. In addition, *in vivo* data suggest both sotorasib and adagrasib are synergistic in combination with VIC-1911 in human KRAS^{G12C}-mutant NSCLC cell line xenograft models. **Methods:** A non-randomized, open-label Phase 1a/1b study of VIC-1911, an aurora kinase A inhibitor, administered as monotherapy and in combination with sotorasib for the treatment of advanced KRAS^{G12C}-mutant NSCLC is in progress. Participants ≥ 18 years, with locally advanced or metastatic KRAS^{G12C}-mutant NSCLC, prior treatment with at least 1 line of PD-1/PD-L1 inhibitor therapy with or without platinum-based chemotherapy and have adequate organ function are eligible. Both KRAS^{G12C} inhibitor naïve and experienced patients are eligible. VIC-1911 monotherapy is given at oral doses of 25–90 mg twice daily in dose escalation and at the VIC-1911 maximum tolerated dose (MTD) in the expansion cohort in patients who are refractory/relapsed on prior KRAS^{G12C} inhibitor therapy. The combination regimen includes dose escalation with VIC-1911 at oral doses of 75, 150 or 200 mg twice daily on days 1-4, 8-11 and 15-18 every 28-day cycle plus sotorasib 960 mg daily in patients who are refractory/relapsed or naïve to prior KRAS^{G12C} inhibitor therapy. In dose escalation, a 3+3 schema is followed with dose limiting toxicity (DLT) criteria for toxicity and a sample size ≤ 36 . For expansion cohorts, the sample size is based on Simon 2-stage optimal design, with a sample size ≤ 104 . VIC-1911 and sotorasib dose modification criteria are provided. Supportive medications are allowed and early stopping rules for toxicity will be followed. VIC-1911 pharmacokinetics will be assessed. Pharmacodynamics will be determined from ctDNA and tumor biomarker analysis. Clinical trial information: NCT05374538. Research Sponsor: VITRAC Therapeutics, LLC.

TPS9139

Poster Session

A phase III, multicenter, double-blinded, randomized, active-controlled study on the efficacy and safety of QL1706 with chemotherapy (CT) as first-line therapy for PD-L1-negative advanced or metastatic non-small-cell lung cancer (NSCLC). *First Author: Li Zhang, Department of Medical Oncology, State Key Laboratory of Oncology in South China; Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University Cancer Center, Guangzhou, Guangdong, China*

Background: PD-(L)1 immunotherapy plus platinum-doublet chemotherapy has been the standard 1L treatment for EGFR/ALK wild-type advanced NSCLC pts. However, pts with PD-L1 negative achieve minimal benefit from the PD-(L)1 immunotherapy plus CT. PD-(L)1 plus CTLA-4 blockade with CT in 1L treatment of PD-L1 negative NSCLC derived an improved median overall survival (OS) versus CT alone in CheckMate-9LA study (Luis Paz-Ares *et al.*, *Lancet Oncol* 2021) and POSEIDON study (M L. Johnson *et al.*, *JCO* 2022). QL1706 is a novel bifunctional antibody, containing a mixture of anti-PD-1 IgG4 and anti-CTLA-4 IgG1 antibodies produced in a fixed ratio (2:1) from the same single cell and manufactured together as one product (MabPair). QL1706 monotherapy or plus CT showed impressive safety and efficacy in advanced NSCLC both in phase I and phase II studies (data have been submitted for publication). Of note, QL1706+CT exhibited promising antitumor activity in advanced PD-L1 negative NSCLC. The phase III study aims to compare the efficacy of QL1706+CT versus anti-PD-1 (tislelizumab) + CT (approved in China for 1L treatment of mNSCLC) as 1L treatment in advanced PD-L1 negative NSCLC. **Methods:** The phase III, multicenter, double-blinded, randomized, active-controlled study is enrolling pts aged 18-75 years with ECOG PS of 0-1, previously untreated, PD-L1 negative (TPS $< 1\%$), EGFR/ALK wild-type, and pathologically identified stage IIIB-IV NSCLC. Eligible pts will be randomized (1:1) to receive 4-cycle treatment of QL1706 (5 mg/kg, Q3W) plus CT or tislelizumab (200 mg, Q3W) plus CT followed with maintenance treatment of QL1706 or tislelizumab monotherapy (squamous), or in combination with pemetrexed (non-squamous), until disease progression, intolerable toxicity, or for up to 2 years of immunotherapy. Stratification factors include histology (squamous vs non-squamous), brain metastasis (yes vs no), and sex (male vs female). Co-primary endpoints are progression-free survival (PFS) and OS. Secondary endpoints include objective response rate (ORR), disease control rate (DCR), duration of response (DOR) assessed by investigator per RECIST v1.1, 6 mo- and 12 mo-PFS, 6 mo- and 12 mo-OS, and safety. Exploratory endpoints include PK characteristics, immunogenicity, PFS2 (defined as time from randomization to progression after first subsequent therapy or any-cause death), and efficacy (iPFS, iORR, iDCR, iDOR) by investigator per iRECIST, biomarker analysis of tumor mutation burden. The study planned to enroll 650 pts to obtain approximately 493 PFS events (HR = 0.69; Power = 94%) and 445 OS events (HR = 0.75; Power = 83%) across the QL1706+CT and tislelizumab+CT arms for the final analyses of PFS and OS, respectively. The alpha was split between PFS ($\alpha = 0.005$) and OS ($\alpha = 0.02$). Enrollment began from Feb 2023. Clinical trial information: NCT05690945. Research Sponsor: Qilu Pharmaceutical Co., Ltd.

TPS9141

Poster Session

STAR-121: A phase 3, randomized study of domvanalimab (DOM) and zimberelimab (ZIM) in combination with chemotherapy vs pembrolizumab (pembro) and chemotherapy in patients with untreated metastatic non-small cell lung cancer (mNSCLC) with no actionable gene alterations. *First Author: Delvys Rodriguez-Abreu, Complejo HU de Canarias, Santa Cruz De Tenerife, Spain*

Background: Although immune checkpoint inhibitors have improved clinical outcomes in mNSCLC, the majority of patients will experience progression and shorter survival. Thus, an urgent need exists for more effective treatment options in mNSCLC. DOM is an anti-TIGIT IgG1, Fc-silent monoclonal antibody designed to inhibit the interaction between TIGIT and its ligand, CD155, thereby reducing immunosuppression of T cells and natural killer cells and promoting antitumor activity. ZIM is an anti-PD-1 IgG4 monoclonal antibody with demonstrated antitumor activity *in vivo* and preliminary clinical activity in multiple tumor types. Preliminary studies have shown that dual blockade of TIGIT and PD-(L)1 increases antitumor activity relative to PD-(L)1 inhibition. In ARC-7, a randomized phase 2 study in PD-L1-high, first-line NSCLC, DOM and ZIM in combination recently demonstrated a higher objective response rate (ORR) and longer median progression-free survival (PFS) than ZIM monotherapy. We hypothesize that DOM and ZIM in combination with chemotherapy will improve clinical outcomes in patients with untreated mNSCLC without EGFR or ALK aberrations regardless of PD-L1 expression. **Methods:** STAR-121 is a phase 3, global, open-label, randomized study to evaluate the safety and efficacy of DOM and ZIM plus chemotherapy vs pembro plus chemotherapy as first-line therapy for patients with mNSCLC with no EGFR or ALK aberrations or other known actionable gene alterations. Approximately 720 patients will be randomized into 3 groups (A, B, or C) in a 4:4:1 ratio and stratified by baseline PD-L1 tumor proportion score ($< 50\%$ vs $\geq 50\%$), histology (squamous vs nonsquamous), and geographic region (East Asia vs non-East Asia). Eligible patients are aged ≥ 18 with untreated mNSCLC with no EGFR or ALK aberrations. Group A will receive DOM 1200 mg + ZIM 360 mg + platinum-doublet chemotherapy (PT), group B will receive pembro 200 mg + PT, and group C will receive ZIM 360 mg + PT. DOM, ZIM, and pembro will be administered until disease progression (PD) as assessed by blinded independent central review (BICR) per RECIST 1.1 or intolerable toxicity or for up to 35 doses. Study treatment will be administered IV every 3 weeks. PT will be chosen by investigators based on tumor histology and administered for the first 4 cycles, after which, pemetrexed can be continued for patients with nonsquamous histology until PD or intolerable toxicities. The primary endpoints are PFS by BICR and overall survival. Key secondary endpoints are ORR and duration of response by BICR, safety, and quality of life. This study is currently enrolling globally. Clinical trial information: NCT05502237. Research Sponsor: Gilead Sciences, Inc.

TPS9142

Poster Session

A phase 2 multi-arm study of magrolimab in combination with docetaxel in patients with locally advanced or metastatic solid tumors: ELEVATE Lung and UC. *First Author: Vivek Subbiah, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Patients (pts) with solid tumors that progress on standard chemotherapy and/or immune checkpoint inhibitors experience limited efficacy with existing standard of care options. These pts have a significant unmet need, and novel agents that safely enhance treatment efficacy are needed. Magrolimab is a monoclonal antibody that blocks CD47, a "don't eat me" signal often overexpressed on solid tumor cells. Magrolimab blockade of CD47 induces macrophage-mediated phagocytosis of tumor cells and has shown preclinical activity and promising clinical efficacy in hematologic malignancies. Certain chemotherapies, including taxanes, enhance phagocytic signals on tumor cells, leading to potential synergistic anti-tumor activity when combined with magrolimab. This study is evaluating the safety, tolerability, and efficacy of magrolimab with docetaxel in metastatic non-small cell lung cancer (mNSCLC), small cell lung cancer (mSCLC), and urothelial cancer (mUC). **Methods:** This open-label study includes a safety run-in and 3 phase 2 cohorts. Pts eligible for the safety run-in must have had ≥ 1 (mNSCLC, mSCLC) or 2 and not more than 3 (mUC) prior lines of systemic anticancer therapy in a locally advanced/metastatic setting and will be treated with magrolimab + docetaxel. In phase 2, pts must have either mNSCLC treated with platinum-based chemotherapy and/or an immune checkpoint inhibitor (ICI), mUC treated with prior systemic chemotherapy and/or an ICI, or mSCLC treated with platinum-based chemotherapy with or without an ICI in a locally advanced/metastatic setting. Pts refractory to prior taxane therapy or who have received a taxane within 12 months of study start are excluded. Pts who had prior treatment with CD47/SIRP α -targeting agents were also excluded. Magrolimab is administered intravenously (IV) as a 1-mg/kg priming dose on cycle 1 day 1 (C1 D1) to mitigate on-target anemia followed by 30 mg/kg on D8 and D15. Magrolimab 30 mg/kg is administered on C2 D1, D8, and D15 and 60 mg/kg on D1 for C3+. The recommended phase 2 dose (RP2D) is determined in the safety run-in, with de-escalation if prespecified dose-limiting toxicity criteria are met. Once the RP2D is determined, the phase 2 cohorts will follow the same dose schedule. Docetaxel 75 mg/m² is administered IV on D1 of each cycle. Reasons for treatment discontinuation may include unacceptable toxicity, disease progression, or pt/investigator choice to discontinue. The primary endpoints are incidence of adverse events by CTCAE v5.0 (safety run-in, phase 2) and investigator-assessed objective response rate by RECIST 1.1 (phase 2 cohorts). Secondary endpoints are magrolimab concentration vs time and antidrug antibodies (safety run-in, phase 2), progression-free survival and duration of response by RECIST 1.1, and overall survival (phase 2 cohorts). Planned enrollment is ≈ 116 pts. Clinical trial information: NCT04827576. Research Sponsor: Gilead Sciences, Inc.

TPS9144

Poster Session

KontRAST-02: A phase III trial investigating the efficacy and safety of the KRAS^{G12C} inhibitor JDQ443 vs docetaxel in patients with previously treated, locally advanced or metastatic, KRAS G12C-mutated NSCLC. *First Author: Federico Cappuzzo, Hematology Department, AUSL della Romagna, Ravenna, Italy*

Background: Kirsten rat sarcoma viral oncogene homolog (KRAS) is the most frequent mutated oncogene in non-small cell lung cancer (NSCLC). KRAS G12C is the most common KRAS variant, present in $\sim 13\%$ of patients (pts) with non-squamous NSCLC. KRAS G12C mutations cause the accumulation of active, GTP-bound KRAS, which leads to activation of downstream pathways involved in cell proliferation and invasiveness. JDQ443 is a potent, structurally novel, selective KRAS^{G12C} inhibitor that irreversibly traps KRAS^{G12C} in its inactive, GDP-bound form. Data from the JDQ443 monotherapy arm of the first-in-human KontRAST-01 study demonstrated encouraging anti-tumor activity and an acceptable safety profile of JDQ443 in pts with previously treated, KRAS G12C-mutated, advanced NSCLC. For pts with advanced NSCLC who progress following first-line immunotherapy or doublet platinum-based chemotherapy, single agent docetaxel remains a standard option, although it presents modest activity and is generally poorly tolerated. In this context, alternative treatment options are needed to improve pt outcomes. **Methods:** KontRAST-02 (NCT05132075) is a global, Phase III, open-label, randomized, multicenter study evaluating JDQ443 as a monotherapy in comparison to docetaxel in pts with KRAS G12C-mutated, advanced NSCLC previously treated with PD-(L)1 inhibitors and platinum-based chemotherapy (either in combination or as sequential treatments). Approximately 360 pts stratified by ECOG performance status (0 vs 1 and 2) and prior therapy (platinum-based chemotherapy and immunotherapy combined vs sequential) will be randomized at 1:1 to receive 200 mg oral JDQ443 twice daily continuously or 75 mg/m² intravenous docetaxel once every 21 days. The primary endpoint of this study is progression-free survival (PFS) per Blinded Independent Review Committee (BIRC) according to RECIST version 1.1. The key secondary endpoint is overall survival (OS); other secondary endpoints include objective response rate, disease control rate, time to response, duration of response, PFS on subsequent therapy, safety of JDQ443 monotherapy, pt-reported outcomes, pharmacokinetics, time to deterioration of ECOG performance status, and safety in pts who crossover from docetaxel to JDQ443. Exploratory objectives include biomarker analyses aimed at investigating predictors of responsiveness to JDQ443. Pts randomized to docetaxel will be allowed to crossover to JDQ443 following confirmed disease progression per BIRC. To allow more pts to be treated with JDQ443, crossover will also be offered to all patients on docetaxel if the primary endpoint (PFS) is met. Treatment beyond progression will be allowed for pts receiving JDQ443 according to investigator judgement. The KontRAST-02 study is currently enrolling pts. Clinical trial information: NCT05132075. Research Sponsor: Novartis Pharmaceuticals Corporation.

TPS9143

Poster Session

ECOG-ACRIN LUNG-MAP S1900E substudy: A phase II study of sotorasib in participants (Pts) with previously treated stage IV or recurrent KRAS G12C mutant non-squamous (Non-sq) non-small cell lung cancer (NSCLC). *First Author: Sukhmani Kaur Padda, Samuel Oschin Cancer Center, Cedars-Sinai Medical Center, Los Angeles, CA*

Background: KRAS mutant NSCLC is further defined molecularly by specific mutation subtypes and co-mutations in tumor suppressor genes. Two targeted therapeutics, sotorasib and adagrasib, are currently approved for the treatment of previously treated advanced KRAS G12C mutant NSCLC. Sotorasib has also demonstrated superiority to docetaxel in the randomized phase III CodeBreak 200 study (*de Langen et al Lancet. 2023 Feb 7 Epub*). The impact of co-mutations in tumor suppressors, including TP53 and STK11, on the efficacy of first generation KRAS G12C inhibitors has been inconclusive. The S1900E substudy aims to prospectively understand, using rigorous biomarker testing/definitions, the impact of co-mutations on the clinical activity of sotorasib in pts with KRAS G12C mutant NSCLC. **Methods:** S1900E is a phase 2 open-label study of sotorasib in biomarker-defined cohorts for pts who have KRAS G12C stage IV/recurrent non-sq NSCLC, received at least one line of systemic treatment, and are naive to KRAS G12C inhibitors. Pts are assigned to S1900E under the Lung-MAP screening protocol (NCT03851445) using FoundationOne F1CDx next generation sequencing assay on tissue (Foundation Medicine, Cambridge, MA). S1900E cohorts include: #1) Presence of TP53 co-mutation AND Wild Type STK11, KEAP1, NFE2L2, CUL3; #2) Presence of STK11 co-mutation AND Wild Type TP53, KEAP1, NFE2L2, CUL3; #3) All pts not eligible for Cohorts 1 and 2 (e.g. dual co-mutations in STK11 and TP53; co-mutations in KEAP1, NFE2L2, CUL3, or others; or lack of any co-mutations). Pts with treated, clinically controlled, and asymptomatic brain metastases are eligible and with amendment 3 (Mar 20 2022), eligibility expanded to pts with asymptomatic untreated brain metastases. Sotorasib is dosed 960 mg oral daily. The primary objective is to evaluate the RECIST 1.1 response rate (ORR) per cohort. For cohorts 1 and 3, the target sample size is 40 eligible pts based on a design with 92% exact power to rule out a 14% ORR at the 1-sided 5% level, if the true ORR were 34%; ≥ 10 responses would rule out a 14% ORR. Cohort 2 has a target sample size of 25 eligible pts with 93% exact power to rule out a 14% ORR at the 1-sided 5% level, if the true ORR were 40%; ≥ 7 responses would rule out a 14% ORR. Secondary endpoints include PFS, OS, duration of response, and toxicity. Circulating tumor DNA is being collected at day 1 of cycle 1, 2, and 3 and at progression. Enrollment started April 2 2021 with conservative accrual targets met, currently with 72% enrolled (84/116) as of Feb 14 2023, including 37, 16, and 31 pts, in cohorts 1, 2, and 3, respectively. Clinical trial information: NCT04625647. Research Sponsor: Multiple Sources: NIH/NCI grants U10CA180888, U10CA180819, U10CA180821, U10CA180820, U10CA180868; and in part by Foundation for the National Institutes of Health; and Amgen, Inc.

TPS9145

Poster Session

REFINE-Lung: A multicentre phase III study to determine the optimal frequency of pembrolizumab in non-small cell lung cancer utilising a novel multi-arm design. *First Author: Michael Seckl, Imperial College London, London, United Kingdom*

Background: Pharmacological and clinical data suggest standard regimens for anti-PD1 agents nivo and pembro result in overtreatment. These agents have high target affinity, saturate PD1 at very low concentrations and maintain receptor occupancy for up to 30 wks following discontinuation. Clinical studies suggest no dose-response relationship in the wide range tested (0.1 – 10 mg/kg) and retrospective data suggest the efficacy of lower doses or longer administration frequency. Given their high costs and important implications for pt quality of life and toxicity, new approaches to optimise treatment regimens are required. However, conventional 2-arm non-inferiority designs require large numbers of patients, explore a single alternative to the standard of care and potentially require multiple trials to establish optimal parameters such as dose or frequency. Here we present a new multi-arm trial design to tackle this problem, implemented in the UK multicentre phase III REFINE-Lung study that aims to determine the optimal treatment frequency of pembro in NSCLC. Pts who are progression free after 6 months of standard therapy are randomised to 5 pembro frequency reduced arms (q6w, q9w, q12w, q15w and q18w). By evaluation of the frequency-response relationship, we will determine the longest frequency that is equivalent to standard of care within a pre-defined margin. **Methods:** The REFINE-Lung trial (NCT05085028) is a multicentre, randomised open-label, phase III trial in advanced NSCLC. REFINE-Lung utilises a novel Multi-Arm Multi-Stage Response Over Continuous Interventions (MAMS-ROCI) design to determine the optimal dose frequency of pembro. 1750 pts aged ≥ 18 and progression free at six months into 1st line pembro and planning to continue, will be enrolled from up to UK 35 hospital groups. Pts will be randomised across 5 arms to determine the optimal dose frequency. To assess safety, pts will initially be randomised 1:1 into q6w (control) and q12w arms. Interim analysis will be conducted once 37 progression free events are observed in the control arm. If PFS in the q12w arm is not significantly reduced, the remaining q9w, q15w and q18w arms will be opened. Pts who progress on a frequency reduced arm may re-escalate to q6w therapy. The primary objective is to determine the optimal continuing dose frequency of pembro, defined as the longest dose interval non-inferior to standard therapy using 2-year survival as the primary outcome. Secondary endpoints include OS, PFS, ORR, duration of response, adverse events, quality of life and cost effectiveness. An exploratory sub-study will explore fundamental aspects of cancer immunotherapy and develop novel biomarkers of response, resistance, toxicity and patient suitability for dose frequency de-escalation. Recruitment is ongoing and the trial is open at 16 centres at time of submission. Clinical trial information: NCT05085028. Research Sponsor: National Institute for Health Research; Lung Cancer Research Charity and North West London Pathology Consortium.

TPS9146

Poster Session

PRESERVE-003: Phase 3, two-stage, randomized study of ONC-392 versus docetaxel in metastatic non-small cell lung cancers that progressed on PD-1/PD-L1 inhibitors. *First Author: Mark A. Socinski, AdventHealth Cancer Institute, Orlando, FL*

Background: For NSCLC without driver mutation, the PD-1/PD-L1 inhibitor as the first-line (monotherapy or in combination with platinum-based doublet agents) or second-line therapy after chemotherapy significantly improved overall survival. However, there remain a significant number of patients who do not have response or have an initial response followed by disease progression to PD-1/PD-L1 inhibitor therapy. CTLA-4 is a proven immunotherapy target in solid tumor, unfortunately no monotherapeutic efficacy has been shown in NSCLC by marketed anti-CTLA-4 antibodies, including ipilimumab and tremelimumab. These anti-CTLA-4 mAbs cause severe toxicity that prevents adequate dosing in cancer patients. In contrast, ONC-392 keeps high-level CTLA-4 on Treg cells through a recycling mechanism and makes Treg cells a better target for antibody-dependent cellular cytotoxicity, particularly in the tumor microenvironment where macrophages are more abundant. The selective elimination of Treg cells in the tumor microenvironment and maintenance of CTLA-4 expression in Treg cells in the peripheral tissues by ONC-392 form the cellular and molecular basis for more potent tumor rejection and low toxicity in animal studies. Our first in human studies have demonstrate safety and clinical activities of ONC-392 in patients with NSCLC and other solid tumors. **Methods:** This is a seamless 2-stage, randomized, open-label, active-controlled, Phase 3 study of ONC-392 for treatment of NSCLC patients who progressed on PD-1/PD-L1 inhibitor (NCT05671510). Approximately 600 patients will be enrolled. Stage 1, the dose-confirmation stage, will assess the efficacy and safety of two ONC-392 dosing regimens (3 mg/kg Q3W and 6 mg/kg Q3W with 2 loading doses of 10 mg/kg Q3W) in comparison to docetaxel 75 mg/m² Q3W. A total of 120 patients will be randomized 1:1 in Stage 1 into one of two ONC-392 dose cohorts or docetaxel cohort. An interim analysis will be conducted at the end of Stage 1 when 120 patients are enrolled. Stage 2 will start when ONC-392 dose is determined and approximately 480 patients will be randomized 1:1 to receive ONC-392 or docetaxel treatment. All enrolled patients who are randomized to the ONC-392 arms will receive ONC-392 at the randomized dose for up to 17 cycles in approximately 1 year or until discontinuation criteria are met. Patients who are randomized to the docetaxel arm will receive docetaxel 75 mg/m² Q3W until disease progression per RECIST 1.1. The primary endpoint is overall survival. The treatment effect will be estimated using a Cox Proportional Hazard model stratified by the randomization stratification factors to calculate the estimated hazard ratio and its 95% CIs. Kaplan-Meier (i.e., product-limit) estimates of median OS time will be presented by treatment arm with two-sided 95% CIs. The analyses will be based on the ITT Population. Clinical trial information: NCT05671510. Research Sponsor: OncoC4, Inc.

TPS9148

Poster Session

ARC-10: A phase 3 study to evaluate zimberelimab + domvanalimab versus pembrolizumab in front-line, PD-L1-high, locally advanced or metastatic non-small-cell lung cancer. *First Author: Christos Chouaid, Centre Hospitalier Intercommunal de Créteil, Créteil, France*

Background: Despite improvements in the management of locally advanced or metastatic non-small cell lung cancer (NSCLC) from programmed cell death/ligand protein 1 (PD-L1) inhibition, there remains an unmet need for improved treatment options. PD-L1 expression is a known biomarker of response to anti-PD-L1 therapies in metastatic NSCLC. The combination of PD-1 inhibition with inhibition of the immunosuppressive T cell Immunoglobulin and ITIM domain (TIGIT) pathway is associated with improved response and prolonged progression-free survival in patients with advanced NSCLC. Domvanalimab (dom) is an Fc-silent humanized IgG1 monoclonal antibody (mAb) that blocks TIGIT, thereby reducing immunosuppression of T/natural killer (NK) cells and promoting antitumor activity. Zimberelimab (zim) is an mAb that binds to PD-1 on T/NK cells, preventing PD-L1-mediated immunosuppressive effects and resulting in tumor cell death. This phase 3 study will investigate the efficacy and safety of combination therapy with dom + zim compared with pembrolizumab monotherapy in patients with PD-L1-high NSCLC. **Methods:** ARC-10 (NCT04736173) is a global, phase 3, randomized, multicenter, open-label study. Eligible patients are adults with histologically confirmed, treatment-naïve, locally advanced or metastatic, squamous or non-squamous NSCLC with ≥ 1 measurable lesion(s) per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, high expression of PD-L1 (tumor cells [TC] $\geq 50\%$), and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Patients must not have genomic tumor aberrations for which targeted therapies are approved and available (eg, *EGFR*, *ALK*, *ROS*, *BRAF*, *NTRK*). Approximately 600 patients will be randomized 1:1 to receive combination therapy with dom + zim (dom 1200 mg intravenous [IV] once every 3 weeks [Q3W] + zim 360 mg IV Q3W) or pembrolizumab monotherapy (200 mg IV Q3W) for 21-day cycles until disease progression, intolerance, or a maximum of 35 cycles. Randomization will be stratified by ECOG performance status (0 vs 1), geographical region (Asia vs non-Asia), and histology (squamous vs non-squamous). The primary efficacy endpoint is overall survival. Secondary efficacy endpoints include blinded independent central review of progression-free survival and confirmed overall response rate according to RECIST v1.1. Safety endpoints include the presence of treatment-emergent adverse events and laboratory parameters. Health-related quality of life will be assessed by measuring the time to first symptom deterioration in the NSCLC-Symptom Assessment Questionnaire total score. Study recruitment is planned in Asia, North and South America, Africa, and Europe. Clinical trial information: NCT04736173. Research Sponsor: Arcus Biosciences.

TPS9147

Poster Session

Phase 1 multicenter dose escalation and dose expansion study of antibody-drug conjugate (ADC) MYTX-011 in subjects with non-small cell lung cancer. *First Author: Alexander I. Spira, NEXT Oncology - Virginia Cancer Specialists, Fairfax, VA*

Background: cMET is a receptor tyrosine kinase and proto-oncogene whose activity is upregulated across a wide range of cancers. In NSCLC, expression of cMET is upregulated by DNA amplification (2% to 5%), exon 14 skipping mutations (2% to 4%), and overexpression (30% to 60%). In NSCLC, cMET upregulation has also been demonstrated to be a resistance mechanism for several approved EGFR-targeted kinase inhibitors, and this may limit their effectiveness. Despite the approval of MET tyrosine kinase inhibitors, almost half of patients do not respond to these inhibitors and resistance is inevitable. MYTX-011 is an ADC incorporating the clinically validated vcMMAE linker-payload conjugated to a novel, pH-dependent anti-cMET antibody. In preclinical studies, MYTX-011, compared to a surrogate of an advanced clinical stage cMET ADC, showed markedly higher (> 3 fold) internalization and increased cytotoxicity in cMET+ tumor cells *in vitro*, which translates to greater (≥ 3 fold) efficacy in high or moderate c-Met+ xenograft models *in vivo*. PK and toxicity studies revealed that MYTX-011 exhibited favorable PK characteristics, and a toxicity profile similar to previously described MMAE-based ADCs. **Methods:** MYTX-011-01 (ClinicalTrials.gov Identifier: NCT05652868) is a first-in-human Phase 1 dose escalation and dose expansion study. MYTX-011 will be administered intravenously every 21 days for a maximum of 2 years. Part 1 (dose escalation) will assess the safety and tolerability of MYTX-011 in patients with advanced NSCLC and identify the recommended Phase 2 dose (RP2D). Part 2 (dose expansion) will include subjects with NSCLC with cMET overexpression or MET amplification/exon 14 skipping mutations. In Part 1, subjects will be enrolled to evaluate the safety of escalating doses of MYTX-011 as a single-agent and to establish the RP2D and/or MTD. The dose escalation scheme is based on a 3-subject cohort minimum Bayesian Optimal Interval (BOIN) design. The RP2D will be selected as a biologically active dose at or below the MTD (or the highest dose tested if an MTD is not identified during the study) and will be informed by safety, tolerability, pharmacokinetic data, and preliminary anti-tumor activity of MYTX-011 based on RECIST 1.1. Part 2 of the study will be initiated once the RP2D has been determined and will enroll subjects into different cohorts based on cMET IHC positivity cutoff and/or presence of MET genetic alterations (MET amplification or exon 14 skipping). All cohorts are defined to explore preliminary anti-tumor activity in populations with different thresholds of cMET positivity that were selected based on data for cMET expression and efficacy observed with MYTX-011 in preclinical models, published data for responses to cMET targeting agents, and on the prevalence of subject tumors with different expression levels. Enrollment in the MYTX-011-01 study is ongoing. Clinical trial information: NCT05652868. Research Sponsor: Mythic Therapeutics.

TPS9149

Poster Session

Phase 2 study of telisotuzumab vedotin (Teliso-V) monotherapy in patients with previously untreated MET-amplified locally advanced/metastatic non-squamous non-small cell lung cancer (NSQ NSCLC). *First Author: Hidehito Horinouchi, Department of Thoracic Oncology, National Cancer Center Hospital, Tokyo, Japan*

Background: Teliso-V is a first-in-class anti-c-Met antibody-drug conjugate composed of the monoclonal antibody telisotuzumab (ABT-700), a cleavable valine-citrulline (dipeptide) linker, and cytotoxic monomethylauristatin E (MMAE; potent microtubule polymerization inhibitor). Direct MMAE payload delivery to c-Met protein over-expressing (OE) cells enables Teliso-V to work independently of c-Met signaling. In NSCLC, while c-Met OE is more common than MET gene amplification (Amp), about 90% of MET Amp tumors will also be c-Met OE. In an ongoing phase 2 trial, Teliso-V showed encouraging efficacy and acceptable safety in previously treated c-Met OE NSQ NSCLC population (Camidge et al. JCO.2022.40.16_suppl.9016). From this study, a retrospective analysis of 10 patients with MET Amp (≥ 1.8 MET gene to chromosome 7 copy number ratio by fluorescence in situ hybridization [FISH]) demonstrated an objective response rate (ORR) of 80%. Described here is an ongoing phase 2 study evaluating efficacy and safety of Teliso-V monotherapy in patients with previously untreated MET Amp locally advanced/metastatic NSQ NSCLC. **Methods:** This is a phase 2, single-arm, open-label, global study (NCT05513703). Eligible patients (≥ 18 years) have histologically documented advanced/metastatic NSQ NSCLC, measurable disease by RECIST v1.1, confirmed MET Amp determined centrally by FISH or locally by FISH, tissue next-generation sequencing (NGS), or plasma NGS using sponsor-approved assays. Additional eligibility criteria include Eastern Cooperative Oncology Group performance status 0 or 1, no alterations in *EGFR*, *ALK*, *ROS1*, or *BRAF* that predict sensitivity to targeted therapy, no prior systemic therapy for locally advanced or metastatic NSCLC, no prior c-Met-targeted antibody therapy. Teliso-V is administered intravenously at 1.9 mg/kg every 2 weeks until disease progression, intolerable toxicity, or other study drug discontinuation criteria are met. Primary endpoint is ORR assessed by independent central review (ICR). Secondary endpoints include duration of response and disease control rate, progression-free survival per ICR, overall survival, patient-reported outcomes (PROs). Tumor assessments (per RECIST v1.1) are performed at baseline and approx. every 6 (year 1), 8 (year 2), and 12 weeks (year 3 and beyond). PROs are assessed through validated questionnaires (EORTC QLQ-LC13, EORTC QLQ-C30, EQ-5D-5L). Safety and tolerability are evaluated by adverse events, physical examinations, laboratory data, and vital signs. Pharmacokinetic and biomarker evaluations may be used for exploratory analyses. The trial intends to enroll approx. 70 efficacy-evaluable patients, with interim analyses planned after 20 and 50 patients are able to be followed for ≥ 6 months. The study was open to enrollment as of Nov 2022. Clinical trial information: NCT05513703. Research Sponsor: AbbVie Inc.

TPS9150

Poster Session

Circulating tumor DNA to guide furmonertinib monotherapy or combination therapy in advanced EGFR mutant non-small cell lung cancer (NSCLC): A randomized, open-label, multicenter study (FOCUS-C). *First Author: Wen-feng Fang, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University Cancer Center, Guangzhou, China*

Background: Detection of EGFR ctDNA after several weeks EGFR-TKIs treatment was an effective method to identify prognosis of advanced EGFR mutant NSCLC patients. Patients with uncleared EGFR ctDNA had shorter progression-free survival (PFS) (*Mack PC et al; CCR 2022*). However, whether they can benefit from EGFR-TKI combination therapy has not been reported. Furmonertinib (AST2818), a potent, orally bioavailable, highly brain penetrant, third generation EGFR-TKI with unique chemical structure designed to improve potency and specificity, showed superior efficacy compared with gefitinib as first-line therapy in EGFR mutant NSCLC along with an acceptable safety profile without new signals (*Shi, YK et al.; Lancet Respir Med 2022*). We hypothesized that monitoring clearance of EGFR ctDNA in blood could rationally guide subsequent monotherapy or combination therapy with furmonertinib and will improve outcomes in patients with uncleared EGFR ctDNA. **Methods:** The FOCUS-C study is a multicenter, open-label, randomized study. Patients who are aged 18 years or older and have histologically confirmed, locally advanced or metastatic, stage IIIB, IIIC, or IV unresectable NSCLC with EGFR exon 19 deletions (19Del) or exon 21 Leu858Arg mutation (L858R) on tissue biopsy and plasma will be treated with furmonertinib. Eligible patients with uncleared EGFR 19Del or L858R ctDNA after 3 weeks furmonertinib treatment will be stratified according to EGFR mutation (19Del or L858R), central nervous system metastases (with or without) and detectable accompanying gene aberrances in plasma (with or without) and randomly assigned (2: 2: 1) to receive furmonertinib or furmonertinib plus chemotherapy (pemetrexed and carboplatin for 4 cycles followed by maintenance pemetrexed) or furmonertinib plus chemotherapy plus bevacizumab (pemetrexed, carboplatin and bevacizumab for 4 cycles followed by maintenance pemetrexed and bevacizumab) in 21-day cycles until disease progression, the occurrence of intolerable toxicities, withdrawal of consent, or other discontinuation reasons judged by the investigators. The primary endpoint is PFS between furmonertinib plus chemotherapy versus furmonertinib alone. Secondary endpoints include PFS, objective response rate, duration of response, disease control rate, overall survival and safety. Several exploratory endpoints will also be evaluated based on ctDNA detection by next-generation sequencing (Genecast, Wuxi, China). The study is enrolling. 34 patients had been enrolled till 2nd Feb 2023. Clinical trial information: NCT05334277. Research Sponsor: Y-2021AST/zd-0053/Beijing Xisike Clinical Oncology Research Foundation, CSCO-Leading Oncology Research Fund.; Shanghai Allist Pharmaceuticals Co., Ltd, Shanghai, China. Genecast Biotechnology Co., Ltd, Wuxi, China. Qilu Pharmaceutical Co., Ltd, Jinan, China.

TPS9152

Poster Session

A phase II multi-cohort single-arm study of tiragolumab with atezolizumab plus bevacizumab in previously treated advanced non-squamous non-small-cell lung cancer. *First Author: Joshua E. Reuss, Georgetown University, Washington, DC*

Background: Checkpoint inhibitor immunotherapy (CPI) offers durable, immune-mediated, anti-tumor responses to a subset of patients (pts) with advanced non-small cell lung cancer (NSCLC), but not all derive meaningful benefit. Two clinical unmet needs where CPI has fallen short include EGFR-mutated NSCLC, where CPI is minimally effective, and NSCLC with intrinsic or acquired resistance to currently available CPI. Novel combination strategies have shown promise. Two agents that have demonstrated synergy with the anti-PD-L1 CPI atezolizumab in NSCLC are bevacizumab, a vascular endothelial growth factor (VEGF)-blocking antibody, and tiragolumab, a T-cell immunoglobulin and ITIM domain (TIGIT) immune checkpoint-blocking antibody. This multi-cohort phase II trial seeks to evaluate the efficacy of tiragolumab with atezolizumab plus bevacizumab in 2 CPI-resistant cohorts - EGFR-wild type, CPI-refractory advanced NSCLC (cohort A) and EGFR-mutated, CPI-naïve advanced NSCLC (cohort B) - incorporating novel genomic and immunologic analyses to deliver mechanistic insight into the biology of CPI-resistance in NSCLC. **Methods:** This open-label, phase II study has two cohorts. Cohort A includes pts with advanced PD-L1+ (TPS $\geq$ 1%), EGFR/ALK/ROS1 wild type NSCLC with progression on prior anti-PD(L)1-based CPI therapy. Cohort B includes pts with targeted therapy-refractory EGFR-mutated NSCLC who are CPI-naïve. Pts must have measurable disease and those with symptomatic and/or untreated brain metastases are excluded. Pts in both arms will receive tiragolumab 600mg IV with atezolizumab 1200mg IV and bevacizumab 15mg/kg IV every 3 weeks until progressive disease or unacceptable toxicity. The primary efficacy endpoint will be assessed separately in each cohort by investigator-assessed objective response rate (ORR) according to RECIST v1.1. Each cohort utilizes a Simon 2-stage design in which a null ORR of 4% is tested against a one-sided alternative of 20%. A sample size of 21 pts/cohort provides 80% power with a one-sided type 1 error rate of 5% to determine a true ORR of 20%. Secondary efficacy endpoints include: duration of response, progression-free survival (PFS), 6-month PFS, overall survival. Blood and tumor specimens will be acquired pre- and on-treatment. Correlative analyses to illuminate the biology of CPI resistance will include multiplex imaging mass cytometry of tumor tissue. In addition, whole exome sequencing, T-cell receptor sequencing, and MANAFEST neoantigen prediction will be used to identify neoantigen-specific T-cells and track these temporally (during/post treatment) and spatially (across biologic compartments). The study is activated and both cohorts are accruing simultaneously with enrollment ongoing. Clinical trial information: NCT04958811. Research Sponsor: Georgetown Lombardi Comprehensive Cancer Center; LUNGevity Foundation; MedStar Health Research Institute; Genentech/Roche.

TPS9151

Poster Session

LUNG-IST-127: A pilot phase II study of maintenance cabozantinib plus pembrolizumab for patients with metastatic squamous non-small cell lung cancer (sqNSCLC) with disease control following induction therapy. *First Author: Ryan Huu-Tuan Nguyen, Department of Hematology Oncology University of Illinois at Chicago College of Medicine, Chicago, IL*

Background: First-line combination chemotherapy with pembrolizumab followed by maintenance pembrolizumab is the standard of care treatment for patients with metastatic sqNSCLC. This was established by the phase III KEYNOTE-407 trial, which demonstrated a median progression-free survival (PFS) of 6.4 months in the experimental arm. Despite these advances, there remains a need to continue to improve upon survival outcomes for these patients. Cabozantinib is a small-molecule inhibitor of multiple tyrosine kinases including MET, VEGFRs, AXL, RET, and ROS, which are receptors involved in tumor cell-proliferation, angiogenesis, and immune cell regulation. Preclinical studies have demonstrated the ability of cabozantinib to modulate both adaptive and innate immune cells and to exhibit synergistic activity when used in combination with immune checkpoint inhibitors. We hypothesize that cabozantinib in combination with pembrolizumab in the maintenance phase of first-line treatment of metastatic sqNSCLC will prolong median PFS with a tolerable toxicity profile. **Methods:** LUNG-IST 127 is a pilot phase II, single-arm clinical trial of maintenance cabozantinib in combination with pembrolizumab for patients with metastatic sqNSCLC who achieved disease control following standard 1L induction therapy with chemotherapy and pembrolizumab. Thirty-six patients will be enrolled at 2 US sites to receive first-line induction therapy with carboplatin, nab-paclitaxel or paclitaxel, and pembrolizumab for four cycles. After induction therapy, those who have achieved disease control based on re-staging imaging will continue onto maintenance therapy with cabozantinib 40mg PO daily in combination with pembrolizumab 200mg IV every 3 weeks. The primary endpoint is PFS estimated by Kaplan-Meier methods with associated 95% confidence intervals. Based on an exploratory power analysis using an elevated one-sided alpha level of 0.40, we hypothesize that the proposed therapy will prolong median PFS from 6.4 to 9 months. Key secondary endpoints include overall survival (OS), overall response rate (ORR), and characterizing the safety and tolerability of cabozantinib in combination with pembrolizumab. Quality of life will also be measured with the EORTC QLQ-C30. Correlative endpoints include characterizing cfDNA from biofluids and assessing the change in circulating immune cells in different phases of treatment in association with PFS and OS. This trial would be the first to address whether there is clinical benefit in utilizing combination cabozantinib and pembrolizumab in the maintenance phase of treatment in metastatic sqNSCLC. Clinical trial information: NCT05613413. Research Sponsor: Exelixis.

TPS9153

Poster Session

Aumolertinib with chemotherapy or alone compared with osimertinib in patients with EGFR-mutant non-small-cell lung cancer (TREBLE). *First Author: Melissa Lynne Johnson, Sarah Cannon Research Institute, Tennessee Oncology, Nashville, TN*

Background: Aumolertinib is a novel third-generation (3G) epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI). Safety and efficacy of aumolertinib have been demonstrated in patients with EGFR-mutated locally advanced or metastatic (LA/m) NSCLC. (Lu, 2021; Lu, 2022) A phase 3 study in these patients in the first-line setting showed a significant improvement in progression-free survival (PFS) for aumolertinib vs gefitinib (median 19.3 months versus 9.9 months; $P < 0.0001$). Aumolertinib was generally well-tolerated. (Lu, 2022) Aumolertinib is approved in China for patients with LA/m NSCLC who have an EGFR T790M resistance mutation upon disease progression and for treatment naïve patients with EGFR-mutated NSCLC. Studies evaluating first-generation EGFR-TKI + chemotherapy (chemo) showed improved PFS in select patient populations. (Hosomi, 2019) It is unclear if the addition of chemo to a 3G EGFR-TKI will improve PFS in patients with EGFR-mutated LA/m NSCLC. As the addition of chemo to a 3G EGFR-TKI may prove warranted, there is a need to understand the relative efficacy and safety in the diversity of patients encountered in routine clinical practice. (Tanaka, 2021). **Methods:** This is a randomized, multi-regional, phase 3 clinical trial comparing aumolertinib + chemo or aumolertinib monotherapy with osimertinib monotherapy. Patients are eligible if they have stage IIIB, IVA, or IVB NSCLC; harbor ex19del or L858R EGFR mutations alone or with other EGFR mutations; and have an ECOG PS of $\leq$ 2. Patients are ineligible if they received prior systemic therapy for mNSCLC or are a candidate for curative intent therapy. Eligible patients will be randomized 2:2:1 and stratified by mutation status (ex19del or L858R), ECOG PS (0 vs 1/2), and race (White vs Asian vs other races combined). Anticipated enrollment is 500 patients; 200 to receive aumolertinib + chemo (110 mg PO QD aumolertinib + investigator's choice chemo), 200 to receive osimertinib (80 mg PO QD), and 100 to receive aumolertinib (110 mg PO QD). The primary endpoint is PFS, by blinded independent review committee (BICR) per RECIST 1.1, for aumolertinib + chemo vs osimertinib. Overall survival (OS) is a key secondary endpoint for aumolertinib + chemo vs osimertinib. Additional efficacy endpoints will be assessed for aumolertinib + chemo vs osimertinib and aumolertinib vs osimertinib, as well as safety and patient reported outcomes. Exploratory endpoints include characterizing mechanisms of acquired resistance across all arms, CNS efficacy, and exposure-response relationship. Enrollment began in July 2022. The study is currently recruiting and will include approximately 200 sites globally. The study design will provide a power of 80% at a 2-sided Type I error of 0.05 for the primary endpoint. If the primary endpoint is statistically significant, a sequential test method will be used to evaluate OS. Clinical trial information: NCT05493501. Research Sponsor: EQRx.

TPS9154

Poster Session

Phase 1b/2a safety and tolerability study of bemcentinib (BEM) with pembrolizumab/carboplatin/pemetrexed in first line (1L) advanced or metastatic non-squamous non-small cell lung cancer (NSCLC) without/with a STK11 mutation. *First Author: Rajwanth Veluswamy, Icahn School of Medicine at Mount Sinai, New York, NY*

Background: The combination of platinum, pemetrexed, and pembrolizumab (CIT) has become the standard of care in 1L non-oncogene addicted NSCLC. Despite an initial improvement in response rate and survival, the 5-year survival of NSCLC remains approximately 20-30%, due to the emergence of primary and acquired resistance. Additionally, the presence of brain metastases occurs in ~30-50% of NSCLC patients and confers a poor prognosis. Among the currently non-actionable mutations, STK11/LKB1 mutations (STK11m) are common (~20%) in NSCLC. Recent evidence suggests that STK11m NSCLC patients have a minimal response to checkpoint inhibitors and to chemo-immunotherapy in the first line setting. STK11m tumors are characterized by an immune-suppressed phenotype which is highly associated with AXL signalling. BEM, a first-in-class, oral, selective AXL inhibitor, has demonstrated the ability to prevent chemoresistance, re-sensitize STK11m NSCLC tumors to pembrolizumab, and enhance efficacy of CIT in preclinical lung models. Moreover, following oral administration, BEM readily distributes in brain tumour tissue in recurrent glioblastoma patients, with a 25.9 mean ratio of drug concentration in brain tissue to plasma. Therefore, the addition of BEM to CIT has the potential to improve 1L treatment outcomes in NSCLC overall and particularly in STK11m tumors. **Methods:** This is an open-label, multi-center, phase 1b/2a study to assess the safety, tolerability, and preliminary anti-tumor activity of BEM + CIT as 1L treatment in patients with advanced (Stage IIb/IIc) or metastatic (Stage IV) non-squamous NSCLC without actionable mutations. Patients with stable brain metastases are eligible to participate. Phase 1b follows a 3+3 design and will explore CIT in combination with one of 3 BEM dose levels: Cohort 1 = 75mg; Cohort 2 = 100 mg; or Cohort 3 = 150 mg. BEM is administered orally once/day on Day 1 of each 21-day treatment cycle. After 4 cycles of CIT + BEM, maintenance with BEM + pemetrexed + pembrolizumab is administered for up to 2 years. An independent data safety monitoring board will assess the safety data at the end of the dose-limiting toxicity period (the first 21 days of treatment for each patient, i.e. cycle 1) of each cohort and will recommend the BEM dose for the phase 2a expansion. In the phase 2a, up to 40 patients harboring a STK11m (regardless of their co-mutational status), in the absence of driver mutations will be enrolled. The study will include extensive co-mutational analyses via next-generation sequencing to identify potential subgroups of patients deriving particular benefit. The trial is open to patient enrolment in phase 1b in the US; recruitment for phase 2a is planned to open in Q2 2023 in Europe and US. *EudraCT 2019-003806-28/NA/124645*. Clinical trial information: NCT05469178. Research Sponsor: BerGenBio ASA.

TPS9155

Poster Session

A phase 1 study to assess BDTX-1535, an oral EGFR inhibitor, in patients with glioblastoma or non-small-cell lung cancer. *First Author: Melissa Lynne Johnson, Lung Cancer Research, Sarah Cannon Research Institute, Tennessee Oncology, Nashville, TN*

Background: The epidermal growth factor receptor (EGFR) is a potent oncogene commonly altered in many cancers, including glioblastoma (GBM) and non-small cell lung cancer (NSCLC). EGFR tyrosine kinase activity driven by common EGFR mutations can be inhibited by small molecules, however, resistance to available agents may be driven by mutations in the EGFR active kinase site or other regions. BDTX-1535 is an orally available, highly potent, selective, irreversible inhibitor of EGFR mutations, including extracellular variants and amplifications commonly expressed in GBM and inhibits the common and uncommon EGFR mutations found in NSCLC, including the C797S mutation acquired following 3rd generation EGFR inhibitor therapy. Preclinical data demonstrated the ability of BDTX-1535 to cross the blood-brain barrier and produce sustained inhibition of EGFR signaling. Preclinical studies suggest that BDTX-1535 has the potential to be clinically active in suppressing tumor growth in patients with GBM and NSCLC with or without CNS metastases, including a potential survival benefit. **Methods:** BDTX-1535-101 (NCT05256290) is Phase 1, open-label, multicenter study to assess the safety, tolerability, PK, CNS activity, and preliminary antitumor activity of BDTX-1535 in recurrent GBM (rGBM) or locally advanced or metastatic NSCLC with or without CNS disease. The Monotherapy Dose Escalation portion will evaluate BDTX-1535 in patients with either rGBM expressing EGFR alterations or locally advanced/metastatic NSCLC harboring sensitizing EGFR mutations with or without CNS disease. Patients with rGBM must have previously received available standard therapy of surgical resection followed by chemo-radiotherapy and/or temozolomide (TMZ). Eligible NSCLC patients must have EGFR mutated NSCLC that has progressed following standard of care EGFR inhibitor therapy. Once a provisional recommended Phase 2 dose (RP2D) has been established, BDTX-1535 monotherapy will be explored in the following Dose Expansion cohorts to further evaluate safety, PK, and preliminary assessment of efficacy: 1) rGBM with confirmed EGFR alterations, 2) NSCLC with uncommon EGFR mutations following EGFR inhibitor therapy; 3) NSCLC with acquired EGFR resistance mutation following a 3rd generation EGFR inhibitor in 1L setting. NSCLC patients may enroll with or without CNS metastases and must not be known to express excluded resistance mutations such as EGFR T790M or MET. BDTX-1535 will also be studied in combination with TMZ to assess safety, tolerability, and a recommended combination dose for the treatment of patients with rGBM harboring EGFR mutations or variants. Enrollment was initiated in 2022 and dose escalation is ongoing. Dose Expansion cohorts are expected to open in 2023. For additional information, please contact BDTX_1535_101_Study@bdtx.com. Clinical trial information: NCT05256290. Research Sponsor: Black Diamond Therapeutics.

TPS9155

Poster Session

VELOCITY-Lung: A phase (Ph) 2 study evaluating safety and efficacy of domvanalimab (dom) + zimberelimab (zim) + sacituzumab govitecan (SG), or etrumadenant (etruma) + dom + zim, or etruma + zim in patients (pts) with treatment-naïve metastatic non-small cell lung cancer (mNSCLC). *First Author: Alexander I. Spira, Virginia Cancer Specialists, Fairfax, VA*

Background: Current standard of care (SOC) for pts with mNSCLC lacking an actionable mutation includes checkpoint inhibitor (CPI), platinum (PT)-based therapy, or a combination of the two, but is associated with poor outcomes. SG is a Trop-2-directed antibody-drug conjugate. SG monotherapy resulted in a 17% objective response rate (ORR), with a manageable safety profile in pts with mNSCLC who had multiple prior therapies (Heist RS, et al. *J Clin Oncol*. 2017), and a Ph 2 study is currently ongoing assessing SG+CPI±PT-based therapy (NCT05186974) in treatment-naïve mNSCLC. Etruma (dual adenosine receptor antagonist), dom (anti-TIGIT), and zim (anti-PD-1) are under clinical investigation for antitumor activity. Substudy-01 is part of the VELOCITY-Lung Ph 2 platform study evaluating novel treatment combinations in pts with treatment-naïve mNSCLC. **Methods:** VELOCITY-Lung (NCT05633667) is an open-label, multicenter, randomized, Ph 2 platform study. Key eligibility criteria for substudy-01 include age ≥18 y; pathologically documented stage IV NSCLC at time of study entry without *EGFR*, *ALK*, or other actionable genomic alterations; no prior systemic treatment for mNSCLC; ECOG PS 0-1; any PD-L1 status. Pts previously treated in the (neo)adjuvant setting may be included if therapy was completed ≥12 mo before study drug initiation. Current treatment arms in the preliminary stage are Arm A: dom+zim+SG; Arm B: etruma+dom+zim; Arm C: etruma+zim. Dosing will be as follows: etruma 150 mg po once daily, dom 1200 mg IV q3wk, zim 360 mg IV q3wk, SG 10 mg/kg IV on D1 and D8 of a 21-D cycle. Randomization will be stratified by histology and baseline PD-L1 status (central testing; ≥50% vs < 50%). Pts are randomized equally between treatment arms (arms can be added to evaluate additional novel combinations) in the preliminary stage. Once the expansion stage opens, pts will be randomized based on the number of experimental arms in the expansion stage, the comparator arm, and any newly added preliminary stage treatment arms. Pts will continue to receive treatment until progressive disease, death, unacceptable toxicity, or initiation of a subsequent anticancer therapy. The primary endpoint is ORR assessed by investigator per RECIST v1.1. Secondary endpoints include progression-free survival, duration of response, overall survival, and safety. During the preliminary stage, efficacy will be compared with historical SOC; during the expansion stage, efficacy will be compared with an active comparator arm within the study. Depending on the number of arms being tested in the expansion stage, this study plans to enroll ~69 to 289 patients globally and is open for recruitment. Clinical trial information: NCT05633667. Research Sponsor: Gilead Sciences, Inc.

ABSTRACT
WITHDRAWN

TPS9158

Poster Session

A phase II trial of JDQ443 in *KRAS G12C*-mutated NSCLC with PD-L1 expression <1% or PD-L1 expression ≥1% and an *STK11* co-mutation. *First Author: Colin R Lindsay, The University of Manchester and The Christie NHS Foundation Trust, Manchester, United Kingdom*

Background: Kirsten rat sarcoma viral oncogene homolog (*KRAS*) is the most frequently mutated oncogene in non-small cell lung cancer (NSCLC). *KRAS G12C*, the most frequent *KRAS* variant, is found in ~13% of patients (pts) with NSCLC. *KRAS* is a GTPase that regulates cell signaling pathways necessary for proliferation, differentiation, and survival. *KRAS* mutation reduces the intrinsic GTPase activity of the enzyme, allowing for the accumulation of active, GTP-bound *KRAS* and hyperactivation of downstream signaling, driving tumorigenesis. JDQ443 is a potent, selective *KRAS^{G12C}* inhibitor that irreversibly traps *KRAS^{G12C}* in its inactive, GDP bound state and blocks downstream signaling. In preliminary data from the Phase Ib part of the KontRASP-01 study (NCT04699188), JDQ443 showed promising antitumor activity and an acceptable safety profile in previously treated pts with *KRAS G12C*-mutated advanced NSCLC. Pts with *KRAS G12C*-mutated NSCLC currently receive the same first-line (1L) treatment as those without driver mutations, consisting of immunotherapy alone or combined with chemotherapy; however, ~30% of pts with NSCLC present with programmed death-ligand 1 (PD-L1) expression <1%, and ~10–20% of pts harbor an *STK11* mutation, both indicators of poor response to immunotherapy. Therefore, alternative 1L treatment options are needed for these pts. Of note, PD-L1 expression and *STK11* mutation do not affect responsiveness to *KRAS^{G12C}* inhibitors, raising interest in the evaluation of these targeted therapies as 1L alternatives to immunotherapy for pts with *KRAS G12C*-mutated NSCLC. **Methods:** KontRASP-06 (NCT05445843) is an open-label, Phase II, single-arm, multicenter study evaluating JDQ443 monotherapy (200 mg JDQ443 twice daily in 21-day cycles) as a 1L treatment for 2 cohorts of adult pts with locally advanced or metastatic, *KRAS G12C*-mutated NSCLC. Cohort A (n=90) includes pts whose tumors have PD-L1 expression <1%, regardless of *STK11* mutation status, while Cohort B (n=30) includes pts whose tumors have PD-L1 expression ≥1% and an *STK11* co-mutation. Local testing for PD-L1 status and *KRAS* and *STK11* mutations is accepted; *KRAS* and *STK11* mutations may be assessed in blood samples. A tissue sample is required for retrospective biomarker status confirmation and exploratory study. The study is currently enrolling pts into both cohorts. The primary endpoint is the overall response rate (ORR) per RECIST version 1.1, assessed by a blinded independent review committee, in Cohort A. Key secondary endpoints are ORR in Cohort B and duration of response in both cohorts. Other secondary endpoints include progression-free survival, overall survival, safety, pharmacokinetics, and p-reported outcomes. A comprehensive biomarker strategy aims to investigate predictors of treatment response and resistance in the study population. © 2023 American Association for Cancer Research®. Reused with permission. Clinical trial information: NCT05445843. Research Sponsor: Novartis Pharmaceuticals Corporation.

TPS9160

Poster Session

Osimertinib then chemotherapy in EGFR-mutated lung cancer with osimertinib third-line rechallenge (OCELOT). *First Author: Daniel Adam Breadner, Schulich School of Medicine and Dentistry, London, ON, Canada*

Background: The results of the FLAURA study established osimertinib as the new first-line standard of care for patients with the two 'common' types of epidermal growth factor receptor mutation-positive (EGFR+) advanced non-small-cell lung cancer (aNSCLC). Second-line (2L) treatment is typically platinum pemetrexed chemotherapy and the standard third-line (3L) treatment is docetaxel throughout much of the globe, which has a modest response rate of 7 – 15%. Previously, when first generation (1G) EGFR tyrosine kinase inhibitor (TKIs) were standard of care in the first-line setting, a number of prospective and retrospective studies examined 3L rechallenge with the same 1G EGFR TKI following 2L chemotherapy, with varying levels of success. Osimertinib is a well-tolerated EGFR TKI which is active against the T790M resistance mutation, which would have limited the efficacy of rechallenge with 1G EGFR TKIs. **Methods:** This is a multicenter international phase II investigator-initiated study of osimertinib in the 3L rechallenge of patients with EGFR+ aNSCLC, following 1L treatment with osimertinib and 2L therapy with platinum pemetrexed chemotherapy. A maximum of 255 patients will be enrolled. Patients with 'common' EGFR exon 19 deletions or L858R mutations will enroll at the start of 2L chemotherapy or 3L osimertinib rechallenge. The primary objective is 3L objective response rate (ORR) in the first 100 evaluable patients, according to RECIST 1.1. Secondary objectives include disease control rate (DCR), progression free survival (PFS), time to treatment failure, overall survival and toxicity for 3L osimertinib rechallenge. Exploratory objectives include assessment of osimertinib resistance based on serial ctDNA samples collected from all participants. The OCELOT study, NCT04335292, is actively enrolling participants. Clinical trial information: NCT04335292. Research Sponsor: AstraZeneca.

TPS9159

Poster Session

A first-in-human, open-label, dose escalation and expansion study of orally administered NX-019 in patients with advanced EGFR mutant cancer. *First Author: Alexander I. Spira, NEXT Oncology - Virginia Cancer Specialists, Fairfax, VA*

Background: CNS involvement, brain metastases and/or leptomeningeal disease, is common in patients with EGFR mutant NSCLC and occurs in 25–50% of patient's journeys. Despite the activity and increased CNS penetration of later generation EGFR inhibitors, management of CNS disease remains a clinical challenge. NX-019 is a broad-spectrum EGFR inhibitor targeting both common and rare mutations including EGFR ex20ins, G719S, and L861Q. NX-019 exhibits selective activity towards mutant vs. wt. EGFR in preclinical studies. Substantial CNS exposure has been demonstrated in animal models, as well as potent anti-tumor activity toward intracranial xenografts with prolonged inhibition of EGFR signaling. Similar drug levels compared to plasma were measured in the brains of rats and mice. NX-019 was readily detectable in the CSF of cynomolgus monkeys, dogs and rats at concentrations similar to the estimated plasma free fraction. **Methods:** NT019-101 is a first-in-human, international, open-label study designed to evaluate single-agent NX-019 in patients with EGFR-mutant, locally advanced or metastatic NSCLC that has progressed following prior treatment. Patients with ECOG performance status 0–2 and EGFR mutant cancers including stable, asymptomatic brain metastases are eligible for Dose Escalation. Patients with known *EGFR C797S* mutations and secondary drivers, e.g., *MET* amplification and *RET* fusions, are excluded. Primary endpoints are to determine recommended phase 2 dose (RP2D), maximum tolerated dose (MTD), safety and tolerability (part 1), and to evaluate antitumor activity at the RP2D by RECIST v1.1 and RANO-BM (part 2). Secondary endpoints are to evaluate pharmacokinetics (PK) and antitumor activity by RECIST v1.1 (part 1) and PK, safety, tolerability, and CNS antitumor activity (part 2). Dose escalation will utilize a 3+3 design with up to 6 patients per cohort in part 1. Part 2 will enroll patients in 5 cohorts (n = 10 or 29 each), including patients with NSCLC who have (1) new or progressing CNS metastases including leptomeningeal disease after treatment with osimertinib, (2) active CNS disease and ex20ins mutations, (3) ex20ins mutations without CNS disease and (4) other rare mutations, based on a Simon 2-stage design. First patient was treated in October 2022 and enrollment is ongoing. The study is planned for approximately 35 centers in North America and Asia-Pacific region. Clinical trial information: NCT05514496. Research Sponsor: Nalo Therapeutics Inc.

TPS9161

Poster Session

LATIFY: Phase 3 study of ceralasertib + durvalumab vs docetaxel in patients with locally advanced or metastatic non-small-cell lung cancer that progressed on or after anti-PD-(L)1 and platinum-based therapy. *First Author: Benjamin Besse, Gustave Roussy, Villejuif, France*

Background: Following progression on first- or second-line immunotherapy ± platinum-based chemotherapy (CT), the prognosis for patients (pts) with metastatic non-small-cell lung cancer (NSCLC) is poor with limited alternative options to docetaxel. Ceralasertib is a selective inhibitor of Ataxia Telangiectasia and Rad3-related (ATR) protein kinase, which is activated in response to DNA damage. Clinical data suggest that ceralasertib may sensitize tumors to immunotherapy by biasing T cells to an immune-effective phenotype. Durvalumab is a selective, high-affinity human IgG1 monoclonal antibody that binds programmed cell death ligand-1 (PD-L1) and inhibits PD-L1-mediated suppression of T-cell activation. Combining ceralasertib with durvalumab may amplify the antitumor immune response, and potentially lead to durable tumor control. In the ongoing phase 2 HUDSON study in pts with locally advanced or metastatic NSCLC who progressed on anti-PD-(L)1 therapy and platinum-doublet regimen, ceralasertib + durvalumab showed promising efficacy with median progression-free survival (PFS) of 6.0 mos (80% CI, 4.6–7.5) and median overall survival (OS) of 15.9 mos (80% CI, 14.1–20.3). **Methods:** LATIFY is a phase 3, open-label, randomized, multicenter study in pts with NSCLC (NCT05450692). Key inclusion criteria are age ≥18 years; ECOG performance status 0–1; documented *EGFR* and *ALK* wild-type, and tumor cell PD-L1 status; and adequate organ and bone marrow function. Stable brain metastases are allowed. Pts should be eligible for second- or third-line therapy, and must have received an anti-PD-(L)1 therapy and a platinum-containing doublet regimen for locally advanced or metastatic NSCLC either separately or in combination, but no other prior therapies. Key exclusion criteria include mixed small-cell lung and NSCLC histology, unresolved toxicities of Grade ≥2 (NCI CTCAE v5.0) from prior therapy, active or prior autoimmune or inflammatory disorders, > 1 line of prior anti-PD-(L)1 therapy (alone or in combination), and > 1 line of platinum-based CT in a metastatic setting. Pts are randomized 1:1 to receive either oral ceralasertib 240 mg twice daily on Days (D) 1–7 with IV durvalumab 1500 mg on D8 (28-day cycle) or IV docetaxel 75 mg/m² (D1, 21-day cycle). The primary objective is to assess efficacy by OS. Secondary objectives include evaluating efficacy by PFS, objective response rate and disease control rate by RECIST v1.1; duration of, and time to, response; time to second progression or death; OS at 12 mos; time to deterioration of health-related quality of life and physical function; determining the pharmacokinetics of ceralasertib; and assessing safety. Approximately 580 pts will be recruited from around 21 countries in the Americas, Europe, and Asia Pacific. Clinical trial information: NCT05450692. Research Sponsor: AstraZeneca PLC.

TPS9162

Poster Session

CAN-2409 plus prodrug with standard of care immune checkpoint inhibitor for patients with stage III/IV NSCLC. *First Author: Charu Aggarwal, University of Pennsylvania, Philadelphia, PA*

Background: Immune checkpoint inhibitors (ICI) are a standard of care (SOC) treatment that have improved outcomes for patients (pts) with non-small cell lung cancer (NSCLC). However, most pts progress, signaling a need for combination approaches to further improve outcomes. CAN-2409 is a replication-defective adenoviral construct encoding the herpes simplex virus thymidine kinase (HSV-tk) gene that is injected intratumorally followed by 2 weeks of prodrug (valacyclovir or acyclovir). HSV-tk converts the prodrug in the tumor microenvironment into a toxic metabolite, resulting in immunogenic cell death, while the adenoviral proteins provide a strong pro-inflammatory signal. Together, this leads to *in situ* vaccination against the patient's own tumor. As a result, CD8+ cytotoxic T cells are educated on how to recognize and kill tumor cells in both the injected tumor and the uninjected metastases. A completed neoadjuvant phase I trial in resectable NSCLC demonstrated safety and immune stimulation (Predina et al 2021), warranting further investigation of CAN-2409 + prodrug as a therapy that can lead to improved long-term outcomes for pts with NSCLC who have a suboptimal response to ICI.

Methods: LuTK02 (NCT04495153) is an open-label, multi-arm, phase II clinical trial to evaluate CAN-2409 + prodrug added to SOC ICI (anti-PD-(L)1) therapy in pts with stage III/IV NSCLC presenting with inadequate response (as defined below) to ICI. Cohort 1 includes pts with nonresponding but stable disease ≥ 18 weeks after starting ICI; cohort 2 includes pts with progressive disease ≥ 18 weeks after starting ICI. Key eligibility criteria include RECIST-evaluable disease; an injectable lesion (via bronchoscopy or US/IR guidance); ability to continue ICI for the treatment period; no change of ICI or prior interruptions of > 4 weeks within 6 months of enrollment; and no focal therapy at > 3 sites of disease within 12 months prior to enrollment. Key exclusion criteria include a history of ICI immune-related adverse events and known alterations in *EGFR*, *ALK*, or *ROS1*. Eligible patients receive 2 injections of CAN-2409 approximately 6 weeks apart followed by prodrug for 14 days. After treatment of ~ 40 evaluable pts in cohort 2 with two injections of CAN-2409, the protocol has been amended to include a new cohort (n ~ 20) of pts treated with three injections of CAN-2409 approximately 4 weeks apart, each followed by prodrug for 14 days, to further define the optimal therapeutic regimen. Primary endpoints are overall response and/or disease control rate per RECIST 1.1 criteria and safety of CAN-2409 + prodrug. Secondary endpoints include duration of response, PFS, OS, and biomarker studies. Exploratory endpoints include evaluation of effects in non-injected lesions, changes in non-target (per RECIST) lesions, tumor growth trajectory, and viral shedding. Clinical trial information: NCT04495153. Research Sponsor: Candel Therapeutics.

9501

Oral Abstract Session

Significant durable response with fiantlimab (anti-LAG-3) and cemiplimab (anti-PD-1) in advanced melanoma: Post adjuvant PD-1 analysis. *First Author: Omid Hamid, The Angeles Clinic & Research Institute, A Cedars-Sinai Affiliate, Los Angeles, CA*

Background: Previous reports have demonstrated that treatment (Tx) with anti-LAG-3 Ab fiantlimab + anti-PD-1 Ab cemiplimab had a 63.8% ORR across two separate cohorts of advanced PD-(L)1 naïve metastatic melanoma (Mel) patients (pts). The benefit the fiantlimab + cemiplimab combination in pts exposed to prior anti-PD-1 Tx as adjuvant (adj) Tx is unknown. Here we present phase 1 safety and clinical activity data from pts with advanced Mel including those who received prior adj systemic Tx. **Methods:** Three separate expansion cohorts of adult pts with unresectable or metastatic Mel (excluding uveal Mel) who were anti-PD-(L)1 Tx-naïve for advanced disease were enrolled. All pts received fiantlimab 1600 mg + cemiplimab 350 mg IV Q3W for 12 months (mos) (optional additional 12 mos if clinically indicated). Study enrollment closed in June 2022. Tumor measurements were performed every 6 weeks (wks) for 24 wks, then every 9 wks. **Results:** 98 pts were enrolled and treated with fiantlimab + cemiplimab as of 01 Nov 2022 data cutoff. Median age was 68.0 years, 60.2% were male, and 89.8% were White. 2.0% of pts had received prior metastatic Tx (not anti-PD-(L)1) and 23.5% had received prior systemic Tx for Mel in the adj/neo-adj setting (disease-free interval > 6 mos), including 13.3% treated with an anti-PD-1 (nivolumab or pembrolizumab). Median follow up was 12.6 mos and median treatment duration was 32.9 wks. Grade ≥3 treatment-emergent adverse events (TEAEs), serious TEAEs, and immune-related AEs (irAEs) occurred in 43.9%, 32.7%, and 65.3% of pts, respectively. 16.3% of pts discontinued Tx due to a TEAE. Rates of irAEs were similar to anticipated rates for PD-1 monotherapy with the exception of adrenal insufficiency (AI) with 12.2% (all grades) and 4.1% (grade ≥3). RECIST 1.1-based investigator-assessed overall ORR was 61.2% (12 complete responses; 48 partial responses), with median DOR (mDOR) not reached [NR] (95% CI: 22.6– not estimated [NE]). KM estimation of median PFS (mPFS) was 15.3 (95% CI: 9.4–NE) mos. In pts with any prior adj Tx, ORR, mDOR, and mPFS was 60.9% (14/23), NR, and 13.3 mos, respectively. In pts with prior anti-PD-1 adj Tx, ORR, mDOR, and mPFS was 61.5% (8/13), NR, and 11.8 mos, respectively. Data from subgroup and correlative biomarker analyses, PK and immunogenicity will be included in the presentation. **Conclusions:** Fiantlimab + cemiplimab in advanced Mel pts showed high clinical activity that compares favorably with other approved combinations of immune checkpoint inhibitors in the same clinical setting. This is the first indication that dual LAG-3 blockade can produce high level of activity with significant ORR in pts with advanced Mel post adj anti-PD-1 Tx. The safety profile of fiantlimab + cemiplimab is similar to anti-PD-1 monotherapy with the exception of AI. A phase 3 trial (NCT05352672) of fiantlimab + cemiplimab in Tx-naïve advanced Mel pts is ongoing. Clinical trial information: NCT03005782. Research Sponsor: Regeneron Pharmaceuticals, Inc.

LBA9503

Oral Abstract Session

Distant metastasis-free survival results from the randomized, phase 2 mRNA-4157-P201/KEYNOTE-942 trial. *First Author: Adnan Khattak, One Clinical Research and Edith Cowan University, Perth, Western Australia, Australia*

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2023, issue of the *Journal of Clinical Oncology*.

9502

Oral Abstract Session

Nivolumab (NIVO) plus relatlimab (RELA) vs NIVO in previously untreated metastatic or unresectable melanoma: 2-year results from RELATIVITY-047. *First Author: Hussein A. Tawbi, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: In RELATIVITY-047 (NCT03470922), NIVO + RELA demonstrated a statistically significant progression-free survival (PFS) benefit vs NIVO; there was an observed improvement in overall survival (OS) although it was not statistically significant. The combination also had a descriptively higher confirmed objective response rate (ORR) assessed by blinded independent central review (BICR) vs NIVO. Here we report updated descriptive analyses (efficacy, safety, and secondary analyses) with longer (~2 years) follow-up. **Methods:** Patients were randomized 1:1 to receive NIVO 480 mg + RELA 160 mg fixed-dose combination or NIVO 480 mg every 4 weeks, as previously described. Primary endpoint of PFS per RECIST v1.1 was assessed by BICR; secondary endpoints included OS and ORR per BICR. Exploratory analyses were performed for melanoma-specific survival (MSS; defined as death due to melanoma, with censoring of deaths due to other causes) and efficacy outcomes on subsequent systemic therapy. **Results:** Patients received NIVO + RELA (n = 355) or NIVO (n = 359). Median follow-up was 25.3 months in this updated analysis (minimum follow-up, 21.0 months). NIVO + RELA continued to show a benefit over NIVO for PFS, OS and ORR (Table). A similar improvement was also observed in MSS. NIVO + RELA was generally favored over NIVO across key subgroups (consistent with previous reports). Subsequent systemic therapy was received by 131 (36.9%) and 136 (37.9%) patients in the NIVO + RELA and NIVO arms, respectively. Treatment-related adverse events (TRAEs; any grade) leading to treatment discontinuation were observed in 61 (17.2%) and 31 (8.6%) patients on NIVO + RELA and NIVO, respectively. Grade 3–4 TRAEs were observed in 78 (22.0%) patients on NIVO + RELA and 43 (12.0%) patients on NIVO. In total, there were 6 treatment-related deaths (NIVO + RELA, n = 4; NIVO, n = 2); no new treatment-related deaths have been reported since the last analysis. **Conclusions:** With 12.3 months of additional follow-up, a consistent benefit was observed with NIVO + RELA vs NIVO for PFS, OS and ORR in the ITT population, as well as in key patient subgroups. MSS was longer with NIVO + RELA compared with NIVO. The safety profile of NIVO + RELA remained consistent with previous reports, with no new or unexpected safety signals. Efficacy outcomes on subsequent systemic therapy (by type of subsequent therapy, including PD-L1/CTLA-4) will be presented. Clinical trial information: NCT03470922. Research Sponsor: Bristol Myers Squibb.

	NIVO + RELA (n = 355)	NIVO (n = 359)
Median PFS, months (95% CI)	10.2 (6.5–14.8)	4.6 (3.5–6.5)
HR (95% CI)	0.81 (0.67–0.97)	
Median OS, months (95% CI)	NR (31.5–NR)	33.2 (25.2–45.8)
HR (95% CI)	0.82 (0.67–1.02)	
OS rate, % (95% CI)		
24 months	61.8 (56.5–66.6)	58.3 (52.9–63.2)
36 months	54.1 (48.6–59.3)	48.4 (42.9–53.8)
48 months	51.5 (45.9–56.9)	42.5 (36.4–48.5)
ORR, % (95% CI)	43.7 (38.4–49.0)	33.7 (28.8–38.9)
Median MSS, months (95% CI)	NR (NR–NR)	46.6 (33.2–NR)
HR (95% CI)	0.77 (0.61–0.97)	

9504

Oral Abstract Session

Association of biomarkers (BMs) with efficacy of adjuvant nivolumab (NIVO) vs placebo (PBO) in patients with resected stage IIB/C melanoma (CA209-76K). *First Author: Georgina V. Long, Melanoma Institute Australia, The University of Sydney, and Royal North Shore and Mater Hospitals, Sydney, NSW, Australia*

Background: Adjuvant NIVO significantly prolonged recurrence-free survival (RFS) over PBO in stage IIB/C melanoma in the randomized, phase III Checkmate 76K trial (HR; 95% CI: 0.42 [0.30–0.59]). For the first time, select BMs and their association with RFS were analyzed in early-stage melanoma treated with an anti-PD-1 agent. **Methods:** Baseline primary tumor and serum BMs were analyzed, including interferon gamma-related gene expression signature (IFN γ -sig), TMB, BRAF mutation, % intratumoral CD8+ T cells, tumor cell PD-L1 expression, and serum CRP levels. BMs were evaluated as continuous variables (high vs low levels) and dichotomized by median or prespecified cutoffs. HRs were estimated using a Cox proportional hazards model. **Results:** Analysis of continuous BM levels within treatment arms showed that higher IFN γ -sig, TMB, and % CD8+ T cells, and lower CRP levels were associated with prolonged RFS with NIVO but not PBO. The same trend was observed in the dichotomized analyses. No clear association between PD-L1 expression and RFS was identified in either arm. Benefit of NIVO over PBO was seen across all BM subgroups, including by BRAF^{V600} mutation status. Patients with higher IFN γ -sig, TMB, and % CD8+ T cells, and lower CRP levels showed numerically greater relative benefit with NIVO, although CIs overlapped (Table). **Conclusions:** Higher IFN γ -sig, TMB, and % CD8+ T cells, and lower CRP levels were associated with longer RFS with NIVO treatment. No BMs assessed were prognostic for RFS in the PBO arm, in contrast to previous reports in melanoma. Prolonged RFS was seen in patients treated with NIVO over PBO across levels of BMs, and irrespective of BRAF mutational status. Composite analyses of BMs with clinical and histopathologic factors will be evaluated for their potential to optimize risk:benefit stratification for NIVO in this patient population. Clinical trial information: NCT04099251. Research Sponsor: Bristol Myers Squibb.

Association between biomarker levels and RFS (unstratified HR ^a).				
	NIVO (within arm) [526]	PBO (within arm) [264]	NIVO vs PBO arms (BM high)	NIVO vs PBO arms (BM low)
IFN γ -sig ^b	0.59 (0.41, 0.86) [425]	0.91 (0.65, 1.27) [213]	0.29 (0.17, 0.48)	0.44 (0.29, 0.66)
TMB, log ₁₀ scale ^b	0.66 (0.49, 0.90) [441]	1.20 (0.89, 1.61) [217]	0.27 (0.17, 0.44)	0.50 (0.33, 0.74)
CD8+ T cells, % ^b	0.60 (0.39, 0.90) [464]	0.97 (0.71, 1.33) [243]	0.35 (0.22, 0.55)	0.56 (0.36, 0.87)
PD-L1, % TC ^b	0.82 (0.60, 1.12) [189]	0.99 (0.87, 1.12) [111]	0.43 (0.24, 0.76)	0.52 (0.28, 0.94)
CRP, log ₂ scale, μ g/mL ^b	1.37 (1.00, 1.88) [493]	0.92 (0.69, 1.24) [246]	0.50 (0.34, 0.74)	0.34 (0.22, 0.52)
BRAF ^{V600K} c	Mut vs WT (0.82, 2.43) [441]	Mut (0.45, 1.35) [217]	Mut (0.30, 1.04) ^d	WT (0.21, 0.53)

^aContinuous HR: high biomarker level over low level from Cox proportional hazards model with arms; (95% CI) [N], except BRAF. ^bContinuous: higher vs lower. ^cBRAF^{V600K} mutation detected (Mut) vs not detected (wild-type; WT).

LBA9505

Oral Abstract Session

Pembrolizumab versus placebo as adjuvant therapy in stage IIB or IIC melanoma: Final analysis of distant metastasis-free survival in the phase 3 KEYNOTE-716 study. *First Author: Jason J. Luke, UPMC Hillman Cancer Center, Pittsburgh, PA*

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2023, issue of the *Journal of Clinical Oncology*.

9506

Oral Abstract Session

Non-comparative, open-label, international, multicenter phase I/II study of nivolumab (NIVO) ± ipilimumab (IPI) in patients (pts) with recurrent/metastatic merkel cell carcinoma (MCC) (CheckMate 358). *First Author: Shailender Bhatia, Division of Medical Oncology, University of Washington and Fred Hutchinson Cancer Center, Seattle, WA*

Background: MCC is a rare and aggressive skin cancer. Programmed death-ligand 1 (PD-L1) is often upregulated in MCC and blockade of PD-L1 or its receptor, PD-1, has improved survival for patients with metastatic MCC. Anti-PD-1 combined with anti-CTLA-4 has been reported to improve outcomes over anti-PD-1 monotherapy (NCT03071406; Kim S et al., *Lancet* 2022), however further investigation is needed. CheckMate 358 (NCT02488759) assessed NIVO ± IPI in 2 non-randomized MCC cohorts. **Methods:** Eligible pts had recurrent or metastatic MCC, ≤ 2 prior therapies, ECOG performance status (PS) 0–1, and no prior immune checkpoint inhibitor (ICI) therapy. Pts were eligible regardless of PD-(L)1 status. Pts received NIVO 240 mg Q2W or NIVO 3 mg/kg Q2W + IPI 1 mg/kg Q6W for ≤ 24 months (m) or until disease progression, unacceptable toxicity, or consent withdrawal. Imaging was conducted Q8W in year 1 and Q12W thereafter. Planned sample sizes were 23 pts for NIVO and 40 pts for NIVO + IPI. The primary endpoint was investigator-assessed objective response rate (ORR). Secondary endpoints included duration of response (DOR), investigator-assessed progression-free survival (PFS), and overall survival (OS). **Results:** 68 pts received NIVO (n = 25) or NIVO + IPI (n = 43) with ≥ 24 m follow-up (median: NIVO, 62.5 m; NIVO + IPI, 24.4 m). In the NIVO arm, median age was 66 yrs (range, 27–88), 10 (40.0%) pts had ECOG PS of 1, and 15 (60.0%) were treatment-naïve. In the NIVO + IPI arm, median age was 70 yrs (range, 48–85), 27 (62.8%) pts had ECOG PS of 1, and 33 (76.7%) were treatment-naïve. Treatment duration was 15.8 m in the NIVO arm, and 7.9 m for NIVO and 6.0 m for IPI in the NIVO + IPI arm. Efficacy and safety outcomes are summarized in the table. ORR was 60.0% (95% CI, 38.7–78.9) in the NIVO arm and 58.1% (95% CI, 42.1–73.0) in the NIVO + IPI arm. The most common reasons for treatment discontinuation were disease progression (NIVO, 28.0%; NIVO + IPI, 32.6%) or study-drug toxicity (NIVO, 20.0%; NIVO + IPI, 25.6%). There was 1 study drug-related death in each arm (NIVO, pneumonitis; NIVO + IPI, gastrointestinal motility disorder). **Conclusions:** Both NIVO and NIVO + IPI show durable clinical efficacy in advanced MCC. While the non-randomized trial design limits comparisons between the arms, results do not suggest additional efficacy benefit with IPI added to NIVO. Higher incidence of grade 3/4 TRAEs observed in the combination arm could have resulted in shorter treatment duration. Clinical trial information: NCT02488759. Research Sponsor: Bristol Myers Squibb.

	NIVO (n = 25)	NIVO + IPI (n = 43)
ORR, n (%) [95% CI]	15 (60.0 [38.7–78.9])	25 (58.1 [42.1–73.0])
Complete response, n (%)	8 (32.0)	8 (18.6)
Partial response, n (%)	7 (28.0)	17 (39.5)
Median DOR, m (95% CI)	60.6 (16.7–NA)	25.9 (10.4–NA)
Median PFS, m (95% CI)	21.3 (9.2–62.5)	8.4 (3.7–24.3)
Median OS, m (95% CI)	80.7 (23.3–NA)	29.8 (8.5–48.3)
Any-grade/grade 3/4 TRAE, %	84.0/28.0	83.7/46.5

NA, not applicable.

9507

Oral Abstract Session

Towards organ preservation and cure via 2 infusions of immunotherapy only, in patients normally undergoing extensive and mutilating curative surgery for cutaneous squamous cell carcinoma: An investigator-initiated randomized phase II trial—The MATISSE trial. *First Author: Charlotte L. Zuur, Department of Head and Neck Surgical Oncology, Netherlands Cancer Institute (NKI-AVL), Amsterdam, Netherlands*

Background: Standard of care for locally advanced cutaneous SCC (CSCC) consists of extensive and mutilating surgery often with adjuvant radiotherapy (RT). To improve clinical prospects of these patients (pts), we tested efficacy of neoadjuvant nivolumab (NIVO) and nivolumab plus ipilimumab (COMBO) in pts with CSCC with an indication for extensive surgery with or without adjuvant RT. **Methods:** 40 pts with T1-4N0-3MO or TxN1-3MO CSCC and an indication for extensive and/or mutilating surgery were needed to reach the primary objective of this trial. Pts were randomized for ARM A: NIVO (3 mg/kg, weeks 0&2, N = 26) or ARM B: NIVO (3 mg/kg, weeks 0&2) + IPI (1 mg/kg, week 0, N = 24) prior to surgery (week 4). Primary objective was pathological response at time of surgery. A major pathological response (MPR) was defined as ≤10% residual viable cancer cells in the surgical resection specimen. Secondary endpoints were tolerability (CTCAE v5.0), survival, and quality of life (QOL). Key exploratory aim for the trial was the serial collection of pre- and on-treatment tumor samples to investigate immunogenomic features correlating with immunotherapy response. **Preliminary results:** 50 pts were enrolled at median age 76, of whom 32% with TxN1-3MO disease. Grade 3-4 irAEs occurred in 6 (12%) pts and were well manageable. 40 pts underwent standard of care surgery w/o adjuvant RT, of whom 40% and 53% reached an MPR upon NIVO and COMBO, respectively. However, 10 pts withdrew consent to undergo surgery and RT, of whom nine pts declined because of self-reported substantial clinical remission upon neoadjuvant immunotherapy. These clinical responses were confirmed via FDG-PET evaluation in week 4. All these 9 pts are currently cancer free at median FU of 12 months (range 4 to 27) with superior QOL compared to MATISSE pts undergoing standard of care. Overall, we found deep clinical responses in 13/26 (50%) and 14/23 (61%) of pts upon NIVO and COMBO, respectively, being either a MPR at time of surgery or a clinical CR in patients declining surgery. **Preliminary conclusions:** The MATISSE trial shows deep responses of 50% and 61% upon neoadjuvant NIVO and COMBO, respectively, with well manageable toxicity in this elderly CSCC population. Nine MATISSE patients have proven the concept that organ preservation and durable complete remissions can be achieved after two infusions of neoadjuvant immunotherapy only, without extensive or mutilating curative surgery and/or RT. Clinical trial information: NCT04620200. Research Sponsor: The MATISSE trial is an investigator-initiated randomized phase II trial, partly funded by Bristol-Myers Squibb; Riki Foundation (private foundation).

9508

Oral Abstract Session

Temozolomide plus cisplatin versus toripalimab (anti-PD-1) as adjuvant therapy in resected mucosal melanoma. *First Author: Bin Lian, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Melanoma and Sarcoma, Peking University Cancer Hospital & Institute, Beijing, China*

Background: Chemotherapy (temozolomide plus cisplatin) has been demonstrated to be a better adjuvant regimen compared to high-dose interferon alpha-2b in resected Mucosal Melanoma (MuM) in the pre-immunotherapy era. Yet in the present immunotherapy era, PD-1 inhibitor was recommended as a standard adjuvant therapy for resected Melanoma. No adjuvant trial comparing chemotherapy with PD-1 inhibitor in resected MuM had been reported. We conducted this study to determine the efficacies of adjuvant chemotherapy versus PD-1 inhibitor in resected MuM. **Methods:** All patients (pts) with resected MuM received chemotherapy (temozolomide 200 mg/m²/day orally on days 1 to 5 plus cisplatin 75 mg/m² i.v. on days 1-3, repeated every 3 weeks for six cycles) or Toripalimab (anti-PD-1, 3 mg/kg every 2 weeks via intravenous infusion) as adjuvant therapy from 2013 to 2019 were included retrospectively. Demographic and clinical characteristics between the two groups were matched with 1:1 by propensity score matching (PSM) to reduce the bias. After PSM, the efficacies of the two groups were compared, and subgroup analysis was performed according to the baseline characteristics. The endpoints were relapse-free survival (RFS), distant metastasis-free survival (DMFS), and overall survival (OS). Kaplan-Meier methods and Cox regressions were used to estimate median RFS, DMFS, OS and HR. **Results:** A total of 247 pts were included, of which 78 were in the Toripalimab group and 169 were in the Chemo group. PSM matched 65 pts from each of the two groups. The baseline characteristics were similar. At a median follow-up of 52.6 months (95%CI, 44.6–60.6 months), patients receiving chemo had a longer median RFS (28.2 vs. 12.0 months; HR=0.64, 95% CI, 0.42 to 0.98; P=0.04), DMFS (42.0 vs. 19.0 months; HR=0.58, 95% CI, 0.36 to 0.92; P=0.02) and OS (93.4 vs. 39.3 months; HR=0.56, 95% CI, 0.33 to 0.94; P=0.03) versus the toripalimab group (Table). **Conclusions:** Adjuvant chemotherapy (temozolomide plus cisplatin) shows remarkable longer RFS, DMFS, and OS than Toripalimab (anti-PD-1). It suggested that adjuvant chemotherapy may be a better option for patients with resected mucosal melanoma even in the present immunotherapy era. Research Sponsor: None.

Characteristics and efficacies of the two groups after PSM.

	Chemo (N = 65)	Anti-PD-1 (N = 65)	P value	HR (Chemo vs anti-PD-1)
Age in years, median (range)	59.0 (33.0–80.0)	60.0 (38.0–74.0)	0.43	
Sex, male, n (%)	29 (44.6)	22 (33.8)	0.21	
Primary site, Head and neck, n (%)	24 (36.9)	25 (38.5)	0.86	
LN metastasis, yes, n (%)	15 (23.1)	15 (23.1)	/	
ECOG ≤1, n (%)	65 (100)	65 (100)	/	
NLR ≤3, n (%)	55(84.6)	57(87.7)	0.61	
Median RFS, mo.(95% CI)	28.2 (17.7 - 38.7)	12.0 (7.1 - 16.9)	0.04	0.64 (0.42 - 0.98)
Median DMFS, mo.(95% CI)	42.0 (31.7 - 52.3)	19.0 (11.6 - 26.4)	0.02	0.58 (0.36 - 0.92)
Median OS, mo.(95% CI)	93.4 (31.6 - 155.2)	39.3 (26.2 - 52.4)	0.03	0.56 (0.33 - 0.94)

9509

Poster Discussion Session

Initial efficacy and safety of RP1 + nivolumab in patients with anti-PD-1-failed melanoma from the ongoing phase 1/2 IGYTE study. *First Author: Bartosz Chmielowski, Jonsson Comprehensive Cancer Center, University of California Los Angeles, Los Angeles, CA*

Background: Patients (pts) with melanoma who progress on anti-PD-1 therapy (anti-PD-1-failed) have limited treatment options. RP1 is an HSV-1-based oncolytic immunotherapy expressing human GM-CSF and a fusogenic protein (GALV-GP-R). Here, we present data from the first 75 pts enrolled into the registration-directed (R-D) cohort in anti-PD-1-failed melanoma (target enrollment N = 125) from the phase 1/2 IGYTE study (NCT03767348). **Methods:** Pts must have locally advanced or metastatic cutaneous melanoma with ≥ 1 measurable and injectable tumor (≥ 1 cm) and confirmed progressive disease (PD) on 2 assessments ≥ 28 days apart while on ≥ 8 consecutive weeks of anti-PD-1 $\pm$ anti-CTLA-4 therapy, with anti-PD-1 being the last treatment received. Pts on prior adjuvant anti-PD-1 therapy must have had PD confirmed by biopsy while on adjuvant therapy. RP1 is initially given intratumorally at 10^6 PFU/mL and then every 2 weeks (Q2W) at 10^7 PFU/mL for ≤ 8 total cycles (≤ 10 mL/dose) combined with nivolumab (nivo; cycles 2-8, 240 mg IV); pts then receive nivo alone (240 mg Q2W or 480 mg Q4W IV) for ≤ 2 years, with the option to reinitiate RP1 if specified criteria are met. **Results:** A total of 91 pts are included in this analysis (initial melanoma cohort, 16 pts; R-D cohort, 75 pts; data cut: Dec 30, 2022). The overall objective response rate (ORR) was 37.4% (initial cohort, 37.5%; R-D cohort, 37.3%) and 18.7% of pts achieved complete response (CR; Table). The response rates seen were also encouraging when evaluated by prior anti-PD-1 therapy setting and disease stage (Table). Responses were seen in uninjected lesions in most responding patients, including in pts with bulky and visceral disease. The majority of responses were observed in pts with PD-L1-negative tumors at baseline (17 of 52 pts with PD-L1-negative tumors responded, compared to 15 of 26 pts with PD-L1-positive tumors, and 2 of 13 pts for whom PD-L1 status was unknown). 85.3% of responses were ongoing 3.7-36.6 months from initiating therapy. Most treatment-related adverse events (TRAEs) were Grade 1-2 with the most common ($>20\%$) being fatigue, chills, pyrexia, and nausea. **Conclusions:** The initial data from this expanded cohort show that RP1 + nivo provides durable and clinically meaningful antitumor activity in pts with anti-PD-1-failed melanoma. Responses were observed in both injected and uninjected lesions, including visceral lesions. The combination continues to be well tolerated, with mostly on-target TRAEs. Additional and updated data will be presented. Clinical trial information: NCT03767348. Research Sponsor: Replimune Inc.

IGYTE response data^a.

	Pts N	CR n (%)	ORR n (%)
All pts	91	17 (18.7)	34 (37.4)
Initial cohort	16	2 (12.5)	6 (37.5)
R-D cohort	75	15 (20.0)	28 (37.3)
Prior anti-PD-1	30	9 (30.0)	15 (50.0)
Adjuvant	61	8 (13.1)	19 (31.1)
Non-adjuvant	31	2 (6.3)	10 (32.3)
Anti-PD-1 + anti-CTLA-4			
Stage	45	13 (28.3)	21 (46.7)
IIb-IVa	46	4 (8.7)	13 (28.3)
IVb-IVc			

^aInvestigator-assessed responses.

9511

Oral Abstract Session

Randomized phase II trial of dabrafenib and trametinib with or without navitoclax in patients (pts) with BRAF-mutant (MT) metastatic melanoma (MM) (CTEP P9466). *First Author: Zeynep Eroglu, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL*

Background: Standard MAPK-targeted therapy (tx) for pts with BRAF MT MM involves combined BRAF and MEK inhibition with high efficacy in advanced melanoma, but durability of response is limited by acquired resistance. One combination, dabrafenib and trametinib (DT), was shown to be less effective in the frontline setting than combined immune checkpoint inhibition (ICI) but did achieve a 48% objective response rate (ORR) after ICI. (Atkins et al., JCO 2022) Preclinical data show that targeting mediators of apoptosis improves response and survival with BRAF-targeted tx. Navitoclax (N) is a BH3-mimetic that inhibits BCL-2, BCL-xL, and BCL-W. We previously demonstrated the safety of DTN in patients with BRAF MT solid tumors in a phase I trial. This randomized phase II study compared DTN to DT. (NCT01989585). **Methods:** Pts with BRAF MT MM were randomized 1:1 to either DT (standard dosing D 150 mg BID and T 2 mg QD) or DTN (standard DT plus N 225 mg QD) and stratified by maximal tumor burden (RECIST 1.1 sum of diameter of target lesions ≥ 100 mm or < 100 mm). The target sample size was 50 evaluable pts (25 per arm). Prior ICI, but not prior BRAF targeted therapy, was permitted. The co-primary endpoints were to estimate complete response (CR) rate for DTN compared to historic controls and to assess maximal tumor shrinkage of pts treated with DTN vs DT. Secondary endpoints included ORR, progression-free survival (PFS) and overall survival (OS). **Results:** Fifty-six pts were enrolled and 50 treated (25 DTN, 25 DT) from 1/11/19 - 3/25/22 at 13 sites. Seventeen pts (68%) in each arm received prior ICI. The ORR was 84% for DTN and 80% for DT. The CR rate for DTN was 20% and 15% for DT; this met pre-specified criteria for success of the primary CR endpoint. There was no difference in the maximal tumor shrinkage in pts treated with DTN vs DT. With median follow up of 25.9 months (mo), there was a trend for improved OS with DTN vs DT (median 36 vs 25 mo, log-rank $p = 0.07$). In the stratification cohort of 37 pts (74%) with smaller baseline tumor burden, there was a statistically significant improvement in OS among pts receiving DTN (log-rank $p = 0.05$), with two-year estimates of OS of 78% (95% CI: 0.46 to 0.93) for DTN and 57% (95% CI: 0.29 to 0.77) for DT. There was no difference in PFS between the two groups. The most common treatment-related toxicities ($> 50\%$ of pts) were nausea (36), diarrhea (31), fatigue (30), fever (28), and vomiting (27), which were not different in pts treated with DTN vs DT. **Conclusions:** In pts with BRAF MT MM, DTN was associated with a CR rate of 20% and ORR of 84%. There was a trend for improved OS in pts treated with DTN compared to DT; the difference in OS was significant in pts with smaller tumor burden. The DTN regimen may be considered for further exploration in the post-ICI setting. Updated data on survival and translational studies will be presented. Clinical trial information: NCT01989585. Research Sponsor: U.S. National Institutes of Health.

9510

Poster Discussion Session

Efficacy and safety of tunlmetinib in patients with advanced NRAS-mutant melanoma: A multicenter, open-label, single-arm, phase 2 study. *First Author: Lu Si, Key laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Renal Cancer and Melanoma, Peking University Cancer Hospital & Institute, Beijing, China*

Background: NRAS-mutant melanoma is an aggressive subtype with worse prognosis. However, no targeted therapy has been approved to date worldwide. Tunlmetinib (HL-085), a novel, potent, selective, oral small-molecule MEK1/2 inhibitor, has showed a favorable pharmacokinetics profile, acceptable tolerability and encouraging antitumor activity in the phase 1 study (BMC Med. 2023 Jan 4;21(1):2). **Methods:** This is an ongoing, multicenter, open-label, single-arm, phase 2 pivotal registration study. Patients (pts) with NRAS-mutant unresectable stage III or IV melanoma were enrolled and received tunlmetinib 12 mg orally twice daily. A historical control of objective response rate (ORR) of 10% was predefined for sample size estimation (100 pts, assuming loss to follow-up rate of 5%) and efficacy evaluation. The primary endpoint was the confirmed ORR per RECIST v1.1 assessed by independent radiology review committee. **Results:** A total of 100 pts were enrolled. All pts were included in the safety analysis set and 95 pts were included in the full analysis set (FAS) for efficacy analysis. At cut-off date (August 17, 2022), median follow-up was 7.9 months (95% CI: 6.6, 9.8). In the FAS, the median age was 58.0 years (range: 24 to 84). Sixty-four pts (67.4%) had received prior immunotherapy (PD-1/PD-L1 inhibitor). Fifty-six pts (58.9%) were acral melanoma, 16 (16.8%) mucosal melanoma and 12 (12.6%) skin melanoma. Fourteen pts (14.7%) were stage III and 81 (85.3%) stage IV. The most frequent NRAS mutation types were Q61R (40.0%), Q61K (29.5%) and G12D (9.5%). Confirmed ORR was 34.7% (95% CI: 25.3%, 45.2%). Median progression-free survival was 4.2 months (95% CI: 3.5, 5.6), overall survival was immature, and 1-year survival rates was 57.2% (95% CI, 44.7%, 67.8%). Subgroup analysis showed that, in pts who had previously received immunotherapy, the confirmed ORR was 39.1% (95% CI: 27.1%, 52.1%). The most frequent treatment related adverse events (TRAEs) were increased blood creatine phosphokinase (CK), diarrhea, peripheral edema, facial edema and increased aspartate aminotransferase. Grade ≥ 3 TRAEs occurred in 68 pts (68.0%), of which 38.0% (38/100) were increased blood CK. Most of pts with CK elevation are asymptomatic and can be managed by dose interruption or reduction without permanent treatment discontinuation. No treatment-related death was reported. **Conclusions:** Tunlmetinib was well tolerated and demonstrated encouraging treatment response rate in pts with advanced NRAS-mutant melanoma. These results indicate that tunlmetinib could be a promising treatment option for NRAS-mutant melanoma, even for those immunotherapy failed pts. Clinical trial information: NCT05217303. Research Sponsor: Shanghai KeChow Pharma.

LBA9512

Poster Discussion Session

Survival after isolated hepatic perfusion as a treatment for uveal melanoma liver metastases: Results from a randomized controlled trial (the SCANDIUM trial). *First Author: Roger Olofsson Bagge, Gothenburg University, Gothenburg, Sweden*

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2023, issue of the *Journal of Clinical Oncology*.

9513

Poster Discussion Session

Tumor infiltrating lymphocyte (TIL) harvest and ex vivo expansion from primary and metastatic (met) uveal melanoma (UM) tumors. *First Author: Sapna Pradyuman Patel, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Adoptively transferred autologous cell therapy using tumor-infiltrating lymphocytes (TIL) is an emerging treatment for met melanoma. Responses have been seen in patients (pts) with checkpoint inhibitor-naïve and -refractory cutaneous melanoma. UM represents a disease subtype that is traditionally less responsive to immune checkpoint blockade (ICB). Preliminary studies have shown clinical utility of TIL in UM pts. However, data describing the success rates of TIL harvest and ex vivo expansion of cells from primary and met UM tumors, and of the treatment of pts with met UM, is limited. **Methods:** Between 2004 and 2019, we conducted a single-center IRB-approved trial (NCT00338377) for TIL harvest in pts age 18 and older with documented met melanoma, including UM pts. The protocol was amended to allow harvest of primary UM tumors in 2015 if the pt was dispositioned for enucleation as primary treatment. **Results:** A total of 96 UM pts underwent TIL harvest; 9 underwent treatment with TIL. Median age was 54 years (range: 28 – 86); 56% of the pts were male; 78% were Caucasian, 9% Hispanic, and 13% unknown ethnicity. Overall successful ex vivo expansion of TIL occurred in 34.8% (32/92) of UM tumors in typical tumor fragment culture with IL-2 (TIL 1.0), with higher rates observed with UM mets (29/65; 44.6%) than UM primary tumors (3/27; 11.1%). Better results were observed with a culture method (TIL 3.0) that includes agonistic stimulation of CD3 and 41BB, with 96.8% (30/31 tumors). Expansion using this new method was successful in 9/10 primary UM tumors and 21/21 UM mets. Average number of days in culture for successful initial ex vivo expansion was 33.0 days for TIL 1.0 and 17.9 days for TIL 3.0 (p -value<0.0001). Overall, the average number of TIL expanded from culture and cryopreserved for clinical use was 130.4 million for TIL 1.0 (range: 34-460) and 326.2 million for TIL 3.0 (range 102-760) (p -value<0.0001). Nine met UM pts received treatment with up to 150×10^9 post-Rapid Expansion Protocol (REP) TIL (5 TIL 1.0, 4 TIL 3.0). Median age was 53, 44% were male, and all had active liver mets with a median of 3 lines of prior treatment for advanced disease. 8 of the TIL products were from UM mets (4 soft tissue, 3 liver, 1 combination of soft tissue and liver tumors), and 1 was from primary UM tumor, for which TIL could only be expanded with TIL 3.0. Best overall response rate per immune-related response criteria was 22% partial response (PR, duration of response was 22.1 months and 16.5 months), 44% stable disease (SD), and 33% progression of disease (PD) for a disease control rate of 66% (PR + SD). Both responding pts had TIL harvests from mets and had previously progressed on ICB, one was treated with TIL 3.0. **Conclusions:** TIL harvest and successful ex vivo expansion of cells is possible from both primary and met UM with TIL 3.0 culture method and can be therapeutically effective. Clinical trial information: NCT00338377. Research Sponsor: U.S. National Institutes of Health.

LBA9515

Poster Discussion Session

Minimal residual disease by circulating tumor DNA as a biomarker of recurrence free survival in resected high-risk melanoma patients treated with mRNA-4157/V940, a personalized cancer vaccine, and pembrolizumab. *First Author: Matteo S. Carlino, Sydney Medical School, Faculty of Medicine and Health Sciences, University of Sydney, Camperdown and Melanoma Institute Australia, Sydney, NSW, Australia, and Crown Princess Mary Cancer Centre, Westmead and Blacktown Hospitals, Westmead, Australia*

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2023, issue of the *Journal of Clinical Oncology*.

9514

Poster Discussion Session

NeoPlus: A phase II study of neoadjuvant lenvatinib and pembrolizumab in resectable mucosal melanoma. *First Author: Lili Mao, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Melanoma and Sarcoma Oncology, Peking University Cancer Hospital & Institute, Beijing, China*

Background: Combination therapy of anti-PD1 agent with VEGFR inhibitor is a promising therapeutic approach in unresectable or metastatic mucosal melanoma. We conducted this study evaluating neoadjuvant lenvatinib and pembrolizumab in pts with resectable mucosal melanoma. **Methods:** This was a single-arm, open-label, single-center, ongoing phase 2 study conducted from Sep 2021. Eligible pts were adults (18-75 yr) with histologically confirmed, resectable mucosal melanoma. Pts received lenvatinib 20mg qd and pembrolizumab 200mg q3w for 2 cycles, followed by surgery. Pembrolizumab (200mg q3w) continued post operatively for further 15 cycles. The primary endpoint was complete pathologic response (pCR). Secondary endpoints were Event free survival (EFS), Overall survival (OS) and safety. **Results:** As of Dec 2022, 19 pts were enrolled with a median follow-up of 49 wks (95%CI, 38 -60). Median age was 57 yrs, 14 were female. Primary sites included: 8 female genital, 6 ano-rectal, 4 head & neck (1 nasal, 3 oral), 1 esophageal. 12 pts were localized disease, 7(37%) were regional lymphatic disease. KIT or NRAS mutations were presented in 2 and 3 pts, respectively. 15 pts underwent surgery, 2 pts had a pCR (13.3 %), 1 MPR, 3 pPR, with a pathologic response rate of 40%(6/15,95%CI 16-67%). 4 pts did not proceed with planned surgery for pts preference. Median EFS has not been reached. IHC data of the resected tumor showed higher CD8+ T cells density in responders ($R=pCR+MPR+pPR$) than non-responders ($NR=pNR$) ($p=0.04$). In 6 pts (one pPR and 5pNR) with paired pre and post treatment samples, CD3+ and CD8+ T cells were significantly increased following treatment ($p=0.03$). Most common AEs were proteinuria (6, 32%), hypothyroidism (6, 32%), dysphonia (5, 26%). One pt(5%, 1/19) had grade 3 ALT elevation. No grade 4-5 toxicities were observed. **Conclusions:** The combination of pembrolizumab plus lenvatinib as neoadjuvant therapy in resectable MM is safe. The preliminary data has shown promising pathologic response with increased CD8+ T cell infiltration, supporting further investigation of neoadjuvant treatment in MM. Acknowledgement: Investigational funding and products are granted from Merck Sharp & Dohme LLC. Clinical trial information: NCT04622566. Research Sponsor: Merck Sharp & Dohme LLC; National Natural Science Foundation of China.

9516

Poster Discussion Session

Revisiting the optimal neoadjuvant immunotherapy regimen in resectable stage III melanoma based on the interferon gamma signature: A pooled analysis. *First Author: Minke W. Lucas, Netherlands Cancer Institute, Amsterdam, Netherlands*

Background: Neoadjuvant anti-PD1 has been shown to be superior to adjuvant administration. Combination of neoadjuvant ipilimumab (IPI) + nivolumab (NIVO) induces even higher pathologic response rates (pRR) and event-free survival (EFS), but at the cost of higher toxicity. We previously showed that the interferon gamma (IFN- γ) signature is associated with a higher pRR after neoadjuvant IPI+NIVO. We hypothesized that IFN- γ high patients (pts) might benefit from less toxic anti-PD1 monotherapy (mono), while IFN- γ low pts might need an escalated regimen with IPI 3mg/kg + NIVO 1mg/kg. **Methods:** In this pooled analysis, pts with macroscopic nodal melanoma who received neoadjuvant NIVO 1mg/kg + IPI 3mg/kg (IPI3/NIVO1), IPI 1mg/kg + NIVO 3mg/kg (IPI1/NIVO3), sequential IPI 3mg/kg and NIVO 3mg/kg (IPI3>NIVO3), or NIVO mono (240mg; IFN- γ high pts only) from the OpACIN-neo, PRADO and DONIMI trials, were analyzed according to their baseline IFN- γ signature. RNA gene expression from baseline tumor biopsies was analyzed using the Nanostring nCounter platform. The IFN- γ scores were calculated using an algorithm and cut-off previously developed at the NKI and prospectively tested in the DONIMI trial. **Results:** Baseline tumor material was available from 151 pts (Table). Median follow-up was 42 months for the entire cohort and 19 months for NIVO mono pts. Combined IPI+NIVO in IFN- γ high pts induced similar major pathologic response (MPR) rates compared to NIVO mono in IFN- γ high pts (71% vs 80%, $p=0.715$), and significantly higher MPR rates compared to IPI+NIVO in IFN- γ low pts (71% vs 45%, $p=0.003$). At 18-months, EFS rates were 87%, 100% and 73% respectively, and overall survival (OS) rates were 98%, 100% and 96%. Notably, IPI3/NIVO1 seemed to induce a higher MPR rate than IPI1/NIVO3 in IFN- γ low pts (64% vs 41%), which was not statistically significant due to small subgroups. At 36 months, EFS was 91% vs 62% and OS was 91% vs 82%. **Conclusions:** Neoadjuvant NIVO mono seems to have equal outcomes as IPI+NIVO in IFN- γ high pts. IFN- γ low pts may benefit from IPI+NIVO with higher doses of IPI. Incorporating baseline biomarkers like the IFN- γ signature algorithm in neoadjuvant treatment decisions will optimize the risk-benefit ratio for these pts. Research Sponsor: BMS and 4SC.

IFN- γ score	Neoadjuvant regimen	No. pts	MPR (%)	EFS	EFS	OS	OS
				18 months (%, 95% CI)	36 months (%, 95% CI)	18 months (%, 95% CI)	36 months (%, 95% CI)
High	NIVO	10	80	100		100	
	IPI/NIVO	63	71*	87 (79-96)	83 (74-92)	98 (95-100)	92 (85-99)
	IPI1/NIVO3	46	74	91 (83-100)	85 (75-96)	100	96 (90-100)
	IPI3/NIVO1	9	78	78 (55-100)	78 (55-100)	89 (71-100)	78 (55-100)
	IPI3>NIVO3	8	43*	75 (50-100)	75 (50-100)	100	88 (67-100)
Low	IPI/NIVO	78	45	73 (64-84)	68 (58-79)	96 (92-100)	85 (77-93)
	IPI1/NIVO3	56	41	70 (59-83)	62 (51-77)	96 (92-100)	82 (73-93)
	IPI3/NIVO1	11	64	91 (75-100)	91 (75-100)	91 (75-100)	91 (75-100)
	IPI3>NIVO3	11	45	73 (51-100)	73 (51-100)	100	91 (75-100)

*1 patient not evaluable.

9517

Poster Discussion Session

Final clinical results and first translational correlates of a phase 2 trial of adaptively dosed nivolumab and ipilimumab based on early radiographic assessment in advanced melanoma (ADAPT-IT). *First Author: James William Smithy, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Initial results from ADAPT-IT (NCT03122522) demonstrated that adaptive dosing of nivolumab (nivo) and ipilimumab (ipi) based on early radiographic assessment was associated with comparable response rates and toxicity compared to historical data for conventional nivo + ipi. Here, we report the final clinical analysis, including median progression-free survival (PFS), and present the first correlative analyses of blood-based biomarkers of response. **Methods:** ADAPT-IT was a multicenter, phase 2 clinical trial with a planned sample size of 60 patients with unresectable melanoma. Patients received two doses of nivo (1 mg/kg) + ipi (3 mg/kg) followed by a computed tomography scan at week 6. Patients with early favorable antitumor effect (FATE; defined as the absence of new lesions and $\leq 4\%$ index lesion tumor growth), discontinued ipi and continued nivo alone. Patients without FATE at week 6 received third and fourth doses of nivo + ipi followed by nivo alone. The primary endpoint was investigator-assessed overall response rate (ORR; defined as the percent of patients with complete or partial responses by RECIST v1.1) at week 12. A Simon two-stage design was employed where a 43% 12-week ORR was considered not promising, a 60% 12-week ORR was considered promising, and the probabilities of type I and type II error were each set at 0.10. Pre- and on-treatment peripheral blood samples were assayed for 1) ten cytokines using a multiplex immunoassay (Meso Scale Diagnostics) and 2) circulating tumor DNA (ctDNA) using the MSK-ACCESS sequencing platform. The Wilcoxon rank sum test and Cox regression modeling were used to evaluate associations between biomarker levels with radiographic response and PFS, respectively. **Results:** 60 patients were enrolled. Week 12 and best ORR were 48% (95% CI, 35-61%) and 58% (95% CI, 45-71%), respectively. Median follow-up was 34 months (interquartile range: 21-36) in survivors, median PFS was 21 months (95% CI: 11-not reached) and the median overall survival was not reached. There were no new Grade 3-5 treatment-related adverse events since the initial report. Higher baseline IL-6 was observed in non-responders compared to responders ($p = 0.03$; $n = 26$) and was associated with shorter PFS (HR for progression or death 1.24; 95% CI: 1.01-1.52; $p = 0.04$). Among 20 patients with detectable ctDNA at baseline (of 25 patients with available samples), an increase in mean adjusted variant allele fraction from baseline to week 6 was associated with shorter PFS (HR 1.14; 95% CI: 1.02-1.27; $p = 0.02$). **Conclusions:** In this updated analysis, now with long-term follow-up, the efficacy of adaptively dosed nivo + ipi resembles that of historical data for standard dose nivo + ipi. Baseline IL-6 and on-treatment changes in ctDNA warrant further prospective study as biomarkers of response to ipi + nivo. Clinical trial information: NCT03122522. Research Sponsor: Bristol Myers Squibb.

9519

Poster Discussion Session

Cemiplimab for kidney organ transplant recipients with advanced cutaneous squamous cell carcinoma: CONTRAC-1. *First Author: Glenn J. Hanna, Dana-Farber Cancer Institute, Boston, MA*

Background: Solid organ transplant recipients are often excluded from immunotherapy trials given the risk of allograft rejection and loss. We report the results of the first prospective study using the PD-1 inhibitor Cemiplimab (Cemi) for kidney transplant recipients (KTR) with advanced, incurable cutaneous squamous cell carcinoma (cSCC), adopting a standardized approach to immunosuppression (IS) with mTOR inhibition and dynamic prednisone (NCT04339062). **Methods:** This single-arm, open-label prospective clinical trial enrolled KTRs (eGFR ≥ 30 mL/min without proteinuria) with advanced cSCC, ECOG ≤ 2 , measurable disease (RECIST v1.1), with no prior immunotherapy exposure. KTRs received mTOR inhibition (target trough 4-6 ng/mL) with a prednisone taper each cycle (40 mg on day -1 to 3, 20 mg days 4-6, 10 mg days 7-20) along with Cemi 350 mg IV every 21-days. Primary endpoint: rate of rejection (futility defined as $\geq 2/3$ or $4/6$ KTRs with rejection events). Secondary endpoints: overall response rate (ORR), duration of response, progression-free survival (PFS), overall survival (OS), infection rates. Exploratory: baseline tumor PD-L1 score, molecular and immunologic predictors of response. **Results:** From 11/2020 to 1/2023, 10 KTRs (median years from transplant: 8, range: 3-31) enrolled including 8 (80%) men, median age 64 (range: 43-86), median eGFR 48 (range: 32-60) often with head and neck primaries (9, 90%) and distant metastases (7, 70%). Six (60%) had prior systemic therapy. For mTOR inhibition, 7 (70%) received sirolimus and 3 (30%) everolimus. At a median follow-up of 6.3 months (range: < 1 -24.9), no patients experienced kidney allograft rejection or loss. Of 8 evaluable patients, ORR was 50% (2 CR, 2 PRs), while 4 had PD. At data cutoff no responder had progressed, with 2/4 in response > 18 months (range: < 1 -22.7+). One patient is pending first restaging; 1 was unevaluable (died before first restaging). One KTR with initial PD experienced a subsequent durable response to cetuximab. Fatigue (40%) and limb edema (30%) were the most common treatment-related adverse events (TRAEs). Grade 3+ TRAEs occurred in 5 (50%) patients including diarrhea, infections ($n = 3$), and electrolyte derangements; there were no Cemi-related deaths. Median PFS was 7.9 mos (95%CI: 1.2-not reached [NR]); the 3-month OS estimate was 61% (95%CI: 27-83). Baseline tumor PD-L1 scores ranged from 0-5%; median TMB was 49 muts/Mb (range: 10-97). Tumor mutations in *TP53*, *CDKN2A*, and *NOTCH1* were common. Exploratory tumor/circulating multiparametric immune profiling and circulating tumor (ct)DNA findings will be presented. **Conclusions:** Using IS with mTOR inhibition and dynamic prednisone resulted in no kidney allograft rejection among KTRs treated with Cemi for advanced cSCC. Durable anti-tumor efficacy was observed. mTOR inhibition with prednisone should be the preferred IS regimen when treating KTRs with anti-PD-1 therapy. Clinical trial information: NCT04339062. Research Sponsor: Regeneron Pharmaceuticals.

9518

Poster Discussion Session

Efficacy of adjuvant therapy in patients (pts) with AJCC v8 stage IIIA cutaneous melanoma. *First Author: Piyush Grover, Melanoma Institute Australia, Sydney, Australia*

Background: Pts with resected AJCC v8 stage IIIA melanoma have been under-represented in clinical trials of adjuvant drug therapy. The benefit of adjuvant targeted and immunotherapy in this population is unclear. **Methods:** In this multicenter, retrospective study, pts with stage IIIA melanoma (AJCC v8) who received adjuvant pembrolizumab or nivolumab (PD1), BRAF/MEK-targeted therapy dabrafenib + trametinib (TT), or no adjuvant treatment (OBS) were included. Recurrence free survival (RFS), distant metastasis free survival (DMFS), and toxicity rates were examined. **Results:** 613 pts from 34 centers across Australia, Europe and USA were included. The median follow-up was 2.6 yrs (IQR, 1.6-3.4 yrs). Pt characteristics and follow-up were similar across the cohorts (Table). Completion rates of 12-month PD1 and TT therapy were 57.0% and 69.2% respectively. 1-yr RFS was 93.3% (95% CI, 90.3-96.4) in PD1, 100% in TT and 91.3% (95% CI, 88.1-94.7) in OBS cohorts. 2-yr RFS was 79.3% (95% CI, 74.1-84.8) for PD1, 100% for TT and 84.3% (95% CI, 79.9-89.0) in OBS cohorts. 2-yr DMFS was 88.4% (95% CI, 84.3-92.8) in PD1, 100% in TT and 91.1% (95% CI, 87.7-94.7) in OBS cohorts. Risk of recurrence was associated with higher Breslow thickness (HR 1.73, 95% CI 1.36-2.20), higher mitotic rate (HR 1.07, 95% CI 1.02-1.12) and neck as the site of nodal metastases (HR 2.71, 95% CI 1.45-5.06) in the overall cohort ($p < 0.05$). Neck nodal metastases were associated with higher risk of recurrence in OBS cohort (HR 3.82, 95% CI 1.91-7.66; $p < 0.05$) but not in the PD1 cohort. Rates of $\geq$ Grade 3 toxicities were 10.9% with PD1 and 20.0% with TT; discontinuation due to toxicity occurred in 25.0% and 30.0%, respectively. No new safety signals were observed. Rates of unresolved toxicity at last follow-up were 26.9% in PD1 and 7.7% in TT cohorts. **Conclusions:** In this large international study, adjuvant PD1 or TT did not significantly improve RFS or DMFS compared to OBS in pts with resected stage IIIA melanoma. Prognosis in stage IIIA melanoma is favourable and outcomes after adjuvant therapy in this population needs further study in prospective randomised trials. Research Sponsor: None.

Baseline pt characteristics and median follow-up.

	PD1, n=256	TT, n=65	OBS, n=292
Male, n (%)	150 (58.6)	31 (47.7)	151 (51.7)
Age, median (years) (IQR)	54 (42-64)	49 (37-58)	58 (46-68)
ECOG PS 0-1, n (%)	246 (96.1)	65 (100)	283 (97.0)
Breslow thickness, median (mm) (IQR)	1.3 (1.1-1.7)	1.3 (1.1-1.5)	1.3 (1.1-1.6)
Mitotic rate, median (per mm ²) (IQR)	3.0 (1.0-5.0)	2.0 (1.8-4.0)	2.0 (1.0-4.0)
Presence of ulceration, n (%)	22 (8.6)	2 (3.1)	8 (2.7)
Lymph node involvement, N1a, n (%)	206 (80.5)	55 (84.6)	253 (86.6)
Maximum diameter of the largest node, median (mm) (IQR)	1.2 (0.5-2.0)	1.0 (0.3-2.0)	0.5 (0.1-1.1)
Complete lymph node dissection, n (%)	55 (21.5)	4 (6.2)	24 (8.2)
<i>BRAF</i> ^{V600} mutation, n (%)	91 (35.5)	65 (100)	90 (30.8)
Follow-up, median (years) (IQR)	2.7 (1.7-3.4)	2.4 (1.5-3.1)	2.6 (1.5-3.4)

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Poster Discussion Session

Role of nivolumab maintenance therapy in advanced melanoma patients following severe immune-related adverse events from combination nivolumab and ipilimumab. *First Author: Anna Maloney, Frank H Netter MD School of Medicine, North Haven, CT*

Background: The combination of ipilimumab (ipi), and nivolumab (nivo) has been shown to be a highly effective treatment for metastatic melanoma. However, immune-related adverse events (irAEs) are common with this treatment, leading to treatment interruption and the use of immunosuppressive agents. There are no data on the impact of resuming single agent nivo on survival outcomes following recovery from the irAE and completion of immunosuppressive treatment. Some physicians hold therapy permanently as done on clinical trials and other physicians resume nivo after steroid taper. **Methods:** In this retrospective analysis, we examined a cohort of patients treated with ipi/nivo who developed irAEs that required treatment interruption and immunosuppressive therapy. The differences in practice patterns among physicians at our institution allowed us to examine the effect of single agent nivo resumption on survival after treatment of irAEs. Multivariate analysis of clinical factors associated with improved survival was performed. **Results:** We identified 165 patients who were treated with ipi/nivo and developed irAEs requiring treatment interruption and immunosuppressive therapy. To remove any impact of immediate disease progression on the analysis patients who progressed on ipi/nivo prior to or during treatment hold were removed from analysis. Of the remaining 131 patients, 45 resumed single agent maintenance nivo following the resolution of toxicity and completion of steroid taper. When stratified by age and adjusted for sex, M-stage, LDH, duration of therapy, and type of irAE causing the treatment pause, the effect of resumption of nivo upon survival remained highly significant ($p = 0.001$). Patients who resumed nivo had an 82% reduction in the hazard of death compared with patients who had not yet or never resumed nivo (HR: 0.18, 95% CI: 0.06 to 0.52). Of the patients who resumed nivo, 12 (26%) patients had subsequent irAEs with 5 patients having grade 3 irAEs (only one of whom had a recurrence of the prior ipi/nivo associated toxicity) and no grade 4 or 5 irAEs were noted. **Conclusions:** The resumption of single agent maintenance nivolumab following a treatment hold for ipi/nivo associated irAE and completion of immunosuppressive therapy increased overall survival compared to discontinuing nivo permanently in patients with metastatic melanoma after stratification for many factors. Toxicity observed post resumption of single agent nivolumab was manageable with no severe irAEs observed. These results suggest that restarting maintenance nivo post irAEs should be studied prospectively. Research Sponsor: Dana-Farber Cancer Institute.

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Poster Session

Real-world treatment patterns and clinical outcomes among subgroups of BRAF-positive metastatic melanoma patients treated with dabrafenib + trametinib. *First Author: Zeynep Eroglu, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL*

Background: Whether disease attributes such as tumor burden or central nervous system (CNS) metastases can affect outcomes for patients with BRAF+ metastatic melanoma (MM) is currently unclear. This study examined real-world patient characteristics, treatment patterns, and clinical outcomes among subgroups of patients with BRAF+ MM treated with dabrafenib + trametinib (dab/tram) in the United States. **Methods:** This retrospective cohort study used the nationwide Flatiron Health electronic health record-derived de-identified database from 1/1/2014 to 9/30/2021. Included patients were aged ≥ 18 years with a diagnosis of BRAF+ MM and received first-line (1L) dab/tram. Patients were stratified into 4 subgroups: high tumor burden (HTB; ≥ 3 sites of metastasis and lactate dehydrogenase [LDH] ≥ 333 IU/L), low tumor burden (LTB; < 3 sites of metastasis and LDH < 333 IU/L), with CNS metastases (prior to 1L dab/tram), and without CNS metastases (prior to 1L dab/tram). Patient characteristics and treatment patterns were evaluated descriptively. Given the potential patient overlap between subgroups, no comparative statistics were conducted. Real-world progression-free (rwPFS) and overall survival (OS) were explored from dab/tram initiation. **Results:** Among 460 included patients (mean age 60 years, 64% male), 66 (14%) had a HTB, 69 (15%) had a LTB, 164 (36%) had CNS metastases, and 296 (64%) did not. Patient characteristics were comparable across the subgroups. Over 60% of HTB patients had documented metastases in each of the liver, lung, bone, lymph nodes, and other sites. Only lung metastases had $> 60\%$ prevalence among patients with a LTB. Overall, 51% of the included patients went on to receive a second-line therapy; LTB patients and those without CNS metastases had a longer time to next therapy. The median rwPFS and OS were significantly shorter among patients with a HTB vs LTB, and among patients with vs without CNS metastases (Table). **Conclusions:** Both tumor burden and presence of CNS metastases appear to have a significant impact on survival among BRAF+ MM patients treated with 1L dab/tram. With growing use of 1L immunotherapy in MM, 1L BRAF/MEK inhibitors are increasingly being used in patients with a worse prognosis, which may explain the lower rwPFS and OS with dab/tram when compared with clinical trials. Research Sponsor: Novartis Pharmaceuticals Corporation.

	Overall (N=460)	HTB (n=66)	LTB (n=69)	CNS metasta- ses (n=164)	No CNS metasta- ses (n=296)
Patients advancing to 2L therapy, n (%)	234 (51%)	33 (50%)	43 (62%)	75 (46%)	159 (54%)
Median time to 2L therapy, days (IQR)	179 (106-335)	140 (100-334)	169 (118-373)	163 (96-307)	181 (108-356)
Median rwPFS, months (95% CI)	5.5 (4.9-6.3)	4.2 (3.3-4.6)	8.4 (5.3-12.4)	3.9 (3.4-4.5)	7.4 (6.3-8.7)
Median OS, months (95% CI)	12.5 (10.5-14.7)	6.1 (4.8-12.9)	15.3 (12.0-21.7)	8.0 (6.0-9.2)	15.3 (12.5-19.0)

2L: second line; CI: confidence interval; IQR: interquartile range.

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Poster Session

The validity of a machine learning algorithm in predicting response to immune checkpoint inhibitors in melanoma. *First Author: Faisal Fa'ak, Laura and Isaac Perlmutter Cancer Center, NYU School of Medicine, Mineola, NY*

Background: We previously reported the development of a machine learning algorithm to predict immunotherapy response in patients with advanced melanoma using retrospectively collected pretreatment histologic slides (Johannet et al, CCR 2021). In this study, we tested the validity of the same algorithm in two independent cohorts of melanoma patients enrolled in phase III clinical trials of immune checkpoint inhibitors (ICI), one metastatic, and one adjuvant. **Methods:** We examined 336 patients enrolled in CheckMate 067(NCT01844505) and CheckMate 238 (NCT02388906). We used deep convolutional neural networks (DCNN) to automatically segment images into three regions of interest: tumor, lymphocytes, and stroma. The algorithm was previously trained and tested to predict the complete and partial response (CR/PR) versus progression of disease (POD) and to predict the probability of progression-free survival (PFS) while on ICI. We tested the performance in the two cohorts; the first (CheckMate 067) included 164 patients with stage III/IV unresectable melanoma who received ipilimumab (n= 49), nivolumab (n = 59), or combination (n= 56) therapy as a first line, then tested whether the algorithm could perform as well in the second cohort (CheckMate 238) which included 172 patients with stage III/IV resectable melanoma who received adjuvant ipilimumab (n = 87) or nivolumab (n = 85) therapy as first line. **Results:** The segmentation classifier identified tumor within slides with an area under the curve (AUC) of 0.99. A combined model of DCCN and treatment predicted POD with an AUC of 0.72 in metastatic melanoma patients enrolled in Checkmate 067. The DCCN classified patients into high and low risk based on their likelihood of PFS (P < 0.0001). However, the same algorithm is not effective in predicting recurrence in patients treated in the adjuvant setting in Checkmate 238 (AUC 0.52). Retraining and testing using only patients treated in the adjuvant setting improved the AUC average to 0.65-0.70. **Conclusions:** Our results show the reproducibility of our previously developed algorithm in predicting response in patients with advanced metastatic melanoma. The inability of the model to predict recurrence in patients treated in the adjuvant setting might reflect the difference in the endpoint tested (response versus recurrence), which requires further training on larger datasets for this particular endpoint prediction, and/or the limited tumor volume in resected disease below a threshold that machine learning can predict a difference. Research Sponsor: U.S. National Institutes of Health.

9522

Poster Session

Subsets of interferon signaling and response to immune checkpoint blockade. *First Author: Daniel Lee, Yale School of Medicine, New Haven, CT*

Background: Interferon (IFN) signaling in tumors is critical for both response and resistance to immune checkpoint inhibitors (ICI). While PD-L1 is an approved biomarker for ICI response in some cancers, most have no approved biomarkers for ICI response. Further, there are no clinical strategies to predict IFN sensitive vs resistant states. We hypothesized that distinct patterns of IFN signaling in melanoma, including STAT1 (precursor to IFN signaling), phosphorylated STAT1 (pSTAT1, marker of active IFN signaling), and PD-L1 (canonical inhibitory output), are associated with response or resistance to ICI. **Methods:** Samples from 2 tissue microarrays of 97 patients total with metastatic melanoma who received ICI from 2011-2017 were randomized into discovery [D] or validation [V] cohorts. Multiplexed immunofluorescent microscopy was used to assess STAT1, pSTAT1, and PD-L1. 54 tumors were assessed for CD3. Signals were quantified via AQUA (Automated Quantitative Analysis). High vs low signals were defined around the discovery cohort median AQUA scores. Treatment response was assessed using RECIST, and 3-year survival was analyzed. For *in vitro* studies, 4 human melanoma cell lines were stimulated with IFN- γ / β , and Western blots were performed for STAT1, pSTAT1, and PD-L1. **Results:** Median follow up time was 20.2 mos (range 0.9-95.4 mos). Higher overall histospot, tumor, and nuclear STAT1 were in responders (CR/PR/SD > 6 mos) compared to non-responders (SD < 6 mos/PD, histospot p = 0.029 [D] and 0.040 [V]) and were associated with improved survival (histospot HR 0.25 [95% CI 0.08-0.76] p = 0.015 [D]; HR 0.32 [95% CI 0.12-0.84] p = 0.021 [V]). PD-L1 and pSTAT1 did not validate as associated with ICI response/survival. While many tumors had concordant high/low STAT1, pSTAT1, and PD-L1, many also had a discordant STAT1 or PD-L1 predominance. To assess the basis of this discordance, we performed IFN stimulation and Western blots of melanoma cell lines. IFN β upregulated STAT1 greater than PD-L1 in both acute and chronic settings (p < 0.001 and < 0.001), while chronic IFN- γ upregulated PD-L1 compared to the acute setting (p = 0.039) but not STAT1 (p = 0.105). Therefore, we hypothesized patients with discordant STAT1 and PD-L1 expression may have differential responses to ICI. In the overall cohort, STA-T1^{high}PD-L1^{high} tumors (IFN engaged) were associated with improved survival compared to STAT1^{low}PD-L1^{low} tumors (IFN low, HR 0.28 [95% CI 0.11-0.70] p = 0.007). Interestingly, STAT1^{high}PD-L1^{low} tumors were associated with improved survival compared to STAT1^{low}PD-L1^{high} tumors (HR 0.28 [95% CI 0.08-0.94] p = 0.04). Accordingly, STAT1^{high}PD-L1^{high} and STAT1^{high}PD-L1^{low} tumors had greater CD3 AQUA scores compared to STAT1^{low}PD-L1^{low} tumors (p < 0.001 and p = 0.018 respectively). **Conclusions:** Combined STAT1 and PD-L1 expression patterns may better predict melanoma response to ICI and provide insight into IFN sensitive versus resistant states. Research Sponsor: U.S. National Institutes of Health; Melanoma Research Alliance / Bristol Meyers-Squibb Young Investigator Award.

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Poster Session

Identification of RPTOR mutation as a novel predictor of efficacious immunotherapy in melanoma. *First Author: Yongzhao Li, Shijiazhuang People's Hospital, Shijiazhuang, China*

Background: mTOR pathway is known to influence cancer immunity by metabolism reprogramming. RPTOR (Regulatory Associated Protein of MTOR Complex 1), one of mTOR pathway genes, which is involving in control of mammalian target of mTORC1 activity for regulating cell growth and survival. Whether mutations of RPTOR are associated with clinical efficacy of immune checkpoint inhibitors (ICIs) in melanoma is still ambiguous. **Methods:** In discovery cohort, we retrospective analyzed the genomic data of 418 melanoma samples which derived from seven immunotherapy studies (<http://www.cbioportal.org/>) to evaluate the relationship between RPTOR mutation status and efficacy of immunotherapy. Then in validation cohort, the predictive value of RPTOR mutation was confirmed in 320 melanomas from MSKCC cohort (<http://www.cbioportal.org/>). TMB was calculated as the total count of nonsynonymous mutations in coding sequence. We used the CIBERSORT to evaluate the 22 types immune cell infiltration status in TCGA melanoma cohort. **Results:** The TMB level of RPTOR-mutant patients was higher than RPTOR-wildtype patients in both discovery (Median [IQR]: 43.11[23.76-140.15] vs. 6.13[2.07-13.66], P < 0.001) and validation (Median [IQR]: 37.38[20.17-84.95] vs. 8.85[3.35-21.07], P < 0.001) cohort. In discovery cohort, compared to RPTOR-wildtype patients, the RPTOR-mutant patients achieved prolonged OS (median OS: not reach, NR vs 22.7 months, HR (95%CI): 0.47(0.22-0.99), P = 0.043). This result was confirmed in validation cohort (median OS: NR vs. 42; HR (95%CI): 0.34 (0.11-1.0); P = 0.049). According to analysis of immune cell infiltration status, the mechanism of the predictive values of RPTOR mutations to ICI efficacy may be activated CD4 memory T cell more abundant in RPTOR-mutant tumors. **Conclusions:** RPTOR mutation is associated with higher TMB in ICI-treated melanoma patients. Survival analysis shows RPTOR mutation have a good link with longer OS after immunotherapy. These findings indicate that RPTOR mutation may serve as a potential predictive biomarker for ICIs in melanoma. Research Sponsor: None.

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Poster Session

CHARLI: A phase Ib/II trial of ipilimumab-nivolumab-denosumab or nivolumab-denosumab in patients with unresectable stage III and IV melanoma. *First Author: Peter Kar Han Lau, Peter MacCallum Cancer Centre, Sir Charles Gairdner Hospital, Harry Perkins Institute for Medical Research, University of Western Australia, Melbourne, Australia*

Background: Denosumab (deno) is an antibody directed against Receptor Activator of NF Kappa-b ligand (RANKL) with established indications as a bone anti-resorptive agent in several cancers. Pre-clinical studies and several case series suggest anti-RANKL can enhance the anti-tumor effect of immune checkpoint inhibitors possibly via modulation of Treg and M2 macrophages. We did a multicentre phase Ib/II trial (NCT03161756) to investigate the safety and efficacy of deno in combination with nivolumab (nivo) or ipilimumab-nivolumab (ipi-nivo). **Methods:** Patients (pts) with unresectable stage III or IV melanoma were recruited to either Arm A (nivo-deno) or Arm B (ipi-nivo-deno) as first-line therapy. In Arm A pts received nivo 3 mg/kg IV q2 weekly for 4 doses and deno 120 mg SC on D1, D8, D15, D29 and then maintenance nivo 480 mg IV with deno 120 mg SC q 4 weekly. In Arm B pts received combined ipi 3mg/kg with nivo 1 mg/kg IV 3 weekly for 4 doses with deno 120 mg SC on D1, D8, D15, D29 followed by 4 weekly maintenance nivo 480 mg with deno 120 mg. Co-primary endpoints were median PFS and grade 3-4 treatment related adverse events (TRAE) of interest. Secondary endpoints were objective response rate (ORR) and overall survival (OS). **Results:** 27 pts (15 males, median age 67 years, 48% (13/27) stage IVM1c, 26% elevated LDH, 31% BRAF^{V600} mutant) were enrolled in Arm A and 24 of 25 evaluable pts (16 males, median age 62, 46% (11/24) stage IVM1c, 13% (3/24) stage IVM1d, 30% elevated LDH and 33% BRAF^{V600} mutant) were enrolled in Arm B. Median follow up was 30.8 months (m) for Arm A and 24.8 m for Arm B. The RECIST 1.1 ORR was 56% (n=15/27, 15% (4/27) complete responses [CR] and 41% (11/27) partial response [PR]) for Arm A and 71% (17/24, 25% (6/24) CR and 46% (11/24) PR) for Arm B. The median PFS in both arms has not been reached with 12 month PFS rates of 59% (95%CI: 43-81) and 63% (95%CI: 46-88) for Arms A & B, respectively. Grade 3-4 TRAE were 11% (3/27) in Arm A and 71% (17/24) in Arm B. Common TRAE (≥10%) in Arm A was rash (52%), pruritus (30%), fatigue (26%), nausea (19%), diarrhoea/colitis (15%), arthralgia (11%), vitiligo (11%), hyperthyroidism (11%). Common TRAE (≥10%) in Arm B included rash (63%), fatigue (54%), diarrhoea/colitis (54%), hepatitis (46%), hyperthyroidism (29%), pneumonitis (29%), pruritus (25%), increased GGT (17%), hypothyroidism (17%), hypocalcaemia (13%). Arm B G3-4 TRAE included diarrhoea/colitis (25%), pneumonitis (17%) and hepatitis (13%). **Conclusions:** Nivo-deno and ipi-nivo-deno had numerically similar G3-4 TRAE compared to nivo and ipi-nivo. The median PFS, 12 month PFS and ORR for nivo-deno and ipi-nivo-deno are encouraging compared with CHECKMATE 067. Clinical trial information: NCT03161756. Research Sponsor: Amgen and Bristol Myers Squibb.

	Arm A (n=27)	Arm B (n=24)
Median age (yr)	67	62
Stage IVM1C %	48	46
Stage IVM1D %	NA	13
High LDH %	26	30
ORR n (%)	15 (56)	17 (71)
CR n (%)	4 (15)	6 (25)
PR n (%)	11 (41)	11 (46)
SD n (%)	4 (15)	1 (4)
mPFS	Not reached	Not reached
PFS 12 m %	59	63

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Poster Session

Preliminary safety and efficacy results from an open-label, multicenter, phase 1 study of RP2 as a single agent and in combination with nivolumab in a cohort of patients with uveal melanoma. *First Author: Joseph J. Sacco, The Clatterbridge Cancer Centre and University of Liverpool, Liverpool, United Kingdom*

Background: Uveal melanoma, although rare, represents the most common primary intraocular tumor in adults and is associated with high risk of liver metastases. Effective treatments are limited as uveal melanoma is an immunologically cold tumor that does not respond well to immunotherapy. RP2 is an enhanced-potency oncolytic herpes simplex virus type 1 expressing human granulocyte-macrophage colony-stimulating factor, fusogenic gibbon ape leukemia virus glycoprotein with the R sequence deleted (GALV-GP-R-), and an anti-CTLA-4 antibody-like molecule. Here, we present updated safety and efficacy data of RP2 monotherapy and RP2 + nivolumab (nivo; anti-PD-1) in patients (pts) with uveal melanoma. **Methods:** Pts ≥18 years old with histologically or cytologically confirmed advanced or metastatic non-neurological solid tumors (including uveal melanoma) who progressed on or could not tolerate standard therapy were included; pts had ≥1 measurable and injectable tumor (≥1 cm). After determination of the recommended phase 2 dose of RP2 (concentration of 10⁶ plaque-forming units [PFU]/mL intratumorally [IT] once followed by up to 7 additional IT doses at 10⁷ PFU/mL; [≤10 mL total/treatment day with amount per lesion determined by tumor diameter]), pts received RP2 monotherapy every two weeks (Q2W) or RP2 Q2W + nivo (NCT04336241). Responses were assessed using modified Response Evaluation Criteria in Solid Tumors version 1.1. **Results:** As of December 30, 2022, 17 pts with uveal melanoma were enrolled (RP2 monotherapy, n = 3; RP2 + nivo, n = 14). The majority of pts received both anti-PD-1 and anti-CTLA-4 therapy (12/17, 70.6%) and 17.6% received ≥3 prior lines of therapy. The overall objective response rate for the 14 pts with sufficient follow up for analysis was 28.6% [4/14] (all partial responses [PRs]; RP2 monotherapy, 1/3; RP2 + nivo, 3/11). The disease control rate (complete response + PR + stable disease [SD]) was 57.1% (8/14; 4 pts with SD in RP2 + nivo cohort). The median (range) duration of response at the data cut-off was 5.8 (1.7–14.7) months. The most common overall Grade 1–2 treatment-related adverse events (TRAEs; ≥20%) were pyrexia, chills, fatigue, and hypotension. The only Grade 3 TRAE occurring in > 1 pt was hypotension (2 pts receiving RP2 + nivo); no Grade 4–5 TRAEs were observed. **Conclusions:** Preliminary RP2 monotherapy and RP2 + nivo data demonstrated a favorable safety profile and meaningful antitumor activity in pts with metastatic uveal melanoma, an immunologically cold tumor with few effective treatment options. These data continue to support the hypothesis that IT oncolytic immunotherapy expressing anti-CTLA-4 in combination with anti-PD-1 may provide clinically meaningful benefit in pts with hard-to-treat/unresponsive tumors. Clinical trial information: NCT04336241. Research Sponsor: Replimune Inc.

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Poster Session

Leveraging longitudinal clinical annotations and panel sequencing to characterize dynamics of organotropism in metastatic melanoma. *First Author: Tyler J Aprati, Dana-Farber Cancer Institute, Boston, MA*

Background: Although metastasis plays a major role in the mortality and morbidity of melanoma, patterns of metastasis and drivers of organotropism have not been well characterized clinically. Although previous efforts have been made to examine genomic drivers of organotropism, a longitudinal examination of metastasis dynamics has not been well characterized clinically. **Methods:** To address these questions, we leveraged a clinico-genomic dataset of patients with metastatic melanoma (Kehl et al. 2021). From this dataset, we assembled a cohort consisting of 26,143 artificial intelligence-annotated imaging reports from 879 patients with metastatic melanoma with an average of 2 years of followup after initial metastatic diagnosis. Annotated metastasis sites included brain, bone, adrenal, liver, lymph node, lung, and mesentery. All patients were evaluated at the Dana-Farber Cancer Institute, and each patient has at least one tumor biopsy sequenced with OncoPanel, a next-generation sequencing panel that identifies mutations in 447 cancer-related genes. Lifetime incidence of metastatic sites was defined as whether a patient ever had a report annotated with that site. Time-to-event analyses on metastatic sites used the acquisition of a metastatic site as the event of interest. For each patient index dates were defined as the date of the first scan with cancer present. We used cumulative incidence models to examine the incidence of each site in our cohort, and both cause-specific hazard models and Fine-Gray modeling to account for competing events and determine the effect of genomic covariates. **Results:** For lifetime metastasis status, the overall incidence varied by site, with LN being the most common, occurring in ~75% of patients, and mesentery the rarest, occurring in ~12% of patients. For lifetime metastasis status, patients with adrenal metastases were positively enriched for mutations in SETD2 (P < 0.005). Among the significant genes for all sites were many genes encoding epigenetic modifiers. In the time-to-event setting, the order of the cumulative incidence functions for each site matched the lifetime frequency of sites. Through time-to-event analysis we found genes whose mutant status were significantly associated with a change in risk and/or rate of certain metastatic sites. Among other results, we found that having a mutation in SETD2 is significantly positively associated with an increase rate and risk of adrenal metastases (cause-specific HR 2.4, P < 0.005, Fine-Gray HR 2.6, P < 0.005), and NRAS mutations were significantly associated with lower rate and risk of liver metastasis (cause-specific HR 0.59 P < 0.05, Fine-Gray HR 0.58 P < 0.01). **Conclusions:** By using time-to-event analysis with longitudinal metastatic annotations, we identify potential drivers of organotropism in melanoma patients. Research Sponsor: U.S. National Institutes of Health.

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Poster Session

Anti-PD1 plus BRAF/MEK inhibitors (triplet therapy) after failure of standard therapy in patients (pts) with advanced melanoma. *First Author: Lisa Zimmer, Department of Dermatology, University Hospital Essen, Essen, Germany*

Background: Preclinical models support the combination of immune checkpoint inhibitors (ICI) with targeted therapy (TT), suggesting a synergistic effect; however, clinical trials evaluating the efficacy of triplet combination in first-line setting showed limited advantage compared to TT only. Early data from the phase II TRIDEANT (NCT02910700) study showed promising clinical activity in anti-PD1 refractory pts. We sought to evaluate the efficacy of combined TT plus anti-PD1 after the failure of standard therapy in pts with advanced melanoma. **Methods:** This retrospective, multicenter study included pts with advanced melanoma who were treated with a BRAF inhibitor and a MEK inhibitor in combination with a PD1 inhibitor after failure of a minimum of one standard therapy in seven major melanoma centers between February 2016 and July 2022. Demographics, disease characteristics, therapy details, and outcome data were evaluated. **Results:** 59 pts were identified; med age was 48 yrs (range, 24-80), 32 pts (54.2%) were males, 20 pts (33.9%) had ECOG PS 1, 46 pts (78%) had 3 or more metastatic sites, 40 pts (67.8%) had brain metastases, and 25 (42.2%) had LDH levels above the upper limit of normal before initiation of triplet therapy. Median follow-up time was 16.2 months (IQR, 6.02-20.81). Median number of previous treatment lines was 2 (range, 1-6); 40 pts (67.8%) were pretreated with at least one line of ICI and TT in any sequence. Of 55 pts who received ICI (n = 41 CTLA4 plus PD1; n = 9 PD1 mono; n = 2 CTLA4 mono; n = 3 PD1-based therapy) prior to triplet therapy, 44 pts (80%) were primary resistant (progressive disease [PD]); stable disease (SD) for < 6 months, and 11 pts (20%) secondary resistant (complete response [CR], partial response [PR], SD for > 6 months) to the ICI therapy. Treatment with triplet therapy resulted in an overall response rate (ORR) of 44.1% (n = 26) and a disease control rate (DCR) of 55.9% (n = 33) with a median duration of response of 13.7 months (range, 5.4-33.2). Median PFS for the entire cohort was 6 months (95% CI, 3.88-8.08), with a 12-month PFS of 29.4% (95% CI, 17.8-42.1) and a 24-month PFS of 20.2% (95% CI, 11.0-32.8). Median OS was 15.7 months (95% CI, 8.1-23.3 months), with a 12-month OS of 52.7% (95% CI, 39.1-65.7) and a 24-month OS of 43.2% (95% CI, 29.6-55.9). Pts with extracerebral PD prior to triplet therapy (40.7%, n = 24) showed an ORR of 50%, pts with intracerebral PD (32.2%, n = 19) of 47.4%, and pts with global PD (27.1%, N = 16) of 31.3%. Treatment-related adverse events (TRAE) of grade ≥3 occurred in 17 of 59 pts (28.8%), of which cytokine release syndrome (n = 7) and hepatitis (n = 3) were the most common. In 16.9% (n = 10) of pts, TRAEs led to treatment discontinuation. **Conclusions:** Triplet therapy has shown promising efficacy in heavily pretreated pts with advanced melanoma and may represent a treatment option after failure of standard therapy with ICI and TT. Research Sponsor: None.

Risk of further progression or death among durable progression-free survivors with melanoma in PD-1 blockade trials: Implications for imaging surveillance. *First Author: Lei Deng, Roswell Park Comprehensive Cancer Center, Buffalo, NY*

Background: Durable progression-free survivors (dPFSors) over 2 years have been reported among melanoma patients treated with PD-1 blockade. However, non-negligible risk of further progression still exists and the optimal imaging surveillance interval is unknown. **Methods:** Individual patient data of progression-free survival (PFS) were extracted from PD-1 blockade clinical trials with follow-up of at least 5 years of PFS events. Co-treatment with anti-CTLA4 antibody was allowed. Patients with PFS of at least 2 years were considered as dPFSors. Conditional risk of progression or death with 95% CI was estimated based on a piece-wise exponential survival model, with the assumption that within each year from the beginning of the third year, the risk of progression/death (P/D) was constant. Conditional risks of P/D every 3, 4, 6, and 12 months in each subsequent year were calculated with 95% confidence interval (CI). We pre-specified three maximal risk levels – 10%, 15%, and 20% at each imaging scanning interval. An interval is considered as acceptable if the 95% CI upper bound of the risk at each scan is lower than a pre-specified risk level. **Results:** Of 1495 melanoma patients from 3 clinical trials, 474 (31.7%) were dPFSors. Among them, the PFS probability for additional 3 years was 76.4%. During the 3 years, no more than 5.0% of patients had P/D in any quarters. The yearly risk of P/D was 15.5% (95% CI 13.7% - 17.3%), 8.8% (6.8% - 10.8%), and 6.3% (3.8% - 8.8%) during the 3rd, 4th, and 5th year, respectively. Under risk at 10%, 15%, and 20%, melanoma dPFSors can be scanned every 6, 6, and 12 months during the 3rd year, every 6, 12, and 12 months during the 4th, and every 12, 12, and 12 months during the 5th, respectively. **Conclusions:** Based on their own risk tolerance level, our findings allow clinicians and dPFSors make data-driven decisions regarding imaging surveillance schedule beyond every 3 months. Research Sponsor: U.S. National Institutes of Health.

Proposed imaging surveillance intervals according to three risk tolerance level per scan.			
	10%	15%	20%
3rd year	Every 6 months (Risk: 8.1%, 95% CI 7.2% - 8.9%)	Every 6 months (Risk: 8.1%, 95% CI 7.2% - 8.9%)	Every 12 months (Risk: 15.5%, 95% CI 13.7% - 17.3%)
4th year	Every 6 months (Risk: 4.5%, 95% CI 3.6% - 5.5%)	Every 12 months (Risk: 8.8%, 95% CI 6.8% - 10.8%)	Every 12 months (Risk: 8.8%, 95% CI 6.8% - 10.8%)
5th year	Every 12 months (Risk: 6.3%, 95% CI 3.8% - 8.8%)	Every 12 months (Risk: 6.3%, 95% CI 3.8% - 8.8%)	Every 12 months (Risk: 6.3%, 95% CI 3.8% - 8.8%)

Encorafenib (enco) + binimetinib (bini) + pembrolizumab (pembro) for unresectable locally advanced or metastatic BRAF V600-mutant melanoma: Results from STARBOARD safety lead-in (SLI). *First Author: Dirk Schandendorf, University Hospital Essen, Essen, Germany*

Background: BRAF inhibitors (BRAFi) + MEK inhibitors (MEKi) (eg, enco + bini) and immune checkpoint inhibitors (CPIs) (eg, pembro) are approved for patients (pts) with BRAF V600-mutant metastatic melanoma. Combinations of BRAFi + MEKi with CPIs further improve outcomes and may offer additional treatment strategies. STARBOARD (NCT04657991) is an ongoing randomized, double-blinded, placebo-controlled, phase 3 study of enco + bini + pembro vs pembro in pts with unresectable locally advanced or metastatic BRAF V600-mutant cutaneous melanoma. Here we present the SLI results. **Methods:** Key inclusion criteria were histologically confirmed unresectable/metastatic BRAF V600E/K-mutant cutaneous melanoma and ≤1 prior systemic therapy for unresectable/metastatic disease. Pts received enco 450 mg QD + bini 45 mg BID + pembro 200 mg IV Q3W (COMBO450+P) or enco 300 mg QD + bini 45 mg BID + pembro 200 mg IV Q3W (COMBO300+P). The primary objective was to identify the recommended phase 3 dose (RP3D). The primary endpoint was dose-limiting toxicity (DLT) incidence; secondary endpoints included safety, objective response rate (ORR), time to response (TTR), and PFS (post hoc). **Results:** 20 pts received COMBO450+P and 17 COMBO300+P (cutoff: Dec 2, 2022). See table for baseline characteristics. 1 pt had a DLT with COMBO450+P: Grade (G) 3 drug-induced liver injury with concurrent G4 ALT increase and G3 bilirubin increase that resolved. 2 pts had DLTs with COMBO300+P: 1 with G3 rheumatoid arthritis flare and 1 with inability to receive drug due to G4 arthralgia, G4 back pain, G4 pyrexia, G3 chills, G3 headache, G3 paraneesthesia, and G3 maculopapular rash. Drug-related AEs led to permanent discontinuation in 4, 5, and 6 pts for enco, bini, and pembro, respectively. 1 pt in the COMBO300+P arm died <28 days after discontinuing all study treatments due to disease progression. See table for antitumor activity data. **Conclusions:** Safety across cohorts was comparable and consistent with the known safety profile of each agent. Both regimens were generally tolerable; COMBO450+P was chosen as the RP3D based on the totality of the safety data. The phase 3 portion of STARBOARD is ongoing. Clinical trial information: NCT04657991. Research Sponsor: Pfizer Inc.

Baseline characteristics and antitumor activity.	COMBO450+P	COMBO300+P
	n=20	n=17
Baseline characteristics		
Median age, y	51.5	54.0
ECOG PS 0, n (%)	15 (75.0)	15 (88.2)
BRAF V600E (local test), n (%)	18 (90.0)	14 (82.4)
Prior adjuvant BRAFi/MEKi, n (%)	2 (10.0)	0
Prior adjuvant CPI, n (%)	2 (10.0)	0
Median FU, months	9.7	10.6
Antitumor activity		
ORR, n (%)	12 (63.2)	8 (50.0)
(95% CI)	(41.0, 80.9)	(28.0, 72.0)
CR	1 (5.3)	1 (6.3)
PR	11 (57.9)	7 (43.8)
SD	4 (21.1)	3 (18.8)
PD	0	1 (6.3)
Not evaluable	3 (15.8)	4 (25.0)
Response duration ≥6 mo, n (%)	6 (50)	6 (75)
Median TTR, wk	9.0	9.2
Median PFS, mo (95% CI)	9.2 (7.1, NE)	NE (4.8, NE)
Pts at risk, n	20	17
Pts with event, n (%)	7 (35)	6 (35.3)

NE, not estimable.

Early safety and efficacy from a phase I clinical study of TWP-101, a novel CD137 agonist antibody, in patients with advanced melanoma and urothelial carcinoma. *First Author: Jun Guo, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Renal Cancer and Melanoma, Peking University Cancer Hospital & Institute, Beijing, China*

Background: CD137 plays the roles as a potent co-stimulator of both adaptive and innate immune cells, being an attractive target for cancer immunotherapy. TWP-101 is a fully humanized agonistic anti-CD137 monoclonal IgG4 antibody, targeting a novel epitope of CD137 with a unique mechanism of actions as a CD137 agonist but not CD137 ligand antagonist. The phase I study of TWP-101 in patient (pts) with advanced melanoma and urothelial carcinoma was initiated (NCT04871334). **Methods:** Enrolled pts were advanced melanoma refractory to standard therapy. Dose-escalation includes accelerated titration (0.01 and 0.03mg/kg) and conventional Fibonacci 3+3 dose levels (0.1, 0.3, 1.0 and 3.0 mg/kg). TWP-101 was administered intravenously every Q2W until confirmed progressive disease, unacceptable toxicity or withdrawal of consent. The primary objectives were to define the safety profile, to determine the maximum tolerated dose and RP2D of TWP-101. Secondary objectives were to evaluate pharmacokinetics (PK), immunogenicity and preliminary clinical efficacy. Exploratory objectives were to determine pharmacodynamics (PD) biomarkers. **Results:** From Feb 2021 to Mar 2022, 13 melanoma pts (median age 54 years, range 39-73; 6 men, 7 women; median 2 prior lines of therapy, range 1-6; 12 with prior immunotherapy) were treated. The following five dose levels had been evaluated from 0.01 to 1.0 mg/kg. 3mg/kg dose escalation is ongoing, no MTD has been reached. The median treatment time was 16 wks. (range 2-59). On cutoff date of October 31, 2022, 13 pts discontinued treatment due to progression disease (n = 12) and protocol deviation (n = 1). No DLTs were observed. 9 pts (69.2%) experienced treatment-related adverse events (TRAE). The most common TRAEs (≥10%) were neutropenia (23.1%), leukopenia (15.4%), hypertriglyceridemia (15.4%), anemia (15.4%), hyponatremia (15.4%). 1 pt experienced grade 3-4 TRAEs: hyponatremia, Asthenia and reduced appetite. In all TRAEs, one grade 1 decreased free triiodothyronine and one grade 2 pyrexia were possibly related, and all other TRAEs, including 2 treatment-related SAEs (1 grade 4 hyponatremia and 1 grade 2 subarachnoid hemorrhage), were identified as possibly unrelated. Deaths were due to progression disease (n = 3). Preliminary PK analysis showed dose-proportional kinetics. For 12 evaluable pts, 2 pts achieved PR (16.7%), 5 pts was SD. DCR was 58.3%. Median PFS was 16 wks. (range 16-60), PFS of 2 PR pts was 24 and 60 wks. **Conclusions:** TWP-101 demonstrated a good safety profile without hepatotoxicity frequently observed with other studied CD137 antibodies. Both favorable tolerability and preliminary antitumor activity warrant further evaluation in pts with advanced melanoma and urothelial carcinoma. Clinical trial information: NCT04871334. Research Sponsor: herawisdom Biopharma Co. Ltd.

A prediction model for response to immune checkpoint inhibition in advanced melanoma. *First Author: Isabella A.J. van Duin, University Medical Center Utrecht, Utrecht, Netherlands*

Background: Immune checkpoint inhibition (ICI) has greatly improved the prognosis for advanced melanoma in the last decade. However, it is still difficult to predict who will benefit from treatment. We aimed to develop a multivariable prediction model for response to ICI, using clinical data including primary melanoma characteristics. **Methods:** We used a population-based cohort of 3525 patients with advanced cutaneous melanoma treated with anti-PD-1-based therapy, originating from the Dutch Melanoma Treatment Registry. The endpoint of the study was objective response to ICI within 6 months after treatment initiation. The model considered 15 candidate predictor variables, was developed with logistic regression using Akaike information criterion-informed backward selection, and was internally validated with bootstrap resampling. Performance evaluation included calibration and discrimination. We used multiple imputation to account for missing data. **Results:** Patients received anti-PD-1 monotherapy (n = 2366) or ipilimumab plus nivolumab (n = 1159) in any treatment line. Median follow-up time was 15 months and 1311 patients (39%) had an objective response within 6 months. The prediction model for response included sex, serum lactate dehydrogenase, World Health Organization performance score, type of systemic therapy, line of systemic therapy, stage of disease, location of primary melanoma, type of primary melanoma, satellites and/or in transit metastases at time of primary diagnosis, and time to first distant recurrence. The model was well-calibrated. The AUC was 0.664 (95% confidence interval [CI] 0.645-0.682), and the over-optimism adjusted AUC was 0.649 (95% CI 0.631-0.667). The range of predicted response probabilities was 6-78%. Based on these probabilities, patients were categorized into quartiles. The median predicted response probability was 25% (interquartile range [IQR] 21-28%) for the lowest quartile and 54% (IQR 50-59%) for the highest quartile. Compared to the lowest response quartile, patients in the highest quartile had a significant longer median PFS (19.9 versus 2.8 months; p < 0.001) and median OS (66.5 versus 8.4 months; p < 0.001). **Conclusions:** We present a model based on both clinical variables and primary melanoma characteristics capable of predicting response to ICI in patients with advanced melanoma. This model can discriminate between patients with a very good and very poor prognosis. Research Sponsor: None.

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Poster Session

A phase I, randomized, controlled, multicentre trial of isolated hepatic perfusion in combination with ipilimumab and nivolumab in patients with uveal melanoma metastases (the SCANDIUM 2 trial). *First Author: Roger Olofsson Bagge, Department of Surgery, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden*

Background: Uveal melanoma is a rare disease characterized by liver metastasis and a very poor prognosis. In patients with metastatic UM, a single treatment with isolated hepatic perfusion (IHP) with high dose melphalan has shown response rates of 40%, while immune checkpoint blockade with ipilimumab (3 mg/kg) in combination with nivolumab (1 mg/kg) every third week (IPI3/NIVO1 q3w) for four cycles followed by nivolumab monotherapy has shown response rates of 11-18%. The impact of these treatments on overall survival, especially if combined, is unclear. This phase I trial investigates the safety and tolerability of the combination of IHP and IPI3/NIVO1. **Methods:** Eligible in this multicenter open, randomized, controlled, phase I trial, were patients with liver dominant metastatic uveal melanoma who had not received previous systemic treatment. Patients were randomized to receive either (Arm A) IHP followed by combination immunotherapy (four cycles IPI3/NIVO1 q3w) or (Arm B) one neoadjuvant cycle of IPI3/NIVO1 prior to IHP followed by three cycles IPI3/NIVO1 q3w. Thereafter, both Arm A and B received monotherapy with nivolumab (480 mg q4w) for up to 1 year. IHP was performed using melphalan 1mg/kg perfused through the liver for 60 minutes under hyperthermia (40°C). The primary endpoint was incidence and severity of adverse events while, secondary endpoints included response according to RECIST v1.1 criteria reported according by the local investigator. **Results:** A total of 18 patients were included and randomized, nine to Arm A and nine to Arm B. Three patients did not undergo IHP as planned, one due to perioperative complications (Arm A), one due to extensive metastatic liver infiltration (> 50% liver volume) (Arm B) and one due to encephalitis related to neoadjuvant IPI3/NIVO1 (Arm B). A total of 20 serious adverse events (SAEs) were reported in eleven patients. There were ten SAEs in each arm, with no treatment related deaths. In total, 11 of 18 patients (six in Arm A and five in Arm B) did not complete the planned four cycles of IPI3/NIVO1, with a mean of 2.4 cycles in Arm A and 3.0 cycles in Arm B. Response was evaluable in 17 patients, with the best clinical responses reported as three complete responses (18%), four partial responses (24%), seven stable disease (41%) and three progressive disease (18%). The overall response rate was 63% in Arm A (5/8) and 22% in Arm B (2/9). **Conclusions:** For previously untreated patients with liver dominant metastatic uveal melanoma, treatment with IHP in combination with IPI3/NIVO1 had a high, yet manageable toxicity profile. The efficacy of this combination treatment is encouraging, however, one cycle of neoadjuvant IPI3/NIVO1 given before IHP did not seem beneficial, neither in regards to safety nor efficacy. Clinical trial information: NCT04463368. Research Sponsor: The Assar Gabriellson Foundation, American Association for Cancer Research, Bristol-Myers Squibb, Knut and Alice Wallenberg Foundation, The Sjöberg Foundation, Swedish Research Council, Swedish Cancer Society.

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Poster Session

Updated results from an ongoing phase 1/2a study of T3011, an oncolytic HSV expressing IL-12 and PD-1 antibody, administered via IT injection as monotherapy or combined with pembrolizumab in advanced solid tumors. *First Author: Jiaxin Niu, Banner MD Anderson Cancer Center, Gilbert, AZ*

Background: T3011 is a recombinant HSV-1 oncolytic virus expressing both IL-12 and anti-human PD-1 antibody. Upon injection, locally produced IL-12 induces IFN- γ production, enhances the oncolytic activity of NK cells and cytotoxic T lymphocytes, promotes anti-angiogenesis and inhibits tumor growth. PD-1 antibodies act as immune checkpoint inhibitors to augment tumor-killing activity of T-cells. Here we report the updated results from an open-label, dose escalation and expansion study of T3011 administered via intratumoral injection as monotherapy or in combination with intravenous pembrolizumab. **Methods:** Pts with pathologically confirmed recurrent or metastatic malignancy after failure of SOC were enrolled and received T3011 monotherapy (1×10^6 - 5×10^7 PFU/mL Q2W) or in combination with pembrolizumab (Lead-in T3011 1×10^6 PFU/mL Q2W monotherapy for 2 cycles followed by combination therapy Q3W). Pts with documented progression on T3011 monotherapy may cross over to receive combination therapy at the discretion of the investigator. The primary endpoints were safety and tolerability. Key secondary endpoints included confirmed ORR, DCR, DOR, PFS by investigator per RECIST1.1; OS; PD and PK. **Results:** As of 17 Jan 2023, 29 pts received T3011 alone or in combination with pembrolizumab, the median follow-up was 14.1 (1.2-27.6) months. No DLTs were reported. Any treatment-related adverse events (TRAEs) occurred in 75.9% (22/29) of pts ($\geq$ G3 in 10.3%). Treatment-related SAEs occurred in 3.4% (1/29). Most frequent TRAEs ($\geq$ 10%) were pyrexia (27.6%), fatigue (20.7%) and chills, injection site pain, arthralgia, nausea, headache (10.3% each). No additional safety signals were observed with combination therapy. 12 advanced melanoma pts failing prior PD-1 or PD-1/CTLA-4 combination treatment received 5×10^7 PFU/mL of T3011 monotherapy. The confirmed ORR and DCR were 25.0% (3/12) and 33.3% (4/12), respectively. 12-month PFS rate was 36.4%. 6 of these pts were re-challenged with immunotherapy with T3011 (5×10^7 PFU/mL) combined with pembrolizumab after progressing on T3011 monotherapy, 1 pt achieved PR after 4 months lasting > 8 months at data cutoff. 15 pts had tumor tissues for PD analysis. Increased CD8+ cells were observed in 46.7% (7/15) of all pts and 50% (5/10) of melanoma pts. It appeared to be more pronounced in pts with PR and SD, 66.7% (6/9) in all pts and 80% (4/5) in melanoma pts, respectively. Notably, the increment of CD8+ cells in 2 melanoma pts with PR was over 15 folds. **Conclusions:** Both T3011 IT monotherapy and combination therapy with pembrolizumab were safe and tolerable. The efficacy of T3011 in immune-resistant melanoma was encouraging. Our data suggest T3011 may modify the tumor microenvironment and overcome immune resistance. Clinical trial information: NCT04370587. Research Sponsor: Immvira Pharma Co., Limited.

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Poster Session

Phase 1b trial of IFx-Hu2.0, a novel personalized cancer vaccine, in checkpoint inhibitor resistant merkel cell carcinoma and cutaneous squamous cell carcinoma. *First Author: Andrew Scott Brohl, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL*

Background: Merkel cell carcinoma (MCC) and cutaneous squamous cell carcinoma (cSCC) exhibit high response rate to immune checkpoint inhibitor (ICI) therapy. However, patients with advanced disease who fail initial ICI therapy have limited treatment options. IFx-Hu2.0 (IFx) is a plasmid DNA encoding for an immunogenic bacterial protein, Emm55, formulated with a transfection agent for direct intratumoral injection. In a phase 1 study in advanced melanoma, biomarker analyses demonstrated robust immune priming effects of IFx administration. As part of an ongoing Phase 1b study, we evaluated the safety and immunologic response of different schedules of IFx intratumoral administration in patients with advanced MCC or cSCC. We report the initial results of the first stage of this study. **Methods:** In the first trial stage (n = 9), IFx was administered intratumorally in up to 3 lesions on 3 schedules; weekly x 1, 2, or 3. We report safety data for these patients. Given the proposed potential for immune priming effects of IFx, we performed an unplanned exploratory analysis of post-protocol treatment efficacy to evaluate for response to ICI rechallenge if given. **Results:** Five patients with advanced MCC and four with cSCC were enrolled. Prior to trial enrollment, all patients with MCC received ICI with pembrolizumab (4) or avelumab (1), all had progressive disease with median 3 months treatment (2.0-4.5mo). All 4 patients with cSCC previously received cemiplimab with median 6 months treatment (3.0-11.5mo). IFx was well tolerated at all dose schedules evaluated with no treatment-related G3-5 adverse events observed. Best response to trial therapy was SD in 2 patients and PD in seven. One MCC patient experienced complete clinical response in 2 injected lesions, but progression of disease overall with development of new disease areas. Following completion of protocol therapy, all 5 MCC patients and 2 of 4 cSCC patients were treated with anti-PD(L)1 therapy as the immediate post-protocol therapy: pembrolizumab (3) or avelumab (2) in MCC and cemiplimab (2) in cSCC. Four of 5 MCC patients and 1 of 2 cSCC patients, or 5 of 7 total (71%), experienced objective response to ICI rechallenge in this setting, with duration of response ongoing in 4 patients (7+, 8+, 9+, 20+ months) and one response lasting 23 months. **Conclusions:** IFx-Hu2.0 is safe and well tolerated at weekly dosing repeated up to 3 weeks. An exploratory analysis showed that five of seven patients (71%) treated with standard of care ICI agents following protocol therapy experienced a durable objective response despite prior failure of this same drug class prior to protocol enrollment. An additional 11 patients are planned for enrollment in the expansion stage of the study using the weekly x3 dosing schedule. Preliminary biomarker analyses from the first nine patients are ongoing and will be presented. Clinical trial information: NCT04160065. Research Sponsor: Morphogenesis, Inc.

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Poster Session

Targeting AMP kinase in melanoma: A phase I trial of phenformin with dabrafenib/trametinib. *First Author: Paul B. Chapman, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: AMP-activated protein kinase (AMPK) can phosphorylate BRAF and block its activation of MEK. AMPK is activated by biguanides such as metformin and phenformin (phen). Preclinical data indicated that phen can enhance the effects of BRAF inhibitors (BRAFi) in sensitive and BRAFi-resistant melanoma (mel) cell lines whereas metformin does not. Phen also can decrease myeloid-derived suppressor cells (MDSCs) enhancing immune reactivity against mel. For these reasons, we designed a phase I trial combining phen with dabrafenib/trametinib (dab/tram) in patients (pts) with metastatic BRAF V600-mutated mel. **Methods:** Bulk phen was provided by the Division of Cancer Treatment and Diagnosis of the National Cancer Institute under a materials transfer agreement. Phen was encapsulated at the Pharmaceutical Product Facility at MSKCC under cGMP procedures and used under an IND held by MSKCC. Eligible pts had metastatic BRAF V600-mutated mel. For the dose-escalation phase, prior BRAFi therapy was allowed. A 3+3 dose escalation design was used starting at a phen dose of 50 mg bid and standard dosing of dab/tram (150 mg bid/2 mg qd). Subsequent planned dose levels were 100 mg bid, 200 mg bid, and 300 mg bid with de-escalation to intermediate doses for toxicity. Plasma PK samples were collected and assayed by MRI Global Inc using a validated, GLP-compliant, HPLC-MS/MS assay. PBMC were collected to measure circulating MDSCs. At the recommended phase 2 dose (RP2D), we planned to treat 10 BRAFi-naïve pts. **Results:** We accrued 18 patients from March 2017 through December 2019. Dose-escalation to 200 mg bid was not tolerable nor was 150 mg bid. Therefore, we determined 100 mg bid to be the RP2D and accrued 2 patients on the dose expansion cohort before further accrual became impossible due to the COVID-19 pandemic. The most common toxicities were gastrointestinal – nausea, vomiting, anorexia, and transaminase and alkaline phosphatase elevation – accounting for 9 DLTs. Two patients were hospitalized due to lactic acidosis. There were also constitutional/inflammatory and skin/mucosal adverse events thought to be related to dab/tram. Weight loss was seen in most patients (median 3.7% at week 8) thought to be related to phen. There were 8 PRs and 2 CRs. Responses were observed in 2/7 pts who had received prior therapy with BRAFi. One CR lasted > 1 year. There were 8/11 (73%) responders among the BRAFi-naïve pts. At the RP2D of 100 mg bid, day 8 median phen plasma level was 73.4 ng/ml (range 32.8-253.2). At the the 50 mg bid dose level, it was 40.8 ng/ml (range 29.7-110.2). MDSC could be analyzed from the 150 mg bid and 200 mg bid dose levels (N = 7 pts). In all but 1 pt, MDSCs decreased while on phen. **Conclusions:** We observed 10/18 (55.5%) total responses with 2/7 among previously treated pts. Circulating MDSCs decreased on treatment. Phen at 100 mg bid can be combined safely with dab/tram and should be explored in future randomized phase II trials. Clinical trial information: NCT03026517. Research Sponsor: MSKCC; U.S. National Institutes of Health.

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Poster Session

Avelumab as second-line or later (2L+) treatment in patients (pts) with metastatic Merkel cell carcinoma (mMCC): Analysis of real-world outcomes in France using the CARADERM registry and the French national healthcare database. *First Author: Astrid Blom Fily, CHU Ambroise Paré, Boulogne-Billancourt, France*

Background: Avelumab, an anti-PD-L1 antibody, has been approved in multiple countries for the treatment of mMCC based on the results of the pivotal phase 2 JAVELIN Merkel 200 trial (NCT02155647). In pts who received avelumab as 2L+ treatment in the trial (part A), median overall survival (OS) was 12.6 months and median progression-free survival (PFS) was 2.7 months. The French health technology assessment agency requested the collection of real-world data from pts with mMCC from a comprehensive registry; data are reported here. **Methods:** This retrospective, noninterventional, real-world study evaluated all pts with mMCC in France using combined data from 2 databases: CARADERM (French national database of rare dermatological cancers) and Système National des Données de Santé (SNDS; national healthcare database). For this analysis, eligible pts were diagnosed with mMCC and initiated 2L+ avelumab outside of a clinical trial between August 2016 and December 2019. Pts were followed for 24 months after initiation of avelumab. Probabilistic linkage was performed to identify pts registered in both databases. OS and PFS were analyzed using Kaplan-Meier methodology. Safety data were not collected. **Results:** A total of 180 pts who received 2L+ avelumab were identified, data were obtained for 112 pts from the CARADERM database and for 68 additional pts after SNDS linkage. Median age at diagnosis was 74.0 years, 66.7% were male, and 98.3% received chemotherapy as first-line treatment. Median follow-up was 13.1 months. 79.5% of CARADERM database pts had discontinued avelumab; the most common reasons specified were progressive disease (36.4%), complete response (17.0%), and death (13.6%). Median OS was 14.6 months (95% CI, 9.9-21.3 months) overall; in CARADERM database pts, median OS was 15.9 months (95% CI, 8.6-28.3 months) vs 13.3 months (95% CI, 6.7-19.1 months) in non-CARADERM database pts. 12- and 24-month OS rates in the overall population were 53.8% (95% CI, 46.2%-60.8%) and 40.5% (95% CI, 33.2%-47.6%), respectively. In CARADERM database pts (data not available in non-CARADERM database pts), median PFS was 3.6 months (95% CI, 2.7-7.5 months), and the objective response rate was 55.3% (95% CI, 45.3%-65.4%), including complete response in 31.9%. Median duration of response was 39.3 months (95% CI, 24.3 months-not estimable). **Conclusions:** In this real-world study of national data from France, outcomes with avelumab as 2L+ treatment for mMCC were similar to those observed in part A of the JAVELIN Merkel 200 trial. These findings confirm the effectiveness of avelumab in pts with mMCC that have progressed following first-line systemic treatment in routine clinical practice. Research Sponsor: This study was sponsored by Merck Santé S.A.S., Lyon, France, an affiliate of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945), as part of an alliance between the healthcare business of Merck KGaA, Darmstadt, Germany and Pfizer.

9539

Poster Session

Economic evaluation for the US of relatlimab and nivolumab (RELA+NIVO) versus nivolumab (NIVO) monotherapy in untreated advanced melanoma. *First Author: Osama Aqel, Center for Health Outcomes and Pharmacoeconomic Research, University of Arizona, Tucson, AZ*

Background: The RELATIVITY-047 trial demonstrated longer median progression-free survival (PFS) with the combination of RELA+NIVO (10.1 months, 95% CI = 6.4 to 15.7) over NIVO (4.6 months, 95%CI = 3.4 to 5.6) in patients with untreated advanced melanoma (hazard ratio for progression or death = 0.75, 95%CI = 0.62 to 0.92). This economic evaluation aimed to estimate the cost-effectiveness/utility of RELA+NIVO vs. NIVO monotherapy in this setting. **Methods:** A two state partitioned survival model (PFS, progressed/death) was developed to compare costs and PFS outcome associated with both treatments. PFS curves were digitized and parametric functions fitted. A 5-year time horizon from a US payer perspective with a 3% discount rate/year was considered. Costs of treatment (average sales price), administration and monitoring parameters were derived from Centers for Medicare & Medicaid Services databases; cost of adverse events (grade 3/4 with rate >5%) were derived from prior advanced melanoma economic evaluations. Incremental costs, PFS life years (PFSLY), and PFS quality adjusted life years (PFSQALY) gained (g) were estimated in base case (BCA) and probabilistic sensitivity analyses (PSA). A cost-effectiveness acceptability curve (CEAC) was plotted to determine the probability of either treatment to be cost-effective over the other at different willingness to pay (WTP) thresholds. **Results:** Exponential regression was used to extrapolate RELA+NIVO and NIVO survival curves. According to the result table shown below, the BCA (PSA) shows an incremental cost of RELA+NIVO over NIVO of \$405,663 (\$402,936), incremental PFSLY of 0.326 (0.325), and incremental PFSQALY of 0.260 (0.256). The BCA (PSA) ICERs indicated an additional \$1,244,365 (\$1,239,803) per PFSLY gained (g) and an additional \$1,560,242 (\$1,573,969) per PFSQALYg. The CEAC curve shows that RELA+NIVO treatment had a 50% probability of being cost-effective regimen at a WTP threshold value of \$1,525,000 and 100% probability at a threshold of \$3,050,000 or above. **Conclusions:** In the setting of advanced melanoma, this economic evaluation showed that RELA+NIVO is associated with improvement in LY and QALY, however, at a marked incremental cost, requiring a very high WTP threshold. Research Sponsor: None.

BCA (PSA).			
	RELA+NIVO	NIVO	Difference
Cost	\$682,148 (\$679,432)	\$276,485 (\$276,496)	\$405,663 (\$402,936)
PFSLY	1.673 (1.665)	1.347 (1.340)	0.326 (0.325)
PFSQALY	1.338 (1.331)	1.078 (1.075)	0.260 (0.256)
ICER			\$1,244,365/PFSLYg (\$1,239,803/PFSLYg)
ICUR			\$1,560,242/PFSQALYg (\$1,573,969/PFSQALYg)

Interpretation of ICER and ICUR: incremental cost to gain resp. 1 LY or 1 QALY.

9538

Poster Session

Immune infiltrates in metastatic uveal melanoma liver metastases and associations with clinical outcomes. *First Author: Katherine Emilie Rhoades Smith, Mayo Clinic, Rochester, MN*

Background: Uveal melanoma has a poor prognosis following metastasis to the liver. Immune checkpoint inhibitors (ICIs) are often utilized in patients with metastatic uveal melanoma (MUM); however, ICIs in MUM have low response rates. We studied the association of immune infiltrates in MUM liver metastases with survival outcomes for all patients, in addition to evaluating if immune infiltrates improve survival for patients treated with ICIs. **Methods:** We included MUM patients with liver metastases who had pre-treatment liver biopsies available at Mayo Clinic Rochester. Demographics, disease characteristics, treatments, and clinical outcomes were obtained from the electronic medical record. Core biopsies of liver metastases were reviewed for the presence of lymphocytes at interface of the tumor and liver parenchyma, and for tumor-infiltrating lymphocytes (TILs). If TILs were present, then additional immunohistochemistry (IHC) staining was performed for CD3, CD4, CD8, PD1, CD25, and FoxP3. Overall survival (OS) was estimated with the Kaplan-Meier method and compared between groups with Cox proportional hazards regression. Median OS and hazard ratios (HR) were calculated and p-values (p) <0.05 were considered statistically significant. **Results:** 140 patients with MUM who had pre-treatment liver biopsies were identified. 122 biopsies were evaluable for the presence of lymphocytes, either at the tumor-liver interface, or for TILs. 80/122 (65.6%) biopsies showed presence of any lymphocyte and 27/80 had TILs. 27 biopsies had sufficient tissue for further IHC classification. CD8+ T cells were identified in 27/27 samples, T cell PD1 positivity $\geq 1\%$ in 4/27 samples, and regulatory T cell markers (CD25 and/or FoxP3) in 18/27 samples. Median OS for the entire cohort was 16 months (mo). Patients still alive at the time of data analysis had at least one year of follow-up available (range 13-124 mo). Univariate analyses (UVA) showed no significant improvement in OS based on the presence of any lymphocytes (HR 1.01, p 0.98), lymphocytes at the tumor-liver interface (HR 1.10, p 0.64), TILs (HR 0.78, p 0.27), >50% CD8+ T cells (HR 0.88, p 0.77), or absence of FoxP3+ T cells (HR 0.68, p 0.40). In the 69 patients treated with ICIs (pembrolizumab, nivolumab, or ipilimumab plus nivolumab), neither the presence of any lymphocytes (HR 1.19, p 0.56) nor TILs (HR 0.68, p 0.24) were associated with an OS benefit. **Conclusions:** We present a large cohort of patients with MUM where we characterized immune infiltrates in liver metastases and evaluated clinical outcomes. OS did not significantly improve with the presence of any lymphocytes, TILs, CD8+ T cells, or with the absence of FoxP3+ T cells. These results were consistent across all patients whether they were treated with ICIs or not. Our findings suggest that lymphocytes in MUM are functionally dormant and highlights the need for novel immune-activating treatment strategies. Research Sponsor: Mayo Clinic.

9540

Poster Session

Interim results from a phase I/II study of duvelisib PI3K δ γ inhibitor and nivolumab in patients with advanced unresectable melanoma who have progressed on anti-PD1 therapy. *First Author: Jingxiao Jin, University of Pittsburgh Medical Center Cancer Center, Pittsburgh, PA*

Background: The majority of unresectable melanoma patients eventually progress on first-line checkpoint blockade therapy. Duvelisib is a potent phosphoinositide 3-kinase (PI3K) δ and γ isoform inhibitor approved for relapsed/refractory CLL. PI3K γ inhibition has been shown to restore anti-PD1 activity in preclinical tumor models through conversion of tumor associated macrophages (TAMs) from an immunosuppressive to a pro-inflammatory state. PI3K δ inactivation has been associated with impaired T regulatory cell (Treg) function and reduced intratumoral Treg numbers. We report study design and results of a phase I study to evaluate the safety and efficacy of duvelisib and nivolumab in anti-PD1 refractory patients. **Methods:** Utilizing a modified 3+3 design with escalating doses of duvelisib (15 mg daily, 25 mg daily, and 25 mg BID), patients with unresectable melanoma were treated with nivolumab and duvelisib until unacceptable toxicity or disease progression. Primary endpoints for the phase I portion were maximum tolerated dose (MTD) and recommended phase II dose (RP2D) of duvelisib. Secondary endpoints include early and late toxicities and anti-tumor activity based on RECIST v1.1. Exploratory endpoints were to evaluate dose-dependent changes in the immune cell populations of peripheral blood and tumor tissue with duvelisib and nivolumab. **Results:** Ten patients have been enrolled (7 at dose level I, 3 at dose level II) with mean age 64. Two patients had BRAF V600E mutation and were previously treated with BRAF/MEK inhibitors. No dose limiting toxicities (DLT) were observed. Grade 3 or higher adverse events (AEs) attributable to study treatment occurred in 4 patients (40%), including G3 neutropenia (10%), G3 diarrhea (10%), G3 vomiting (10%) and G4 hepatitis (20%). Both instances of hepatitis resolved rapidly with 1-2mg/kg of prednisone. In one patient, hepatitis and nausea/vomiting led to discontinuation of treatment. Out of 6 patients who had follow-up imaging, 4 exhibited progressive disease, one stable disease, and one had partial response of 11 months duration. Given the published data on the regulation of macrophages and Tregs by PI3K δ γ inhibitors, we are utilizing multispectral imaging to measure the spatial interactions of key immune cells within the tumor microenvironment (T cells, B cells, and macrophages) in all matched pre-/post-treatment paraffin-embedded tissues, for which results will be presented. **Conclusions:** The combination of duvelisib and nivolumab was well-tolerated in patients with advanced unresectable melanoma refractory to ICI without DLTs to date at 15 and 25mg daily dosages. Significant anti-tumor activity was noted in one patient. Enrollment at dose level II is ongoing. Clinical trial information: NCT04688658. Research Sponsor: Secura Bio, Inc.

9541

Poster Session

Updated safety and efficacy results from the phase I study of either LBL-007 (an anti-LAG-3 antibody) in combination with toripalimab (an anti-PD-1 antibody) or LBL-007 in combination with toripalimab and axitinib in patients with advanced melanoma. *First Author: Xue Bai, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Renal Cancer and Melanoma, Peking University Cancer Hospital & Institute, Beijing, China*

Background: Initial safety and efficacy data of LBL-007 plus toripalimab in patients with advanced melanoma (Part A) have been reported in 2022 ASCO (Abstract 9538). Here we present the updated results of part A and the preliminary results of part B (LBL-007 plus toripalimab with axitinib). Median follow-up was 9.7 months at cut-off data (January 11, 2023). **Methods:** Patients with advanced melanoma with or without prior therapy were enrolled during Jan 2021 - Aug 2022. This trial comprised 2 parts: Part A, patients received LBL-007 (0.25 - 10 mg/kg for dose escalation; 3 or 6 mg/kg for dose expansion) plus toripalimab at 3 mg/kg (both i.v. Q2W); and Part B, patients received LBL-007 at 3 or 6 mg/kg plus toripalimab at 3 mg/kg (both i.v. Q2W) and axitinib at 5 mg BID. The primary objective was safety, the second objectives were pharmacokinetics, pharmacodynamics and efficacy (per RECIST v1.1). **Results:** In part A, 68 patients in total (57 treatment-naïve) were enrolled including 20 patients in dose escalation and 48 patients in dose expansion, and among which, 31 additional patients have been enrolled since 2022 ASCO report. Nineteen (27.9%) patients occurred grade ≥ 3 TEAEs, the common grade ≥ 3 TEAEs was anaemia (11.8%). No new safety signals were detected. Among 55 efficacy evaluable treatment-naïve patients (41 with acral, 7 mucosal, 7 others), ORR was 23.6%, DCR was 58.2%, and mPFS was 5.7 months (95% CI: 3.7, 9.5). In part B, 11 patients (10 mucosal, 1 acral) were enrolled. No DLT was observed. Five patients (45.5%) occurred grade ≥ 3 TEAEs, the common grade ≥ 3 TEAEs included blood pressure increased (18.2%) and transaminases increased (18.2%). One (9.1%) patient discontinued treatment due to TEAEs. ORR was 45.4% (including 4 mucosal and 1 acral), DCR was 72.7%, and mPFS was 5.5 months (95% CI: 1.8, 9.1). **Conclusions:** LBL-007 plus toripalimab continued to show promising antitumor activity and manageable safety profile in patients with treatment-naïve melanoma, which support further development in this indication. LBL-007/toripalimab/axitinib combination demonstrated acceptable safety profile and encouraging antitumor activity in patients with mucosal melanoma. Acknowledgements: Junshi Biosciences. Clinical trial information: NCT04640545. Research Sponsor: Nanjing Leads Biolabs Co., Ltd.

9543

Poster Session

The effect of LNS8801 alone and in combination with pembrolizumab in patients with metastatic uveal melanoma. *First Author: Alexander Noor Shoushtari, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: LNS8801 is an oral, selective, small molecule agonist of the G-protein coupled estrogen receptor (GPER). LNS8801 treatment results in increased melanocytic differentiation, reduced c-Myc protein levels in cancer cells, inhibition of proliferation, suppression of invasion, and enhancement of immune recognition. In preclinical models, LNS8801 has demonstrated increased activity in combination with immune checkpoint inhibitors (ICIs). In the first-in-human dose escalation study, LNS8801 was safe and tolerable alone and in combination with pembrolizumab in patients with advanced solid tumors (NCT04130516). **Methods:** Patients with measurable metastatic uveal melanoma (mUM) received LNS8801 (125 mg, QD, PO) alone or with pembrolizumab (200 mg, Q3W, IV) (NCT04130516). The primary objective was safety and tolerability assessed according to NCI CTCAE v5.0. Secondary endpoints include pharmacokinetic, pharmacodynamics, objective response rate (ORR) and disease control rate (DCR, CR+PR+SD) per RECIST v1.1. Presence of a consensus, fully-functional, germline GPER coding sequence was assessed via Sanger sequencing on DNA extracted from blood as a potential predictive biomarker. **Results:** As of 1/25/23, 15 patients with mUM were treated with LNS8801 alone (n = 8) or a combination of LNS8801 and pembrolizumab (n = 7). Patients were previously treated with a median of 2 prior lines of systemic therapy. 4 of 8 monotherapy patients had AEs potentially related to study drug (all grade 1), with no AEs occurring in more than one patient. 6 of 7 combination patients had AEs potentially related to study drugs (grades 1-2), with fatigue occurring in more than one patient. Of the 14 patients evaluable for efficacy (7 mono, 7 combo), 7 had disease control (4 mono, 3 combo) resulting in a disease control rate of 50%. 1 patient treated with combination achieved a confirmed partial response. Consensus germline GPER was present in 2 of 12 sequenced patients (1 mono, 1 combo), and both of these patients have ongoing disease control lasting longer than 24 weeks. **Conclusions:** LNS8801 alone and in combination with pembrolizumab is tolerable without unanticipated toxicities and demonstrates encouraging anti-tumor activity in patients with mUM. The hypofunctional germline GPER variant appears over-represented in this cohort compared to the normal population, suggesting a potential significant role for GPER in the development of mUM. These data support further development of LNS8801 alone and in combination with pembrolizumab as a therapeutic approach to treat mUM patients, especially for patients with consensus germline GPER. Clinical trial information: NCT04130516. Research Sponsor: Linnaeus Therapeutics.

9542

Poster Session

Durable clinical outcomes in patients (pts) with advanced melanoma and progression-free survival (PFS) ≥ 3 y on nivolumab (NIVO) $\pm$ ipilimumab (IPI) or IPI in checkmate 067. *First Author: F. Stephen Hodi, Dana-Farber Cancer Institute, Boston, MA*

Background: NIVO + IPI has demonstrated durable clinical benefit at 7.5 y in pts with advanced melanoma in the phase 3 CheckMate 067 study. PFS curves plateaued at ~ 3 y in this study, suggesting that being alive and progression-free for ≥ 3 y (PFS ≥ 3 y) may be a good surrogate for long-term clinical benefit. We conducted analyses to quantify this association. **Methods:** Pts with treatment (tx)-naïve, unresectable stage III/IV melanoma (stratified by PD-L1 expression, BRAF mutation status, and metastasis stage) received NIVO 1 mg/kg + IPI 3 mg/kg for 4 doses Q3W, followed by NIVO 3 mg/kg Q2W (n = 314); NIVO 3 mg/kg Q2W + placebo (n = 316); or IPI 3 mg/kg Q3W for 4 doses + placebo (n = 315) until progression or unacceptable toxicity. Exploratory post hoc analysis was performed in pts with PFS ≥ 3 y. **Results:** In the NIVO + IPI, NIVO, and IPI arms, respectively, 99 (32%), 78 (25%), and 21 (7%) pts had PFS ≥ 3 y. Objective response rates (ORRs) in these pts were $\geq 95\%$ (table). The majority of responses were complete responses (CRs; table); in almost all pts with partial responses (PRs) on NIVO + IPI or NIVO, target-lesion size decreased by $\geq 50\%$. At 7.5 y of follow-up among pts alive and progression-free at 3 y, PFS rates were $\geq 68\%$, overall survival (OS) rates were $\geq 85\%$, and melanoma-specific survival (MSS) rates were $\geq 95\%$ in the 3 tx groups (table). Among pts in this group who died after 3 y on study, the majority of deaths were unrelated to disease (table). The majority of pts with PFS ≥ 3 y who were alive and in follow-up were tx-free at the 7.5-y data cutoff (77/84, 57/64, and 13/16). Pts who received NIVO + IPI were off tx (median) for 75.5 mo (NIVO, 55.7 mo; IPI, 59.2 mo). Among pts with PFS ≥ 3 y in the 3 tx groups, 4%, 5%, and 19% received subsequent systemic tx (table). No new safety signals were observed in pts with PFS ≥ 3 y. **Conclusions:** This exploratory post hoc analysis suggested that PFS ≥ 3 y may be a good surrogate for long-term MSS with NIVO + IPI or NIVO, with very few occurrences of progression or death due to melanoma in this population through 7.5 y. Most pts were tx-free without having received subsequent systemic tx after demonstrating PFS ≥ 3 y. Further study of pts with PFS ≥ 3 y may allow the burden of imaging and follow-up visits to be reduced in this group. Clinical trial information: NCT01844505. Research Sponsor: Bristol Myers Squibb.

Outcomes at 7.5 y in pts with PFS ≥ 3 y.

	NIVO + IPI (n = 99)	NIVO (n = 78)	IPI (n = 21)
ORR, % (95% CI)	100 (96-100)	99 (93-100)	95 (76- <100)
Best overall response, n (%)			
CR	57 (58)	50 (64)	12 (57)
PR	42 (42)	27 (35)	8 (38)
Stable disease	0	1 (1)	1 (5)
PFS rate, % (95% CI)	84 (73-90)	85 (73-92)	68 (41-84)
Pts with PFS event after 3 y, n	13	11	6
MEL-unrelated deaths	7	3	2
OS rate, % (95% CI)	89 (80-94)	95 (87-98)	85 (60-95)
Deaths after 3 y, n	11	5	3
MEL-unrelated deaths	8	3	1
MSS rate, % (95% CI)	98 (92-99)	97 (89-99)	95 (68-99)
Subsequent tx, n (%)			
Any	12 (12)	12 (15)	7 (33)
Systemic	4 (4)	4 (5)	4 (19)
Radiotherapy	4 (4)	2 (3)	4 (19)
Surgery	10 (10)	9 (12)	3 (14)

MEL, melanoma.

9544

Poster Session

Breaking primary checkpoint inhibitor resistance: Interim analysis of a multicenter phase II study by intermittent application of an alkylating agent among patients with metastatic melanoma. *First Author: Lucie Heinzerling, Department of Dermatology, Ludwig-Maximilians-Universität München, München, Germany*

Background: Patients with BRAF wildtype (wt) metastatic melanoma with primary resistance to immune checkpoint inhibitors (ICI) have a dismal prognosis. Chemotherapy has been shown to induce mutations, alter the tumor microenvironment as well as the microbiome, and modulate the immune system. This prospective phase II trial investigates whether two applications of an alkylating agent (dacarbazine/DTIC) can render ICI non-responsive patients with metastatic melanoma responsive to the same checkpoint inhibitor regime. **Methods:** The PROMIT trial (NCT04225390) targets patients with histologically confirmed BRAFwt metastatic melanoma showing primary resistance to ICI therapy. Applying an optimal two-step design, the uninteresting responder rate was set to 5% with an expected rate of 20%. Response is defined as complete or partial response by week 14 according to RECIST 1.1. Design foresaw 29 assessable patients at first step and 38 patients overall (alpha one-sided 5%, 90% power). After showing primary resistance to ICI, patients received 2 doses of DTIC (850 mg/m² i.v.) on days 1 and 21, and were subsequently re-exposed to the same ICI therapy they had previously shown resistance to. **Results:** In total, 38 patients were screened at 4 skin cancer centers. Interim analysis was performed after 29 patients who had received at least one ICI re-exposure were assessable for efficacy. Overall response rate was 24% (90%CI 12-41%) with 7 out of 29 patients showing a partial response; disease control rate was 38%. Application was well tolerated with 16% grade 3 or more adverse events and no new safety signals. **Conclusions:** Interim analyses results indicate that this approach of a short-term chemotherapy can break resistance in a subgroup of patients and allows us to continue the phase II trial to assess relevance of this treatment approach for metastatic melanoma. Enrollment is ongoing. Clinical trial information: NCT04225390. Research Sponsor: German Cancer Aid; University hospitals.

9545

Poster Session

Real-world comparison between 6 weeks versus 3 weeks adjuvant pembrolizumab in high-risk stage IIB-IIID cutaneous malignant melanoma: Experience from an academic cancer center. *First Author: Manan Shah, The James Cancer Hospital and Solove Research Institute, Columbus, OH*

Background: The KEYNOTE-555 trial demonstrated similar efficacy and safety profile of 6-week (q6w) pembrolizumab (400 mg/m²) vs 3-week (q3w) in unresectable and metastatic melanoma leading to FDA's approval of this dosing schedule for adults in 2020. Limited real-world data is available on the use of 3 weeks vs 6 weeks pembrolizumab in the adjuvant setting in cutaneous melanomas. Q6w is hypothesized to cause more adverse effects due to higher drug concentration. **Methods:** We conducted a retrospective study of surgically resected Stage IIB-IIID cutaneous melanomas receiving adjuvant pembrolizumab from 2019-2022 at The James Comprehensive Cancer Center with a follow-up of ~1 year. Fifty patients [n=35 (q6w) and n=15 (q3w)] were included. The primary objectives were to compare disease free survival (DFS) and safety profile based on the NCI-CTCAE (v 5.0) criteria. Kaplan-Meier curves were generated for DFS comparisons between the two groups. Fisher's exact test was used to compare the safety profile between the two groups. Accuracy of the sample size for final analysis was planned based on log rank test. With 15 patients (q3w) and 35 patients (q6w), our study had 80% power to detect differences in clinical outcomes. A *p*-value of less < 0.05 was considered statistically significant. The secondary objective was to compare overall survival (OS) which will be reported later with a longer follow-up. **Results:** The mean age in the q6w and q3w groups was 59 years and 69 years, respectively. The median follow up was ~ 9 months with males predominating in both groups (54% and 18%). In the q6w group, 68% had ECOG status 0 (vs.30% in q3w) and most of our patients (32%) were stage IIB (vs. 6% in q3w) and 28% were stage IIIC (vs 12% in q3wk). *BRAF* mutation was present in 32% in q6w vs. 2% in q3w. Toxicity profile was noted to be similar in both groups with no significant statistical difference (*p*-value=0.4), though there were more Grade-3 immune-related toxicities in 7 patients in the q6w group (vs 3 in q3wk). The most common grade 3 toxicity noted was colitis (n=4, q6w; n=1, q3w). Notably, no significant difference was noted in the DFS between the two groups (*p*-value=0.6). At the time of analysis, 3/15 (20%) patients in q3w and 7/35 (20%) in the q6w group had disease progression with the most common site being the regional lymph-nodes. At the time of the last follow up, 96% of the patients were alive with only 2 deaths occurring due to non-cancer related causes. **Conclusions:** We demonstrate comparable efficacy of q6w and q3w adjuvant pembrolizumab for advanced stage melanoma, with a trend towards increased immune-mediated colitis events in q6w. Research Sponsor: None.

Characteristics		q6w n=35(%)	q3w n=15(%)
Age (years)		59 (21-87)	69 (54-84)
Gender	Male	19 (54)	9 (60)
	Female	16 (46)	6 (40)
TNM stage	II B-C	-	5
	III A-D	35 (100)	10 (66.67)
Colitis	Grade 1-2	2	0
	Grade 3	4	1
Fatigue	Grade 3	1	1
Hepatitis	Grade 3	1	1

9547

Poster Session

Retreatment and rechallenge with BRAF/MEK inhibitors in patients with metastatic melanoma: Results from the observational study GEM1801. *First Author: Pablo Ayala de Miguel, Medical Oncology Department, Hospital Universitario San Pedro de Alcntara, Caceres, Spain*

Background: Most patients with BRAF-mutant melanoma eventually develop resistance to therapy with BRAF/MEK inhibitors and immune-checkpoint blockade. Alternative treatment strategies are required in these patients since further therapy options lack survival benefit. Small series have shown promising activity from re-exposure to BRAF/MEK inhibitors after a treatment free interval of targeted therapy (TT), probably due to regression of resistant tumors and proliferation of clones that maintain sensitivity to BRAF/MEKi. However, prospective evidence for this approach is limited. Here we report the results of 30 patients who received a second course of TT at relapse after adjuvant therapy (retreatment) or after first progression on TT in the advanced setting (rechallenge). **Methods:** GEM1801 is a prospective observational study from the Spanish Melanoma Group (GEM) including 893 patients with melanoma treated in 37 centers. This is a descriptive analysis of basal characteristics, response rates (RR), progression free survival (PFS) and overall survival (OS) from 30 patients that received retreatment or rechallenge with BRAF/MEKi in GEM1801 study. **Results:** 4 patients received retreatment and 26 rechallenge. For retreatment, BRAF/MEKi median free interval from end of adjuvant TT to subsequent retreatment was 17.8 months (range: 12.4 - 57.7). RR with retreatment were 25%, with a median PFS and OS of 5.7 and 8.5 months. For rechallenge, RR was 38.5% and median PFS and OS 11.1 and 22.2 months respectively. Patients who were selected for rechallenge had higher complete response (CR) rates to first TT (26.9% vs 20.3%; *p*= 0.026). Patients who experienced deeper responses with 1st TT in the metastatic setting showed a correlation to longer PFS to 2nd TT with 12-m PFS rates of 66.7% versus 35.7% (HR 9.09 [95%CI: 1.42-58]; *p*= 0.02). OS showed a not statistically significant improvement in patients who reported CR to first TD (24-m OS rate of 75% versus 40.7% respectively). BRAF/MEKi free interval since first progression and retreatment or rechallenge was not associated with prognosis. Prognostic factors as LDH and number of metastatic sites did not correlate with the efficacy of retreatment. **Conclusions:** Retreatment or rechallenge with BRAF/MEKi in the metastatic setting achieved encouraging efficacy and may be a valid therapeutic strategy in a selected group of patients. Response to first treatment, retreatment and rechallenge with BRAF/MEKi. Clinical trial information: NCT03605771. Research Sponsor: GEM through industry partners: Novartis, Pierre Fabre, Incyte, BMS, Roche and MSD.

	First treatment N = 245		Retreatment (after adjuvant) N = 4		Rechallenge (after metastatic) N= 26	
	n	%	n	%	n	%
Complete Response	45	18.4	0	0	4	15.4
Partial Response	89	36.3	1	25	6	23.1
Stable Disease	33	13.5	0	0	3	11.5
Progression Disease	25	10.2	2	50	6	23.1
Not Evaluable	53	21.6	1	25	7	26.9
ORR	134	54.7	1	25	10	38.5
DCR	167	68.2	1	25	13	50

9546

Poster Session

Neoadjuvant T-VEC + nivolumab combination therapy for resectable early metastatic (stage IIIB/C/D-IV M1a) melanoma with injectable disease: NIVEC trial. *First Author: Lisanne P. Zijlker, Division of Surgical Oncology, Netherlands Cancer Institute, Amsterdam, Netherlands*

Background: Neoadjuvant systemic treatment with checkpoint inhibitors (ICI) has shown high response rates in patients with resectable metastasized melanoma. In patients with unresectable stage IIIB-IVA melanoma; intralesional treatment with talimogene laherparepvec (T-VEC) has also shown high and durable response rates. In this trial we investigated the safety and efficacy of neoadjuvant treatment with a combination of nivolumab and T-VEC in regionally metastasized melanoma. **Methods:** In this single arm phase II open-label trial (NCT04330430), 24 patients with resectable stage IIIB-IVA melanoma were included. Inclusion criteria were a RECIST 1.1 measurable lesion of ≥10mm and no prior systemic therapy. Treatment consisted of four doses of intralesional T-VEC (dose in ml according to the size of the lesions) and three doses of nivolumab 240 mg flat dose every two weeks, followed by surgery. The primary endpoint was pathological response rate according to the International Neoadjuvant Melanoma Consortium (INMC) criteria, secondary endpoints were delay or failure to perform surgery, event free survival (EFS) from time of randomization and safety. **Results:** Baseline characteristics are presented in the table. The overall pathological response rate was 74%, with a major pathological response (MPR = pathologic complete response (pCR) + near-pCR (max 10% viable tumor cells) in 15 patients (65%), a partial response in two patients (9%), a non-response in 4 patients (17%) and progression of disease (PD) in two patients (9%). In one patient the response was not evaluable because surgery was delayed due to a vena cava thrombosis. The two patients with PD had evidence of distant metastasis on preoperative imaging and therefore did not proceed to surgery as planned. Grade 2 treatment related adverse events (trAE) occurred in 7 patients (29%) and grade 3 in 2 (8%). There were no grade 4-5 trAEs. The 1-year EFS was 75% (95%CI 0.55-1). **Conclusions:** Neoadjuvant combination therapy of nivolumab and T-VEC for patients with regionally metastasized melanoma (satellite/in-transit +/- lymph node metastases) has an acceptable toxicity profile and has shown a significant major pathological response rate of 65%. Clinical trial information: NCT04330430. Research Sponsor: AMGEN.

Baseline characteristics of patients included in NIVEC trial.		All patients (n=24)
Gender		
- Male		13 (54%)
- Female		11 (46%)
Age (median, IQR)		67 (56-73)
WHO performance score		
- 0		23 (96%)
- 1		1 (4%)
Stage		
- IIIB		14 (58%)
- IIIC		8 (33%)
- IIID		2 (9%)
BRAF status		
- Positive		11 (46%)
- negative		13 (54%)
Number of lesions (mean)		2.2 (2 unknown*)
Maximum diameter target lesion (median, IQR)		22 mm (18-34)(2 unknown*)

*Revision pending.

9548

Poster Session

A phase 1 study of fianlimab (anti-LAG-3) in combination with cemiplimab (anti-PD-1) in patients with advanced melanoma: Poor-prognosis subgroup analysis. *First Author: Inderjit Mehmi, The Angeles Clinic & Research Institute, A Cedars-Sinai Affiliate, Los Angeles, CA*

Background: Co-blockade of LAG-3 improves the effectiveness of anti-PD-1 treatment (Tx) in advanced melanoma (Mel) patients (pts). We previously reported high clinical activity of the combination immunotherapy of anti-LAG-3 (fianlimab) and anti-PD-1 (cemiplimab) in pts (N = 80) with anti-PD-1/PD-ligand (L)1-naïve advanced Mel enrolled in two expansion phase 1 cohorts. The objective response rate (ORR) (N = 80) and disease control rate (DCR) was 63.8% and 80.0%, respectively with median duration of response (mDOR) not reached (NR). Factors associated with poor prognosis include elevated lactate dehydrogenase (LDH) levels and sites of metastases, including liver or other visceral organs (M1c). Here we present updated efficacy data in poor prognosis pts from three phase 1 advanced Mel expansion cohorts: cohort 6 and 15 of anti-PD-(L)1/systemic Tx-naïve pts and cohort 16 of pts previously exposed to adjuvant (adj) or neo-adj systemic Tx including anti-PD-1. **Methods:** Pts with advanced Mel (excluding uveal Mel) were treated with fianlimab 1600 mg + cemiplimab 350 mg intravenously every 3 weeks for 12 months (+ additional 12 months if clinically indicated). Tumor measurements were assessed by RECIST 1.1 every 6 weeks for 24 weeks, then every 9 weeks. **Results:** 40 pts each in cohort 6 and 15, and 18 pts in cohort 16 (total N = 98) were enrolled and treated with fianlimab + cemiplimab as of 01 Nov 2022 data cutoff. In the adj/neo-adj setting, 23.5% of pts had received prior systemic Tx for Mel including 15.3% with prior exposure to immune checkpoint inhibitors (iCPIs). Median follow up was 12.6 months and median Tx duration was 32.9 weeks. ORR among all 98 pts and in 15 pts with prior iCPIs was 61.2% and 60.0%, respectively. In pts with LDH > upper limit of normal (ULN) (N = 32, 32.7%), ORR, DCR, and mDOR were 53.1%, 71.9%, and NR (95% CI, 7.4–not estimated [NE]), respectively, and median progression-free survival (mPFS) was 11.8 months (95% CI, 3.7–NE). In pts with liver mets at baseline (BL) (N = 21, 21.4%), ORR, DCR, and mDOR were 42.9%, 57.1%, and 9.0 months (95% CI, 2.8–NE), respectively, and mPFS was 4.2 months (95% CI, 1.2–NE). In pts with any M1c disease and LDH > ULN at BL (N = 17, 17.3%), ORR, DCR, mDOR were 35.3%, 58.8%, and NR (95% CI, 5.7–NE), respectively, and mPFS was 7.1 months (95% CI, 1.2–NE). Overall, 43.9% and 32.7% of pts reported grade ≥3 Tx-emergent adverse events (TEAEs) and serious TEAEs. Correlative biomarkers analyses are in progress and will be included in the presentation. **Conclusions:** The combination of fianlimab and cemiplimab showed high activity in pts with advanced Mel and poor prognosis features at BL. The ORR and DCR observed in these subgroups compare positively with the available data for approved combinations of iCPIs in the same clinical setting. A phase 3 trial (NCT05352672) of fianlimab + cemiplimab in Tx-naïve advanced Mel pts is ongoing. Clinical trial information: NCT03005782. Research Sponsor: Regeneron Pharmaceuticals, Inc.

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Poster Session

Determinants of racial disparities in immune-related adverse events (irAE) with checkpoint inhibition (ICI) in melanoma. *First Author: Milad Ibrahim, New York University, New York, NY*

Background: We recently reported that a pretreatment autoantibody (AutoAb) signature predicts immune-related adverse events (irAE) with an AUC of ~0.80 in melanoma patients enrolled in two phase III clinical trials of adjuvant ICI (Johannet *et al. CCR* 2022). The vast majority of those patients were non-Hispanic whites (NHW). We hypothesized that underrepresented minority (URM) melanoma patients might have a different baseline autoAb profile compared to NHW patients, as their site-specific irAEs differ (Xue Bai *et al. Br J of Derm* 2022) and autoimmune disease is generally more common in underrepresented minorities (Roberts MH, Erdei E. *Autoimmune Review* 2020). We also explored the possibility that differences in the immuno-biology of acral melanoma (AM) and cutaneous melanoma (CM) – most commonly detected in URM and NHW patients, respectively – might inform our understanding of the racial differences in irAEs. **Methods:** We compared pre-treatment sera autoAb from URM melanoma patients (n=35) to NHW patients (n= 185) enrolled in Checkmate-238 (NCT02388906), Checkmate-915 (NCT03068455) or the NYU melanoma program database using the CDI and Sengenics proteomic platforms, and analyzed their association(s) with the development of grade 3-4 irAEs. We carried out single cell RNA-seq in AM versus CM tumor tissues to test whether expression of genes whose proteins were associated with irAE were preferentially expressed in AM tissue. We also compared RNA-seq of an immunoregulatory gene panel in AM versus CM tumors. **Results:** We identified autoAbs that were only detected in sera from URM patients with grade 3-4 irAEs (e.g. *ALDOA*, *BANK1*, *LDHB* and *RNF7*) and autoAbs that were only detected in NHW patients with grade 3-4 irAEs (e.g. *GMEB2*, *YWHA* and *ANKRD45*). A subset of these autoAb targets was preferentially expressed in AM or CM tissues, while other targets were undetected in these melanoma subtypes. Cytokine signaling pathways were enriched in sera from URM but not NHW patients, and expression of genes known to modulate irAEs and response to ICI were significantly more expressed in AM than CM tumors, e.g. *FOXP3* ($P=0.01$), *IL2* ($P=0.00547$), *IL4* ($P=0.0221$) and *IL10* ($P=0.0126$). **Conclusions:** Our data suggest that URM patients have an altered tumor immune microenvironment that defines their response to ICI and risk of developing irAE. An integrative analysis of both the tumor and systemic immune environments is needed to better understand molecular links between response to ICI and irAEs in URM and NHW melanoma patients. A multi-center study is planned to address these questions. Research Sponsor: U.S. National Institutes of Health.

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Poster Session

Final results: Dose escalation study of a personalized peptide-based neo-antigen vaccine in patients with metastatic melanoma. *First Author: Sofie Kirial Mørk, National Center for Cancer Immune Therapy (CCIT-DK), Department of Oncology, Copenhagen University Hospital, Herlev, Denmark, Herlev, Denmark*

Background: Despite the advances made with CPIs such as aPD-1/aPD-L1, aCTLA4 and aLAG-3 there still is a significant unmet medical need for patients with metastatic cancers. As it has been shown that the effect of CPIs are mediated by tumor specific T cells, one strategy for increasing treatment success is to actively induce tumor specific T cells. Here, we report on a first-in-human clinical trial evaluating a personalized neoantigen vaccine (EVX-01) in patients with metastatic melanoma. **Methods:** Stage-IV metastatic melanoma patients were treated with standard aPD-1 in combination with a personalized tumor-specific neo-antigen vaccine. The vaccine consisted of multiple 15-27mer peptides comprising one or more patient specific neoantigens identified from tumor DNA and mRNA sequencing data by an integrated AI-platform; PIONEER and delivered together with the novel liposomal adjuvant CAF09b to potentiate immune responses. **Results:** Vaccines were designed and manufactured for each patient in less than 7 weeks. In total, 12 eligible patients received either 500ug (5 patients, reported in PMID: 35036074), 1000ug (3 patients) or 2000ug (4 patients) total peptide load keeping the peptide:CAF09b ratio constant. Four patients had stable disease on aPD-1 treatment for at least 4 months before enrolment in the study, whereas the remaining patients were treatment naïve. All patients received monotherapy with pembrolizumab (11) or nivolumab (1) during the vaccine manufacturing period. The personalized vaccine was shown to be safe and well tolerated with fatigue and injection site reactions being the most frequently reported events and only grade 1-2 events being related to the vaccine. Response was evaluated by RECIST 1.1, according to the investigator's assessment with 8 patients (67%) having objective response (CR: n = 2, PR: n = 6), of which 1 patients had response initiation before addition of the vaccine. Importantly the vaccine induced neoantigen specific T cells in all patients analyzed. Both CD4+ and CD8+ T cells were detected, with the majority of responses being CD4+ T cell mediated. Interestingly, we report a significant correlation between the PIONEER prediction score and induced immunogenicity. Furthermore, the breadth of the neoantigen recognition seemed to be important for the clinical effect of the vaccine as responders demonstrated T cell recognition of more epitopes within the vaccine compared to non-responders. We found, in our cohort, that the neo-antigen scores effectively separated responders and non-responders, as opposed to the TMB (by FDA guidelines). **Conclusions:** aPD-1 treatment combined with a peptide-based personalized neo-antigen-based vaccine was shown to be feasible and safe with promising signs of efficacy, warranting further study. Further, the neo-antigen selection method appeared crucial for designing an efficacious vaccine. Clinical trial information: NCT03715985. Research Sponsor: Innovation Fund Denmark; Evaxion Biotech.

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Poster Session

Phase II clinical trial of camrelizumab combined with famitinib for advanced acral and mucosal melanoma. *First Author: Lili Mao, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Melanoma and Sarcoma, Peking University Cancer Hospital and Institute, Beijing, China*

Background: Acral and mucosal melanoma were rarely seen in Caucasians but common in Asians. Previous studies revealed that acral and mucosal melanoma are more aggressive than cutaneous melanoma with a high unmet need for effective treatments. Camrelizumab plus anti-angiogenic agents have shown promising antitumor activity in previously untreated melanoma. Famitinib, a selective multiple-target tyrosine kinase inhibitor that exhibits both anti-angiogenesis and anti-proliferative effects via targeting VEGFR-2, PDGFR, c-kit, FGFR and so on, combined with camrelizumab had been proven effective in multiple cancers. This study aimed to assess the antitumor activity and safety of camrelizumab plus famitinib in both immunotherapy naïve and experienced advanced mucosal or acral melanoma. **Methods:** This single-center, open-label phase II study recruited patients (pts) with advanced acral and mucosal melanoma. Pts who were immune checkpoint inhibitors (ICI) treatment naïve were in cohort 1, while pts experienced ICI in cohort 2. In both cohorts, pts received camrelizumab (200 mg i.v. q3w) and famitinib (20 mg po qd) until disease progression or intolerable toxicity. The primary endpoint was objective response rate (ORR) per RECIST1.1. Secondary endpoints included progression free survival (PFS), disease control rate (DCR), overall survival (OS), and safety. This analysis focused on cohort 2. **Results:** As of January 12, 2023, 18 pts (9 mucosal and 9 acral histology subtypes) were enrolled in cohort 2. The median age of all pts was 58 yrs (ranged 38-71 yrs); 9 pts (50.0%) were female; prevalence of mutations: BRAF (11.1%), C-KIT or NRAS (16.7% each); 38.9% received ≥ 2 prior treatments. All pts progressed after anti-PD-1/L1 monotherapy (27.8%) or combinational therapy (66.7%), except one progressed after 4-1BB mAb monotherapy. The combination drugs included anti-LAG-3/CTLA-4 antibodies (38.9%), oncolytic viruses (11.1%), c-kit inhibitors, chemotherapy and anti-angiogenic agents (5.6% each). The median follow-up was 7.3 months (ranged 4.6-14.7 months). At the data cutoff, 5 pts remained on treatment. 17 pts were evaluable. The ORR and DCR were 17.6% and 64.7%, including two pts with confirmed PR, and one with unconfirmed PR, all of which were acral subtype. The median PFS was 6.0 months. The median OS was not reached. Of 18 pts, the incidence of treatment-related adverse events (TRAEs) was 88.9%. The most common grade 3 TRAEs was neutrophil count decreased (11.1%). No grade 4 TRAEs and no treatment-related deaths occurred. **Conclusions:** Camrelizumab plus famitinib showed promising antitumor activity in ICI-experienced advanced acral and mucosal melanoma pts, and was generally well tolerated. Clinical trial information: NCT05051865. Research Sponsor: None.

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Poster Session

Efficacy and safety of first-line (1L) nivolumab plus relatlimab (NIVO + RELA) versus NIVO plus ipilimumab (NIVO + IPI) in advanced melanoma: An indirect treatment comparison (ITC) using patient-level data (PLD). *First Author: Dirk Schadendorf, University Hospital Essen, University Duisburg-Essen, West German Cancer Centre (WTZ), and German Cancer Consortium, Partner Site Essen, Essen, Germany*

Background: NIVO + RELA and NIVO + IPI are approved as dual checkpoint inhibitor, 1L treatment options for patients (pts) with advanced melanoma based on results from the RELATIVITY-047 (NIVO + RELA vs NIVO; enrollment, 2018–2020) and CheckMate 067 (NIVO + IPI or NIVO vs IPI; enrollment, 2013–2014) trials, respectively. However, there is no head-to-head trial comparing the combinations; therefore, this ITC was conducted using PLD. **Methods:** To adjust for cross-trial imbalances in baseline characteristics, inverse probability of treatment weighting (IPTW) was used. Database locks were selected to best align follow-ups in RELATIVITY-047 (min., 21 mo; median, 25 mo) and CheckMate 067 (min., 28 mo; median, 29 mo). Efficacy and safety outcomes were selected based on data availability, including progression-free survival (PFS) per investigator, confirmed objective response rates (ORRs) per investigator, overall survival (OS), treatment-related adverse events (TRAEs), and TRAEs leading to discontinuation (DC). Efficacy was also evaluated in key subgroups. PFS and OS were compared for NIVO + RELA vs NIVO + IPI using Kaplan–Meier curves and hazard ratios (HRs); ORRs were compared using odds ratio (OR). As an internal validation of the ITC and matched assessments, the weighted NIVO cohorts from both trials were compared. **Results:** After IPTW, key baseline characteristics were balanced for NIVO + RELA (n = 340) and NIVO + IPI (n = 298). PFS, confirmed ORR, and OS after IPTW were similar between the treatments (table). Efficacy outcomes appeared to be similar between the treatments across subgroups, although trends favoring NIVO + IPI were observed for certain subgroups, such as pts with *BRAF* mutant disease or lactate dehydrogenase more than twice the upper limit of normal. Grade 3/4 TRAEs occurred in 23% and 61% of pts receiving NIVO + RELA and NIVO + IPI, respectively; any-grade TRAEs leading to DC occurred in 17% and 40% of pts. Efficacy outcomes were similar between the NIVO cohorts (table). **Conclusions:** In the absence of head-to-head trials, this ITC suggests that 1L treatment with NIVO + RELA may have comparable efficacy to, and better tolerability than, NIVO + IPI in pts with advanced melanoma. Similar outcomes between the NIVO cohorts support the ITC methodology. Results should be interpreted with caution given differences in study design and changes in treatment landscape over time. Research Sponsor: Bristol Myers Squibb.

	NIVO + RELA (n = 340)	NIVO + IPI (n = 298)	HR/OR (95% CI)	NIVO RELATIVITY- 047 (n = 338)	NIVO Check- Mate 067 (n = 287)	HR/OR (95% CI)
Median PFS, mo (95% CI)	12.0 (8.2–15.8)	11.2 (8.4–17.5)	1.07 (0.87–1.31)	6.7 (4.6–10.2)	5.7 (3.1–8.9)	0.93 (0.76–1.13)
Confirmed ORR, %	48	50	0.93 (0.74–1.17)	40	39	1.03 (0.81–1.32)
Median OS, mo (95% CI)	NR (37.0–NR)	NR (31.9–NR)	0.94 (0.74–1.19)	36.8 (27.3–NR)	32.4 (25.8–NR)	0.95 (0.76–1.20)

NR, not reached.

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Poster Session

Melanomas lacking HLA class I expression and response to checkpoint inhibitor. *First Author: Paul B. Chapman, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: The current paradigm of how checkpoint inhibitors (CPIs) mediate anti-tumor effects relies on $\alpha\beta$ T cells as the effector cells. However, HLA class I allele expression loss is common in melanoma, and in some cases, both β 2-microglobulin (β 2m) alleles are silenced, which results in complete loss of HLA I expression. We reasoned that if CPI therapy requires $\alpha\beta$ T cells as the effector cells, melanoma tumors with biallelic loss of β 2m could not present antigen to $\alpha\beta$ T cells and should never respond to CPI. **Methods:** We screened the 2754 melanoma patients (pts) whose tumors had been genotypically analyzed using MSK-IMPACT, a hybridization capture-based next-generation assay for targeted deep sequencing of all exons and selected introns of up to 505 genes, including β 2m. We identified 13 pts who had been treated with CPI, were evaluable for response and progression-free survival, and whose pre-treatment melanoma was found to have biallelic loss of β 2m. In 1 pt, only a post-treatment tumor was available for genetic testing for β 2m loss but lack of β 2m expression in a pre-treatment tumor was confirmed by immunohistochemistry (IHC). Pts were assessed for clinical responses using RECIST 1.1. We recorded best overall response, duration of response, and overall survival. When available, pre-treatment tumor tissue was assessed by IHC for β 2m and HLA class I expression, and for lymphocytic infiltrates expressing CD3, CD4, CD8, and CD56. **Results:** Anti-tumor responses were observed in 3/13 patients (23%); 2 PRs, 1 metabolic CR lasting for 24, 9.4, and 6.4 months, respectively. Responses were to ipilimumab (ipi) (N=2) and ipi/nivolumab (N=1). One pt responding to ipi had progressed on pembrolizumab; the other 2 responders were treatment-naïve. One pt died 11.5 months after starting treatment; the other 2 pts remain alive 5.5 and 8.9 years after starting treatment. IHC confirmed the lack of cell surface expression of β 2m and HLA class I in all 5 tumors available for IHC staining. IHC evaluations of lymphocyte infiltrates in tumors from 1 responder and 4 non-responders showed variable degrees of CD3⁺ tumor infiltrating lymphocytes (TIL) with CD4⁺ T cell predominance. Interestingly, the 1 responder had the least dense pretreatment TIL among the 5 cases. In all 5 tumors, CD56⁺ lymphocytes, indicating NK cells, were rare-to-absent. **Conclusions:** Melanomas lacking HLA class I expression can respond to CPI therapy. Although all patients ultimately progressed, some responses were long-lived and 2 of 3 patients remain alive >5yrs. It seems unlikely that traditional CD8⁺ T cells are mediating these responses but more work needs to be done to identify the effector cells in these cases. Research Sponsor: None.

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Poster Session

High dose ipilimumab (Ipi) plus temozolomide (TMZ) after progression on standard or low dose Ipi in advanced melanoma. *First Author: Julie Williamson, Department of Internal Medicine, University of Utah, Salt Lake City, UT*

Background: Despite advancements in checkpoint inhibitor-based immunotherapy (IO), patients (pts) with advanced melanoma who have progressed on Ipi + nivolumab (Nivo) continue to have poor prognosis. Several studies support a dose-response activity of Ipi. One promising combination for these pts is Ipi 10mg/kg (Ipi10) + TMZ. TMZ depletes regulatory T cells and suppresses their function, and it may enhance the antitumor activity of Ipi. We studied outcomes of pts with advanced melanoma treated with Ipi10+TMZ in the IO refractory/resistant setting, using a cohort of similar pts treated with Ipi3+TMZ as comparison. **Methods:** Clinical data of pts with IO refractory melanoma treated with Ipi+TMZ was collected retrospectively following IRB approval. Molecular profiling by WES and RNAseq of tumors harvested throughout one responder's treatment were analyzed: the primary skin lesion (P1), a liver metastasis (M2) 2 days after low-dose Ipi1+Nivo, and a soft tissue metastasis (M3) after Ipi10+TMZ. **Results:** Overall 12 pts met eligibility: 6 received Ipi10 and 6 received Ipi3. All pts in Ipi10 cohort had progressed on prior Ipi+Nivo. Two pts (33% ORR) with CNS involvement demonstrated extraordinary near complete responses to Ipi10+TMZ despite progressing on prior therapies, including regular or low dose Ipi+Nivo. With a median follow up of 119 days, pts treated with Ipi10+TMZ had statistically significant longer median progression free survival (PFS) of 144.5 days (range 27–219) vs 44 (26–75) for Ipi3+TMZ, $p = 0.04$. There is a trend for longer median PFS for pts who had > 1 cycle of treatment, and for those who had progressed on prior Ipi+Nivo. There is a trend for longer median overall survival (OS) of 154.5 days (27–537) with Ipi10 vs 89.5 (26–548) for Ipi3 +TMZ. In those previously exposed to Ipi3+Nivo, median OS in the Ipi10+TMZ group was 154.5 days (27–537) vs 39 (26–55) in Ipi3+TMZ group. WES of one responder's tumors revealed only 12 shared somatic mutations among P1, M2 and M3, including BRAF V600E, suggesting common lineage but significant clonal evolution. Genes involved in several important immune response pathways were mutated in M2 and M3 but not in P1. RNAseq showed enrichment of inflammatory signatures, including interferon responses in both M2 and M3 compared to P1, and downregulated negative immune regulators such as Wnt and TGF β signaling. M2 is a responding liver lesion to prior Ipi1+Nivo but disease progressed to bones and brain that subsequently responded to Ipi10+TMZ. **Conclusions:** Ipi10+TMZ demonstrated efficacy including dramatic responses in pts with advanced melanoma refractory to standard or low doses of Ipi + anti-PD1, even with CNS metastases. Molecular data suggest a potential threshold of Ipi dose for activation of sufficient anti-tumor immune response, and higher dose Ipi is required for some pts. Research Sponsor: None.

9554

Poster Session

Safety and preliminary efficacy of intrathecal (IT) and intravenous (IV) nivolumab (N) for patients (pts) with leptomeningeal disease (LMD). *First Author: Isabella Claudia Glitza, MD Anderson Cancer Center, Houston, TX*

Background: Pts with LMD have a dismal prognosis, with median overall survival (OS) < 3 months, no approved therapies and extremely limited clinical trial options. We previously reported initial safety findings from the dose escalation of an open label, single arm, single center phase I/II trial (NCT03025256) for pts with metastatic melanoma (MM), in which IT/IV N were well tolerated, without any CNS-specific or unexpected toxicity. Here we report an update on safety, maximum tolerated dose (MTD), and dose expansion cohort (including 2 pts with NSCLC) and preliminary efficacy. **Methods:** Pts aged ≥ 18 with evidence of LMD by MRI and/or CSF cytology, ECOG PS ≤ 2 were treated with IT/IV N. Dexamethasone (dexa) ≤ 4 mg/daily and concurrent BRAF/MEK inhibitor(i) therapy (tx) were allowed. For cycle 1, IT N was administered via ommaya reservoir on day (D)1. For subsequent cycles (every 14 days) pts received IT N on D1, followed by IV N 240 mg on D2. IT N doses evaluated were 5, 10, 20, and 50 mg. Blood and CSF were collected at multiple time points for translational research. The primary objectives were to determine safety and/or recommended dose/MTD of IT N given with IV N in pts with LMD and the safety of the MTD in an expansion cohort. OS was a secondary objective. Bayesian mTPI methodology was used to define the MTD. **Results:** 50 pts were treated: 17 in the dose escalation (2 at 5; 3 at 10; 6 at 20; 6 at 50 mg IT N), 8 in the initial expansion of 20mg, and 25 at the MTD 50 mg IT N. 48 pts had a diagnosis of MM, 2 NSCLC. Median age at LMD was 49 (19–74); 27 pts are male. All pts had radiographic evidence of LMD; 26 pts had positive baseline CSF cytology. 46 pts received prior systemic tx including checkpoint inhibitors (n = 42) and targeted tx (n = 34). 39 pts had prior CNS radiation (RT), including whole brain RT (n = 14). 18 pts used concurrent steroid, with a median dose of 2mg (0.9–4) dexa equivalent and 27 pts used concurrent targeted tx with BRAF/MEKi. The median number of IT N doses was 6 (1–92). The combination regimen was well tolerated by all evaluable pts (n = 50), with 9 pts (18%) experiencing grade (gr) 3 AEs and no reported gr 4 or 5 toxicities. Rash (58%), nausea (44%), vomiting (34%), and dizziness (22%) were the most common AEs. Thirty pts (60%) experienced AEs after IT N administration, all gr 1/2 and 1 gr 3 (vasogenic edema). At a median follow-up of 4.6 months (mths) (0, 54.8 mths), median OS was 7.0 mths. OS was 66.6% at 3 mths, 53.1% at 6 mths and 34.8% at 12 mths. **Conclusions:** IT + IV nivo was safe and well-tolerated in MM pts with LMD, with no unexpected toxicities of the 50 mg MTD of IT N. OS rates at 6 and 12 mths are encouraging and support further evaluation of IT immunotherapy for LMD, including in other tumor types. Overall results also demonstrate the feasibility of prospective clinical trials in pts with LMD. Final presentation will also include immunological analysis of longitudinally collected CSF samples collected in the trial. Clinical trial information: NCT03025256. Research Sponsor: BMS; AMRF (Foundation); Dr. Miriam and Sheldon G. Adelson Medical Research Foundation; U.S. National Institutes of Health; BMS.

9558

Poster Session

The impact of emotional distress on pathologic response and survival after neoadjuvant combination immune checkpoint blockade (ICB) in high-risk stage III melanoma. *First Author: Irene L.M. Reijers, Netherlands Cancer Institute, Amsterdam, Netherlands*

Background: Neoadjuvant ICB has been shown to induce high pathologic response rates in high-risk stage III melanoma, outperforming adjuvant ICB with respect to survival benefit. Biomarkers that have been shown to predict ICB efficacy, including the interferon-gamma (IFN- γ) signature and tumor mutational burden (TMB), do not completely explain why some patients (pts) fail to benefit from neoadjuvant ICB. Emerging evidence in preclinical and clinical studies suggests that emotional distress (ED) negatively affects tumor progression and anti-tumor immune responses, mediated by β -adrenergic and glucocorticoid signaling. Here, we investigate the association between ED prior to neoadjuvant ICB and pathologic response and survival in pts with stage III melanoma treated in the PRADO trial. **Methods:** PRADO tested neoadjuvant ipilimumab + nivolumab followed by a response-directed surgical and adjuvant treatment regimen in stage III melanoma pts. The European Organization for Research and Treatment of Cancer (EORTC) scale for emotional functioning was used to identify pts with ED, based on established clinically relevant thresholds. Association between ED and pathologic response or survival was assessed using multivariable logistic or Cox regression analysis. Potential effects of ED on the tumor and its microenvironment were examined in baseline tumor biopsies using RNA sequencing. **Results:** Pts who completed the baseline EORTC questionnaire were included and defined as pts with ED (n = 28) or without ED (n = 60). Baseline characteristics, IFN- γ signature expression and TMB were comparable. Pts with ED showed a trend towards achieving less major pathologic responses (MPR; $\leq 10\%$ viable tumor) compared to pts without ED (46% vs 65%, $p = 0.099$). Multivariable analysis showed a significant association between ED and MPR (OR 0.20, $p = 0.043$) when adjusted for age, sex, IFN- γ signature (OR 9.36, $p = 0.002$) and TMB (OR 13.21, $p = 0.003$). Pts with ED also had a significantly lower relapse-free survival (RFS) compared to pts without ED (2-year RFS 74% vs 91%, $p = 0.011$), and ED at baseline remained associated with relapse in multivariable regression (HR 3.81, $p = 0.034$) when adjusting for IFN- γ signature (OR 0.34, $p = 0.109$) and TMB (OR 1.02, $p = 0.972$). Analyses investigating the relation between ED with β -adrenergic and glucocorticoid signaling and factors representing anti-tumor immune responses are ongoing and will be presented at ASCO. **Conclusions:** Emotional distress was identified as baseline marker associated with impaired clinical outcomes after neoadjuvant combination ICB in pts with high-risk stage III melanoma. This data warrants further investigation in independent cohorts and into the potential effect of pharmacological and psychosocial interventions, e.g. adrenergic receptor blockade, on the anti-tumor immune response and patient outcomes. Clinical trial information: NCT02977052. Research Sponsor: BMS.

9559

Poster Session

A phase 2 study of alrizomadlin (APG-115) in combination with pembrolizumab in patients with unresectable or metastatic cutaneous melanoma that has failed immuno-oncologic (IO) drugs. *First Author: Montaser F. Shaheen, University of Texas Health Science Ctr, San Antonio, TX*

Background: Alrizomadlin is a novel, orally active small-molecule MDM2 inhibitor that activates p53-mediated apoptosis in tumor cells, also functions as a host immunomodulator, and may restore antitumor activity in patients with cancer that has progressed on PD-1/PD-L1 inhibitors. Alrizomadlin is currently being investigated for treatment of patients with unresectable or metastatic cutaneous melanoma that progressed on prior immunotherapy. **Methods:** This multicenter clinical trial was conducted in the United States and Australia in patients with unresectable or metastatic cutaneous melanoma that had progressed on PD-1/PD-L1 immunotherapy. Eligible patients had an ECOG performance status of 0-2. Alrizomadlin 150 mg was administered orally every other day for 2 consecutive weeks, with 1 week off, and pembrolizumab 200 mg intravenously for 30 minutes on Day 1 of a 21-day cycle. **Results:** As of December 12, 2022, preliminary and interim results are reported for 31 patients with cutaneous melanoma, of whom 21 were male and 10 female, with a median (range) age of 65 (27-84) years. Treatment-related adverse events (TRAE) of any grade (> 10%) for either alrizomadlin or pembrolizumab were reported in 30/31 (96.8%) patients. These AEs included nausea (71%), vomiting (38.7%), fatigue (35.5%), thrombocytopenia (32.3%), diarrhea (25.8%), neutropenia (19.4%), decreased appetite (16.1%), and decreased leukocyte count (12.9%). A total of 4/31 (12.9%) patients reported treatment-related serious AEs, including anemia, thrombocytopenia, deep vein thrombosis, joint effusion, pulmonary embolism, and vomiting. In 26 efficacy-evaluable patients, the confirmed overall response rate (ORR; partial response [PR] + complete response [CR]) was 23.1%, including 2 patients reporting CRs and 4 reporting PRs based on RECIST v.1.1. The initial analysis indicated that the ORR observed in patients whose disease had failed IO treatment was primarily due to alrizomadlin combined with pembrolizumab, not the delayed effect of prior immunotherapy. **Conclusions:** Alrizomadlin combined with pembrolizumab is well tolerated and demonstrates clinical efficacy in these patients with highly refractory unresectable or metastatic cutaneous melanoma that had progressed on PD-1/PD-L1 immunotherapy. Internal study identifier: APG-115-US002. Clinical trial information: NCT03611868. Research Sponsor: Ascentage Pharma Group Corp Ltd. (Hong Kong) and Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

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Poster Session

Correlation of DNA methylation signatures with response to immune checkpoint inhibitors in metastatic melanoma. *First Author: Julia Maria Ressler, Department of Dermatology, Medical University of Vienna, Vienna, Austria*

Background: Immune checkpoint inhibitors (ICIs) have revolutionized the treatment of metastatic melanoma with objective response rates of 40-58%. However, reliable biomarkers to predict treatment response are lacking. Tumor tissue methylation profiles were recently proposed to have predictive value in various solid organ tumor entities. **Methods:** Patients with metastatic melanoma, American Joint Committee on Cancer (AJCC; 8th Edition) stage IV, receiving first-line ICI-based therapy, were retrospectively identified and formalin-fixed paraffin-embedded tumor tissue samples (FFPE) prior to ICI therapy were retrieved. We analyzed DNA methylation profiles of > 850,000 CpG sites in tumor specimens by Infinium MethylationEPIC microarrays. DNA methylation profiles were then correlated with radiological response (iRECIST). **Results:** 71 patients with metastatic melanoma (44 (62.0%) male, 27 (38.0%) female) were investigated; median progression free survival (PFS) was 8.5 months (range: 0 – 104.1 months) and median overall survival (OS) was 30.6 months (range: 0 – 104.1 months), respectively. 29 (40.8%) patients achieved an objective response to ICIs. Microarray analyses revealed a methylation signature including mainly hypomethylation, corresponding to the response to ICIs. Based on the 500 mostly differentially methylated genes, a total of 3 clusters were identified with the majority of responders being in cluster 2 (12/12) and 3 (12/22). The predictive performance of the methylation signature was high with 80% sensitivity, 81% specificity, and an AUC of 0.853. **Conclusions:** Our findings suggest that tumor DNA methylation profiling may be useful to predict response to ICIs in patients with metastatic melanoma. Research Sponsor: Christian Doppler Research Association and the Austrian Federal Ministry for Digital and Economic Affairs, the National Foundation for Research, Technology and Development.

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Poster Session

Machine learning (ML)-based quantification of tumor-infiltrating lymphocytes (TIL) and clinical outcomes of patients with melanoma treated with immune-checkpoint inhibitors (ICI). *First Author: Elio Adib, Brigham and Women's Hospital, Boston, MA*

Background: TIL quantification has shown promising prognostic and predictive impact in various tumors treated with ICI. More recently, TIL therapy has become an emerging treatment agent for ICI-refractory melanoma. In this work, we studied the effect of intrinsic TILs on clinical outcomes of patients with melanoma treated with ICI and quantified its utility as a biomarker in combination with tumor mutational burden (TMB). **Methods:** We applied a previously developed ML model to process digital whole-slide images of hematoxylin and eosin slides to quantify TIL density (TIL/mm²) in 182 metastatic melanoma samples treated with ICI at the Dana-Farber Cancer Institute. All samples underwent next-generation targeted-panel sequencing and had available TMB data (mutations/megabase). Overall survival (OS) was calculated from the date of ICI initiation to the date of death. TTF was calculated from the date of ICI initiation to the date of next line treatment or death. Alive patients were censored at the date of last follow-up. Multivariable cox regression was used to estimate adjusted hazard ratios (adj-HR) and p-values (adj-p), with TMB, prior lines of treatment and regimen type (single vs. combination ICI) used as covariates. TMB-high (TMB-H) group was defined as samples with TMB ≥ 10. TIL-high (TIL-H) group was defined as samples with TIL density higher than the median. **Results:** Of 182 patients, 60% (110/182) were male and the median age at ICI start was 65.5 years. 63% (115/182) of patients received single-agent ICI (anti-PD1 or anti-CTLA4). Of 182 tumor specimens assessed for TILs, 47 (25.8%) were obtained from the primary site. There was no difference in TIL density (medians 583 vs. 817 TILs/mm², p=0.57; 709 TIL/mm² for full cohort) or TMB (medians 11.4 vs 12.2 mutations/megabase) between primary and metastatic samples, respectively. Moreover, there was no correlation between TIL density and TMB (pearson's correlation coefficient = 0.92, p=1) across all samples. Compared to patients in the TIL-low (TIL-L) category, patients in TIL-H had significantly longer median TTF (33.9 [15.9-NR] versus 13.0 [7.8-18.6] months, adj-HR: 0.53 (95% CI: 0.36-0.78); adj-P=0.0012), while there was no difference in OS (P=0.57). In fact, patients in the TMB-H/TIL-H group had the longest TTF, followed by TMB-H/TIL-L, TMB-L/TIL-H then TMB-L/TIL-L (table). **Conclusions:** Our results support the potential use of ML-based TIL scoring as a novel and independent biomarker to predict time to failure on ICI. There is ongoing effort to validate our findings in an external dataset. Research Sponsor: None.

Group	Median OS (months)	Median TTF (months)
TMB-H/TIL-H	74.0 [45.7 – NR] months	49.0 [26.6 – NR] months
TMB-H/TIL-L	NR [43.2 – NR] months	23.3 [14.4 – NR] months
TMB-L/TIL-H	50.5 [24.5 – NR] months	15.5 [8.1 – 33.9] months
TMB-L/TIL-L	29.0 [18.1 – NR] months	6.4 [5.0 – 12.9] months

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Poster Session

Association of ultra-sensitive ctDNA assay to identify actionable variants and response to immune checkpoint inhibitor (ICI) therapy in metastatic melanoma. *First Author: Christoffer Gebhardt, Skin Cancer Center, University Medical Center Hamburg-Eppendorf (UKE), Hamburg, Germany*

Background: Detection of molecular residual disease (MRD) via circulating tumor DNA (ctDNA) can identify therapeutic response/resistance months in advance of imaging, and monitoring clinically actionable variant dynamics in ctDNA may be important for guiding treatment. Despite this, adoption has been slow due to the reduced sensitivity and reproducibility of current approaches. Here, we profile melanoma patients receiving ICI over several years using an ultra-sensitive, tumor-informed ctDNA platform, and correlate the findings with clinical outcome. **Methods:** Over 150 plasma samples from 23 advanced melanoma patients (stage IV) were collected during ICI treatment (up to 40 months) and profiled with NeXT Personal, a tumor-informed ctDNA assay that leverages whole-genome sequencing of tumor/normal samples to generate personalized liquid biopsy panels. Each bespoke panel consists of up to 1,800 selected variants which enable sensitive MRD detection, and a fixed set of 2,100 known clinically actionable and resistance loci for detection of variants emerging under therapeutic pressure. MRD signal and variant dynamics were then correlated with RECIST assessments and outcome. **Results:** In this cohort, ctDNA was detected across a broad dynamic range (2.3-100,000 PPM; median limit of detection = 1.97 PPM) with 37% of detections occurring below 100 PPM. Baseline ctDNA was detected in 94% (17/18) of patients, and was significantly correlated with S100B and metastatic burden (Spearman's rho, 0.73 and 0.5; p, 0.0002 and 0.025). The mutation-rate normalized count of melanoma-specific driver genes detected at baseline predicted reduced overall survival (OS) (p = 0.03). 94% (17/18) of ctDNA+ patients displayed dynamic variant allele frequency (VAF) shifts, impacting 149 loci across 37 ICI-related genes including BRAF, CDKN2A, KIT, MAP2K1, and NRAS. Delta ctDNA from baseline to the first on-treatment time point correlated with PFS (log rank p = 0.004). Treatment elicited greater than 3-fold reduction in average PPM, and the magnitude was significantly correlated with progression (p = 0.0005). VAF increases in known ICI-related genes (JAK1, ALK, etc) predicted shortened OS (p = 0.007) and fewer variants in genes conferring sensitivity to (NRAS, BRAF, etc) ICI were detected on-treatment in progressing patients (p = 0.025). **Conclusions:** We tracked both tumor-informed MRD and tumor-agnostic evolution of ICI related variants over the course of treatment using a single liquid biopsy platform. We achieved ultra-sensitive ctDNA detection down to 2.3 PPM and dynamics in ctDNA signals were predictive of clinical outcome. Furthermore, we demonstrated that ctDNA measurements and VAF dynamics of clinically actionable and resistance variants correlated with response as well as resistance to ICI. Research Sponsor: University Medical Center Hamburg-Eppendorf (UKE); Hiege Stiftung - German Skin Cancer Foundation.

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Poster Session

Interim analysis of a phase II study of nivolumab/ipilimumab plus cabozantinib in patients with unresectable advanced melanoma. *First Author: Geoffrey Thomas Gibney, Georgetown - Lombardi Comprehensive Cancer Center, Washington, DC*

Background: Nivolumab/ipilimumab (Nivo/Ipi) is a standard therapy in patients with unresectable stage III/IV melanoma, demonstrating an objective response rate (ORR) of 58% and 12-month progression free survival (PFS) rate of 49% [Wolchok J, NEJM 2017]. c-MET/VEGFR2 inhibition with cabozantinib (Cabo) has modest clinical activity in melanoma and can augment antitumor immunity by increasing CD8+ T cell and macrophage tumor infiltration, decreasing intratumoral regulatory T cell levels, and increasing tumor cell MHC antigen presentation. Nivo/Ipi plus Cabo showed clinical activity and acceptable toxicity profile in GU malignancies [Apolo AB, JCO 2020]. We performed a study of Nivo/Ipi plus Cabo in advanced melanoma patients aimed at improving efficacy. **Methods:** We conducted a multicenter phase II study of induction Nivo 3mg/kg IV and Ipi 1mg/kg IV and Cabo 40mg PO daily every 3 weeks for 4 cycles, followed by Nivo 480mg IV plus Cabo 40mg PO daily every 4 weeks for up to 2 years, until disease progression or unacceptable toxicity/patient withdrawal. Patients with unresectable stage III/IV melanoma and no prior anti-PD-1 or CTLA-4 exposure (unless in adjuvant setting > 6 months since last dose) were included. Uveal melanoma excluded. Primary endpoint was 12-month PFS rate. Secondary endpoints included ORR, overall survival (OS), and adverse events (AEs). Interim analysis was preplanned after first 14 subjects were evaluated in a Simon 2 stage design (goal >8 subjects 12-month progression free). **Results:** As of 1/2023, 14 subjects were enrolled across three cancer centers within the Georgetown-Lombardi Comprehensive Cancer Center Consortium. Median age 66.5 years, all stage IV disease, 10 with cutaneous primary site, 5 with elevated LDH, and 6 with BRAF V600 mutant tumor. Median follow up was 10.6 mos. 12-month PFS rate was 30% (3/10 evaluable subjects); 3 subjects pending PFS evaluation; median PFS 10.3 mos. ORR was 46% (6/13 evaluable subjects) with 2 CR, 4 PR, and 1 SD. Responders had cutaneous (5) or unknown (1) primary sites. 9 patients were alive at last follow up. 12-month OS rate was 67% (6/9 evaluable subjects). Reasons for treatment discontinuation included AEs (4), patient withdrawal (1), and disease progression (6). 3 subjects remain on study drug(s). Treatment related AEs (TRAEs) were observed in 13 subjects; 9 experienced a grade 3-4 TRAE (most frequent were elevated AST/ALT 29% and hypokalemia 14%). Most frequent grade 2 TRAEs were diarrhea (35%) and palmar-plantar-erythrodysesthesia (29%). No treatment related deaths occurred. **Conclusions:** Clinical activity was observed with Nivo/Ipi plus Cabo in advanced melanoma but did not meet the predefined threshold to advance to the second stage of enrollment. TRAE profile was similar to prior reports. Biomarker analyses are planned to identify patient profiles associated with particular benefit from this regimen. Clinical trial information: NCT04091750. Research Sponsor: Exelixis.

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Poster Session

Expression of lymphoid structure-associated cytokine/chemokine gene transcripts in tumor and protein in serum: Outcomes for patients with melanoma. *First Author: Lilit Karapetyan, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL*

Background: Proinflammatory chemokines/cytokines support development and maturation of tertiary lymphoid structures (TLS) within the tumor immune micro-environment (TIME). In the current study, we sought to investigate the prognostic value of TLS-associated chemokine/cytokine (TLS-kine) expression levels in melanoma patients (MEL PTs) by performing serum protein and tissue transcriptomic analyses, and to then correlate these data with PT tumor clinicopathological and TIME characteristics. **Methods:** Levels of TLS-kines in PT sera were quantitated using a custom Luminex Multiplex Assay. The Cancer Genomic Atlas MEL cohort (TCGA-SKCM) and a Moffitt MEL cohort were used for tissue transcriptomic analyses. Associations between target analytes and survival outcomes, clinicopathological variables, and correlations between TLS-kines were statistically analyzed. **Results:** Serum of 95 PTs with MEL were evaluated; 48 (50%) female, median age of 63, IQR 51-70 years. Serum levels of APRIL/TNFSF13 were positively correlated with levels of both CXCL10 and CXCL13. Tumors with brisk/non-brisk tumor-infiltrating lymphocytes (TIL) vs. absence of TIL exhibited significantly higher levels of APRIL/TNFSF13 ($p = 0.01$), CCL19 ($p = 0.01$) and CXCL13 ($p = 0.01$). In multivariate analyses, high levels of serum APRIL/TNFSF13 were associated with improved event-free survival after adjusting for age and stage (HR = 0.64, 95% CI 0.43-0.95; $p = 0.03$). High expression of APRIL/TNFSF13 transcripts was significantly associated with improved OS in TCGA-SKCM ($n = 448$) (HR = 0.69, 95% CI 0.52-0.93; $p = 0.01$) and in Moffitt MEL PTs ($n = 134$) (HR = 0.51, 95% CI: 0.32-0.82; $p = 0.006$). Further incorporation of CXCL10 and CXCL13 transcript levels in a 3-gene index revealed that high APRIL/CXCL10/CXCL13 expression was associated with improved OS in the TCGA SKCM cohort (HR = 0.42, 95% CI 0.19-0.94; $p = 0.035$). High coordinate expression of the TNFSF13/CXCL10/CXCL13 transcripts in MEL was correlated with an increased presence of naïve B cells, plasma B cells, CD8⁺ T cells, and M1 macrophages and decreased levels of M2 macrophages and mast cells as well as a reduced neural network gene signature. **Conclusions:** Serum protein and tumor transcript levels of APRIL/TNFSF13 are associated with improved survival outcomes. PTs exhibiting high coordinate expression of APRIL/CXCL10/CXCL13 transcripts in their tumors displayed superior OS. MEL differentially expressed genes positively associated with high coordinate APRIL/CXCL10/CXCL13 expression were linked to tumor infiltration by a diverse array of proinflammatory immune cell types. Further investigation of TLS-kine expression profiles related to clinical outcomes is warranted. Research Sponsor: Melanoma Center Internal Funding at the University of Pittsburgh Medical Center, NIH P01 CA234212-01A1 (Walter Storkus); Conquer Cancer Foundation of the American Society of Clinical Oncology.

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Poster Session

Analysis of overall survival (OS) and progression-free survival (PFS) in the phase 1b clinical trial of anti-PD-1 ab (toripalimab) plus intrahepatic injection of orienX010 in stage IV melanoma with liver metastases. *First Author: Chuanliang Cui, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Melanoma and Sarcoma, Peking University Cancer Hospital & Institute, Beijing, China*

Background: Advanced melanoma with liver metastasis has a lower response rate and survival even in immunotherapy era which might because of its immunosuppressive tumor microenvironment. CPI combined with TVEC had showed a remarkable in cutaneous melanoma. The initial results of the phase 1b trial, systemic toripalimab (anti-programmed cell death-1 antibody) combined with Intratumoral injection of liver with OrienX010 - a HSV-1-derived oncolytic virotherapy with expression of GM-CSF in liver metastasis patients without extra-hepatic injectable lesions had shown its efficacy. Here we present the PFS and overall survival (OS) outcomes. **Methods:** Eligible pts included those over 18 with injectable liver metastasis confirmed by biopsy with or without extra-hepatic metastasis; the ocular melanoma and brain metastasis were excluded. Pts received intravenous toripalimab Q2W combined with ultrasound guided intratumoral injection of OrienX010 Q2W (8×10^7 pfu/ml, 10ml per injection) until intolerance or disease progression per iRECIST criteria. Liver biopsy would be performed at baseline and first tumor evaluation (8-12 weeks). The primary endpoint was toxicity; secondary endpoints included ORR, disease control rate (DCR), PFS and OS. Clinical trial information: NCT04206358. **Results:** From Jul 2019 to Feb 2023, 30 pts enrolled. 60.0% pts primary from mucosal; 73.3% got extra-hepatic metastasis; median size of injected lesions: 24mm (10-94mm); median number of liver metastasis: 7 (1-10); median number of injection: 10 (3-36). Among these pts, 29 pts could be evaluated for efficacy. The median PFS was 7.0 months (95% CI: 4.7-9.3 months) and the median OS was not reached. The 3-year OS rates 51.5%. The global ORR by investigator was 20.7% (6/29), DCR 48.3% (14/29); the response rate was 31.0% (9/29) for injected lesions, 30.0% (6/20) for non-injected lesions in liver, and 27.8% (5/18) for extra-hepatic metastases. For pts (21.7% (2 PR and 3 SD)) with no melanoma cells residual by immunohistochemistry in biopsies the median PFS was 14.0 months (95% CI: 3.7-24.4 months), and it was much longer than that of other pts which was 4.1 months (95% CI: 1.4-6.8 months). The median OS of the pts with no melanoma cells was 19.7 months (95% CI: 7.5-31.9 months). Most adverse events (AE) were grade 1-2 and manageable. The grade 3-4 treatment-related AE included elevated transaminase (3 [10.0%]), nausea (1 [3.3%]), pulmonary embolism (1 [3.3%]) and vomiting (1 [3.3%]). No treatment-related deaths occurred. **Conclusions:** Systemic toripalimab combined with intrahepatic OrienX010 injection has shown remarkable long PFS, OS and ORR in melanoma pts with liver metastases with manageable toxicity. Clinical trial information: NCT04206358. Research Sponsor: None.

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Poster Session

Exploring the clinical significance of specific immune-related adverse events (irAE) in patients with melanoma undergoing immune checkpoint inhibitor (ICI) therapy. *First Author: Nethanel Asher, Ella Lemelbaum Institute for Immuno Oncology and Melanoma, Sheba Medical Center, Ramat-Gan, Israel*

Background: Several studies have demonstrated that patients who experience irAE as a result of ICI treatment, exhibit significantly improved outcomes compared to patients without toxicity. However, data regarding the impact of specific irAE is currently lacking. **Methods:** This is a real world single-site cohort of advanced melanoma patients who were treated with ICI as first line between 2014 and 2020. This study explores the effects of specific irAE on treatment efficacy. **Results:** Three hundred and ninety-five (395) patients were treated with either monotherapy anti PD-1 (65.4%), combination ICI (24.3%), or anti CTLA-4 (10.3%). Median age was 68 years (12-99y), and 57% were male. The median follow up was 24.5m. Any-grade irAEs were seen in 72% ($n = 299$), and 26% experienced high-grade irAE ($n = 104$). The most frequent irAE were dermatologic ($n = 110$, 27.8%), vitiligo ($n = 48$, 12.1%), rheumatologic ($n = 68$, 17.2%), gastro-intestinal ($n = 66$, 16.7%), and endocrine ($n = 61$, 15.4%). The development of irAE was associated with a significantly longer median PFS (19.3m vs 4.5m; HR 0.46, $p < 0.001$) and median OS (55m vs 16.9m; HR 0.44, $p < 0.001$). Specific irAE that were significantly associated with survival benefit were rheumatologic (HR 0.34 for PFS, $p < 0.001$; HR 0.38 for OS, $p < 0.001$), dermatologic (HR 0.58 for PFS, $p < 0.001$; HR 0.54 for OS, $p = 0.001$), vitiligo (HR 0.30 for PFS, $p < 0.001$; HR 0.29 for OS, $p < 0.001$) and endocrine (HR 0.6 for PFS, $p = 0.01$; HR 0.52 for OS, $p < 0.001$). After adjustment for ECOG performance status, LDH level, type of ICI protocol and M-stage - the rheumatologic, dermatologic and vitiligo irAE remained significant on multivariate analysis for both PFS and OS. **Conclusions:** The development of rheumatologic, vitiligo and other dermatologic irAE during ICI treatment, is correlated with a noteworthy survival advantage. These irAE may reflect a hyper-activated immune response and thus can serve as meaningful clinical biomarkers. Research Sponsor: None.

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Poster Session

Transforming growth factor-b1 and soluble co-inhibitory immune checkpoints as putative drivers of immune suppression in advanced basal cell carcinoma. *First Author: Bernardo Leon Rapoport, Department of Immunology, Faculty of Health Science, University of Pretoria, Pretoria, South Africa*

Background: BCC rarely metastasizes and the mortality rate is low; however, the disease is associated with substantial morbidity. Transforming growth factor-b1 (TGF-b1) is a key player in cell proliferation, differentiation, apoptosis, and immune regulation. TGF-b1 is associated with immunosuppression and resistance to immunotherapeutic drugs. Immune checkpoint proteins (ICMs) maintain self-tolerance and modulate the immune responses of effector cells. The current study compared the levels and possible associations between systemic soluble ICMs (sICMs) and a group of humoral modulators of immune suppressor cells in a cohort of patients with advanced basal cell carcinoma (BCC, n=40) and a group of healthy control subjects (n=20). **Methods:** We measured sICMs and immunosuppressive humoral modulators by using multiplex bead array or ELISA procedures, with plasma as the matrix. The sICMs comprised seven co-inhibitory (CTLA-4, BTLA, LAG-3, PD-1, PDL-1, PDL-2, and TIM-3) and eight co-stimulatory (CD27, CD28, CD40, CD80, CD86, GITR, GITRL, and ICOS) proteins, as well as the two dual-active sICPs, HVEM and TLR2. The seven humoral modulators of immunosuppressor cells included arginase 1, fibroblast activation protein (FAP), RANTES (Regulated upon Activation Normal T Cell Expressed and Presumably Secreted) also known as CCL5, interleukin-10 (IL-10), TGF-b1, and the M2-type macrophage biomarkers, soluble CD163 (sCD163) and sCD206. Ethics approval was granted by The Research Ethics Committee, Faculty of Health Sciences, University of Pretoria (Ethics Committee Approval Numbers 356/2020). **Results:** The plasma levels of six co-inhibitory sICPs, sCTLA-4, sLAG-3, sPD-1, sPDL-1, and sTIM-3 and sPD-L2 were significantly elevated in the cohort of BCC patients ($p < 0.001$ - $p < 0.00001$), while that of sBTLA was significantly decreased ($p < 0.006$). Of the co-stimulatory sICPs, sCD27 was significantly increased ($p < 0.0002$) in the cohort of BCC patients, with the levels of the others essentially comparable with those of the control patients; of the dual active sICPs, sHVEM, sTLR2 was significantly elevated ($p < 0.00001$) and TLR2 comparable with the control group. Although the plasma levels of the seven modulators of immune suppressor function were not significantly different between the BCC and control groups, correlation heat maps revealed selective, strong associations of TGF-b1 with seven co-stimulatory ($z = 0.618468$ - 0.768131) and 4 co-inhibitory ($z = 0.674040$ - 0.808365) sICPs, as well as with sTLR2 ($z = 0.696431$). **Conclusions:** Notwithstanding the association of BCC with selective elevations in the levels of a large group of co-inhibitory sICPs, our novel findings also imply the probable involvement of TGF-b1 in driving immunosuppression in this malignancy, possibly via activation of regulatory T cells. Research Sponsor: Department of Immunology, University of Pretoria.

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Poster Session

Overall survival after the introduction of adjuvant treatment in stage III melanoma: A nationwide registry based study. *First Author: Hildur Helgadóttir, Department of Oncology-Pathology, Stockholm, Sweden*

Background: Adjuvant treatments with PD-1 and BRAF+MEK inhibitors significantly prolong recurrence-free survival in stage III cutaneous melanoma. However, the effect on overall survival is still unclear. After the approval of adjuvant treatments with PD-1 inhibitors and BRAF+MEK inhibitors, based on recurrence-free survival data, these treatments have been widely implemented. However, there are significant side effects and costs of the treatment, and the overall survival effect remains a highly anticipated outcome. **Methods:** Clinical and histopathological parameters were obtained from the Swedish Melanoma Registry that covers nearly all (99%) primary cutaneous melanomas diagnosed. Information on deaths was received from the Cause of Death Registry, a virtually complete register of all deaths in Sweden. Patients diagnosed with stage III melanoma between 2016 and 2020 were included and divided depending on if they were diagnosed before or from July 2018, the timepoint when adjuvant treatment was introduced in Sweden (designated as pre- and post-cohorts). In Sweden, approved treatments are freely available for all residents and there is a high-adherence to national treatment guidelines. Data was retrieved for the age and sex of the patients, the site, histopathological subtype, Breslow thickness and ulceration of the primary melanoma, type of locoregional spread and numbers of affected lymph nodes. Patients were followed until the end of 2021. Melanoma-specific and overall survival were calculated using the Kaplan-Meier method and Cox regression analyses. **Results:** There were 1371 patients diagnosed with stage III melanoma in Sweden in 2016-2020. The median time of follow-up in the pre-cohort was 57 months (range 42-72 months) and in the post-cohort 27 months (range 12-42 months). The 2-year overall survival rates, comparing the 634 patients in the pre-cohort and the 737 in the post-cohort, were 84.3% (95% CI 81.4-87.3) and 86.1% (95% CI 83.4-89.0), respectively, with an adjusted HR 0.91 (95% CI 0.70-1.19, $P = 0.51$). Further, no significant overall or melanoma-specific survival differences were seen when comparing the pre- and the post-cohort in different subgroups depending on the age, sex or tumor characteristics. **Conclusions:** To our knowledge, this study is the first to assess the impact on overall survival from a national introduction of adjuvant treatment in stage III melanoma. In this nationwide, population and registry-based study, no survival benefit was detected in the cohort receiving adjuvant therapy. Considering also the significant side effects and costs, these findings encourage a careful assessment of the current recommendations on adjuvant treatment. To offer close follow-up, and only treat if relapse occurs, should be an option discussed with patients with fully resected stage III melanoma. Research Sponsor: Swedish Cancer Society, Region Stockholm, Radiumhemmet Forskningsfonder.

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Poster Session

De-correlating immune checkpoint inhibitor toxicity and response in melanoma via the microbiome. *First Author: Nyellia Williams, Division of Medical Oncology, Department of Internal Medicine, The Ohio State University, Columbus, OH*

Background: Immune-checkpoint inhibitor (ICI) immunotherapy increases survival in patients with melanoma. Yet only half of the patients respond, and 10-40% of patients experience immune-related adverse events (irAEs). Previous studies have found a correlation between the development of an irAE and treatment response. Modifying the gut microbiome could positively affect response to ICIs and reduce toxicities. We sought to determine if the microbiome at the onset of treatment, during an irAE, and at 12 weeks, can predict the response or toxicity during ICI treatment for metastatic melanoma. **Methods:** Melanoma patients (pts) > 18 yo treated with ICI enrolled in a prospective observational cohort study at The Ohio State University Comprehensive Cancer Center Skin Cancer Clinic. Excluded were patients on corticosteroids at the start of ICI cycle 1, except for adrenal physiologic replacement. Stools were collected at baseline, within 2 days of an adverse event assessed by physician chart review using CTCAE (Common Terminology Criteria for Adverse Events) v5.0, and at 12 weeks. Response (ORR) to ICIs was assessed by Response Evaluation Criteria in Solid Tumors (RECIST v1.1) q12 weeks and progression-free survival recorded. Metagenomic whole-genome shotgun sequencing was performed on an Illumina NovaSeq 6000 and classified using HUMAnN3. The effect of microbe relative abundances on irAEs was modeled by logistic regression with the R package glm. **Results:** Of the 88 patients enrolled, 48 had metastatic disease with 32 assessable for response. ORR at 12 weeks was 28% (1 CR, 8 PR, 17 SD, and 6 PD) and 24 patients showed PFS at 12 months. Grade > 2 irAEs were observed in 11/48 pts. Abundance of *Bacteroides dorei* (False Discovery Rate Corrected p-value = 9.5E-07) and *Blautia species CAG:257* (padj = 0.001) were enriched in responders, *Prevotella Stercora* (padj = 1.1E-07) and a phage with a predicted target of *Salmonella* (padj = 8.3E-09) in non-responders. Responders with an irAE had enrichment of *Bacteroides plebeius* (padj = 4.2E-13) and *Bacteroides coprophilus* (padj = 0.0002) whereas responders without irAE had enrichment of *Eubacterium siraeum* (padj = 7.2E-05). **Conclusions:** Longitudinal and event-driven biospecimen collection in patients treated with ICIs showed several bacteria and viruses but no fungi associated with response, with and without the development of an irAE. The abundance of the two high-taxonomic rank microbe groups is significantly associated with irAEs. The association with the *Bacteroides* Genus is consistent with previous studies and is associated with response to ICIs. A microbiome abundant in *Bacteroides* and lacking *Prevotella* is associated with response to ICI. An abundance of *Bacteroides* could be a biomarker for irAEs, and an abundance of *Eubacterium*, a biomarker for response without irAEs. Future analyses are necessary to assign causal roles for microbe biomarkers with specific irAEs. Clinical trial information: NCT05102773. Research Sponsor: Pelotonia.

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Poster Session

Population-based validation of the melanoma institute australia (MIA) and the memorial sloan-kettering cancer center (MSKCC) predictive tool for sentinel node status in patients with melanoma. *First Author: Rasmus Mikiver, University of Linköping, Linköping, Sweden*

Background: Patients with primary cutaneous melanoma are selected for sentinel lymph node biopsy (SLNB) based upon their risk of a positive SLN being identified. To improve upon stage-based categorization, the Memorial Sloan Kettering Cancer Center (MSKCC) and Melanoma Institute Australia (MIA) developed predictive models. Which model is more clinically useful is currently unclear. **Methods:** Consecutive patients undergoing SLNB from 2007-2021 were identified from the Swedish Melanoma Registry (SweMR), which covers 99% of patients with invasive cutaneous melanoma in Sweden. The predicted probability of SLN positivity was calculated using the MSKCC and limited MIA models (using mitotic rate as absent/present instead of count and excluding the optional variable lymphovascular invasion) for each patient. The operating characteristics of the models were assessed and compared. The "clinical utility" of each model was assessed using decision curve analysis (DCA) and compared with a strategy of performing SLNB on all patients. **Results:** In total 10,089 patients were included; the median Breslow thickness was 1.8 mm, 33.7% were ulcerated, and 1,802 patients had a positive SLN (17.9%). Both the MSKCC and limited MIA models were well calibrated across the full range of predicted probabilities, and had similar external area under curve (AUC), MSKCC 70.8% (95% CI 69.5-72.1%) and MIA 70.3% (95% CI 68.9-71.7%). When new models were constructed to compare the incremental value of the additional parameters of either nomogram over Breslow thickness alone, the AUCs were 70.1%, 71.6% and 72.0% for Breslow alone, MIA parameters and MSKCC parameters, respectively. At a risk threshold of 5%, DCA indicated no added net benefit for either model compared to performing SLNB for all patients. At risk thresholds of 10% or higher, both models added net benefit compared to SLNB for all. The greatest benefit was observed from use of the models in patients with T2 melanomas when a threshold of 10% was used to select patients for SLNB. In that setting, use of the nomograms led to a net reduction in seven avoidable SLNBs per 100 patients for the limited MIA nomogram and eight for the MSKCC nomogram, when compared to a strategy of SLNB for all. **Conclusions:** This study confirms the statistical performance of both the MSKCC and limited MIA models in a large, nationally-representative dataset. However, clinical utility as assessed by DCA demonstrated that using the models only improved selection for SLNB when a risk threshold of at least 10% was employed, and then mainly for T2 melanomas. Either further development of the nomograms, or other strategies, are needed to improve selection at lower risk thresholds. Research Sponsor: Knut and Alice Wallenberg Foundation, Wallenberg Centre for Molecular and Translational Medicine, University of Gothenburg, Sweden.

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Poster Session

Tumor-informed circulating tumor DNA (TI-ctDNA) based molecular residual disease (MRD) detection and relapse risk for patients with stage II-IV melanoma in surgical remission: A single center experience. *First Author: Logan Rhea, Virginia Commonwealth University Health System, Richmond, VA*

Background: Melanoma is associated with significant risk of relapse after surgery. While the odds of relapse increase with advancing stage, long term relapse free survival (RFS) is possible without adjuvant therapy in a significant subset of patients as shown by AJCC v8 staging long term survival data. TI-ctDNA (Signatera™) is a non-invasive biomarker for MRD detection and functions by sequencing the patient's own tumor for the creation of a customized panel of PCR probes based upon a tumor's unique mutational profile. Positive TI-ctDNA testing is significantly associated with relapse after surgical resection in colorectal cancer and may help inform treatment decision-making, allowing for intensification or de-intensification of patient management. This study describes the operating characteristics of TI-ctDNA in monitoring for relapse in patients with resected melanoma. **Methods:** This is a single center retrospective analysis of patients with stage IIb-IV melanoma in surgical remission. Between January 2021 and January 2023, male and female patients presenting in surgical remission were monitored with TI-ctDNA at 6- or 12-week intervals. Surveillance imaging for relapse was performed according to standard of care guidelines appropriate for tumor stage. Patients were treated with immunotherapy, targeted therapy, or melanoma specific anti-tumor vaccine. Duration of RFS from surgery to detectable TI-ctDNA was recorded, along with duration of RFS from surgery to confirmed melanoma relapse. **Results:** 45 eligible patients were included in the analysis. 10 patients had detectable TI-ctDNA during the study period. 7 patients had confirmed relapse, 6 of whom were TI-ctDNA positive and 1 who was TI-ctDNA negative. The total relapse rate in TI-ctDNA positive patients (6/10) was significantly higher than the relapse rate in TI-ctDNA negative patients (1/35) [p = 0.0002]. Time to detection of positive TI-ctDNA was variable and ranged from 0 to 664 days (median 73 days). **Conclusions:** TI-ctDNA testing demonstrated preliminary ability to differentiate melanoma patients at the highest risk of relapse. Prospective evaluation of TI-ctDNA monitoring for determination of patients at high versus low risk of relapse is warranted and may help to inform future clinical trial designs by allowing for patient stratification to low risk (undetectable TI-ctDNA) and high risk (detectable TI-ctDNA) disease states. Research Sponsor: None.

9574

Poster Session

Intralesional therapy, limb infusion/perfusion, and immune checkpoint inhibitors as first-line therapy in surgically unresectable melanoma in-transit metastases. *First Author: Danielle K DePalo, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL*

Background: Surgery remains the gold standard for resectable melanoma in-transit metastases (ITM). Unresectable ITM is a heterogeneous disease with multiple treatment (tx) options including systemic therapies such as immune checkpoint inhibitors (ICI), regional therapies such as isolated limb infusion or perfusion (ILI/P), and intratumoral therapies such as talimogene laherparepvec (IT). Until now, there has been no direct comparison of these first-line tx for unresectable ITM. **Methods:** A retrospective chart review of patients (pts) with ITM treated first-line with IT, ILI/P, or ICI was performed at 11 institutions. Pts with unresectable ITM, synchronous nodal or distant metastatic disease were excluded. **Results:** 560 pts (54% women) were identified, 86 received IT, 353 received ILI/P, and 121 received ICI from 1990-2022. ICI pts were youngest, IT pts were oldest (p<0.001). Limb was the most common site of ITM. There was no difference in largest ITM size, but number of lesions (burden of disease (BOD)) was highest in ILI/P pts and lowest in IT pts (p=0.003). Toxicity (tox) requiring <90 days (p<0.001) or > 90 days (p=0.034) of pharmacologic tx as well as tox requiring hospitalization (p<0.001) was greatest in ICI pts. Lymphedema was more likely in ILI/P pts (p=0.016). Median follow-up was much longer for ILI/P pts at 8.0 yrs compared to 2.5 yrs for IT pts and 3.1 yrs for ICI pts. Overall response rate (ORR) was 82.2% in ILI/P pts, significantly higher than IT (72.1%, p=0.047) or ICI pts (63.6%, p<0.001). Overall survival was similar between modalities (p=0.167); however, ILI/P pts had worse progression-free survival (PFS) (p<0.0001) and melanoma-specific survival (MSS) (p=0.003). On multivariable analysis of MSS by number of ITM present, MSS remained worst if ILI/P was used for low BOD, ≤3 ITM (p=0.005), but no difference was seen between tx modalities for higher BOD, >3 ITM (p=0.211). **Conclusions:** ICI was used more often in younger pts with less BOD, IT in older pts with less BOD, and ILI/P in older pts with high BOD. Short and long-term tox was greater in ICI. ILI/P had the best ORR, but ICI and IT resulted in greater overall MSS. Multidisciplinary consideration of risks and benefits of each modality should guide ITM tx selection. Research Sponsor: None.

Patient and tumor characteristics, toxicity, and outcomes by treatment modality.					
	IT n=86	ILI/P n=353	ICI n=121		p-value
Age (yrs, median)	74	67	64		p<0.001
Number of ITM (mean)	4.2	12.6	7.1		p=0.003
Tox Requiring <90 Days Pharmacologic Tx (%)	18.0	20.4	44.1		p<0.001
Tox Requiring >90 Days Pharmacologic Tx (%)	0.0	12.7	16.9		p=0.034
Tox Requiring Hospitalization (%)	1.4	9.2	22.1		p<0.001
ORR (%)	72.1	82.2	63.6	IT vs. ILI/P p=0.047 ILI/P vs. ICI p<0.001 ICI vs. IT p=0.231	
Median Follow-Up (yrs)	2.5	8.0	3.1		p<0.0001
Median PFS (yrs)	2.1	0.7	1.2		p=0.003
MSS (cumulative incidence, events/total)	13/85	148/347	15/106		

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Poster Session

Discovery and validation of AMBLor as a prognostic biomarker for non-ulcerated cutaneous AJCC stage I/II melanoma. *First Author: Penny Lovat, Newcastle University, Newcastle upon Tyne, United Kingdom*

Background: Cutaneous melanoma incidence continue to increase, with a particular increase in the number of patients diagnosed with thin, < 1mm tumours with reduced probability of recurrence-free survival. The inability of current AJCC staging criteria to identify genuinely low risk subsets of patients with AJCC stage I/II tumours thus emphasises the acute need for credible prognostic biomarkers to stratify patient follow-up based on personalised risk. The combined immunohistochemical (IHC) expression of AMBRA1 and Loricrin (AMBLor) in the epidermis overlying non-ulcerated AJCC stage I melanomas has recently been identified as a prognostic biomarker and valuable pre SLNB test. The aim of the present study was to evaluate the potential for AMBLor as a prognostic biomarker for both AJCC stage I and II non-ulcerated melanoma. **Methods:** Prospective analysis of AMBLor was performed in two independent retrospective cohorts of non-ulcerated AJCC (8th edition) stage I and II cutaneous melanomas derived from the USA and Australia (discovery cohort) and Spain and the UK (Validation cohort) following validated automated immune-histological staining and binary scoring analysis to define at risk vs low risk subgroups. Each cohort was powered to represent rates of 10% or up to 20% metastasis for stage I or stage II disease respectively. **Results:** Data revealed retention of AMBLor in the discovery cohort of 541 melanomas correlated with significantly increased recurrence-free survival (RFS) of 96% compared to 87% for patients with stage I/II melanomas in which AMBLor was lost (P = 0.06; HR 3.6, 95% CI 1.99-6.84, NPV 96%). Subsequent AMBLor analysis in the validation cohort of 303 tumours, further confirmed retention of AMBLor was associated with increased RFS of 98% compared to 81% for patients with stage I/II tumours in which AMBLor was lost (P = 0.01; HR 8.16, 95% CI 3.68-18.07). **Conclusions:** Collectively data from this multi-international study confirm AMBLor as a prognostic biomarker marker able to identify genuinely low risk subsets of AJCC stage I/II melanomas. Inclusion of AMBLor into clinical melanoma management may therefore aid stratification of patient follow up, enable significant savings on healthcare resources and improve patient anxiety. Research Sponsor: NIHR i4i funding, UK; AMLo Biosciences, A Newcastle University Spin out company.

9575

Poster Session

Nature and management of melanoma recurrences following adjuvant anti-PD-1 (PD1) therapy. *First Author: Rachel Woodford, Melanoma Institute Australia, Wollstonecraft, Australia*

Background: Despite improved outcomes with the use of adjuvant PD1 therapy, approximately 50% of patients (pts) develop recurrent disease by 5 years. Data to define best management of recurrences is lacking, including whether retreatment with PD1 has benefit. **Methods:** This was a multicentre, international retrospective study of pts with resected stage II-IV melanoma who commenced adjuvant PD1 therapy before January 2022 and then recurred. Demographics, disease characteristics, treatment, toxicity, recurrence patterns, management and outcomes were collected. **Results:** 711 pts from 17 sites were included. Med age was 60 [range 16-92], 64% (N=451) were male. 641 (91%) pts were stage III (A 7%, B 24%, C 54%, D 3%), 18 (2%) stage II, 51 (7%) stage IV. 80% (N=536) underwent SLNB prior to PD1, of which 44% (N=236) went onto CLND. 635 pts (90%) received PD1, 74 (10%) PD1 + other. Med time to recurrence was 6.2 months (m) (0-68.5); 63% (N=444) recurred ON PD1, while 36% (N=257) recurred OFF. 338 pts (48%) recurred within 6m of starting adjuvant, 166 (23%) between 6-12m, 140 (20%) 12-24m and 59 (8%) after 24m. Initial recurrences were locoregional (LR) alone in 315 (44%), 307 (43%) distant alone, and 78 (11%) both. Patients with LR recurrences alone underwent definitive surgery, or surgery + radiation in 98 (31%) and 42 (13%) respectively. After initial LR management, 164 (52%) had a further local and 129 (41%) distant recurrence. Those with initial distant recurrences were managed with definitive surgery (21, 7%), surgery + radiation (8, 3%) and radiation alone (14, 5%). Further 'second' adjuvant therapy was given in 27% (N=86) of LR and 6% (N=25) of distant recurrences. Definitive systemic therapy at first recurrence was given in 77% (N=296) distant and 23% (N=73) LR recurrences (Table). **Conclusions:** Patients recurring after adjuvant PD1 therapy do so early, and often while on drug. Patients with resected recurrences often receive "second adjuvant" therapy, although whether adjuvant or definitive, outcomes are poor. Novel drug therapies and clinical trials are required for those who recur despite PD1 therapy. Research Sponsor: None.

	RFS2*†	DMFS2*†	PFS2*†	OS*
Second adjuvant (N=119)				
BRAF/MEK1 (N=62)	24.9 (7.8-66.0)	16.2 (5.0-42.3)	15.3 (0.5-42.3)	23.4 (1.3-56.8)
PD1 (N=42)	11.7 (2.9-58.1)	3.7 (1.3-24.3)	9.0 (1.2-44.0)	19.9 (0.7-76.1)
(ON PD1; N=23)	3.2 (0.5-22.8)	18.1 (0.7-76.1)	6.8 (0.7-47.5)	27.0 (0.7-76.1)
(OFF PD1; N=19)	17.5 (2.6-52.5)	17.5 (2.6-72.7)	13.3 (2.9-61.2)	16.6 (5.5-72.7)
Definitive systemic therapy (N=378)	ORR (%)	DOR*	PFS*	OS*
PD1 alone (N=46)	24	6.3 (2.7-14.4)	17.4 (2.3-44.3)	15.2 (1.0-69.7)
(ON PD1, N=18)	17	11.9 (9.8-14.0)	9.4 (1.4-54.8)	21.3 (3.0-54.8)
(OFF PD1, N=28)	32	-	7.9 (2.7-34.0)	11.5 (3.3-51.1)
CTLA4 alone (N=19)	11	-	9.8 (4.9-50.5)	12.7 (2.0-35.7)
CTLA4 + PD1 (N=157)	34	5.6 (0-21.7)	13.5 (1.9-55.3)	14.4 (1.0-69.7)
BRAF/MEK1 (N=105)	65	3.4 (0-29.3)	14.8 (0.6-73.5)	15.6 (1.3-67.4)

*Med (range), m. †From start of second adjuvant, m.

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Poster Session

NEO-CESQ study: Neoadjuvant plus adjuvant treatment with cemiplimab in surgically resectable, high risk stage III/IV (M0) cutaneous squamous cell carcinoma. First Author: Paolo Antonio Ascierto, Melanoma, Cancer Immunotherapy and Development Therapeutics Unit, Istituto Nazionale Tumori IRCCS "Fondazione G. Pascale", Naples, Italy

Background: In the last years, the treatment of locally advanced and/or metastatic cutaneous squamous cell carcinoma (CSCC) has been revolutionized by the introduction of cemiplimab, an anti-PD-1 antibody, which showed a 50% overall response rate and long term benefit (1). Recently, a phase II trial of neoadjuvant cemiplimab in resectable CSCC patients (2), showed a major pathological response (MPR) rate of 63.3%. In the current multicenter, phase II trial we evaluated the efficacy of neoadjuvant plus adjuvant immune checkpoint inhibitor in patients with surgically resectable, high-risk stage III/IV (M0) CSCC. **Methods:** Patients with surgically resectable high-risk stage III/IV (M0) CSCC received cemiplimab at a dosage of 350 mg every 3 weeks for two cycles prior surgery and for one year after surgery. The study primary endpoint was MPR [pathological complete response (pCR) or near pCR (< 10% remaining viable tumour cells in the surgical pathology sample)] per independent central pathology review. Key secondary endpoints included recurrence-free survival (RFS), overall survival (OS), safety and the analysis of predictive biomarkers. **Results:** From May 2021 to October 2022 twenty-three patients were enrolled in 6 centers. pCR was observed in 9 (39%) patients and near pCR in 2 (8%) patients, while pathological partial response (10-50% remaining viable tumour cells) and no pathologic response was observed in 1 patient and 11 patients, respectively. At data lock of 31st January 2023, only one patient was discontinued due to clinical progression. Furthermore, it was observed n = 60 (57%) any adverse events (AE) and n = 29 (30%) treatment-related AE. No any G3/G4 AE were observed. **Conclusions:** Neoadjuvant cemiplimab induced a pathological response in 52% of stage III/IV (M0) CSCC patients with a MPR in 48%. The study is still ongoing to evaluate the impact of combined neoadjuvant and adjuvant immunotherapy on RFS and biomarkers analysis. Clinical trial information: NCT04632433. Research Sponsor: SANOFI.

9577

Poster Session

Association of circulating tumor DNA kinetics with disease recurrence in patients with stage IIIB/C/IV melanoma treated with adjuvant immunotherapy in Checkmate 238. First Author: Mahrukh M. Syeda, New York University School of Medicine, New York, NY

Background: In patients (pts) with resected, stage III/IV melanoma receiving adjuvant immunotherapy, pre-treatment (pre-Tx) and on-treatment (on-Tx) circulating tumor DNA (ctDNA) combined with tumor features were evaluated to predict recurrence risk. **Methods:** We used analytically validated, mutation-specific droplet digital PCR (ddPCR) assays to measure ctDNA in pre- and on-Tx plasma samples from pts with resected stage IIIB/C/IV melanoma enrolled in CheckMate 238 (NCT02388906) receiving either adjuvant Nivolumab (NIVO) or Ipilimumab (IPI). Assay choice was based on detection of one of the 7 melanoma hot-spot mutations in pt tumors: BRAF V600E/K, NRAS Q61R/L/K, or TERT C228T/C250T. We evaluated associations between ctDNA detection, recurrence free survival (RFS), distant metastasis free survival (DMFS), and known immunotherapy tumor biomarkers including PD-L1, IFNg gene signature, CD8, and tumor mutational burden. Associations between ctDNA kinetics and RFS/DMFS were analyzed using Kaplan-Meier and Cox regression models. **Results:** Mutations were identified in 87% of tumors. ctDNA was detected in pre-Tx samples from 94/753 (12.5%) pts. Pre-Tx ctDNA was significantly associated with higher stage of disease, LDH $\geq$ ULN, PD-L1 < 5%, and tumor IFNg-RNA signature expression below the median. Detection of pre-Tx ctDNA was associated with shorter RFS and DMFS in both NIVO and IPI arms compared to undetectable ctDNA (Table). ctDNA detection on-Tx (week (w) 3, 7, 13, 25, 37, 49) was also associated with shorter RFS. Refined subgroup predictions that potentially impact therapy were achieved by incorporating pre- and on-Tx time points. Of those with baseline and w7 ctDNA results, pts in the NIVO arm with undetectable pre-Tx ctDNA (n=308) that became positive at w7 (n=22) had shorter RFS (median RFS 20.68 mos [95% CI, 2.79, NR]) than pts in whom on-Tx ctDNA remained undetectable (n=286) (median RFS, NR [95% CI, 61.1, NR]). Pts with positive pre-Tx ctDNA (n=42) that remained positive at w7 (n=23) had markedly shorter RFS (median RFS, 3.35 mos [95% CI, 2.73, 20.44]) vs pts in whom on-Tx ctDNA became undetectable (n=19) (median RFS, NR [95% CI, 14, NR]). Similar results were observed in the IPI arm. **Conclusions:** Pre- and on-Tx ctDNA measurements are associated with melanoma recurrence risk during adjuvant checkpoint inhibitor therapy. Incorporation of ctDNA with other tumor molecular features may improve prediction of RFS and DMFS in this setting. Clinical trial information: NCT02388906. Research Sponsor: U.S. National Institutes of Health; Bio-Rad; Bristol Myers Squibb.

	Patients, n	Pre-treatment ctDNA status	Median RFS, mos (95% CI)	RFS HR (95% CI)	Median DMFS, mos (95% CI)	DMFS HR (95% CI)
NIVO	49	+	16.7 (4.7, 41.6)	2.09	24.48 (8.54, NR)	2.27
	327	-	NR (61, NR)	(1.43, 3.06)	NR (NR, NR)	(1.51, 3.42)
IPI	45	+	5.91 (2.86, 15.90)	2.17	6.70 (2.92, 22.08)	2.59
	332	-	30.9 (19.8, 54.5)	(1.49, 3.18)	NR (52, NR)	(1.75, 3.84)

CI, confidence interval; HR, hazard ratio; NR, not reached.

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Poster Session

Melanoma disparities in urban vs rural communities in the era of immunotherapy: An NCDB analysis. First Author: Rachel Akers, Rush University Medical Center, Chicago, IL

Background: Several barriers to care exist for melanoma patients including distance to specialty care, transportation, and cost. Additionally, differences in rural and urban melanoma incidence have not been fully investigated. Using a large nationwide database, we aim to investigate the relationship between urban and rural locations in stage of melanoma presentation and access to adjuvant systemic treatment. **Methods:** The National Cancer Database (NCDB) was queried for all adult patients ($\geq$ 18 years old) with diagnosis of cutaneous melanoma from 1/1/2011 – 12/31/2020. For receipt of adjuvant immunotherapy, diagnosis from only 1/1/2017 - 12/31/2020 was analyzed. Demographic, socioeconomic, tumor-related, and treatment-related factors were analyzed using SPSS Statistics, with Chi-square analysis performed for categorical variables and ANOVA performed for continuous. **Results:** Between 2011 and 2020, 558,445 patient cases were identified and included in the analyses. The average age was 63.7 years, and patients predominantly identified as White (97.6%) and non-Hispanic (96.2%). Patients in urban areas were more likely to present with melanoma of the extremities (40.8% vs 36.2%, $p < 0.001$), while patients in rural areas presented with head and neck melanoma (26.2% vs 31.0%, $p < 0.001$). Additionally, patients in urban areas were more likely to have an early-stage melanoma (0, 1, or 2) melanoma (51.4% vs 48.5%, $p < 0.001$). Patients in rural areas traveled an average of 68 miles for care, in contrast to urban patients who traveled an average of 20 miles ($p < 0.001$). There was no significant difference when comparing receipt of immunotherapy for stage 3 or stage 4 patients. **Conclusions:** In rural areas, patients with melanoma tended to present with a higher portion of head and neck melanoma and of later stage. Rural patients also had to travel farther for care. However, these differences did not result in fewer patients in rural areas receiving immunotherapy for appropriate treatment. Further studies are needed to evaluate how these presentation differences influence care outcomes. Research Sponsor: None.

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Poster Session

A pilot study of the neoadjuvant use of vemurafenib plus cobimetinib in patients with BRAF-mutant melanoma with palpable lymph node metastases: Survival results. First Author: Teresa M. Petrella, Sunnybrook Hospital, Toronto, ON, Canada

Background: Melanoma patients with palpable nodal metastases have a very poor prognosis with the majority recurring within the first 2-3 years post-resection with survival ranging from 20-50% at 5 years. We aimed to ascertain if patients with a BRAF V600 mutation that receive vemurafenib and cobimetinib before surgery (neoadjuvantly) have a higher probability of resectability, pathologic complete response (pCR), and a lower risk of local recurrence and a longer disease free survival (DFS), distant metastatic free survival (DMFS) and overall survival (OS). **Methods:** This was a single arm, prospective, multi centre phase II study in patients with histologically confirmed, BRAF V600 mutated Stage IIIB and IIIC melanoma (AJCC 7th Edition) with palpable nodal disease. Patients received vemurafenib 960mg PO BID and cobimetinib 60mg PO OD for 4 months prior to resection followed by 8 months of adjuvant therapy post-surgery. CTscans were performed at baseline and before resection and every 6 months for the first 3 years and yearly in year 4 and 5. Biopsies for correlative studies and diagnosis were performed at baseline prior to starting therapy. The primary outcomes were the proportion of patients achieving resectability, radiologic response as per RECIST and the proportion of patients achieving a pCR. Presented here are the LRFS, DMFS, DFS and OS. **Results:** Twenty-four patients were enrolled and received neoadjuvant vemurafenib and cobimetinib and 21 underwent resection. Following resection and pathological evaluation 12 (57%; 95% CI 34.02-78.18) patients achieved a pCR, 8 (38%; 95% CI 18.11-61.56) had a partial pathologic response and 1 had no pathologic response. Of the 24 patients, 2 patients (8%) developed local recurrence, 6 patients (25%) developed distant metastasis, and 8 patients (33%) had either local or distant recurrences. 7 patients (29%) died due to metastatic disease. At 60 months, LRFS was 89.5% (76.7-100%), DMFS was 75.0% (59.5-94.5%), DFS was 85.7% (72.0-100%), and OS was 63.9% (95% CI 43.5-93.8). Among total 20 evaluable patients, 17 patients had CR/PR and 3 had PD/SD as best response. There was no significant difference between patients with CR/PR or SD/PD (log-rank p-value = 0.0548) with 48 month survival of 82.4% for CR/PR population compared to 33.3% with SD or PD. **Conclusions:** In this small phase II study, neoadjuvant vemurafenib and cobimetinib led to a higher LRFS, DMFS, DFS and OS of all resected patients with bulky nodal disease compared to historical survival rates. Clinical trial information: NCT02036086. Research Sponsor: Roche; institutional funding.

9580

Poster Session

Prognostic significance of immune-related adverse events and immunosuppression in patients with melanoma receiving adjuvant anti-PD-1 therapy. *First Author: Andrew David Knight, University of Pittsburgh Medical Center, Pittsburgh, PA*

Background: Treatment with anti-Programmed Death-1 (PD-1) therapy reduces the risk of recurrence for patients (PT) with resectable Stage IIB-IV melanoma (MEL). This treatment is associated with the development of immune-related adverse events (irAEs), which may necessitate use of immunosuppressive therapy and treatment discontinuation. This project investigates the impact of irAE and immunosuppressive therapy in survival outcomes of PTs with MEL. **Methods:** PTs with stage IIB-IV resectable MEL who received adjuvant or neoadjuvant treatment with anti-PD-1 therapy were enrolled from the University of Pittsburgh Melanoma Center biospecimen repository. The association between irAEs/immunosuppressive therapy and recurrence-free survival (RFS) and overall survival (OS) were evaluated by univariate and multivariate Cox proportional hazards regression models. **Results:** A total of 6059 PT were consented to the repository: stage III = 1,328, stage IIB = 403, and stage IIC = 269 PT. Of these PT, 180 men and 93 women received adjuvant anti-PD-1 therapy. Average age at diagnosis was 61. BRAF mutation present in 94 PTs: V600E = 71 PT, V600K = 11 PT. Documented irAEs occurred in 50.9% of PTs. Cutaneous irAEs were most common (65/139, 46.8%), followed by endocrine (45/139 32.4%), and visceral organ (37/139, 26.6%). Of the 32 visceral organ irAEs, 15 were gastrointestinal, 10 pulmonary, 5 hepatic, and 1 renal. Systemic corticosteroids > 10mg of prednisone equivalent were administered during adjuvant therapy for 24.9% of PT. In the univariate model, development of irAEs was associated with improved OS (HR = 0.38; CI 0.18-0.83, p = 0.015). In a multivariate analysis after adjusting for age and sex, irAE development continued to be associated with improved OS (HR = 0.38; CI 0.17-0.82, p = 0.014). RFS did not differ for patients that developed irAEs (HR = 0.9; CI 0.59-1.4, p = 0.67). Steroid treatment was not associated with a change in OS (HR = 1.04; CI 0.46-2.4, p = 0.93) or RFS (HR = 0.96; CI 0.59-1.56, p = 0.87). **Conclusions:** Half of stage IIB-IV resectable MEL PT receiving adjuvant anti-PD1 therapy developed irAEs, of which 24% required steroid therapy. Development of irAE was associated with improved OS and corticosteroid use for irAE did not mitigate adjuvant therapy outcome benefits. Research Sponsor: None.

9582

Poster Session

Longitudinal circulating tumor DNA monitoring for detection of molecular residual disease in patients with surgically resected stage II/III melanoma. *First Author: Revathi Kollipara, Rush University Medical Center, Chicago, IL*

Background: Over the past decade, advances in immunotherapy (IO) have dramatically improved overall survival (OS) for patients with metastatic melanoma. Immune checkpoint inhibitors and BRAF/MEK inhibitors also became standard of care for surgically resected stage III melanoma, and most recently pembrolizumab was approved for stage IIB/C patients. Although the phase III trials that led to their respective approvals met their primary endpoints for relapse-free survival, no benefit in OS has been observed. Given that a large proportion of early-stage melanoma patients are cured with surgery alone, the decision to proceed with adjuvant therapy should be weighed against the risk of potential life-altering toxicity. There is a high unmet need to develop biomarkers to accurately select patients who are most likely to benefit from adjuvant IO while sparing a group of low risk patients from unnecessary treatment. In this study, we evaluated the prognostic value of personalized, tumor-informed circulating tumor DNA (ctDNA) testing in patients with resectable stage II/III melanoma. **Methods:** In this real-world study, longitudinal plasma samples (n = 159) were analyzed in real-time from 45 stage IIA-IIID cutaneous melanoma patients treated at Rush University between 03/30/2021 and 01/12/2023. A personalized, tumor-informed ctDNA assay (Signatera bespoke, mPCR-NGS assay) was used for detection and quantification of ctDNA in plasma samples. **Results:** Personalized, tumor-informed ctDNA assays were successfully designed for 93% (42/45) of patients using tissue samples from either surgical resection (14/42, 33%) or biopsy (26/42, 67%; 16 shave, 10 excisional, 1 punch, 1 core). ctDNA was detectable at one or more time points in 36% (15/42) of patients. We observed a higher ctDNA-positivity rate in stage III patients (11/20, 55%) compared to stage II patients (4/22, 18%). Twelve of the 15 ctDNA-positive patients received adjuvant IO/treatment escalation after a positive ctDNA result; 6 patients had sustained ctDNA clearance, 2 had transient clearance, and 4 continue to receive adjuvant IO and follow-up ctDNA testing. Radiographic recurrence was observed in 7/42 patients, 6 of whom were ctDNA-positive. Ninety-six percent (26/27) of patients with persistent ctDNA-negativity remain clinically and radiographically progression-free. **Conclusions:** Our data suggest that molecular residual disease detection using a personalized, tumor-informed ctDNA assay is highly prognostic in melanoma patients undergoing curative resection. Sustained clearance of ctDNA was achieved with adjuvant therapy in a subset of this cohort. Prospective studies evaluating the utility of ctDNA to aid clinical decision-making regarding adjuvant treatment intensification or de-escalation are warranted. Research Sponsor: None.

9581

Poster Session

Intralesional oncolytic virotherapy with talimogene laherparepvec in patients with cutaneous lymphomas and non-melanoma skin cancers. *First Author: Egle Ramelyte, Department of Dermatology, University Hospital of Zurich, Zurich, Switzerland*

Background: Cutaneous lymphomas (CL) and non-melanoma skin cancers (NMSC) present with skin lesions and can often be treated with local therapies. However, some do not respond or relapse, underlining the need for new treatment options. Intralesional oncolytic virotherapy with genetically modified Herpes simplex 1 virus called Talimogene laherparepvec (T-VEC) was approved for cutaneous melanoma. Given previous reports on oncolytic virotherapy in non-melanoma tumors, we investigated the effect of intralesional T-VEC in patients with CL and NMSC. **Methods:** Patients with CL and NMSC without extracutaneous spread were eligible (NCT03458117). They were treated according to the standard for up to 8 injections. We assessed clinical response of injected and, whenever possible, non-injected lesions using response criteria for intratumoral therapies (iTRECIST). Safety was assessed using CTCAE v5 criteria. To evaluate T-VEC induced changes, we collected tumor biopsies at baseline, after 2 and 5 injections. We performed multiplex immunohistochemistry for CD3, CD8, CD79a, CD56, CD11c and FoxP3 and evaluated the changes using Akoya Bioscience technology. **Results:** Twenty-seven patients were enrolled into the study: 19pts with cutaneous B-cell lymphoma (CBCL), 5pts with cutaneous T-cell lymphoma, 1pt with cutaneous squamous cell carcinoma and 1pt with Merkel cell carcinoma. The mean age was 61.9yrs. In total, 26pts have received at least one intralesional T-VEC, one patient has withdrawn consent before the first infusion. Patients received median of 7 injections, 11pts (44%) have received 8 planned injections. Therapy was well tolerated with treatment related fever, flu-like symptoms and ulceration of the injected tumor being the most common treatment related adverse events (AE) (34% each). Three patients (12%) had grade 3 AE. Of the injected lesions, 84% demonstrated response, with reduction of the elevation in 84% and reduction of redness of the tumor in 68%. Non-injected response was 40% and overall response was 32%. Tissue samples of 18pts were available for analysis. Following T-VEC injections, responding lesions had an increase of CD8+ and decrease of FoxP3+ cells, while all lesions had an increase of CD56+ cells and slight reduction of CD79a+ cells. Responding CBCL samples had increased CD3+ cells, whereas all samples had an initial reduction of CD79a+ and CD11c+ cells, independent of response. **Conclusions:** Oncolytic virotherapy with intralesional T-VEC induces clinical responses and is tolerated without any unexpected toxicities in patients with locally advanced cutaneous lymphomas and NMSC. T-VEC induces activation of immune response, with differences in responding and non-responding lesions. T-VEC represents a viable treatment option for patients with CL and NMSC, and should be investigated in larger controlled clinical trials. Clinical trial information: NCT03458117. Research Sponsor: Amgen.

9583

Poster Session

Expanded cohort and extended follow-up of neoadjuvant plus adjuvant (neo + adj) dabrafenib (D) and trametinib (T) in patients (pts) with surgically resectable stage (stg) III/IV melanoma. *First Author: Tarin Hennegan, MD Anderson Cancer Center, Houston, TX*

Background: Most melanoma pts are diagnosed with earlier-stage, surgically resectable disease. Although there are approved adjuvant immunotherapy (IT) and targeted therapy (TT) options available, neoadjuvant systemic treatment (NST) has demonstrated improved outcomes based on pathologic complete response (pCR). We previously reported outcomes from a randomized trial comparing neo + adj DT vs upfront surgery followed by adj DT in pts with surgically resectable stage III/IV BRAF mutated melanoma. After enrolling 21 pts, the randomized study was closed by the Data Safety Monitoring Board due to rapid disease progression in pts randomized to upfront surgery. The trial continued as a single-arm study to evaluate neo + adj DT. With a median follow up of 35 mos (range 6-97 mos), we report the updated outcomes for the pts evaluable for the primary endpoint. **Methods:** We conducted a single-center, phase II clinical trial (NCT02231775) evaluating neo + adj DT in pts with surgically resectable, RECIST measurable clinical stg III or oligometastatic stg IV BRAF V600E/K mutated melanoma. Study objectives included determination of pCR and survival outcomes based on INMC path response. Pts received oral D 150mg BID and T 2mg daily for 8 wks prior to surgery and 44 wks of adjuvant DT starting 1wk post-surgery. Imaging was performed prior to surgery to determine the RECIST 1.1 objective response rate (ORR) and then every 12 wks to monitor for recurrence. **Results:** Of the 51 pts who received neo DT, 49 were considered evaluable for the primary endpoint unrelated to progression prior to surgery. Median age was 56 (IQR 45-66). 10 pts received prior adj IT. All but 1 pt underwent surgery on time with delay due to treatment related toxicity. The radiographic ORR was 78%, including 6 (12%) CR. 17 (35%) pts achieved a pCR, 7 (14%) near pCR, 12 (24%) partial path response, and 13 (27%) path non-response. 47 (96%) pts initiated adj treatment; 23 (47%) completed all planned adj treatment, 7 (14%) discontinued adj treatment due to recurrence and 12 (24%) due to toxicity. Median RFS for all pts was 17.6 mos (95% CI: 14.40.1) and was improved for pts with pCR versus non-pCR [median Not Reached (NR) vs 11.3 mos; p = 0.0002]. Median distant metastasis free survival (DMFS) for all pts was 48.9 mos (95% CI: 24.1, NA) and was also improved for pCR pts (median NR vs 17.5 mos; p = 0.0004). Median OS was not reached for all pts and was improved in pCR pts (p = 0.03). No new safety signals were seen. **Conclusions:** Neo + adj DT is feasible and safe in pts with surgically resectable BRAF mutated melanoma. With a median follow-up of 35 mos, median RFS, DMFS, and OS have not been reached for pts with a pCR after neo DT, and are all significantly prolonged compared to non-pCR pts. These results demonstrate durable benefit for neo + adj DT in this high-risk pt population that achieve a pCR. Clinical trial information: NCT02231775. Research Sponsor: Novartis; Melanoma Research Alliance and Rising Tide Foundation.

9584

Poster Session

[¹⁸F]FDG-PET to identify pathological responses upon neoadjuvant immune checkpoint blockade in cutaneous squamous cell carcinoma. *First Author: Sabine Breukers, The Netherlands Cancer Institute (NKI), Amsterdam, Netherlands*

Background: To improve clinical prospects of patients with locally advanced cutaneous SCC (CSCC), we tested the efficacy of neoadjuvant nivolumab with or without ipilimumab prior to standard of care curative surgery ± radiotherapy; the MATISSE trial (NCT04620200). Neoadjuvant immunotherapy-response prediction via FDG-PET imaging was demonstrated feasible in the IMCISION trial (PMID 34937871), where a decrease of ≥12.5% in total-lesion glycolysis (TLG) upon immunotherapy identified deep pathological responders to immunotherapy in head and neck SCC prior to surgery with 95% accuracy. The current research investigates the predictive power of FDG-PET to identify deep pathological responses to neoadjuvant immunotherapy in MATISSE patients. **Methods:** 26 patients with primary CSCC (stage I–IVa) were treated with neoadjuvant nivolumab with (n = 14) or without (n = 12) ipilimumab (weeks 0 and 2). FDG-PET/CT scans were evaluable at baseline and shortly before surgery (week 4) in 20 patients. Images were analysed for SUV_{max}, metabolic tumor volume (MTV), and TLG. Responders to immunotherapy were defined as having a major or partial pathological response to immunotherapy (MPR and PPR, showing ≤ 10% and 11–50% remaining viable cancer cells at time of surgery, respectively). **Results:** Overall, median SUV_{max}, MTV, and TLG decreased upon immunotherapy at the primary tumor site in responders (n = 15), whereas median SUV_{max}, MTV and TLG increased in non-responders (Table). Three patients with stable or increased SUV_{max}, MTV and TLG, also showed a pathological response and were classified as pseudo-progressive. Another patient with a MPR had an increase in SUV_{max}, but a decrease in MTV and TLG. All patients with any decline in SUV_{max}, MTV or TLG at the primary tumor site showed a pathological response (PPV 100%) and none of them developed a relapse at median follow-up 9.0 months. **Conclusions:** Primary tumor response assessment using FDG-PET-based ΔSUV_{max}, ΔMTV and ΔTLG accurately identifies pathological responses early upon neoadjuvant immunotherapy in cutaneous SCC. FDG-PET could, upon validation, select CSCC patients for response-driven treatment adaptation in future trials. FDG-PET-CT upon neoadjuvant immunotherapy in CSCC, changes in PET-parameters and predictive values of any decline in SUV_{max}, MTV or TLG. Clinical trial information: NCT04620200. Research Sponsor: The MATISSE trial is an investigator-initiated phase-2 clinical trial, partly funded by Bristol-Myer-Squibb (BMS) and KIKI-foundation (private).

	Responders n=15	Non-responders n=5	p-value	PPV (%)	NPV (%)	Sens (%)	Spec (%)
ΔSUV _{max} median (range)	-32.5 (-78.9 – +230.8)	+15.2 (+1.0 – +50.3)	0.02 ^a	100	55	73	100
ΔMTV median (range)*	-95.4 (-100.0 – +90.0)	+187.0 (+14.1 – +272.0)	<0.002 ^a	100	57	77	100
ΔTLG median (range)*	-95.8 (-100.0 – +69.6)	+215.7 (+19.9 – +312.8)	<0.002 ^a	100	57	77	100

^a p = p-values calculated with Mann-Whitney U test. PPV = positive predictive value, NPV = negative predictive value, Sens = sensitivity, Spec = specificity. *based on 13 responders and 4 non-responders.

9586

Poster Session

Successful management of Australian patients with locally advanced keratinocyte cancer (KC) and/or extensive skin field cancerization (ESFC), using widefield volumetric arc radiation therapy (VMAT): Report with 24-month follow-up. *First Author: Andrew Potter, GenesisCare, Adelaide, SA, Australia*

Background: Keratinocyte cancer (KC) diagnoses are associated with an elevated risk of developing new skin lesions. Patients with extensive skin field cancerization (ESFC) have large areas (generally ≥50cm²) of actinic keratoses and often, frequent keratinocyte cancers, necessitating repeated interventions. Volumetric modulated arc radiation therapy (VMAT) can precisely target large, complex surfaces with modulated doses, as required, leading to its increasing application to ESFC +/- KC. This is a follow-up 24-month report on the efficacy, safety, cosmetic, and quality of life outcomes of VMAT in the management of patients with ESFC +/- KC at Australian facilities. **Methods:** Two hundred and twenty-four fields for 194 patients with ESFC +/- KC have been prescribed widefield VMAT and prospectively enrolled in the National (Australian) Dermatology Radiation Oncology Registry (NDROR). One hundred and six fields are now beyond 24-months post-treatment. Over 80% of patients had received up to 4 prior non-radiotherapy interventions. Fields included lower and upper limb, face, scalp, or trunk regions. 3-, 6-, 12-, 18-, and 24-month follow-up assessments rated the percentage of field clearance, lesion response, new lesion events, cosmesis using the Lovett's scale, toxicity based on CTCAE, and quality of life as assessed using a EQ-5D-5L visual analogue scale (VAS). **Results:** Median dose delivered to ESFC-only and ESFC + KC fields were 45 Gy (16.2–60 Gy) and 47 Gy (22–60 Gy), respectively, in 25 daily fractions (7–30) across 7 weeks (2–13). At 24-month follow-up of 106 fields, 96% and 94% of ESFC-only and ESFC + KC fields, respectively had clinical success, defined as > 90% field clearance. Cosmesis was graded excellent or good in 98% of fields. The incidence of new KC within the field out to 24-months was 11%. Grade 1–2 radiation dermatitis was induced in all fields during treatment, but resolved by 3-month follow-up. Six percent of fields exhibited grade 3 dermatitis. Twelve percent of patients discontinued treatment due to acute toxicities (Median 88% dose delivered). The most common persistent toxicity at 24-month follow-up was localized grade 1–2 xerosis (51%), alopecia (43%), and/or pruritis (8%). Quality of life was sustainably improved in patients at 24-month follow-up (3.67; p = 0.026). **Conclusions:** Widefield VMAT has a promising profile of clinical efficacy, safety, and cosmesis in patients with ESFC +/- KC for whom other therapies had failed. Treatment was also associated with significant and durable improvements in quality of life. While long-term follow-up of patients continues, these results provide further support for widefield VMAT as a suitable option for patients with increasingly unmanageable presentations of ESFC and locally-advanced KC. Clinical trial information: ACTRN12618000627257. Research Sponsor: GenesisCare.

9585

Poster Session

FDG-PET/CT response and prediction of pathological response to neoadjuvant nivolumab and ipilimumab for clinical stage III melanoma. *First Author: Milton Jose De Barros E Silva, A.C. Camargo Cancer Center, São Paulo, Brazil*

Background: Neoadjuvant immunotherapy with nivolumab 3mg/kg and ipilimumab 1 mg/kg (N3+I1) for two cycles for clinical stage III melanoma have shown rates of major pathological response (MPR) of approximately 60%. The prognosis of this group seems to be excellent so far. On the other hand, patients classified as pathological non-responders have a worse outcome and early identification of this group may allow us to tailor the treatment before surgery. **Methods:** We conducted a multicenter retrospective analysis of patients with clinical stage III melanoma treated with neoadjuvant N3+I1 for two cycles who did baseline and pre-operative 18F-FDG-PET/CT. The total number of FGD avid lesions and the percentual difference between the maximum SUV per lesion was calculated. The pathological results were correlated to FGD-PET/CT findings. **Results:** Between January 2019 and January 2023, 28 patients with clinical stage III melanoma treated with N3+I1 who had baseline and preoperative 18F-FDG PET were identified. Gender: 20 (71%) males, median age (range): 55 (34–78), BRAFV600E/K mut: 15(53%), positive nodes on baseline PET/CT: 1 = 26 (92%), 2 = 1(4%), and 3 = 1(4%). All known lesions identified by CT scan were also captured by FGD-PET/CT. Site of node(s): axilla = 12 (43%), cervical = 10 (36%), and inguinal = 6(21%). All but one patient received 2 cycles of N3+IP1 (1 patient had grade 3 toxicity and received only one cycle). Pathological response: MPR = 19(68%), non-MPR: 8 (28%), and 1(4%) did not undergo surgery due to widespread progression. An increase in maximum SUV and/or appearance of new lesion(s), n = 8(28%), was correlated to non-MPR or metastatic disease in all cases, including a patient who developed sarcoidosis-like reaction with increase of SUV in the index lesion (+68%) and appearance of inflammatory mediastinal lymph-nodes. The median increase was (range): +73% (+11% to 483%). Reduction or stable maximum SUV with no appearance of new lesion, n = 20 (72%), was associated with MPR in 19 patients (95%). One patient, who had G3 colitis with the need of infliximab, had 32% of reduction in maximum SUV but 100% of viable tumor cells on pathological report. The median decrease (range) was -76% (-1.2% to -100%). **Conclusions:** FGD-PET/CT may help to predict pathological response in patients with clinical stage III melanoma who undergo to neoadjuvant nivolumab and ipilimumab. Research Sponsor: None.

9587

Poster Session

Comprehensive genomic profiling (CGP) of clinically advanced and metastatic cutaneous adnexal carcinomas (CAs; MCADCA): A genomic landscape study. *First Author: Maroun Bou Zerdan, SUNY Upstate Medical University, Syracuse, NY*

Background: Cutaneous adnexal tumors are a large group of malignant neoplasms that exhibit morphologic differentiation towards one of the four primary adnexal structures present in normal skin: hair follicles, sebaceous glands, sweat-apocrine glands, and sweat-ecrine glands. **Methods:** 276 cases of MCADCA underwent hybrid capture-based CGP to evaluate all classes of genomic alterations (GA). Microsatellite instability (MSI) status, tumor mutational burden (TMB), genomic loss of heterozygosity (gLOH), genomic ancestry prediction and COSMIC genomic signature were determined from sequencing results. PD-L1 was measured by IHC (TPS; Dako 22C3). Fisher exact method was used for statistical analysis with the false discovery rate corrected using Benjamini-Hochberg adjustment. **Results:** Sequencing was performed on the primary cutaneous tumor in 131 (47.4%) and on a local recurrence or metastatic site biopsy in 145 (52.5%) MCADCA. Male preponderance (64–81%) and age distributions mean (59–63 yrs) were similar in all groups with apocrine (APO) older than eccrine (ECC) (72 vs 62 yrs; p = .001). There were 173 (62.7%) sweat gland (SWG) derived, 55 (19.9%) were sebaceous gland (SEB) derived, 14 (5.1%) were hair follicle (HRF) derived and 34 (12.3%) were unclassified (UNK). 150/173 (86.7%) of SWG were ECC and 23 (13.3%) were APO. The SWG cases included 12 (6.9%) digital papillary ca's (DPA), 11 (6.3%) mucinous ca's (MAC), 19 (11.0%) porocoma's (POR), 14 (8.1%) spiradenoma's (SPR), 10 (5.8%) syringadenoma's (SRNG) and 77 (44.5%) unclassified ca's (UNC). GA/tumor were highest in SEB vs SWG (7.9 vs 4.9; p = .004) and lowest in DPA (2.1 vs 5.0 non-DPA; p = .03). There were no ancestry distribution differences. When compared with the SWG group, the SEB group had higher frequencies of RB1 GA (38.2% vs 8.1%; p < .0001) and TP53 GA (76.4% vs 43.4%; p = .0002) indicating likely neuroendocrine differentiation. The MAC group had significantly higher PTCH1 GA than the non-MAC group (36.4% vs 1.8%; p = .044). MSI-High status was highest in the SEB group vs all other groups (SEB 15.7% vs SWG 1.2%; p = .005). gLOH > 16% was most frequent in SEB when compared with SWG (19.6% vs 7.2%; p = .081). The MMR signature was more frequent in SEB than SWG (32.0% vs 2.1%; p = .005). The mean TMB was high in all MCADCA ranging from 10.4 mut/Mb in HRF to 38.8 mut/Mb in MAC with the exceptions of APO (2.7 mut/Mb; p = .001 and DPA 1.4 mut/Mb; p = .003). PD-L1 expression was not significantly different in all the MCADCA with low positive scores SWG vs SEB (37.0% vs 33.3%; NS). **Conclusions:** As there is limited evidence on the treatment of MCADCA, we provide a repertoire of common GA found. An increased frequency of GA is observed in SEB MCADCA. Clinical trials are needed to evaluate MCADCA-based biomarkers prognostic of ICI response. Only then can we successfully incorporate novel therapeutic strategies in the evolving landscape of treatment. Research Sponsor: None.

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Poster Session

A phase Ib study of endogenous T cell therapy using SLC45A2-specific CD8 T cells for patients with metastatic uveal melanoma. *First Author: Suzanne Phillips, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Overall survival (OS) for patients (pts) with advanced uveal melanoma (UM) is poor compared with outcomes in cutaneous melanoma. Roughly half of all pts with UM will develop distant metastatic disease despite effective treatment of the primary tumor. Antigen-specific endogenous T cells (ETC) can be expanded and infused successfully in pts with many different types of cancer. Our group has identified epitopes of SLC45A2, a melanosomal transport protein, which are highly expressed in UM and are present at low levels in normal melanocytes. *In vitro*, we showed that cytotoxic T cells against SLC45A2 were able to kill HLA-matched UM cell lines. *In vivo*, we hypothesize that infused ETC can traffic to tumor sites. **Methods:** Between 6/2017 and 12/2022, we conducted a single-center, IRB-approved, first-in-human phase Ib dose escalation study of ETC targeting SLC45A2 in pts with metastatic UM (NCT03068624). Eligible pts with metastatic UM who express HLA-A*02:01 or A*24:02 underwent apheresis to collect peripheral T cells which were then selected and expanded (Turnstile 1). For Turnstile 2, conditioning with low-dose cyclophosphamide (300 mg/m²) occurred on Day -2. For pts in the radiation cohort, radiation occurred between Day -7 and Day -1. Infusion of ETC was done via hepatic arterial or central venous catheter on Day 0 followed by low dose subcutaneous interleukin-2 (IL-2) twice daily for 14 days +/- ipilimumab. The study utilized a 3+3 design with a starting dose level of 3.3 x 10⁹ cells/m² of ETC alone. The primary objective was to evaluate the safety and tolerability of infusing ETC targeting SLC45A2. Secondary objectives were to evaluate the *in vivo* persistence and anti-tumor efficacy of this regimen. **Results:** With a median age of 58 years (30-77), 34 pts were enrolled, 16 (47%) men and 18 (53%) women. 33 (97%) pts underwent apheresis and 11 (32%) received infusion of ETC. One dose limiting toxicity (DLT) thought to be unrelated to treatment or underlying cancer (cardiac disorder Grade 5) occurred at the starting dose level with no additional DLTs. The maximum tolerated dose was established as 1 x 10¹⁰ cells/m². The most common treatment-related grade 3 and 4 toxicities were lymphocyte count decrease 9 (82%), hyponatremia 1 (9%), and hypophosphatemia 1 (9%). Per immune-related response criteria (irRC), 4 (36%) pts had stable disease (SD), 6 (55%) had progression of disease (PD), and 1 (9%) was not evaluable for best response. Median overall survival (OS) was 8.9 weeks (wks). OS was 91% at 4 wks, 55% at 8 wks and 46% at 13 wks. Median progression-free survival was 5.9 wks. In the 4 patients with stable disease, the median duration of SD was 5.7 months. **Conclusions:** ETC targeting SLC45A2 is safe and well-tolerated in pts with metastatic UM. Further analyses are underway to evaluate T cell trafficking and persistence. Clinical trial information: NCT03068624. Research Sponsor: U.S. National Institutes of Health; Cancer Prevention and Research Institute of Texas CPRIT: RP170317.

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Poster Session

Survival outcomes associated with liver-directed therapies in patients with metastatic uveal melanoma. *First Author: Michael M Caplan, Columbia University Irving Medical Center, New York, NY*

Background: Metastatic uveal melanoma (mUM) is characterized by a hepatotropic pattern of spread and poor outcomes. Tebentafusp, the only FDA approved therapy, is restricted to patients (pts) with the HLA-A*02:01 genotype. As a result, a variety of liver-directed therapies (LDT) are commonly used for management of hepatic metastases. **Methods:** Pts with mUM with hepatic metastases who underwent LDT, including radiofrequency ablation, microwave ablation, hepatic metastasectomy, Yttrium-90 radio-embolization (SIRT), transarterial chemoembolization (TACE), bland embolization, and immunoembolization (IE), were identified from an institutional database. Data collected included: age, gender, tumor location and size, baseline liver function tests (LFT) and lactate dehydrogenase (LDH), molecular tumor characteristics (where available), type(s) of LDT received, systemic therapies received, and vital status. Time from onset of hepatic metastasis until death (Liver-OS), as well as time from initial diagnosis of primary uveal melanoma until death (Ocular-OS) were calculated. **Results:** A total of 119 pts were identified. The median age at diagnosis was 53.8 years (range 26-83), 47% were female. At the time of LDT initiation, 33% had bilobar disease and 16% had extrahepatic metastasis. 18% pts had elevated LFTs and 55% had elevated LDH. 72% of pts had M1a disease, 24% had M1b and 4% had M1c disease. 45% of pts received more than one form of LDT. SIRT (31%) was the commonly administered initial LDT, followed closely by IE (26%) and TACE (9%). 86% of pts received systemic therapy including 42% who received immune checkpoint blockade overlapping with LDT. Molecular profiling in 26 pts revealed recurrent mutations in BAP1 (n = 18) and SF3B1 (n = 8). The median ocular-OS across all pts was 71.0 months (95% confidence intervals (CI), 62.8-99.4). The median liver-OS across all pts was 31.8 months (95% CI 25.2-35.3). In pts who received TACE, IE, or SIRT exclusively (n = 44), the median Liver-OS was 15.2 months (95% CI 12.8-NA) for TACE (n = 8), 23.3 months (95% CI 15.8-NA) for SIRT (n = 28), and 28.2 months (95% CI 22.6-NA) for IE (n = 8). **Conclusions:** Our results provide additional support for the utilization of LDT in pts with mUM, as demonstrated by improved OS compared to historical survival data. Research Sponsor: None.

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Poster Session

Early ctDNA reduction may identify patients with stable disease and long OS on tebentafusp. *First Author: Dan Feng, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Tebentafusp, a bispecific (gp100 × CD3) ImmTAC showed significant overall survival (OS) benefit (HR 0.51) versus investigator's choice in a Phase (Ph) 3 trial in first line (1L) HLA-A*02:01+ adult patients (pts) with metastatic uveal melanoma (mUM) (Nathan NEJM 2021). In Ph2 and Ph3 trials of tebentafusp, OS was improved regardless of RECIST best response and the degree of early reduction in ctDNA was a better predictor of OS (Cavajal Nat Med 2022; Sullivan AACR 2023). Here we explored whether early on-treatment reduction in ctDNA could distinguish pts with stable disease (SD) and long OS vs those with SD and short OS in a Ph3 trial of tebentafusp in 1L mUM pts. **Methods:** 1L HLA-A*02:01+ pts with mUM received 68 mcg tebentafusp weekly intravenously after intra-patient dose escalation (NCT03070392). Response was assessed by investigators per RECISTv1.1. Sera collected at baseline (BL) and week 9 on tebentafusp were analyzed for ctDNA using targeted mPCR-NGS assay for mutations in 15 genes including GNAQ, GNA11, SF3B1, CYSLTR2, PLCB4 and EIF1AX. Landmark OS from week 9 was analyzed in subsets with ≥0.3 log reductions in mean tumor molecules (MTM) per ml of serum on treatment. Data cutoff 11-Nov-2022. **Results:** 76/245 (36%) tebentafusp-treated pts had best response of SD, with a median OS of 29 months and were evaluable for ctDNA. Baseline tumor burden as assessed by sum of longest lesion diameters and percentage of pts with elevated BL serum LDH were greater in the subset with < 1 year (yr) OS (median 70 mm and 64%, respectively) than in subsets with OS ≥ 1 yr (median 42 mm, 11%) or OS ≥ 2 yrs (median 31 mm, 9%). Almost half (36/76; 47%) of all SD pts had detectable ctDNA mutations in one or more UM genes at baseline. Baseline ctDNA levels were similar across survival groups. By week 9 on-treatment, ctDNA reduction was observed in 34/36 (94%) evaluable SD pts, including 29/36 (81%) with ≥ 0.5 log reduction, 18/36 (50%) with ≥ 2 log reduction and 16/36 (44%) with undetectable ctDNA (clearance). Deeper reductions in ctDNA were associated with better OS (Table). **Conclusions:** In this Ph3 trial, ctDNA reduction by week 9 on tebentafusp was strongly associated with improved OS in pts with best RECIST SD. Early ctDNA reduction may predict SD patients with long OS on tebentafusp. Research Sponsor: Immunocore.

ctDNA subset	N (%)	OS hazard ratio (95% CI)*	≥ 1-year OS %	≥ 2 year OS %
All stable disease with evaluable ctDNA	76 (100%)	NA	73%	51%
ctDNA detected at baseline	36/76 (47%)	NA	78%	48%
ctDNA not detected at baseline	40/76 (53%)	NA	90%	72%
No decrease by week 9	2/36 (6%)	NA	50%	50%
Any (>0 log) decrease by week 9	34/36 (94%)	1.02 (0.14-7.67)	79%	48%
≥0.5 log	29/36 (81%)	0.61 (0.23-1.64)	83%	53%
≥2 log	18/36 (50%)	0.33 (0.14-0.78)	89%	72%
≥3 log (ctDNA clearance)	16/36 (44%)	0.28 (0.12-0.67)	94%	75%

*HRs estimated from Kaplan-Meier analysis for subsets above vs below ctDNA reduction threshold.

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Poster Session

Long-term outcomes of chronic immune-related adverse events from adjuvant anti-PD-1 therapy for high-risk resected melanoma. *First Author: Rachel S Goodman, Vanderbilt University School of Medicine, Nashville, TN*

Background: Adjuvant anti-PD1 improves relapse-free survival in high-risk, resected melanoma, but can lead to irAEs, which become chronic in up to 41% of patients (Patrinely et al, JAMA Onc 2021). Given the expanding use of anti-PD-1 in earlier settings in many tumors, it is imperative to assess their long-term effects. We aimed to determine the incidence, characteristics, and long-term outcomes, including resolution vs persistence, of chronic irAEs from adjuvant anti-PD1. **Methods:** We retrospectively analyzed patients (pts) treated with adjuvant anti-PD1 for resected stage III-IV melanoma from 2015-2022 from 6 institutions; all pts had at least 18 month follow up post-anti-PD1 discontinuation. Demographics, disease characteristics, treatment and recurrence details, and outcomes were collected. Type, grade, duration, treatment, and resolution of acute (onset during treatment) and chronic irAEs (defined as those extending 6+ months after treatment cessation) were characterized. **Results:** Among 318 pts, 226 (64%) developed acute irAEs arising during treatment, including 44 (20%) with grade 3-5 irAEs. Chronic irAEs developed in 147 (46%) pts, of which 74 (50%) were grade 2+, 6 (4%) were grade 3-5, and 100 (68%) were symptomatic. With long-term follow-up (median 35 months), 52 (35%) pts experienced resolution of chronic irAEs while 95 (30% of the full cohort) had persistent chronic irAEs at last follow-up. Among these 95 pts with persistent chronic irAEs, 43 (45%) were grade 2+, 42 (44%) were symptomatic, 24 (16%) were on steroids, and 42 (29%) were on other management. The most common persistent chronic irAEs were hypothyroid (n = 38), arthritis (n = 18), dermatitis (n = 9), and adrenal insufficiency (n = 8). Of 37 pts with chronic irAEs who received additional immunotherapy, 12 (32%) had a flare, 10 (27%) had no effect, and 20 (54%) had a distinct irAE. **Conclusions:** In this large cohort of anti-PD1 treated pts, chronic irAEs were common (46%) and frequently were persistent with long-term follow up (30%, most often hypothyroid and arthritis). Prolonged monitoring and management are needed for these long-term survivors. Research Sponsor: Burroughs Wellcome Fund; Susan and Luke Simons Directorship for Melanoma, the James C. Bradford Melanoma Fund, the Van Stephenson Melanoma Fund; U.S. National Institutes of Health.

N (% of pts with chronic irAEs)			
Any chronic irAE	147		
Resolved	52 (35)		
irAE	N (% of total pts)	Ongoing at last follow up (> 1.5 years) (% of pts with chronic irAE)	
Adrenal insufficiency	8 (3)	8 (100)	
Arthritis	26 (8)	18 (69)	
Dermatitis	21 (7)	9 (43)	
Xerostomia	10 (3)	6 (60)	
Hypophysitis	8 (3)	8 (100)	
Pneumonitis	8 (3)	3 (38)	
Hypothyroid	48 (15)	38 (79)	

TPS9592

Poster Session

ARTISTRY-6: Nemvaleukin alfa monotherapy in patients with advanced mucosal and cutaneous melanoma. *First Author: Jeffrey S. Weber, Laura and Isaac Perlmutter Cancer Center, NYU Langone Health, New York, NY*

Background: Despite improved outcomes in melanoma with the introduction of checkpoint inhibitors (CPIs), ~50% of patients do not respond. A subset of responders ultimately progress and have limited treatment options, underscoring a high unmet need for novel treatments with durable benefit. Patients with mucosal melanoma exhibit response rates and progression-free survival ~2 times lower than those with cutaneous melanoma. Nemvaleukin alfa (nemvaleukin, ALKS 4230) is a novel, engineered cytokine that selectively binds to the intermediate-affinity interleukin-2 receptor complex to preferentially activate CD8⁺ T and natural killer cells, with minimal expansion of regulatory T cells. Nemvaleukin has been granted Orphan Drug designation for the treatment of mucosal melanoma by the US FDA. In the ARTISTRY-1 study, the intravenous (IV) recommended phase 2 dose (RP2D) for nemvaleukin monotherapy (6 µg/kg on days 1-5 of a 21-day cycle) demonstrated durable antitumor activity in patients with advanced melanoma, including mucosal melanoma, previously treated with a CPI (N = 46, overall response rate [ORR] 13.0% [95% CI 4.9-26.3], median duration of response 8.1 weeks [range 6.1-79.0]). In the ARTISTRY-2 study, the subcutaneous (SC) RP2D was identified as 3 mg every 7 days, which demonstrated pharmacodynamic effects consistent with those of IV delivery. Data from these studies support further evaluation of nemvaleukin monotherapy among patients with advanced mucosal or cutaneous melanoma. Additionally, a less frequent IV nemvaleukin dosing schedule is being evaluated in patients with advanced solid tumors in the ARTISTRY-3 study. **Methods:** ARTISTRY-6 (NCT04830124) is an ongoing phase 2, global, multicenter, open-label study that is currently enrolling. Eligible patients will have had prior anti-PD(L)1 therapy with or without anti-CTLA-4 therapy, an Eastern Cooperative Oncology Group performance status of 0 or 1, and adequate hematologic reserve and hepatic and renal function. In Cohort 1, patients with advanced cutaneous melanoma will receive nemvaleukin at the SC RP2D of 3 mg every 7 days. In Cohort 2, patients with advanced mucosal melanoma will receive nemvaleukin at the IV RP2D of 6 µg/kg on days 1-5 of a 21-day cycle. In Cohort 3 (added as a protocol amendment), patients with advanced cutaneous melanoma will receive IV nemvaleukin in 1 of 2 less frequent dosing schedules of 1 or 2 doses per cycle. The dosing schedules for Cohort 3 will be determined when a less frequent IV RP2D has been established in ARTISTRY-3. Patients will receive nemvaleukin until progression or intolerable toxicity. The primary objective is to evaluate the antitumor activity of nemvaleukin monotherapy defined by ORR. Additional objectives include evaluation of safety, health-related quality of life, predictive biomarkers, pharmacokinetics, immunogenicity, and pharmacodynamic effects. Clinical trial information: NCT04830124. Research Sponsor: Alkermes, Inc.

TPS9594

Poster Session

A phase 2/3 trial in progress on tebentafusp as monotherapy and in combination with pembrolizumab in HLA-A*02:01+ patients with previously treated advanced non-veal melanoma (TEBE-AM). *First Author: Diwakar Davar, UPMC Hillman Cancer Center, Pittsburgh, PA*

Background: Tebentafusp is a bispecific (gp100 x CD3) ImmTAC that can redirect T cells to target gp100+ melanoma cells. In a Phase (Ph) 3 trial, tebentafusp demonstrated an overall survival (OS) benefit (HR 0.51) compared to investigator's choice (IC) in first line HLA-A*02:01+ patients with metastatic uveal melanoma (mUM). Gp100, which has limited expression in normal cells, is overexpressed in melanoma, including skin melanoma, supporting the investigation of tebentafusp in non-veal melanoma. In a first-in-human trial, tebentafusp monotherapy demonstrated a promising 1-year OS (~74%) in anti-PD(L)1 naïve HLA-A*02:01+ patients with metastatic cutaneous melanoma (mCM). In a subsequent Ph1 trial, tebentafusp combined with anti-PDL1, with or without anti-CTLA4, demonstrated a 1-year OS of 75% in patients with mCM who progressed on prior anti-PD(L)1 therapy, which compares favorably with recent benchmarks (1-year OS 38%-57%) in similar patient populations.¹⁻³ The promising activity of tebentafusp as monotherapy and in combination with anti-PD(L)1 agents in advanced melanoma (AM) provides the rationale to conduct a Ph2/3 trial of tebentafusp (TEBE-AM; NCT05549297) in patients who have progressed on standard of care therapies. In mUM trials, RECIST response underestimated the OS benefit of tebentafusp, whereas a strong association was shown between OS and early reduction in ctDNA levels relative to baseline.⁴ As an early measure of changes in tumor burden, ctDNA reduction is included as an innovative dual primary endpoint with OS for the Ph2 part of this study. **Methods:** TEBE-AM is a multicenter, open-label, seamless Ph2/3 study in HLA-A*02:01+ patients with non-veal AM who have progressed on prior anti-PD(L)1, received prior ipilimumab, and a prior BRAF/MEK inhibitor regimen if actionable BRAF mutation is present. Patients are randomly assigned (1:1:1) to receive tebentafusp monotherapy, tebentafusp combined with pembrolizumab, or IC. In the IC arm, patients may enroll in clinical trials of investigational agents, receive local standard of care, or receive best supportive care, while being followed for key endpoints. Randomization into the Ph3 portion will commence immediately following completion of accrual into the Ph2 portion. Efficacy from the Ph2 portion may inform changes to the Ph3 design. Primary endpoints are ctDNA reduction relative to baseline and OS in Ph2 and OS in Ph3. Ph2 enrollment opened in Jan 2023 in the US and is expected to open in other countries mid-2023. Clinical trial registration: NCT05549297. 1. Zimmer L, et al. Eur J Cancer 75:47-55, 2017. 2. Silva IPD, et al. J Clin Oncol 38:10005-10005, 2020. 3. Arance AM, et al. J Clin Oncol 39: S9504, 2021. 4. Carvajal RD, et al. Nat Med 28:2364-2373, 2022. Clinical trial information: NCT05549297. Research Sponsor: Immunocore.

TPS9593

Poster Session

Camrelizumab combined with anlotinib and nab-paclitaxel in patients with untreated advanced mucosal melanoma: A single-arm, multicenter, exploratory study. *First Author: Di Wu, Cancer Centre, The First Hospital of Jilin University, Changchun, China*

Background: Anti-programmed cell death-1 (PD-1) monotherapy is a part of the standard treatment for cutaneous melanoma, but its efficacy in mucosal melanoma is not ideal. In vivo studies have demonstrated that co-inhibition of the VEGF receptor (VEGFR) and PD-1 pathways increased T cell infiltration and suppressed tumor growth synergistically. Early phase trial data confirmed that PD-1 inhibitors combined with anti-angiogenic drugs showed efficacy in the treatment of advanced mucosal melanoma, but still did not meet clinical needs. Previous studies have shown that chemotherapy combined with anti-angiogenic drugs has significantly improved median PFS and median OS compared with chemotherapy alone, and has a certain effect as a salvage treatment for progression after PD-1 inhibitor treatment. In addition, previous retrospective analysis showed that PD-1 inhibitors combined with chemotherapy drugs such as nab-paclitaxel were superior to anti-PD-1 monotherapy in the treatment of advanced mucosal melanoma. In summary, the combination of anti-PD-1, anti-angiogenic drugs and chemotherapy may bring new hope for the treatment of advanced mucosal melanoma. **Methods:** This is a single-arm, multicenter, exploratory study to evaluate the efficacy and safety of camrelizumab combined with anlotinib and nab-paclitaxel as first-line therapy in patients with advanced mucosal melanoma. The trial is expected to enrol 66 patients. Key Inclusion Criteria are pts with confirmed recurrence, unresectable or metastatic mucosal melanoma after surgery (stage III/IV) and ECOG performance status of ≤1. Pts with previous adjuvant therapy or neoadjuvant therapy (except PD-1/PDL1 monoclonal antibody and VEGFR TKI) at least 4 weeks before the first administration of the study drug are allowed. Patients received intravenous camrelizumab (200 mg) on day 1, intravenous nab-paclitaxel (260mg/m²) on day 1, and oral anlotinib (8mg) on days 1-14 every 3 weeks. The primary endpoint is objective response rate (ORR). Secondary endpoints include disease control rate (DCR), progression-free survival (PFS), and 2-year overall survival (OS). Clinical trial information: NCT04979585. Research Sponsor: Jiangsu Hengrui Medicine Co., Ltd.

TPS9595

Poster Session

Phase Ib/II study of XmAb23104 (PD1 X ICOS) and XmAb22841 (CTLA-4 X LAG3) combination in metastatic melanoma refractory to prior immune checkpoint inhibitor therapy with and without CNS disease. *First Author: Saya Jacob, UCSF Hem/Onc Fellowship, San Francisco, CA*

Background: Immune checkpoint inhibitors (ICI) have greatly improved outcomes for patients by targeting programmed cell death protein 1 (PD1), cytotoxic T-lymphocyte-associated antigen 4 (CTLA4) and Lymphocyte Activation Gene-3 (LAG-3) to increase immune-mediated anti-tumor response. Despite these advances, ~50% of patients with metastatic melanoma do not respond to standard of care ICI. We strive to address this unmet clinical need through a Phase Ib/II, first-in-human, multi-center trial of two bispecific antibodies targeting four different immune checkpoints: XmAb23104 (PD1 X ICOS) and XmAb22841 (CTLA-4 X LAG3) in patients with melanoma refractory to ICI. This is the first trial of quadruple checkpoint inhibitor therapy. Furthermore, bispecific antibodies may allow simultaneous checkpoint blockade on the same cell and have been shown to heighten T cell activation in pre-clinical models. Two ongoing phase I trials of these bispecific antibodies with PD1 therapy have observed an immune related adverse event (irAE) rate of 20-24% with efficacy analysis ongoing (NCT03752398; NCT03849469). We postulate that treatment with XmAb23104 and XmAb22841 will enhance immune activation, overcome resistance, and improve disease control for patients refractory to traditional ICI. **Methods:** Eligible patients must have advanced/metastatic melanoma and have progressed on prior PD1/PD-L1 inhibitor or PD1/CTLA4 dual inhibition. Cutaneous, acral, mucosal and melanoma of unknown origin are allowed. Patient with CNS metastasis are allowed if these are asymptomatic and stable on MRI imaging obtained within 4 weeks of enrollment. Patients with prior unresolved irAE or irAE ≥ grade 3 are not allowed. XmAb23104 and XmAb22841 will be given on D1 and D15 of a 28-day cycle for 4 cycles, after which XmAb23104 (PD1 X ICOS) will be given alone for a total of 2 years. The phase I portion will be a dose escalation using standard 3+3 design of XmAb22841 (CTLA-4 X LAG3) with three dose levels (0.3 mg/kg, 1 mg/kg and 3 mg/kg). The dose of XmAb23104 (PD1 X ICOS) will remain at 10 mg/kg. These doses were selected based on results of prior early phase trials when these agents were combined with PD1. Once the P2RD of XmAb22841 (CTLA-4 X LAG3) is established, we will move on to dose escalation using a Simon's 2-stage design. This portion will include two arms: Arm A consisting of 17 patients without CNS disease and Arm B consisting of 17 patients with CNS disease (total 34). Primary endpoints include dose limiting toxicities (DLT)/irAE and Objective Response Rate (ORR) at the time of best response by RECIST 1.1. Secondary endpoints include progression-free survival, overall survival, CNS response. At the time of this abstract submission, Cohort 1 of dose escalation has begun with the first few patients still within the DLT observation window. Clinical trial information: NCT05695898. Research Sponsor: Xencor.

TPS9596

Poster Session

Phase II study of niraparib in patients with advanced melanoma with genetic homologous recombination (HR) mutation/alteration. *First Author: Kevin B. Kim, California Pacific Medical Center, San Francisco, CA*

Background: There are a limited number of therapeutic options available for metastatic melanoma patients progressing on the checkpoint inhibitor(s) and BRAF-targeting drugs. PARP inhibitors have been approved in the setting of BRCA1/2 germline mutations, and have demonstrated activity in the setting of HR deficiency in other cancers. Documentation of PARP inhibitors in melanoma would have clear clinical impact. We have previously shown that 21-34% of metastatic melanomas harbor at least 1 molecular aberration in the HR pathway, considered pathogenic, and likely leading to HR deficiency. Previously, we demonstrated dramatic regression of tumors harboring HR mutation(s) with PARP inhibitor treatment in a PDX model. These findings provide a strong rationale to evaluate the clinical efficacy of a PARP inhibitor in patients with advanced melanoma with HR deficiency. **Methods:** This is a single arm, open-label, multi-center phase II trial. The primary objective of the study is: To evaluate the clinical efficacy of niraparib in advanced melanoma patients with HR deficiency. The secondary objectives is to evaluate PFS, OS, and safety profile of niraparib. The key eligibility criteria: Advanced melanoma patients with mutation in any of the following: ARID1A/B, ARID2, ATM, ATR, ATRX, BARD1, BRCA1/2, BAP1, BRIP1, CHEK2, FANCD2, MRN11A, RAD50, RAD51, RAD54B, PALB2 (requires a genetic analysis result performed at any CLIA-certified laboratory) disease progression on PD1-antibody therapy and if BRAF mutant, BRAF/MEK inhibitors ≥ 18 years of age; ECOG PS ≤ 1 ; prior systemic cytotoxic therapy ≤ 1 regimen; no limit on number of prior immunotherapy or targeted therapy regimens. No symptomatic brain metastasis; active brain lesions ≥ 6 mm size, or requiring steroid treatment. Patients will be treated with oral niraparib once daily (28-day cycle); the dose will be 300 mg (if weight ≥ 77 kg and platelet counts of $\geq 150,000$ μ L); otherwise 200 mg RECIST 1.1 will be used to evaluate clinical response every 8 weeks. Adverse events will be recorded according to CTCAE version 4.03. The primary study endpoint is overall response rate. Simon's optimal 2-stage design is proposed. With significance level of 5% and 80% power, our null hypothesis that the true response rate is 0.10 will be tested against a one-sided alternative: $H_0: p \leq 10\%$, a response rate of no real interest VS $H_1: p \geq 30\%$, a response rate that would be of considerable interest. 10 patients will be analyzed for a response evaluation in the first stage of the study, and 19 in the second stage, for a total of 29 patients. If the response rate is 10% (1/10) or less at the end of the first stage, further accrual will be terminated. With 2 or more responses in the first stage, accrual will continue to a total of 29 patients for this cohort. The null hypothesis will be rejected if ≥ 6 responses are observed in a cohort of 29 subjects. Clinical trial information: NCT03925350. Research Sponsor: Glaxo Smith Kline.

TPS9598

Poster Session

A phase 3 trial comparing fianlimab (anti-LAG-3) plus cemiplimab (anti-PD-1) to pembrolizumab in patients with completely resected high-risk melanoma. *First Author: Timothy J. Panella, University of Tennessee Medical Center at Knoxville, Knoxville, TN*

Background: Melanoma (Mel) accounts for the majority of skin cancer-related deaths. Most patients (pts) with a newly diagnosed Mel have resectable disease and are potentially cured by surgery. However, regional nodal and/or distant relapses can occur after curative-intent resection. Postoperative adjuvant therapy with immune checkpoint inhibitors improves relapse-free survival (RFS) and distant metastasis-free survival (DMFS) of pts at high risk of Mel. Fianlimab (anti-LAG-3) and cemiplimab (anti-PD-1) are both high-affinity, fully human, IgG4 monoclonal antibodies (MAbs) that combined have shown high clinical activity in pts with advanced Mel in a phase 1 study. Additionally, combination of relatlimab (anti-LAG-3) and nivolumab (anti-PD-1) have shown superiority over nivolumab for PFS in advanced Mel. These observations provide a rationale for use of fianlimab and cemiplimab combination in high-risk adjuvant Mel. **Methods:** Our study (NCT05608291) is a three-way, double-blind, phase 3 trial to compare fianlimab + cemiplimab to pembrolizumab in the adjuvant therapy (Rx) of high-risk, resected Mel. The primary objective is RFS, and the secondary objectives are overall survival, safety, pharmacology, and immunogenicity. This international trial will be conducted at 200 sites. Pt eligibilities: (1) ≥ 12 years of age; (2) Stage IIc, III or IV (all M-stages) and histologically confirmed Mel, completely resected ≤ 12 weeks prior to randomization; (3) no prior systemic anti-cancer Rx or radiation Rx for Mel in the previous 5 years; (4) no evidence of metastatic disease on staging investigations; and (5) an Eastern Cooperative Oncology Group performance status (PS) of 0 or 1 (for adult pts), Karnofsky PS > 70 (pts > 16 years) or Lansky PS > 70 (pts < 16 years). Study arms (all Rx every 3 weeks intravenously for one year): A. fianlimab (1600 mg) + cemiplimab (350 mg); B. fianlimab (400 mg) + cemiplimab (350 mg); C. pembrolizumab (200 mg) + saline/dextrose placebo. The placebo controlled trial will enroll about 1530 pts, randomized 1:1:1 to Arms A:B:C, treated for up to 1 year. The trial will stratify by disease stage (stage IIIA vs IIC-IIIB-IIIC vs IIID-IV [M1a/b] vs IV [M1c/d]), and geography (North America vs Europe vs Rest of World). The primary endpoint is investigator-assessed RFS. The secondary endpoints include efficacy (overall survival, DMFS, melanoma-specific survival), safety [treatment-emergent adverse events (TEAEs), interruption or discontinuation of drugs due to TEAEs], pharmacokinetic (concentrations of fianlimab and cemiplimab in serum over time), immunogenicity (anti-drug Abs and neutralizing Abs in serum against fianlimab or cemiplimab), and patient reported outcomes. The first analysis will be performed when 242 RFS events have been observed. Clinical trial information: NCT05608291. Research Sponsor: Regeneron Pharmaceuticals, Inc.

TPS9597

Poster Session

Phase 1 study of SGN-BB228, an investigational CD228 x 4-1BB costimulatory antibody anticalin bispecific, in patients with advanced melanoma and other solid tumors (SGNBB228-001). *First Author: Jason Timothy Henry, Sarah Cannon Research Institute at HealthONE, Denver, CO*

Background: SGN-BB228 is an investigational costimulatory Antibody Anticalin bispecific (Mabcalin) molecule directed to CD228 and 4-1BB. CD228 is a tumor-associated antigen selectively expressed by multiple tumor types including melanoma, mesothelioma, pancreatic, colorectal, and lung cancers with minimal expression in normal tissue. 4-1BB is an inducible costimulatory receptor expressed on activated T cells and other immune cell populations. The clinical development of 4-1BB agonist antibodies has been hampered by limited efficacy and/or poor tolerability at active doses (Segal et al 2017, Segal et al 2018). SGN-BB228 is designed to deliver a potent costimulatory bridge between tumor-specific T cells and tumor cells, potentially localizing antitumor activity to the tumor microenvironment and expanding the therapeutic window for 4-1BB agonism. In vitro, SGN-BB228 shows potent CD228-conditional 4-1BB stimulation and cytotoxic T cell activation (Updegraff et al 2022) providing rationale for evaluating SGN-BB228 in patients (pts) with melanoma or other solid tumors. **Methods:** SGNBB228-001 (NCT05571839) is a phase 1, open label, multicenter study designed to evaluate the safety, tolerability, PK, and antitumor activity of SGN-BB228 in adults ≥ 18 years of age with advanced melanoma or other solid tumors. The study includes dose escalation (Part A), dose and schedule optimization (Part B; optional), and dose expansion in disease-specific cohorts (Part C). Parts A and B will enroll pts with histologically or cytologically confirmed metastatic or unresectable cutaneous melanoma, and Part C will enroll pts with cutaneous melanoma, mesothelioma, pancreatic, colorectal, or non-small cell lung cancer. Pts must have disease that is relapsed, refractory, or intolerant to standard of care therapies, ECOG PS 0-1, and adequate organ function. Pts with known active CNS metastases or prior use of agents targeting CD228 or 4-1BB are excluded. Pts with cutaneous melanoma must have received anti PD(L)-1 agent as monotherapy or in combination. Pts with a targetable BRAF mutation must have received, been intolerant to, or declined treatment with BRAF/MEK targeted therapy prior to study entry. Primary endpoints include rate of adverse events, laboratory abnormalities, dose-limiting toxicities, and cumulative dose-level safety. Secondary endpoints are PK, ORR, DOR, PFS, OS, and incidence of antidrug antibodies. Safety and antitumor activity endpoints will be assessed by dose, schedule, and tumor type using descriptive statistics. The ORR and its 95% CI will be estimated. DOR, PFS, and OS will be estimated using Kaplan-Meier method. Enrollment is ongoing in the US and planned in Europe. Clinical trial information: NCT05571839. Research Sponsor: Seagen Inc.

TPS9599

Poster Session

OMNIA-1: A phase I/II study, an IL-2R- $\beta\gamma$ targeted antibody-IL-2 fusion protein, as monotherapy or in combination with anti-PD-1 or anti-CTLA-4 antibodies, in patients with advanced melanoma. *First Author: Paolo Antonio Ascierto, Istituto Nazionale Tumori IRCCS "Fondazione G. Pascale", Naples, Italy*

Background: ANV419 is a potent and selective IL-2R $\beta\gamma$ targeted antibody IL-2 fusion protein, designed to enable the delivery of high dose interleukin-2 (IL-2) to patients in order to stimulate anti-tumour response and minimise toxicities. Recombinant IL-2 (proleukin) induces durable responses in approximately 10% of patients with melanoma. Signalling through IL-2R α expressing cells is believed to limit its therapeutic potential in cancer. By eliminating binding to IL-2R α , ANV419 could lead to increased anti-tumor effect while increasing tolerability. The ANV419-001 first-in-human study (NCT 04855929) demonstrated that ANV419 preferentially stimulates cytotoxic CD8+ T and natural killer (NK) cells over immunosuppressive regulatory T cells, with a significantly longer half-life than that of conventional IL-2. The safety and tolerability data from this study confirmed that ANV419 delivers high molar equivalents of IL-2 in a tolerable and convenient way. **Methods:** ANV419 is being evaluated in a global multicentre, open-label, randomized Phase I/II study in patients with unresectable or metastatic cutaneous melanoma to assess the safety and efficacy of intravenous ANV419 as monotherapy and in combination with anti-PD1 or anti-CTLA-4 antibodies. The OMNIA-1 study leads in with a monotherapy dose expansion part, followed by a combination dose-finding with either anti-PD-1 or anti-CTLA-4 and a combination dose expansion part. ANV419 is administered intravenously every 2 weeks as monotherapy and every 3 weeks when given in combination. Patients with advanced cutaneous melanoma, no active brain metastases and whose disease has progressed on or following at least 1 line of standard of care immunotherapy are eligible. In Part 1, a total of 30 patients will be randomised and evaluated for response to Q2W ANV419 monotherapy (108 μ g/kg or 243 μ g/kg). In Part 2, escalating doses of Q3W ANV419 are evaluated to define the maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D) in combination with pembrolizumab (200 mg) or ipilimumab (3 mg/kg). In Part 3, the efficacy and safety of ANV419 in combination with the approved doses pembrolizumab or ipilimumab will be evaluated using a Simon's 2-stage design. Up to 130 patients are planned to be enrolled. Patients will be stratified according to BRAF mutation status. AEs are assessed according to CTCAE V5.0. Tumour response is determined using RECIST 1.1 criteria. The study is conducted at sites in the US, France, Spain, Germany, Italy, and UK. The first patient was dosed in December 2022. Preliminary monotherapy efficacy data are expected by Q1/2024. Clinical trial information: NCT05578872. Research Sponsor: Anaveon.

TPS9600

Poster Session

NOTOS: A pivotal study of navtemadlin, a first-in-class mouse double minute 2 inhibitor (MDM2i), in patients (pts) with *TP53* wild-type (*TP53*^{WT}) Merkel cell carcinoma (MCC) for whom anti PD-1/L1 therapy has failed. *First Author: Michael K.K. Wong, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: There are no approved therapies for pts with MCC for whom an anti PD-1/L1 agent has failed. The high rate of non-responsive disease after anti PD-1/L1 therapy together with high mortality rate and the absence of a standard of care in this setting highlight the urgent unmet need for effective novel therapies. Approximately 80% of MCC tumors carry the oncogenic Merkel cell polyoma virus (MCPyV) and most cases are *TP53*^{WT}. Oncoproteins from MCPyV inhibit p53 tumor suppressor functions by activating MDM2. Navtemadlin, a potent, selective, orally available MDM2i, overcomes MDM2 dysregulation by restoring p53 activity and inducing apoptosis of *TP53*^{WT} MCC tumors. Navtemadlin is the first targeted therapy to show single-agent activity in pts with metastatic MCC for whom anti-PD-1/L1 has failed (Wong ASCO 2022). In the dose finding study, evaluable pts (n=8) receiving the recommended phase 2 dose of navtemadlin (180 mg QD on Day 1-5/28-day cycle) demonstrated a 25% confirmed objective response rate (ORR), 38% unconfirmed + confirmed ORR, and 63% disease control rate. The median duration of response was not reached (range, 6-16.2+ months [mos]) and median time to treatment response was 4.1 mos (range, 1.2-7). Responses to navtemadlin were highest in those pts with no prior chemotherapy (chemo; Wong ASCO oral 2022). In pts receiving navtemadlin at doses of ≥ 180 mg, an ORR of 40% was reported with no prior chemo (n=15) versus 14% in those who received prior chemo (n=14, Wong ASCO oral 2022). Navtemadlin demonstrated an acceptable safety profile with the most common treatment emergent adverse events (TEAEs) cytopenias, nausea, vomiting, diarrhea, and fatigue. Grade 3/4 TEAEs were 32% anemia, 32% lymphopenia, and 19% thrombocytopenia (Wong 2022). Based on this encouraging data, the NOTOS study (navtemadlin induces p53-driven apoptosis in Merkel cell carcinoma) will evaluate the safety and efficacy of navtemadlin in two post PD-1/L1 treated cohorts: chemo-naïve pts and chemo treated pts. **Methods:** Adults with MCC for whom anti PD-1/L1 therapy has failed, who have ≥ 1 measurable lesion per RECIST v1.1, ECOG PS 0-1 and *TP53*^{WT} MCC by central testing will receive 180 mg QD on days 1-5 of a 28-day cycle until disease progression, unacceptable toxicity, death or withdrawal of consent. The primary endpoint is ORR per RECIST v1.1 by blinded independent review. Secondary endpoints include ORR per investigator, duration of response, progression-free survival, overall survival, clinical benefit rate (including stable disease for ≥ 10 wk, partial response or complete response), and safety. The NOTOS trial is currently enrolling (NCT03787602). Clinical trial information: NCT03787602. Research Sponsor: Kartos Therapeutics.

TPS9602

Poster Session

A phase 3 trial of fiantlimab (anti-LAG-3) plus cemiplimab (anti-PD-1) versus pembrolizumab in patients with previously untreated unresectable locally advanced or metastatic melanoma. *First Author: Ana Baramidze, Todua Clinic, Tbilisi, Georgia*

Background: Fiantlimab (anti-lymphocyte activation gene 3 [LAG-3]) and cemiplimab (anti- programmed cell death-1 [PD-1]) are both high-affinity, fully human, IgG4 monoclonal antibodies (Abs). Concurrent blockade of anti-LAG-3 and anti-PD-1 has shown enhanced efficacy (increase in progression free survival [PFS]) in advanced melanoma (Mel). We previously presented data from a phase 1 study showing a 63.8% objective response rate (ORR) across two separate cohorts of advanced PD-(L)1 naïve metastatic Mel patients (pts) treated with fiantlimab plus cemiplimab with an acceptable risk-benefit profile. **Methods:** This is a randomized, double-blind, phase 3 study to evaluate fiantlimab plus cemiplimab compared to pembrolizumab in pts with previously untreated unresectable locally advanced or metastatic Mel (NCT05352672). This study will be conducted globally, at approximately 200 sites. Key inclusion criteria are: (1) ≥ 12 years of age; (2) histologically confirmed unresectable Stage III and Stage IV (metastatic) Mel (3) no prior systemic therapy for advanced unresectable disease, prior (neo) adjuvant therapies are allowed with treatment/disease-free interval of 6 months; (4) measurable disease per Response Evaluation Criteria in Solid Tumors version 1.1; (5) valid LAG-3 results; (6) Eastern Cooperative Oncology Group performance status (PS) of 0 or 1 (for adult pts), Karnofsky PS ≥ 70 (pts ≥ 16 years) or Lansky PS ≥ 70 (pts < 16 years); and (7) anticipated life expectancy of at least 3 months. There are 4 arms to the study: (1) Arm A: fiantlimab (1600 mg) + cemiplimab (350 mg) every 3 weeks (Q3W), intravenously (IV); (2) Arm A1: fiantlimab (400 mg) + cemiplimab (350 mg) Q3W, IV; (3) Arm B: pembrolizumab (200 mg Q3W, IV) + saline/dextrose placebo (placebo); (4) Arm C: cemiplimab (350 mg Q3W, IV) + placebo. The trial is expected to enroll approximately 1590 pts. The primary endpoint is progression-free survival. The key secondary endpoints are overall survival and objective response rate. The additional secondary endpoints include disease control rate, duration of response, safety, pharmacokinetics of cemiplimab and fiantlimab, and immunogenicity (incidence and titer of anti-drug Abs and neutralizing Abs). The study is currently open for enrollment. Clinical trial information: NCT05352672. Research Sponsor: Regeneron Pharmaceuticals, Inc.

TPS9601

Poster Session

Phase III study of adjuvant encorafenib plus binimetinib versus placebo in fully resected stage IIB/C BRAFV600-mutated melanoma: COLUMBUS-AD study design. *First Author: Alexander Christopher Jonathan Van Akkooi, Melanoma Institute Australia, Wollstonecraft, Australia*

Background: Significant progress has been made in the treatment of advanced BRAFV600-mutant melanoma. Encorafenib in combination with binimetinib is a well-tolerated and effective treatment option, providing sustained progression-free and overall survival benefit in unresectable or metastatic setting. The focus has shifted to early-stage disease in order to prevent recurrence. 18% of stage IIB and 25% stage IIC patients die due to melanoma within 10 years from the diagnosis [Gershenwald and al 2017], indicating an unmet medical need. Currently only immunotherapy has been approved in first countries across the world in this setting. There is a need for more treatment options for BRAF-mutated stage II disease. We report here the rationale and design of COLUMBUS-AD (NCT05270044). **Methods:** COLUMBUS-AD study is an international randomized, placebo-controlled, triple-blind, multicenter Phase III trial evaluating adjuvant encorafenib + binimetinib against placebo in patients with fully resected stage IIB/C BRAF V600-mutant melanoma. Approximately 815 patients will be enrolled. More than 170 sites in up to 26 countries worldwide will participate in the study conducted in collaboration with the European Organisation for Research and Treatment of Cancer (EORTC). Patients will receive encorafenib + binimetinib or placebo for 12 months, or until disease recurrence and will be followed monthly during treatment period, then every 3 months up to year 3, and then at regular intervals. The participants will be followed for a total of 10 years. Patients included in the study must have undergone resection of a stage IIB/C cutaneous melanoma with a BRAFV600E/K mutation, confirmed on resected tumor sample by a central laboratory, and a negative result on sentinel node biopsy. Patients must have recovered from surgery, have an ECOG 0/1, and adequate hematologic, hepatic, cardiac, coagulation and renal functions. Eligible patients will be randomized 1:1 to receive either encorafenib 450 mg once daily plus binimetinib 45 mg twice daily or matching placebos. The primary objective of the study is to evaluate the efficacy of the combination of encorafenib+ binimetinib for prolonging recurrence-free survival (RFS). The secondary objectives are to compare distant metastasis-free survival (DMFS), overall survival (OS), health-related quality of life (QoL), and safety and tolerability between the two arms and to provide additional pharmacokinetic data. **Conclusion:** COLUMBUS-AD is the first phase 3 randomised trial to evaluate adjuvant BRAFi/MEKi in stage IIB/C melanoma. This study will evaluate whether the combination of encorafenib and binimetinib can decrease the risk for recurrence and improve distant metastasis-free survival and overall survival versus placebo in completely resected IIB/C BRAFV600E/K-mutant cutaneous melanoma. Clinical trial information: NCT05270044. Research Sponsor: Pierre Fabre Medicament.

TPS9603

Poster Session

A randomized phase 2 trial of encorafenib + binimetinib + nivolumab vs ipilimumab + nivolumab in BRAFV600-mutant melanoma brain metastases: SWOG S2000. *First Author: Zeynep Eroglu, Moffitt Cancer Center and Research Institute, Tampa, FL*

Background: While anti-PD-1 and anti-CTLA4 immunotherapies are widely used in the treatment of metastatic melanoma, including melanoma brain metastases (MBM), their efficacy in patients with symptomatic MBM is very limited. In the Checkmate-204 trial of ipilimumab with nivolumab in MBM, the 6-month progression free survival (PFS) rate was 19% with a median PFS of only 1.2 months in symptomatic participants (those with neurological symptoms including steroids up to 4 mg/day of dexamethasone, n=18). (Tawbi, Lancet et al., 2021) In the COMBI-MB study of BRAF/MEK-inhibitors in BRAF-V600 mutant MBM, median PFS was 5.5 months in those with symptomatic metastases (n=17). (Davies et al., Lancet Oncol, 2017) The combination of anti-PD-1/PD-L1 therapy with BRAF/MEK inhibitors has been tested in various trials. The single-arm phase 2 TRICOTEL study explored the triplet regimen of vemurafenib + cobimetinib + atezolizumab in MBM; in the symptomatic brain met cohort, 6-month PFS was 57% (n=24). (Dummer et al., Lancet Oncol 2022). **Methods:** SWOG S2000 is a randomized phase 2 trial exploring the efficacy of a triplet regimen of BRAF/MEK inhibitors with PD-1 therapy (encorafenib 450 mg qday + binimetinib 30 mg BID + nivolumab 480 mg IV q4 weeks) versus ipilimumab 3 mg/kg + nivolumab 1 mg/kg q3 weeks in patients with symptomatic BRAF-mutant MBM. (The study was amended to exclude patients with asymptomatic MBM.) Eligible patients are ≥ 18 years old, ECOG 0-2, and prior neoadjuvant or adjuvant anti-PD-1, CTLA-4, or BRAF/MEK-inhibitors is permitted. Steroids up to 8 mg of dexamethasone/day (or equivalent), leptomeningeal spread, and prior local therapy (radiation or surgery) for brain mets are permitted, if a patient has at least one measurable, progressing brain met ≥ 0.5 cm in size. Primary objective is to compare PFS per (RECIST 1.1) between the two study arms. Secondary objectives include overall survival, toxicity profile, objective tumor response, intracranial response and duration per modified RECIST 1.1, modified RANO-BM, and iRANO criteria, and evaluation of radiographic response criteria by centralized review of banked images. This study is powered to detect an increase in estimated 6-month PFS from 20% to 52% with 80% power and type I error rate of 10%, with 24 eligible patients required. Total sample size is 28 to account for ineligible patients. Available blood, tissue, CSF and stool samples are banked for future correlative studies. The study is currently enrolling patients through SWOG, ECOG and NRG centers. Funding: NIH/NCI grants U10CA180888, U10CA180819, U10CA180820 U10CA180868; and in part by Pfizer, Inc. Clinical trial information: NCT04511013. Research Sponsor: U.S. National Institutes of Health.

TPS9604

Poster Session

A pilot, open study to assess efficacy and safety of ON-01910 (rigosertib) in patients with recessive dystrophic epidermolysis bullosa associated locally advanced/metastatic squamous cell carcinoma. *First Author: Lauren Banner, Department of Dermatology and Cutaneous Biology, Thomas Jefferson University, Philadelphia, PA*

Background: Recessive Dystrophic Epidermolysis Bullosa (RDEB) is an extremely rare, severe blistering disease driven by mutations in collagen seven (COL7A1). Besides the skin and mucosal blistering, this genodermatosis is also characterized by aggressive cutaneous squamous cell carcinomas (cSCCs) arising from patients' chronic wounds. The cumulative risk of death from these cSCCs is 70% by age 45. There are limited effective treatment options for advanced (unresectable/metastatic) RDEB-associated cSCCs. While the standard of care for any advanced cSCC is immune checkpoint inhibitors, only half of the treated patients had responses in clinical trials. Their use for RDEB-associated SCCs been limited to case reports, and our own experience has not been positive. Conventional chemotherapy in RDEB-associated cSCC is another proposed treatment strategy, however, case reports demonstrated limited response rates without lasting effects. Currently it is recommended palliatively, although there are concerns about adverse effects. Other existing options are tyrosine kinase inhibitors, resulting in mixed responses to treatment for advanced cSCCs of any type, and epidermal growth factor receptor inhibitors, demonstrating limited effectiveness in a small number of case reports on RDEB-associated cSCCs. More effective therapeutic modalities for advanced/metastatic RDEB-associated cSCCs are needed. We previously demonstrated that RDEB SCC keratinocytes are specifically affected by polo-like kinase-1 (PLK-1) siRNA. Eight PLK-1 inhibitors were screened for cytotoxicity. Of the 8 candidates, ON-01910 was superior as it demonstrated the largest therapeutic window for distinguishing between tumor versus normal cells. The ON-01910 clinical trial is in progress in patients with RDEB with advanced/metastatic cSCCs. **Methods:** ON-01910 is being evaluated in both oral and intravenous formulations in an open-label, non-randomized phase 2 study in RDEB patients with advanced, treatment resistant cSCC. The trial explores the anti-tumor activity of ON-01910 and evaluates its safety and tolerability. Secondary objectives are to assess the impact on quality of life and to perform biomarker analysis on patient tissue. This study began in August 2021 and is ongoing. One patient is currently enrolled in the oral arm at Thomas Jefferson University in the USA. Safety is assessed according to the CTCAE v5. Tumor response in lymph nodes is determined per the RECIST 1.1 and in skin via clinical examination with serial tumor measurements. Key eligibility criteria include 1) diagnosis of RDEB and associated measurable, advanced cSCC confirmed histologically 2) failure to respond to standard of care including excision for localized disease 3) no concomitant cancer therapies. Clinical trial information: NCT04177498. Research Sponsor: Dystrophic Epidermolysis Bullosa Research Association of America; Onconova Therapeutics.

TPS9606

Poster Session

A pilot trial of autologous tumor infiltrating lymphocytes (lifileucel, LN-144) for patients with asymptomatic melanoma brain metastases. *First Author: Allison Betof Warner, Stanford Cancer Institute, Stanford, CA*

Background: Melanoma brain metastases (MBM) are a leading cause of morbidity and mortality for patients with advanced melanoma. Modern systemic therapies are insufficient at controlling MBM, and median overall survival (OS) for pts with MBM is < 1 year. Adoptive T cell therapy using tumor infiltrating lymphocytes (TIL) has demonstrated efficacy in advanced melanoma. Lifileucel (LN-144), an autologous TIL product, was recently shown to be safe and effective for patient with PD-1 refractory melanoma. Patients with active MBM were excluded from lifileucel trials to date. **Methods:** This single-center pilot trial (NCT05640193) is enrolling up to 10 pts with asymptomatic MBM from non-veal melanoma to receive lifileucel. Patients must have ≥ 1 intracranial lesion measuring 5-30mm visible on MRI to be used as a target lesion for modified (m)RECIST measurement, progression on prior anti-PD-1 therapy (with or without anti-CTLA-4), progression on targeted therapy if BRAF V600E/K-mutated, ECOG PS ≤ 1 , ≥ 1 resectable lesion(s) (≥ 1.5 cm), recovered from prior surgery/anticancer treatment-related AEs (grade ≤ 1). Patients are not eligible if they have symptomatic MBM and/or require corticosteroids of ≥ 10 mg/day of prednisone or equivalent. Lifileucel is generated from resected tumor in a centralized GMP process. The regimen includes nonmyeloablative lymphodepletion, lifileucel infusion, and a short course of high-dose IL-2. The primary endpoint is feasibility, defined as $\geq 7/10$ patients who undergo tumor harvest receiving lifileucel infusion. Secondary endpoints are safety, feasibility of manufacturing lifileucel in patients with MBM, and brain metastasis response rate (BMRR) per mRECIST 1.1. Exploratory endpoints include overall objective response rate by mRECIST 1.1, best extracranial response rate, intracranial progression-free survival (PFS), overall PFS, OS. Extensive correlative analyses of peripheral blood mononuclear cells, plasma, tumors, and cerebrospinal fluid are planned to better understand MBM growth, treatment resistance, and response of the central nervous system to lifileucel. Clinical trial information: NCT05640193. Research Sponsor: Iovance Biotherapeutics; Conquer Cancer Foundation of the American Society of Clinical Oncology; Melanoma Research Foundation; Memorial Sloan Kettering Cancer Center K12 Grant.

TPS9605

Poster Session

Phase II study of nivolumab (nivo) in combination with relatlimab (rela) in patients (pts) with active melanoma brain metastases (MBM). *First Author: Suzanne Phillips, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: More than half of all pts diagnosed with metastatic melanoma (MM) will develop brain metastases. Despite this prevalence, pts with MBM are excluded from the majority of clinical trials, preventing them from potential benefit of novel therapies. Long-term outcomes of the CheckMate 204 study combining ipilimumab (ipi) (3mg/kg) plus nivo (1 mg/kg) for asymptomatic MBM reported an intracranial (IC) response in 54% of pts. The 36-month IC progression-free survival (PFS) was 54% and overall survival (OS) was 72%. Grade 3 or 4 treatment-related adverse events (TRAEs) occurred in 55% of pts. RELATIVITY-047, a global phase II/III randomized study, reported on the fixed-dose combination of nivo (480 mg) and rela (a LAG-3-blocking antibody, 160 mg) compared to nivo (480 mg) alone for pts with advanced unresectable and untreated melanoma. The combination demonstrated significantly improved PFS and improved OS and objective response rate (ORR) compared to monotherapy. At 19.3 months of median follow-up, only the PFS benefit was statistically significant with a hazard ratio (HR) of 0.78 (95% CI 0.64-0.94). The OS benefit was not statistically significant (HR 0.8, 95% CI 0.64-1.01), and the descriptive ORR was 43.1% compared to 32.6% for single agent nivo. Grade 3 or 4 TRAEs occurred in 21% of pts in the combination group compared to 11% in the monotherapy group with no new safety signals. The nivo/rela combination has been FDA approved for the treatment of pts with MM but has not been studied in pts with MBM. We hypothesize that nivo/rela will be safe and tolerable for pts with MBM and demonstrate favorable outcomes compared to nivo monotherapy with fewer AEs in contrast to ipi/nivo combination. **Methods:** This single arm, single center, open-label phase II trial will evaluate the safety and efficacy of nivo/rela in pts with MBM (NCT05704647). 30 MBM pts who are treatment naïve to anti-PD-1 therapy will be enrolled. At least one unirradiated parenchymal brain metastasis at least 5 mm or larger is required for inclusion. Asymptomatic pts not requiring steroids for the management of their neurological symptoms are eligible. Pts requiring urgent local therapy with radiation or surgery are not eligible. Pts will be treated with nivo (480 mg)/rela (160 mg) every 4 weeks for up to 25 cycles, disease progression, or unacceptable toxicity. The primary objective is to evaluate IC ORR (CR + PR) by MRI per modified RECIST 1.1 criteria. Monitoring for fertility will be performed using the Bayesian Optimal Phase 2 (BOP2) design. Thirty evaluable patients will provide 82% power to detect a difference between the historical IC ORR of 20% for nivo alone to a targeted ORR of 40% for nivo/rela. Longitudinal research blood, tissue, and microbiome samples will be collected along with neurocognitive assessment and quality of life surveys. Clinical trial information: NCT05704647. Research Sponsor: Bristol-Myers Squibb Company (BMS); MD Anderson Cancer Center Melanoma Moon Shots.

TPS9607

Poster Session

A phase 3 study (TILVANCE-301) to assess the efficacy and safety of lifileucel, an autologous tumor-infiltrating lymphocyte cell therapy, in combination with pembrolizumab compared with pembrolizumab alone in patients with untreated unresectable or metastatic melanoma. *First Author: Daniel Olson, University of Chicago, Chicago, IL*

Background: Most patients (pts) with advanced (unresectable or metastatic) melanoma receiving front-line immune checkpoint inhibitor (ICI) therapy progress within a year (Robert *Lancet Oncol* 2019; Larkin *NEJM* 2019; Tawbi *NEJM* 2022). Early-line therapies are needed to improve the rate of deep and durable responses and increase the proportion of pts with long-term benefit. Lifileucel demonstrated an ORR of 31.4% and median DOR not reached (median 36.5 mo follow-up) in pts with post-ICI advanced melanoma (Sarnaik *SITC* 2022). Earlier-line treatment with lifileucel plus pembrolizumab (pembro) in pts with ICI-naïve advanced melanoma demonstrated an ORR of 67%, including a CR rate of 25% (Iovance Press Release, April 5, 2022; O'Malley *JITC* 2021). TILVANCE-301 will evaluate the efficacy and safety of lifileucel plus pembro compared with pembro alone in pts with untreated advanced melanoma. **Methods:** TILVANCE-301 (NCT05727904) is a phase 3, multicenter, randomized, open-label, parallel group, treatment study that will randomize ~670 pts (1:1) to either Arm A: lifileucel plus pembro (study intervention includes tumor tissue resection, pembro, nonmyeloablative lymphodepletion [NMA-LD], lifileucel infusion, an abbreviated course of high-dose IL-2, and thereafter, continued pembro) or Arm B: pembro alone. Pts in Arm B who receive pembro and experience confirmed progressive disease verified by blinded independent review committee (BIRC) have the option to receive lifileucel as the immediate next line of treatment. Eligible adults have histologically confirmed advanced melanoma (Stage IIIC, IIID, or IV); ECOG PS of 0 or 1; estimated life expectancy > 6 mo; ≥ 1 resectable lesion ~1.5 cm in diameter postresection to generate lifileucel and ≥ 1 measurable lesion (RECIST v1.1); and adequate hematologic parameters and organ function. Neoadjuvant or adjuvant treatment including ICI meeting protocol-specified criteria may be allowed. Exclusion criteria include prior therapy for metastatic disease; symptomatic untreated brain metastases; organ allograft or prior cell transfer therapy; uveal/ocular melanoma; chronic systemic steroid therapy; active systemic infections; cardiovascular, respiratory, or immune system illnesses; primary/acquired immunodeficiency; or other primary malignancy in the last 3 y. The dual primary efficacy endpoints are BIRC-assessed (RECIST v1.1) ORR and PFS. Key secondary efficacy endpoint is OS. Additional secondary efficacy endpoints include BIRC-assessed CR rate, DOR, and EFS; investigator-assessed ORR, PFS, CR rate, DOR, EFS, and PFS2; and safety as characterized by severity and seriousness of TEAEs, and relationship to study drug. The study will enroll globally. Clinical trial information: NCT05727904. Research Sponsor: This study is sponsored by Iovance Biotherapeutics.

TPS9609

Poster Session

The DIET study: A randomized controlled trial of a high fiber diet in cancer patients (pts) receiving immune checkpoint blockade (ICB). *First Author: Rachel Farias, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Gut microbiome modulation is a promising strategy to enhance response to ICB. Fecal microbiota transplant studies have shown positive signals of improved outcomes in both ICB naïve and refractory melanoma; however, this strategy is challenging to scale. Diet is a key determinant of the gut microbiota and we have previously shown that a) habitual high dietary fiber intake is associated with improved response to ICB and b) fiber manipulation in mice impacts anti-tumor immunity. We recently demonstrated feasibility of a controlled high-fiber dietary intervention (HFDI) conducted in melanoma survivors with excellent compliance and tolerance. Building on this, we are now conducting a single center Phase II randomized trial of HFDI versus healthy control diet in cancer pts receiving ICB (NCT04645680). **Methods:** 57 pts starting standard of care (SOC) ICB will be enrolled in 4 cohorts: 3 melanoma cohorts in the adjuvant (n = 21), neoadjuvant (n = 12), and unresectable (n = 12) settings and 1 metastatic renal cell carcinoma (RCC) cohort (n = 12). Key inclusion criteria include BMI 18.5-40 kg/m², and willingness to exclusively eat the diet. Key exclusion criteria include diabetes mellitus, inflammatory bowel disease, total colectomy or bariatric surgery, recent use of prebiotic/probiotic supplements, steroids (within 14 days), antibiotics (within 21 days), current smoker or heavy drinker, and dietary fiber > 20g/day. Pts are randomized 2:1 to the HFDI (target fiber 50g/day) or control diet (fiber 15-20g/day) stratified by BMI and cohort. Both diets have same macronutrient composition but differ in fiber content. The primary objective is to establish the effects of a dietary intervention on the structure and function of the gut microbiome. Secondary endpoints include change in circulating and stool metabolites, systemic and tumor immunity, and safety and tolerability of dietary intervention. As a controlled feeding study, all meals are isocaloric and prepared by MD Anderson Bionutrition Research Core for up to 11 weeks. Meals follow American Cancer Society and American Institute for Cancer Research recommendations which include whole foods plant-forward diet, little to no processed meats or added sugars, and no alcohol consumption. Meals are shipped weekly within the contiguous United States and include breakfast, lunch, dinner, and snacks. The HFDI group start at 30g fiber/day, up titrated every 2 weeks up to 50g/day based on tolerance. Blood and stool samples are collected longitudinally. Tumor biopsies are required in the neoadjuvant cohort and optional in unresectable. A Fitbit is provided to monitor physical activity and a scale to measure daily weight. 24 of the planned 57 pts have been enrolled: n = 13 adjuvant, n = 5 neoadjuvant, n = 5 unresectable, n = 1 RCC. 14 treated with PD1 monotherapy, 9 with ipilimumab + nivolumab, and 1 with nivolumab + relatlimab. Clinical trial information: NCT04645680. Research Sponsor: Seerave Foundation; Elkins Foundation, Rising Tide Foundation, Mark Foundation.

TPS9611

Poster Session

KEYVIBE-010: Adjuvant coformulated vibostolimab with pembrolizumab versus adjuvant pembrolizumab in patients with high-risk stage II-IV melanoma. *First Author: Georgina V. Long, The University of Sydney, Sydney, NSW, Australia*

Background: Pembrolizumab is an anti-PD-1 monoclonal antibody that has been shown to significantly improve recurrence-free survival and distant metastasis-free survival when used as adjuvant therapy in patients with high-risk resected melanoma (Long GV, et al. *Lancet Oncol.* 2022;23:1378-88; Eggermont AMM, et al. *Lancet Oncol.* 2021;22:643-54). Combining pembrolizumab with other therapies may further improve outcomes in this setting. Vibostolimab is an anti-TIGIT monoclonal antibody that showed antitumor activity and manageable safety when used in combination with pembrolizumab in patients with advanced solid tumors in the phase 1 KEYVIBE-001 study (Niu J, et al. *Ann Oncol.* 2022;33:169-80). The randomized, double-blind, phase 3 KEYVIBE-010 study (NCT05665595) is designed to evaluate the efficacy and safety of adjuvant coformulated vibostolimab and pembrolizumab (MK-7684A) versus pembrolizumab alone in patients with resected high-risk stage IIB-IV melanoma. **Methods:** Eligible patients are ≥12 years of age (weighing ≥40 kg if <18 years), with surgically resected stage IIB or IIC (pathologic or clinical), III, or IV cutaneous melanoma per AJCC 8th edition guidelines, and an Eastern Cooperative Oncology Group performance status of 0 or 1 (Lansky play-performance scale ≥70 if <16 years; Karnofsky performance status ≥70 if ≥16 to <18 years). Patients must not have received any prior systemic therapy beyond complete resection and no more than 12 weeks can have elapsed between final surgical resection and randomization. Patients with ocular, mucosal, or conjunctival melanoma, and prior allogeneic tissue/solid organ transplant are excluded. Patients will be stratified by risk. Approximately 1560 patients will be randomly assigned 1:1 to receive intravenous coformulated vibostolimab 200 mg with pembrolizumab 200 mg or pembrolizumab 200 mg (2 mg/kg up to a maximum of 200 mg for adolescents) every 3 weeks. Treatment will continue for 17 cycles or until disease recurrence, unacceptable toxicity, or withdrawal. The primary end point is recurrence-free survival by investigator review. Secondary end points are distant metastasis-free survival by investigator review, overall survival, safety and tolerability, and quality of life. Hazard ratios and 95% confidence intervals will be estimated using a stratified Cox regression model with the Efron method of handling ties, with treatment as a covariate. Between-treatment differences will be evaluated using a stratified log-rank test. Enrollment is ongoing. Clinical trial information: NCT05665595. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

TPS9610

Poster Session

A phase 2 study to determine the pathological (path) response to neo-adjuvant nivolumab (nivo) and relatlimab (rela) in high-risk stage II cutaneous melanoma: NeoReNi II. *First Author: Maria Gonzalez, Melanoma Institute Australia, Sydney, Australia*

Background: Patients diagnosed with stage II melanoma account for ~50% of those who develop metastatic disease and die (Poklepovic et al., 2020). Neoadjuvant therapy (NAT) is a powerful treatment platform to rapidly assess drug activity in resectable cancers using the International Neoadjuvant Melanoma Consortium (INMC) path response criteria (Tetzlaff et al., 2018), wherein a major path response (≤10% viable tumor) correlates with low risk of recurrence in resectable stage III melanoma (Menzies et al., 2021). Other benefits include early insight into response, feedback to pts regarding their individual response and prognosis, ability to tailor subsequent management, and collection of translational specimens to explore mechanisms of response and resistance (Amaria et al., 2019). NAT for stage II melanoma is an opportunity to improve survival rates beyond the gains achieved with adjuvant therapy, as illustrated by the phase II SWOG 1801 trial (Patel et al., 2022) for pts with stage III melanoma. The NeoReNi II trial will examine whether combination PD-1 blockade plus lymphocyte-activation 3 (LAG3) checkpoint inhibition will achieve a high rate of path response with manageable toxicity. **Methods:** Pts with histologically confirmed AJCC (8th ed.) clinical stage IIA (T2b, T3A), IIB (T3b, T4a), or IIC (T4b) primary cutaneous melanoma from a partial biopsy, with residual macroscopic disease at study entry, are eligible (N = 20). Pts with IIA disease must have an estimated ≥20% risk of recurrence at 5 years, according to the Melanoma Institute Australia stage II risk calculator (melanomarisik.org.au). All pts undergo wide excision and sentinel lymph node resection (RES) at wk 6 following NAT with 2 doses of nivo (480 mg, IV) plus rela (160 mg, IV). Pts with no (> 50% viable tumor) or partial path response (> 10% - ≤50% viable tumor) receive a further 11 cycles (Q4W) of adjuvant nivo (480 mg) plus rela (160 mg), and radiological and clinical surveillance. Pts with complete (pCR; 0% viable tumor) or near-complete (≤10% viable tumor) path response will undergo radiological and clinical surveillance after RES. All pts will be followed for recurrence (6 monthly CT) and survival for 10 years. Lymphatic mapping, dermoscopy, in vivo confocal microscopy, CT, and FDG PET/CT will be performed at baseline (BL) and prior to RES to measure response to NAT. Tumour and fecal samples are collected at BL, RES, and recurrence. Blood samples are collected at BL, wk 4, RES, and recurrence. The primary endpoint is the rate of pCR at RES after 6 wks of NAT using INMC response criteria (Tetzlaff et al., 2018). Secondary endpoints include assessing the feasibility of NAT in a stage II pt population, RFS, OS, safety/tolerability, surgical outcomes, changes in confocal microscopy and dermoscopy, rate of sentinel node positivity and changes in lymphatic mapping, QOL, and biomarker analyses. Clinical trial information: NCT05418972. Research Sponsor: BMS; Melanoma Institute Australia.

TPS9612

Poster Session

NADOM trial: Neoadjuvant/adjuvant trial of darovasertib in ocular melanoma (OM). *First Author: Roderick O'day, Royal Victorian Eye and Ear Hospital, Melbourne, Australia*

Background: Darovasertib (Daro) is a novel inhibitor of PKC, that has pre-clinical activity in GNAQ/GNA11 tumours including ocular melanoma. A recently completed clinical trial of Daro monotherapy in metastatic OM with a response rate of 11%, and DCR of 78% with only mild manageable toxicity, suggesting utility in localized disease and in the adjuvant setting. **Methods:** NADOM is an investigator-initiated window-of-opportunity phase 2 clinical trial open in 3 centers across Australia. Eligible patients include patients planned for enucleation, ECOG 0-1 with adequate organ function. The primary objective is the feasibility and safety of neoadjuvant Daro in a pilot cohort of 12 patients. Secondary objectives include the effect of Daro on circulating biomarkers (including CTCs and ctDNA), imaging assessments (MRI, FDG-PET and ocular ultrasound), pharmacokinetic and pharmacodynamic correlates and radiographic PFS in the adjuvant setting. Treatment comprises a neo-adjuvant period of treatment of up to 6 months at ophthalmologist discretion with Daro (300mg bid) before definitive management. Patients who demonstrated radiological, biomarker or clinical response are then offered an adjuvant period of treatment for up to 6 months following integrated consensus at multi-disciplinary ocular oncology meetings. DSMB meetings are scheduled to ensure clinical and peri-operative safety regularly. Enrollment commenced in November 2022 and accrual is ongoing in the 6 month neo-adjuvant cohort. **Results:** To date, an initial safety cohort of 1 month of neo-adjuvant treatment has been cleared following DSMB review. **Conclusions:** Recruitment is ongoing and expected to complete in late 2023. Clinical trial information: NCT05187884. Research Sponsor: Ideaya Biosciences.

TPS9613

Poster Session

PLUME: A single-arm phase II trial evaluating the combination of pembrolizumab and lenvatinib in metastatic uveal melanoma (mUM) patients (pts) previously treated or not with tebentafusp. *First Author: Manuel Rodrigues, Medical Oncology Department, Institut Curie, Paris, France*

Background: Up to 50% of pts with uveal melanoma (UM) develop metastases, mainly hepatic, with poor overall survival and limited treatment options as response rate to first-line immune checkpoint inhibitors (ICI) is low in mUM pts. Tebentafusp, a bispecific T-cell engager, was recently approved in this setting but only in HLA A*02-01+ mUM patients. Lenvatinib is a tyrosine kinase inhibitor targeting multiple growth factor receptors including vascular endothelial growth factor receptors (VEGFRs), fibroblast growth factor receptors (FGFRs) and colony-stimulating factor receptor (CSF1-R), which are key pathways in UM. Lenvatinib showed an immune-modulating effect in preclinical models. The combination demonstrated synergic clinical anti-tumor activity in various tumor types including microsatellite-stable endometrial cancers, kidney cancers and ICI-resistant skin melanomas. We hypothesize that combining pembrolizumab with lenvatinib in mUM may lead to an improved immune response in mUM patients. **Methods:** Fifty-four, ICI-naïve, metastatic UM pts will be enrolled in this monocentric, single-arm phase II trial at Institut Curie, Paris, France. Because previous exposure to tebentafusp might increase the activity of subsequent ICI, the combination will be assessed in two independent cohorts: cohort 1 with HLA A*02-01^{neg}, tebentafusp-naïve patients (22 assessable patients), and cohort 2 with HLA A*02-01^{pos} pts previously treated with tebentafusp (28 assessable patients). Up to 54 patients may be included according to an 8% drop-out rate. Each participant will receive pembrolizumab (200 mg Q3W, maximum of 35 cycles) plus lenvatinib (starting at 20mg QD) until reaching a discontinuation criterion. Liver MRI and chest-abdomen-pelvis CT will be performed every 9 weeks until progressive disease. Primary objective is to evaluate the progression-free survival (PFS) after nine cycles of treatment (27 weeks) as assessed by the investigator using the RECIST v1.1. Secondary objectives include PFS according to immune RECIST (iRECIST), overall survival, overall response rate, safety and tolerability, quality of life. Inclusion period started mid-July 2022 for two years. To date, twenty-four (21 in cohort 1, 3 in cohort 2) of planned 54 pts have been enrolled in six months. Biospecimens (longitudinal blood samples and tumor tissue at inclusion) will be collected during the study to allow biomarker research. Clinical trial information: NCT05282901. Research Sponsor: INCa PHRC-K 2020; Merck Sharp & Dohme LLC.

TPS9614

Poster Session

CemiplimAb-rwlc survivorship and epidemiology (CASE): A prospective study of safety and efficacy of cemiplimab in patients with advanced basal cell carcinoma in a real-world setting. *First Author: Soo J Park, University of California San Diego, La Jolla, CA*

Background: Basal cell carcinoma (BCC) is the most common form of non-melanoma skin cancer in the United States. Surgical excision is the standard treatment, with < 1% of cases progressing to locally advanced or metastatic disease. Hedgehog pathway inhibitors (HHIs) are the first-line therapy for advanced BCC (aBCC); the US Food and Drug Administration and European Medicines Agency have approved the use of cemiplimab (a programmed cell death-1 inhibitor) in advanced BCC (aBCC) patients previously treated with (or are inappropriate for) HHI. Limited real-world data exist on the clinical characteristics, disease management and progression, and survivorship of patients with aBCC. The ongoing C.A.S.E. study aims to evaluate the efficacy, safety, disease evolution, survivorship, and patient reported outcomes (PRO) in patients treated with cemiplimab in the real-world setting. **Methods:** This trial in progress (NCT03836105) aims to describe the effectiveness and safety of cemiplimab 350 mg administered every 3 weeks for treatment of patients with aBCC in real-world clinical settings. Up to 100 adult patients with aBCC who are prescribed commercially available cemiplimab from ~65 study sites in the United States will be included. The duration of follow-up will be 24 months. Endpoints for this study relate to real-world efficacy, including overall survival; progression-free survival; objective response rate, (partial or complete response); and disease control rate, defined as the percentage who do not progress for ≥ 6 months; Time to response, duration of response, time to treatment failure, and disease-specific death will also be assessed. Real-world safety outcomes will also be captured, including immune-related adverse events, infusion-related reactions, and serious adverse events. Patient selection criteria and treatment patterns will be analyzed using descriptive statistics. This study also aims to describe the patient experience of real-world treatment with cemiplimab. PROs including global quality of life, functioning, and symptoms will be captured at baseline and follow-up visits via the EORTC QLQ-C30 and the Skin Care Index. Recruitment for this trial is ongoing. Clinical trial information: NCT03836105. Research Sponsor: Regeneron Pharmaceuticals, Inc.

10000

Oral Abstract Session

High risk neuroblastoma (HR-NB) with MNA and age <18 months: Results from the HR-NBL1/SIOPEN trial. *First Author: Ruth Lydia Ladenstein, St. Anna Children's Hospital and St. Anna Kinderkrebsforschung, Department of Paediatrics, Medical University Vienna, Vienna, Austria*

Background: The INES 99.4 trial (JCO 2009, 27(7):1014-9) for MYCN amplified (MNA) infants using 6 courses of CBDCA-Vp16/CADO showed early progressions or non-response in 30%. Two-year overall survival (OS) was 30% (SE, 0.08) with median survival of 12 months. Aims are to report risk factors and outcomes for patients < 18 months with MNA neuroblastoma treated on HR-NBL1/SIOPEN. **Methods:** From 2006-2022, patients < 18 months with MNA INSS stages > 1 were eligible. All infants received Rapid Cojec induction, eventually 2 TVDs, Busulfan-Melphalan as high-dose treatment and could receive Dinutuximab- beta immunotherapy. Toddlers (12-18 months) followed the HR-NBL1/SIOPEN respective eligibility criteria. **Results:** Median age at diagnosis was 1.2 years in 414 patients (median follow up 7 years): 56% were male; 18.6% had localised tumours, 6.8% stage 4S and 75% stage 4. The predominant primary tumour site was abdominal (85%). Rapid Cojec was used in 85%, BUMEL in 89% and 26% received Dinutuximab-beta. Multiple metastatic compartments were reported in 82% of stage 4. Five-year event-free (5y-EFS) and overall survival (5y-OS) was 0.46 ± 0.03 and 0.51 ± 0.03 . Stage 2,3&4S patients had a better 5y-EFS of 0.64 ± 0.03 ($p < 0.005$) (5y-OS: 0.66 ± 0.06), compared to stage 4 with 0.41 ± 0.03 (OS: 0.46 ± 0.03). Infants' 5y-EFS was superior with 0.53 ± 0.04 (5y-OS: 0.57 ± 0.04) ($p = 0.015$) over the toddlers with 5y-EFS 0.42 ± 0.03 (5y-OS: 0.46 ± 0.03). Patients with bone marrow (BM) and skeletal metastases > other sites (MS) did worse ($p < 0.005$) with a 5y-EFS of 0.31 ± 0.04 (5y-OS: 0.36 ± 0.04) whilst other metastatic combinations revealed outcomes above 0.50 ± 0.03 . LDH ($2x > \text{normal}$) predicted a worse 5y-EFS of 0.43 ± 0.03 (5y-OS: 0.46 ± 0.03) ($p < 0.001$) versus normal LDH (5y-EFS 0.71 ± 0.07 ; 5y-OS: 0.80 ± 0.06). EFS multivariable analysis at diagnosis (MVA) showed independent significance for stage 4 (p-value 0.0139; HR: 1.608) and LDH (p-value 0.0042; HR: 2.237), but not for age. In stage 4 patients MVA on EFS found LDH (p-value 0.0098; HR: 2.567) and BM/skeleton involvement (p-value 0.0024; HR: 1.693) as independent risk predictors. In maintenance Dinutuximab-beta had a major impact on 5y-EFS in stage 4 patients with 0.69 ± 0.05 (5y-OS: 0.71 ± 0.05) vs. 0.41 ± 0.07 (0.46 ± 0.07) for those treated with 13-cis retinoic acid ($p = 0.002$ & $p = 0.001$), but not on others. **Conclusions:** In HR-NBL1/SIOPEN outcomes improved with almost half of patients alive at 5 years and only few late events. Clinical trial information: NCT01704716. Research Sponsor: EC 5th Frame Work Grant SIOPEN-R-NET EC grant no. QLRI-CT-2002-01768; St. Anna Kinderkrebsforschung; Pierre Fabre Médicament, Apeiron Biologics.

10002

Oral Abstract Session

A multicenter cooperative group study of late effects after high-risk neuroblastoma: COG ALTE15N2—LEAHRN study. *First Author: Tara O. Henderson, The University of Chicago, Chicago, IL*

Background: Aggressive therapies for high-risk neuroblastoma (HRNBL) have resulted in increased survival, but late effects have not been well-characterized. **Methods:** Comprehensive cross-sectional evaluation of health outcomes in HRNBL survivors enrolled on the COG Neuroblastoma Biology Study after 1/1/2000 and ≥ 5 years from primary diagnosis, using medical record abstraction and in-person clinical assessments. Descriptive and multivariable analyses identified extent of and risk factors for late toxicity. **Results:** There were 375 participants from 88 COG centers, 205 (55%) male; 92 (26%) non-white; 45 (13%) Hispanic. Median age at neuroblastoma diagnosis was 2.5 years (range: 0.2-15.8), at enrollment was 12.0 years (range: 5.0-24.0). All had received chemotherapy; 94% received cisplatin (median dose: 398 mg/m²). Other exposures included: radiation (95%), isotretinoin (91%), anti-GD2 antibody therapy (64%), MIBG (7%), single (79%) or tandem autologous transplantation (ASCT; 20%). ASCT conditioning included: Busulfan/Melphalan (BuMel) (18%), Carboplatin/Etoposide/Melphalan (CEM) (73%), Thiotepa/Cytosan (19%), and total body irradiation (5%). Severe ototoxicity (requiring hearing aids) was observed in 58% of participants. Physician-reported late effects included hypothyroidism (17%), pulmonary hypertension (1%), congestive heart failure (2%), and hypertension (6%). Pulmonary Function Studies revealed restrictive lung disease [RLD - Total Lung Capacity < 70% predicted] in 8% of subjects. Laboratory study showed elevated creatinine in 7% and Hemoglobin A1c in 7%. Growth failure (height Z-score < -1.7) was observed in 34%. Subsequent malignant neoplasms (SMN) developed in 15 participants (4%; 4 sarcomas, 3 MDS/t-AML, single instance of 8 other malignancies). Adjusting for sex, follow-up time, age, and race, there were no differences in risk of SMN, severe ototoxicity, growth failure, or RLD for participants who received BuMel vs. CEM-based conditioning, or among those who received anti-GD2 antibody therapy vs. those who did not. Use of carboplatin during ASCT was not associated with increased ototoxicity risk for any category of cisplatin induction dose. Comparing subjects who received CEM as a component of tandem ASCT (vs. single CEM), there was increased risk of growth failure [OR (95%CI) = 4.2(2.1, 8.4); $p < 0.0001$], but not RLD. Exposure to isotretinoin was not associated with increased risk of growth failure. Further multivariable analyses will be presented, exploring risks for late toxicity associated with conditioning regimens, radiation therapy, surgical approaches, and acute and chronic complications of therapy. **Conclusions:** The burden of late toxicity in HRNBL survivors is substantial. Anti-GD2 immunotherapy and isotretinoin do not appear to be associated with SMN, ototoxicity, growth failure, or RLD. Research Sponsor: St. Baldrick's Foundation.

10001

Oral Abstract Session

Irinotecan and temozolomide combined with dasatinib and rapamycin for patients with relapsed or refractory neuroblastoma: Results of the prospective randomized RIST trial. *First Author: Selim Corbacioglu, University Hospital of Regensburg, Regensburg, Germany*

Background: Relapsed or refractory neuroblastoma (r/rNB) are associated with a dismal outcome. RIST is the acronym for irinotecan and temozolomide (I/T) as backbone in combination with dasatinib (S) and rapamycin (R) aligned in a molecular targeted, metronomic design. **Methods:** RIST-rNB-2011, an open label randomised Phase II trial (NCT01467986), compared RIST (experimental arm) with I/T (control arm; CA). Patients with high-risk r/rNB (stage 4 and all MYCN amplified stages; MYCN+) were randomized with a block-wise (block length of 6) randomization stratified by MYCN. RIST treatment consists of courses of R/S (4 days/week) followed by I/T (5 days/week). Phase 1 is defined by 4 cycles with one R/S and one I/T course (8 weeks). In phase 2 each of the 4 cycles comprise 2 R/S and 1 I/T course (12 weeks). CA consisted of I/T courses only. The primary endpoint was progression-free survival (PFS), analysed by a Cox proportional hazards model adjusted for MYCN- to test the null hypothesis of a hazard ratio of 1 assuming proportional hazard rates at a two-sided 5% significance level. A point estimate and a two-sided 95% confidence interval was provided. A sample size of N = 114 patients was calculated. Primary analysis was based on the intention-to-treat principle (ITT). Toxicity was assessed in all participants who received at least one dose of protocol therapy. **Results:** Subjects (N = 124) eligible for follow-up were enrolled from 08/2012 – 09/2020. Median age was 5.37 years (y) (range 1.1 – 24.6 y). Disease characteristics were relapse in 80% (< 18 months (m) after diagnosis: 40%) and refractory disease in 20%, MYCN+ was present in 39%. Median overall follow-up was 72 m. In the ITT population median PFS was 11 m in RIST vs 5 m in CA (HR: 0.62 (95%-CI: 0.42, 0.92), $p = 0.019$), and 16 m in RIST vs 4 m in the CA (HR: 0.53 (95%-CI: 0.31, 0.90), $p = 0.018$) in the per protocol (PP) population. Subgroup analyses showed a selective effect in the MYCN+ (HR: 0.45 (95%-CI: 0.24, 0.84), $p = 0.012$) compared to MYCN- patients (HR: 0.84 (95%-CI: 0.51, 1.38), $p = 0.492$). PFS at 2 y in MYCN+ was 38% vs 8% in CA (ITT) and 50% vs 6% (PP), respectively. In MYCN+ patients with a relapse < 18 m from initial diagnosis (N = 33) PFS remained significantly better ($p = 0.048$). Median overall survival (OS) for RIST vs CA was 20 m vs 16 m in ITT (HR: 0.68 (95%-CI: 0.45, 1.04), $p = 0.073$) and 26 m vs 16 m in PP (HR: 0.55 (95%-CI: 0.32, 0.98), $p = 0.041$). OS was significantly better in MYCN+ patients: 11 m vs 6.5 m in ITT (HR: 0.51 (95%-CI: 0.27, 0.96), $p = 0.037$) and 17 m vs 5 m in PP (HR: 0.34 (95%-CI: 0.14, 0.83), $p = 0.018$). In MYCN- no differences were observed neither in PFS nor in OS. R/S did not add additional toxicity to I/T. **Conclusions:** RIST was well tolerated and led to a significantly improved PFS and OS in MYCN+ patients, allowing a targeted approach for this high-risk population. Clinical trial information: NCT01467986. Research Sponsor: Deutsche Krebshilfe.

10003

Oral Abstract Session

Biological medicines for diffuse intrinsic pontine glioma (DIPG) eradication (BIOMEDE): Final results of an international randomized phase II platform trial comparing 3 targeted therapies in combination with radiotherapy from ITCC, SIOPE-Brain and ANZCHOG. *First Author: Jacques Grill, Gustave Roussy, Villejuif, France*

Background: DIPG is the most aggressive brain cancer in children and adolescents with a median survival of 9 months. Surgery is not possible due to the invasive nature of the disease in a critical area of the brain; only radiotherapy has shown a transient palliative effect on disease progression and no adjuvant therapy has proven to increase disease control. **Methods:** We launched a large randomized biomarker-driven platform trial to compare three targeted therapies (erlotinib, everolimus and dasatinib) in combination with 54 Gy radiotherapy, in newly diagnosed patients with DIPG (NCT02233049). A central pathological review was performed prior to study entry to confirm the diagnosis of DIPG with H3K27me3 loss (with or without H3K27M mutation) and assess biomarkers. The randomization was designed so that a drug could not be allocated if the corresponding biomarker was absent in the tumor (EGFR overexpression for erlotinib, mTOR activation for everolimus, no specific biomarker for dasatinib). Tumors underwent whole genome sequencing and RNAseq to evaluate prognostic and theranostic biomarkers. Primary endpoint was overall survival. **Results:** Among the 279 DIPG patients screened for the randomized trial between October 2014 and September 2019, 233 were enrolled in 45 centers in 7 countries; among the 46 screen failures, the diagnosis of DIPG could not be confirmed in 23 patients. No biopsy- or treatment-related death was reported. Serious adverse events ≥ 3 unrelated to disease progression were reported in 40% of patients, 34%, 36% and 46%, in the erlotinib, everolimus and dasatinib arms, respectively ($p = 0.32$). With a median follow-up of 5.3 years, median overall survival (OS) from the date of randomization was 9.0 (95% confidence interval, 7.4-14.4), 11.3 (10.3-13.4) and 9.4 (7.7-10.7) months for erlotinib, everolimus and dasatinib, respectively ($p = 0.45$). OS were not statistically different from those of a historical biopsy-proven cohort. The molecular profiling with copy number aberrations (CNA) had a strong impact on survival (log-rank test, $p = 0.0001$) as shown by the preliminary analysis of the first hundred patients identifying a group of tumors with very poor prognosis with a HR for death of 1.96 (1.07-3.64) characterized by TP53 mutations ($p = 3.05e-11$) associated with more CNA ($p < 0.0001$). **Conclusions:** This trial demonstrated the feasibility and safety of a large randomized trial for DIPG based on biomarker information from a stereotactic biopsy at diagnosis in an international multicenter setting and generated new tumor biological insights to further develop innovative therapies. Clinical trial information: NCT02233049. Research Sponsor: French National Cancer Institute; Imagine4Margo; Roche, BMS, Novartis.

10004

Oral Abstract Session

10005

Oral Abstract Session

Clinical activity of pan-RAF inhibitor tovorafenib in the registrational pediatric low-grade glioma arm of the phase 2 FIREFLY-1 (PNOC026) study.
First Author: Lindsay Baker Kilburn, Children's National Hospital, Washington, DC

Background: Pediatric low-grade gliomas (LGGs) are the most common brain tumors of childhood. Genomic alterations of *BRAF* (*KIAA1549-BRAF* fusions, 50–60% and *BRAF* V600E mutations, 5–15%) are the most frequent oncogenic drivers in pLGGs. Tovorafenib is an investigational, oral, selective, brain-penetrant, small molecule, type II pan-RAF inhibitor. Tovorafenib has demonstrated clinically meaningful responses in 24/35 patients (2 CR, 7 PR and 15 SD) in the pediatric phase 1B PNOC014 (NCT03429803) trial in patients with *RAF*-altered cancers (Wright, SNO 2022). **Methods:** FIREFLY-1 (NCT04775485) is a multicenter phase 2 study evaluating the efficacy and safety of tovorafenib monotherapy in patients with *BRAF*-altered cancers. Registrational arm 1 of FIREFLY-1 includes patients 6 months–25 years of age with recurrent or progressive LGG previously treated with ≥ 1 prior line of systemic therapy. Tovorafenib 420 mg/m² (not to exceed 600 mg) is administered weekly, in 28-day cycles, (tablet or liquid suspension formulation) until progression. The primary end-point of arm 1 is ORR, as defined by Response Assessment in Neuro-Oncology (RANO) criteria and determined by blinded independent review. **Results:** As of September 28, 2022, arm 1 had enrolled 77 patients and is fully accrued. All patients had ≥ 6 months of follow-up. Median age at enrollment was 8 years (range 2–21). Patients were pretreated with a median of 3 prior lines of systemic therapy (range: 1–9); 60% had received prior MAPK pathway-targeted agents. The most common tumor site was optic pathway (51%). Sixty-four patients harbored a *BRAF* fusion/rearrangement (83%) in their tumors, and 13 (17%) had a *BRAF* V600E mutation. Median duration of tovorafenib treatment is 8.4 months (range 0.7–16.8), with 59 patients (77%) remaining on treatment at the time of data cutoff. Per independent assessment in 69 RANO-evaluable patients, ORR was 64%, [3 CR, 41 PR (10 unconfirmed) and 19 SD] with a clinical benefit rate of 91%. Responses were achieved in tumors with *BRAF* fusions and V600E mutations, including those previously treated with MAPK inhibitors. The most common treatment-related adverse events (TRAEs) of any grade were hair color changes (75%), increased creatine phosphokinase (64%), anemia (46%), fatigue (42%) and maculopapular rash (42%). Tovorafenib dose modifications occurred in 16 (21%) and discontinuations in 2 (3%) patients due to TRAEs. Updates from a longer follow-up on the 77 patients in arm 1 will be presented at the meeting. **Conclusions:** Tovorafenib was generally well tolerated and showed encouraging evidence of antitumor activity in children and young adults with recurrent/progressive *BRAF*-altered pLGG. LOGGIC/FIREFLY-2 (NCT05566795), a global, phase 3 trial is evaluating once-weekly tovorafenib monotherapy in newly-diagnosed patients with pLGG harboring a known activating *RAF* alteration. Clinical trial information: NCT04775485. Research Sponsor: Day One Biopharmaceuticals.

10006

Oral Abstract Session

Palbociclib in solid tumor patients with genomic alterations in the cyclin D-CDK4/6-INK4a-Rb pathway: Results from NCI-COG pediatric MATCH trial Arm I (APEC1621I).
First Author: Margaret E Macy, Department of Pediatrics, University of Colorado and Center for Cancer and Blood Disorders, Children's Hospital Colorado, Aurora, CO

Background: The NCI-Children's Oncology Group (COG) Pediatric Molecular Analysis for Therapy Choice (MATCH) trial assigns patients aged 1 to 21 years with relapsed or refractory solid tumors, lymphomas, and histiocytic disorders to phase 2 treatment arms of molecularly-targeted therapies based on genetic alterations detected in their tumor. Arm I evaluated palbociclib, a reversible, selective oral small molecule inhibitor of CDK 4 and 6 in tumors harboring specified genomic alterations in the cyclinD-cdk4/6-INK4a-Rb pathway: amplification of *CDK4*, *CDK6*, *CCND1*, *CCND2*, or *CCND3*. Positive Rb expression by IHC was required. **Methods:** Palbociclib was administered on days 1–21 at 75 mg/m² once daily in 28-day cycles for up to 2 years, until disease progression, or intolerable toxicity. Response assessment occurred every 2–3 cycles. The primary endpoint was objective response (OR) rate; secondary endpoints included safety/tolerability and progression-free survival (PFS). **Results:** Twenty-three patients (median age 15 yrs; range 9–21) were enrolled between August 2018 and May 2022. Twenty patients received protocol therapy and were evaluable for response. Of treated patients, osteosarcoma was the most common diagnosis (9/20, 45%), with amplification of *CCND3* detected in 6/9 patients, *CDK4* in 2, and *CDK6* in 1. Rhabdomyosarcoma was next most frequent (6/20, 30%), with all tumors harboring *CDK4* amplifications. Other diagnoses were high grade glioma (n = 2), soft tissue sarcoma (n = 2), and neuroblastoma (NB) (n = 1). Additional genomic alterations were detected in 9/20 tumors, most frequently *TP53* mutations (n = 4, including 2 patients with Li-Fraumeni syndrome). Palbociclib was generally well tolerated with hematologic toxicities being the most common treatment related events and no related grade 5 events. Neutropenia was the most common grade 3–4 adverse event (n = 10, 50%) followed by thrombocytopenia (n = 8, 40%), leukopenia (n = 7, 35%), and anemia (n = 5, 25%). Four patients came off study for toxicity (3 for prolonged thrombocytopenia (cycle 1 (x2) and cycle 2) and 1 for prolonged grade 4 neutropenia (cycle 3)). Non-hematologic toxicities were mild (grade 1–2). No ORs were seen. Two patients with tumors harboring *CDK4* amplifications had stable disease (SD): one with NB had SD for 5 cycles and one with sarcoma had SD for 3 cycles but came off therapy for toxicity. Six-month PFS was 10% (95% CI: 1.7%–27.2%) and six-month overall survival was 65% (95% CI: 40.3%, 81.5%). **Conclusions:** The CDK4/6 inhibitor palbociclib at 75mg/m² PO daily was well tolerated in this heavily-pretreated cohort. No objective responses were observed in these biomarker-selected patients with treatment-refractory solid tumors. Further evaluation of this agent in combination with chemotherapy in the pediatric population is ongoing. Clinical trial information: NCT03526250. Research Sponsor: U.S. National Institutes of Health.

Treatment of focal anaplastic Wilms tumor (FAWT): A report from the Children's Oncology Group (COG) AREN0321 and AREN03B2 studies.
First Author: Amy E. Armstrong, Washington University in St Louis, St. Louis, MO

Background: FAWT represents tumors with circumscribed small areas of anaplastic nuclear changes confined to the kidney within an otherwise favorable histology WT. In National Wilms Tumor Study-5, patients with stage I FAWT treated with vincristine and dactinomycin (VA) without flank radiation had 4-year event-free survival (EFS) and overall survival (OS) of 67.5% and 88.9%, respectively. Patients with stage II–IV FAWT were treated with VA plus doxorubicin and radiation (DD4A). Of the 20 patients with stage II–III FAWT, 4 had a relapse and 3 died. The 4-year EFS and OS for stage IV FAWT/upfront nephrectomy were 61.4% and 71.6%, respectively. The COG AREN0321 study evaluated whether intensifying therapy for stage I and IV FAWT would improve survival of these patients. **Methods:** Tumor histology and stage were confirmed for all patients by real-time central pathology, surgery, and radiology review on protocol AREN03B2, the COG renal tumor classification, biology, and banking study. Patients then enrolled on AREN0321 with stage I–III FAWT received DD4A and those with stage IV FAWT received vincristine, doxorubicin, cyclophosphamide, carboplatin and etoposide with radiation (UH-1). We analyzed outcomes of patients with FAWT treated on AREN0321 and those enrolled only on AREN03B2 who received the same chemotherapy regimens. **Results:** A total of 46 patients (25 AREN0321 and 21 AREN03B2) were included in the analyses. Of the 25 AREN0321 patients, 17 (68%) had upfront nephrectomy and all 25 received radiation. Of the 5 AREN0321 patients with stage IV FAWT, 4 had metastasis to lung and 1 to lung and liver. Of the 21 AREN03B2 patients, 19 (90%) had upfront nephrectomy and 17 (81%) reported receiving radiation. The 2 AREN03B2 stage IV patients had lung only metastases. The 4-year EFS and OS are displayed in the table below. No events occurred in stage I–II AREN0321 patients nor in any AREN03B2 patients. Of 10 patients with stage III FAWT on AREN0321, 3 had a relapse. None of the 7 stage IV FAWT patients who received UH-1 had a relapse, but one patient died due to toxicity. **Conclusions:** Patients with stage I and II FAWT had outstanding survival when treated with DD4A and radiation. Intensification of therapy may be warranted for stage III FAWT and appears to have improved patient survival for stage IV FAWT but with increased risk of toxicity. Strategies to alleviate toxicity of UH-1 therapy have been incorporated into the ongoing COG trial for high-risk patients. Clinical trial information: NCT00335556. Research Sponsor: Children's Oncology Group.

Disease stage	AREN0321 FAWT cohort				AREN0321 + enrolled only on AREN03B2 FAWT combined cohort			
	4-year EFS (%) (95% CI)		4-year OS (%) (95% CI)		4-year EFS (%) (95% CI)		4-year OS (%) (95% CI)	
	n		n		n		n	
Stage I	8	100	100	15	100	100	100	100
Stage II	2	100	100	6	100	100	100	100
Stage III	10	70 (46.7-100)	78.8 (56.4-100)	18	83.3 (67.8-100)	88.1 (73.9-100)	88.1 (73.9-100)	88.1 (73.9-100)
Stage IV	5	80 (51.6-100)	80 (51.6-100)	7	85.7 (63.3-100)	85.7 (63.3-100)	85.7 (63.3-100)	85.7 (63.3-100)
Overall	25	84 (70.8-99.7)	87.8 (75.8-100)	46	91.2 (83.3-99.8)	93 (85.7-100)	93 (85.7-100)	93 (85.7-100)

10007

Oral Abstract Session

Erdafitinib in patients with FGFR-altered tumors: Results from the NCI-COG Pediatric MATCH trial arm B (APEC1621B).
First Author: Alice Lee, Children's Hospital at Montefiore, Bronx, NY

Background: The NCI-Children's Oncology Group (COG) Pediatric Molecular Analysis for Therapy Choice (MATCH) trial assigns patients aged 1–21 years with relapsed or refractory solid tumors, CNS tumors, lymphomas, and histiocytic disorders to phase 2 treatment arms of molecularly-targeted therapies based on genetic alterations in their tumor. Arm B (APEC1621B) evaluated the orally bio-available FGFR inhibitor erdafitinib in patients whose tumors harbored activating alterations in FGFR 1/2/3/4. **Methods:** Patients received oral erdafitinib 4.7 mg/m²/dose (Max dose: 8 mg) daily for 28-day cycles until disease progression or drug related dose limiting toxicity (Max 26 cycles). Disease assessments were performed every 2–3 cycles. The primary endpoint was objective response rate; secondary endpoints included progression free survival (PFS). **Results:** A total of 20 evaluable patients (median age: 15 yrs) were enrolled from June 2018 to July 2022 in this first study of erdafitinib in pediatric patients. The most common diagnosis (n = 17) was glioma or glioneuronal tumor (11 low grade and 6 high grade). Three patients had non-CNS solid tumors (1 each with neuroblastoma, osteosarcoma, and rhabdomyosarcoma). FGFR alterations detected consisted of activating hotspot mutations in *FGFR1* (n = 16), *FGFR2* (n = 1), *FGFR4* (n = 1), and *FGFR1* fusions (n = 2; *FGFR1:TACC1*, *FGFR1:TACC3*). Partial responses were confirmed by central review in 2/20 patients (10%, 90%CI: 3.4%, 26.2%), both with low grade gliomas or glioneuronal tumors (LGG, LGGNT) and *FGFR1* hotspot mutations (K687E and N577K). A best response of stable disease (SD) was observed in 6 additional patients with gliomas with a median duration of SD of 6.5 cycles. Six-month PFS was 45% (95% CI: 23.1%, 64.7%) and six-month OS was 89.7% (95%CI: 64.8%, 97.3%). Treatment related adverse events included those previously reported with FGFR inhibitors including hyperphosphatemia and nail changes or infections. Grade 1 vision changes were also reported. There was one Grade 3 spinal cord compression and one Grade 4 intracranial hemorrhage. **Conclusions:** Erdafitinib was generally well tolerated in this heavily pre-treated cohort of children with relapsed tumors harboring FGFR alterations. Partial responses or stable disease were observed in the majority (6/11, 54%) of patients with *FGFR1*-mutant low grade gliomas or glioneuronal tumors, suggesting the possible benefit of FGFR inhibitor therapy for these patients. Further studies would be necessary to more thoroughly evaluate the activity of erdafitinib for patients with other histologies and FGFR alteration types or combination approaches that include other targeted and/or cytotoxic agents. Clinical trial information: NCT03210714. Research Sponsor: U.S. National Institutes of Health.

10008

Oral Abstract Session

Phase 2 study of larotrectinib in children with newly diagnosed infantile fibrosarcoma (IFS): Children's Oncology Group (COG) ADVL1823 cohort A. *First Author: Theodore Willis Laetsch, Division of Oncology, Children's Hospital of Philadelphia, and Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA*

Background: *NRK1/2/3* gene fusions (TRK fusions) occur in a range of pediatric cancers and are the canonical molecular alterations in IFS. Larotrectinib is a highly selective TRK inhibitor that is FDA-approved for TRK fusion solid tumors in patients with no satisfactory alternative treatments or whose cancer has progressed following initial treatment. ADVL1823 (NCT03834961) evaluated larotrectinib in children with newly diagnosed TRK fusion positive solid tumors in two histology-based cohorts. Cohort A enrolled patients with IFS and is the focus of this analysis. **Methods:** Newly diagnosed patients ≤ 30 years old with unresectable or metastatic IFS and a locally identified *NRK* gene fusion were eligible for Cohort A utilizing a Simon 2-stage design. Patients received larotrectinib at a dose of 100 mg/m²/dose BID (max of 100 mg/dose) continuously in 28-day cycles until disease progression, unacceptable toxicity, the tumor becoming surgically resectable following a minimum of 6 cycles of therapy, or completion of 12 cycles (for those with CR) or 26 cycles (for those with PR) of therapy. The primary endpoint was the centrally confirmed objective response rate within 6 cycles according to RECIST 1.1; response assessment occurred every 2 cycles for the first 6 cycles. The data cutoff was December 31, 2022. **Results:** Between October 2019 and May 2022, 18 patients with IFS were enrolled from 14 centers. The median age was 2 months (range <1 month to 4.6 years). *NRK* fusions included presumed/confirmed *ETV6:NRK3*, *n*=15, *NRK3* (partner unconfirmed), *TMP3:NRK1* and *DCTN1:NRK1*, *n*=1 each, and were identified by FISH (*n*=8), NGS (*n*=7), and PCR (*n*=3). 17 of 18 patients (94%) demonstrated confirmed objective responses (16 PR and 1 CR,) resulting in closure to enrollment after meeting the pre-specified efficacy threshold. The only patient without confirmed response demonstrated 79% tumor reduction after cycle 2, but no confirmatory scan was obtained within the first 6 cycles. No patient discontinued therapy within the first 6 cycles due to disease progression or toxicity. Four (22%) patients had dose limiting toxicities: 2 neutropenia (both CTCAE V5 grade (G4) and 1 each G3 AST increase and G3 weight loss. All patients resumed therapy following a dose reduction. Treatment-related grade ≥ 3 toxicities occurred in 7 patients, most commonly neutropenia (*n*=5, 3 G3, 2 G4). **Conclusions:** Larotrectinib is highly active and well tolerated in newly diagnosed patients with IFS. Enrollment of this very rare molecularly defined patient population was feasible within the COG. Ongoing follow-up will evaluate durability of response after treatment discontinuation at protocol specified response-adapted timepoints with or without surgical resection of tumor. Clinical trial information: NCT03834961. Research Sponsor: U.S. National Institutes of Health; St. Baldrick's Foundation; Bayer.

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Oral Abstract Session

Feasibility and acceptability of social determinants of health data collection in the context of a Children's Oncology Group trial. *First Author: Emily Jones, Dana-Farber/Boston Children's Cancer and Blood Disorders Center, Boston, MA*

Background: Children who are Black, Hispanic or of proxied low socioeconomic status experience inferior survival outcomes despite receipt of uniform treatment on Children's Oncology Group (COG) trials. Investigation of mechanisms underlying these disparities and evaluation of interventions to address them has been limited by inadequate data. Prior COG trials have collected child race, ethnicity, insurance and zip code—non-modifiable data elements that are prone to misclassification bias—as proxies for exposure to adverse social determinants of health (SDOH). Collection of parent-reported SDOH data provides key information not previously assessed in COG trials, including modifiable exposures such as household material hardship (HMH): food, housing, utility or transportation insecurity. We report the preliminary feasibility and acceptability of the first COG trial to prospectively embed SDOH data collection. **Methods:** ANBL1531 (NCT03126916), the current frontline, groupwide COG trial for patients with high-risk neuroblastoma, was amended in September 2019 to include an opt-in, correlative aim to evaluate parent-reported SDOH. Parents of patients < 18 years could opt-in during initial ANBL1531 consent to complete a brief, single-timepoint survey at their enrolling site during Induction Cycle 1. Survey domains included parent-reported demographics, HMH, household income, and social support. Paper/pencil surveys available in English, Spanish or French were self-completed or read-aloud by site personnel and could be administered in any language with an interpreter. Surveys were submitted to a central disparities study team for data cleaning and entry into an electronic database. **Results:** As of December 31, 2022, 360/413 eligible participants opted-in to the embedded SDOH aim across 101 COG sites (87.2% consent rate). Among participants, 316 surveys (87.8%) were completed a median of 11 days post-enrollment. Four (1.1%) parents declined survey completion (3 withdrew consent). Reasons for non-completed surveys included: survey still pending within protocol-specified window (*n* = 10), institutional COVID-19 restrictions (*n* = 6), site scheduling issues (*n* = 6), patient came off ANBL1531 protocol (*n* = 5) and unknown (*n* = 13). Data missingness for HMH, the primary SDOH of interest, was 0.8%. Surveys were administered in English, Spanish, French, Vietnamese, Arabic, Mandarin and Tamil. **Conclusions:** Collection of parent-reported SDOH data as an optional, embedded component of a groupwide COG trial is feasible and acceptable, as demonstrated by remarkable willingness to participate and infrequency of missing data. Incorporation of this approach in future National Clinical Trials Network trials is essential to inform impactful health equity research, including the development and evaluation of targeted interventions to address outcome disparities. Research Sponsor: Philanthropic Funds.

10009

Oral Abstract Session

Feasibility of the Poverty-Targeted Pediatric Cancer Resource Equity (PediCARE) intervention. *First Author: Haley Newman, Children's Hospital of Philadelphia, Philadelphia, PA*

Background: Children with cancer living in poverty are more likely to relapse and die, even when treated uniformly on clinical trials. No evidence-based interventions targeting poverty as a risk factor for disparate outcomes exist in pediatric oncology. We previously developed and refined the Pediatric Cancer Resource Equity (PediCARE) intervention—a centrally-delivered, household material hardship (HMH)-targeted intervention that provides transportation and groceries to low-income pediatric oncology families. We report feasibility of administering PediCARE as a randomized intervention across 2-centers. **Methods:** We conducted a pilot randomized controlled trial (RCT) of PediCARE versus usual care at Dana-Farber Cancer Institute (DFCI) and University of Alabama Birmingham (UAB) between May 2019 and August 2021 (NCT03638453). Eligible participants included children age < 18 years with *de novo* cancer diagnosed in the prior 2-months, who were planned to receive at least 4-cycles of chemotherapy and lived in a household that screened positive for HMH (food, housing, utility or transportation insecurity). Participants were randomized 1:1 by site to receive PediCARE or usual care for 6-months. Parent/guardians completed a household survey at baseline and at completion of the 6-month intervention. The primary outcome was feasibility defined *a priori* as a recruitment and consent to randomization rate of $\geq 75\%$ and $< 20\%$ attrition per arm—endpoints intended to justify the feasibility of a subsequent efficacy RCT. Secondary outcomes included proportion of recipients who successfully received the intervention and intervention acceptability. **Results:** A total of *N* = 40/40 eligible families (*n* = 12 UAB; *n* = 28 DFCI) were approached and offered an opportunity to participate (100% consent rate). Among participants, there was 0% attrition in either arm following randomization and the 6-month intervention period; 100% of parent/guardians completed both baseline and 6-month surveys. Among those randomized to PediCARE, 100% (*n* = 20) successfully received grocery and transportation resources; 100% reported that it was "easier to buy food for my family," 85% reported it was easier to get to and from the hospital, and 95% reported they would be "very likely to recommend the intervention to other families". **Conclusions:** Stark disparities exist in pediatric oncology. Advancement in health equity science must include establishment of a robust, evidence-based portfolio of scalable health equity interventions for evaluation in the Children's Oncology Group (COG) drug trial setting. Findings from this pilot RCT support feasibility and utility of a poverty-targeted intervention from the clinical oncology setting—as evidenced by 100% of parent/guardians consenting to randomization with 0% attrition across 2-centers. Immediate next steps include randomized efficacy evaluation in a COG trial-embedded study. Clinical trial information: NCT03638453. Research Sponsor: Charles Hood Foundation and Family Reach Foundation.

10011

Oral Abstract Session

Medicaid enrollment changes among U.S. adult survivors of childhood cancer following medicaid expansion: A report from the Childhood Cancer Survivor Study (CCSS). *First Author: Xu Ji, Emory University School of Medicine, Atlanta, GA*

Background: Little is known about whether Medicaid expansion under the Affordable Care Act (ACA) affected insurance coverage among adult survivors of childhood cancer, a population at high-risk for poor health outcome. We addressed this gap by evaluating the association between ACA Medicaid expansion and Medicaid enrollment among participants in the Childhood Cancer Survivor Study (CCSS). **Methods:** The CCSS cohort of 5-year survivors of childhood cancer was linked to administrative Medicaid insurance data in 2010-2016. We identified 13,895 adult survivors (aged 18-64 years) diagnosed with cancer under age 21 and between 1970 and 1999. Outcomes included (1) percentage with any Medicaid enrollment by year; and (2) Medicaid-covered days (number of days when a survivor was enrolled in Medicaid) during each year. Multivariable difference-in-differences (DD) models were used to examine outcome changes pre vs. post ACA Medicaid expansion, in expansion- vs. non-expansion states, adjusting for age, sex, race/ethnicity, income, education, and chronic conditions. Multivariable models were conducted overall and then stratified by cancer type, race/ethnicity, income, and education. **Results:** Medicaid enrollment rates increased more in expansion states (17.6% pre-expansion to 24.1% post-expansion) than non-expansion states (16.4% to 16.9%), leading to a net increase in enrollment of 6.6 percentage points (ppt; 95% CI = 5.5-7.7) in the multivariable DD model. Multivariable DD model showed a net increase of 18.4 days (95% CI = 13.8-23.1) in Medicaid-covered days in expansion states relative to non-expansion states. The expansion-associated increase in Medicaid enrollment rates was greatest among survivors of leukemia (multivariable DD estimate: 8.9 ppt, 95% CI = 6.9-11.0) and non-Hodgkin lymphoma (8.0 ppt, 95% CI = 5.0-10.9). Greater increases in Medicaid enrollment were seen in non-Hispanic Black (13.5 ppt, 95% CI = 8.0-19.1) and Hispanic survivors (15.8 ppt, 95% CI = 10.6-21.0) than non-Hispanic White peers (5.1 ppt; 95% CI = 4.0-6.2); in survivors with $< \$20K$ household income (11.7 ppt, 95% CI = 8.9-14.4) compared to those with $\geq \$60K$ household income (2.9 ppt, 95% CI = 1.6-4.2); and in survivors with high school or lower education (9.3 ppt, 95% CI = 6.9-11.8) compared to those with a college or higher degree (3.9 ppt, 95% CI = 2.6-5.3). Similar patterns were observed across survivor subgroups when examining Medicaid-covered days. **Conclusions:** We provide the first evidence on increased Medicaid enrollment and longer coverage duration among adult survivors of childhood cancer following Medicaid expansion, with greater increases seen among survivors of underrepresented racial/ethnic populations, those with low socioeconomic status, and high medical need survivors. Research Sponsor: U.S. National Institutes of Health.

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Oral Abstract Session

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Oral Abstract Session

Enhancing prediction of cancer therapy-related cardiomyopathy from surveillance echocardiograms: A Children’s Oncology Group (COG) report. *First Author: Eric Jessen Chow, Fred Hutchinson Cancer Center, Seattle, WA*

Background: Many childhood cancer patients receive cardiotoxic therapies and need surveillance for therapy-related cardiomyopathy (CM). (Echo)cardiography is used to screen for cardiac dysfunction but has relatively poor discriminatory ability to predict who will develop CM. We sought to identify combinations of echo parameters that can better predict which patients subsequently develop CM. **Methods:** Longitudinal echos (obtained per routine care) of patients diagnosed with cancer < 21y who subsequently met CM criteria (left ventricular [LV] ejection fraction $\leq 50\%$ / fractional shortening $\leq 28\%$, ≥ 2 times, with ≥ 1 time after completion of cancer therapy) plus clinical data were collated from COG sites. Echos and data from patients without CM were also collated. All echos were centrally remeasured for 42 routinely reported parameters in blinded fashion. We applied least absolute shrinkage and selection operator (LASSO) to fit logistic models to identify the most influential predictors for CM development within 2 and 5y of echo, plus age and sex. Data were randomly split into training (85%) and test (15%) sets with 10-fold cross validation. Prediction accuracy was calculated using area under the ROC curve (AUC), based on the model that provided the minimum mean cross-validated error. **Results:** Echos from 88 CM cases (248 echos predating CM) and 126 non-cases (518 echos) were available. Patients (n = 214) were diagnosed at mean age 7.7 ± 5.2 y with mean 9.5 ± 4.0 y follow-up. Mean doxorubicin equivalent doses for cases and non-cases were 350 ± 188 and 272 ± 199 mg/m², respectively. For 2y CM prediction, models achieved training AUC 0.85 (95%CI 0.78-0.92; 261 echos) and test AUC 0.74 (95% CI 0.74-0.90; 46 echos). Factors selected included age, 2-dimensional (2D) measurements of LV geometry (LV systolic and end-systolic dimensions, and posterior wall thickness), systolic function (M-mode fractional shortening), diastolic function (mitral inflow E wave, septal E', septal A'), and a measurement of combined systolic and diastolic function (myocardial performance index). For 5y CM prediction, models achieved training AUC 0.90 (95%CI 0.85-0.95; 175 echos) and test AUC 0.89 (95%CI 0.78-0.99; 30 echos). Age, LV end-systolic dimension (2D and M-mode), M-mode LV posterior wall thickness, 2D wall thickness-dimension ratio, mitral inflow E, septal E', septal A', and the myocardial performance index were selected. At both times 2D end-systolic dimension was the most influential parameter. Inclusion of anthracycline and chest radiotherapy dose did not meaningfully improve the AUCs. **Conclusions:** Prediction models that incorporate conventional echo data may be able to accurately identify childhood cancer patients at high risk of developing CM 2-5y prior to CM diagnosis. This may provide a window of opportunity to introduce interventions that may arrest or slow CM progression. Research Sponsor: Rally Foundation; U.S. National Institutes of Health.

10014

Oral Abstract Session

Clonal hematopoiesis in survivors of childhood cancer. *First Author: Danielle Novetsky Friedman, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Subsequent malignancies and cardiovascular (CV) disease are the leading cause of premature death in childhood cancer survivors, a population also at risk for premature aging. Clonal hematopoiesis (CH), the age-related clonal expansion of mutated hematopoietic stem cells, is a prominent risk factor for early-onset malignant and CV disease. Data are lacking on the prevalence of CH in childhood cancer survivors. **Methods:** We evaluated the prevalence of CH in a retrospective case-control study of childhood cancer survivors and matched controls (all ≥ 13 years of age). Cases included individuals diagnosed with a solid tumor or lymphoma at age ≤ 25 years who were ≥ 6 -months from completion of chemotherapy and/or radiotherapy. Age-matched controls (5-year age bins) with and without a history of cancer were included, given evidence of shared genomic risk factors between cancer and CH. Samples were batched and sequenced at an average depth of 19,830x using a custom, targeted amplicon-based UMI sequencing platform (ArcherDX), which included full exons of DNMT3A, TET2, ASXL1, TP53, CHEK2 and targeted regions of PPM1D, SRSF2, SF3B1, JAK2. Mutations at a variant allelic frequency (VAF) $\geq 0.02\%$ were identified with VAF $> 2\%$ considered clinically significant. Logistic regression adjusted for age, gender, and race was used to test for an association between CH and case-control status. **Results:** Samples were analyzed from 104 childhood cancer survivors (median age 19 years [y], range, 13-49y; median time since end-of-therapy: 10y, range 0.5-39y), 71 controls with untreated, newly diagnosed cancer (median age 25y, range 8-48y), and 68 healthy controls (median age 23y, range, 15-51y). The frequency of CH was higher in childhood cancer survivors compared to controls across ages with CH detected in 36.5% of survivors and 20.1% of controls (OR 3.2, 95% CI, 1.6-6.1). The enrichment of CH in survivors was observed both relative to healthy controls (OR 2.3, 95% CI 1.1-5.3) and treatment-naïve solid tumor controls (OR 5.0, 95% CI, 2.1-13.7). A trend toward a stronger association for CH mutations with VAF $> 2\%$ (OR 10.9, 95% CI, 1.9-60.7) compared to VAF $< 2\%$ (OR 2.7, 95% CI, 1.4-5.2) was observed. The most commonly mutated genes were in the DTA (*DNMT3A*, *TET2* and *ASXL1*) and DDR (*PPM1D*, *TP53* and *CHEK2*) classes. While a higher proportion of both DTA and DDR mutations was noted among survivors compared to controls, the enrichment of DDR mutations was stronger than DTA (OR 7.1, 95% CI 2.8-18.3 for DDR; OR 2.3, 95% CI 1.1-4.6 for DTA). A sub-analysis of 5 year survivors showed a higher frequency of CH in this cohort compared to controls (OR 2.8, 95% CI, 1.3-5.9). **Conclusions:** Childhood cancer survivors have higher frequencies of CH than age-matched controls, which persists for years after treatment. These data suggest that CH may, in part, drive the long-term premature multimorbidity seen in survivors. Longitudinal assessment of CH among survivors may be indicated to elucidate these associations. Research Sponsor: Society of MSK Research Grant; Meg Berte Owen foundation; U.S. National Institutes of Health; The MSK Precision Interception Program, the Evans Center for MDS at MSKCC, and the Center for Pediatric Immunology at St. Louis Children’s Hospital and Washington University.

Carvedilol for prevention of heart failure in anthracycline-exposed survivors of childhood cancer: Results from COG ALTE1621. *First Author: Saro Armerian, City of Hope, Duarte, CA*

Background: Carvedilol improves cardiac function in patients with heart failure (HF), but remains untested as cardioprotective therapy in long-term childhood cancer survivors at risk for HF due to high-dose anthracycline exposure. We hypothesized that low-dose carvedilol would be safe and efficacious in reducing anthracycline-related heart failure risk in long-term survivors without evidence of HF. **Methods:** This was a randomized, double-blind, placebo-controlled phase 2B trial (NCT02717507) conducted at 28 sites. Eligibility included ≥ 250 mg/m² cumulative anthracycline exposure by age 21 years (y), ≥ 2 y from completion of cancer treatment, and preserved systolic function (ejection fraction [EF] $\geq 55\%$ and/or fractional shortening [FS] $\geq 28\%$) at enrollment. Patients were randomized 1:1 to take low-dose carvedilol (12.5 mg/day) or placebo for 2y; dose up-titration started at 3.125 mg/day. The primary objective was to determine the impact of carvedilol on echocardiographic indices of HF risk: standardized left ventricular (LV) wall thickness/dimension ratio (LVWT/Dz; primary endpoint), LV end-systolic wall stress (ESWS), LV chamber diameters, systolic and diastolic function. These indices were obtained every 6 months and measured centrally in a blinded fashion. Common Terminology Criteria for Adverse Events (CTCAE v4.0) was used to assess toxicity. Cardiac event was defined as relative EF/FS decline $< 20\%$ from baseline or both $< 55\%$ [EF] and $< 28\%$ [FS]. Treatment effects were analyzed using the Generalized Estimating Equation for normally distributed data, assuming linear time-trend. Group differences were evaluated by treatment*time interaction. **Results:** Of 196 participants enrolled, 182 were eligible and randomized. Characteristics (median, range): age at enrollment, 24.7y (10.4-53.9); time from cancer diagnosis, 13.4y (2.9-43.6); anthracycline dose, 374 mg/m² (250-1760); 19% had received chest-directed radiotherapy. There were no group differences in baseline participant demographics, cardiotoxic treatment exposure, or cardiac endpoints. LVWT/Dz was similar (+0.053, p = 0.15) between arms at 2y. However, treatment effects varied by time since diagnosis (p = 0.008) suggesting greater efficacy among longer-term survivors. Compared to placebo, carvedilol arm participants had significantly better LV end-diastolic diameter (-0.16 cm, p = 0.005) and LVESWS (-7.53, p = 0.027) at 2y. There were no CTCAE grade ≥ 3 events; all except 2 participants tolerated full dose escalation. Six out of eight cardiac events occurred on the placebo arm; longer-term follow-up of study participants is ongoing. **Conclusions:** In this randomized trial of long-term survivors of childhood cancer treated with high-dose anthracyclines, low-dose carvedilol was safe and effective in reducing established biomarkers of HF risk and could serve as a risk reduction strategy. Clinical trial information: NCT02717507. Research Sponsor: U.S. National Institutes of Health; Leukemia & Lymphoma Society, St. Baldrick’s Foundation, Rally Foundation, Altschul Foundation, STOP Cancer Foundation.

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Oral Abstract Session

Genomic determinants of outcome in acute lymphoblastic leukemia: A Children’s Oncology Group study. *First Author: Ti-Cheng Chang, St. Jude Children’s Research Hospital, Memphis, TN*

Background: While cure rates for childhood acute lymphoblastic leukemia (ALL) exceed 90%, half of relapses arise in those originally classified with standard risk (SR) disease. **Methods:** We performed genome/transcriptome sequencing of diagnostic and germline samples of children with SR (n=1381) B-ALL or high-risk (HR) B-ALL with favorable cytogenetics (*ETV6:RUNX1* or double trisomy (DT) of chromosomes (chr) 4+10; n=115) to identify predictors of relapse. We used a case-control study to analyze 439 patients who relapsed and 1057 who remained in complete remission for > 5 years. **Results:** Genomic subtype was associated with relapse. Unbalanced *ETV6:RUNX1* translocations were more common than balanced in relapse patients (OR=2.01, CI=1.25-3.20, P=0.002). Conversely, balanced *TCF3:PBX1* translocations were more often associated with relapse than unbalanced in *TCF3:PBX1* ALL (OR=0.11, CI=0.01-0.50, P=0.003). A striking finding was the high relapse rate in PAX5 altered ALL (57 of 116 cases (49%); OR=3.29, CI=2.16-5.01, P=3.49x10⁻⁸). The nature of the heterogeneous PAX5 driver alterations in this subtype influenced relapse risk, with internal PAX5 amplifications and biallelic PAX5 alterations associated with the highest risk. Specific chr gains influenced outcome in hyperdiploid ALL, with gain of chr 10 and disomy of chr 7 associated with favorable outcome (OR=0.27, CI=0.17-0.42, P=8.02x10⁻¹⁰, St Jude Children’s Research Hospital (SJCRH) validation cohort: OR=0.22, CI=0.05-0.80, P=0.009), while disomy of chr 10 and 17 and gain of chr 6 were enriched in patients that relapsed (OR=7.16, CI=2.63-21.51, P=2.19x10⁻⁵; SJCRH cohort: OR=21.32, CI=3.62-119.30, P=0.0004). Genomic alterations were also associated with relapse in a subtype-dependent manner, including alterations of *INO80* in *ETV6:RUNX1*, *IKZF1* and *CREBBP* in hyperdiploid, and *FHIT* in Ph-like ALL. **Conclusions:** Genetic subtype, aneuploidy patterns, and secondary genomic alterations influence risk of relapse in children otherwise classified with SR ALL, or HR ALL with favorable genetics. Comprehensive genomic analysis is required for optimal risk stratification and treatment allocation, and particularly to study reduction of therapy in the lowest risk patients. Research Sponsor: U.S. National Institutes of Health; St Baldrick’s Foundation; American Lebanese Syrian Associated Charities of St. Jude Children’s Research Hospital.

Association of driver genetic alterations with relapse in the most common MP2PRT subtypes*.

Genetic Driver	Odds Ratio	Confidence Interval	N (remission)	N (relapse)	p-value
ETV6:RUNX1 (557)	1.00	N/A	428	129	N/A
Hyperdiploid with DT (319)	0.65	0.45-0.93	264	55	1.66x10 ⁻²
Hyperdiploid, no DT (195)	1.75	1.21-2.51	129	66	2.79x10 ⁻³
PAX5alt (116)	3.29	2.16-5.01	59	57	3.49x10 ⁻⁸
DUX4 (54)	1.16	0.60-2.15	39	15	6.56x10 ⁻¹
TCF3-PBX1 (54)	1.39	0.73-2.53	37	17	3.04x10 ⁻¹
B-Other (44)	4.39	2.34-8.34	19	25	4.88x10 ⁻⁴
ETV6-RUNX1-like (36)	3.99	2.01-7.96	17	19	9.52x10 ⁻⁴
Ph-like (36)	2.14	1.04-4.28	22	14	3.82x10 ⁻²

*Only subsets with > 35 cases are included; all compared to ETV6:RUNX1.

10016

Oral Abstract Session

A phase 3 trial of inotuzumab ozogamicin for high-risk B-ALL: Second safety phase results from Children's Oncology Group AALL1732. *First Author: Maureen Megan O'Brien, Cincinnati Children's Hospital Medical Center, Cincinnati, OH*

Background: Inotuzumab ozogamicin (InO) is effective in adults and children with relapsed/refractory (R/R) CD22+ B-acute lymphoblastic leukemia (B-ALL). Children's Oncology Group AALL1732 is a phase 3 randomized trial evaluating InO for newly diagnosed patients (pts) with high-risk B-ALL. Given known hepatic, hematologic, and infectious toxicities, two safety phases were completed. **Methods:** Pts with residual marrow disease < 0.01% by end consolidation are randomized to chemotherapy (Arm A) or chemotherapy plus 2 cycles of InO (Arm B) after consolidation and interim maintenance 1 (IM1). Modifications after safety phase 1 [SP1; McNeer et al. *Blood* (2021) 138 (Suppl 1):3398] included reducing InO to 1.2mg/m²/cycle, increasing hydration during IM1 on Arm B, and enhancing supportive care in delayed intensification (DI) with antimicrobials. Safety phase 2 (SP2) assessed methotrexate (MTX) clearance, treatment delays and infectious/hepatic toxicity. Planned interim analysis is reported. **Results:** Fifty pts were randomized and evaluable (25 Arm A, 25 Arm B). There was no difference in gr ≥3 ALT or bilirubin elevations. Sinusoidal obstruction syndrome (SOS) occurred in 4 Arm B pts during DI including 3 (1 gr 3, 2 gr 4) in DI part 2 (DI2). IM1 day 1 MTX clearance was similar 65.4 (range 52.6-154) vs 70.2 hrs (range 56.5-267) on Arm A vs B, p = 0.27. Mean duration of IM1 was 74.8 (sd 11.8) vs 84 days (sd 13.3) on Arm A vs B, p = 0.013. Arm B IM1 duration in SP2 was shorter than SP1 [90 days (sd 15.3)]. DI part 1 (DI1) duration was similar between Arms. Arm B DI2 was longer than Arm A [53.8 (sd 20.2) vs 42.6 days (sd 9.5), p = 0.025]. Sepsis occurred in DI1 in 0 Arm A and 5 Arm B pts and in DI2 in 1 Arm A and 5 Arm B pts (Table). In DI2 1 pt on each Arm had gr 5 multiorgan failure (MOF) with sepsis. In DI1 50% of Arm A and 87.5% of Arm B pts had absolute neutrophil count (ANC) < 500 (p = 0.011). In DI2 all Arm A and 92.5% of Arm B pts had ANC < 500 with longer duration on Arm B [19.3 (sd 8.1) vs 7.8 days (sd 12.4), p = 0.015]. Compliance with prophylactic antibiotics was higher on Arm B (DI1 Arm A 41.7% vs Arm B 80.9%; DI2 Arm A 52.2% vs Arm B 85%). **Conclusions:** While SP2 modifications improved MTX clearance and duration of IM1, SOS and infections remain concerning on Arm B, particularly during DI. Most SOS events occurred proximal to thioguanine in DI2. Neutropenia was more pronounced in DI on Arm B but compliance with antimicrobials was high. Higher sepsis rates, primarily gr 3, were observed on Arm B with no increase in gr 5 infections. Additional modifications are planned for Arm B to further mitigate toxicity during post InO chemotherapy blocks. Clinical trial information: NCT03959085. Research Sponsor: U.S. National Institutes of Health.

Adverse Event	Block	Arm A (N; Gr3/ Gr4/Gr5)	Organism	Arm B (N; Gr3/ Gr4/Gr5)	Organism
Sepsis	DI1	0		5; 5/0/0	<i>C parapsilosis</i> <i>C albicans</i> <i>R mucilaginosa</i> <i>E coli</i> <i>S epidermidis</i> <i>E coli</i> x 3
	DI2	1; 0/1/0	<i>E coli</i>	5; 4/1/0	<i>K pneumoniae</i> <i>Aspergillus</i> & <i>C sartagiforme</i> <i>S Choleraesuis</i>
MOF	DI2	1; 0/0/1	<i>C difficile</i> & COVID-19	1; 0/0/1	

10018

Poster Discussion Session

Frequency and spectrum of clinically significant molecular alterations detected by tumor gene panel testing for pediatric cancer patients in the Texas KidsCanSeq study. *First Author: Frank Y. Lin, Texas Children's Cancer and Hematology Center, Baylor College of Medicine, Houston, TX*

Background: Tumor sequencing has the potential to inform diagnosis, prognosis, and treatment of childhood cancer patients. Prospective data are needed to evaluate the clinical utility of these tests. **Methods:** Patients less than 18 years of age with extracranial solid tumors (ST), central nervous system tumors (CNS), lymphomas and histiocytic disorders (L/H) were enrolled in the Texas KidsCanSeq clinical genomics study at six Texas institutions. Available tumor samples from a subset of patients designated as high risk (based on poor prognosis at diagnosis or tumor recurrence) were sequenced using pediatric cancer-focused targeted DNA (initially 124 genes; expanded to 169 genes) and RNA (81 genes) panels developed at Texas Children's Hospital. DNA variants (single nucleotide variants, insertion/deletions, splice site variants, copy number alterations) and fusion genes detected by RNA testing were analyzed. Tumor alterations were classified by molecular pathologists and oncologists as carrying strong (Tier 1) or potential (Tier 2) clinical significance following consensus guidelines from the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists. **Results:** A total of 626 patients were enrolled between 2018 and 2021, of whom 380 were designated as high risk. Tumor samples adequate for molecular testing were available from 342 of the 380 (90%) high risk patients (196 ST [57%], 132 CNS [39%] and 14 L/H [4%]). Clinically significant alterations were identified in 246 of 342 (72%) tumors: 165 (48%) from DNA testing only, 34 (10%) from RNA testing only, and 47 (14%) from both modalities. The frequency of clinically significant alterations was similar across tumor cohorts (74% ST, 68% CNS, 71% L/H). Alterations relevant to therapy-choice were reported in 127 of 342 (37%) tumors (35% ST, 26% CNS, 57% L/H); 87 of these 127 (69%) were not known from prior clinical testing. The most frequently altered therapeutic gene alterations (Table) involved *BRAF* (n=25), *CDKN2A/B* (n=20), *SMARCB1* (n=17), *GFR1/2/3/4* (n=14), *NF1* (n=13), *PIK3CA* (n=11), *ALK* (n=10), *CDK4* (n=9), and *RET* (n=7). One hypermutated tumor was identified: a high-grade glioma (tumor mutation burden > 190 mut/Mb) in a patient with Lynch syndrome due to a germline *MSH6* variant. **Conclusions:** Tumor alterations of clinical significance according to consensus guidelines were reported in a large proportion of children with diverse high risk or recurrent cancer diagnoses, the majority of which were not detected by other standard pathologic analysis. These data further support broader adoption of tumor molecular profiling for these patients. Research Sponsor: U.S. National Institutes of Health.

Therapeutic tier I and II gene alterations.				
Gene	SNV/indel	CNV	Fusion	Total
<i>BRAF</i>	16	0	9	25
<i>CDKN2A/B</i>	4	16	0	20
<i>SMARCB1</i>	5	12	0	17
<i>GFR1/2/3/4</i>	11	1	2	14
<i>NF1</i>	13	0	0	13
<i>PIK3CA</i>	11	0	0	11
<i>ALK</i>	4	1	5	10
<i>CDK4</i>	0	9	0	9
<i>RET</i>	1	0	6	7

10017

Oral Abstract Session

Preliminary results from the first-in-child phase II trial (ITCC-054/COG-AAML1921) of bosutinib in pediatric patients with newly diagnosed (ND) chronic myeloid leukemia (CML). *First Author: Edoardo Pennesi, Erasmus MC, Rotterdam, Netherlands*

Background: Bosutinib is a tyrosine kinase inhibitor (TKI), approved for adults with Philadelphia Chromosome (Ph+) CML; at the standard initial dose of 400 mg/day in ND patients, and 500 mg/day in resistant/intolerant (R/I) patients, administered orally once daily (QD) with food. Compared to the TKIs already approved in pediatrics, bosutinib has a different tolerability profile, and preclinical data suggest that longitudinal growth is potentially less impaired. Study NCT04258943 is an international, open-label, phase I/II trial, sponsored by the Erasmus Medical Center and the Children's Oncology Group, and funded by Pfizer Inc. The phase II arm enrolled ND patients, as well as R/I ones. The latter are not included in this analysis. **Methods:** ND patients aged 1-18 years with chronic phase CML, without evidence for organ toxicities, were enrolled. Main exclusion criteria included known T315I or V299L BCR-ABL1 mutations, and use of proton pump inhibitors and CYP3A inducers/inhibitors. The primary objectives of the phase II part of the study were to assess the safety and pharmacokinetics (PK) of bosutinib at the recommended phase II dose, which is body surface area adjusted, and consists of 300 mg/m² QD for ND patients (max 500 mg/day), as determined in the phase I part of the study. Based on regulatory authorities requirements, at least 35 patients have to be enrolled in phase II, with a total of 50-60 patients in phase I and II combined. This allows for pooled AE rates to be estimated with a maximum standard error of 0.071 and 0.065, respectively. **Results:** On 20/12/2022, 25 ND patients were screened, and 24 were enrolled: 15 males, median age 13 years (range: 5-17). The median follow up was 14 (range: 0.9-31) months. The most common non-hematological adverse events (AEs) were diarrhea (n = 16, Grade (Gr) ≤ 2 = 13), abdominal pain (n = 10, Gr ≤ 2 = 10), and nausea/vomiting (n = 8/8, Gr ≤ 2 = 7/8). Most common hematological AEs included platelet count decrease (n = 11, Gr ≤ 2 = 5), and anemia (n = 10, Gr ≤ 2 = 4). At 6 and 12 months, the cumulative incidence of Major Cytogenetic Response (MCyR) was 85% (95%CI 49%-96%) and 92.5% (95%CI 39%-99%), while for Complete CyR it was 77% (47%-91%) and 88.3% (95%CI 55%-98%), and for Major Molecular Response it was 23% (95%CI 7%-46%) and 30% (95%CI 10%-54%), respectively. Three patients permanently discontinued bosutinib due to intolerance, four due to unsatisfactory response per investigator's judgment, 17 were still on treatment at time of dataset lock. **Conclusions:** Bosutinib was well tolerated, despite common grade 1-2 gastrointestinal AEs. The preliminary efficacy seems comparable to published data from other second generation TKIs in children and to ND adult patients treated with bosutinib. Clinical trial information: NCT04258943. Research Sponsor: Pfizer Inc provided financial support.

10019

Poster Discussion Session

Comprehensive nationwide study on the prescription of experimental anticancer therapies for compassionate use in children and adolescents in France. *First Author: Pablo Berlanga, Gustave Roussy Cancer Campus, Villejuif, France*

Background: Compassionate use prescriptions of innovative anticancer therapies are common in pediatric oncology, although rarely reported and activity/safety information mainly based on single/limited institutional retrospective experiences. **Methods:** In France, early drug access before marketing authorization is granted by the French National Agency for the Safety of Medicines and Health Products (ANSM) in case on unmet need, positive benefit/risk balance of preliminary data and no access within clinical trials. All anticancer prescriptions approved by the ANSM from 01/01/2020 to 31/12/2022 for patients < 18 years-old were analyzed. Patients safety and activity data were collected through the SACHA France study (NCT04477681) in the 2020-2021 period. 2022 data analysis is currently ongoing and will be included in the presentation at ASCO. **Results:** In the study period, 1022 anticancer compassionate use prescriptions were authorized by ANSM. The most frequently prescribed drug was methotrexate drinkable solution (n = 526) and 383 prescriptions were within the inclusion criteria of the SACHA study (anti-cancer innovative therapies not approved in Europe or new formulation of an already approved drug after 2007). In the 2020-2021 period, 28 different therapies were prescribed to 188 patients in a French Society of Pediatric Oncology (SFCE) center. Of them, 14 patients never received the prescribed drug, mainly due to early death. 107 of 174 (61%) eligible patients from 21 SFCE centers were included in the SACHA study (56% in 2020 and 67% in 2021). Median age at inclusion was 6.0 years (range: 0.3 -17.3). Main cancer types were central nervous system (CNS) tumors (69), followed by non-CNS tumors (24) and leukemia/lymphoma (14). Main prescribed therapies targeted MEK/BRAF (66), EZH2 (11), BCL2 (7) and ALK/ROS1/MET (5). In 40/107 patients (37%) at least a grade ≥2 clinical and/or grade ≥3 biological adverse drug reaction (ADR) was reported, leading to delayed therapy in 15 % of patients. Overall, 10 serious ADRs were reported in 10 patients. At last news, 53/107 patients had stopped their drug, mainly due to disease progression (33), followed by physician decision (11) and toxicity ± physician decision (8). 12-months PFS was 49% (95 IC: 38-60 %), with a median of 334 days of follow-up for patients on therapy. **Conclusions:** To our knowledge, this is the first comprehensive nation-wide study on compassionate use prescriptions of experimental anticancer therapies to children and adolescents with cancer with prospective safety/activity information in more than 60% of patients. This study underscores the importance, and feasibility, of the close collaboration between academia and regulatory authorities to ensure adequate real-life monitoring of these prescriptions. Supported by Imagine for Margo, Association Hubert Guoin, Fondation du LEEM and the SFCE. Research Sponsor: Imagine for Margo, Association Hubert Guoin, Fondation du LEEM and the SFCE.

10020

Poster Discussion Session

Prognostic factors of early mortality in children and adolescents enrolled in oncology trials with a dose-finding part in the era of targeted and immune therapies: An Innovative Therapies for Children with Cancer (ITCC) study. *First Author: Fernando Carceller, The Royal Marsden NHS Foundation Trust, Sutton, United Kingdom*

Background: Phase I/II trials play a key role for children with relapsed/refractory tumors. Life expectancy beyond 8-12 weeks is a common eligibility criterion. However, there are no objective means to determine life expectancy for trial candidates. A better understanding of the risk factors associated with early mortality on trial could maximize the efficiency of such trials, whilst ensuring the ethical aspects of recruitment. **Methods:** Patients with relapsed/refractory solid tumors or lymphomas aged < 18 years and participating in interventional clinical trials with a dose-finding part between 2000-2018 in 14 ITCC centers (across 5 European countries) were eligible. The mortality at 30 and 90 days (30-DM and 90-DM, respectively) from Cycle1-Day1 (C1D1) and its association with clinical, laboratory and efficacy data were assessed. Validated prognostic scores (RMH, MDACC) were correlated with early mortality rates. **Results:** Overall, 527 cases were included in the study; 19 subjects had participated in > 1 trial, leaving a total of 507 subjects enrolled in their first phase I/II trial. Median age at C1D1 was 11.6 years (range, 0.5-17.9); male:female ratio 1.2:1; central nervous system (CNS) tumors (40%) Vs extra-CNS tumors (60%); 75% cases were treated in trials with at least one targeted therapy. The 30-DM (24/507) and 90-DM (116/507) were 4.7% (95%CI 3.1-7.0) and 23.0% (95%CI 19.3-26.8), respectively. At baseline the clinical variables which correlated with higher 90-DM in the univariate analysis were: performance status (Lansky or Karnofsky) $\leq 80\%$, no school/work attendance, requirement of opioids, ≥ 3 metastatic sites, Hb < 100 g/dL and Total Bilirubin, LDH or AST above normal levels (up to the maximum permitted according to protocol eligibility criteria). Higher RMH and MDACC scores also correlated with higher 90-DM. **Conclusions:** To our knowledge this is the largest case series of children and adolescents participating in pediatric phase I/II trials to date, in which most of the patients were treated with targeted or immuno-oncology agents. The reported 30-DM and 90-DM will serve as a reference benchmark for future trials. Performance status $\leq 80\%$, no school/work attendance, requirement of opioids and ≥ 3 metastatic sites correlated with higher 90-DM. Adult prognostic scores (RMH, MDACC) showed good correlation with 90-DM in the pediatric population. Prognostic factors of early mortality should be given appropriate relevance at the time of study design, informing families and recruiting patients to these studies. Research Sponsor: None.

10022

Poster Discussion Session

Identifying osteosarcoma signatures in cell free DNA using 5-hydroxymethylcytosine profiling. *First Author: Evan W Neczypor, University of Chicago Pritzker School of Medicine, Chicago, IL*

Background: Osteosarcoma is the most common primary bone tumor in children and adolescents. Prognostic biomarkers are limited, and post-treatment surveillance relies heavily on radiologic imaging. Capture and analysis of cell-free DNA (cfDNA) from the bloodstream is an emerging technique that could be used to provide additional prognostic information and track residual disease following treatment. 5-hydroxymethylcytosine (5-hmC) is an epigenetic marker of open chromatin and active gene expression, and tumor specific patterns of global 5-hmC deposition are identifiable in several cancers and vary according to disease burden. We profiled 5-hmC using plasma-derived cfDNA from osteosarcoma patients and healthy children to assess its utility as a biomarker of disease status. **Methods:** cfDNA was isolated from patients diagnosed with osteosarcoma and well child controls. Nano-hmC-Seal, a technique developed to isolate 5-hmC-modified DNA fragments, was used to generate sequencing libraries of cfDNA. Genomic DNA from osteosarcoma cell lines was serially diluted with healthy donor-derived cfDNA. DESeq2 was used to identify genes with high 5-hmC deposition in osteosarcoma cell line DNA relative to serial dilutions. In patient cfDNA samples, the relative abundance of 5-hmC deposition on these osteosarcoma genes was determined using gene set variation analysis (GSVA). GSVA returns a score ranging from -1 to 1, with positive values indicating a relative abundance of 5-hmC deposition on osteosarcoma genes. **Results:** The cohort consisted of 33 healthy children and 17 patients with osteosarcoma including 53 serially collected samples from these patients. 139 osteosarcoma genes were identified and used for GSVA analysis. Patients with osteosarcoma had significantly higher GSVA scores than well children (0.26 vs -0.38; $p < 0.001$). Hierarchical clustering identified two clusters of samples from children with osteosarcoma. Cluster 1 contained samples with scores correlating with osteosarcoma-derived DNA compared to Cluster 2 (0.14 vs -0.18; $p < 0.001$). Furthermore, Cluster 1 contained 17 of 23 samples from patients with active disease on clinical imaging (sensitivity = 74%, specificity = 57%). High 5-hmC deposition on *MYC* was readily identified in one sample obtained at diagnosis from the only patient with a *MYC* amplified tumor. Additional samples from this patient during treatment showed decreasing 5-hmC deposition on *MYC*, consistent with a treated tumor shedding less DNA into the blood. Additionally, decreased disease burden following surgical resection was identifiable in 5-hmC profiles (presurgical GSVA score 0.22 vs postsurgical -0.08; $p = 0.004$). **Conclusions:** Osteosarcoma 5-hmC signatures can identify patients with active disease. Monitoring cfDNA in osteosarcoma using 5-hmC profiling is a promising technique that warrants further investigation with larger patient cohorts. Research Sponsor: U.S. National Institutes of Health.

10021

Poster Discussion Session

Intensity at the end of life in pediatric neuro-oncology patients: The case for pediatric palliative care. *First Author: Chinwe Udemgba, University of Chicago, Chicago, IL*

Background: Although pediatric cancer is rare, it is the leading cause of death by disease after infancy for children and adolescents in the United States. Children exist in the context of a family; hence, excellent care for a child must also include attention to the needs of the family. Palliative care aims to enhance quality-of-life for these children living with life threatening illnesses and their families. Among pediatric cancers, brain tumors have high disease-related mortality rates; therefore, early introduction of palliative care to these patients is critical. This study aims to evaluate the association of palliative care during the terminal admissions of pediatric neuro-oncology patients and intensity of care provided at the end of life. **Methods:** Pediatric patients with brain tumors were identified using the Pediatric Health Information System (PHIS). Inclusion criteria were age <18, diagnosis of brain tumor as defined by ICD-10 codes, discharged as deceased, and hospital admission between 1/1/2017 and 12/31/2021. Intensity of care measures included: pediatric intensive care unit (PICU) admission, mechanical ventilation, total parenteral nutrition (TPN), and extracorporeal membrane oxygenation (ECMO). **Results:** 567 patients met the inclusion criteria. 359/567 (63%) patients had an inpatient palliative care consultation during their terminal hospital stay. Patients receiving a palliative care consultation had a lower percentage of PICU admission (64.9 vs 83.2, $p < 0.001$), mechanical ventilation use (51.0 vs 76.0, $p < 0.001$), and TPN use (18.1 vs 25.5, $p = 0.027$). There were no significant differences in length of stay (22.07 vs 22.25 days, $p = 0.181$) and ECMO use (0.28% vs 1.92%, $p = 0.450$). **Conclusions:** Pediatric patients receiving palliative care consultations during their terminal admission received less intense care while having comparable lengths of stay. Palliative care should be offered to all families, even with aggressive goals, to help incorporate quality of life and comfort in the treatment plan and to ensure bereavement support is available if needed. Similar to data in the adult palliative care literature, this data demonstrates reduced resource utilization among pediatric patients receiving palliative care. Palliative care has been shown to be a supportive service that has the potential to improve the quality of life of patients. The first step toward equitable healthcare is to ensure that all children with a potentially terminal cancer diagnosis have access to full supportive services, including palliative care. Research Sponsor: U.S. National Institutes of Health.

10023

Poster Discussion Session

A multicenter, open-label, single-arm phase 1/2 study to evaluate the safety and efficacy of FCN-159 in pediatric participants with neurofibromatosis type 1. *First Author: Xiaojie Hu, Department of Plastic and Reconstructive Surgery, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University, School of Medicine, Shanghai, China*

Background: Neurofibromatosis type 1 (NF1) is an autosomal dominant genetic disease characterized by multiple progressive tumor and non-tumor manifestations, with abnormal activating MAPK pathway. Plexiform neurofibromas (PN) presents in 20-50% of NF1 patients (pts) and may cause serious complications. Selumetinib was approved for pediatric pts with NF1-related PN in US and EU, but therapeutic options remain limited in China. FCN-159 is a highly potent selective anti-tumorigenic inhibitor of MEK1/2, potentially effective in NF1-related PN. **Methods:** This multicenter, open-label phase 1/2 clinical trial is the first-in human study to assess safety and efficacy in pediatric pts with NF1-related PN. The primary objective was to determine the dose limiting toxicity (DLT) and recommended phase 2 dose (RP2D) in the dose escalation, followed by a dose expansion phase 2 to evaluate safety and efficacy. The starting dose in pediatric pts was determined according to the adults in the dose-escalation phase (previously published in ASCO 2022, abstract no. 3011). Here, we first present the safety and efficacy results in pediatric participants. **Results:** As of data cut-off (November 21, 2022), 65 pts were enrolled, 19 pts in phase 1 and 45 pts in phase 2. A dose of 4 mg/m² (10 pts) and 5 mg/m² (9 pts) were evaluated in phase 1 and no DLT was observed. Pediatric pts in the 5 mg/m² cohort achieved similar exposure to the 8 mg adult cohort. AUC simulation from population PK model at different BSA ranges were also similar to the adults of 8 mg. Therefore, the RP2D was determined to be 5 mg/m². Treatment-emergent adverse events (TEAEs) were reported in 62 pts (95.4%). Common TEAEs ($\geq 20\%$) were mouth ulcer (43.1%), sinus arrhythmia (36.9%), upper respiratory tract infection (35.4%), folliculitis (21.5%), paronychia (21.5%), and increased blood creatine phosphokinase (20%). 5 pts (7.7%) experienced grade ≥ 3 treatment-related AEs (TRAEs), including 2 pts (2/10, 10%) in the 4 mg/m² group and 3 pts (3/55, 5.5%) in the 5 mg/m² group. Grade 3 TRAEs were increased aspartate aminotransferase (1.5%), electrocardiogram QT prolongation (1.5%), folliculitis (3.1%), and dermatitis acneiform (1.5%). No grade ≥ 4 TRAEs were observed. 2 pts (3.1%) reported treatment-related serious adverse events (one case of rhabdomyolysis and dermatitis acneiform each). TEAEs led to dose interruption (26.2%), and discontinuation (1.5%). No reported TEAE led to dose reduction or death. Of the 19 pts with at least one tumor assessment data after baseline, 8 (42%) pts had partial response, 11 (57.8%) with stable disease and none with disease progression. The median DOR could not be evaluated. **Conclusions:** Overall, FCN-159 was well-tolerated and demonstrated promising anti-tumor activity in pediatric participants with NF1-related PN. Long-term efficacy and safety follow-up are ongoing. Clinical trial information: NCT04954001. Research Sponsor: Shanghai Fosun Pharmaceutical Industrial Development Co., Ltd.

10024

Poster Discussion Session

A phase 2 study of sirolimus in combination with metronomic chemotherapy (CHOAnome) in children with recurrent and/or refractory solid and CNS tumors. *First Author: Thomas Cash, Aflac Cancer & Blood Disorders Center, Children's Healthcare of Atlanta, Emory University School of Medicine, Atlanta, GA*

Background: Multiple low-dose, anti-angiogenic (metronomic) chemotherapy regimens have demonstrated activity in pediatric solid and central nervous system (CNS) tumors. The mTOR pathway is activated in many human cancers and provides an attractive therapeutic target. We previously conducted a phase 1 trial establishing the dose (2 mg/m²), safety and tolerability of sirolimus in combination with metronomic chemotherapy. In the current study, we conducted a prospective, multi-institutional phase 2 trial to determine the objective response rate (ORR) in pediatric patients with recurrent and/or refractory (R/R) solid and CNS tumors treated with this regimen (NCT02574728); herein we report the results of the CNS tumor stratum. **Methods:** Patients aged 12 months to 30 years with R/R CNS tumors of all world health organization (WHO) grades were eligible. After completion of the trial's first stage, patients with diffuse intrinsic pontine glioma (DIPG) were excluded due to lack of efficacy. Patients were required to have measurable disease and no known curative therapeutic options. Treatment consisted of continuous sirolimus (2 mg/m²/dose PO daily), celecoxib (100 mg PO BID), and oral etoposide (50 mg/m²/day; max dose: 100 mg) alternating every 21 days with oral cyclophosphamide (2.5 mg/kg/day; max dose: 100 mg) in 42-day cycles. Sirolimus was dose-adjusted to maintain a serum trough concentration of 10-15 ng/ml. Response was determined using a modified Response Assessment in Neuro-Oncology (RANO) criteria. Enrollment proceeded using a Fleming's two-stage design based on best overall response (BOR), which required two objective disease status determinations. **Results:** Twenty-two CNS tumor patients were enrolled; 20/22 were evaluable for response. Median age was 11.2 years (range: 5.9 – 18.1); 6 (30%) were female. Diagnoses included DIPG (N = 5), medulloblastoma (N = 3), high-grade (HG) glioma (N = 5), HG/malignant neuroepithelial tumor (N = 3) and one each of diffuse midline glioma, atypical teratoid/rhabdoid tumor (ATRT), choroid plexus carcinoma, and pineoblastoma. Median number of cycles was 2 (range: 1-6). Best response after any cycle was partial response (PR) in 4 [medulloblastoma (N = 3); pineoblastoma (N = 1)], stable disease (SD) in 4, and progressive disease (PD) in 12 for an ORR of 20%; all patients with DIPG had PD at or before their first disease evaluation. BOR was PR in 3 (15%), SD in 2 (10%), PD in 14 (70%), and unknown in 1 (5%). Four patients had SD or response for ≥ 6 months [medulloblastoma (N = 1), pineoblastoma (N = 1), and HG glioma (N = 2)]. **Conclusions:** The combination of sirolimus with metronomic chemotherapy showed activity in pediatric patients with some R/R CNS tumors, producing objective responses in medulloblastoma and pineoblastoma. Patients with DIPG did not benefit from this regimen and should be offered alternative treatments. Clinical trial information: NCT02574728. Research Sponsor: Cannonball Kids cancer Foundation; Hyundai Hope on Wheels.

10026

Poster Discussion Session

Pediatric oncologist referral practices for CAR T-cell therapy: A mixed methods study. *First Author: Anurekha Gollapudi Hall, Seattle Children's Hospital, University of Washington, Seattle, WA*

Background: Chimeric antigen receptor (CAR) T-cells are a promising therapy for children with relapsed/refractory B-acute lymphoblastic leukemia. However, few centers provide CAR T therapy, which may lead to disparate access, particularly for those from disadvantaged populations. Referral by pediatric oncologists is an essential step in this process—and one susceptible to bias—but prior literature evaluating referral practices for CAR T therapies is limited. **Methods:** We conducted a mixed methods study to better understand oncologists' perspectives on barriers and facilitators to referral for CAR T therapies and possible biases in referral practice. Oncologists who previously referred patients for CAR T at five CPCI pediatric hospitals were emailed a survey. Descriptive statistics illustrated oncologist characteristics and factors influencing the referral process. We developed multivariable models to examine the association between oncologist characteristics, familiarity with CAR T, and referral practices. We conducted semi-structured interviews with a subset of participants and used thematic analysis to code transcripts. **Results:** 68 oncologists participated in the survey; 79% practiced at institutions with > 50 new pediatric oncology diagnoses per year. Factors identified as most significantly influential in the decision to refer included goals of care (75%), family interest in CAR T (35%), support from enrolling site (25%), insurance (22%), and family resources (20%). 77% of oncologists expressed being 'very familiar' with CAR T and 'very comfortable' providing information about CAR T to patients and families. In multivariate analysis, Hispanic oncologists and those at institutions with fewer than 50 new diagnoses per year were less likely to express familiarity with CAR T (OR 0.02 (CI: 0.0001-0.91), p = 0.04 and OR 0.04 (CI: 0.003-0.30), p = 0.005). 38% considered non-clinical patient and family-level factors (compliance, social support, resources, insurance, language, education, and race or ethnicity) to be significantly influential in referral decisions. Oncologists who were Hispanic and those practicing for at least 20 years were more likely to consider these factors significantly influential (OR 14.52 (CI: 1.49-358.66), p = 0.04 and OR 6.76 (CI: 1.18-50.5), p = 0.04) in multivariate analysis. Nine oncologists completed in depth interviews; important factors in the referral process included ease of insurance approval and established partnership with CAR T center. **Conclusions:** Many oncologists consider factors in addition to medical criteria when deciding to refer patients for CAR T, raising concern for bias in the referral process. Familiarity with available CAR T therapies may also affect eligible patient referral. Future work should focus on identifying ways to improve familiarity with CAR T in order to optimize patient access, while ensuring equitable referral practices. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology; U.S. National Institutes of Health.

10025

Poster Discussion Session

Physical and emotional quality of life in children with B-acute lymphoblastic leukemia randomized to every 4- vs. 12-week vincristine/dexamethasone during maintenance: Children's Oncology Group AALL0932. *First Author: Lyn M. Balsamo, Yale University, New Haven, CT*

Background: Children with B-acute lymphoblastic leukemia (B-ALL) undergo 2-3 years of treatment that impacts their quality of life. AALL0932 randomized reduction in vincristine and dexamethasone pulses (VCR/DEX every 4 weeks vs. every 12 weeks) during maintenance in the average-risk (AR) subset of NCI standard risk (SR) B-ALL. We longitudinally measured physical and emotional function overall and by treatment. **Methods:** SR AR B-ALL patients enrolled on AALL0932, aged ≥4 years, with English-speaking parents were evaluated at 5 timepoints (T1-T5: end consolidation, maintenance month 1, maintenance month 10, maintenance month 18 for boys/end of therapy for girls, end of therapy for boys). Parents completed the Pediatric Quality of Life Inventory Generic Core Scales 4.0 and a survey of supportive services received. Age- and sex-matched z scores and proportion impaired (> 2 SD below normative mean; 2.5% expected in normative population) on the emotional and physical function subscales were measured longitudinally and compared by treatment with the Fisher's exact test and repeated measures logistic regression. **Results:** Consent and data were obtained from 555 participants (mean/sd age = 6.0 ± 1.6 years, 46.8% female). Among randomized participants with completed evaluations, 31.3% had impaired physical function at T1 decreasing to 12.5% at T4. Emotional function was impaired in 24.5% of patients at T1 decreasing to 9.8% at T4. Overall 34.9-43.8% received special education/accommodations at T1-T5; there was low use of other services (Table). In adjusted analysis, treatment group was not associated with physical or emotional function. T2 impairment predicted increased risk of impairment at T4 for physical (OR = 4.7, 95% CI 2.3-9.7, p < 0.0001) and emotional (OR = 4.7, CI 2.3-9.5, p < 0.0001) function. **Conclusions:** Impaired physical and emotional function were prevalent early in SR AR B-ALL therapy, improved by the end of therapy, but remained higher than norms. Outcomes did not vary with VCR/DEX frequency. Patients with early emotional and physical impairment are at elevated risk of later impairment. Clinical trial information: NCT01190930. Research Sponsor: U.S. National Institutes of Health; St. Baldrick's Foundation.

	Timepoint									
	T1*		T2		T3		T4		T5	
	AB	CD	AB	CD	AB	CD	AB	CD	AB	CD
Impaired physical function N (%)	63 (30.1)	58 (32.6)	20 (10.8)	19 (11.9)	21 (11.8)	15 (10.3)	19 (11.5)	18 (13.7)	14 (18.4)	5 (9.1)
Impaired emotional function N (%)	50 (23.9)	45 (25.1)	27 (14.6)	15 (9.4)	23 (12.9)	20 (13.8)	16 (9.7)	13 (9.9)	11 (14.5)	1 (1.8)
Special education/ accommodations N (%)	76 (36.0)	70 (38.9)	77 (41.0)	63 (38.9)	70 (38.9)	64 (43.8)	66 (37.9)	59 (42.7)	29 (34.9)	25 (39.7)
Occupational/physical therapy N (%)	2 (0.9)	1 (0.6)	10 (5.3)	7 (4.3)	8 (4.4)	9 (6.2)	5 (5.2)	6 (4.4)	3 (3.6)	3 (4.8)
Mental health services N (%)	1 (0.5)	0 (0)	1 (0.5)	2 (2.5)	1 (0.6)	2 (1.4)	1 (0.6)	2 (1.4)	1 (1.2)	1 (1.6)

*Prior to randomization. AB = VCR/DEX every 4 weeks. CD = VCR/DEX every 12 weeks.

10027

Poster Discussion Session

Efficacy and safety of pembrolizumab (pembro) in children and young adults with newly diagnosed classical Hodgkin lymphoma (cHL) with slow early response (SER) to front-line chemotherapy (chemo) in the phase 2, open-label, KEYNOTE-667 study. *First Author: Luciana Vinti, IRCCS Ospedale Pediatrico Bambino Gesù, Rome, Italy*

Background: Patients (pts) with cHL with SER to initial chemo are at higher risk of relapse, and chemo dose intensification and radiotherapy (RT) can increase the burden of late organ toxicities. The open-label, phase 2 KEYNOTE-667 study (NCT03407144) is evaluating pembro plus chemo in pts with cHL and SER to front-line chemo. Results of an interim analysis in pts with high-risk cHL (group 2) and SER are presented. **Methods:** Pts were aged 3-17 (children) or 18-25 y (young adults) with newly diagnosed stage IIEB, IIIEA, IIIEB, IIIB, IVA, or IVB cHL. Pts received induction with 2 cycles of vincristine, etoposide, prednisone/prednisolone, and doxorubicin (OEPA). Response was assessed after induction (early) and consolidation (late) therapy by PET/MRI/CT. After induction, pts with rapid early response at the early response assessment (ERA) received nonstudy therapy and pts with SER at ERA received consolidation with 4 cycles cyclophosphamide, vincristine, prednisone/prednisolone, dacarbazine (COPDAC-28) plus pembro 2 mg/kg up to 200 mg IV every 3 weeks (Q3W; aged 3-17 y) or 200 mg IV Q3W (aged 18-25 y). Pts with PET positivity (Deauville score 4-5) after consolidation (late response assessment [LRA]), received involved-site RT (28.8 Gy) to late PET-positive residua; RT was omitted in pts with PET negativity. All pts with SER received maintenance pembro Q3W for a total of 17 doses. Primary end point was ORR by blinded independent central review (BICR) per Cheson 2007 International Working Group criteria in pts with SER. Secondary end points included PET negativity after consolidation and safety. **Results:** At data cutoff (Sep 02, 2022), median follow-up was 15.3 mo (range, 3.2-30.5); 49 pts with high-risk cHL with SER were included. Median age was 15 y (range, 6-22), 24 (49%) pts had bulky disease, and 31 (63%) had Ann Arbor stage IV disease. 22 (45%) pts completed treatment and 24 (49%) were ongoing on consolidation/maintenance treatment. Median time on pembrolizumab was 10.4 mo (range, 0.5-11.8). 42 (86%) of 49 pts had a LRA, of whom 27 (64%) were PET negative by BICR (30 [71%] PET negative by investigator). All-cause adverse events (AEs) occurred in 42 (86%) pts, with 30 (61%) having a treatment-related AE. Grade ≥3 AEs occurred in 13 (27%) pts, with 7 (14%) having a serious AE. Grade ≥3 treatment-related AEs occurred in 6 (12%) pts. 4 (8%) pts had immune-mediated AEs (2 grade 1 hypothyroidism; 2 grade 2 hypothyroidism). **Conclusions:** In pediatric pts with high-risk cHL and SER to standard OEPA induction, pembro plus COPDAC-28 consolidation had manageable safety and resulted in 64% of pts having a PET-negative response at end of chemo and being spared RT. These results suggest adding pembro to COPDAC-28 consolidation may augment responses in this high-risk population. Clinical trial information: NCT03407144. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

10028

Poster Discussion Session

Accelerated brain age and associated neurocognitive impairments in adult survivors of childhood cancer. *First Author: Nicholas Steve Phillips, St. Jude Children's Research Hospital, Memphis, TN*

Background: Structural brain aging assessed from routine clinical MRI exams is associated with neurologic and neurocognitive impairments in older non-cancer populations yet is unexplored in childhood cancer survivors. **Methods:** Neurocognitive assessments and clinical 3-D T1 MRI whole brain images were obtained on 253 childhood cancer survivors (acute lymphoblastic leukemia = 118; brain tumor = 49; Hodgkin lymphoma = 86) and 43 community controls. Brain age was estimated using open-source Gaussian process regression software (BrainAgeR) on visually inspected, segmented, and normalized MRI scans. Benjamin-Hochberg adjusted T-tests were used to compare age-adjusted neurocognitive z-scores between controls and survivors. Linear regression tested associations between brain age acceleration (brain age-chronological age) and treatment (multivariable), and neurocognitive outcomes (univariable). **Results:** Survivors (mean(SD) age 31.2 [8.9]) had poorer executive function (Trails B survivors -0.72 vs controls 0.32, $p < 0.0001$), processing speed (Grooved Peg Board -0.77 vs 0.05, $p < 0.0001$), memory (visual selection -0.73 vs -0.10, $p = 0.0010$; digit backward span -0.45 vs 0.08, $p = 0.0304$), vocabulary (WASI vocabulary -0.43 vs 0.14, $p = 0.0007$), and reading (WJ letter word -0.43 vs -0.05, $p = 0.0006$) compared to controls. In survivors, mean[95%CI] brain age was 7.5 [6.4 to 8.6] years older than chronologic age; 0.65[-1.0 to 2.3] years for controls. Compared to males without cranial radiation, for females age $\geq$ 10 years at cancer diagnosis treated with $\geq$ 40Gy cranial radiation, brain age acceleration was 13.35 years ($p < 0.001$), which worsened by an additional 9.81 years ($p = 0.017$) for those diagnosed < 10 years. Greater brain age acceleration was associated with a worse performance in executive function ($\beta = -1.73$, $p < 0.001$), processing speed ($\beta = -2.18$, $p < 0.001$), memory ($\beta = -2.07$, $p < 0.001$; $\beta = -1.78$, $p < 0.029$), vocabulary ($\beta = -2.04$, $p < 0.001$), and reading ($\beta = -3.77$, $p < 0.001$). **Conclusions:** Survivors of childhood cancer experience significant brain age acceleration that is associated with impairments in neurocognitive function. In non-cancer populations, accelerated brain age has been shown to predict late morbidities and mortalities. BrainAge is a promising surrogate biomarker that could predict cognitive decline and improve early detection of dementia risk. Finally, it highlights the risk of cranial radiation in < 10 -year-old female cancer survivors. Research Sponsor: U.S. National Institutes of Health; ALSAC.

10030

Poster Session

Adherence to mercaptopurine (6-MP) and habit strength in pediatric acute lymphoblastic leukemia (ALL). *First Author: Mira Yang, Department of Medical Education, Northwestern University Feinberg School of Medicine, Chicago, IL*

Background: Rates of adherence to mercaptopurine (6-MP) below 90% have been associated with increased relapse in pediatric patients with acute lymphoblastic leukemia (ALL). Habit strength has been associated with medication adherence through multiple mechanisms, including self-efficacy and social norms. The goal of this study was to investigate the relationship between habit strength, adherence to 6-MP, and health-related quality of life domains. **Methods:** This was a single center, cross-sectional study. A total of 52 participants, including 11 patients (ages 12-23, mean age 16 ± 4 , 45% Female) and 41 parents/caregivers (ages 25-43, mean age 37 ± 5 , 80% Female) of patients with ALL under the age of 18. Participants completed the Visual Analogue Scale (VASdose), PROMIS Medication Adherence Scale (PMAS), Self-Regulated Habit Index (SRHI), and PROMIS quality of life measures (PROMIS-CAT). Spearman's rho correlations were used to assess relationships between variables. Eleven semi-structured interviews of patients and caregivers were conducted and analyzed using Grounded Theory coding and thematic analysis. **Results:** Overall, 81% ($n = 42/52$) of participants surveyed had high adherence to 6-MP (VASdose $\geq 95\%$); 91% ($n = 10/11$) of patients and 78% ($n = 32/41$) of parents/caregivers reported high adherence. The median VASdose and PMAS score were 100% (IQR 97-100) and 39.5 (IQR 38-40) across all participants, respectively. Participants with higher adherence, VASdose $\geq 95\%$ and PMAS ≥ 39.5 , reported less physiological stress ($p = 0.02$), and better cognitive function ($p = 0.09$) and peer relations ($p = 0.08$), compared to those with lower adherence. No significant correlation was found between medication adherence rate and habit strength. Emerging themes from qualitative coding included the influence of routine and automaticity on 6-MP as well as adherence strategies. Strategies such as reminders, care team communication, and developing personalized tools were cited by participants as potentially improving adherence in taking or administering 6-MP. Other facilitating participant characteristics included experience with medication administration, self-efficacy, and access to social support. Financial burden, scheduling conflicts, and medication access were common barriers cited by participants. **Conclusions:** Nearly one-fifth of our participants reported lower adherence to 6-MP (VASdose $< 95\%$), which increases risk of relapse. Medication adherence to 6-MP was not associated with habit strength, but our results show preliminary associations between adherence rates and quality of life outcomes, such as physiological stress. Behavioral interventions are needed to better optimize adherence to 6-MP and improve health outcomes in pediatric ALL. Research Sponsor: None.

10029

Poster Discussion Session

Genetic study of type 2 diabetes risk in diverse populations of survivors of childhood cancer: A report from the St. Jude Lifetime Cohort (SJLIFE) and the Childhood Cancer Survivor Study (CCSS). *First Author: Cindy Im, University of Minnesota, Minneapolis, MN*

Background: Type 2 diabetes (T2D) is an established late effect of cancer treatment among long-term survivors of childhood cancer. Genetic factors underpinning T2D in diverse populations of survivors have not been well studied. **Methods:** We conducted a multi-ancestry genome-wide association study (GWAS) for clinically ascertained T2D among survivors of European (EUR; $N = 3,102$ with 261 cases) and African (AFR; $N = 574$ with 43 cases) ancestry from SJLIFE. Replication analyses were performed between ancestries in SJLIFE and in EUR survivors in CCSS ($N = 5,965$; 270 self-reported cases). Two published T2D polygenic risk scores (PRSs) were assessed in survivors: a 338-variant multi-ancestry PRS ($N \sim 1.4$ million; 49% non-EUR descent) and a ~ 6.9 million-variant EUR-only PRS ($N \sim 160K$; DIAGRAM Consortium and UK Biobank Study). Treatment-related T2D risk effect modification was evaluated for abdominal irradiation and alkylating agents. **Results:** In SJLIFE AFR survivors, one novel locus with suggestive significance was identified (5p15.2: OR = 10.19, $P = 5.1 \times 10^{-7}$), replicating in both SJLIFE EUR ($P = 0.011$) and CCSS EUR survivors ($P = 0.021$). A EUR-specific genome-wide significant association at 8q11.21 (*SNTG1* intronic variant; OR = 1.99; $P = 4.4 \times 10^{-8}$) was replicated in CCSS ($P = 8.1 \times 10^{-3}$). Two other loci with suggestive associations ($P < 5 \times 10^{-6}$) in SJLIFE EUR survivors replicated in SJLIFE AFR survivors ($P < 0.05$), achieving genome-wide significance in multi-ancestry meta-analysis (2p25.3: OR = 2.05, $P = 4.5 \times 10^{-8}$; 19p12: OR = 2.43 $P = 5.7 \times 10^{-9}$). Each of the three novel trans-ancestral loci overlapped putative Polycomb-repressed regions, i.e., chromatin-based gene regulation elements, in pancreatic cells and displayed treatment-related effect heterogeneity across ancestry groups. Notably, AFR survivors with risk alleles experienced disproportionately greater T2D risk if treated with alkylating agents (2p25.3: OR = 3.95; 19p12: OR = 5.74; 5p15.2: OR = 17.81). Increases in the T2D odds per multi-ancestry PRS standard deviation were consistent in survivors across ancestries (SJLIFE EUR: OR = 1.84, $P = 1.1 \times 10^{-16}$; SJLIFE AFR: OR = 1.80, $P = 2.8 \times 10^{-3}$, CCSS EUR: OR = 1.60, $P = 8.4 \times 10^{-13}$). However, T2D risk association with the EUR-only PRS was absent in AFR survivors (OR = 0.97, $P = 0.95$). **Conclusions:** Multi-ancestry genetic analyses revealed three novel T2D risk alleles associated with disproportionately greater alkylating agent-related risk among African-ancestry survivors. Furthermore, an external multi-ancestry T2D PRS was associated with increased risk in diverse ancestry survivors, whereas a EUR-only PRS was not useful for African-ancestry survivors. This study supports precision diabetes surveillance and survivorship care for all childhood cancer survivors, including those in minority ancestry groups. Research Sponsor: U.S. National Institutes of Health.

10031

Poster Session

Real-world use of tisagenlecleucel in children and young adults with relapsed or refractory B-cell lymphomas. *First Author: Jonathan Bender, Cincinnati Children's Hospital Medical Center, Cincinnati, OH*

Background: Survival for pediatric B-cell lymphomas (BCL) exceeds 90% with modern regimens, however outcomes remain poor for patients with relapsed or refractory (R/R) disease. Tisagenlecleucel is a CD19-directed CAR T-cell therapy (CAR T) that is FDA approved for adults with R/R BCL. No data exists for use of tisagenlecleucel in R/R pediatric BCL. **Methods:** We surveyed 48 sites in the Pediatric Real-World CAR Consortium to retrospectively describe use and outcomes of tisagenlecleucel for pediatric patients with R/R BCL. This cohort included 10 patients from 7 centers aged ≤ 25 years who were infused between 2019-2022 and were ≥ 3 months from CART. We aimed to describe response rates, as determined by each institution based on positron emission tomography, bone marrow evaluation, and/or cerebrospinal fluid (CSF) studies, along with toxicity and outcomes in this population. **Results:** Ten patients received CART with a median age at infusion of 19 (range, 7-24) years. Five patients had B-lymphoblastic lymphoma (B-LyL), 2 had primary mediastinal BCL, and 1 each had Burkitt lymphoma, diffuse large B-cell lymphoma (DLBCL), and post-transplant lymphoproliferative disorder related DLBCL. Five patients had primary refractory disease, and 5 were in $\geq 2^{nd}$ relapse. Three had received prior hematopoietic stem cell transplant (HSCT). Two had CSF involvement, and 1 had central nervous system parenchymal disease at time of infusion. CART was well tolerated with 1 patient experiencing grade 3 cytokine release syndrome and 2 patients experiencing neurotoxicity (grade 2 $n = 1$, grade 3 $n = 1$), both of whom had CSF involvement at time of CART infusion. Best overall response was complete response (CR) for 6, partial response (PR) for 2, and refractory disease for 2. Two patients, both with B-LyL, underwent allogeneic HSCT while in CART-mediated CR with B-cell aplasia. Both patients with PR (1 DLBCL, 1 Burkitt) subsequently relapsed with CD19-negative disease; the patient with DLBCL subsequently achieved CR with salvage immuno-chemotherapy and HSCT. All 6 CR patients remain in remission at a median time to follow-up of 31 (range, 14-47) months. **Conclusions:** This multicenter case series of CD19-directed CART for R/R pediatric BCL suggests that tisagenlecleucel may be safe and active in this population with all CR patients currently in sustained remission. Larger studies are needed to understand how best to incorporate CART into treatment for R/R pediatric BCL. Research Sponsor: None.

Prior # Therapies, median (range)	4 (1-8)
Prior HSCT	3/10 (30%)
Best Overall Response of Complete Response	6/10 (60%)
B-Lymphoblastic	4/5 (80%)
Burkitt	0/1 (0%)
Diffuse Large B-Cell	1/2 (50%)
Primary Mediastinal B-Cell	1/2 (50%)
Disease Status at Last Assessment	Alive, No Disease 7 (70%) Alive, With Disease 1 (10%) Deceased 2 (20%)
Cytokine Release Syndrome: Any Grade Grade ≥ 3	7 (70%) 1 (10%)
Neurotoxicity: Any Grade Grade ≥ 3	2 (20%) 1 (10%)

10032

Poster Session

Outcomes in pediatric relapsed/refractory anaplastic large cell lymphoma: A multi-institutional retrospective analysis. First Author: Lianna Jean Marks, Stanford University School of Medicine, Palo Alto, CA

Background: Treatment options for relapsed or refractory (R/R) anaplastic large cell lymphoma (ALCL) have increased in the era of targeted therapies such as brentuximab vedotin (BV) and Anaplastic Lymphoma Kinase (ALK)-inhibitors. However, there is no standard treatment and limited published data evaluating their use in this patient population. **Methods:** We conducted a retrospective, multi-institutional study of patients <22 yrs old at initial diagnosis with R/R ALCL treated between 2011-2021 across 18 institutions. **Results:** We identified 85 patients with R/R ALCL (median age at initial diagnosis 12 yrs, 67% male, 96% ALK+). Treatment for initial diagnosis included ALCL99 (31%), ANHL12P1 + BV (32%), ANHL12P1 + crizotinib (CZ) (11%), ANHL0131 (14%), or other (13%). Median time from diagnosis to relapse was 0.7 yrs (range 0.2-10.8 yrs) with sixteen patients (18%) relapsing on initial chemotherapy. Stage at relapse for 82 ALK+ patients: I (9%), II (15%), III (41%), IV (35%). Initial re-induction regimens shown in the table. Fifty-nine (72%) patients received a hematopoietic stem cell transplant (HSCT), 11 autologous and 49 allogeneic with one receiving both. Of 59 transplanted patients, 10 relapsed (6 allo 4 auto) and 7 died. All but one of the patients who relapsed post-HSCT responded to additional therapy and remain alive. Of 23 ALK+ patients who never had a transplant, 4 patients died and 19 are alive in remission. Eleven remain on active therapy (6 CZ, 3 BV, 1 BV+CZ, 1 vinblastine) with eight off therapy. Patients who received a transplant more likely to be off therapy and alive. Duration of treatment for patients receiving BV or the ALK-inhibitor CZ varied widely (BV 1-11 yrs; CZ 2-10 yrs) with 20 patients continuing on therapy at the time of data collection. Five-year overall survival for patients with or without transplant was 91% (CI 84-99%) and 86% (CI 73-100%) respectively. **Conclusions:** This is the largest collection of patients with R/R ALK+ ALCL treated in the era of targeted therapy. Patients achieved excellent responses to ALK-inhibitor or BV monotherapy, but questions remain about duration of therapy. Transplant may not be necessary for all R/R patients including those with high-risk disease. Research Sponsor: Stanford Maternal & Child Health Research Institute Award.

Characteristic	Overall N = 82	Not transplanted N = 23	Transplanted N = 59
Time to first relapse in yrs, Median (IQR)	0.7 (0.5 - 1.2)	0.8 (0.5 - 2.0)	0.7 (0.5 - 1.1)
First re-induction regimen, n (%)			
ALK-inhibitor	39 (48)	11 (48)	28 (47)
Brentuximab	17 (21)	5 (22)	12 (20)
Chemo	13 (16)	4 (17)	9 (15)
Chemo + Targeted	9 (11)	2 (8.7)	7 (12)
Vinblastine	4 (4.9)	1 (4.3)	3 (5.1)
Achieved CR, n (%)	76 (93)	19 (83)	57 (97)
Second relapse, n (%)	14 (17)	4 (17)	10 (17)
Treatment outcome, n (%)			
Alive off	51 (62)	8 (35)	43 (73)
Alive on	20 (24)	11 (48)	9 (15)
Dead	11 (13)	4 (17)	7 (12)
Death, n (%)			
Death due to ALCL progression	4 (4.9)	3 (13)	1 (1.7)
Death due to treatment toxicity	4 (4.9)	0 (0)	4 (6.8)
Death due to other cause	3 (3.7)	1 (4.3)	2 (3.4)

10034

Poster Session

Single-agent activity of the anti-GD2 antibody dinutuximab beta given as a long-term infusion in relapsed and refractory neuroblastoma (APN311-304).

First Author: Holger N. Lode, University Medicine Greifswald, Pediatric Hematology and Oncology, Greifswald, Germany

Background: Severe pain is a common side effect associated with short-term infusions of anti-GD2 antibodies in combination with cytokines and isotretinoin and was reduced by the long-term infusion (LTI) strategy. We investigated efficacy and tolerability of a single-agent dinutuximab beta (DB)-LTI in patients with primary refractory or relapsed (R/R) stage 4 neuroblastoma (NB). **Methods:** Patients with R/R-NB were enrolled into an open label phase II trial. Previous anti-GD2 antibody therapies were allowed, if anti-DB antibody could not be detected. Patients received 5 cycles of DB-LTI (100 mg/m²/10 days). The primary endpoint was objective INRC response 24 weeks after the end of cycle 5. A sample size of 40 patients provides at least 80% power to reject the null hypothesis of an objective response in < 10% of patients if the true objective response rate observed was 25% (overall 1-sided significance level 0.05, exact binomial test). Secondary endpoints included safety, morphine use, best response and duration of response, pharmacodynamics and pharmacokinetics, 3-year progression-free (PFS) and overall survival (OS). **Results:** 40 patients were treated and 38 patients had evaluable response. The objective response rate 24 weeks after the end of cycle 5 was 26% (10/38) (CR/PR) (p = 0.0034) and 32% (12/38) (CR/PR/MR), with a higher response rate in refractory vs. relapsed patients (50% vs 25%; p = 0.0159). The best response rate was 53% (20/38). Of 14 patients with bone marrow involvement, 13 patients responded (93%) (12 CR, 1 PR). The median duration of response (CR/PR) was 238 days (95% CI [108-290d]). The 3-year probability of PFS was 31% (95% CI [0.17-0.47]) and of OS was 66% (95% CI [0.47-0.79]). Survival was higher for patients with refractory compared to relapsed disease (PFS 47% vs 19%, OS 93% vs 50%; p = 0.015). Grade 3 treatment emergent adverse events (TEAE) were pain (18%), diarrhea (5%), and hypokalemia (5%) and grade 3 hypotension, capillary leak and neurotoxicity were not observed. In patients who experienced pain, mean pain scores (scale 0-10, where 0 is no pain) were low and decreased between cycles 1 and 2: pain score at rest decreased from 1.01 to 0.30, and at stress from 1.45 to 0.28. There were no grade 4 or 5 TEAEs. The morphine usage decreased from cycle 2 to 5 (C2 95%; C3 12%; C4 0%; C5 0%). DB peak serum concentration in cycle 1 was 10.8±0.7 µg/ml and patients showed 7- and 11-fold increase of antibody-dependent cell-mediated (ADCC) and complement-dependent cytotoxicity (CDC), respectively. Anti-DB antibodies were found in 24% of patients. There was no association and no trend between exposure to DB (area under the curve, peak or trough level) and response rate or survival in this cohort. **Conclusions:** Single-agent treatment with single agent dinutuximab beta given as long LTI without cytokines and without isotretinoin is effective and highly tolerable in R/R-NB. Clinical trial information: NCT02743429. Research Sponsor: Apeiron Biologics; Hector Stiftung; University Medicine Greifswald; EUSA Pharma; Kinderkrebsstiftung.

10033

Poster Session

Impact of fludarabine exposure on the depth and duration of lymphopenia and CAR T-cell outcomes. First Author: Keagan Lipak, Pediatric Oncology Branch, Center for Cancer Research (CCR), National Cancer Institute, NIH, Bethesda, MD

Background: Chimeric antigen receptor (CAR) T-cells are highly effective for patients with relapsed or refractory B-ALL. Lymphodepletion has been paramount to CAR T-cell expansion and efficacy. Recent data identified an association of fludarabine exposure with reduced relapse rates, longer leukemia free survival, and more prolonged B-cell aplasia following tisagenlecleucel. However, the relationship of fludarabine exposure to lymphopenia and the mechanism by which dosing impacts outcomes following CAR T-cells remains unknown. **Methods:** We conducted a retrospective review of children and young adults with B-ALL who received fludarabine for lymphodepletion (LD) prior to infusion of anti-CD19, anti-CD22, or anti-CD19/22 bispecific CAR T-cells. The primary objective of this study was to investigate the impact of fludarabine on the depth and duration of lymphopenia. Secondary objectives included examining the impact of fludarabine exposure on: 1) overall clinical response, and 2) CAR T-cell expansion. All patients in the analysis cohort received fludarabine 25 mg/m²/day x 3 days (= 75 mg/m² cumulative dosing). Fludarabine exposure (AUC per dose) for each patient was predicted using a validated population PK model and analyzed with various responses/endpoints using the 3-day cumulative exposure/patient. **Results:** Of 137 children and young adults, the median cumulative AUC was 8.3 mg*hr/mL (range, 3.00-13.83 mg*hr/mL). The overall complete response (CR) rate was: 67.9% (93/137). The median duration of lymphopenia (defined as an absolute lymphocyte count (ALC) ≤ 150 K/uL) was 5 days (range, 0-15); and the median ALC on Day 0 was 80 K/uL (range, 0-1250 K/uL). When stratified by the median fludarabine exposure, there was no difference in depth or duration of lymphopenia or CAR T-cell expansion collectively or per trial. The median fludarabine exposure also did not differ between responders and non-responders. However, depth and duration of lymphopenia did differ in the CD22 CAR T-cell trial. Specifically, in those achieving CR, the duration of lymphopenia was longer than in non-responders (7 days versus 4 days, p = 0.030). Similarly, CAR T-cell expansion was higher if lymphopenia duration was greater than 5 days (p = 0.019). These findings were not seen across our less persistent CD19 or CD19/22 CAR T-cell trials. **Conclusions:** Although lymphodepletion impacts CAR T-cell response, we did not find an association between CR rate, depth of lymphopenia, or duration of lymphopenia with varying fludarabine exposures. This raises additional questions regarding the impact of LD therapy on CAR T-cell outcomes—especially since a more prolonged lymphopenia was associated with high CR rates and greater peak expansion in at least one of our studies (CD22 CAR T-cells). Future analysis will evaluate the impact of fludarabine on Day 0 cytokines and other immune parameters. Clinical trial information: NCT03448393. Research Sponsor: U.S. National Institutes of Health.

10035

Poster Session

Comprehensive genomic profiling and individual therapeutic planning in high-risk/refractory pediatric solid tumors: A single-center real-world study.

First Author: Ondrej Slaby, Masaryk University, Faculty of Medicine, CEITEC, Brno, Czech Republic

Background: Despite major improvements in the survival of pediatric cancer patients that were achieved through the intensification of chemotherapy and the perfection of supportive care in the past decades, treatment outcomes for high-risk, relapsed, and refractory solid cancers remain unsatisfactory. Accelerating the progress of pediatric oncology requires both therapeutic advances and attention to reducing the long-term cytotoxic treatment-related side effects. This could be achieved by targeting specific molecular changes that drive pediatric malignancies. **Methods:** From September 2016 to August 2020, a total of 192 patients with pediatric high-risk solid tumors successfully underwent comprehensive genomic profiling. Since more than thirty patients had two or more biopsies from recurrent relapses, the total number of samples examined was 295. In the cohort, there were 78 cases of central nervous system tumors, 68 sarcomas, 14 neuroblastomas, 10 lymphomas, and 22 tumors of other histology. Whole-exome sequencing was performed in all patients, fusion gene analysis in 96% of patients, whole-transcriptome profiling in 84% of patients, and CNV analysis in 63% of patients. **Results:** The diagnostic yield of therapeutically actionable findings was 40%, with single-nucleotide variants and small insertions/deletions being the most common actionable alteration types. In 23% of patients, a clinically relevant gene fusion was identified. The majority of the identified fusions were of diagnostic significance, and 18% of those were therapeutically targetable gene fusions involving BRAF, RAF1, ALK, FGFR1, or NTRK2. Four patients were eligible for immunotherapy based on high tumor mutational burden (> 10 mut/Mb). Lymphomas and CNS tumors showed the highest rate of patients with therapeutically actionable findings (60% and 56%, respectively), followed by neuroblastomas (36%), sarcomas (25%), and other solid tumors (23%). All results and individual treatment plans were discussed and approved at multidisciplinary molecular tumor boards. **Conclusions:** Precision medicine in pediatric oncology has rapidly developed over the last decade and resulted in new therapeutic options based on molecular biomarkers and increased our understanding of the complexity of pediatric malignancies. Supported by the Ministry of Health of the Czech Republic, grant nr. NU20-03-00240 and the project National Institute for Cancer Research (Programme EXCELES, ID Project No. LX22NP05102) - Funded by the European Union - Next Generation EU. Research Sponsor: Czech Government.

10036

Poster Session

A phase 1b study of crizotinib in combination with temsirolimus in pediatric ALK- or MET-aberrated relapsed or refractory neuroblastoma (ITCC-053): Results of the phase 1 part. *First Author: Kim Schellekens, Department of Pediatric Oncology, Erasmus MC-Sophia Children's Hospital and Princess Máxima Center for Pediatric Oncology, Rotterdam, Netherlands*

Background: Preclinical data in neuroblastoma (NBL) models provided evidence that the addition of an mTOR inhibitor with crizotinib may overcome the relative resistance to ALK inhibitors (Berry et al., 2012, Cancer Cell). The primary objective of this phase 1b trial was to establish the recommended phase 2 dose (RP2D) of crizotinib in combination with the mTOR inhibitor temsirolimus in pediatric NBL patients. **Methods:** Patients aged 1-21 years with relapsed/refractory ALK/MET aberrant NBL were eligible to enroll onto stratum 2 of the CRISP trial (EudraCT: 2015-005437-53, ITCC-053), sponsored by Erasmus MC. This was an open-label, non-randomized, two-stage phase 1b dose finding study. Crizotinib was dose escalated using the EWOC method in four dose levels (DL) ranging from 100 mg/m² to 280 mg/m² twice daily (BID) in 28 day cycles. Temsirolimus was administered intravenously in a fixed dose of 60 mg/m²/week. Both starting doses were reduced compared to the single agent RP2D because of an expected CYP3A4 interaction. Primary endpoint was dose limiting toxicity (DLT) during cycle 1. Radiological disease assessments and blood sampling for pharmacokinetics were scheduled per protocol. **Results:** Nine NBL patients were enrolled onto stratum 2 between 06-2018 and 12-2022. Eight patients with a median age of 4 years (range: 1-12) received trial treatment. The temsirolimus dose was reduced to 40 mg/m² after the first 3 patients based on unexpected toxicity. DLTs occurred in 2/3 patients treated with crizotinib at DL2 (200 mg/m² BID); grade 3 elevated ALT (alanine aminotransferase) and grade 3 gastritis (temsirolimus dose; see table). No DLT occurred in 5 patients treated with crizotinib DL1 (150 mg/m² BID). Dose re-escalation of crizotinib to DL2 was considered not feasible. The RP2D was established at 150 mg/m² BID crizotinib with 40 mg/m² temsirolimus. Frequent grade 3 treatment-related adverse events were anorexia, gastritis, oral mucositis (n = 2) and anemia (n = 3). Treatment, toxicity and response are summarized in table. **Conclusions:** We established a RP2D of 150 mg/m² BID crizotinib in combination with 40 mg/m² temsirolimus. The expansion cohort is currently open for enrollment. Clinical trial information: EUCR2015-005437-53. Research Sponsor: Pfizer; Go4Children.

Summary of treatment, toxicity and response.

Pt	Crizotinib dose (mg/m ² BID)	Temsirolimus dose (mg/m ²)	ALK status	DLT	Completed cycles	Reason for trial discontinuation	Disease evaluation	Last disease status
1	150	60	F1174L	No	1	Withdrawal of consent	NE	DOD
2	200	60	F1174L	No	1	Non-DLT toxicity	NE	DOD
3	200	60	Amplification	Yes, ALT elevation gr 3	0	DLT	NE	DOD
4	200	40	R1275L	Yes, gastritis gr 3	0	DLT	NE	AWD
5	150	40	F1174L	No	1	PD	PD	AWD
6	150	40	F1245V	No	1	PD	PD	AWD
			Copy number gain					
7	150	40	F1245C	No	2, ongoing	-	SD	AWD
8	150	40	I1170N	No	1, ongoing	-	NE	AWD

NE: not evaluated. PD: progressive disease. SD: stable disease. DOD: died of disease. AWD: alive with disease.

10038

Poster Session

Healthcare resource use for pediatric low-grade glioma care: A cohort of linked electronic health records and claims data. *First Author: Tab Cooney, Dana-Farber/Boston Children's Cancer and Blood Disorders Center, Boston, MA*

Background: Pediatric low-grade glioma (pLGG) is the most common brain tumor in children and is associated with persistent long-term tumor- and treatment-related morbidities. This study aims to characterize the costs associated with the treatment of pLGG. **Methods:** A retrospective study using the Optum de-identified Market Clarity Dataset linked claims (commercial, Medicare Advantage and Managed Medicaid beneficiaries) and electronic health records (EHRs) of cases ≤ 18 years of age, with an ICD-10 code for brain neoplasm and ≥ 1 physician notes between January 2017 and June 2018 was performed. Index date was the first claim or EHR with an ICD-10 code for brain neoplasm. Natural language processing was used to identify pLGG-relevant data from physician notes. The observation period included 3 months prior to index date and 6-month segments from index date for 36 months. Cases had either continuous insurance coverage or continuous EHR activity during this period. Results for procedures and medication use were reported as averages throughout the 36-month post-index follow-up period. **Results:** A total of 154 patients with pLGG were identified. Median age was 11 years (range 2-18). Among the cohort, 49% (n=76) were female; 75% (n=116) were non-Hispanic white, 13% (n=20) Hispanic, 5% (n=7) African American, 1% (n=1) Asian and 6% (n=10) other/unknown. Of benefits, 56% had commercial and 44% Medicaid. Brain imaging and neuropsychological evaluations were performed at least once in 85% and 57% of the cohort, respectively. Among pLGG relevant medications, 57% of the cohort used analgesics, 45% anti-emetics, 32% anxiolytics, and 29% anticonvulsants. A total of 100 patients received ≥ 1 pLGG disease control treatments: Of these, 53% underwent emergency brain surgery, 24% had planned brain surgery, 14% received chemotherapy, and 6% received targeted therapy. Of the 100 patients who received disease control treatments, 57% relapsed after first-line treatment; 37% of patients received 2 lines of therapy, and 20% of patients received ≥ 3 lines of therapy. **Conclusions:** Our findings show that patients with pLGG often require long-term medical care and high levels of healthcare resources to treat their disease and its sequelae. Additionally, a majority will relapse and face a higher burden of disease. Further studies using integrated data sources are warranted to help us understand the burden of pLGG and inform evidence-based health care planning for these patients. Research Sponsor: Day One Biopharmaceuticals.

10037

Poster Session

Stage 4N neuroblastoma before and during the era of anti-GD2 immunotherapy. *First Author: Brian H. Kushner, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Patients with stage 4N neuroblastoma (distant metastases limited to lymph nodes) stand out as virtually the only survivors of high-risk neuroblastoma (HR-NB) before myeloablative therapy (MAT) and immunotherapy with anti-GD2 monoclonal antibodies (mAb) became standard. No report presents results with contemporary treatment programs for 4N. The only large study to date (from the International Neuroblastoma Risk Group) analyzed patients diagnosed 1990-2002, found 4N to have significantly better event-free (EFS) and overall survival (OS) compared to other stage 4 patients, and recommended considering less intensive therapy for 4N.

Methods: We conducted a retrospective analysis of patients treated at our center from 1985-2021 to analyze our large experience to fill the gap in the literature on treatment of 4N, namely, results with contemporary multi-modality therapy including MAT and anti-GD2 mAbs. **Results:** We found and reviewed 48 pediatric 4N patients (< 18 years old) treated 1985-2021 at our center. Biological features included segmental chromosomal aberrations in 21/21 MYCN-non-amplified patients, mutations of ALK in 4/22 (18%), ATRX in 4/16 (25%), and TERT in 4/12 (33%) patients. Among 33 MYCN-non-amplified high-risk patients (> 18 months old), 19 are relapse-free 1.6+ to 36.9+ (median 12.2+) years post-diagnosis, including 13 without prior MAT and 3 with no mAb, while 14 patients (7 without prior immunotherapy) relapsed (all in soft tissue initially). Eleven of the 14 died, including 3 who developed late osteomedullary metastases after 3-5 relapses in soft tissue alone. Of 13 MYCN-amplified 4N patients, 6 are relapse-free 4.5+ to 25.8+ (median 11.7+) post-diagnosis (all received mAbs; 3 underwent MAT) and 3 are in 2nd remission 4.4+ to 21.1+ years post-relapse (all soft tissue). For all high-risk 4N patients, 5/10-year EFS was 55%/52%, and OS was 76%/64%. MAT was not prognostic. The 2 patients with intermediate-risk 4N (14 months old) are relapse-free 7+ years post-resection of primary tumors; distant disease spontaneously regressed. **Conclusions:** The natural history of 4N is marked by NB confined to soft tissue without early relapse in bones or bone marrow, sites where mAbs have proven efficacy. These findings plus the possibility of survival without MAT and/or mAb immunotherapy, as seen elsewhere and at our center, support consideration of treatment reduction for selected MYCN-non-amplified 4N patients. Research Sponsor: None.

10039

Poster Session

Recommended phase 2 dose (RP2D) for abemaciclib in combination with irinotecan (IRN) and temozolomide (TMZ) in pediatric patients with relapsed/refractory solid tumors (JPCS Part A). *First Author: Alvaro Lassaletta, Hospital Infantil Universitario Niño Jesús, Madrid, Spain*

Background: There remains an unmet need to improve outcomes for pediatric patients (pts) with relapsed/refractory solid tumors. Abemaciclib is an orally administered, selective cyclin-dependent kinase (CDK) 4 & 6 inhibitor approved for breast cancer. Based upon preclinical data and the role of CDK4 & 6 in multiple pediatric solid tumor types, we hypothesized that abemaciclib in combination with IRN and TMZ would demonstrate clinical activity to support further pediatric development. This Phase 1b study aimed to determine the RP2D of abemaciclib in combination with IRN and TMZ in this pt population. **Methods:** This dose escalation study was part A of study JPCS (NCT04238819), and enrolled pts ≤ 18 years, weighing ≥ 10 kg, with a body-surface area ≥ 0.5 m², and with relapsed/refractory solid tumors, including CNS tumors, that progressed on standard treatment or experienced disease recurrence. IRN (50 mg/m²) and TMZ (100 mg/m²) were administered on days 1-5 of 21-day cycles and remain the same for all dose levels, while abemaciclib was tested on four dose levels: 55, 70, 90, and 115 mg/m² twice daily (BID). The starting dose was 70 mg/m² BID for abemaciclib. The maximum tolerated dose was defined as the highest dose level at which < 33% of pts experienced a dose-limiting toxicity (DLT) during Cycle 1. The primary objective, determination of the abemaciclib RP2D, was defined based on the totality of safety, tolerability, and pharmacokinetic (PK) results, and confirmed in an expansion cohort. Secondary objectives included safety and response assessments. **Results:** At the data cut-off of 13 June 2022, a total of 20 pts received abemaciclib at 70 mg/m² (n = 7) or 55 mg/m² (n = 13). The most frequent diagnoses (≥ 3 pts) were medulloblastoma (n = 4), malignant glioma (n = 3), and rhabdomyosarcoma (n = 3). At the starting dose of 70 mg/m², DLTs were experienced by 3 pts (neutropenia [n = 3; 43%]; gamma glutamyltransferase increased [n = 1; 14%]). The dose was de-escalated to 55 mg/m², at which one pt (8%) experienced a DLT (thrombocytopenia). High grade adverse events (AEs) were mostly hematological. Discontinuations due to AEs occurred in 2 pts (29%) at 70 mg/m² and 0 pts at 55 mg/m². Five pts (71%) at 70 mg/m² and 4 pts (31%) at 55 mg/m² achieved a best overall response of stable disease; 1 pt (8%) at 55 mg/m² achieved a complete response (rhabdomyosarcoma). No partial responses were observed. PK concentrations of abemaciclib at 55 mg/m² achieved average plasma abemaciclib concentrations of ~ 150 ng/mL and the abemaciclib C_{trough} concentrations appeared reasonably constant over time at ~ 100 ng/mL. PK concentrations of IRN and TMZ were as expected. **Conclusions:** The RP2D of abemaciclib is 55mg/m² BID in combination with IRN and TMZ. This combination appears tolerable with plasma concentrations within the range associated with efficacy in adult studies. Clinical trial information: NCT04238819. Research Sponsor: Eli Lilly and Company.

10040

Poster Session

Safety and PK (pharmacokinetic) profile of niraparib (nir) + dostarlimab (dost) in pediatric patients (pts) with recurrent or refractory (RR) solid tumors: SCOOP study. *First Author: Francois Doz, Institut Curie and University of Paris, Paris, France*

Background: Combination therapies may improve clinical outcomes in pediatric pts with tumors with single-agent resistance. Emerging preclinical and clinical data have shown a positive effect for combination PARP/immune checkpoint inhibition. The SCOOP study was designed to evaluate combination nir+dost in pediatric pts with non-central nervous system (CNS) RR solid tumors. Herein we present the safety, dose-limiting toxicities (DLTs), PK, and recommended phase 2 dose (RP2D) of nir+dost. **Methods:** SCOOP is a phase 1, multicenter, open-label, dose-escalation, and cohort-expansion study in pts aged ≥ 6 mo to < 18 y with non-CNS tumor types reported to have a *BRCA* gene signature. Part 1A comprised multiple dose-level cohorts (0, 1A, 1B, and 2; Table) of pts ≥ 20 kg able to swallow nir tablets. The primary endpoint was determination of the RP2D of nir+dost based on DLT incidence during the first 2 cycles. Plasma concentrations were compared with simulated adult concentrations using population PK models. **Results:** A total of 23 pts with non-CNS RR solid tumors were enrolled with 16 evaluated for DLTs and 23 for PK analysis (see Table for dose-level cohorts and observed DLTs). Grade (Gr) ≥ 3 drug-related (DR) treatment-emergent adverse events (TEAEs) in part 1A included hematologic toxicities, decreased appetite, and fatigue, with DR serious TEAEs of immune-mediated encephalitis, headache, nausea, vomiting, cerebral hemorrhage, and hyponatremia. Observed plasma nir concentrations at 100 and 200 mg once daily (QD) in pediatric pts were similar to simulated adult concentrations at 200 or 300 mg QD. Observed dost concentrations at 7.5 mg/kg every 3 weeks (Q3W) in pediatric pts were in the expected range for adults at 500 mg Q3W. **Conclusions:** Observed DLTs were consistent with the individual safety profile of each drug; overall no unexpected safety issues were observed. Based on these results, nir 100 mg QD + dost 7.5 mg/kg Q3W was selected as the RP2D for the SCOOP expansion cohorts in neuroblastoma and osteosarcoma. Pts in the expansion study will receive nir+dost at the RP2D until disease progression. Clinical trial information: NCT04544995. Research Sponsor: GSK.

Cohort	Dosage	DLTs observed
0 (n=11; 8 evaluable ^a)	Nir 100 mg QD + dost 3 mg/kg Q3W	n=1; Gr 3 anemia requiring blood transfusion
1A (n=7; 6 evaluable ^a) Selected as RP2D	Nir 100 mg QD + dost 7.5 mg/kg Q3W	n=1; Gr 3 vomiting, nausea, and anorexia and Gr 5 immune- mediated encephalitis
1B (n=5; 2 evaluable ^{a,b})	Nir 200 mg QD + dost 3 mg/kg Q3W	n=2; 1 Gr 4 thrombocytopenia requiring transfusion, 1 Gr 3 cerebral hemorrhage
2 Did not open for enrollment as 1B was not deemed safe	Nir 200 mg QD +dost 7.5 mg/kg Q3W	

^aDLT-evaluable population comprises pts who completed the DLT observation period or experienced a DLT. ^bTwo additional pts in cohort 1B experienced Gr 3 neutropenia leading to interruption and reduction of nir dose, resulting in inadequate dosing compliance.

10042

Poster Session

Reduction in curie score in neuroblastoma patients treated with naxitamab. *First Author: Jaume Mora, Pediatric Cancer Center Barcelona, Hospital Sant Joan de Déu, Barcelona, Spain*

Background: Patients with high-risk neuroblastoma (HR-NB) most frequently present with metastases in the bone marrow (BM; 70–89%) and bone (56–65%). Approximately 15% of HR-NB patients will be refractory to induction therapy and 50% will relapse. Naxitamab is a humanized GD2-binding monoclonal antibody approved in the US with granulocyte-macrophage colony-stimulating factor (GM-CSF) for treatment of patients ≥ 1 -yr with refractory/relapsed (R/R) HR-NB in the bone or BM with partial response, minor response, or stable disease to prior therapy. Curie Score (CS) is an important tool for assessing extent of disease and treatment response. The reduction in CS by baseline disease status, i.e., refractory or relapsed, from Trial 201 pre-specified interim analysis (data cut-off 31-dec-2021) is reported. **Methods:** Ongoing Trial 201 (phase II, NCT03363373) evaluates naxitamab+GM-CSF in patients with R/R HR-NB with residual disease limited to bone/BM. Soft tissue and actively progressing disease were addressed prior to enrollment. Naxitamab was administered (intravenously) at 3mg/kg/day over 30-60 min on Days 1/3/5 with GM-CSF (subcutaneous) on Days -4 to 5 at 4-week cycles. ¹²³I-MIBG scans were used to assess CS and treatment response according to INRC criteria per independent review. **Results:** Interim analysis included 52 (efficacy group) and 74 (safety) patients. The primary endpoint achieved an overall response rate (ORR) of 50% [95% CI: 35.8–64.2] with complete response rate (CR) of 38%. A summary of changes in overall CS by disease status is reported in the table. Median change in CS from baseline to end of treatment (EOT) was -1 across refractory and relapsed subgroups and ranged from -18 to 18 . Baseline CS (≤ 2 vs. ≥ 3) did not affect the safety profile. The most common adverse events were pain, hypotension, urticaria, and bronchospasm. The frequency of Grade 3 or higher and serious related adverse events was lower for patients with refractory vs. relapsed disease, i.e. lower rates of severe hypotension (51% vs. 68%), increased ALT (0% vs. 14%), and hypoxia (3% vs. 16%). **Conclusions:** Clinically meaningful reductions in CS were seen in patients regardless of baseline disease status (relapsed or refractory HR-NB). Baseline CS did not affect the safety profile. Refractory patients had a lower frequency of severe and serious related adverse events. Clinical trial information: NCT03363373. Research Sponsor: Y-Mabs Therapeutics.

Summary of Curie Score (CS) overall and by disease status.

	Overall (n=47*)	Refractory (n=24)	Relapsed (n=23)
Median Baseline CS (range)	3 (1-20)	3 (1-20)	3 (1-19)
Mean Baseline CS	5.6	5.5	5.7
Median end of treatment (EOT) CS (range)	1 (0-24)	1 (0-6)	1 (0-24)
Mean EOT CS	2.9	1.3	4.5
Median change from baseline (range)	-1.0 (-18 to 18)	-1.0 (-18 to 1)	-1.0 (-17 to 18)
Mean change from baseline	-2.7	-4.2	-1.2

*In the efficacy group, 2 patients had BM only disease and 3 patients did not have EOT CS.

10041

Poster Session

Clinical application of ctDNA detection in Chinese pediatric patients with soft tissue sarcoma (STS). *First Author: Jia Zhu, Sun Yat-sen University Cancer Center, Guangzhou, China*

Background: Circulating tumor DNA (ctDNA) is an effective and noninvasive supplementary approach for assessing minimum tumor burden in a range of solid tumors; however, studies on pediatric soft tissue sarcoma (STS) are limited. The purpose of the study was to assess the utility of ctDNA detection in predicting patient response and recurrence, and to inform treatment strategies through dynamic monitoring of ctDNA during the treatment of various types of pediatric STS. **Methods:** From January 2022 to January 2023, a total of 27 tissues and 112 plasma samples were obtained at baseline and during treatment. Utilizing the next-generation sequencing approach, ctDNA profiling was performed on tissue and plasma samples from 48 pediatric STS (< 18 years old) with a panel of 481 sarcoma-specific genes (Nanjing Geneseeq Technology Inc.). **Results:** The study included thirty patients with rhabdomyosarcoma, nine Ewing sarcoma, and nine other subtypes of sarcoma, with 52.1% (n = 25) female. Seven patients were stages I-II, and 24 were stages III-IV. At baseline, ctDNA was identified in 56.25 % (18/32) of plasma before chemotherapy and 87.50 % (14/16) of plasma before surgery. Comparable mutational burdens were seen in baseline tissue and plasma samples, with an average of 3.8 and 3 mutations per sample, respectively. The concordance of detected mutations between tissue and plasma was 64.3%. The average plasma abundance (p = 0.007), maximum abundance (p = 0.0045), ctDNA concentration (hGE/ml) (p = 0.0005), and relative ctDNA abundance (p = 0.0083) of stage IV patients (n = 5) were higher than those of stage I-III patients (n = 6). Following surgical resection, four patients (25 %, 4/16) had detectable ctDNA. In the longitudinal monitoring, we found a high correlation (75.86 %, 22/29) between ctDNA trend and clinical response. Notably, ctDNA positive in Ewing sarcoma had the strongest correlation with clinical response. The inconsistency between ctDNA detection and clinical response could be attributed to the presence of bone lesions (57.1%, 4/7). One patient was observed to have positive ctDNA before any radiological findings. **Conclusions:** Our findings showed that it is feasible to use ctDNA to dynamically monitor tumor burden in pediatric soft tissue sarcoma, especially Ewing sarcoma. ctDNA may serve as a safe, non-invasive option complementary to imaging assessment of sarcoma, and further clinical benefits are being investigated. Research Sponsor: None.

10043

Poster Session

Effect of bispecific B7H3 x CD19 CAR T cells on host CD19 expression and CAR T cell engraftment. *First Author: Navin R. Pinto, University of Washington, Seattle, WA*

Background: Our experience of B7H3 chimeric antigen receptor T cells (CAR-T) revealed modest engraftment (max 4.9 cells/uL) and no objective responses on first infusion. Previous CD19 CAR T cell trials have revealed that host B cell CD19 can drive robust engraftment and persistence even in the absence of malignant CD19 expression. We therefore developed a bispecific B7H3xCD19 CAR T cell with the intent of using host CD19 expression to drive better engraftment of the B7H3-targeting CAR. **Methods:** Young patients with relapsed/refractory solid tumors (R/RST) were enrolled onto a Phase 1 trial (NCT04483778) to examine the safety of autologous T cells lentivirally transduced to express either or both scFv-IgG4hinge-CD28tm-4-1BB-zeta B7H3-specific and CD19-specific CARs. The B7H3 CAR construct contained the methotrexate resistance/selection cassette DHFR^{td} and the tracking/suicide construct EGFRt and the CD19 CAR construct containing the tracking/suicide construct HER2tg, allowing for differential CAR tracking. CAR T cells were cultured in low-dose methotrexate to select for B7H3 containing CAR T cells and limit exposure to monospecific CD19 CAR T cells. All patients received lymphodepleting fludarabine and cyclophosphamide prior to infusion of cryopreserved CAR-T at the prescribed dose level. The maximal tolerated dose or biologically effective dose (BED) was determined based upon observed toxicity through day 28 from initial CAR-T infusion and using a 3+3 statistical design. **Results:** 11 subjects (age 5-23, median 18 years) enrolled and received dose level (DL) 0B (0.5 x 10⁶ TOTAL CAR-T/kg, n = 7) or DL1B (1 x 10⁶ TOTAL CAR-T cells/kg, n = 4). One subject experienced dose limiting toxicities at DL1 of transaminitis, hyponatremia, worsening of a pericardial effusion and hypoxia. Most common toxicities were cytokine release syndrome (CRS) (n = 4, maximum CTCAE grade 2). No occurrence of ICANS was noted. Maximum total circulating CAR-T expansion on first infusion was 796.3 cells/uL and max B7H3 expansion was 374.2 cells/uL with 7/11 continuing with ongoing detection of CAR T cells in the peripheral blood at time of last follow up (21 days to 8 months). CAR engraftment was predominated by the B7H3 CAR single expressing CAR T cells in all subjects. All subjects developed B cell aplasia which is ongoing in 10/11 subjects at time of last check (range of 21 days to 8 months). Best overall response of Stable Disease was observed in 2 of the 11 subjects infused. **Conclusions:** B7H3xCD19 CAR T cells robustly engraft and expand in patients with R/RST and are safe, but despite ongoing detection of the CAR T cells, no objective responses were observed. It is likely that additional measures will be required to enhance the activity of CAR-T cells to achieve objective responses. STRIVE-02 Arm C will explore the addition of pembrolizumab post bispecific CAR infusion to evaluate the effect of PD1 blockade on anti-tumor activity. Clinical trial information: NCT04483778. Research Sponsor: Seattle Children's Therapeutics.

10044

Poster Session

Neurosurgical morbidity in pediatric supratentorial midline low-grade glioma: Results from the German LGG studies. *First Author: Michèle Simon, Department of Pediatric Oncology and Hematology, Charité-Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt Universität zu Berlin, Berlin, Germany*

Background: Surgical resection is a mainstay of treatment for pediatric low-grade glioma (LGG) within all current therapy algorithms, yet associated morbidity is scarcely reported. As supratentorial midline (SML) interventions are particularly challenging, we investigated the frequency of neurosurgical complications/new impairments aiming to identify their risk factors. **Methods:** Records were retrospectively analyzed from 318 patients with SML-LGG from successive German multicenter LGG studies, undergoing surgery between May 1998 and June 2020. **Results:** 537 operations (230 resections, 167 biopsies, 140 non-tumor procedures) were performed in 318 patients (54% male, median age: 7.6 years at diagnosis, 9.5 years at operation, 11% NF1, 42.5% optic pathway glioma). Surgical mortality rate was 0.93%. Applying the Drake classification, postoperative surgical morbidity was observed in 254/537 (47.3%) and medical morbidity in 97/537 (18.1%) patients with a 40.1% 30-day persistence rate for newly developed neurological deficits (65/162). Neuroendocrine impairment affected 53/318 patients (16.7%), visual deterioration 34/318 (10.7%). Postsurgical morbidity was associated with patient age <3 years at operation, tumor volume ≥80cm³, presence of hydrocephalus, complete resection, surgery in centers with less than median reported tumor-related procedures and during the earlier study period between 1998-2006, while the neurosurgical approach, tumor location, NF1 status or previous non-surgical treatment were not. **Conclusions:** Neurosurgery-associated morbidity was frequent in pediatric patients with SML-LGG undergoing surgery in the German LGG-studies. We identified patient- and institution-associated factors that may increase the risk for complications. We advocate that local multidisciplinary teams consider the planned extent of resection and surgical skills. Research Sponsor: None.

Postsurgical morbidity according to the classification by Drake et al.* (n=537 interventions).			
	All	Surgical morbidity	Medical morbidity
Resections	260	324 incidences (170 patients)	85 incidences (69 patients)
Biopsies	167	76 incidences (57 patients)	19 incidences (15 patients)
Other interventions	140	36 incidences (27 patients)	13 incidences (13 patients)

*Drake JM et al. Prospective surveillance of complications in a pediatric neurosurgery unit. J Neurosurg Pediatr. 2010.

10046

Poster Session

¹⁸F-MFBG PET imaging in patients with neuroblastoma: Lesion targeting and comparison with MIBG. *First Author: Shakeel Modak, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: ¹²³I-MIBG gamma camera imaging (MIBG) is routinely used for the imaging of neuroblastoma. Limitations include need for two-day imaging schedule and lack of quantitative uptake measurements. Phase I study showed that ¹⁸F-MFBG (MFBG), a positron-emitting analog of MIBG, is safe and feasible (PMID:28705916). In the follow-up phase II trial (NCT02348749) we evaluated MFBG PET imaging, comparing neuroblastoma lesion between the two modalities. **Methods:** Patients with known neuroblastoma underwent whole-body PET CT or PET-MR imaging one hour post-injection with 8mCi/1.7m2 of MFBG. All patients had concurrent MIBG scan with planar and SPECT-CT imaging without intervening therapy. MFBG and MIBG images were independently analyzed for lesion targeting; lesion number, site and uptake was noted for each patient and compared. Discordant lesions were further investigated with correlative imaging and/or clinical follow up. MFBG score was generated, similar to the modified Curie score for MIBG, for each patient. **Results:** 25 patients (median age 8 y) underwent MFBG scans at a median of 2 (range 0-24) days after MIBG scans; in one patient MFBG scan was performed 1 day before MIBG scan. No MFBG-related adverse events were noted. 24 patients had both MIBG and MFBG positive scans while 1 patient had both MIBG and MFBG negative scans. A total of 367 lesions were visualized on MFBG as against 217 on MIBG. There were no MIBG-positive that were negative on MFBG. A median number of 11 (range 0-57) lesions per patient were detected on MFBG scan. Uptake was noted in osteomedullary only, (n=13), soft tissue only (n=1) and both soft tissue and osseous lesions (n=10). MFBG detected a median of 6 (range 1-24) additional lesions in 19 patients. In 16/19 patients where follow up was available, the discordance was related to true positive disease, including at least 116 sites. Respective median curie scores were 3 (range: 0-22) and 9 (range:0-24) with MIBG and MFBG respectively. **Conclusions:** MFBG scan detected disease in all patients with MIBG positive disease. MFBG detected similar or more lesions compared to MIBG in patients with neuroblastoma, with overall increased scores. Further analysis to evaluate impact on patient management is underway. Clinical trial information: NCT02348749. Research Sponsor: U.S. National Institutes of Health.

10045

Poster Session

Quality of cancer family history taking in pediatric solid tumor patients. *First Author: Benjamin Hu, Stanford University School of Medicine, Palo Alto, CA*

Background: Approximately 10% of childhood solid tumors occur in individuals with a cancer genetic predisposition. Identifying cancer predisposition permits interventions for prevention and early detection of future cancers in the child and their affected family members and may have other important medical care implications. The American Society of Clinical Oncology (ASCO) guidelines recommend reviewing family history (FHx) to identify high-risk patients who should be offered genetic testing. To our knowledge, adherence to ASCO guidelines by pediatric oncology providers (POPs) has not been studied. **Methods:** Retrospective chart review of solid tumor patients <18 years of age referred for genetic counseling 1/1/2017-1/31/2019. POP and genetic counselor (GC) FHx documentation was assessed for adherence with the ASCO minimum quality metrics: 2 generation pedigree, patient ethnicity, cancer genetic testing results in relatives (GTRR), and cancer type, age at diagnosis, and lineage (maternal/paternal) for each relative with cancer (RWC). Comparisons of FHx quality between POPs and GCs were evaluated with 1-sided t-tests. Ethnicity was considered assessed if both maternal and paternal ethnicities were documented. GTRR was considered assessed if the results of all relatives who had undergone genetic testing were noted. Cancer type, age at diagnosis, and lineage were considered assessed if they were checked for all RWCs. Whether or not the child underwent genetic testing and their testing results were also documented. **Results:** Of 129 eligible patients, 102 underwent germline genetic testing. Twelve (12%) had pathogenic alterations in cancer predisposition genes. The POP failed to document FHx in 20 patients (16%), including 2 with pathogenic germline alterations. The POP missed first/second degree RWCs in 32 of 88 patients with RWCs (36%). GCs achieved >99% on each of the 6 ASCO quality metrics, whereas POPs performed significantly more poorly (Table). In patients with RWCs, GCs achieved all 6 metrics in more cases than POPs (99% vs. 3%, p<0.001). **Conclusions:** POPs performed significantly worse than GCs in documenting family history compliant with ASCO minimum family history guidelines, raising concern for missed genetic cancer predisposition syndrome diagnoses in those not referred to a GC. Routine referral of pediatric solid tumor patients to a GC for family history review and interventions to improve the quality of family history taking by POPs may improve germline cancer predisposition detection, improving care of both patients and their affected family members. Research Sponsor: None.

Family History Quality Metric	Proportion Achieving Metric		p-value
	POP	GC	
All Patients (n=129)			
2 generation pedigree	58%	100%	<0.001
Ethnicity	9%	99%	<0.001
Cancer genetic testing results in relatives (GTRR)	8%	100%	<0.001
Patients with ≥ 1 RWC (n=88)			
RWC cancer type	76%	100%	<0.001
RWC age at cancer diagnosis	30%	100%	<0.001
RWC lineage	76%	100%	<0.001

10047

Poster Session

Adherence to surveillance guidelines in survivors of hodgkin lymphoma: A report from the Childhood Cancer Survivor Study (CCSS). *First Author: Jamie Michelle Shoag, Cleveland Clinic, Cleveland, OH*

Background: Pediatric Hodgkin lymphoma (HL) is a highly curable disease. However, survivors are at high risk for long-term complications of therapy. The impact of sociodemographic and clinical factors on adherence to late effects surveillance guidelines is unknown. **Methods:** The CCSS is a retrospective cohort with prospective follow-up of survivors diagnosed from 1970-1999. HL survivors enrolled in CCSS who responded to a 2017 questionnaire were included. We assessed adherence to the Children's Oncology Group surveillance guidelines for cardiomyopathy, breast cancer, colorectal cancer, and skin cancer. Multivariate logistic regression was used to estimate adjusted odds ratios and 95% confidence intervals (aOR [95% CI]) for sociodemographic and clinical risk factors associated with adherence. Estimates were adjusted for area deprivation index (ADI); chronic health conditions; recent (≤2 years) routine check-up, cancer center or survivorship clinic visit; and possession of a survivorship care plan (SCP). **Results:** 1,380 HL survivors (45.6% male; median age 43.6 years, range 21.6-65.9 years) responded, of whom 55.5% were at elevated risk for cardiac dysfunction, 71.0% for breast cancer, 83.5% for skin cancer, and 39.4% for colorectal cancer. Of those at elevated risk, 42.7%, 19.9%, 31.3% and 48.9% were adherent to the guidelines for cardiac, breast, skin, and colorectal screening, respectively. Predictors of adherence to cardiac dysfunction guidelines were male sex (aOR 1.7 [1.1-2.6]), having children (aOR 1.6 [1.1-2.4]), recent routine checkup (aOR 4.0 [1.3-13.1]), recent visit to a cancer center or survivorship clinic (aOR 6.2 [3.9-10.0]), and possession of a SCP (aOR 3.1 [1.9-5.0]). Adherence to breast cancer guidelines was higher in those who were unmarried (aOR 2.1 [1.0-4.1]), had a recent visit to a cancer center or survivorship clinic (aOR 3.7 [2.0-7.0]), and possessed a SCP (aOR 3.5 [1.5-8.3]). Adherence to skin cancer guidelines was higher in those > 14 years at diagnosis (aOR 1.8 [1.3-2.4]), living in a low deprivation area (ADI 1-24.9) compared to a high deprivation area (ADI 75-100) (aOR 3.4 [1.9-5.9]), employed (aOR 1.8 [1.1-2.9]), > 30 years from diagnosis (aOR 2.4 [1.6-3.6]), with a recent routine check-up (aOR 3.6 [1.1-12.5]), and recent cancer care (aOR 2.4 [1.6-3.5]). Adherence to colorectal cancer guidelines was higher in those with grade 3-4 chronic health conditions (aOR 1.9 [1.1-3.3]). **Conclusions:** Less than 50% of HL survivors are adherent to screening guidelines. Sociodemographic risk factors are significant predictors of non-adherence, particularly to skin cancer screening guidelines. This threatens to potentiate outcome disparities among HL survivors. Research Sponsor: None.

10048

Poster Session

Financial hardship among siblings of long-term survivors of childhood cancer: A Childhood Cancer Survivor Study (CCSS) report. *First Author: Timothy James Daeun Ohlsen, Cancer and Blood Disorders Center, Seattle Children's Hospital, Seattle, WA*

Background: Siblings of children with cancer may experience adverse household economic and psychosocial impacts during and after treatment. While many long-term survivors of childhood cancer experience financial hardship, financial outcomes of siblings in later adulthood are unknown. **Methods:** We surveyed randomly selected nearest age siblings of survivors (aged 18-64y) enrolled in the CCSS to estimate the prevalence of financial hardship, using 20 items adapted from validated national surveys grouped into 3 domains (material, psychological, behavioral). We calculated the prevalence of reporting any hardship within each domain. Multivariable logistic regression estimated associations between sibling sociodemographic characteristics and each domain of hardship. For individual financial hardship items with a matching item in the contemporaneous National Health Interview Survey (n = 21,271) or Behavioral Risk Factor Surveillance System (n = 259,901), we compared siblings with national survey respondents aged 18-64, calculating adjusted prevalence ratios to sample-weighted responses, adjusted for sex, race, ethnicity, household income, education, and marital status. **Results:** 1,008 siblings participated (of 1,590 approached; 63%) with median age of 46y (IQR 39–53y). Siblings were 57% female, 89% non-Hispanic White, 69% college-educated, and 74% married. The prevalence of reporting any material, psychological, and behavioral hardship among siblings was 34%, 28%, and 23%, respectively. Sibling factors associated with reporting material financial hardship included: female sex (OR 1.7, 95% CI 1.2–2.4), age (30–39y vs 21–29y: OR 2.61, 95% CI 1.1–6.5), household income (\$50,000–\$74,999 vs $\geq$ \$75,000: OR 2.3, 95% CI 1.4–3.6), lack of health insurance (OR 2.4, 95% CI 1.1–5.1), presence of severe/disabling chronic medical conditions (OR 1.7, 95% CI 1.1–2.8), out-of-pocket medical expenses $\geq$ 10% of income (vs <10%: OR 4.9, 95% CI 1.9–12.3), and increased non-medical/non-home debt (for example, \$25,000–\$49,999 vs none: OR 5.2, 95% CI 3.2–8.6). Associations with psychological and behavioral hardship were similar. Compared with national survey respondents, siblings were more likely to report financial hardship on several individual items: difficulty paying medical bills (PR 1.2, 95% CI 1.0–1.4), worries about bills (PR 1.1, 95% CI 1.1–1.2), foregoing medical care (PR 1.3, 95% CI 1.0–1.6) and dental care (PR 1.4, 95% CI 1.2–1.6) due to cost, and worries about affording nutritious foods (PR 1.7, 95% CI 1.5–2.0). **Conclusions:** Adult siblings of childhood cancer survivors are more likely to experience multiple aspects of financial hardship than US adults in the general population, suggesting that childhood cancer may have life-long impact on siblings. Increased support for families across the trajectory of cancer treatment may help prevent or reduce financial hardship. Research Sponsor: U.S. National Institutes of Health.

10050

Poster Session

Demographic predictors of successful transition to adult survivorship care for survivors of pediatric cancer. *First Author: Renee Gilbert, University of Kansas Clinical Child Psychology Program, Lawrence, KS*

Background: There is a growing number of childhood cancer survivors in the U.S. (Chow et al., 2020) who are at risk for experiencing negative long-term health outcomes (Oeffinger et al., 2006). Current guidelines state the importance of receiving risk-based follow-up at adult survivorship clinics, yet available estimates suggest that less than 50% of survivors receive yearly survivorship care (Landier et al., 2004; Daly et al., 2018). The transition from pediatric to adult care is a difficult process, with various factors acting as barriers (Devine et al., 2017). The present study sought to evaluate demographic predictors of successful transition to adult survivorship care in a Midwestern clinic serving a large urban and rural catchment area. **Methods:** The study includes adult survivors of childhood cancer (n = 203) who received pediatric or adult survivorship care in a Midwestern metropolitan area from 2015 to 2022. For this study, successful transition to adult care was defined as attending at least one appointment in the adult survivorship clinic. Dates of clinic attendance, cancer diagnosis, insurance data, and zip code were abstracted from the medical record. 86.2% of survivors had commercial insurance, 13.8% had government-sponsored insurance, self-pay or other insurance. Participant zip codes were 66.7% urban, 19.5% metropolitan (low and high commuting), 9.2% micropolitan, and 4.6% rural. Survivor ages ranged from 20 to 68 years (M = 29.48, SD = 7.74) and 53.2% were female. Participant-reported race/ethnicity was 90.1% White, 5.4% Hispanic, 3.4% Black and 1% Other. **Results:** 66% of the sample attended at least 1 appointment in the adult survivorship clinic. Chi-square analyses revealed a significant relationship between insurance type and attendance at the clinic, $X^2(1) = 16.60$, $p < .001$, such that a greater proportion of survivors with commercial insurance transitioned to adult survivorship care (71%), compared to government-assisted (Medicare), self-pay or other insurance (32%). Analyses revealed a significant relationship between rurality and transition, $X^2(3) = 14.11$, $p < .01$, such that a greater proportion of survivors from urban areas transitioned (74%) compared to rural areas (22%). Race/ethnicity, gender and cancer type were not significantly associated with transition. **Conclusions:** Results suggest that a lack of commercial insurance and rurality served as risk factors for not successfully transitioning to an adult survivorship clinic, highlighting opportunities for improvement in clinic reach. Research Sponsor: None.

10049

Poster Session

Associations between psychosocial and lifestyle factors and biological age acceleration among long-term survivors of childhood cancer: A prospective study from the St. Jude Lifetime Cohort. *First Author: Brennan Streck, National Cancer Institute, Rockville, MD*

Background: Survivors of childhood cancers may be at risk for premature, or accelerated, biological age aging, which is associated with cancer treatment exposures. However, life course theory and a growing body of evidence suggest that psychosocial and lifestyle factors may also contribute. The objective of this study was to explore associations between psychosocial and lifestyle factors and biological age acceleration in the St. Jude Lifetime Cohort. **Methods:** In this cross-sectional study, we applied physiology-based methods (Klemera-Doubal method and Phenotypic Age) and DNA methylation-based epigenetic clocks (Horvath's, Hannum's, Levine's PhenoAge, GrimAge, and DunedinPACE clocks) to compare biological age acceleration, estimated as the residual from regressing biological age on chronological age, among survivors (n = 4,117) and age- and sex-frequency-matched non-cancer community controls (n = 606). We compared psychosocial and lifestyle factors between survivors and controls using t-tests/Wilcoxon rank sums, and chi-square. Multivariable linear regression was used to assess associations of self-reported smoking, alcohol use, physical activity, overweight/obesity, and depressive symptoms with biological age acceleration in survivors, adjusted for age, race/ethnicity, sex, education, and cancer treatment. **Results:** Childhood cancer survivors at a mean chronological age of 35.1 years (SD 10.2) were biologically older than controls according to KDM-BA, Phenotypic Age, Hannum's clock, Levine's PhenoAge clock, and DunedinPACE, with biological age acceleration ranging from 1.7–4.7 years ($p < 0.05$). A greater proportion of survivors reported elevated depressive symptoms (10.3% v. 8.7%), current smoking (17.8% v. 12.3%), < 150 minutes of physical activity (47.3% v. 38.2%), and were overweight/obese (66.0% v. 59.9%) compared to controls (p 's < 0.001). In survivors, < 150 minutes of physical activity (B's (difference in biological age acceleration [years]) = 1.10–2.68), current (B's = 1.18–5.96) and former smoking (B's = 2.53–4.29) were consistently associated with higher biological age acceleration across measures (p 's < 0.05). Risky drinking and higher depressive symptoms were associated with higher biological age acceleration, but only for KDM (B = 1.26, $p < 0.021$) and DunedinPACE measures (B = 0.15, $p < 0.001$), respectively. **Conclusions:** Biological aging in childhood cancer survivors is associated with psychosocial and lifestyle factors. Interventions designed to optimize healthy behaviors and mitigate poor emotional health may have potential to prevent or remediate this phenotype in childhood cancer survivors. Research Sponsor: U.S. National Institutes of Health.

10051

Poster Session

Treatment and treatment-related toxicity following subsequent breast cancer: A report from the Childhood Cancer Survivor Study (CCSS). *First Author: Cindy Im, University of Minnesota, Minneapolis, MN*

Background: Long-term survivors of childhood cancer are at high risk for treatment-related breast cancer and have elevated mortality risk after a breast cancer diagnosis than the general population. There is no standard of care for women with treatment-related breast cancer, and treatment patterns and risk for toxicity are not known. **Methods:** Female survivors in CCSS diagnosed and treated for childhood cancer between 1970–1999 who developed a subsequent breast cancer (N = 344) were matched with females with sporadic breast cancer (multi-institution sampling; 1:1 matching ratio) on age at breast cancer diagnosis, breast cancer treatment decade, race/ethnicity, histology, and hormone receptor status. Conditional logistic regression evaluated univariate associations with treatments, toxicities, and synchronous breast cancer (≤ 12 months from diagnosis). Hazard ratios (HR) for metachronous disease risk (> 12 months from diagnosis) were estimated using proportional hazard models with robust variance estimation. **Results:** Among survivors, the median time between the primary cancer and initial breast cancer diagnosis at median age 40 years (IQR 35–45) was 26 years (IQR 21–30). Two-thirds received chest radiation therapy (RT) and 44% were treated with anthracyclines for their childhood cancer. In the matched sample, breast cancer clinical features were similar between survivors vs. controls, but the odds of synchronous bilateral disease at diagnosis was 4.8-fold greater (95% CI 2.2–10.2) among survivors. Surgical interventions (99% vs. 98%, $P = 0.22$) and treatment with chemotherapy (46% vs. 45%, $P = 0.43$) were similar between groups. However, women with sporadic breast cancers were more likely to receive RT (OR 4.4, 95% CI 2.9–6.8) or anthracyclines (OR 2.4, 95% CI 1.5–3.8). Survivors were more likely to undergo mastectomy (OR 3.0, 95% CI 2.1–4.2) and experience surgical complications (OR 2.2, 95% CI 1.4–3.4), and had 1.4-fold greater odds (95% CI 1.01–1.98) of experiencing any treatment-related toxicity compared to controls. The 15-year cumulative incidence of developing a metachronous breast cancer was 20% (95% CI 13–25%) in survivors versus 9% (95% CI 5–13%) in controls ($P < 0.001$). Risk of metachronous disease remained higher among survivors (HR 2.4, 95% CI 1.5–4.0) after adjusting for breast cancer treatments (mastectomy, RT, and anthracyclines). **Conclusions:** Female survivors of childhood cancer who develop subsequent treatment-related breast cancer are more likely to develop synchronous and metachronous breast cancer compared to controls. Despite similar biologic characteristics, survivors are treated differently from females with sporadic breast cancer and are more likely to experience treatment-related toxicities. Further study of how treatment of subsequent breast cancers and corresponding toxicities impact prognosis and survival is needed. Research Sponsor: U.S. National Institutes of Health.

10052

Poster Session

Mortality and the burden of subsequent malignant neoplasms in survivors of childhood cancer beyond age 50: A report from the Childhood Cancer Survivor Study (CCSS). *First Author: Rusha Bhandari, City of Hope, Duarte, CA*

Background: The first generation of survivors of childhood cancer is now older than 50 years (y) of age. There is a paucity of information on the risk for late mortality and the evolving burden of subsequent malignant neoplasms (SMNs) in these aging survivors. **Methods:** We assessed cause-specific mortality (National Death Index) and self-reported SMNs (excluding nonmelanoma skin cancers) among CCSS participants diagnosed between 1970-1999, conditional on having survived to 50y by 12/31/2017. There were 4,772 survivors alive at 50y eligible for mortality analyses. Of the 3,355 who completed a baseline CCSS questionnaire, 2,273 also completed a follow-up questionnaire at ≥50y and were included in the SMN analyses. Cumulative mortality, standardized mortality ratios (SMRs), and, for SMNs, cumulative burden, standardized incidence ratios (SIRs), and relative rate (RR) with 95% confidence intervals (CIs) were calculated, compared with the general US population and by survivor subgroups. Piecewise-exponential multivariable regression was used to identify risk factors associated with the development of SMNs after 50y. **Results:** Mean age at diagnosis was 14y (standard deviation 4.2y). Mortality: Among survivors who attained 50y of age, the subsequent 5y, 10y, and 15y incidences of all-cause mortality were 9%, 19%, and 35%, respectively, (overall SMR 3.7 [95% CI 3.4-4.1]). SMRs were highest for SMN (SMR 5.1 [95% CI 4.4-5.9]), pulmonary (SMR 4.7 [95% CI 3.3-6.5]) and cardiovascular (SMR 3.9 [95% CI 3.2-4.8]) causes of death. The highest SMR (SMR 9.2 [95% CI 7.7-10.8]) was seen in female survivors of Hodgkin lymphoma. SMN: By age 50y, 14% of CCSS participants reported >1 SMN. History of SMN <50y was independently associated with the rate of developing another SMN at >50y (RR 1.6 [95% CI 1.1-2.3]). The most frequent SMNs ≥50y were breast (41%) in females and prostate (21%) in males, followed by gastrointestinal cancers in both (14% [females], 19% [males]). The cumulative burden of SMNs in survivors treated with radiation therapy (RT) increased sharply with age and exceeded 50 per 100 survivors by 65y (SIR 3.3 95%CI 2.0-5.2). Survivors who did not receive RT had a SMN rate comparable to the general population (Table). **Conclusions:** This sentinel population of survivors of childhood cancer is at high risk for poor outcomes as they enter older adulthood. RT exposure and history of SMN <50y are associated with increased risk for developing SMNs after 50y. The evolving burden of late morbidity attributed to SMNs may be lower for contemporary survivors projected to have less RT exposure. Research Sponsor: U.S. National Institutes of Health.

At age (y)	Cumulative burden of SMN per 100 survivors (95%CI)		SIR for SMN (95%CI)	
	RT	No RT	RT	RT No
55	26.8 (23.7-29.8)	15.0 (11.9-18.5)	2.7 (2.1-3.4)	1.2 (0.7-2.0)
60	34.3 (30.0-38.5)	20.5 (15.8-26.0)	1.9 (1.3-2.7)	1.4 (0.7-2.5)
65	53.4 (42.5-66.0)	21.7 (16.4-27.4)	3.3 (2.0-5.2)	0.4 (0.0-2.3)

10055

Poster Session

Predictors of cancer center-based follow-up among pediatric and adolescent/young adult cancer survivors. *First Author: Emily Pang, Stanford University School of Medicine, Stanford, CA*

Background: Though guidelines recommend lifelong follow-up for pediatric and adolescent/young adult (AYA) cancer survivors, this has been challenging to implement in clinical practice. We constructed an institutional cohort of pediatric/AYA cancer survivors in order to evaluate follow-up patterns and identify predictors of cancer center-based follow-up. We hypothesized that follow-up would be lower for patients with greater individual- and area-level socioeconomic disadvantage and longer time since treatment. **Methods:** This retrospective cohort study used EHR data at an academic medical center. We included all patients who completed cancer treatment between 2010-2019 and were aged 0-29 years at last treatment date. Treatment was defined by diagnosis/procedure codes and medication records for chemotherapy, radiation, stem cell transplant, and cancer surgery. The primary outcome of cancer center-based follow-up was defined by clinic visits in an oncology department through 12/31/2022. Patients who died were excluded after the date of death. Multivariate logistic regression models (overall, age 0-19, age 20-29) evaluated the association of follow-up with age, sex, race/ethnicity, treatment intensity, insurance type, primary language, distance to cancer center, and area deprivation index (ADI, a composite measure of socioeconomic disadvantage). **Results:** 2210 patients were included with an overall rate of cancer center-based follow-up that decreased from 94% 1 year after treatment to 61% at 2-3 years, 45% at 4-5 years, and 35% at 6-7 years. Follow-up was not significantly associated with race/ethnicity, insurance type, primary language, or ADI for overall or age-specific cohorts. Patients >100 miles away had lower odds of follow-up. Increasing age was associated with decreased odds of follow-up, and this trend persisted over time since treatment (Table). **Conclusions:** Patterns of decreased pediatric/AYA cancer survivor follow-up were largely predicted by age and time since treatment. Further work is ongoing to understand drivers of follow-up disparities, including transfers of care and insurance type among AYA patients and the role of community support and telemedicine in healthcare access and health promotion. Research Sponsor: Stanford University School of Medicine.

Association of age/distance and odds of cancer center follow-up 2-7 years after treatment completion.			
	OR at 2-3 years (95% CI)	OR at 4-5 years (95% CI)	OR at 6-7 years (95% CI)
Age 25-29	0.30 (0.19-0.45)	0.20 (0.12-0.33)	0.32 (0.18-0.59)
Age 20-24	0.47 (0.31-0.71)	0.29 (0.18-0.46)	0.31 (0.17-0.55)
Age 15-19	0.67 (0.44-1.03)	0.42 (0.26-0.67)	0.34 (0.19-0.62)
Age 10-14	0.99 (0.64-1.53)	0.62 (0.39-0.99)	0.73 (0.40-1.31)
Age 5-9	1.42 (0.91-2.21)	1.03 (0.63-1.67)	1.39 (0.76-2.54)
Age 0-4	(ref)	(ref)	(ref)
>100 mi from cancer center	0.68 (0.47-0.96)	0.61 (0.40-0.94)	0.53 (0.29-0.94)
51-100 mi	1.07 (0.79-1.44)	0.89 (0.64-1.26)	1.02 (0.66-1.59)
0-50 mi	(ref)	(ref)	(ref)

10054

Poster Session

Longitudinal associations between peripheral neuropathy and neurocognitive decline in long-term survivors of pediatric cancer treated without central nervous system (CNS) directed therapy. *First Author: AnnaLynn Williams, University of Rochester School of Medicine and Dentistry, Rochester, NY*

Background: Survivors of pediatric cancer treated without CNS-directed therapy are at risk of neurocognitive impairment and peripheral neuropathies. Using the St. Jude Lifetime Cohort, we investigated longitudinal associations with neuropathy to inform contributors to long-term cancer-related neurocognitive decline. **Methods:** Survivors of pediatric cancer (N=899 mean age 32 [SD 12], 24[10] years from diagnosis) treated without CNS-directed therapy completed neurocognitive testing and medical assessments at two timepoints (T1, T2 4.4[2.3] years apart). Peripheral sensory and motor neuropathy subscales combined with functional tasks were severity graded using a modified CTCAE (no neuropathy = none or grade 1 at T1 and T2; new onset = new grade 2 or 3 at T2; persistent = grade 2 or 3 at T1 & T2). Linear regression models estimated change in neurocognitive Z-score associated with neuropathy groups, adjusted for diagnosis age, time between visits, sex, race/ethnicity, high-dose intravenous methotrexate & baseline neurocognitive Z-score. **Results:** New onset sensory (n=33, 3.6%) and motor (n=35, 3.9%) neuropathy was associated with a 0.33 standard deviation (SD) decline in visual-motor processing speed (Table). New onset motor neuropathy was associated with a 0.50 SD decline in sustained attention as well as significant declines in verbal recall, working memory, and cognitive flexibility (p's<0.05). Persistent sensory neuropathy (n=25, 2.8%) was associated with large declines in focused attention and cognitive flexibility (p's<0.05). Persistent motor neuropathy (n=18, 2.0%) was associated with a 0.50 SD decline in sustained attention, verbal recall, and working memory (p's<0.05). **Conclusions:** Peripheral neuropathies are associated with future neurocognitive decline in adult survivors of pediatric cancer. Research is needed to understand shared mechanisms (e.g. pain, inflammation) to inform targeted interventions to improve neuropathic symptoms and neurocognitive function. Research Sponsor: U.S. National Institutes of Health; ALSAC.

	New Onset (vs No Neuropathy)		Persistent (vs No Neuropathy)	
	Sensory	Motor	Sensory	Motor
Sustained Attention	-0.35(-0.70,0.01)	-0.49(-0.83,-0.16)	-0.41(-0.84,0.02)	-0.59(-1.05,-0.13)
Focused Attention	-0.43(-0.71,-0.14)	-0.45(-0.73,-0.17)	-0.81(-1.15,-0.47)	-0.07(-0.46,0.31)
Visual Motor Processing Speed	-0.29(-0.51,-0.07)	-0.34(-0.56,-0.12)	-0.42(-0.67,-0.17)	-0.19(-0.47,0.10)
Verbal Recall	-0.18(-0.49,0.14)	-0.32(-0.63,-0.02)	-0.43(-0.79,-0.07)	-0.53(-0.95,-0.11)
Working Memory	-0.06(-0.33,0.20)	-0.31(-0.56,-0.05)	-0.59(-0.89,0.28)	-0.49(-0.84,-0.13)
Cognitive Flexibility	-0.31(-0.67,0.05)	-0.64(-0.98,-0.30)	-0.75(-1.17,-0.33)	-0.29(-0.76,0.17)

10056

Poster Session

Outcomes of childhood, adolescent, and young adult cancer survivors (CAYACS) with solid organ transplants: A population-based study. *First Author: Sumit Gupta, Division of Haematology/Oncology, The Hospital for Sick Children, Toronto, ON, Canada*

Background: Organ toxicity requiring solid organ transplant (SOT) is a rare but serious effect of cancer treatment. Given restricted donor organ supply, teams must assess CAYACS requiring SOT in relation to potential recipients with non-malignant indications; decisions are limited by scant long-term outcome data. We compared long-term outcomes for CAYACS requiring SOT with other SOT recipients. **Methods:** All Ontario, Canada children < 18 years at cancer diagnosed 1986-2021 at pediatric centres, and AYA aged 15-21 diagnosed at adult centres for acute leukemia, lymphoma, sarcoma, or testicular cancer between 1992-2012 were identified using population-based clinical databases. Patients with SOT prior to their primary cancer diagnosis were excluded. SOT was identified through linkage to healthcare databases; patients were matched 1:2 to non-malignant SOT recipients by sex, SOT year and type, and birth year. Post-SOT outcomes including overall survival (OS) and post SOT cancers were compared between CAYACS and SOT controls. **Results:** Among 16,533 CAYA with cancer, 85 received SOT: 46 liver, 18 kidney, 11 lung, and 10 heart. Among liver recipients, 33 (71.7%) were for primary cancer treatment (e.g. hepatoblastoma) vs. 13 (28.3%) for organ toxicity. Median age at original cancer diagnosis was 4 years [interquartile range (IQR) 1-13] and at SOT was 13 (IQR 3-20). CAYACS with SOT as treatment for long-term toxicity (liver subset plus all renal, lung, heart, N = 52) had a median time from cancer diagnosis to SOT of 9 years (IQR 4-16) and experienced lower 10-year OS from time of SOT [67.7%, 95th confidence interval (95CI) 50.8-79.9] vs. SOT matched controls [86.0% (74.8-92.5); hazard ratio (HR) 3.9; 95CI 1.6-9.7; p = 0.003]. When stratified by SOT type, similar trends were seen but were only statistically significant among lung SOT recipients (Table). The 5-year cumulative incidence of primary cancer relapse from time of SOT among those who received liver SOT for primary cancer therapy was 15.9% (95CI 5.6-30.8). Among CAYACS who require SOT following organ toxicity, 10-year cumulative incidence of second cancers was 8.6%±4.2%; this was similar to the incidence of first cancer among SOT controls (6.4%±2.6%; HR 1.6, 95CI 0.6-4.0; p = 0.34). **Conclusions:** Though CAYACS requiring SOT have inferior survival compared to other SOT patients, the majority achieve long-term cancer-free survival. These data can inform discussions on the suitability of CAYACS for SOT. Research Sponsor: None.

	10-year OS		HR (95CI)	p
	CAYACS	Control SOT		
Liver	75.0 (58.1-85.8)	89.1 (80.0-94.2)	2.1 (0.8-5.1)	0.11
Primary cancer therapy	78.0 (56.7-89.7)	86.7 (75.0-93.2)	1.4 (0.5-4.1)	0.51
Late treatment toxicity	68.4 (35.9-86.8)	94.1 (65.0-99.1)	7.1 (0.8-64)	0.08
Kidney	79.6 (37.1-94.9)	88.6 (57.7-97.4)	2.3 (0.4-14)	0.37
Lung	42.4 (10.8-71.9)	74.5 (43.5-90.1)	10 (1.2-86)	0.04
Heart	66.7 (27.1-88.1)	79.1 (47.0-92.9)	2.0 (0.4-9.8)	0.40

10057

Poster Session

Outcomes among survivors of childhood cancer in low- and middle-income countries: A systematic review. *First Author: Avram Denburg, Division of Haematology/Oncology, The Hospital for Sick Children, Toronto, ON, Canada*

Background: Low- and middle-income countries (LMICs) account for most of the global childhood cancer burden. Though cure rates lag behind those in high-income countries (HICs), a substantial proportion of LMIC children do survive. Long-term side effects of cancer or cancer therapy (late effects) are well-documented among childhood cancer survivors (CCS) in HICs, but whether prevalence and risk factors of late effects are comparable in LMICs is unclear. We thus conducted a systematic review to assess LMIC CCS outcomes. **Methods:** Five major health sciences databases were searched from inception to November 2022 in all languages. We included observational studies conducted in LMICs (World Bank 2021 classification) that evaluated outcomes in CCSs diagnosed with any malignancy. Mean or median length of follow-up must have been ≥ 5 years from original cancer diagnosis. Meta-analyses were precluded by cohort and outcome heterogeneity. **Results:** Of 1,994 studies identified, 113 underwent full-text review and 21 met inclusion criteria (16 full articles and 5 conference abstracts). Studies were conducted in lower-middle income (N = 12, 57%) or upper-middle income (N = 9, 43%) countries; no low-income country data were found. Study regions were mainly South and East Asia (N = 10, 48%) and the Americas (N = 8, 38%). Almost half (N = 9, 43%) of studies were conducted in India and only one African study from Cameroon was identified. Over half (N = 12, 57%) of studies were cross-sectional in design. Only five (24%) cohorts were comprised entirely of 5-year survivors. CCS of all childhood cancer types were evaluated in 12 (57%) cohorts, and 9 (43%) were specific to one cancer type. Ten (48%) studies were conducted in a survivorship clinic. Second cancers, followed by endocrine, reproductive, and cardiovascular late effects were most frequently assessed. Second cancers were reported in 1%-11% of CCS cohorts (N = 10 studies). The prevalence of hypothyroidism and metabolic syndrome ranged from 2%-49% (N = 6 studies) and 4%-17% (N = 5 studies), respectively. Gonadal dysfunction ranged from 2%-82% (N = 6 studies). Cardiac dysfunction and hypertension ranged from 1%-16% (N = 3 studies) and 5-19% (N = 3 studies), respectively. Late effects of the musculoskeletal (N = 4 studies) and urinary (N = 4 studies) systems were least investigated. **Conclusions:** Substantial knowledge gaps exist in LMIC childhood cancer survivorship. Few LMIC-based studies were identified, with no low-income country data available. In middle-income countries, variability existed in how late effects were defined and assessed; data was also limited by selection bias and small sample sizes. Additional systematically collected data on LMIC CCS cohorts are urgently needed. Research Sponsor: None.

10060

Poster Session

Leveraging a community-academic partnership to evaluate the needs of Latinx AYA cancer survivors. *First Author: Stephanie M Smith, Division of Hematology/Oncology, Department of Pediatrics, Stanford University School of Medicine, Stanford, CA*

Background: Adult survivors of childhood cancer have an increased risk of late death and treatment-related comorbidities, yet < 20% of survivors receive guideline concordant risk-based care. Individual-level disadvantages and population-level measures of deprivation contribute to unequal health outcomes among survivors. We aimed to explore the experiences of adolescent/young adult (AYA) cancer survivors and their parents in a region in California with low socioeconomic status and high rates of non-English language preference. **Methods:** We formed a community-academic partnership with Jacob's Heart, a nonprofit organization that provides material/psychosocial support to predominantly Hispanic/Latino (Latinx) families of children with cancer. Between Feb-July 2022, we conducted semi-structured interviews in-person or by video or phone with English- or Spanish-speaking AYA survivors of childhood cancer (age ≥ 15 years, ≥ 5 years post-diagnosis), parents, and Jacob's Heart staff members, with assistance from certified medical interpreters. Data were analyzed qualitatively using reflexive thematic analysis based on grounded theory and the constant comparative method. Themes were refined through team discussions with our community partners. **Results:** We interviewed 12 AYAs (11 Latinx and bilingual), 11 parents (8 Latinx, 7 non-English preferred), and 7 organization staff (5 Latinx and bilingual). AYAs (5 female, 7 male) were median age (min-max) 20 (16-32) and 9 (5-19) years post-diagnosis; parents (9 female, 2 male) were median age 48 (40-60) and 14 (6-23) years post-child's diagnosis. Cancer types were leukemia (6 AYAs, 9 parents), CNS tumors (1 AYA, 2 parents), other solid tumors (3 AYAs), lymphoma (2 AYAs). Key themes across interviews included gratitude and trust in the pediatric cancer care team and Jacob's Heart staff, challenges obtaining healthcare outside of the pediatric cancer setting, lasting effects of cancer on the family (e.g., parental job loss, financial strain, impact on siblings, prolonged fear of recurrence in parents, unmet mental health needs in parents and AYAs), and communication barriers between Latinx families and clinicians (e.g., hesitancy to ask questions, overwhelmed by medical information) and between AYAs and parents (e.g., avoidance of talking about cancer history, cancer-related stigma, differing language preferences of AYAs and parents). **Conclusions:** Childhood cancer has long-lasting effects on families and those with fewer socioeconomic resources face additional burdens. Communication gaps experienced by Latinx families may be a target for intervention to improve AYA survivorship care. Future steps include sharing results with participants and partnering with the community to co-design interventions to facilitate triadic communication among Latinx AYAs, parents, and clinicians. Research Sponsor: Stanford Maternal and Child Health Research Institute Structural Racism, Social Injustice & Health Disparities Pilot Grant.

10058

Poster Session

Subsequent meningiomas in survivors of childhood cancer: A report from the Childhood Cancer Survivor Study (CCSS). *First Author: Tab Cooney, Dana-Farber/Boston Children's Cancer and Blood Disorders Center, Boston, MA*

Background: Meningiomas are the most common subsequent central nervous system tumor among aging survivors of childhood cancer, yet incidence across the lifespan, occurrence of multiple meningiomas, and risk for mortality are not established. **Methods:** Meningiomas were identified by self-report and validated with pathology/medical records. Twenty-year cumulative incidence of meningioma (95% confidence interval) was estimated and multivariable models assessed demographic- and treatment-related meningioma risk factors. **Results:** Among 24,902 5-year survivors of childhood cancer diagnosed 1970-1999, we identified 472 survivors with 710 meningiomas, 145 (20.4%) of which were WHO grade 2/3. Among survivors with meningioma, 137 (28%) had ≥ 2 meningiomas, and 80 (16%) met criteria for meningiomatosis. The median latency from childhood cancer to first meningioma diagnosis was 26.2 years (range 5.6-48.2), and the median time from first to second meningioma (among those without meningiomatosis) was 1.4 years (range 0-30.2 years). The twenty-year cumulative incidence did not significantly decrease between survivors diagnosed in the 1970s (0.58, 95% CI 0.41-0.79) and the 1990s (0.42, 95% CI 0.32-0.55). In multivariable analysis, female sex (HR 1.52, 95% CI 1.21-1.91) and all cranial radiotherapy dose levels (> 0.30 Gy, HR 57.0, 95% CI 7.93-419.60; 30.1-50 Gy, HR 228.90, 95% CI 30.89-1695.99; > 50 Gy, HR 113.29, 95% CI 15.09-850.34) were associated with increased meningioma risk, while older age at diagnosis (10-14 years, HR 0.60, 95% CI 0.44-0.82; 15-20 years, HR 0.35, 95% CI 0.22-0.55) was associated with reduced meningioma risk. Among 71 deaths in survivors with meningioma, the most prevalent cause of death was meningioma (N = 25, 35.2%). The 5-year all-cause mortality from first meningioma diagnosis was 4.20% (95% CI: 2.44-5.96%). **Conclusions:** In conclusion, cranial radiation, younger diagnostic age and female sex were identified as independent meningioma risk factors in, to our knowledge, the largest study to date. The risk for meningioma-associated mortality argues for assertive meningioma surveillance and treatment in this population. Research Sponsor: None.

10061

Poster Session

Influence of genetic predisposition and lifestyle on modifiable cardiovascular risk factors among survivors of childhood cancer. *First Author: Carmen L Wilson, St. Jude Children's Research Hospital, Memphis, TN*

Background: We aimed to evaluate associations between polygenic risk score (PRS), and lifestyle with cardiovascular risk factors (CVRFs) assessed as continuous phenotypes (LDL, HDL, triglycerides, fasting glucose [FG], systolic [SBP] and diastolic blood pressure [DBP]) among childhood cancer survivors. **Methods:** Participants included 2,347 White survivors (mean age=35.5 (± 9.3) years) enrolled in the St. Jude Lifetime Cohort. Phenotype-specific PRS (derived from general population) were divided into tertiles and survivors classified as being at low-, intermediate-, or high-genetic risk. Lifestyle, classified as good, intermediate, or poor, was assessed based on four factors (smoking [yes/no], physical activity [meeting CDC guidelines for physical activity], diet quality [Healthy Eating Index score > 59], and obesity [BMI ≥ 30 kg/m²]). A general linear model was created for each CVRF in which the effect of lifestyle (good, intermediate, poor) was examined within genetic risk group (low, intermediate, high), adjusting for sex, age, cancer therapies and current medication use. **Results:** The table shows worsening CVRF profiles associated with declining lifestyle and with increasing genetic risk. For example, among survivors with poor lifestyle-high genetic risk, SBP and DBP were higher on average by 14 (95% CI = 9-18) and 9 (95% CI = 6-12) mmHg respectively, compared to survivors with good lifestyle-low genetic risk. In analyses restricted to survivors with high genetic risk, mean SBP (7, 95% CI=2-12) mmHg, DBP (4, 95% CI=1-7) mmHg, triglyceride (61, 95% CI=5-117) mg/dL, and FG (7, 95% CI=4-10) mg/dL values were higher among survivors with poor versus good lifestyle, while mean HDL was lower (-13, 95% CI= -18) mg/dL. **Conclusions:** While the risk of CVRFs among cancer survivors are associated with high genetic risk and cancer therapies, healthy lifestyle choices may partially ameliorate perturbations in CVRFs even among those with high genetic risk. Our findings highlight the importance of developing interventions targeting modifiable behaviors in this high-risk population. Research Sponsor: U.S. National Institutes of Health.

Genetic Risk	Lifestyle	HDL (mg/dL) Beta (95%CI)	LDL (mg/dL) Beta (95% CI)	TG (mg/dL) Beta (95%CI)	SBP (mmHg) Beta (95% CI)	DSP (mmHg) Beta (95% CI)	FG (mg/dL) Beta (95% CI)
Low	Good	Ref	Ref	Ref	Ref	Ref	Ref
	Intermediate	-13 (-9,-17)*	6 (-5, 17)	7 (-21, 36)	4 (0.6, 8)*	3 (1, 6)*	1 (-2, 4)
	Poor	-24 (-19,-27)*	6 (-7,19)	46 (12, 81)*	2 (-2, 7)*	5 (2, 7)*	4 (1, 8)*
Intermediate	Good	-16 (-11, -20)	18 (6, 29)*	15 (-15, 45)	2 (-2, 6)	3 (1, 6)*	5 (1, 8)*
	Intermediate	-22 (-18, -26)	27 (16, 37)	49 (23, 76)*	6 (3, 10)*	5 (3, 7)*	5 (2, 8)*
	Poor	-28 (-23, -32)	32 (21, 42)	76 (47, 104)*	9 (5, 13)*	6 (4, 8)*	5 (2, 9)*
High	Good	-22 (-16, -27)	37 (23, 51)	60 (21, 98)*	7 (2, 12)*	5 (2, 8)*	2 (-2, 6)
	Intermediate	-28 (-24, -32)	44 (33, 55)	89 (60, 117)*	7 (3, 11)*	7 (5, 9)*	6 (2, 9)*
	Poor	-35 (-30, -40)	39 (26, 52)	121 (87, 155)	14 (9, 18)*	9 (6, 12)*	9 (5, 13)*

*p<0.05.

10062

Poster Session

Racial disparities in treatment and outcomes of pediatric hepatoblastoma. *First Author: Taylor Billion, Creighton University School of Medicine, Omaha, NE*

Background: Hepatoblastoma is the most common malignant liver tumor which affects pediatric patients. However, the incidence is rare with 100 cases reported per year.¹ Current management consists of surgery and adjuvant cisplatin chemotherapy and radiation depending on tumor histology, resectability, and metastasis.² However, due to its rarity, optimal treatment protocol remains unclear. The 5-year overall survival rate in the US is approximately 57-69%.¹ **Methods:** The National Cancer Database (NCDB) was used to identify patients diagnosed with hepatoblastoma from 2004 to 2020 using the histology codes 8970 as assigned by the Commission on Cancer Accreditation program. Kaplan-Meier, Chi-Square, and ANOVA tests were performed. Data was analyzed using SPSS version 27 and statistical significance was set at $\alpha = 0.05$. **Results:** This study identified 1215 patients with hepatoblastoma. Black patients had a significantly lower median survival rate compared to White and other race patients (126.2 months vs 165.4 months vs 166.1 months; all $p < 0.05$). Black patients were more likely to be from low-income households than White patients (29.6% vs 17.3%; $p < 0.05$). The mean age of diagnosis was higher for Black patients compared to White patients (2.42 vs 1.99; $p < 0.05$). Black patients were less likely to receive surgery (63.5% vs. 75.4%; $p < 0.05$). Black patients on average had shorter distances to travel from their residence to the hospital (30.61 vs. 59.52 miles; $p < 0.05$). Black patients had longer mean stay times compared to white patients (16.7 days vs 11.2 days; $p < 0.05$). There was no significant difference in survival across incomes. When comparing Black and White patients there was no significant difference in insurance type, surgical margins, grade, stage, size of tumor, regional lymph nodes and time of diagnosis to treatment. No significant difference was shown between adjuvant therapies including chemotherapy and radiation. **Conclusions:** This study showed Black patients experienced inferior overall survival when diagnosed and treated for hepatoblastoma compared to White patients. This population was less likely to receive surgery, older when diagnosed, and had longer hospital stays. Poorer outcomes suggest a disparity in hepatoblastoma treatment. References: 1. Rangaswami, Arun A. "Pediatric Hepatoblastoma Treatment & Management: Medical Care, Surgical Care, Consultations." *Pediatric Hepatoblastoma Treatment & Management: Medical Care, Surgical Care, Consultations*, Medscape, 9 Dec. 2021, <https://emedicine.medscape.com/article/986802-treatment>. 2. Pritchard J, Brown J, Shafford E, et al.: Cisplatin, doxorubicin, and delayed surgery for childhood hepatoblastoma: a successful approach—results of the first prospective study of the International Society of Pediatric Oncology. *J Clin Oncol* 18 (22): 3819-28, 2000. Research Sponsor: None.

10064

Poster Session

Expansion of the fertility preservation program to all newly diagnosed prepubertal oncology patients at a pediatric hospital. *First Author: Antonia Pryor Leavitt, Duke University School of Nursing, Durham, NC*

Background: As the majority of pediatric oncology patients survive their disease, generating a population of over 500,000 survivors in the United States, it is imperative to minimize the lifelong consequences of treatment, which includes temporary or permanent infertility caused by certain cancer treatments. Fertility preservation (FP), the opportunity to preserve one's ability to have genetically-related children prior to damaging the reproductive system, is a young but rapidly expanding field and recent scientific advances have led to an expansion of options for prepubertal patients. A fertility consultation at diagnosis can provide patients and families with the opportunity to be informed regarding likelihood of gonadal dysfunction and to consider FP. **Methods:** After our pediatric hospital started to offer tissue cryopreservation, we initiated this evidence-based interventional quality improvement project. Our primary aim was to ensure that all newly diagnosed prepubertal oncology patients who met criteria for FP were correctly identified and offered an educational consultation and preservation. Inpatient admission lists and provider schedules were reviewed daily to identify patients. Treatment plans were discussed with providers to calculate infertility risk. All procedures were to be completed at the time of another procedure to increase likelihood of insurance coverage and minimize delays. **Results:** Between 07/15/22 and 11/30/22, 54 newly diagnosed prepubertal patients' treatment plans were evaluated to determine treatment-related infertility risk using the Oncofertility Consortium Pediatric Initiative Network's Risk Assessment tool. 15 patients were at a high level of significantly increased risk and were therefore eligible for consultation. 7 patients and their families received an educational consultation and 6 elected to undergo FP (3 TTCs; 3 OTCs). FP procedures did not cause a delay in starting treatment for any of these patients. 8 patients did not receive consultations. Reasons included the provider electing to proceed with treatment without consultation (4), the patient's comorbidities (1), the inability to bundle FP with another procedure (1), and the family decision to decline consultation (1). **Conclusions:** Of the patients at high risk of infertility, only 46% received consultation with lack of referral prior to initiating treatment as the primary reason. Of the patients offered preservation methods, 86% elected to preserve their fertility, illustrating patient and family interest. Providers must acknowledge changes in practice and be informed on the impact that high-risk treatment protocols can have on fertility. An FP program with established policies processes can increase the likelihood that prepubertal patients at high risk for infertility are correctly identified, educated, and offered preservation. Research Sponsor: None.

10063

Poster Session

Clinical course and native antibody development after COVID-19 infection in 50 pediatric oncology patients. *First Author: Maeve Smart, Dana-Farber Cancer Institute, Boston, MA*

Background: Pediatric oncology patients are at higher risk for severe COVID-19 infection compared to healthy children. However, pediatric cancer patients appear to be at lower risk of severe infection compared to adults with cancer. Lower rates of native antibody development have been seen in adults with hematologic malignancies particularly those with a history of transplant or anti-CD20 therapy. Data on the clinical characteristics of COVID-19 and antibody development after infection in children with cancer are limited. This study aims to describe the clinical manifestations of COVID-19 infection in pediatric cancer patients, identify variables associated with severe infection, and evaluate native antibody development. **Methods:** REsearch on COVID-19 in Oncology to Inform Recovery and Mitigate Future Risk (RECOVER) is an IRB approved institutional cohort study at Dana-Farber Cancer Institute. Pediatric patients with cancer who had COVID-19 are eligible 1-12 months following qPCR confirmed infection. Blood samples are collected at 2 timepoints (3-12 months after COVID-19 infection and 6-9 months later) and undergo research analysis as well as clinical Anti-SARS-CoV-2 (antibody response only to native infection) testing. **Results:** We report on the first 50 patients enrolled on the RECOVER study from March 2021 to December 2022 (COVID infection between March 2020 and November 2022). In this cohort, 56% (28/50) were male, 60% (30/50) had hematologic malignancies, 28% (14/50) had solid tumors, and 12% (6/50) had CNS tumors. Median patient age was 10.4 years (range 1-22 years). Most patients (86%; 43/50) were on active cancer treatment, of which 76% (33/43) had modifications in cancer-directed therapy due to COVID-19 infection. 76% of patients with COVID-19 were symptomatic and 26% (13/50) were hospitalized for COVID-19 symptoms. COVID-19 directed treatments were administered to 44% (22/50) of patients, most commonly antivirals ($n = 12$), monoclonal antibodies ($n = 9$), steroids ($n = 3$) and IVIG ($n = 2$). Native COVID-19 antibody testing 3-12 months post infection was performed for 88% (44/50) of patients, with 64% (28/44) seropositive at a median time of 5 months post-infection. Repeat antibody testing at timepoint 2 was available for 20 patients, with 14/14 remaining seropositive, 6/7 remaining seronegative, and 1 converting from seronegative to seropositive. **Conclusions:** The clinical characteristics of COVID-19 seen in this cohort of 50 pediatric oncology patients is consistent with prior reports, highlighting a high risk of hospitalization in this population. This study is the first to evaluate COVID-19 antibody development in pediatric cancer patients and showed that 63% of patients developed antibodies. Pediatric enrollment is ongoing and additional analyses are underway to assess factors associated with severe COVID-19 infection and/or associated antibody response. Research Sponsor: Dana Farber Cancer Institute.

10065

Poster Session

Self-reported sleep difficulties and association with cognitive function in pediatric cancer survivors. *First Author: Pete Stavinocha, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Preventing and ameliorating cognitive impairment following treatment for pediatric cancer remains a persistent challenge, with recent literature examining lifestyle factors as possible targets for intervention. An association between sleep and cognitive impairment has been identified in adult cancer patients and survivors, yet information is limited for pediatrics. Thus, the primary goal of our retrospective study was to explore self-reported sleep difficulties in pediatric patients and survivors with mixed cancers. A secondary aim was to explore the impact sleep problems on specific cognitive functions. **Methods:** Children and adolescents who completed neuropsychological assessments at two large pediatric cancer centers ($N = 298$) were identified via medical record review. In addition to demographic data, clinically collected cognitive tests included Wechsler Working Memory (WM), Processing Speed (PSI), and General Ability (GAI) indices. Objective attention measures included Conners Continuous Performance Test (versions II and 3) Omissions (O), Commissions (C), and Reaction Time (RT). Sleep Disturbance (SD) and Sleep-Related Impairment (SRI) were captured using pediatric self-report PROMIS scales. PROMIS cut points were used to categorize sleep issues within the study population and PROMIS scores were compared to reference population means. Multiple linear regression was used to identify relationships between cognitive domains and sleep factors. Common cancer-related clinical and demographic characteristics were controlled as covariates. **Results:** 21.5% of patients reported severe SD, while 12.8%, 15.9% and 49.7% reported moderate, mild, and within normal limits (WNL) SD, respectively. For SRI, 13.3% reported severe SRI, while 20.0%, 15.9% and 50.8% reported moderate, mild and WNL SRI, respectively. Mean SD and SRI were higher than in the reference populations ($p = 0.000$ for both measures). Pearson correlation results suggested a moderate relationship between SD and SRI ($r = 0.489$, $p = 0.000$). After controlling for covariates, multiple linear regressions indicated significant relationships between SD and GAI ($p = 0.006$), SD and O ($p = 0.018$), and SRI and WM ($p = 0.006$). **Conclusions:** Results suggested that ~50% of our pediatric cancer patients and survivors reported SD and SRI. SD was correlated with SRI in our sample, and regression analysis indicates a significant relationship between sleep problems and O, WM, and GAI in our sample. Findings from this retrospective study suggest a relationship between sleep problems and cognitive performance in pediatric cancer survivors. As a potentially modifiable factor to improve cognitive function in pediatric cancer survivors, sleep difficulties warrant more research to potentially guide interventions to better manage and improve cognitive function in this population. Research Sponsor: None.

TPS10066

Poster Session

Phase 1/2 study of tiragolumab and atezolizumab in patients with relapsed or refractory SMARCB1 or SMARCA4 deficient tumors. *First Author: Mary Frances Wedekind, Pediatric Oncology Branch, NCI, NIH, Bethesda, MD*

Background: The SMARCB1/A4 gene products are core subunits of the SWI/SNF chromatin remodeling complex. Tumors with defects in SWI/SNF are histologically distinct aggressive cancers occurring in children and young adults. SMARCB1/A4 deficient tumors, particularly rhabdoid tumors, poorly differentiated chordoma, epithelioid sarcoma, and medullary renal cell carcinoma, have immune cell infiltrates and programmed death ligand 1 (PD-L1) expression. Response to immune checkpoint inhibition (ICI) has been observed in SMARCB1/A4 deficient tumors; however, responses are not durable. T cell immunoreceptor with Ig and ITIM domains (TIGIT) is a novel inhibitory receptor expressed on multiple immune cells. TIGIT inhibits T and NK cells by binding to its ligand poliovirus receptor (PVR) and Nectin2 on tumor cells and antigen-presenting cells. Utilizing RNAseq data, SMARCB1/A4 deficient tumors demonstrate high expression of PVR and Nectin2. Tiragolumab is an antibody to the TIGIT receptor. In patients with non-small cell lung cancer, tiragolumab with atezolizumab increased survival compared to atezolizumab alone. Thus, data suggest that SMARCB1/A4 deficient tumors are susceptible to ICI; however, monotherapy is unlikely to achieve durable responses; the addition of tiragolumab may enhance response rates. **Methods:** This is a phase 1/2 trial of tiragolumab monotherapy and in combination with atezolizumab in patients ≥ 12 months of age with SMARCB1/A4 deficient tumors administered IV on Day 1 of 21-day cycles. Part A will evaluate the safety of tiragolumab monotherapy (300 mg if ≤ 15 kg; 420 mg if > 15 to ≤ 40 kg; 600 mg if > 40 kg or ≥ 18 yrs) based on cycle 1 DLTs in up to 6 evaluable patients < 18 yrs of age. Part B will estimate the antitumor activity of tiragolumab in combination with atezolizumab (15 mg/kg [max 1200 mg]) if < 18 yrs or 1200 mg if ≥ 18 yrs) in 6 histology-specific cohorts (renal medullary carcinoma, malignant rhabdoid tumor, atypical teratoid rhabdoid tumor, poorly differentiated carcinoma, epithelioid sarcoma, and other) Each cohort will be conducted using a 6+4 Simon's 2 stage design. Up to 13 patients may enroll in each cohort allowing for invaluable patients (maximum n=78). Enrollment of patients ≥ 18 yrs on Part B may occur concurrently with enrollment of patients < 18 yrs on Part A. If the pediatric dose of tiragolumab is deemed safe, patients < 18 yrs old may be enrolled on Part B. Cycle 1 toxicities of the combination therapy will be monitored in Part B using a Bayesian Optimal Interval Design in patients < 12 yrs of age. The secondary objectives are to characterize pharmacokinetics/anti-drug antibody and estimating progression free survival, overall survival, and duration of response. Enrollment is open for all Pediatric Early Phase Clinical Trial Network sites. Clinical trial information: NCT05286801. Research Sponsor: PEP-CTN Grant UM1CA228823; Genentech, Member of the Roche group supports drug supply and funding; Cookies for Kids' Cancer.

TPS10068

Poster Session

Phase 1b/2 study of abemaciclib combined with chemoimmunotherapy in pediatric and young adult patients with relapsed/refractory neuroblastoma (JPCS Part C). *First Author: Emily Gustava Greengard, University of Minnesota, Eden Prairie, MN*

Background: Survival for high-risk neuroblastoma (NBL) remains poor with over 50% of patients experiencing disease relapse. The addition of dinutuximab (DIN) and granulocyte macrophage colony-stimulating factor (GM-CSF) to irinotecan (IRN) and temozolomide (TMZ) in patients with first relapse achieved an overall response rate of 42% in the study ANBL1221¹ and is now standard of care. However, there remains a significant unmet need to improve outcomes for children with relapsed/refractory NBL. Deregulation of the Cyclin D/cyclin-dependent kinase (CDK) 4 & 6 pathway has been observed in NBL, rendering CDK4 & 6 inhibition logical to explore. Abemaciclib is an orally administered, selective CDK4 & 6 inhibitor approved to treat breast cancer. JPCS (NCT04238819) is designed to assess the pharmacokinetics, safety, and tolerability of abemaciclib added to standard treatment regimens for relapsed/refractory pediatric solid tumors. Part A defined the recommended phase 2 dose (RP2D) of abemaciclib in combination with IRN and TMZ. In Part C, the addition of DIN + GM-CSF to the JPCS Part A regimen will be evaluated. The co-primary objectives of Part C are to determine the RP2D and to estimate the anti-tumor activity of abemaciclib added to the ANBL1221 chemoimmunotherapy backbone in patients with first relapse/refractory NBL. **Methods:** JPCS Part C is a two-stage, non-randomized, open-label, Phase 1b/2 study for patients < 21 years of age with first relapse/refractory NBL. Stage 1 aims to identify the maximum tolerated dose (MTD) of abemaciclib at a starting dose of 55 mg/m² combined with DIN, GM-CSF, IRN and TMZ using a 3+3 design. One dose de-escalation (30 mg/m²) will be possible if the starting dose is not tolerated. Further tolerability and initial anti-tumor activity will be evaluated in an expansion cohort at the MTD. Up to 11 evaluable patients will enroll in Stage 1 at the MTD; the MTD will be declared the RP2D if adequate safety and tolerability are observed and ≥ 6 patients achieve minimal response or better per International Neuroblastoma Response Criteria (INRC). Following determination of the RP2D, Stage 2 will enroll 35 patients. If ≥ 26 of 46 total patients achieve an INRC minimum response or better, further investigation of this regimen could be warranted. As of 31 Jan 2023, Part C is open for enrollment at one site (US) and additional sites are being evaluated. References: Mody et al. J Clin Oncol. 2020; 38(19):2160-2169. Clinical trial information: NCT04238819. Research Sponsor: Eli Lilly and Company.

TPS10067

Poster Session

LOGGIC/FIREFLY-2: A phase 3, randomized trial of tovorafenib vs. chemotherapy in pediatric and young adult patients with newly diagnosed low-grade glioma harboring an activating RAF alteration. *First Author: Cornelis Martinus van Tilburg, Hopp Children's Cancer Center Heidelberg (KITZ), Heidelberg University Hospital and German Cancer Research Center (DKFZ), Heidelberg, Germany*

Background: Pediatric low-grade gliomas (pLGGs) are the most common CNS tumors of childhood. Genomic alterations of *BRAF* are oncogenic drivers in almost all pLGGs. Approximately 50%–60% of pLGGs harbor a *KIAA1549-BRAF* fusion and 5%–15% a *BRAF* V600E mutation. Tovorafenib is an investigational, oral, selective, CNS-penetrant, small molecule, type II pan-RAF inhibitor. The registrational, phase 2 FIREFLY-1 (NCT04775485) study of tovorafenib in pediatric patients with recurrent/progressive LGG is ongoing and interim analysis has shown encouraging anticancer activity. **Methods:** LOGGIC/FIREFLY-2 (NCT05566795) is a registrational, 2-arm, randomized, multicenter, global (~ 100 sites across Australia, Canada, Europe, New Zealand, Singapore, South Korea, and USA), phase 3 trial being conducted in collaboration with the SIOPE Brain Tumor Group LOGGIC Consortium. The study is evaluating the efficacy, safety, and tolerability of tovorafenib vs. standard of care (SoC) chemotherapy in patients < 25 years old with pLGG harboring an activating *RAF*-alteration and requiring first-line systemic therapy. Approximately 400 patients will be randomized 1:1 to receive oral tovorafenib, 420 mg/m² (≤ 600 mg) once weekly (tablet or liquid suspension), or an investigator's choice of SoC chemotherapy: COG-V/C regimen (60 weeks), SIOPE-LGG-V/C regimen (81 weeks), or single-agent vinblastine (70 weeks). Tovorafenib will be continued until the occurrence of radiographic progression (based on Response Assessment in Neuro-Oncology [RANO] criteria as determined by the investigator and confirmed by independent review) or unacceptable toxicity; patients with radiographic progression may be allowed to continue tovorafenib if, in the opinion of the treating investigator, they are deriving clinical benefit from study treatment. Patients who progress in the SoC arm during or after completion of chemotherapy are eligible to cross-over to receive tovorafenib. The primary endpoint is the objective response rate based on RANO criteria, as determined by independent review. Key secondary endpoints are progression-free survival and duration of response per RANO criteria by independent review and overall survival. Other secondary endpoints include efficacy assessments per Response Assessment in Pediatric Neuro-Oncology (RAPNO) criteria, changes in neurological and visual function, and safety and tolerability. Exploratory endpoints include efficacy assessments per investigator, tumor volume, adaptive behavior and quality of life. Prognostic and predictive molecular biomarkers, including senescence profiles for treatment outcome, response prediction, and treatment resistance, will be explored in parallel studies. Clinical trial information: NCT05566795. Research Sponsor: Day One Biopharmaceuticals.

TPS10069

Poster Session

Evaluation of palbociclib in combination with topotecan and cyclophosphamide in pediatric patients with recurrent or refractory neuroblastoma. *First Author: Theodore Willis Laetsch, Division of Oncology, Children's Hospital of Philadelphia, and Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA*

Background: Palbociclib is an orally administered, highly selective, reversible, small molecule cyclin-dependent kinases 4/6 (CDK4/6) inhibitor. Inhibition of CDK4/6 reduced growth of neuroblastoma cell lines. The phase 1 portion of the study, conducted and funded by Pfizer in collaboration with the Children's Oncology Group, established the recommended phase 2 dose (RP2D) of palbociclib with topotecan and cyclophosphamide (TOPO/CTX) in children with solid tumors. Per study protocol, if 2 or more patients from the phase 1 study show a confirmed objective response (OR) in a specific tumor type, an open-label, non-randomized tumor-specific cohort (TSC) may be opened. **Methods:** A neuroblastoma TSC has been opened to evaluate the preliminary antitumor activity of palbociclib with TOPO/CTX in the treatment of patients with recurrent/refractory neuroblastoma using a modified Simon's 2-stage optimal design. Up to 21 patients will be enrolled and receive palbociclib with TOPO/CTX. The primary endpoint is OR, as assessed by investigator using International Neuroblastoma Response Criteria (INRC). Secondary efficacy endpoints include duration of response, progression-free survival, and overall survival. Key eligibility criteria include: recurrent/refractory neuroblastoma, measurable disease as defined by INRC, aged ≥ 2 and < 21 years at the time of study entry, adequate blood counts organ function, and performance status. Patients may have received prior TOPO and/or CTX, provided their disease did not progress on this regimen. Prior treatment with a CDK4/6 inhibitor is exclusionary. Patients will receive palbociclib at the RP2D of 75 mg/m² orally once daily on days 1–14 of each 21-day treatment cycle. CTX (250 mg/m²) followed by TOPO (0.75 mg/m²) will be administered intravenously once daily on days 1–5. Concurrent radiotherapy or surgery for local control will be permitted. Treatment will continue until disease progression, patient and/or legal guardian refusal, unacceptable toxicity, or up to 24 months of treatment, whichever occurs first. Enrollment in the neuroblastoma TSC was initiated in December 2022 (NCT03709680). Clinical trial information: NCT03709680. Research Sponsor: Pfizer Inc.

TPS10070

Poster Session

Phase 1/2, first-in-child study of sonodynamic therapy (SDT) using low intensity focused ultrasound and 5-aminolevulinic acid (ALA) for patients with diffuse intrinsic pontine glioma. *First Author: Hasan R Syed, Children's National Hospital, Washington, DC*

Background: Diffuse intrinsic pontine glioma (DIPG) is a devastating pediatric brain tumor with poor prognosis. Sonodynamic therapy (SDT) with ALA is a non-invasive strategy that sensitizes target tissues with a non-toxic chemical agent followed by exposure to low intensity MR-guided focused ultrasound (MRgFUS). Preclinical studies have shown that ALA is preferentially taken up by glioma cells and metabolized to protoporphyrin IX (PpIX). SDT activates protoporphyrin IX and induces tumor cell death via photodynamic effect (lipoperoxidation, apoptosis). Suheiro et al and Wu et al demonstrated that SDT killed tumors via apoptosis and lipoperoxidation in rodent glioma models with minimal damage to surrounding normal brain.^{1,2} ALA SDT was well-tolerated in an ongoing first-in-human trial in adults with recurrent high-grade gliomas and demonstrated biomarker evidence of the photodynamic effect.³ **Methods:** A Phase 1/2, multicenter, open label study (NCT05123534) is enrolling patients at Children's National Hospital. The study employs the Bayesian optimal interval (BOIN) algorithm to evaluate safety and tolerability of treatment with SDT in newly diagnosed DIPG subjects to determine the maximum tolerated dose (MTD) or recommended phase 2 dose (RP2D) of MRgFUS energy in combination with ALA. The study will evaluate 3 ALA doses and 3 acoustic energy doses. ALA is administered IV six to nine hours prior to MRgFUS with the Exablate type-2 device. The first cohort, B1C1, evaluates the lowest drug-device dose combination and if no dose-limiting toxicity (DLT) is encountered after 3 patients, ascending dose-escalation will proceed to the second cohort, B2C1, treated with lowest dose of ALA with the second level of MRgFUS energy. Again, if no DLT is experienced, the next cohort will receive a higher dose combination. The initial patient in each cohort is treated in 2 sessions 21 to 28 days apart, each covering one-half of the pons. Subsequent patients are treated in 1 session to the whole pons. The primary objective is to evaluate the safety and tolerability of SDT in DIPG subjects. Secondary outcomes include preliminary efficacy assessments, pharmacokinetics of ALA and PpIX, mechanical performance of the Exablate Type-2 device, and radiographic evidence of tumor physiological changes associated with SDT. All patients at least 5 years of age with newly diagnosed, radiographically typical DIPG between 4-24 weeks after completion of standard radiotherapy are eligible for the trial. Patients with evidence of disease progression, diagnosis of porphyria, or prior or concurrent therapy with any other anticancer or investigational intervention will be excluded. Cohort 1 has been completed without DLT. References: 1. Suheiro et al. *J Neurosurg* 2018;129:1416-1428. 2. Wu et al. *Sci Rep* 2019;9:10465. 3. Sanai et al. *NeuroOnco* 2022;24(4):vii72-vii73. Clinical trial information: NCT05123534. Research Sponsor: SonALAsense; Focused Ultrasound Foundation.

TPS10072

Poster Session

A multicenter, phase II trial of maintenance sirolimus in combination with metronomic chemotherapy in children and adolescents with high-risk solid tumors. *First Author: Kathryn S. Sutton, Aflac Cancer and Blood Disorders Center, Children's Healthcare of Atlanta, Emory University School of Medicine, Atlanta, GA*

Background: Risk of relapse for children with high-risk solid tumors (ST) remains unacceptably high despite aggressive multimodal therapy. Maintenance therapy is an emerging option to improve outcomes. Sirolimus, an inhibitor of mammalian target of rapamycin, is a potent immunosuppressant with antiproliferative and antiangiogenic effects. Low-dose metronomic chemotherapy along with the cyclooxygenase-2 inhibitor celecoxib also decreases neovascularization in *in vitro* and *in vivo* systems. The maximum tolerated dose (MTD) of sirolimus in combination with celecoxib and etoposide alternating with cyclophosphamide was determined in a phase I study in pediatric patients with relapsed/refractory ST. The regimen was well-tolerated and showed best response of stable disease in 8/18 subjects and partial response in 1/18. The efficacy of this regimen in relapsed/refractory ST is being tested in a Phase II study (NCT02574728). We hypothesize that patients with high-risk ST administered a 12-month course of this maintenance regimen will have improved 2-year progression-free survival (PFS) when compared to matched historical patients who were observed following completion of upfront therapy. **Methods:** This is a phase II study of sirolimus in combination with celecoxib and alternating low-dose etoposide and cyclophosphamide delivered as maintenance therapy. Sirolimus will be given at the MTD of 2mg/m²/day with celecoxib 100mg twice daily and oral etoposide 50mg/m²/day (max 100mg) alternating every 21 days with oral cyclophosphamide 2.5mg/kg/day (max 100mg). This study includes: 1) a prospective cohort of patients with high-risk ST in first complete remission (CR), 2) a prospective cohort of patients with recurrent ST in second CR, and 3) a historical cohort matched 2:1 with cohort 1 on diagnosis, age, metastatic sites, and date of diagnosis treated with observation following upfront therapy. The study will enroll up to 38 patients in cohort 1. Eligible subjects are children (1-30 years) with a diagnosis of high-risk extracranial ST (metastatic sarcoma, desmoplastic small round cell tumor, malignant rhabdoid tumor) in first CR or any ST in second CR. Patients enrolled in upfront clinical trials are excluded. Primary endpoint is 2-year PFS of cohort 1 compared to the historical cohort. Secondary endpoints are median PFS of cohort 1, 2-year PFS and overall survival of cohorts 1 and 2, incidence of severe toxicities, and feasibility of completing the 12-month course following standard upfront therapy. Exploratory objectives include evaluation of circulating tumor DNA (ctDNA) in this population of patients in CR or with minimal disease burden and correlation of clinically obtained tumor molecular profiling with outcomes. As of January 2023, 12 subjects are enrolled, 9 in cohort 1 and 3 in cohort 2. Clinical trial information: NCT04469530. Research Sponsor: Peach Bowl LegAcY Fund (Children's Healthcare of Atlanta).

TPS10071

Poster Session

Update for NCI-COG Pediatric MATCH: Active trial cohorts for children, adolescents and young adults with refractory cancers. *First Author: Donald Williams Parsons, Texas Children's Cancer and Hematology Center, Baylor College of Medicine, Houston, TX*

Background: The National Cancer Institute-Children's Oncology Group Pediatric Molecular Analysis for Therapy choice (MATCH) trial seeks to facilitate evaluation of molecular-targeted therapies in biomarker-selected cohorts of childhood and young adult patients with cancer by screening tumors for actionable alterations. The Pediatric MATCH screening protocol and first seven treatment arms were activated in July 2017 for patients treated at COG sites across the United States; six additional treatment arms were activated between 2017 and 2020. In 2022 a major screening protocol amendment discontinued centralized tumor testing at MATCH laboratories and mandated use of molecular profiling reports from outside laboratories to determine treatment arm eligibility. **Methods:** The trial assigns patients aged 1 to 21 years with relapsed or refractory solid tumors, lymphomas, and histiocytic disorders to phase 2 treatment arms of molecularly-targeted therapies based on the genetic alterations detected in their tumor. Starting in January 2022, a clinical tumor molecular profiling report from a CAP/CLIA-approved laboratory has been required for patients to enroll in the screening protocol. The treating site indicates which molecular alteration in the submitted report is believed to be actionable as well as the open Pediatric MATCH study arm for which the patient is proposed to be eligible. The submitted report is then reviewed by the study Molecular Review Committee to determine if an actionable alteration is present (based upon study-defined levels of preclinical and clinical evidence); if so, the patient is assigned to the relevant MATCH treatment arm. Other treatment arm eligibility requirements are typical of phase 2 pediatric trials including adequate patient performance status and standard washout periods for prior therapy. Each treatment arm follows a one (arms A, D, F, M, N) or two (arm K) stage design with a 20 patient primary cohort and option for histology-specific expansion cohort(s) if at least 3 objective responses are seen in a tumor histology. The primary endpoint is objective response rate; secondary endpoints include safety/tolerability and progression-free survival. Therapy is discontinued if there is evidence of progressive disease or drug related dose-limiting toxicity that requires removal from therapy; therapy may otherwise continue for up to 2 years. As of January 2023, 6 of the 13 Pediatric MATCH treatment arms remain open to enrollment (Table). Clinical trial information: NCT03155620. Research Sponsor: U.S. National Institutes of Health; St. Baldrick's Foundation.

Arm	Agent	Actionable alterations	Enrolled
A	larotrectinib	<i>NTRK1, NTRK2, NTRK3</i> fusions	8
D	samotolisib	<i>TSC1, TSC2, MTOR, PTEN, PIK3CA, or PIK3R1</i> mutations	17
F	ensartinib	<i>ALK</i> fusions or mutations, <i>ROS1</i> fusions	11
K	ivosidenib	<i>IDH1</i> mutations	3
M	tipifarnib	<i>HRAS</i> mutations	5
N	selipratinib	<i>RET</i> fusions and mutations	1

TPS10073

Poster Session

A pilot clinical study of oral irinotecan HCl (VAL-413) in patients with recurrent pediatric solid tumors. *First Author: Jeffrey A. Bacha, Edison Oncology Holding Corp., Menlo Park, CA*

Background: Intravenous irinotecan hydrochloride (IRN-IV) is approved for the treatment of adult colorectal cancer and also used off-label to treat a range of adult and pediatric tumors including recurrent Ewing sarcoma, rhabdomyosarcoma, neuroblastoma, hepatoblastoma, Wilms tumor, gynecologic cancers, lung cancer and medulloblastoma. Previously, a regimen of IRN-IV administered as a 60-min i.v. infusion daily for 5 days, bi-weekly in combination with other agents such as temozolomide has been recommended use in treating children with solid tumors (*Blaney. ClinCanRes, 2001*). Protracted administration schedule of IRN-IV is inconvenient for patients, so oral regimens utilizing IRN-IV have been developed and implemented with favorable tumor response (*Wagner. ClinSarcRes, 2015*). Unfortunately, the palatability of the IRN-IV is poor, leading to reduced compliance especially in younger pediatric patients. Development of an advanced formulation to improve tolerability and patient compliance is an important unmet need. VAL-413 is a novel formulation developed to improve palatability of oral irinotecan. This pilot trial will examine the safety and tolerability of this novel formulation and assess pharmacokinetics compared to current oral regimen. **Methods:** Eligibility: Up to 20 patients $\geq$ 1 year of age or $\leq$ 30 years of age with recurrent pediatric solid tumors and adequate bone marrow, renal and liver function, for whom irinotecan therapy is a treatment option will be enrolled. Trial Design: Two different dose levels of VAL-413, 90mg/m²/day or 110mg/m²/day will be studied in combination with fixed-dose temozolomide using a standard 3 + 3 phase I design. In the event the starting dose of 90 mg/m²/day is not tolerable due to toxicity, a lower dose of 75 mg/m²/day may be implemented. Treatment: During the first cycle of treatment, each patient will receive 4 daily doses of VAL-413 and one daily dose of the intravenous preparation of irinotecan taken orally (IRN-IVPO). During all subsequent cycles, only VAL-413 will be given with temozolomide in 5-day courses administered every 21 days, as tolerated. Outcome Measures: Toxicity is assessed by NCI CCTCAEv5; tumor response is assessed by RECIST 1.1. A palatability survey instrument will assess palatability of VAL-413 vs. IRN-IVPO; comparative intra-patient pharmacokinetics of irinotecan and its metabolites will be assessed. This trial is ongoing (CT.gov: NCT04337177), with no DLT observed to date. Clinical trial information: NCT04337177. Research Sponsor: Valent Technologies LLC; Edison Oncology Holding Corp.

10500

Oral Abstract Session

Germline genetic testing use and results after a cancer diagnosis. *First Author: Allison W. Kurian, Stanford Cancer Institute, Stanford University School of Medicine, Stanford, CA*

Background: Germline genetic testing is increasingly essential for cancer prevention and treatment. There is a growing call for universal germline testing after a cancer diagnosis. In this evolving context, little is known about genetic testing use and results across cancer types at the population level. **Methods:** All patients aged ≥ 20 years, diagnosed with any cancer type and reported to statewide Surveillance Epidemiology and End Results (SEER) registries in Georgia and California from 2013-2019, were linked to 2013-2021 results from four laboratories providing nearly all germline testing in these regions. Testing use was evaluated in patients diagnosed with all cancer types reported by SEER. Pathogenic variant (PV) and variant of uncertain significance (VUS-only) results were evaluated across cancer types. Tested genes were grouped by major cancer associations and by clinical guidelines for testing and results management after a cancer diagnosis, as follows: breast/ovarian including *BRCA1/2*; gastrointestinal including the Lynch syndrome genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*); other hereditary cancer syndromes; and preliminary evidence genes with no clinical guidelines. Genetic testing trends were analyzed with logistic regression modeling. **Results:** Among 1,369,660 patients, 6.8% linked to genetic testing results. Genetic testing use was highest among patients with male breast cancer (50.0%), followed by ovarian cancer (38.6%), female breast cancer (26%), multiple primary cancers (7.5%), endometrial cancer (6.4%), pancreatic cancer (5.6%), colorectal cancer (5.6%), prostate cancer (1.1%) and lung cancer (0.3%). Genetic testing use increased over time, notably ten-fold for pancreatic cancer (2013 diagnoses, 1.2%; 2019 diagnoses, 18.6%). Most (67.5-89.6%) of identified PVs were in genes with clinical guidelines for testing and management, and had an established association with the patient's cancer type (breast/ovarian including *BRCA1/2*: 79.5% of PVs in patients with female breast cancer, 83.8% in patients with male breast cancer, 82.0% in patients with ovarian cancer; gastrointestinal including Lynch syndrome genes: 68.3% of PVs in patients with colorectal cancer, 71.8% in patients with endometrial cancer). Preliminary evidence genes comprised 5.1%-28.1% of PVs detected across cancer types. Compared to non-Hispanic Whites (NHW), patients from other racial/ethnic groups received less testing (Black, odds ratio (OR) 0.58, 95% confidence interval (CI) 0.55-0.63; Hispanic, OR 0.62, CI 0.58-0.66; Asian OR 0.71, CI 0.58-0.66) without improvement over time, and more VUS-only results (NHW, 24.9%; Black 39.0%; Asian, 40.0%), a difference which increased over time. **Conclusions:** At the population level, germline testing use is low across cancer types, falling short of guidelines. Racial/ethnic disparities in testing use and clarity of test results persisted over time. These gaps are priorities for intervention. Research Sponsor: U.S. National Institutes of Health; Centers for Disease Control.

10502

Oral Abstract Session

Incidence round screening performance among women with dense breasts undergoing abbreviated breast MRI and digital breast tomosynthesis (ECOG-ACRIN EA1141). *First Author: Christiane K. Kuhl, Rheinisch-Westfälische Technische Hochschule Aachen, Aachen, Germany*

Background: The sensitivity of mammography, including digital breast tomosynthesis (DBT), is limited by breast density. Abbreviated breast MRI (AB-MR) significantly increases breast cancer detection in women with dense breasts. In the prevalence (baseline) screening round of the EA1141 trial, AB-MR offered a 2.45-fold higher cancer detection rate (CDR) than DBT. Here we report the CDR and diagnostic accuracies of AB-MR and DBT during the EA1141 incidence screening round and the overall interval cancer rate. **Methods:** Informed consent was obtained from all participants. Asymptomatic average risk women aged 40-75 years with mammographically dense breasts scheduled for routine screening with DBT were enrolled. All women underwent DBT and AB-MR at baseline (prevalence) and year 1 (incidence) screens which were interpreted independently by 2 different radiologists blinded to the other modality. Women were contacted 11-13 months after the year 1 screen to assess for a subsequent breast cancer diagnosis. Pathology of biopsy was the reference standard for CDR and positive predictive value of biopsy (PPV3). Interval cancers reported during 11-13 months of follow-up until the next annual screening were included in the reference standard for sensitivity and specificity. A post hoc adjustment was made for multiple testing using the Bonferroni method; p-values are reported for comparisons which met the adjusted significance threshold (0.05/5 = 0.01). Reported 95% confidence intervals were not adjusted for multiplicity. **Results:** Of 1516 enrolled subjects, 1444 completed the baseline and 1291 also the incidence screen. During the latter, 9 women were diagnosed with breast cancer. DBT detected cancer in 5 women (3 DCIS, 2 invasive) for a CDR of 3.9/1000 (5/1291, CI 1.7, 9.0). AB-MR detected cancer in 6 women (0 DCIS, 6 invasive), 4 of which were not detected on DBT, for a CDR of 4.6/1000 (6/1291, CI 2.1, 10.1). The additional imaging (subject-level) rate for DBT was 7.9% (102/1291, CI 6.6%, 9.5%) vs 3.7% (48/1291, CI 2.8%, 4.9%) for AB-MR ($p < 0.001$). The PPV3 (lesion-level) for DBT was 29.4% (5/17, CI 13.5%, 52.6%) and 15.0% (6/40, CI 6.9%, 29.6%) for AB-MR. During the 2 years of study screening (baseline and year 1), there was 1 interval cancer (palpable lump 348 days after year 1 screen), for an overall interval cancer rate of 0.37/1000 person-years (1/2677 person-years, CI 0.05, 2.65). Sensitivity and specificity were 50.0% (5/10, CI 23.7%, 76.3%) and 98.5% (1261/1280, CI 97.7%, 99.0%) for DBT vs 60% (6/10, CI 31.3%, 83.2%) and 93.3% (1193/1278, CI 91.8%, 94.6%, $p < 0.001$) for AB-MR. **Conclusions:** On the incidence screening round, AB-MR detected additional invasive breast cancers not seen on DBT. In addition, a low overall interval cancer rate was observed with combined screening. Although the need for additional imaging was lower for AB-MR, specificity was higher for DBT. Clinical trial information: NCT02933489. Research Sponsor: U.S. National Institutes of Health; Bracco Diagnostics, Monroe/NJ.

10501

Oral Abstract Session

Breast cancer risk associated with missense variants in *BRCA2*. *First Author: Siddhartha Yadav, Mayo Clinic, Rochester, MN*

Background: Greater than 90% of missense variants in *BRCA2* are classified as variants of uncertain significance (VUS). In addition, among the few known missense pathogenic variants (PVs) in *BRCA2*, breast cancer risk has been reported to be lower compared to pathogenic truncating variants (PTVs) (Li et al., 2022). Herein, we aim to reclassify several missense variants in *BRCA2* and investigate the associated breast cancer risk. **Methods:** A total of 450 *BRCA2* missense variants in the C-terminal DNA binding domain (DBD) were evaluated for functional effect utilizing a previously validated homology-directed DNA double-strand repair (HDR) assay. The results of the functional evaluation along with clinical, structural, and in-silico data were applied to the rules-based ACMG/AMP criteria for variant classification to identify pathogenic/likely pathogenic (P/LP) variants and benign/likely benign (B/LB) variants. A pooled case-control analysis was performed comparing the frequency of reclassified P/LP missense variants among 82,372 women with breast cancer within the Ambry Genetics database as cases and 174,167 unaffected women within gnomAD, CARRIERS, and BRIDGES datasets as controls to evaluate associated breast cancer risk. Separate case-control analysis and comparisons with *BRCA2* DBD PTVs, exon 11 PTVs, and known missense PV standards in ENIGMA were also performed. **Results:** From the 450 missense variants in the DBD, 137 (30.4%) were noted to be functionally deleterious and 313 (69.6%) were functionally neutral by the HDR assay. Incorporation of the functional and other data into an ACMG/AMP model led to the reclassification of 439 (97.6%) variants, with 131 as P/LP and 308 as B/LB variants. In a pooled case-control analysis, reclassified *BRCA2* missense P/LP variants were associated with clinically significant increased risks of breast cancer (Odds Ratio (OR): 5.6, 95%CI: 3.9-8.0), whereas B/LB missense variants were not (OR: 1.1, 95%CI: 1.1-1.2). Similarly elevated risks of breast cancer were observed for *BRCA2* PTVs in the DBD (OR: 6.8, 95%CI: 5.1-9.0) and missense PV standards in ENIGMA (OR: 7.8, 95%CI: 4.1-14.7). However, PTVs in exon 11 of *BRCA2* were associated with a lower risk of breast cancer (OR: 4.4, 95%CI: 3.8-4.9) compared to PTVs in DBD, confirming the ovarian cancer cluster region effect in *BRCA2*. **Conclusions:** The study demonstrates that the HDR functional assay in conjunction with other clinical and genomic data can be a powerful tool that can aid in the reclassification of $> 95\%$ of missense variants in *BRCA2*. In addition, missense PVs in DBD were noted to have a similarly elevated risk of breast cancer as PTVs. The reclassification of the *BRCA2* missense VUS and identification of associated breast cancer risk in this study will significantly influence breast cancer risk assessment and management strategies among carriers of these missense variants. Research Sponsor: U.S. National Institutes of Health.

10503

Oral Abstract Session

Second primary breast cancer in young breast cancer survivors. *First Author: Kristen D Brantley, Harvard School of Public Health, Boston, MA*

Background: Prior data suggests that the risk of second primary breast cancer (SPBC) is higher among women diagnosed with primary breast cancer (BC) before age 40. There is evidence that risk differs by primary tumor characteristics, cancer treatments, and genetic predisposition. However, studies investigating risk of SPBC by clinical risk factors are often limited by low numbers of young women and lack of complete patient data, particularly regarding germline genetic risk. **Methods:** Using the Young Women's BC Study (YWS), a prospective cohort of 1,302 women ≤ 40 years diagnosed with BC from 2006-2016, we sought to compare clinical and treatment characteristics among women who developed an SPBC vs. those who did not. The analytic cohort included women diagnosed with Stage 0-III BC who did not undergo bilateral mastectomy ($N = 685$). Demographics, genetic testing and results, clinical events, and treatment data were collected through self-report on baseline and follow-up surveys (every 6 months for 3 years, then annually). Detailed tumor and treatment information, confirmation of genetic testing results, and new and recurrent cancer events were obtained through regular and triggered medical record review. Univariate and multivariate Cox proportional hazards models were used to examine associations of age, race, genetic testing results, hormone receptor status, stage, and grade of primary tumor, and cancer treatments with SPBC. Participants were censored at the time of local recurrence, metastasis, death, or loss of follow-up. **Results:** At a median follow-up time of 9.9 years [inter-quartile range (IQR) = 6.6-12.0 y], 17 patients developed an SPBC (2.5%), in whom 3 occurred in the ipsilateral breast after lumpectomy as primary BC surgery. Median time from primary BC diagnosis to SPBC diagnosis was 4.2 years (IQR = 3.3-5.6 y). Compared to those who did not develop an SPBC, a greater percentage of women who developed an SPBC had *in situ* disease as their primary BC (24% v. 6%) and were of Ashkenazi descent (12% v. 5%). In the 577 women who had had genetic testing, 544 (94%) were non-carriers of pathogenic variants. Risk of SPBC was 2.2% ($N = 12$) in non-carriers and 9.1% ($N = 3$) in the 33 carriers. In Cox univariate analyses, carriers had a 4.1 times higher risk of SPBC compared to non-carriers (HR = 4.14, 95% confidence interval (CI) = 1.67-14.66, $p = 0.03$), and primary diagnosis with *in situ* BC was associated with a 5-fold increased risk of SPBC (HR = 5.02, 95% CI = 1.63-15.41, $p = 0.005$). Both factors remained strongly associated with SPBC when tested together in a multivariate model. **Conclusions:** This prospective study demonstrated a low risk of SPBC in the first 10 years after diagnosis of early BC in young women who are not germline pathogenic variant carriers. The finding that risk of SPBC was higher after *in situ* primary BC at a young age warrants further investigation. These findings have important implications for the treatment and follow-up care of young women with BC. Research Sponsor: Susan G. Komen; Breast Cancer Research Foundation.

10504

Oral Abstract Session

Ancestry-adjusted genomic analysis to identify known and novel associations with single and multiple cancer phenotypes. *First Author: Vijai Joseph, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Germline cancer risks are impacted by cancer type, stage, specific mutation, and ancestry. This study aims to determine the magnitude of genetic risks for commonly tested genes across patients with single and multiple primary cancers (MPC). **Methods:** We conducted a partially de-identified, retrospective cohort study of all patients consented to using the MSK-IMPACT, a matched tumor-normal sequencing assay, over a five-year period. Approximately 83% of IMPACT testing is derived from patients with metastatic disease. We collected data on demographics and clinical cancer features through cBioPortal and institutional databases. MPC were classified based on the IARC guidelines. Clinically actionable, pathogenic variants in cases and gnomAD non-cancer controls were identified using PathoMAN. Statistical methods incorporated ancestry adjusted, weighted generalized linear model, and ancestry specific methods to estimate risk. Biallelic losses were analyzed from paired tumors. **Results:** We analyzed 28,000 individuals across 35 cancer types, where germline variants were discovered within 100 cancer predisposition genes. 16% carried pathogenic, clinically actionable variants in known and novel cancer predisposition genes (15% in those with single primary and 21% in MPC). We discovered statistically significant novel associations of germline variants with several cancer phenotypes, including *BRCA2* and biliary cancer (OR = 4.5, CI = 2.2-8); *ATM* and *BRCA2* with mesothelioma (OR = 4.8, CI = 2.1-9.2; OR = 8, CI = 3.1-16.6, respectively); *NF1* and breast cancer (OR = 5.8, CI = 2.4-12.1); *NBN* and lung cancer (OR = 4.2, CI = 2.3-6.9), bladder with *ATR* and others. We replicated known associations and discovered pleiotropy of *BRCA1/2*, *NF1*, *ATM*, *TP53* with several cancer types. We failed to replicate reported associations such as *PALB2* and ovarian cancer and *CHEK2* and colon cancer. Amongst cancer pairs of multiple primaries, we observed mismatch repair genes *MSH2*, *MSH6* and *MLH1* to be associated with increased risks for stomach, bowel, and uterine cancer pairs, and *TP53* in breast MPC compared to breast single primaries. **Conclusions:** An ancestry adjusted, weighted analysis of a large real-world case-cohort enriched with metastatic disease did not confirm some prior genotype-phenotype correlations, while suggesting novel associations with hereditary cancer types. Research Sponsor: Robert and Kate Niehaus Center for Inherited Genomics; Niehaus Center Fund.

10506

Oral Abstract Session

Integrating polygenic risk scores into clinical breast cancer models: Influence on prediction in diverse cohorts. *First Author: George B.J. Busby, Allelica Inc, Oxford, United Kingdom*

Background: Breast cancer (BC) is the second leading cause of cancer death in women worldwide. Periodic mammography screening has been shown to reduce breast cancer mortality by around 20% in average-risk women and several BC risk models are currently used to identify women at higher risk who can be targeted with increased or earlier screening. However, despite their broad use, these models display only moderate discrimination performance (AUC ranging between 0.51 to 0.68). Here we explore the potential of integrating PRS into a BC risk model using a testing dataset comprising over 175,000 women of diverse ancestry in the UK Biobank and Women Health's Initiative Cohorts. **Methods:** We built and validated novel ancestry-specific BC PRSs utilizing novel methodology that leverage multiple Genome Wide Association Studies (GWASs) and linkage disequilibrium maps. We assessed genetic ancestry from 5 continental level ancestry groups across all individuals and applied the PRSs to our testing dataset to assess the clinical implications of integrating genetic information to the Tyrer-Cuzick (TC) breast cancer clinical risk model. **Results:** The PRSs were well calibrated and displayed high risk stratification (Odds Ratios per Standard Deviation: 1.41 (1.28-1.62) to 1.76 (1.40-2.20; Table) which were comparable or better than benchmarking comparisons with previously published PRS panels. Across genetic ancestries, integrating PRS led to a relative increase of women identified at high lifetime BC risk (20% or higher) from between 1.7 fold (East-Asian ancestry) to around 3 fold (European ancestry). The Net Reclassification Improvement compared to the TC-only model was around 12% for East-Asian (0.001-0.254), European (0.111-0.133), and Admixed American ancestries (0.002-0.228), 17% (0.079-0.266) for South-Asians, and 5% (0.008-0.094) for African ancestry individuals (Table). **Conclusions:** Our results demonstrate that optimizing PRSs for genetic ancestries and integrating them into BC risk models can lead to a significant improvement in risk stratification. This can enable more targeted use of enhanced screening and prevention strategies improving their cost/benefit ratio. Research Sponsor: Allelica Inc.

Predictive performance of ancestry adjusted PRSs for breast cancer.						
Genetic Ancestry	Controls (N)	Cases (N)	OR per SD (CI)	AUC (CI)	Brier Score (CI)	NRI* (CI)
African	4,579	327	1.41 (1.28-1.62)	0.60 (0.56-0.62)	0.063 (0.061-0.064)	0.05 (0.01-0.10)
Admixed American	1,645	82	1.76 (1.40-2.20)	0.63 (0.56-0.70)	0.045 (0.044-0.046)	0.11 (0.01-0.23)
East Asian	1,674	77	1.58 (1.23-1.92)	0.61 (0.55-0.69)	0.043 (0.042-0.043)	0.13 (0.01-0.25)
European	165,044	10,095	1.71 (1.70-1.74)	0.67 (0.67-0.67)	0.053 (0.053-0.053)	0.14 (0.13-0.16)
South Asian	4,311	193	1.56 (1.36-1.76)	0.63 (0.60-0.68)	0.041 (0.040-0.041)	0.17 (0.08-0.27)

*Categorical NRI was calculated using 0-15%, 15-20% and >20% as risk categories.

10505

Oral Abstract Session

Polygenic risk score calibration and association with breast cancer in diverse ancestries. *First Author: Matthew Kucera, Myriad Genetics, Inc., Salt Lake City, UT*

Background: Polygenic risk scores (PRS) have been shown to substantially improve breast cancer (BC) risk prediction when incorporated into traditional risk assessment models. However, PRS developed primarily in women of European ancestry have shown poor performance when applied to non-European populations. We previously described development and validation of a multiple-ancestry PRS (MA-PRS) that is based on individual ancestral genetic composition. MA-PRS has been incorporated into the Tyrer-Cuzick model for use in clinical practice and has been shown to provide independent value to the model. Here, we describe performance of the MA-PRS in a large cohort of women from diverse ancestral backgrounds. **Methods:** The study cohort included 203,586 patients who were referred for hereditary cancer testing and negative for pathogenic variants in genes associated with BC. MA-PRS was calculated as previously described based on 149 SNPs (93 BC and 56 ancestry-informative). Association of MA-PRS with invasive BC status (affected vs unaffected) was analyzed using logistic regression adjusted for personal and family cancer history, age, and ancestry. Calibration was assessed by examining the MA-PRS distribution within unaffected patients, and through goodness-of-fit tests. All analyses were conducted within the full cohort and within ancestral subpopulations. Odds ratios (ORs) are reported per standard deviation. **Results:** One-fifth (43,782/203,586, 21.5%) of patients were diagnosed with invasive BC, and 60,657 (29.8%) of patients reported BC in a first degree relative. The MA-PRS distribution was centered around zero among unaffected patients overall and within each subpopulation. MA-PRS significantly improved BC risk prediction over clinical factors in the full cohort (OR = 1.43, 95% CI: 1.41-1.44) and within each ancestral subpopulation (Table). The strongest associations were observed in Ashkenazi Jewish (OR = 1.56, 95% CI: 1.39-1.76) and South Asian (OR = 1.49, 95% CI: 1.23-1.81) populations. The top decile of the MA-PRS consistently identified patients with two-fold increased risk of developing BC. Goodness-of-fit tests showed that the MA-PRS was well calibrated and predicted BC risk accurately in the tails of the distribution for both European and non-European women. **Conclusions:** The breast cancer MA-PRS based on genetic ancestral composition is well-calibrated and strongly associated with BC in all tested ancestral populations. Incorporation of PRS adds independent information to risk models and supports equitable access to personalized BC risk management. Research Sponsor: Myriad Genetics, Inc.

Population	Total Patients	OR	95% CI
All Ancestries	203,586	1.43	(1.41, 1.44)
Ashkenazi Jewish	2,257	1.56	(1.39, 1.76)
East Asian	4,048	1.35	(1.24, 1.47)
South Asian	1,009	1.49	(1.23, 1.81)
Black/African	25,330	1.24	(1.20, 1.28)
Hispanic/Latina	19,784	1.43	(1.37, 1.50)
White	134,288	1.47	(1.45, 1.49)
Mixed Ancestry	13,501	1.40	(1.32, 1.48)

10507

Oral Abstract Session

Whole exome sequencing and machine learning germline analysis of individuals presenting with phenotypes of extreme high and low risk of developing tobacco-induced lung adenocarcinoma. *First Author: Jose Luis Perez-Gracia, Department of Oncology, Clinica Universidad de Navarra, Pamplona, Spain*

Background: Tobacco is the main risk factor for developing lung cancer. Yet, while some heavy smokers develop lung cancer at young age others never develop it, even at advanced age. This suggests a remarkable variability in the individual susceptibility to the carcinogenic effects of tobacco. We characterized the germline profile of subjects presenting these extreme phenotypes with Whole Exome Sequencing (WES) and Machine Learning (ML). **Methods:** We sequenced germline DNA from heavy smokers who either developed lung adenocarcinoma at early age (*extreme cases*) or did not develop it at advanced age (*extreme controls*). The discovery and validation cohorts included respectively 50 and 66 extreme cases and 50 and 83 extreme controls, selected from databases including > 6,000 subjects. We selected individual coding variants and variant-rich genes showing a significantly different distribution between extreme cases and controls. We trained ML models (Logistic Regression, Random Forest, Support Vector machine Classifier (SVC)) on the discovery cohort to classify subjects into their respective phenotypes and tested them on the validation cohort. **Results:** Mean age for extreme cases and controls in both cohorts was 50.2 and 78.4 years. Mean tobacco consumption was 38.1 and 59.1 pack-years. We validated 16 significant individual variants. The most significant variants were in *ADAMTS7* (2 variants) in cases and *TMEM191B* (1) in controls. We validated 33 genes enriched with significant variants. The genes harboring more variants were *HLA-A* (4 variants) and *ADAMTS7* (2) in cases; and *PLIN4* (2) in controls (Table). We trained several ML models on the discovery cohort using as input the 16 significant individual variants and the number of variants in the 33 enriched genes. We tested them in the validation cohort obtaining accuracy of 72% and AUC-ROC of 87.4% with the best model (SVC), using 16 variants as input, confirming their association with the phenotypes. Functions of validated genes included oncogenes, tumor-suppressors, DNA repair, maintenance of genomic stability, HLA mediated antigen presentation and regulation of proliferation, migration, apoptosis and inflammatory pathways. **Conclusions:** Individuals presenting phenotypes of extreme high and low risk of developing tobacco-induced lung adenocarcinoma have different germline profiles. Our strategy may allow to identify high-risk subjects and to develop new therapeutic approaches. Research Sponsor: Spanish Society of Medical Oncology, Fundación SEOM and Fundación Salud 2000.

	Discovery		Validation		Function
	N.variants	p	N.variants	p	
<i>Genes(cases)</i>					
<i>HLA-A</i>	4	3.5 E-07	4	1.7 E-06	Antigen presentation
<i>ADAMTS7</i>	2	0.02	2	3.1 E-05	Metalloproteinase
<i>SPINK5</i>	2	0.002	1	0.044	Tumor suppressor
<i>REXO4</i>	2	0.0002	1	0.046	DNA repair
<i>Genes(controls)</i>					
<i>PLIN4</i>	2	0.0006	2	0.002	Lipid droplet metabolism
<i>ZNFX14</i>	2	6.7 E-05	1	0.03	Transcriptional regulation
<i>KRT18</i>	1	0.03	2	0.003	Ras activated oncogene

10508

Oral Abstract Session

Lung cancer metabolomics: A pooled analysis in the cancer prevention studies. First Author: Ziyin Tang, Emory University, Atlanta, GA

Background: Lung cancer is a heterogeneous disease, often diagnosed at advanced stages, with low overall survival rate. To better understand the lung cancer etiology and discover screening and early detection biomarkers, we performed a nested case-control study to examine the metabolic perturbation related to lung cancer. **Methods:** This study included 741 case-control pairs (mean age = 67 years) from the ongoing Cancer Prevention Study (CPS) cohorts. Participants completed a comprehensive exposure and health questionnaire at enrollment. Pre-diagnosis blood samples were collected between 1998-2001 in CPS-II and 2006-2013 in CPS-3. Cases and controls were 1:1 matched on date of birth, blood draw date, gender, and race/ethnicity. All eligible controls were cancer-free at the time of case diagnosis. Odds ratios (ORs) per standard deviation and 95% confidence intervals (CIs) were estimated using conditional logistic regression, controlling for potential confounders including body mass index, fruit and vegetable consumption, smoking status, and hormone use. We further performed stratified analyses by smoking status (never/former/current) and follow-up time (i.e., within 3 years/ beyond 3 years between blood draw and diagnosis). Statistical significance was determined as false discovery rate (FDR) < 0.2. **Results:** Sphingomyelin (d18:0/22:0), a bioactive sphingolipid of cell membranes, was associated with lung cancer risk (OR:1.32, 95% CI: 1.15, 1.53), FDR = 0.12). When stratified by follow-up time, participants diagnosed within 3 years of blood draw had a 59% higher risk of lung cancer per standard deviation increase in sphingomyelin (d18:0/22:0) (OR:1.58, 95% CI: 1.16, 2.15, $p = 0.004$) and 25% higher risk for those diagnosed beyond 3 years (OR:1.27, 95% CI: 1.08, 1.50, $p = 0.005$). Metabolites associated with lung cancer at raw p -value < 0.05 indicated the perturbation mostly in lipid, amino acid, and xenobiotics metabolism. We observed variants in perturbed metabolic pathways between never-smoker lung cancer cases and current-smoker lung cancer cases. **Conclusions:** This is the largest prospective study examining lung cancer risk and metabolic response using an untargeted metabolomics platform. These findings provide preliminary support for sphingomyelin (d18:0/22:0) as a potential screening and early detection biomarker for lung cancer. Results also highlight that lipid metabolism including sphingolipid and bile acid metabolism may play an important role in lung cancer etiology. Research Sponsor: U.S. National Institutes of Health; American Cancer Society.

10510

Clinical Science Symposium

Redefining early-onset cancer and risk of hereditary cancer predisposition. First Author: Zsafia Kinga Stadler, Memorial Sloan Kettering Cancer Center, New York, NY

Background: For most solid tumors, early age of onset, a marker for potential increased inherited risk, has been arbitrarily defined as a diagnosis of cancer at age < 50. However, this disregards the variation in mean age of diagnoses across solid tumors resulting in the potential misclassification of patients at increased risk of germline alterations. **Methods:** 25,305 prospectively ascertained cancer patients, representing 32 solid tumor types, underwent sequencing analysis of up to 90 cancer predisposition genes using next-generation genetic analysis with reporting of germline likely pathogenic (LP) and pathogenic variants (P). Mean age of diagnosis by cancer type, with standard deviations (STD), were calculated according to Surveillance, Epidemiology, and End Results Program (SEER) data. Early-onset (EO-CA), average-onset (AO-CA), and late-onset (LO-CA) cancers were defined as cancers diagnosed < -1 STD, -1 < STD > 1, and > 1 STD around the mean age at diagnosis for the specific cancer type, respectively. Prevalence of LP/P variants was classified according to age of onset. Statistical analyses were performed using STATA. **Results:** Among 25,305 patients with 32 solid tumor types classified as per SEER data, 31% ($n = 7,854$) of patients were categorized as having EO-CA. Overall prevalence of germline alterations varied as a function of age at diagnosis with 19.2% ($n = 1509$), 15.9% ($n = 2588/16,299$), and 12.9% (149/1152) of EO-CA, AO-CA, and LO-CA patients harboring a germline LP/P variant ($p < 0.0001$). The enrichment of variants in EO-CAs was driven by high- and moderate-penetrance genes with 13.2%, 9.2% and 5.1% of EO-CA, AO-CA, and LO-CA patients having an LP/P variant ($p < 0.0001$); low-penetrance germline alterations were static across the age groups (6%, 6.7%, 7.8%). An age cutoff of 50 for early-onset cancer was > 1 STD below the mean age at diagnosis in 20 cancer types resulting in 2,226 patients who would not have been classified as having EO-CA inclusive of 394 patients who tested positive for a germline LP/P, representing 26.1% of all germline EO-CA positives. **Conclusions:** Early-onset cancer should be defined taking into consideration the mean age at diagnosis for a specific cancer type as an arbitrary cutoff of age < 50 misses over 25% of patients with an inherited cancer predisposition syndrome. Due to the high prevalence of inherited predisposition syndromes, genetic testing of all patients with EO-CA, irrespective of tumor type, is warranted. Research Sponsor: Precisions Interception and Prevention Program; Marie-Josée and Henry R. Kravis Center for Molecular Oncology.

10509

Clinical Science Symposium

Effect of germline mutations on somatic alteration landscapes in BRCA-associated cancers. First Author: Ali Arafa, University of Minnesota, Minneapolis, MN

Background: The interaction between germline alterations in homologous recombination repair (gHRR) genes and tumoral genomic landscapes is poorly understood. We hypothesized that gHRR alterations may influence somatic mutational landscapes in BRCA-associated cancers. **Methods:** Using a large de-identified real-world dataset of patients undergoing matched tumor/normal next-generation DNA sequencing (Tempus xT), we compared somatic genomic landscapes of tumors arising in individuals with germline HRR mutations (gBRCA1, gBRCA2, gPALB2, gATM, gCHEK2) versus their sporadic counterparts, across four BRCA-associated cancers (breast, ovary, pancreas, prostate). **Results:** In breast cancer ($N = 6955$; gHRR-altered 5.9%, sporadic 94.1%), somatic TP53 muts were enriched in gBRCA1 pts, and depleted in gATM and gCHEK2 pts (all $P < 0.001$). ESR1 muts were depleted in gBRCA1 pts, and enriched in gATM and gCHEK2 pts (all $P < 0.05$). PIK3CA muts were depleted in gBRCA1/2 pts, and enriched in gATM and gCHEK2 pts (all $P < 0.05$). FGFR1 muts were depleted in gBRCA1/2 and gPALB2 pts, and enriched in gATM pts (all $P < 0.01$). HER2 and CDH1 alterations were depleted in gBRCA1 pts ($P < 0.05$). In ovarian cancer ($N = 4244$; gHRR-altered 6.2%, sporadic 93.8%), somatic TP53 muts were enriched in gBRCA1/2 pts, and depleted in gATM and gCHEK2 pts (all $P < 0.05$). ESR1 muts were enriched in gATM pts ($P < 0.001$). PIK3CA muts were depleted in gBRCA1/2 pts, and enriched in gATM pts (all $P < 0.05$). KRAS muts were depleted in gBRCA1/2 pts ($P < 0.05$). In pancreatic cancer ($N = 5386$; gHRR-altered 3.9%, sporadic 96.1%), somatic TP53 muts were enriched in gBRCA1 pts, and depleted in gATM and gPALB2 pts (all $P < 0.05$). KRAS muts were enriched in gBRCA1/2 and gATM pts ($P < 0.05$). Unexpectedly, ESR1 muts were enriched in gPALB2 and gCHEK2 pts ($P < 0.05$). In prostate cancer ($N = 4378$; gHRR-altered 4.5%, sporadic 95.5%), somatic TP53 muts trended higher in gBRCA1 pts, and lower in gATM and gPALB2 pts ($P = NS$). TMPRSS2-ERG fusions were depleted in gBRCA1 and gBRCA2 pts ($P < 0.05$). FOXA1 muts were enriched in gBRCA2 pts ($P < 0.05$), while BRAF and CDK12 muts were enriched in gCHEK2 pts ($P < 0.05$ and $P = 0.07$). Median TMB was higher in BRCA-associated cancers with gBRCA1/2 and gPALB2 muts relative to sporadic cancers (all $P < 0.05$), but not in pts with gATM or gCHEK2 muts. There were no differences in MMR mutations or MSI status. **Conclusions:** Across four BRCA-associated cancers, TP53 muts are enriched in BRCA1 pts and depleted in gATM pts. In breast/ovarian cancers, PIK3CA muts are depleted in gBRCA1/2 pts, while ESR1 muts are enriched in gATM pts. KRAS muts are enriched in gBRCA1/2-altered pancreas cancers, but are depleted in gBRCA1/2-altered ovarian cancers. gBRCA2-altered prostate cancers are enriched in FOXA1 muts, and depleted in ERG fusions. These data suggest that gHRR-mutated cancers have distinct genomic landscapes compared to their sporadic counterparts; this may influence therapeutic considerations. Research Sponsor: None.

10511

Clinical Science Symposium

POT1 germline pathogenic variants and evolving understanding of tumor spectrum: Evidence for lung cancer predisposition. First Author: Michael Francis Walsh, Memorial Sloan Kettering Cancer Center, New York, NY

Background: As a critical component of the shelterin complex, the protection of telomeres 1 protein (POT1) plays important roles in telomere length regulation and tumorigenesis. POT1 germline pathogenic/likely pathogenic variants (PVs) have been primarily linked to the development of melanoma, chronic lymphocytic leukemia, and glioma. Recent studies report POT1 PVs also predispose to other tumors such as certain sarcomas and thyroid cancer. **Methods:** To better understand the role of POT1 in the development of solid tumors, we explored the spectrum of POT1 germline variants in 6644 patients with POT1 sequencing performed utilizing the MSK-IMPACT assay. **Results:** In total, 91 POT1 germline rare variants (population frequency < 0.01%) were identified in our cohort in 90 patients across 47 cancer types. We found 16 POT1 PVs including frameshift variants (p.Ile49fs, p.Gln358fs, p.Asp617fs), a nonsense variant (p.Arg363Ter), a missense variant (p.Asp224Asn), and splice site variants (c.10-2A > C, c.1369+1G > T). One cutaneous melanoma patient, one uveal melanoma patient, and one glioma patient were identified to have POT1 PVs. Interestingly, 8 patients with germline POT1 PVs were diagnosed with lung cancer (7 with lung adenocarcinoma and one with small cell lung cancer). Three of these 7 patients with lung adenocarcinoma had biallelic inactivation of POT1 in their tumor. The proportions of POT1 PVs in MSK lung adenocarcinoma compared to the gnomAD non-cancer control cohort were statistically significantly different (odds ratio = 16.28, 95%CI = 6.52-33.54, $P = 2.87e-06$). Moreover, of the 90 patients with rare germline POT1 variants, 22 had POT1 biallelic inactivation, and 9 of these 22 were diagnosed with lung adenocarcinoma. **Conclusions:** Taken together, our study refines the role of POT1 germline variants in solid tumors and highlights an apparent association of POT1 PVs with lung adenocarcinoma development. Research Sponsor: Marie-Josée and Henry R. Kravis Center for Molecular Oncology and Niehaus Center for Inherited Cancer Genomics; U.S. National Institutes of Health.

10512

Clinical Science Symposium

Germline alterations in patients with lung cancer. *First Author: Ramaswamy Govindan, Washington University School of Medicine, St. Louis, MO*

Background: Despite extensive knowledge about genomic alterations in tumor cells, less is known about germline alterations in patients with lung cancer. In this study, we explore the association between germline alterations in cancer-predisposing genes across lung cancer patients with different tumor histologies and smoking status. **Methods:** To compare the alterations in cancer-predisposing genes through germline profiling, we analyzed 11,740 tumors from primary Lung patients (any stage/ subtype) sequenced with Tempus xT tumor/normal matched assay (DNA-seq of 648 genes at 500x coverage, full transcriptome RNA-seq). Prevalence of pathogenic/likely pathogenic (P/LP) germline alterations in 46 genes was compared between smokers and non-smokers, non-smoker somatic *EGFR* altered (sEGFRalt) and non-smoker somatic *EGFR* wild-type (sEGFRwt), non-small cell lung histology (NSCLC) and small cell histology (SCLC), and lastly NSCLC sEGFRalt and NSCLC sEGFRwt. Due to the low prevalence of germline, most differences were insignificant, although statistics of interest are reported. **Results:** Of 10,419 lung cancer patients with known smoking status (89%) 8845 were smokers and 1574 non-smokers. *MUTYH* germline alterations were detected in 1.3% vs. 1.1%, *ATM* 0.7% vs. 1.0%, and *EGFR* < 0.1% vs. 0.4% in smokers and non-smokers with lung cancer respectively. Among non-smokers, 549 were sEGFRalt and 1025 were sEGFRwt. *MUTYH* germline alterations were detected in 1.1% non-smoker sEGFRalt vs. 1.1% non-smoker sEGFRwt, *ATM* 0.7% vs. 1.1%, and *EGFR* 1.1% vs. 0%. Germline *EGFR* was significant after FDR adjustment ($q < 0.037$). There were 10115 patients identified with NSCLC histology and 595 with SCLC histology. *MUTYH* germline alterations were detected in 1.3% NSCLC vs. 0.3% SCLC, *ATM* 0.8% vs. 0.3%, and *BRCA2* 0.7% vs. 0%. Of note, SCLC was more likely to be smokers than NSCLC (93% vs. 85%, $p < 0.001$). Among NSCLC, 1,141 were sEGFRalt and 8,974 were sEGFRwt. *MUTYH* germline alterations were detected in 1.6% NSCLC sEGFRalt vs. 1.3% NSCLC sEGFRwt, *ATM* 0.5% vs. 0.8%, *EGFR* 1.3% vs. 0%, and *BRCA2* 0.8% vs. 0.6%. Germline *EGFR* was significant after FDR adjustment ($q < 0.001$). A separate analysis of the United Kingdom Biobank data found the prevalence of P/LP germline alterations in the same 46 genes in 4.3% of 1132 smokers with lung cancer and 5.1% in 198 never-smokers with lung cancer. The most common germline alterations involved *ATM* (0.8%), *BRCA 2* (0.79%), *MUTYH* (0.62%) among smokers and *MUTYH* (1.5%), and *CHEK2* (1.01%) among non-smokers. **Conclusions:** Currently, there are no standard guidelines for germline analysis for patients with lung cancer. The Tempus database enables the identification of pathogenic or likely pathogenic germline alterations in a variety of lung cancer subtypes along with their distribution frequency among various groups. The findings suggest that germline P/LP alterations in the select panel of 46 genes occur infrequently across subgroups of lung cancer. Research Sponsor: Tempus.

10514

Poster Discussion Session

Lorpicutinin (JNJ-64251330) in patients with familial adenomatous polyposis (FAP): Results from a phase 1b study. *First Author: Robert Hüneburg, Department of Internal Medicine I, University Hospital Bonn, Bonn, Germany; National Center for Hereditary Tumor Syndromes, University Hospital Bonn, Bonn, Germany*

Background: FAP is the most common hereditary adenomatous polyposis syndrome and, if left untreated, will lead to colorectal cancer development in nearly all patients. Chronic inflammation, driven in part by the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway, may promote polyp formation. Enteric-selective inhibition of the JAK/STAT pathway may provide a treatment for FAP. Lorpicutinin is an oral, small molecule, potent pan-JAK inhibitor with favorable enteric-selective properties. Here, we report the efficacy, safety, and pharmacokinetic (PK) results from a phase 1b study of lorpicutinin in patients with FAP (NCT05014360). **Methods:** Patients aged ≥ 18 years with ≥ 6 polyps ≥ 2 mm in diameter in the rectum or colon with FAP (*APC* germline mutation or obligate carrier) received lorpicutinin 75 mg twice daily for 24 weeks. The primary objective was to evaluate the effect of lorpicutinin on colorectal polyp burden at Week 24, assessed by endoscopy at baseline and Week 24. Secondary objectives were safety, PK, and biomarker assessments of lorpicutinin activity. **Results:** Overall, 42 (23 pre-colectomy; 19 post-colectomy) patients with FAP were enrolled, with a median age of 33 (range, 19-61) years. No clear effect on polyp burden was observed at Week 24. Gut mucosal and polyp concentrations of lorpicutinin were much higher than plasma concentrations, indicating an enteric-selective distribution. Mean sigmoid colon, rectum, and polyp concentrations of lorpicutinin at Week 8 were 112-, 473-, and 108-fold higher, respectively, than the observed maximum plasma concentration at Week 8 (1 hour). At Week 8, lorpicutinin achieved JAK tyrosine kinase inhibition in mucosal biopsies as evidenced by a median 37% reduction in normalized pSTAT-3 levels. Lorpicutinin reduced serum-based inflammatory biomarkers such as C-reactive protein and serum amyloid A by Week 16 of therapy. Some patients reported an improvement of clinical symptoms such as less frequent bowel movements and less blood in the stool. The most common adverse events (AEs) were abdominal pain (16%), bilirubin increased (13%), headache (13%), lipase increased (13%), and diarrhea (13%). There were no treatment-related serious AEs, grade 3 treatment-emergent AEs, serious infections, or venous thromboembolisms. **Conclusions:** These results show that lorpicutinin had no clear effect on polyp burden. The study found that lorpicutinin is safe and exhibits an enteric-selective distribution in FAP patients. Inhibition of JAK tyrosine kinase signaling was associated with reduced STAT-3 phosphorylation in mucosal biopsies from FAP patients. While reductions observed in polyp burden were not clinically significant, lorpicutinin treatment lowered levels of several serum inflammatory biomarkers. Treatment with lorpicutinin was safe and well tolerated, and may improve clinical symptoms associated with FAP. Clinical trial information: NCT05014360. Research Sponsor: Janssen Research & Development, LLC.

10513

Poster Discussion Session

Famitinib for familial adenomatous polyposis-associated aggressive desmoid tumors: A single-center exploratory study. *First Author: Sai Ge, Department of Gastrointestinal Oncology, Key laboratory of Carcinogenesis and Translational Research (Ministry of Education), Peking University Cancer Hospital & Institute, Beijing, China*

Background: Desmoid tumour (DT) is a common extra-intestinal manifestation of familial adenomatous polyposis (FAP), with high risk of recurrence and became the second leading cause of FAP patients' death. The treatment of FAP-associated DTs are limited. Famitinib is an orally bioavailable, tyrosine kinase inhibitor against VEGFR-2, PDGFR, c-kit, and FGFR, and has shown antitumor activity in these patients (pts). **Methods:** This is a prospective, single arm study of FAP pts with progressing DT per RECIST v1.1, treated with famitinib 20 mg QD since 11/2021. The primary endpoint was objective response rate (ORR), with secondary endpoints of safety, progression-free survival (PFS), and quality of life (EORTC QLQ C30). We also collected the FFPE slices of DTs to test both genetic and proteomic backgrounds of pts with different therapeutic results. **Results:** Between Nov 24, 2021 and Aug 8, 2022, 11 pts were enrolled and evaluated every 9 weeks. The median follow-up time was 9.4 m (6.6 to 14.9 m). The median age was 36 (28-53) and 45% were male. Nine pts were diagnosed with intra-abdominal (IA) tumors while two had extra-abdominal (EA) DTs. Eight had stage III-IV DTs with rapid growth and severe symptoms. 10 of them had history of intestinal resection. Two pts were treated with dacarbazine and epirubicin before enrollment, while one patient received radiotherapy before famitinib. Five pts achieved partial response (PR) and six achieved stable disease (SD), with a median time to response of 7.0 months. The ORR was 45.5% and the disease control rate (DCR) was 100%. The 6-month PFS rate was 91%. The ORR of pts with IA DTs was 55.6%. Of adverse events (AEs) with famitinib, 87% were grade 1/2, the most frequently reported being hypertension (73%), neutropenia (64%), bilirubinemia (55%) and proteinuria (36%). Mean global health status/QoL before and after 6 months' treatment was 58.3 vs 75.8 ($P = 0.09$). Of all 11 pts, germline APC mutations scattered from codon 457 to 1578, and five of them detected somatic APC mutations from codon 547 to 1896 in DTs. Correlative study analysis will be presented. **Conclusions:** Famitinib demonstrated promising efficacy and a favorable safety profile in FAP-associated aggressive DTs. Research Sponsor: National Natural Science Foundation of China (No. 81902514).

10515

Poster Discussion Session

Real-world outcomes and safety in patients with VHL associated tumors receiving belzutifan. *First Author: Anusha Chidharla, University of Kansas Cancer Center, Kansas City, KS*

Background: Belzutifan, a small molecule HIF-2 α inhibitor was FDA approved for the treatment of VHL-associated renal cell carcinoma (RCC), CNS hemangioblastomas and pancreatic NET (pNET). The approval was based on the results from the phase 2, open-label, single-group trial, enrolling 61 patients at approximately 12 study sites (Srinivasan, 2021). Objective responses were seen in 49% patients with VHL-associated RCC, 63% patients with VHL-associated CNS hemangioblastomas, and 83% of patients with VHL-associated pNET. Common adverse events included anemia, fatigue, renal dysfunction, nausea, and elevated glucose levels. There is currently very limited data on real-world outcomes using belzutifan in VHL patients. **Methods:** After obtaining IRB approval, we retrospectively evaluated the efficacy and safety of Belzutifan for patients with VHL disease and renal cell cancer and/or VHL-associated tumors who received Belzutifan between August 2021 and January 2023 at KU Cancer center. **Results:** A total of 16 patients are started on Belzutifan treatment. The baseline characteristics include median age of 45 years, including 8 (50%) females and 8 (50%) males. Patients with VHL-associated RCCs were seen in 15 patients ($n = 15$), VHL-associated pNET ($n = 13$), and CNS hemangioblastomas ($n = 13$). Patients were started on belzutifan 120mg daily. The patients underwent bloodwork and clinic follow-up every 6-8 weeks, and response assessment was done in 11/15 patients who had follow-up scans at 6-month intervals. Objective Response to Belzutifan in any of these VHL-associated tumors was seen in 9 of 11 patients (81%), and 1/11(9%) had progressive disease (PD). Objective response in patients with VHL-associated RCC was observed in 8/11 (72%) patients and 2/11 (18%) with partial response (PR), and 6/11 (54%) with stable disease (SD). Responses observed in patients with pancreatic lesions were 1/11 patients (9%) with CR, 1/11 (9%) with PR, and 5/11 (45%) with SD. Patients with CNS hemangioblastomas 4/9 (44%) had SD. Safety was assessed in all the patients. The predominant side effect was anemia 12/16 (75%) and fatigue 11/16 (68%). Other side effects reported are foggy 4/16 (25%), nausea 2/16 (12.5%), dizziness 2/16 (12.5%), and shortness of breath 2/16 (12.5%). Dose reduction to 80mg was needed in 2/16 (12.5%) patients due to moderate fatigue, hypoxia in one, and dysgeusia, respectively. **Conclusions:** Our real-world outcomes analysis of patients with VHL-associated tumors who are treated with Belzutifan shows an improved objective response when compared to the initial clinical trials, which is promising for patients. The analysis based on our real-world data shows the superior objective response in VHL-associated RCCs with Belzutifan, with a manageable safety profile. These findings reinforce Belzutifan as an effective treatment option for this patient population but warrant confirmation in a larger sample. Research Sponsor: None.

10516

Poster Discussion Session

Neoplasia detection via colonoscopic surveillance among young patients with MSH6 and PMS2-associated Lynch syndrome. *First Author: Alicia Latham, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Lynch syndrome (LS) is the most common colorectal cancer (CRC) predisposition syndrome. While patients (pts) with *MLH1/MSH2*-associated LS are recommended to start colonoscopy between age 20-25, recent guidelines recommend delaying initiation in pts with *MSH6/PMS2*-associated LS to age 30-35. However, data on findings from colonoscopic surveillance in young *MSH6/PMS2*-LS pts are limited. **Methods:** We performed a retrospective review of a multi-institutional cohort of pts with *MSH6/PMS2*-associated LS who underwent any colonoscopic surveillance prior to age 50, and assessed corresponding pathology results. Neoplastic lesions were defined as a CRC, adenomas, or non-hyperplastic serrated lesions. Clinicopathologic variables were reported with summary statistics and compared using non-parametric tests at the patient level and among pooled procedures. **Results:** We identified 285 pts [161(56%) *MSH6*; 124(44%) *PMS2*] with history of colonoscopic surveillance prior to age 50. 190 (67%) pts were female, with similar sex distribution among the *MSH6* and *PMS2* groups. 107 (38%) pts had personal history (hx) of any cancer, 67 (42%) *MSH6* and 40 (32%) *PMS2*, including 58 (20%) with CRC [35(22%) *MSH6*; 23 (19%) *PMS2*]. Median age at CRC diagnosis (dx) was 39 and did not differ between groups (41 *MSH6* vs. 37 *PMS2*, $p = 0.47$) with 16 (5.6%) pts dx prior to age 35. 157 (57%) pts had a family hx of CRC, and there was no difference in the rate of CRC between pts with or without family hx of CRC [50% (n = 25) vs 60% (n = 31), $p = 0.33$]. Pts underwent a median of 2 colonoscopic surveillance procedures (range 1-12) with 824 total procedures, 806 (98%) colonoscopies and 18 (2%) sigmoidoscopies, with 691 (85%) occurring at an academic/tertiary center. Among the 824 pooled procedures, there were 194 (24%) procedures with neoplastic lesions identified, including 19 (2.3%) with advanced adenomas or advanced serrated lesions and 34 (4.1%) with CRC. Among 247 procedures completed at age < 35, 43 (18%) detected neoplastic lesions, including 4 (1.6%) with advanced adenomas or advanced serrated lesions and 9 (3.6%) with CRCs. Notably, in 123 procedures performed prior to LS diagnosis, 43 (35%) had a neoplastic finding with 28 (23%) showing CRC. These findings did not differ between the *MSH6* and *PMS2* groups. **Conclusions:** Among this large, multi-institutional cohort of pts with *MSH6/PMS2*-associated LS with history of colonoscopic surveillance performed prior to age 50, colonoscopic surveillance was found at similar rates in both *MSH6* and *PMS2*-associated LS. 20% of overall pts had CRC, with 48% presenting prior to LS dx. In surveillance procedures performed < age 35, the upper threshold of initiation of colonoscopic surveillance as per NCCN, 18% found a neoplastic finding with 3.6% finding CRC, highlighting the need to optimize the age of colonoscopic surveillance initiation in *MSH6/PMS2*-associated LS. Research Sponsor: U.S. National Institutes of Health; Robert and Kate Niehaus Center for Inherited Cancer Genomics, Romeo Milio Lynch Syndrome Foundation, Fieldstone Family Fund, Jason and Julie Borrelli Lynch Syndrome Research Fund, King Family Fund for Lynch Syndrome Education, Outreach and Impact, The Lesswitz Fund for Lynch Syndrome, The Terry T. Sweet Fund for Lynch Syndrome, The Sweet Family Fund.

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Poster Discussion Session

High-risk constitutional *MLH1* methylation as a cause of early-onset colorectal and endometrial cancers displaying mismatch repair deficiency and *MLH1* methylation. *First Author: Megan Philippa Hitchins, Cedars-Sinai Medical Center, Los Angeles, CA*

Background: Mismatch repair deficiency (MMRd) occurs in ~15% of colorectal (CRC) and ~30% of endometrial (EC) cancers, of which ~20% are caused by Lynch syndrome (LS). Universal screening of all incident CRC and EC for MMRd uses *MLH1* methylation (in tumors with *MLH1*-loss by immunohistochemistry) to omit common sporadic cases from follow-up germline testing for LS. However, this overlooks unusual cases with constitutional *MLH1* methylation (epimutation), a poorly-recognized high-risk mechanism for LS-type cancers that are *MLH1* methylated. We aimed to determine the role and prevalence of constitutional *MLH1* methylation among CRC and EC cases with tumor *MLH1* methylation from clinical and population-based series and if age limits could be used to triage cases warranting additional germline methylation testing. **Methods:** We screened blood DNA for constitutional *MLH1* methylation by pyrosequencing and methylation-specific qPCR in patients with *MLH1*-loss, *MLH1* methylated CRC and EC ascertained from: i) cancer clinics, referred by oncologists and genetic counselors; ii) Ohio population-based "Columbus" and "OCCPI" cohorts. Bisulfite sequencing confirmed constitutional *MLH1* methylation. **Results:** In clinical cases, constitutional *MLH1* methylation was identified in 3/7 EC and 3/8 CRC cases < 60 years. In population-based cohorts, constitutional *MLH1* methylation was identified in 4/95 (4.2%) and 4/281 (1.4%) CRC cases of all ages from Columbus and OCCPI, respectively. Highest rates of detection with the majority of cases detected were at age ≤55 years, with 3/4 (75%) in Columbus and 4/17 (23.5%) in OCCPI ≤55 years. For EC, constitutional *MLH1* methylation was identified in 0/68 Columbus cases of all ages and 1/24 OCCPI cases < 60 years (age-limited testing). She was one of six (~17%) cases < 50 years in the combined cohorts. EC was the first/dual-first presenting "sentinel" cancer in three female patients with constitutional *MLH1* methylation. Of the 14 cases with constitutional *MLH1* methylation, nine had hemiallelic methylation (~50% alleles methylated, affecting a single parental allele) and five had mosaicism across various normal tissues. Somatic "second-hits" affecting the unmethylated allele were found in the tumors of mosaic cases, demonstrating causation. **Conclusions:** A correct diagnosis of constitutional *MLH1* methylation at first cancer presentation is important as it will significantly alter clinical management of these high-risk patients. Although rare overall, high rates of detection were found ≤55 years for CRC and ≤50 years for EC cases with a MMRd, *MLH1* methylated tumor, entailing minimal extra screening. Testing for constitutional *MLH1* methylation is warranted in patients with young-onset CRC or EC, or syn/metachronous cancers at any age, with MMRd and *MLH1* methylated tumor(s). Research Sponsor: U.S. National Institutes of Health.

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Poster Discussion Session

Clinical and molecular characterization of microsatellite stable (MSS) tumors in patients with Lynch syndrome (LS). *First Author: Emily Harrold, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: LS, caused by germline pathogenic variants in DNA mismatch repair genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*), is characterized by near universal microsatellite instability (MSI)/mismatch repair deficiency (dMMR) of associated tumors. Accurate MSI/dMMR assessment is critical to determine immune checkpoint blockade (ICB) eligibility but discordant MSI and immunohistochemical analysis of MMR status (IHC) is described. We sought to characterize MSS tumors in LS pts. **Methods:** Cancer-associated LS pts consented to tumor and matched normal DNA sequencing via MSK-IMPACT (NCT01775072), from 01/2014 to 10/2022 were identified with MSI status inferred via MSLens. Microsatellite stable (MSS) or indeterminate (MSI-I) tumors were further assessed using MiMSI, a multiple instance learning tool demonstrating high sensitivity for MSI even with low sample tumor purity. MSLens and MiMSI status were correlated with MMR IHC. **Results:** Of 405 LS cancer-affected pts, 120 had MSS, 59 MSI-I and 226 MSI-H tumors using MSLens. Tumor MSI status varied by LS gene with *MSH6* (MSS: 33 % (40/120), MSI-I: 42 % (25/59), MSI-H: 14%, (33/226)) and *PMS2* (MSS: 42% (50/120), MSI-I: 12% (7/59), MSI-H: 12%, (28/226)) more frequently associated with MSS/MSI-I than MSI-H tumors ($p = 0.005$) Utilizing orthogonal analysis 43% (63/147) of MSS/MSI-I tumors were re-classified as either MSI or dMMR. MiMSI was available on 106/147 MSS/MSI-I tumors resulting in the re-classification of 36 (28/38 MSI-I, 8/68 MSS tumors) as MSI. IHC was concordant with reclassified MSI status in 23/36 tumors. 5/36 reclassified cases (MSI-I on MSLens) had pMMR on IHC, in 2 of these cases MSI was driven by POLE/POLD1 somatic mutations. IHC was unavailable for 8/36 tumors reclassified by MiMSI. 18/36 (50%) tumors reclassified by MiMSI had low tumor content in profiled samples a known limitation of MSLens. Tumors reclassified as MSI on MiMSI included those considered part of the LS cancer spectrum (8 CRC, 3 gastroesophageal, 8 endometrial, 3 ovarian, 3 urothelial, 2 brain) in addition to cancers not clearly LS associated. 6 tumors classified as MSS/MSI-I on MSLens were MSI-I on MiMSI, 2/6 were dMMR on IHC. Amongst the 41 MSS/MSI-I tumors on MSLens for which only orthogonal IHC was available, 25 (11 MSS, 14 MSI-I) demonstrated protein loss consistent with the implicated LS gene. Low tumor content was noted in 44% (11/25) of tumors reclassified by IHC. Of 34 tumors found to be both MSS and MMR-proficient on orthogonal analysis, the majority (88%) were in *PMS2* or *MSH6* carriers, representing 9 tumor types of which 4 are considered part of the LS cancer spectrum. **Conclusions:** MSS tumors occur in LS pts, especially in lower-penetrance *MSH6* and *PMS2* carriers. Given increasing ICB utilization for MSI/dMMR tumors, orthogonal testing methods are critical to comprehensively identify all LS pts who may derive benefit from ICB particularly when sample tumor purity is low. Research Sponsor: MSK Cancer Center Core grant (P30 CA008748), the Molecular Diagnostics Service in the Department of Pathology, and the Marie-Josée and Henry R. Kravis Center for Molecular Oncology.

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Poster Discussion Session

Early real-world (RW) experience with a multi-cancer early detection (MCED) test. *First Author: Candace Westgate, Adventist Health, Saint Helena, CA*

Background: An MCED test (Galleri, GRAIL, LLC, Menlo Park, CA) intended to complement recommended screening has been in clinical use since 04/2021. Here, we report RW clinical experience across age, sex, ordering site, and use case with the initial ~53,000 tests. **Methods:** This cell-free DNA-based MCED test uses a targeted methylation assay and a machine learning classification algorithm to detect a cancer signal (CS) and predict CS origin (CSO). This report includes tests returned from 04/20/2021 to 12/31/2022 on individuals aged ≥22 years (yrs) and excludes tests from clinical studies and sites limiting external data sharing, and repeat tests. Systematic collection of outcomes for cases with a "CS detected" (CSD) result was completed for a limited subset and continues via a rigorously controlled quality assurance (QA) program. **Results:** Tests were ordered and processed from across all US states (results returned, 98.9%; mean turnaround time, 6.7 business days). Among the 53,134 tests with results returned, CSD rate (CSDR) was 1.0% (95% CI, 0.9-1.0; 51,053/53,134), generally higher in males (1.1% [1.0-1.2; 313/29201]) vs females (0.8% [0.7-0.9; 197/23933]), and comparable to expected CSDR (males 1.07%; females 0.96%) as modeled based on MCED test performance and cancer incidence from SEER. CSDR increased with age (Table), which was a significant predictor of CSDR ($p < 2e-13$). In males and females, 67.4% and 61.9% of CSOs represented cancers without (w/o) recommended population screening, respectively. Early data from the QA program from an initial limited subset of CSD cases showed that a CSD result was associated with a diagnosis of invasive cancer across multiple cancers (eg, anus, breast, esophagus, head and neck, liver/bile duct, lymphoma, ovary, pancreas, plasma cell neoplasm, prostate, sarcoma), including stage I and II cancers. **Conclusions:** RW experience with the MCED test was consistent with previous large-scale clinical studies with an average CSDR of 1.0%, which increased with age. The test detected a CS and predicted CSO across multiple cancers, including early-stage cancers and cancers w/o recommended screening. This indicates that the MCED test can reliably detect a CS, which is essential to support population screening. Follow-up of CSD cases is ongoing through the QA program and will allow for future reporting of RW outcomes. Research Sponsor: GRAIL.

CSDR (%) by sex and decade with most frequent top-one CSOs.

	<50	50-59	60-69	70-79	>80	Most Frequent First CSO (all ages; %)
Male	0.2 (0.1-0.4) (14/5775)	0.5 (0.3-0.6) (41/9058)	1.2 (1.0-1.4) (95/8034)	2.3 (1.9-2.7) (119/5244)	4.0 (2.9-5.4) (44/1090)	1. Lymphoid neoplasm (21.1) 2. Prostate (16.6) 3. Colon/Rectum (15.0) 4. Head/Neck (13.4) 5. Pancreas/Gallbladder (8.0)
Female	0.5 (0.3-0.7) (22/4736)	0.4 (0.3-0.6) (33/7667)	1.0 (0.7-1.2) (65/6742)	1.5 (1.2-2.0) (63/4072)	2.0 (1.1-3.3) (14/716)	1. Breast (23.9) 2. Lymphoid neoplasm (16.2) 3. Colon/Rectum (13.7) 4. Lung (10.2) 5. Uterus (9.1)

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Poster Discussion Session

Clinical evaluation of cancer signal origin prediction and diagnostic resolution following multi-cancer early detection testing. *First Author: Eric A. Klein, GRAIL, LLC, a subsidiary of Illumina, Inc., currently held separate from Illumina, Inc., under the terms of the Interim Measures Order of the European Commission dated 29 October 2021, Menlo Park, CA*

Background: PATHFINDER (NCT04241796) was a prospective, interventional return of results study that enrolled 6,662 participants (pts) from 7 US institutions to assess clinical implementation of a blood-based multi-cancer early detection (MCED) test. Test results for those with a cancer signal detected also included a cancer signal origin prediction designed to help guide diagnostic evaluations. We analyzed whether the diagnostic evaluations in PATHFINDER were appropriately directed by cancer signal origin predictions, assessed the residual risk of cancer after negative initial evaluation, and examined the role of whole-body imaging (WBI), defined as PET/CT or CT chest/abdomen/pelvis) in diagnostic evaluation. **Methods:** Analysis included pts with a cancer signal detected result from the two different versions of an MCED test evaluated in PATHFINDER. Prespecified criteria blinded to study results were used to define expected diagnostic evaluations by cancer signal origin prediction. These criteria were then used to judge concordance between cancer signal origin predictions and the diagnostic evaluation actually performed. Definitive cancer or no cancer diagnosis (cancer status at end of study [EOS]) was assessed at 12 months after enrollment (EOS). **Results:** 39 pts had cancer signal detected results by both test versions. Diagnostic evaluations were consistent with cancer signal origin in 30/39 (77%) cases. Diagnostic resolution was achieved in 32/39 (82%) pts after initial evaluation, while 7/39 (18%) required additional workup. 25 of the 32 (78%) pts who achieved diagnostic resolution after initial evaluation had a cancer signal origin-guided workup. Additional evaluation of the 7 pts not achieving initial diagnostic resolution was based on persistent clinical suspicion of cancer due to prior cancer history (n = 1) or abnormal/equivocal findings on initial evaluation (n = 6). Additional workup led to diagnostic resolution in all 7 cases (3 with cancer and 4 with no cancer confirmed at EOS). WBI was ordered in 27 cases, of whom 9 had a prior cancer history, 10 had non-localizing cancer signal origin (hematologic or indeterminate), and 1 had both. WBI was equivocal or had no impact on diagnostic resolution in 8/27 (30%) cases. **Conclusions:** Most cases resulted in diagnostic resolution after cancer signal origin-directed diagnostic workup. In pts with a cancer history and negative initial evaluations, and those with equivocal initial evaluations, there was still a risk of cancer, suggesting the need for additional evaluation. WBI was used mostly in those with a cancer history or non-localizing cancer signal origins, and had no impact on diagnosis in almost one-third of pts. Clinical trial information: NCT04241796. Research Sponsor: GRAIL.

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Poster Discussion Session

Germline mutations and the presence of clonal hematopoiesis of indeterminate potential (CHIP) in 20,963 patients with BRCA-associated cancers. *First Author: Catherine Handy Marshall, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University School of Medicine, Baltimore, MD*

Background: The contribution of germline genetics on the emergence of CHIP in patients with solid tumor malignancies is not well understood. We hypothesized that those with germline (g) alterations in homologous recombination repair genes (gHRR) and BRCA-associated cancers (breast, ovarian, prostate, pancreas) would have different rates of CHIP than those without. **Methods:** We analyzed a large real-world Tempus multimodal database of paired germline and somatic DNA sequencing results. CHIP was calculated based on the presence of pathogenic or likely pathogenic alterations in any one of 16 CHIP-associated genes (ASXL1, BCOR, BCORL1, CBL, CREBBP, CUX1, DNMT3A, GNB1, JAK2, PPM1D, PRPF8, SETDB1, SF3B1, SRSF2, TET2, U2AF1) with a variant allele frequency of at least 2%. Patients with g alterations in BRCA1, BRCA2, ATM, CHEK2, and PALB2 were compared to those without gHRR alterations (sporadic). **Results:** In breast cancer, patients with gBRCA1 (n = 104) mutations were younger (med 43 yrs) at diagnosis compared to sporadic cases (n = 6,546 med 56yrs) but had similar rates of CHIP (3% vs 5%). Those with gPALB2 (n = 42 med age 55) had the highest rate of CHIP (14%). gBRCA2 (n = 148; med age 52), gATM (n = 57 med age 52), and gCHEK2 (n = 57 med age 53) and similar rates of CHIP (3%, 4%, 7%). In ovarian cancer, patients with gBRCA1 (n = 137 med age 53) were younger at diagnosis than sporadic cases (n = 3,979 med age 63) with similar rates of CHIP (4% vs 3%). Those with gBRCA2 (n = 83 med age 61) were similar (4%) and gPALB2 (n = 11 med age 68) had the highest rate of 9%. CHIP was not detected among patients with gATM (n = 23 med age 61) or gCHEK2 mutations (n = 9, med age 59). In prostate cancer, 4% of patients with sporadic cases had CHIP (n = 4, 183 med age 66) compared to 4% in gBRCA2 (n = 109 med age 63) and 5% in gATM (n = 44 med age 66). gCHEK2 had 17% prevalence of CHIP (n = 12 med age 66) followed by gPALB2 (n = 12 med age 69). There were no CHIP mutations found among those with gBRCA1 (n = 16 med age 64). In pancreatic cancer, patients with gBRCA2 (n = 89 med age 64) and PALB2 (n = 20 med age 62) were younger at diagnosis, compared to sporadic cases (n = 5,176 med age 67) with lower rates of CHIP (1% gBRCA2, 0 PALB2, 5% sporadic). The highest proportion was in gBRCA1 patients (n = 20 med age 63) with 10%, gCHEK2 (n = 16 med age 68) with 6% and gATM (n = 60 med age 66) with 5%. **Conclusions:** Despite younger age at diagnosis, patients with gBRCA1 had similar or higher rates of CHIP within breast and ovarian cancer. Women with gPALB2 alterations and breast and ovarian cancer, as well as men with gCHEK2 mutations and prostate cancer, had higher rates of CHIP. These data suggest that gHRR mutations may influence the prevalence of CHIP among patients with BRCA-associated cancers and more research is needed. Research Sponsor: Tempus Labs; Commonwealth Fund.

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Poster Discussion Session

Real-world performance of a multi-cancer early detection test based on integrative analysis of cell-free DNA whole-methylome sequencing. *First Author: Yulong Li, Genecast Biotechnology Co., Ltd., Beijing, China*

Background: Early detection and diagnosis is key to reducing cancer-related mortality. We developed a blood-based multi-cancer early detection test, called THEMIS, using multimodal analysis of plasma cell-free DNA (cfDNA) methylation, fragmentation, and copy number alteration features by whole-methylome sequencing (WMS). The real-world performance of THEMIS was investigated with a prospective cohort of high-risk populations and the preliminary results were reported here. **Methods:** A total of 1,374 adults over 65 y with additional cancer risk factors for five common cancers (colorectal, esophageal, liver, lung, or stomach cancer) were recruited in the city of Wuxi, Jiangsu province, China. Additional risk factors included fecal occult blood, smoking history, H. pylori infection, HBV infection, and serum protein biomarkers. Participants had no known cancer diagnosis at the time of administration. Blood samples were collected and subject to low-pass WMS assay (~2X) and cancer probability was predicted by the THEMIS model, which was developed and locked in previous studies. Participants predicted as cancer positive by THEMIS were followed up until positive cancer diagnosis in a clinic or one year after receiving the test report, whichever was earlier. **Results:** At a fixed cutoff rendering 99% training specificity, THEMIS predicted 58 (4.15%) positive cases, among whom 19 participants consented to and completed follow-up. Ten participants received confirmed cancer diagnosis within the follow-up period, including five lung cancers, three liver cancers, one esophageal cancer, and one colorectal cancer. These results yielded a positive predictive value (PPV) of 52.6%. Those who declined follow-up upon a positive THEMIS report were predicted with digestive tract cancers, which need gastrointestinal endoscope for diagnostic confirmation. **Conclusions:** The noninvasive blood-based THEMIS test demonstrated promising performance and patient compliance for clinical utility to detect cancer early and improve patient outcome. Given that clinical follow-ups were only conducted with a subset of participants, future investigations of the precise real-world performance of THEMIS are needed with more complete patient follow-up. Research Sponsor: None.

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Poster Discussion Session

Prevalence of unexpected actionable germline pathogenic variants identified on broad-based multi-gene panel testing in a cohort of cancer patients. *First Author: Kara K. Landry, University of Vermont Larner College of Medicine, Burlington, VT*

Background: Broad-based germline multi-gene panel testing (MGPT) for inherited predisposition has become increasingly common for cancer patients. Both indications for germline testing and the spectrum of genes on MGPT have expanded. We sought to examine the frequency of an unexpected pathogenic/likely pathogenic variant (P/LPV) in patients with a variety of solid and hematologic malignancies undergoing MGPT. **Methods:** A retrospective review of patients with a history of cancer who underwent MGPT at a single institution from 2015 to 2021 with MGPT of > 20 cancer predisposition genes. Low penetrance genes and genes with a recessive inheritance pattern were excluded. Deidentified pedigrees were analyzed by genetic counselors for clinical diagnostic criteria and gene-specific national testing guidelines to determine whether clinical suspicion of the P/LPV was present. **Results:** 10,975 cancer patients underwent MGPT. 1,180 (10.9%) patients were found to have > 1 P/LPV in a moderate or highly penetrant cancer susceptibility gene. 357 (3.3%) of the P/LPV were unexpected based on patient's personal cancer history alone. 208 (1.9%) of the P/LPV remained unexpected after patient and family cancer histories were considered. Most common cancer subtypes with an unexpected P/LPV were breast [1.5% (83/5691)], prostate [2.1% (28/1300)], colorectal [2.2% (18/823)], ovarian/fallopian [1.7% (13/781)] and uterine [2.8% (10/352)] cancer. Most frequent unexpected P/LPV were PMS2 (n = 19), MTF (n = 18), ATM (n = 18), BRIP1 (n = 17), CHEK2 (n = 14), HOXB13 (n = 13), SDHA (n = 12), BRCA2 (n = 7), MSH6 (n = 7), SDHC (n = 7), TP53 (n = 7), and PALB2 (n = 6). No predictor of having an unexpected P/LPV was identified in multivariable logistic regression analysis. Low penetrance or recessive variants were found in 521 (4.8%) patients. Variants of uncertain significance (VUS) were found in 3,774 (35.0%) patients. **Conclusions:** This large retrospective analysis of cancer patients undergoing MGPT identified an overall rate of 1.9% of P/LPV in actionable cancer predisposition genes. Findings were more often unexpected (3.3%) when considering only the patient cancer history, endorsing the importance of family cancer history for consideration of more targeted genetic testing. Identification of moderate or highly penetrant P/LPV in cancer patients is increasingly important in guiding treatment decisions, cancer screening in survivors and testing of at-risk family members. These findings may justify consideration of broader MGPT panels especially when family cancer history is uncertain or unavailable. MGPT also detected a high rate of VUS, reinforcing the importance of physician education to ensure appropriate interpretation and management. Research Sponsor: None.

CDH1 incidental findings in patients with personal or family history of breast cancer. *First Author: Hiam Abdel-Salam, Clinical Cancer Genetics Program, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Pathogenic variants in *CDH1* (*CDH1*+) are associated with hereditary diffuse gastric cancer (HDGC), with an increased risk for DGC (~40-83%) and lobular breast cancer (BC) (~64%) [1]. The National Cancer Center Network recommends the inclusion of *CDH1* in multi-gene panel testing (MGPT) for patients with significant history of BC, given its classification as a high-risk BC gene [2]. Management includes prophylactic gastrectomy or consideration of annual endoscopic biopsies and high-risk breast screening, with consideration of prophylactic mastectomy. Several studies have identified *CDH1* patients who do not meet the International Gastric Linkage Consortium's diagnostic criteria for HDGC [3,4,5,6]. These studies have brought concerns of *CDH1* pathogenic variants in patients with low risk phenotypes, given the potential for total gastrectomy to reduce DGC risk. Our study aims to investigate our cohort of patients with a personal and/or family history of BC to determine if there is a significant number of *CDH1* patients with a non-classical presentation of HDGC. **Methods:** 17,208 families with a history of BC who underwent MGPT were seen in a Clinical Cancer Genetics (CCG) high-risk breast clinic between August 2013 and July 2022. They were identified using a prospectively maintained MD Anderson Cancer Center CCG database. Families were categorized by their history of GC and *CDH1* status. **Results:** Among the families, 10,202 (59%) had a proband with a personal history of BC, with a mean age of onset of 51 years. 49 families (0.28%) were *CDH1*+. 21 *CDH1* families (43%) had no personal and/or family history of GC. Overall, 0.12% of families within the cohort were *CDH1* and had no family history of GC. A chi-square goodness of fit test was performed comparing observed (O) versus expected frequencies (E) (O/E) of families that were: 1) *CDH1* and had a history of GC (28/28), 2) *CDH1* and no history of GC (21/21), 3) *CDH1* - (benign variant or variant of unknown significance (VUS)) and a history of GC (180/164), and 4) *CDH1* - and no history of GC (16,979/16,995). O was determined by using a general population risk of GC (0.81%) and estimated risk of DGC for *CDH1* individuals (58.2%). The χ^2 was determined to be 1.576, with a p-value of 0.66483. **Conclusions:** In comparison to the expected frequency of incidental *CDH1* families identified via MGPT, we found that there was not a significant difference in expected and observed frequencies of families based on *CDH1* status and presence of GC. These results likely reflect the incomplete penetrance and variable expressivity of HDGC, in addition to reported cases of occult signet ring cell carcinomas in biopsy samples or surgical pathology that has been reported in low risk presenting families [7]. We seek to validate these results with cohort of patients in which the diffuse gastric cancer pathology is known and to expand the analysis in patients specifically with a personal history of lobular breast cancer. Research Sponsor: None.

Twenty-year patterns in area deprivation index and risk of metastatic prostate cancer at initial diagnosis among men in Ohio. *First Author: Jennifer Cullen, Case Western Reserve University School of Medicine, Cleveland, OH*

Background: Men diagnosed with prostate cancer (PCa) have a 5-year overall survival (OS) rate of 98%. However, this rate plummets to approximately 30% for men diagnosed with metastatic PCa. Furthermore, PCa exerts a greater burden on African American men with a higher incidence and a higher mortality rate than other races. These disparities have been contributed to a result of interactions among genes, health behaviors, and access to care. In our study, we examined Social Determinants of Health (SDoH) – social risk factors that contribute to disparities in cancer mortality. Area deprivation index (ADI) is one of the assessments used to measure these social risk factors. ADI can assess a geographic area's level of socioeconomic deprivation and is associated with health outcomes on the census block level. Variables used in ADI are grouped into 4 domains – education, income, employment, and housing quality. Most of the communities will fall between a standardized score of 40 to 160. In this study, we used a large population-based cancer database to examine the impact of ADI on risk of metastatic PCa at diagnosis in Ohio. **Methods:** The Ohio Cancer Incidence Surveillance System (OCISS) data were examined for the period 1996 to 2016 to predict the odds of distant stage at diagnosis. Generalized additive models were constructed with age and year of cancer diagnosis, area deprivation index, race, and Hispanic ethnicity as predictors. The relationship between continuous variables and odds of distant diagnosis was modeled via penalized cubic splines. Odds ratios were calculated for race and Hispanic ethnicity. To summarize the results for variables modeled via splines, predicted probabilities were calculated with other variables held at their average or reference values. **Results:** We identified 112,023 men with PCa in OCISS database. The median age was 67 (IQR 61-67) years old. Subjects were 85.3% White, 13.8% Black, and 0.9% other races. Only 0.6% of men were Hispanic. By stage, 84.6% (N=94753) had localized PCa, 10.4% (N=11640) had regional PCa, and 5.0% (N=5571) had distant PCa. The median ADI was 93.9 (IQR 83.6-106.5). Our analysis showed that Black men had 41.8% higher odds of having metastatic PCa at diagnosis than White men. Furthermore, our analysis showed similar risk of metastatic PCa at diagnosis in lower ADI values but higher risk at higher ADI values (Table). **Conclusions:** Higher ADI values were associated with higher risk of metastatic PCa at diagnosis. Interventions should target populations with socioeconomic deprivation and aim to improve patient access to prostate cancer prevention, screening, and treatment services. Research Sponsor: Department of Defense.

1. Variables	OR (95%CI)
Race: Black	1.418 (1.306-1.538)
Race: Other	1.148 (0.833-1.582)
Ethnicity: Hispanic	0.955 (0.665-1.373)
2. ADI value	Predicted Probability (95%CI)
ADI= 60	0.02 (0.02-0.02)
ADI=80	0.02 (0.02-0.02)
ADI=120	0.03 (0.03-0.03)
ADI=140	0.04 (0.03-0.04)

The impact of climate change on cancer incidence in U.S. women: Who is most affected? *First Author: Caitlin Ruth Johnson, California Pacific Medical Center Research Institute, San Francisco, CA*

Background: To determine the association between cancer incidence and regional climate change among U.S. women. **Methods:** Data on climate change-associated cancers (breast, lung, melanoma) were obtained from the United States Cancer Statistics (USCS) database from 2001-2019. Climate change data were obtained from federal reports, insurance companies, and nonprofits. States greatly impacted by, moderately affected by, and most resistant to climate change were analyzed. SEER*Stat 8.3.9.2 and Joinpoint regression program 4.9.0.0 were used to calculate cancer incidences and trends per 100,000. Average annual percentage change (AAPC) was used to describe trends. Age-adjusted incidences were adjusted by the U.S. 2000 standard population. **Results:** Prior studies suggest that breast, lung, and skin cancers are associated with climate change. States greatly impacted by climate change were FL, TX, LA, CA, SC, OK, KS, UT, AR, GA, NC, AL, and MO. States most resistant to climate change were VT, MN, ME, NH, MI, HI, RI, PA, MA, CO, AK, IL, and WY. Breast cancer incidence decreased overall by -0.12% per year from 2001-2019 (p = 0.001). Of states with significant AAPCs, those greatly impacted and moderately affected by climate change had increases of 0.34% (p = 0.008) and 1.31% (p = 0.002) while incidence among resistant states decreased at -0.31% (p = 0.03) per year. Regarding race, minority populations in greatly impacted states had higher increases at 0.83% for Blacks (p < 0.001), 2.21% for Asians (p = 0.003), and 2.38% for Hispanics (p = 0.01) and remained unchanged for Whites (p = 0.4). Melanoma incidence increased overall by 1.59% per year from 2001-2019 (p = 0.008). Of states with significant AAPCs, those greatly impacted by climate change had the largest increases at 2.82% (p = 0.002) while moderately affected and climate-resistant states had increases of 2.37% (p < 0.001) and 2.24% (p < 0.001). Incidence decreased at -1.10% for the overall Black population (p = 0.007). In climate-impacted states, incidence increased for Whites at 2.23% (p < 0.001) and remained unchanged for Asians (p = 0.9), Hispanics (p = 0.9), and Blacks (p = 0.3). Lung cancer incidence decreased overall by -0.73% per year from 2001-2019 (p < 0.001). Moderately affected and climate-resistant states had larger AAPC decreases at -1.24% (p = 0.004) and -1.34% (p < 0.001). In states greatly impacted by climate change, overall incidence only decreased by -0.94 (p < 0.001) with incidence decreasing for Blacks at -1.56% (p < 0.001), Hispanics at -6.78% (p < 0.001), and Whites at -0.41% (p = 0.02) while remaining unchanged for Asians (p = 0.1). **Conclusions:** This data suggests that women in states greatly impacted by climate change had larger increases in climate change-associated cancers. Particularly regarding breast cancer, climate change appears to negatively impact racial minorities when compared to White populations. Further studies are warranted to better understand these trends. Research Sponsor: None.

Trends in diagnosis of de novo metastatic hormone sensitive prostate cancer in US Veterans, 2002-2021. *First Author: Nada Al masalmeh, St. Louis University, St. Louis, MO*

Background: The incidence of non-localized prostate cancer in the US has been increasing since 2011. While the etiology of this increase is unknown, improved detection of metastatic disease and changes in prostate-specific antigen (PSA) screening may be contributing factors. In this retrospective study, we report the frequency and characteristics of veterans with de novo metastatic prostate cancer to understand changes in the diagnosis over time. **Methods:** The study population consisted of veterans diagnosed with de novo metastatic Hormone Sensitive Prostate Cancer (mHSPC) with a biopsy between 2002 and 2021 in the Veterans Health Affairs Prostate Cancer Data Core were included. All patients had no prior diagnosis of prostate cancer and were classified as SEER stage 'distant'. We collected the highest PSA within 3 months of diagnosis, age, race, and calculated the Charlson Comorbidity Index. Year of diagnosis was categorized into 5-year periods and differences over time were assessed by chi-square linear by linear ANOVA test for linearity as appropriate. **Results:** 15,485 patients were diagnosed with de novo mHSPC between 2002 and 2021. The mean age was 72.9 years and the median PSA was 88.0 ng/mL. There was a 39% increase of the number of patients diagnosed with mHSPC (from 3,274 between 2002-2006 to 4,560 between 2017-2021). Mean age increased from 71.6 years between 2002-2006 to 74.4 between 2017-2021 (p < 0.001). Median PSA decreased from 96.6 ng/mL in 2002-2006 to 80.3 ng/mL in 2006-2021 (p < 0.001). The percentage of patients who were identified as black decreased from 29.8% between 2002-2006 to 25.4% between 2017 and 2021 (p < 0.001). Mean comorbidity index increased from 3.2 between 2002-2006 to 4.5 between 2017-2021 (p < 0.001). BMI increased from 26.2 between 2002-2006 to 27.2 between 2017-2021 (p < 0.001). Median overall survival improved from 26.7 months in 2002-2006 to 31.7 months in 2016-2021 (p < 0.001). **Conclusions:** Over a 20-year period, the Veterans diagnosed with prostate cancer were older, with higher comorbidities and with decreased PSA at diagnosis. Additionally, overall survival improved from 26.7 to 31.7 months. The findings of this study are consistent with a reduction in screening and more sensitive imaging modalities to detect metastatic disease combined with changes in the veteran population and improvements in treatment of mHSPC. Further study is warranted to understand these trends over the same time period. Research Sponsor: Department of Defense grant W81XWH-22-1-0602 and Prostate Cancer Foundation Young Investigator Award.

	2002-2006	2007-2011	2012-2016	2017-2021	Overall
De novo mHSPC (n)	3274	3590	4061	4560	15485
Age (mean years, SD)	71.6, 10.5	72.1, 11.0	73.0, 10.5	74.4, 9.5	72.9, 10.4
Median PSA ng/mL (IQR)	94.7 (25.8-403)	89.3 (23.5-363)	89.9 (24.0-355)	81.0 (22.1-303)	88.0 (23.7-347.4)
Black race n, (%)	977 (29.8%)	977 (27.2%)	1071 (26.4%)	1160 (25.4%)	4185 (27.0%)
Charlson Index mean (IQR)	3.2 (2-3)	3.7 (2-4)	4.0 (3-5)	4.5 (3-6)	3.9 (3-5)
Overall Survival (months)	26.7	26.4	30.3	31.7	28.9

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Poster Session

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Poster Session

Breast cancer: Global patterns of incidence, mortality, and trends. *First Author: Ephrem Tadele Sedeta, Department of Medicine, One Brooklyn Health Brookdale University Hospital, Brooklyn, NY*

Background: The global burden of cancer incidence and mortality including that of female breast cancer continues to increase largely because of the growth and aging of the population and adoption of western lifestyle behaviors that increase cancer risk. In this study, we summarize the current burden, trends, and survivorship of female breast cancer that account for nearly 12% of the cancer burden worldwide. **Methods:** Estimates of incidence and mortality in the year 2020 were obtained from Global Cancer Observatory (GLOBOCAN) database. GLOBOCAN provides country-specific estimates of cancer incidence, mortality, and prevalence for 185 countries or territories and 36 cancer types by age group and sex. For US rates, data from Surveillance, Epidemiology, and End Results (SEER) program were assessed. Rates are age-standardized (ASRs) (per 100,000 person-years) using the 1966 Segi-Doll World Standard Population. Geographic variability was assessed using 20 predefined world regions, and the 4-tier Human Development Index (HDI). Finally, we provide a prediction of the future burden of female breast cancer in 2040 based on demographic projections. **Results:** Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death in females worldwide, with an estimated 2.3 million new cancer cases (1 in 4 new cancer cases) and 685,000 cancer deaths (1 in 6 deaths) in 2020. Breast cancer incidence rates varied by nearly 4-fold across WHO areas. The highest incidence rates (per 100,000) were found in Australia/New Zealand (95.5), Western Europe (90.7), and Northern America (89.4), while the lowest rates were in South-Central Asia (26.2), Middle and Eastern Africa (33), and Central America (39.5). In contrast, the highest breast cancer mortality rates were recorded in Melanesia (37.5), Polynesia and Western Africa (22.3), and the Caribbean (18.9), while the lowest rates were found in Eastern Asia (9.8), Central America (10.4), and Australia/New Zealand (12.1), a 2.8-fold difference. In the United States, the age-standardized breast cancer incidence rate (per 100,000) increased from 106 (1975) to 142 (1999), decreased to 128 (2004), and then slowly increased to 137 (per 100,000) in 2019. Similar broad temporal trend patterns were observed in other western countries. Incidence rates are rising in South America, Africa, and Asia where rates were historically low. Worldwide, an estimated 2,964,197 new female breast cancer cases are projected to occur in 2040, a 31% increase from the corresponding 2,260,127 cases in 2020. **Conclusions:** There is significant variation in female breast cancer incidence and mortality rates worldwide. Breast cancer incidence is increasing at different rates in various regions of the world. Mortality rates in many high HDI countries have been on the decline, in contrast to increasing rates in low HDI countries. This study also shows a substantial increase in new breast cancer diagnoses over the next two decades. Research Sponsor: None.

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Poster Session

Epidemiologic effectors on the breast tumor microenvironment: Results from the Cancer Prevention Study-II and -3 cohorts. *First Author: Maha AT Elsebaie, John H. Stroger, Jr. Hospital of Cook County, Chicago, IL*

Background: Despite breast cancer being the leading cancer among women, we have a poor understanding of the impact of epidemiologic risk factors on its tumor microenvironment (TME). We examined risk factors for TME favorability using a novel aggregate marker: the Histomic Prognostic Score (HiPS). **Methods:** Data were from whole slide image (WSI) scans of hematoxylin & eosin slides from women in the Cancer Prevention Studies CPS-II and -3, diagnosed with nonmetastatic breast cancer. Diagnoses occurred between enrollment and the last administrative date (1992/1993 to 2011 in CPS-II and 2006–2013 to 2018 in CPS-3). Median year of diagnosis was 2004 in CPS-II and 2014 in CPS-3. Using the WSI, a deep-learning model was trained to extract features and summarize the morphology of the epithelium, stroma, and tumor-infiltrating lymphocytes within the TME. These features, along with demographic, tumor biomarkers, and survival data, were then used to generate the HiPS, a novel measurement of “prognostic favorability” of TME, ranging from 0 (favorable) to 10 (unfavorable). Multivariable linear models estimated associations between the HiPS score and epidemiologic risk factors: hormone replacement therapy use (HRT; current vs. former/never), cigarette smoking (current vs. former/never), alcohol intake (>1 drink vs. <1 drink/day), aspirin intake (daily vs. not daily) controlled for, age at diagnosis, body mass index (BMI), race, and cancer detection method (screen-vs. self-detected). **Results:** We included 1264 CPS-II and 651 CPS-3 participants in the analysis. Compared to CPS-II, CPS-3 participants were younger (mean (± sd) age 54.7 ± 7.6 vs. 72.2 ± 7, p<0.001), heavier (mean (± sd) BMI 27.1 ± 5.8 vs. 26 ± 4.8, p<0.001), and more diverse (7.4% vs. 2.1% non-White, p<0.001). Most breast cancers (69.9% of CPS-II and 64.1% of CPS-3) were screen-detected, p=0.206. Increasing age and BMI were associated with higher HiPS score in both cohorts, Table. Daily aspirin use and current HRT use were associated with lower HiPS scores in CPS-3 only. The inverse association for HRT use was lost in the following subgroups age < 50, ER-, HER2+, TNM stage-1, and screen-detected cancers. **Conclusions:** Increasing age and BMI have independent adverse effects on breast TME. Daily aspirin intake and current HRT use were only associated with a favorable TME in the younger, more contemporary cohort. Additional studies are needed to confirm these findings and better understand the role of these epidemiologic factors on the TME. Research Sponsor: U.S. National Institutes of Health.

Multivariable models*				
	CPS-II		CPS-3	
	Coeff	p-value	Coeff	p-value
Age (years)	0.04	< 0.001	0.05	< 0.001
BMI (kg/m ²)	0.05	< 0.001	0.09	< 0.001
Screen vs. self-detected	-0.69	< 0.001	-0.85	< 0.001
Daily vs. never aspirin use	-0.10	0.336	-0.55	0.005
Current vs never HRT use	-0.11	0.283	-0.68	0.004

* Each variable was controlled for a standard set of covariates: age at diagnosis, BMI, race, and detection method.

Comparison of 5- and 10-year breast cancer risk predictions. *First Author: John L. Hopper, Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, University of Melbourne, Melbourne, VIC, Australia*

Background: Breast cancer risk assessment is valuable in personalizing risk-reduction and screening approaches for the general population. Maximizing the benefits while reducing the harms associated with current breast cancer screening and risk-reduction recommendations should increase the efficacy of these paradigms. Because healthcare providers have limited time with their patients, we developed a risk prediction model, BRISK, which uses the most important clinical risk factors for breast cancer (in an easily collected format), polygenic risk and mammographic density. We previously validated BRISK 5-year risk predictions and found that it performed better than IBISv7 and BCRAT. **Methods:** The dataset comprised 241,633 women (mean age at baseline assessment = 56.6 years). We included all races/ethnicities available in the UK Biobank. There were 3726 women affected during the first five years of follow-up and 7482 women affected during the full 10 years of follow-up. We compared the performance of the 5-year and 10-year risk predictions by assessing the association with breast cancer using Cox regression to estimate the hazard ratio (HR) per SD of risk, discrimination using calculating Harrell’s C-index and calibration using logistic regression to estimate the slope and the intercept of the logit of the risk predictions. Nelson–Aalen estimates of the hazard function by quintiles of risk and standardized incidence ratios (SIRs) of the number of breast cancer cases expected were used to illustrate performance. **Results:** The predictive performance of BRISK was consistent for 5-year and 10-year risk predictions. Discrimination was similar, with a Harrell’s C-index of 0.645 (95% CI = 0.636, 0.654) for the 5-year risk and of 0.638 (95% CI = 0.632, 0.645) for the 10-year risk. We used Nelson–Aalen cumulative hazard estimates to compare breast cancer incidence by risk quintile for both 5 and 10-year risk. Both risk scores overestimated risk in the top two deciles with the 5-year expected risks of 2.8% and 5.0% corresponding to observed risks of 2.3% and 3.3%. The 10-year expected risks for the top two deciles were 5.6% and 9.8% while the corresponding observed risks were 4.6% and 6.4%. Finally, we used clinically actionable thresholds to show the standard incidence ratios (SIR) of 1.77 (95% CI = 1.69, 1.85) for women ≥3% 5-year risk and 2.05 (95% CI = 1.93, 2.18) ≥8% 10-year risk. **Conclusions:** The BRISK 5-year and 10-year risk prediction perform equally well. There is an overestimation of risk for the top decile in both models. This is important to consider in risk-management conversations between clinician and patient. While the observed risk of the top decile remained above the 3% 5-year risk threshold used in the United States, the top decile observed risk dropped below the 8% 10-year risk threshold used in the United Kingdom. Risk scores are not used in isolation, but it may be preferable to err on the side of overestimation rather than underestimation. Research Sponsor: Genetic Technologies Ltd.

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Poster Session

Clinical characteristics of interval breast cancer within 12 months and 13-24 months in Utah. *First Author: Mei Wei, University of Utah, Salt Lake City City, UT*

Background: A breast cancer (BC) that emerges following a negative/benign screening mammogram (SMG) but before the next expected SMG is referred to as an interval breast cancer (IBC). Current guidelines vary in the recommended frequency of SMG: some guidelines support SMG every 12 months, others every 24 months, and many adapt the 12- or 24-month recommendation by age. This study compared the clinical characteristics of IBC that developed within a 3-12 month interval (12m IBC) and a 13-24 month interval (24m IBC) in a statewide population. **Methods:** This is a retrospective cohort study using demographic/medical records in the Utah Population Database linked to the Utah Cancer Registry, a Surveillance, Epidemiology, and End Results (SEER) registry. Index SMG refers to the SMG just prior to a diagnostic mammogram or other clinical encounter, which led to a BC diagnosis before the next, expected SMG. Women ages ≥38y who underwent SMG during 2005–2019 at Intermountain Healthcare and University of Utah Health, had no history of BC prior to first SMG, and had BI-RADS assessment of normal or benign finding at index SMG were included. Clinical characteristics of 12m IBC and 24m IBC were compared using multivariable logistic regression to provide odds ratio estimates with covariate adjustment for age at diagnosis, stage, tumor size, grade, histology, biomarkers, breast density, body mass index, family history of breast cancer, and age at first birth. Women who developed IBC during the 3-12 month interval were not counted in the 24m IBC group. **Results:** A total of 7776 BC were observed in this study, among which 2122 were IBC; 486 (6.3%) 12m IBC and 1636 (21.0%) 24m IBC. Women with 12m IBC and 24m IBC had similar rates of a first-degree family history of breast cancer (16% and 17%, respectively). Women 70 and older were the least likely to develop IBC in 12 months as compared to 24 months (OR 2.34, 95% CI: 1.61–3.40, p< 0.01). The odds of having axillary lymph node metastases (regional disease) at the time of BC diagnosis was higher among 12m IBC than 24m IBC (OR 1.68, 95% CI: 1.29–2.19, p< 0.01). A total of 41 women with IBC had distant metastatic disease at the time of diagnosis (5% 12m IBC, 1% 24m IBC). Among those, the odds that metastatic IBC would be a 12m IBC were significantly higher than 24m IBC (OR = 4.07, CI 2.03–8.29, p< 0.01). The 12m IBC group was more likely to be HER2 positive (OR 2.10, 95% CI: 1.36–3.22, p< 0.01) or triple negative (OR 2.08, 95% CI: 1.26–3.39, p< 0.01) than the 24m IBC group. Extremely dense breast tissue at SMG increased the odds of developing 12m IBC compared to 24m IBC (OR 2.05, 95% CI: 1.13–3.80, p< 0.01). **Conclusions:** Compared to 24m IBC, 12m IBC appeared to be more advanced and aggressive. Women with extremely dense breast tissue were more likely to develop 12m IBC than 24m IBC. These results suggest that women with extremely dense breast tissue or age < 70y may benefit from annual SMG instead of biennial SMG. Research Sponsor: Breast Gynecology Disease Group Research Funding.

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Poster Session

Trends in mortality caused by neoplasms of the heart in the United States between 2000 and 2019: An observational analysis of disparities by gender and race. *First Author: Abhishek Shahapurkar, Department of Internal Medicine, Mount Auburn Hospital, Cambridge, MA*

Background: Neoplasms of the heart, primary and metastatic, are relatively rare diseases in the US. Metastatic neoplasms are 30 times more common than primary neoplasms and constitute more than 99.3% of the total neoplasms of the heart. Only a few studies have evaluated the mortality trends of this rare disease. Therefore, we aim to analyze the trends of mortality caused by benign and malignant neoplasms of the heart from 2000-2019 and compare them based on gender and race. **Methods:** We utilized the CDC WONDER database to extract data on Heart Benign Neoplasms (ICD 10 D15.1), Heart Malignant Neoplasms (C38.0), and overlapping lesions of Heart, Mediastinum, and pleura (C38.8) mortality in the United States between 2000 to 2019. ICD codes were applied to multiple causes of death. Age-standardized mortality rates (ASMR) per 1,000,000 with a 95% confidence interval were presented for the total population, stratified by gender and race. We assessed the mortality trends using joinpoint trend analysis. **Results:** From 2000 to 2019, 3493 deaths were reported due to neoplasms of the heart, out of which 1672 (47.86%) were due to benign neoplasms, and 1821 (52.13%) were due to malignant neoplasms. Overall, total deaths and ASMR decreased from 221 to 139 and 0.82 to 0.35, respectively, with an Average Annual Percentage change (AAPC) of -3.5. Out of 3493, the majority were females (2254, 64.5%). On evaluating ASMR based on gender, it decreased from 0.65 to 0.32 (AAPC -2.6) for males and from 0.89 to 0.35 for females (AAPC -3.9). On dividing based on racial subgroups, 2962 deaths were in whites, 413 were in African Americans (AA), and 118 were from other races (Asian, Pacific Islanders, Native Indians). On further comparison between Whites and AA, ASMR was found to be higher in AA throughout the study period. For AA, ASMR decreased from 1.18 to 0.51 (AAPC -4.9), and for Whites, from 0.76 to 0.33 (AAPC -2.5). **Conclusions:** This study has shown a decline in overall mortality trends across genders and races. This could be attributed to increased cardiac workups for cardiovascular conditions and advances in imaging modalities, cardiac oncology, and therapeutic interventions. Although the mortality trend in females is decreasing, they still have higher mortality rates than males. At the same time, although AA showed a higher rate of reduction in ASMR, they showed an overall higher ASMR throughout the study period. Further studies are needed to assess if increased screening, early detection, and management plans are causing a decrease in overall mortality in neoplasms of the heart. Research Sponsor: None.

Year	2000	2019	% change	absolute change
Overall total	0.82	0.35	-57.31	-0.47
Females (total)	0.89	0.35	-60.67	-0.54
Males (total)	0.65	0.32	-50.76	-0.33
African Americans (Males + Females)	1.18	0.51	-56.77	-0.67
Whites (Males + Females)	0.76	0.33	-56.57	-0.43
White females	0.84	0.38	-54.76	-0.46
White males	0.58	0.37	-36.20	-0.21

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Poster Session

Cardiorespiratory fitness and BMI in youth and site-specific cancer mortality in men: A population-based cohort study with register linkage. *First Author: Aron Onerup, University of Gothenburg, Gothenburg, Sweden*

Background: There is insufficient evidence on the associations between cardiorespiratory fitness (CRF), body mass index (BMI), and site-specific cancer mortality. **Methods:** We collected data on all men who underwent military conscription 1968-2005 in Sweden at ages 16-25. CRF was assessed as maximal aerobic workload on a cycle ergometer test and classified as low, moderate, or high. BMI (kg/m²) was classified as underweight (< 18.5), normal weight (18.5-24.9), overweight (25-29.9), or obesity (≥30). Data was cross-linked on individual level through the Swedish identification number with national registers with high validity for information on cancer mortality. Follow-up was from conscription until death, emigration, or end of follow-up (12/31/2019). Cox regression analyses included CRF and BMI as well as age, year, and site of conscription, parental education, and muscle strength. Primary analyses tested linear trends for CRF and BMI, with effect sizes for categorical comparisons for interpretation. **Results:** 1,083,738 men were included in the analyses and were followed for a mean of 33 years, during which 8,912 cancer-specific deaths occurred. Lower CRF and higher BMI were linearly associated with any cancer mortality as well as with several site-specific cancer mortalities (table). However, death in some major cancer sites (prostate, CNS) were not associated with CRF or BMI and higher CRF was associated with higher mortality from malignant skin cancer. **Conclusions:** Higher CRF and lower BMI was associated with lower cancer mortality for some, but not all cancer sites. These results could be used as a further incentive for working with modifiable risk factors in public health. Research Sponsor: The Swedish state under the ALF agreement; Assar Gabrielsson's Foundation.

	Prostate	Malignant skin	Bronch and lung	Head & Neck	Esophagus	Stomach	Pancreas	Liver	Colon	Rectum	Kidney	Bladder	Central nervous system	Leukemia	Myeloma	Non-Hodg-kin's lymphoma	Any cancer mortality
Deaths, n	491	547	1,060	385	374	353	774	497	740	441	324	166	1,002	320	191	298	8,912
High vs low	0.95	1.45	0.50	0.55	0.51	0.87	0.80	0.56	0.89	0.89	0.70	1.03	1.17	1.48	0.85	0.80	
low CRF	(0.75)	(1.16)	(0.42)	(0.42)	(0.39)	(0.66)	(0.67)	(0.43)	(0.73)	(0.69)	(0.66)	(0.47)	(0.87)	(1.00)	(0.63)	(0.75)	
HRR (95% CI)	1.20	1.81	0.59	0.71	0.68	1.15	0.97	0.71	1.08	1.14	1.20	1.04	1.22	1.57	2.19	1.15	0.84
p-value for linear trend for CRF	1.00	0.02	< 0.001	< 0.001	< 0.001	0.03	< 0.001	< 0.001	0.10	0.09	0.28	0.17	0.62	0.92	0.03	0.52	< 0.001
Obesity vs normal weight	0.91	0.34	1.84	1.21	3.18	2.35	1.35	1.76	1.63	2.83	3.02	2.35	0.94	1.35	1.17	1.79	1.77
low BMI	(0.34)	(0.08)	(1.15)	(0.50)	(1.73)	(1.20)	(0.70)	(0.93)	(0.94)	(1.58)	(1.54)	(0.86)	(0.53)	(0.55)	(0.29)	(0.79)	(1.51)
I, HRR (95% CI)	1.37	1.37	2.94	2.94	5.85	4.61	2.62	3.32	2.84	5.07	5.92	6.43	1.07	3.31	4.70	6.08	2.07
p-value for linear trend for BMI	0.26	0.11	0.07	0.007	< 0.001	< 0.001	< 0.001	< 0.04	< 0.001	0.001	0.001	0.81	0.58	0.10	0.30	0.003	< 0.001

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Poster Session

Epidemiological and clinicopathological features of patients (pts) with early-onset (EOPC) and late-onset pancreatic cancer (LOPC): A mono-institutional retrospective analysis. *First Author: Maria Bensi, Oncologia Medica, Comprehensive Cancer Center, Fondazione Policlinico Universitario Agostino Gemelli-IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy*

Background: PC is mostly diagnosed in the 7th decade of life. Recent evidence suggests a rising incidence of both EOPC and LOPC. However, there are few data about their specific characteristics. The aim of our study is to determine the incidence of EOPC and LOPC and their correlation with epidemiological and clinicopathological features. **Methods:** Real world data were extracted and analyzed by the Gemelli GENERATOR within the Gemelli Science and Technology Park (G-STeP). Study population was identified from health records matching main inclusion criteria: hospitalized pts with a diagnosis of PC (International Classification of Disease 9, ICD-9 codes captured from structured data source) or pts with at least one anatomic pathology report including PC evidence (selected using clinically validated text mining techniques from unstructured data source). Two subgroups were defined: EOPC (< 50 years old) and LOPC (> 75 years old) pts. Epidemiological and clinicopathological variables (gender, age, BMI, diabetes, history of pancreatitis, histology, primary tumor site, primary tumor surgery) were extracted using SAS (SAS(R) Institute suite for ETL). Statistical analyses were conducted using R (v4.2.1). **Results:** From January 2018 to December 2020, a total of 1606 PC pts treated at our Institution were included in the analysis. The median age was 69 years, 51% were male and the median BMI was 25. Regarding comorbidities, only 4% and 3% of pts had diabetes and history of pancreatitis, respectively. Adenocarcinoma (1120/1126; 99%) was the most common histotype and pancreatic head (576/901, 64%) was the most frequent primary tumor site. Two hundred and ninety-three pts (18%) underwent primary tumor surgery. Concerning the two subgroups, 92 (6%) pts had EOPC and 510 (32%) had LOPC. The median age was 43 years in EOPC group and 81 years in LOPC group. No difference between the two groups was found in gender (p 0.83), BMI (p 1) and tumor histology (p 1). Diabetes was present in 1% and 7% of EOPC and LOPC pts (p 0.07) and pancreatitis history in 3% and 2% (p 0.79), respectively. The primary tumor site was pancreatic head in 78% and 65% (p 0.06) of LOPC and EOPC, respectively. Regarding primary tumor surgery, a significant difference was observed between the two groups (27% in EOPC pts vs 11% LOPC pts; p < 0.001). **Conclusions:** In our study, we did not observe a different epidemiology or a distinctive clinicopathological profile between EOPC and LOPC pts. Despite the retrospective nature of our analysis and single-institution evaluation, our findings showed that EOPC pts more frequently underwent primary tumor surgery, probably related to better clinical conditions. Additional analyses on survival outcomes, molecular and genetic features may help to clarify differences between the two groups. Research Sponsor: None.

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Poster Session

Examining the potential for lead-time bias by estimating stage-specific proportions of deaths due to diagnosed cancer. *First Author: Ellen T. Chang, GRAIL, LLC, a subsidiary of Illumina, Inc., currently held separate from Illumina, Inc., under the terms of the Interim Measures Order of the European Commission dated 29 October 2021, Menlo Park, CA*

Background: Lead-time bias occurs when cancer is detected earlier in time, but with no change in lifespan. Cause of death is not susceptible to lead-time bias; therefore, stratifying cause of death by cancer stage informs the potential for lead-time bias in early detection across cancer types. **Methods:** Using recent data from 17 US Surveillance, Epidemiology, and End Results (SEER) cancer registries for 1 152 610 first incident primary cancers among patients aged 50-84 years at diagnosis in 2006-2010, we evaluated proportional causes of death by cancer type and uniformly classified stage at diagnosis (American Joint Committee on Cancer, 6th edition), following or extrapolating all patients until death. **Results:** A minority of cancer patients diagnosed at stages I-II (27%) went on to die from their index cancer, whereas most stage IV cancer patients (85%) did. For patients diagnosed with stage I cancer at all sites combined, an estimated 26% of deaths were due to the index cancer, 61% due to non-cancer causes, and 12% due to a subsequent primary (non-index) cancer. At stage II, 27% of deaths were due to the index cancer, 60% due to non-cancer causes, and 13% due to a non-index cancer. In contrast, at stage IV, 85% of deaths were attributed to the index cancer, with 13% non-cancer and 2% non-index-cancer deaths. Index cancer mortality from stages I-II cancer was proportionally lowest for thyroid, melanoma, uterus, prostate, and breast, and highest for pancreas, liver, esophagus, lung, and stomach. Leading causes of non-index cancer death (lung, pancreas, and colorectal) and non-cancer death (heart disease and COPD) at each stage were similar to those in the general US population. Non-White racial/ethnic groups, including Hispanics and non-Hispanic Blacks, Asian Americans/Pacific Islanders, and American Indians/Alaska Natives, experienced a higher percentage of deaths from stages I-II cancer than non-Hispanic Whites. **Conclusions:** Across all cancer types, the percentage of patients who went on to die from their cancer was three times greater at stage IV than at stages I-II. As mortality patterns are not influenced by lead-time bias, these data suggest that earlier stage at diagnosis is broadly, if not uniformly, associated with substantially reduced risk of cause-specific death from cancer; therefore, early detection is likely to improve outcomes across cancer types, including those currently unscreened. Research Sponsor: GRAIL, LLC, a subsidiary of Illumina, Inc., currently held separate from Illumina, Inc., under the terms of the Interim Measures Order of the European Commission dated 29 October 2021.

Causes of death (extrapolated if not observed) by stage for first incident primary cancer cases aged 50-84 years at diagnosis in 2006-2010, followed for mortality through 2019, SEER 17.

Stage	Index cancer		Cause of death*		Other cancer		Non-cancer	
	n	%	n	%	n	%	n	%
I	70 717	26%	33 221	12%	164 466	61%		
II	88 757	27%	42 535	13%	194 428	60%		
III	95 374	63%	10 015	7%	46 980	31%		
IV	172 202	85%	4 351	2%	25 783	13%		
Unknown/missing	121 365	60%	11 454	6%	71 051	35%		

*Percentages may not sum to 100% due to rounding.

10536

Poster Session

Obesity and breast cancer in women under age 40. *First Author: Rabia Cattie, Ochsner Health System, New Orleans, LA*

Background: Obesity is a well-established risk factor for postmenopausal hormone-receptor positive breast cancer (BC). The role of obesity in premenopausal BC, especially in women under the age of 40, is not well understood. Multiple studies have shown a decreased rate of premenopausal BC with increasing body mass index (BMI), notably for estrogen receptor positive tumors. Even though there is an inverse association between obesity and premenopausal BC, it has been suggested that obesity has a negative prognostic role in premenopausal BC. This may be explained if premenopausal obese women develop more aggressive tumors. Obesity is associated with triple negative and Luminal B cancers in premenopausal women. We sought to evaluate the relationship between premenopausal breast cancer and obesity in a diverse patient population. **Methods:** We assembled a 10-year database of women diagnosed with breast cancer before age 40 in a single health system. Data collected included age at diagnosis, self-identified race, breast cancer subtype, BMI, and stage at diagnosis. The control group was all women under the age of 40 presenting to our health system in the same time period. Stratification analysis was performed using Mantel-Haenszel Risk Estimation. **Results:** The risk ratio between the standardized estimates of BC patients under 40 with BMI ≤ 30 to BMI > 30 is 0.7924, 95% CI (0.683 – 0.920), P = 0.0022. This implies that young BC patients are more likely to be obese than all young women presenting to our health system. There are more obese Black patients compared to White patients. The effect of obesity on BC diagnosis was more pronounced in Black patients, with a risk ratio of 0.59 compared to 0.96. **Conclusions:** The data presented here challenge previous research which had shown that obesity seemed to be protective against breast cancer in premenopausal women. Here, we see a statistically significant increase in obesity among young women < 40 years presenting with breast cancer. The increased risk of breast cancer diagnosis was particularly pronounced in obese Black women. Previous studies have had a very low proportion of Black women represented, which may cause underestimation of risk in this patient population. These data suggest that obesity is a risk factor for breast cancer in young women, especially in Black patients. Research Sponsor: None.

Race	BMI ≤ 30	BMI > 30	Risk Ratio	95% CI
White	0.00156	0.00163	0.957211	0.790612-1.15892
Black	0.00108	0.00183	0.590699	0.463669-0.75253

10538

Poster Session

Association between excess body mass index trajectory and change in monoclonal protein level in patients diagnosed with monoclonal gammopathy of undetermined significance. *First Author: Lawrence Liu, City of Hope National Comprehensive Cancer Center, Duarte, CA*

Background: Obesity is a known risk factor for the development of multiple myeloma (MM) and for progression of its asymptomatic premalignant state, monoclonal gammopathy of undetermined significance (MGUS) to MM. Prior studies have demonstrated that monoclonal protein (M-spike) at MGUS diagnosis as well as high M-spike velocity within a year following MGUS diagnosis predict progression of MGUS to MM, making M-spike a useful, readily available, and less invasive (compared to bone marrow biopsy) marker to assess progression risk. However, no studies have evaluated to what extent exposure to high body mass index (BMI) over time influences M-spike trajectory. **Methods:** Patients diagnosed with MGUS from 1999-2021 in the Veterans Health Administration were identified. We used a natural language processing-based algorithm to confirm MGUS diagnosis and progression to smoldering MM or MM. MGUS patients without IgM or IgD subtype or Diabetes Mellitus and were black or white were included in the analysis. Other exclusion criteria were progression within 5 years of MGUS diagnosis, patients without M-spike level within a year before or after MGUS diagnosis, and patients without BMI data 3 years or more after MGUS diagnosis. The exposure was the trajectory of excess BMI (defined as BMI > 25 kg/m²), defined by an area under the curve (AUC) of excess BMI during the 5 years following MGUS diagnosis. The outcome was continuous M-spike trajectory post-MGUS diagnosis since a prior study demonstrated that this was a reliable marker for progression risk. A multivariable mixed model was used to estimate the association of excess BMI trajectory AUC with M-spike trajectory to control for correlation between M-spike values overtime. The covariates included BMI at MGUS diagnosis, M-spike level (> = 1.5g/dL) at MGUS diagnosis, age at MGUS diagnosis, sex, race, MGUS heavy chain subtype, and light-chain MGUS. **Results:** After applying the inclusion and exclusion criteria, the analytic cohort consisted of 6757 MGUS patients. Our multivariable analysis demonstrated a positive association between excess BMI trajectory and increasing M-spike trajectory (β = 0.005, p = 0.007). **Conclusions:** In patients diagnosed with MGUS, increasing BMI over time following MGUS diagnosis was associated with increasing M-spike level. This further supports the relationship between obesity and weight gain in the pathway of MGUS to MM progression. Research Sponsor: U.S. National Institutes of Health.

10537

Poster Session

The impact of high body mass index on hepatocellular carcinoma in viral hepatitis and cirrhosis. *First Author: Moonho Kim, Department of Hematology and Oncology, University of Ulsan College of Medicine, Gangneung Asan Hospital, Gangneung, South Korea, Gangneung, South Korea*

Background: The impact of a high body mass index (BMI) on hepatocellular carcinoma (HCC) has been unclear in patients with viral hepatitis and liver cirrhosis (LC). Our aim is to investigate the association between BMI and HCC in patients with viral hepatitis and LC. **Methods:** We conducted a population-based cohort study. In total, 156,143 Korean adults who underwent routine health examinations during 2003-2006 were followed up until December 2019 via linkage to the national hospital discharge records. Multivariable-adjusted hazard ratios (HRs) per each 5 kg/m² increase in BMI for HCC risk were calculated using Cox proportional hazard models. **Results:** BMI was positively associated with HCC in hepatitis B virus (HBV) patients with BMI range of 27.5~29.9 kg/m² and BMI ≥30 kg/m² and LC patients with a BMI range of 27.5~29.9 kg/m². Assuming linear associations, HRs were 1.17 for HBV, 1.08 for hepatitis C virus (HCV), and 1.11 for LC. In the subgroup analysis for the LC, the HR were 1.19 in the HBV-LC, 1.38 in the HCV-LC, 1.36 in the alcoholic LC, and 1.59 in the fatty liver LC. Women showed stronger positive associations between BMI and HCC than men in the HBV (HR, 1.45 vs 1.06) and LC (1.27 vs. 1.02). The positive association seemed to be stronger in younger age (< 65 years) in HBV (1.17 vs 1.05) and HCV (1.33 vs 0.77) patients compared to older age (> 65 years). **Conclusions:** In the BMI range of ≥25 kg/m², a higher BMI was associated with an increased risk of HCC in LC and HBV. The associations between BMI and HCC risk are different according to liver disease, sex and age. Research Sponsor: Medical Research Promotion Program through the Gangneung Asan Hospital funded by the Asan Foundation.

10539

Poster Session

County-level food insecurity to predict cancer incidence and mortality in the United States, 2015-2020. *First Author: Krista Y. Chen, Johns Hopkins School of Medicine, Baltimore, MD*

Background: Modifiable dietary patterns incorporating inexpensive, calorie-dense, processed foods and meals low in fiber and other nutrients are associated with development of cancer. Inadequate access to quality nutrition is a crucial but underappreciated social determinant of health and predictor of poor cancer outcomes. We investigated the impact of county-level food insecurity on age-adjusted incidence and mortality rates (AAIR, AAMR) for all cancers. **Methods:** We linked county-level cancer incidence and mortality rates for 2015-2020 from NCI State Cancer Profiles to food insecurity measures from Feeding America and County Business Patterns. Measures included percentage of individuals experiencing food insecurity (as defined by USDA), percentage on Supplemental Nutrition Assistance Program (SNAP) benefits, average cost per meal, and density of fast-food restaurants. AAIR and AAMRs of all cancers per 100,000 individuals were compared between 1st and 4th quartiles for each measure using robust linear regression models with log transformation and population weights. **Results:** There was an annual average of 1,728,431 cancer diagnoses with AAIR 449 and 599,666 deaths with AAMR 149. Highest AAIRs were observed in >50y (1351), men (488), non-Hispanic Whites (467), and urban counties (459). This differed from highest AAMR groups including >50y (502), men (178), non-Hispanic Blacks (175), and rural counties (168) suggesting factors of increased disease severity or decreased access to care in the latter. Both AAIRs and AAMRs increased significantly when moving from least to most insecure counties, as defined by overall food insecurity, higher proportion of population on SNAP, higher fast-food density, and lower meal cost. AAMRs and AAIRs for lung cancer and CRC, and for rural residents were most exacerbated by changes in all measures of food insecurity, even when adjusting for screening rates for CRC in low access areas. **Conclusions:** Our study highlights the most food insecure counties have higher cancer incidence and even greater mortality burden. We recognize food insecurity as a proxy for socioeconomic disadvantage prior to and during cancer treatment. These results encourage prioritization of policies that optimize food assistance programs and clinical practices that incorporate food insecurity-related screenings in care delivery models. Research Sponsor: None.

Rate ratios* between least (Q1) and most (Q4) food insecure counties.		Food Insecurity			
			SNAP	Meal Cost	Fast Food
AAIR	Overall	1.03	1.04	0.97	1.03
	Black	1.05	1.04	0.97	1.01*
	Rural	1.04	1.10	0.94	1.05
	Lung	1.38	1.30	0.75	1.19
	CRC	1.16	1.13	0.87	1.11
AAMR	Overall	1.25	1.23	0.83	1.13
	Black	1.09	1.08	0.93	1.08
	Rural	1.13	1.12	0.88	1.07
	Lung	1.17	1.17	0.86	1.14
	CRC	1.08	1.02	0.98	1.09

*Rate ratios obtained as described in methods. All corresponding 95% CI (not shown due to space limits) were statistically significant unless noted with a *.

10541

Poster Session

The role of metabolic perturbations in mediating the effects of ambient air pollution on lung cancer in the cancer prevention studies. *First Author: Donghai Liang, Emory University, Atlanta, GA*

Background: Exposure to ambient air pollution is an established risk factor for lung cancer. Investigation on the underlying mechanisms of air pollution carcinogenicity remains challenging due to the complex composition of air pollution and a lack of sensitive biomarkers to accurately measure exposure and corresponding response. To address the knowledge gaps, we applied high-resolution metabolomics to identify metabolic signatures of exogenous air pollution exposures and endogenous processes involved in lung carcinogenesis. **Methods:** A total of 683 matched lung cancer and control pairs within the established Cancer Prevention Study-II (CPS-II) Nutrition and CPS-3 cohorts were included in this study. The plasma metabolome was profiled with ultrahigh-performance liquid chromatography-tandem mass spectrometry. Assessment of exposure to six ambient air pollutants, including carbon monoxide (CO), nitrogen dioxide (NO₂), particulate matter (PM₁₀), fine particulate matter (PM_{2.5}), sulfur dioxide (SO₂), and ozone (O₃), was conducted using spatiotemporally-resolved models based on residential address at blood draw and calculated based on yearly average levels. We conducted metabolome-wide association studies with multiple linear regression models to assess associations of ambient air pollution and lung cancer with a meet-in-the-middle approach. Models controlled for potential confounders and covariates including age at blood draw, sex, race, body mass index, alcohol consumption, smoking status, passive smoke exposure, vegetable and fruit intake, and educational level. Metabolites significant at the FDR < 0.2 level in the air pollution model were analyzed in the lung cancer model. High-dimensional mediation analysis was used as a secondary analysis to compare results from the meet-in-the-middle analysis. **Results:** Among 1,204 metabolic features extracted from the blood samples, seven features were significantly associated with air pollution exposure and lung cancer incidence at the FDR < 0.2 level in the meet-in-the-middle analysis. Six features were significant at the p < 0.01 level through high-dimensional mediation analysis. All confirmed metabolites are enriched within peptide, lipid, and amino acid pathways. Gamma-glutamylglutamine and gamma-glutamylmethionine were statistically significantly associated with CO, NO₂, and PM₁₀ exposure and lung cancer incidence in both analyses. **Conclusions:** This is the largest prospective metabolomics study examining biological perturbations associated with air pollution exposure and lung cancer incidence. Peptide metabolism may play an important role in mediating the association between air pollution and lung cancer. Findings from this study will lay the foundation for future studies to further understand the biological mechanisms underlying the carcinogenicity of air pollution. Research Sponsor: U.S. National Institutes of Health; American Cancer Society.

10543

Poster Session

Impact of social media messages on perceived risk and severity of adverse effects and regret of HPV vaccination: The moderating role of decision-making preference. *First Author: Jorge Villegas, University of Illinois Springfield, Springfield, IL*

Background: The HPV vaccine has proven to be a highly effective and safe public health intervention for reducing the risk of various types of cancer. Despite its efficacy and safety, misinformation and negative opinions about the vaccine on social media can lead to negative emotions such as regret among those who have received it. This study investigated the impact of different content of social media messages on perceived risk and severity of adverse effects and regret of HPV vaccination. **Methods:** An experiment was designed to expose participants to messages posted on social media that manipulated the number of Vaccine Adverse Effects and the appeal used (narrative vs. statistics). The study measured the effect of the message on decisional regret and also assessed preferred level of involvement with medical decision-making. The online study was implemented among college students enrolled in a Midwestern or a South Texas university. We used structural equation modeling (SEM) to systematically test the relationships between the variables of interest. **Results:** A total of 721 participants were exposed to the experimental materials and completed the questionnaire. The results of the SEM (with overall good fitness of RMSEA = 0.015, CMIN/df = 1.172) suggest that messages that contained more numeric information (standardized regression weights [Std Reg Wght = 0.161]) and more adverse effects of the HPV vaccine (Std Reg Wght = 0.076) led to a higher perception of the risk of vaccine adverse effects. The severity of adverse effects was significantly associated with the number of side effects in the message (Std Reg Wght = 0.147). This increase in perceived risk (Std Reg Wght = 0.182) and severity of side effects of the vaccine (Std Reg Wght = 0.163) seem to increase decisional regret. However, this relationship was moderated by individuals' preferences for making their own medical decisions. Individuals with a higher preference to make their own health decisions were less likely to experience decisional regret (Std Reg Wght = -0.238). **Conclusions:** Messages on social media can exacerbate negative emotions and lead to hesitation in following future medical advice. Encouraging individuals to play a more active role in their medical decision-making appears to reduce this negative emotion and increase their confidence in health decisions. Research Sponsor: None.

10542

Poster Session

Global burden and economic impact of vaccine-preventable cancer mortality. *First Author: Goran Bencina, Center for Observational and Real-World Evidence, MSD Spain, Madrid, Spain*

Background: Cancer has a high clinical and economic burden, with ~10 million deaths globally in 2020. In Europe, the total cost of cancer was €199 billion in 2018. Infections are responsible for approximately 13% of cancer cases worldwide. Human papillomavirus (HPV) and hepatitis B (HBV) are among the most important infections associated with cancer for which vaccines are available. However, global vaccination rates for these cancer-causing infections remain low (~12% for HPV; 42% for HBV). Elimination of vaccine-preventable cancers is a public health priority, and the World Health Organization (WHO) has proposed a strategy to eliminate cervical cancer and viral hepatitis by 2030. This analysis aims to estimate the global burden and economic impact due to vaccine-preventable cancer mortality. **Methods:** The number of deaths and Years of Life Lost (YLL) in 2019 from liver cancer caused by hepatitis B (ICD-10 C22), head and neck cancers (ICD-10 C00-14 and C32), and cancer of the cervix uteri (ICD-10 C53) were sourced from the Institute for Health Metrics Evaluation (IHME) Global Burden of Disease. Deaths and YLL were applied to attributable fractions for each vaccine-preventable cancer based on published data. The Value of YLL (VYLL) was estimated by multiplying the GDP per capita (World Bank, in USD) and YLL for each cancer, in each WHO region. Sensitivity and scenario analyses were performed to test the robustness of results. **Results:** In 2019, there were 479,750 potentially vaccine-preventable cancer deaths and 14,561,049 YLL (38% in males) across WHO regions (Table). The estimated economic impact due to vaccine-preventable cancer deaths was over \$171 billion globally with the Americas and European region accounting for 63% of the total cost (\$107 billion). Cervical cancer had the highest mortality burden (52% of total deaths). Globally, 78% of non-cervical HPV-related cancer deaths were in males. **Conclusions:** In 2019, 1,314 people died per day due to vaccine-preventable cancers leading to substantial YLL and economic impact. The overall burden is likely to be higher since several other HPV-related cancers were not included in this analysis. Improved implementation of HPV and HBV vaccination programs should be prioritized to decrease this burden. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

Deaths, YLL and VYLL due to vaccine-preventable cancers.

Region	Deaths (total)	Deaths (% Male/% Female)	YLL (total)	YLL (% Male/% Female)	VYLL (\$)
African	56,777	11/89	1,948,911	11/89	6,781,797,190
Eastern Mediterranean	16,466	36/64	548,777	34/66	8,977,158,196
European	51,816	34/66	1,377,083	34/66	53,957,605,778
The Americas	51,150	14/86	1,492,493	13/87	53,659,526,030
South-East Asia	101,136	30/70	3,197,870	29/71	36,719,638,991
Western Pacific	202,406	58/42	5,995,916	60/40	11,768,800,297
Global*	479,750	39/61	14,561,049	38/62	171,864,526,482

*Sum of all WHO regions.

10544

Poster Session

The impact of HPV vaccination in Florida compared to New York. *First Author: Thanuja Neerukonda, HCA Florida Brandon Hospital, Brandon, FL*

Background: HPV is responsible for cancers including anus, penis, vulvovaginal, and oropharyngeal but cervical cancer is the most common cancer caused by HPV. To study the impact of HPV vaccination, we compared age-adjusted cervical cancer incidence and death rates in New York, a state with a high HPV vaccination rate, to Florida, a state with a lower vaccination rate, prior to HPV vaccination and 10 years post HPV vaccination availability. **Methods:** This is an ecologic study observing the cervical cancer incidence and death rates prior to (2005) and after (2016) the introduction of the HPV vaccination using state wide healthcare cancer registries. **Results:** The HPV vaccine became available in the United States in 2006. Historically, Florida was found to have a low HPV vaccination rate in 2009 with less than 40% compared to New York which had a high rate of 50% in 2009. By 2016, Florida's HPV vaccination rate improved to 55% but was still low compared to New York with a rate greater than 70%. New York had a decline of cervical cancer incidence of 9.7 per 100,000 in 2005 to 8.3 in 2016. New York had a decrease in death rate from 3.0 in 2005 to 2.7 in 2016. In Florida, the cervical cancer incidence rate from 2005 to 2016 increased from 9.7 to 9.9 and the mortality was 3.0 in 2005 and 2.9 in 2016. When comparing New York's cervical cancer incidence rates, there was a statistically significant drop in age-adjusted incidence before HPV-vaccination compared to 10 years post vaccination availability. When analyzing cervical cancer incidence in 2016, significant increase in cases between Florida's incidence compared to New York's. **Conclusions:** Since the introduction of the HPV vaccination, age-adjusted incidence rate of cervical cancer has declined in New York but not in Florida. This may be due to lagging HPV vaccination rates in Florida in addition to other sociodemographic or healthcare factors. There has been minimal change in cervical cancer death rates between both states, likely attributed by the low death rate associated with cervical cancer. The medical community needs to work together to address the barriers to HPV vaccination and promote programs to increase vaccination rates which will reduce the incidence and mortality of cervical, anus, penis, vagina, vulva, and oropharyngeal cancer. Research Sponsor: None.

Directly standardized cervical cancer age-adjusted incidence and death rates effects in 2005 and 2016: Florida and New York.

State/Year	Comparison	Incidence Rate Ratio (95% CI)	Mortality Rate Ratio (95% CI)
Florida/2005	New York/2005	1.0033 (0.91545-1.09947)	0.994 (0.84280-1.17233)
Florida/2016	New York/2016	1.1941 (1.09003-1.30818)	1.071 (0.90901-1.26185)
Florida/2005	Florida/2016	0.9965 (0.91151-1.08939)	1.065 (0.90771-1.24950)
New York/2005	New York/2016	1.2096 (1.10131-1.32848)	1.178 (0.99470-1.39591)

10545

Poster Session

Barriers to cervical cancer screening in a developing Middle Eastern country: A nationwide survey. *First Author: Ahmed A Abdulelah, University of Jordan, Amman, Jordan*

Background: In addition to being ranked as the 4th leading malignancy worldwide, cervical cancer is associated with considerable morbidity and mortality resulting in significant burden. However, cervical cancer screening is available and has been proven to significantly minimize the associated morbidity and mortality through early detection. The identification of the barriers towards cervical cancer screening in Jordan, a developing middle eastern country, is of outstanding significance towards effective intervention and minimizing the collective health and socio-economic burden imposed. **Methods:** The first consecutive 695 females aged 25 years and above with no prior history of cervical cancer and residing in Jordan across the different regions were enrolled via random probability sampling through a self-reporting survey that comprises of extensive questions regarding the participant's demographics, medical history, awareness about cervical cancer and its screening methods. Single females were not included in the study due to culture unacceptability of performing pap smears on unmarried females. Statistical analysis was performed to identify the key barriers towards cervical cancer screening in Jordan. **Results:** The mean age of the enrolled participants was 42 ± 9 years with the majority of the participants having a higher level of education (84.5%), are medically insured (72.4%), and are non-smokers (74.7%). The majority of the participants, 77.7%, did not report a family history of cervical cancer. 472 participants (67.9%) were aware of the availability of a screening modality for cervical cancer, with the majority being informed through awareness campaigns (64.7%). Nonetheless, only 30.1% of the participants previously underwent pap smear for screening purposes. When the participants who did not undergo previous cervical cancer screening were compared with those who did, the participants who did not undergo any prior screening were more likely to identify the lack of information and knowledge towards screening (49.0% vs 9.6%) (p-value < 0.001), fear of the results (81.5% vs 7.2%) (p-value = 0.016), lack of belief in screening and its efficacy (2.1% vs 0.0%) (p-value = 0.037) as crucial and leading barriers. Additionally, the presence of a positive family history for cervical cancer was identified as a statistically significant promoter for screening uptake (p-value = 0.004). Nonetheless, there was no statistically significant difference between the two groups when evaluating the financial aspects of screening or embarrassment from the test as potential barriers, p-value = 0.159 and 0.738, respectively. **Conclusions:** Lack of knowledge towards screening and belief in its efficacy, and fear of the results were identified as driving barriers towards screening. Effective formulation of comprehensive awareness campaigns is pivotal towards successful intervention to the reported barriers. Research Sponsor: None.

10547

Poster Session

Sex differences in cancer incidence rates by race and ethnicity: Results from the surveillance, epidemiology, and end results (SEER) Registry (2000-2019). *First Author: Sararat Tosakoon, National Cancer Institute, Rockville, MD*

Background: Sex differences in cancer incidence are pronounced, with men having 2-3 times the rate of most non-reproductive cancers than women. However, whether the male predominance is due to differences in biological factors or behavior remains not well understood. This study investigated sex differences in cancer incidence by race and ethnicity to provide a greater understanding of whether differences are driven by biological factors or environmental exposures. **Methods:** Cancer incidence data from the Surveillance, Epidemiology and End Result (SEER) program (2000-2019) was used to calculate male-to-female incidence rate ratios (MF IRR) for each cancer site and histological subtype, stratified by race and ethnicity (non-Hispanic White, non-Hispanic Black, non-Hispanic Asian/Pacific Islander, American Indian/Alaskan Native, and Hispanic), and age-standardized to the 2000 U.S. population for individuals ages ≥ 20 years. **Results:** Most non-reproductive cancers had a male predominance across race and ethnicity, with the largest MF IRR seen for cancers of the tonsil, hypopharynx, larynx, and Kaposi sarcoma (MF IRR > 4). Three cancers, gallbladder; peritoneum, omentum, mesenter; and thyroid, were more common among females than males across all race and ethnicity. Females had a higher incidence of anal cancer than males for all racial and ethnic groups except for non-Hispanic Black individuals where the MF IRR was >1. Cancers of the stomach, skin (excluding basal and squamous cell), melanoma skin, and other non-epithelial, and myeloma had greater MF IRR among non-Hispanic White adults than all other racial and ethnic groups. Non-Hispanic Black individuals had higher MF IRR of cancers of the liver and lung and bronchus, compared to other racial and ethnic group. Non-Hispanic White males had the highest MF IRRs for esophagus adenocarcinoma and gastric cardia adenocarcinoma and the lowest MF IRR for esophagus SCC compared to other races and ethnicity. **Conclusions:** The MF IRR for most cancers in this study did not differ by race and ethnicity, suggesting the influence of biological factors. Differences in the MF IRR across race and ethnicity may indicate carcinogenic exposure differences leading to the development of non-sex-specific cancers. Further research is needed to identify biological drivers of cancer incidence for most non-reproductive cancers. Funding: Intramural Research Program of the Division of Cancer Epidemiology and Genetics in the National Cancer Institute, National Institutes of Health. Research Sponsor: U.S. National Institutes of Health.

10546

Poster Session

Incomplete HPV vaccination among individuals aged 27-45 years in the United States: A mixed effect analysis of individual and contextual factors. *First Author: Victor Adekanmbi, University of Texas Medical Branch, Galveston, TX*

Background: In the United States, the Human papillomavirus (HPV) vaccine is approved for use up to age 45. Incomplete HPV vaccination rates among those over age 26, however, remain high. The aim of this study was to examine the independent effects of individual- and neighborhood-level factors on incomplete HPV vaccine series in the United States (US) among those aged 27-45 years. **Methods:** This retrospective cohort study used administrative data from Optum's Clinformatics DataMart Database to identify individuals aged 27-45 years who received 1 or more doses of HPV vaccine between July 2019 and June 2022. Multilevel multivariable logistic regression models were applied to the data on 7,662 individuals aged 27-45 years who were fully vaccinated against HPV or not, nested within 3839 neighborhoods across the US. **Results:** More than half of the participants in this study (52.93%) were not completely vaccinated against HPV. About 64% of the eligible participants aged 27-30 years did not complete their HPV vaccine series. After adjusting for all other covariates in the final model, being older than 30 years old decreased the odds of incomplete HPV vaccine series. Participants living in neighborhoods of South region of the US had enhanced odds of incomplete HPV vaccine series compared to those residing in Northeast region (aOR 1.21; 95% CrI 1.03-1.42). There was significant clustering of incomplete HPV vaccine series at the neighborhood level. **Conclusions:** This study revealed that individual- and neighborhood-level factors significantly influence HPV vaccination incompleteness in the US. Interventions to improve HPV vaccination uptake and completion should take into consideration both individual- and contextual-level characteristics during design, planning and implementation of policies and programs to improve HPV vaccination coverage and completion in the US and other similar countries. Acknowledgement Dr. Adekanmbi is supported by a research career development award (K12HD052023: Building Interdisciplinary Research Careers in Women's Health Program-BIRCWH; Berenson, PI) from the National Institutes of Health/Office of the Director (OD), National Institute of Allergy and Infectious Diseases (NIAID), and Eunice Kennedy Shriver National Institute of Child Health & Human Development (NICHD). Dr. Guo is currently supported by an award (K07CA222343) from the National Institutes of Health, National Cancer Institute (NIH/NCI). Dr. Berenson is supported by an award (PP2000048) from the Cancer Prevention and Research Institute of Texas (CPRIT). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or CPRIT. Conflict of Interest: All authors report no conflicts of interest. Research Sponsor: U.S. National Institutes of Health.

10548

Poster Session

Polygenic risk scores in assessing lung cancer susceptibility in non-Hispanic White and Black populations. *First Author: Matthew R Trendowski, Wayne State University School of Medicine, Detroit, MI*

Background: Polygenic risk scores (PRS) have become an increasingly popular approach to evaluate cancer susceptibility, but have not adequately represented Black patients in model development. We used previously identified single nucleotide polymorphisms (SNPs) and annotated SNPs in associated gene regions to develop PRS in non-Hispanic Whites and Blacks using the INHALE dataset. **Methods:** Using the Multi-Ethnic Genotype Array, 1,204 SNPs for non-Hispanic Whites and 1,515 SNPs for Blacks were evaluated for their association with lung cancer risk adjusting for age, sex, total pack-years, family history of lung cancer, history of COPD and the top five PCs for genetic ancestry. Gene region-specific significant SNPs (p < 0.05) were used to develop race-specific PRS. **Results:** The race-specific PRS included different sets of significant SNPs and were highly associated with lung cancer risk in both non-Hispanic Whites (OR = 1.07, 95% CI: 1.05-1.09, p = 3.44×10^{-9}) and Blacks (OR = 1.12, 95% CI: 1.08-1.17, p = 9.14×10^{-8}). These models remained significant for both Whites (OR = 1.05, 95% CI: 1.03-1.09, p = 0.0004) and Blacks (OR = 1.08, 95% CI: 1.01-1.15, p = 0.01) who currently do not meet USPSTF screening guidelines. AUC analysis demonstrated the Black-specific model (AUC = 0.68) outperformed the White-specific model (AUC = 0.57) (p = 0.03) when examined exclusively in the Black cohort. **Conclusions:** Using previously validated SNPs and gene regions, we developed race-specific PRS in non-Hispanic White and Black INHALE participants. Further validation of PRS could enable the incorporation of genetic risk modeling into lung cancer screening to identify patients who do not have traditional risk factors for lung cancer, as well as stratify patients into different levels of risk based on their genetic profile. Through the development of a reliable genetic risk factor prediction model, clinicians will have another method by which to evaluate lung cancer susceptibility, potentially leading to earlier diagnoses that portend more favorable treatment outcomes. Research Sponsor: U.S. National Institutes of Health; Herrick Foundation.

10549

Poster Session

Racial disparities in germline testing among men with pancreas, breast and metastatic prostate cancers in two health systems. *First Author: Jeffrey Shevach, University of Pennsylvania-Abramson Cancer Center, Philadelphia, PA*

Background: Germline genetic testing is a guideline-based practice for men with pancreas, breast and metastatic prostate cancers. Emerging evidence in female breast and ovarian cancers suggests that Black patients are less likely to receive germline genetic testing, but it is unclear how disparities extend to male cancers and vary by health system. We examined differences by race in germline genetic testing for men with pancreas, breast and metastatic prostate cancers in equal-access and non-equal access systems. **Methods:** We conducted a retrospective cohort study of men with newly diagnosed pancreas, breast and metastatic prostate cancers between January 1, 2019, and September 30, 2021. We studied two national cohorts: 1) Veterans receiving care in the Veterans Health Administration (VHA), an equal-access health system, and 2) commercially insured beneficiaries. Data consisted of claims and electronic health record data from the VHA Corporate Data Warehouse and claims data from Optum's De-Identified Clinformatics Data Mart Database (2007-2021). Current Procedural Terminology codes $\pm$ laboratory orders and results, and genetic services notes were used to ascertain germline testing prior to the end of the study period. Cox proportional hazards models were used to test the association of non-Hispanic White vs. Black race with the primary outcome of germline genetic testing completion, adjusted for baseline covariates (age, cancer subtype, census region, diagnosis year, Elixhauser comorbidity index and Agent Orange exposure [VHA only]). **Results:** Our cohort consisted of 7,894 men (5,142 commercially-insured; 2,752 Veterans), including 1,589 Black men (779 [15.1%] commercially-insured; 810 [24.9%] Veterans). Among commercially-insured beneficiaries, one-year germline genetic testing rates were higher in White compared with Black men (18.8% vs. 13.1%; log-rank $p < 0.001$). Among Veterans, one-year germline genetic testing rates were similar for White and Black Veterans (13.1% vs. 16.9%; log-rank $p = 0.335$). After adjusting for baseline covariates, Black race was associated with a lower hazard of testing among commercially-insured beneficiaries (adjusted hazard ratio [aHR] 0.72; 95% confidence interval [CI] 0.58 – 0.90; $p = 0.004$), but not among Veterans (aHR 0.99; 95% CI: 0.79 – 1.25; $p = 0.960$). **Conclusions:** This is the first study to examine disparities in germline genetic testing across equal-access and non-equal access healthcare systems, and the largest national study examining germline genetic testing completion in men. While overall rates of testing were similar between Veterans and commercially-insured beneficiaries, racial disparities in testing were observed in non-equal-access settings but not in equal-access settings. Access to care, cost, and other sequelae of structural racism may impact access to guideline-based germline testing. Research Sponsor: Bassett Center for BRCA; U.S. National Institutes of Health.

10551

Poster Session

Characterizing medical mistrust (MM) in a socio-demographically diverse sample of patients with cancer. *First Author: Cindy Park, Temple University, Lewis Katz School of Medicine, Philadelphia, PA*

Background: Genetic and genomic testing are increasingly recognized as essential to high quality cancer care. Despite expanded eligibility for testing in recent years, barriers to genomic medicine persist. Notably, growing political and social mistrust risks negatively impacting views of medical institutions, medical professionals and complex technologies, and could undermine acceptance of genetic/genomic testing to guide treatment and identify risk in families. Prior studies have documented disparities and increased MM of genetic counseling and testing among underserved minorities which have been associated with delays or avoidance to care. We sought to identify individual characteristics associated with MM among cancer patients. **Methods:** A cross-sectional survey of cancer pts from the Fox Chase Cancer Center (FCCC) Burholme Campus (n=105, mixed urban/suburban, primarily insured) and Broad street campus (n=95, primarily urban underserved population) was conducted from 6/22-12/22, using a maximum variation (purposeful) sampling approach. Surveys queried MM using the LaVeist MM Index (MMI, range 0-10, measures healthcare/institution MM) and the Thompson Group Based MM Scale (GBMMS, range 1-5, measures race/ethnic specific MM; suspicion, discrimination, and lack of support subscales). Demographic and disease factors, as well as psychosocial measures (general/genetic health literacy, social support, self-advocacy, conspiratorial thinking, relationship with doctor, and trust in information sources) were also assessed. Medical decision making preference and health literacy were assessed with single validated items. The study was approved by the FCCC IRB #22-8003. **Results:** Participants had a median age of 62 yrs (range 25-91); 62% were female, 47% African American (AA), 15% Hispanic, 42% married, 47% high school graduate or less, 52% had household income $< \$50K/yr$. Breast (28%), colorectal (16%), and GYN/GU (12%) cancers were the most commonly reported, and 23% reported > 1 previous cancer diagnosis. Mean GBMMS was 2.11 (SD 0.80) and mean MMI was 4.63 (SD 1.54). See the table for significant associations. **Conclusions:** High levels of healthcare institution and race-based MM are associated with socio-demographic vulnerabilities, putting the most vulnerable cancer patients at high risk of making poor health decisions. Research Sponsor: U.S. National Institutes of Health; ECOG ACRIN.

Predictor	MMI Healthcare institution mistrust	GBMMS Race-based medical mistrust	Comparators
Age	NS	$p=0.04$	Younger>older
Race/ethnicity	$p=0.04$	$p<0.001$	AA>Hispanic>White
Stage (Early/Late/Unsure)	$p=0.04$	NS	"Unsure" highest
Education	$p=0.03$	NS	< high school highest
Insurance type	$p=0.04$	NS	Medicaid highest
Annual household income	NS	$p=0.05$	< \$25K highest
Site (urban/suburban)	NS	$p=0.03$	Urban higher
Health literacy	NS	NS	
Medical decision making preference	$p=0.0015$	$p=0.07$	"I make the decisions without MD input" highest

10550

Poster Session

Disparities in germline genetic testing results from a cohort of 493,515 black and white patients. *First Author: Rachel Wyatt, UT Health San Antonio, San Antonio, TX*

Background: When undergoing germline genetic testing (GGT), Black patients (pts) are more likely than non-Hispanic White (NHW) pts to receive uncertain results and less likely to receive definitive molecular diagnoses as the Black genome is less well-characterized. As GGT is increasingly pertinent to cancer care, it is important to explore the scope of these disparities. **Methods:** A retrospective cohort of clinician-reported Black and NHW pts who underwent GGT (43-84 genes) from 2015-2022 was evaluated. Frequencies of pathogenic/likely pathogenic (P/LP) and variant of uncertain significance (VUS) results were compared between Black and NHW pts. Rate and type of VUS reclassifications were also compared. Differences in proportions were determined using Chi-square test and significance was set at 0.05. **Results:** The cohort consisted of 493,515 pts (48,684 [10%] Black and 444,831 [90%] NHW). VUS results were significantly more frequent and P/LP results significantly less frequent for Black compared to NHW pts (46% vs. 32% and 9 vs. 13%, respectively). This was also true for pts who reported a history of cancer, across all common hereditary cancer types (Table). Comparing Black to NHW pts, there were more unique instances of VUS reclassifications over time (13% of 13,629 vs. 9% of 53,195 unique VUS), including 12% vs. 8% downgraded to benign/likely benign and 0.9% vs. 1.3% upgraded to P/LP. **Conclusions:** Lower rates of actionable results limit risk-reducing interventions for Black pts and their families. However, VUS rates continue to decline, particularly in Black pts, as more individuals (of any race or ethnicity) are sequenced. Clinicians can be reassured that most (but not all) VUS that are reclassified are downgraded to benign. Research Sponsor: Invitae.

Test result yield by cancer type among black and white pts.

	Cancer type # of pts (%)							
	Breast	Ovarian	Endometrial/ Uterine	Colorectal	Prostate	Pancreatic	Gastric	Renal
Black	20000	1389	1261	3070	3253	1456	454	616
P/LP	1923 (10)	187 (14)	136 (11)	403 (13)	260 (8)	138 (10)	58 (13)	42 (7)
VUS*	8858 (44)	622 (45)	560 (44)	1325 (43)	1540 (47)	684 (47)	194 (43)	292 (47)
NHW	169875	16679	13920	31102	21255	14675	2581	6769
P/LP	21305 (13)	2806 (17)	2087 (15)	4942 (16)	3115 (15)	2179 (15)	473 (18)	967 (14)
VUS	54416 (32)	5083 (31)	4238 (30)	9687 (31)	7127 (34)	4799 (33)	783 (30)	2313 (34)

Note: Negative results make up the remaining percentages within columns.

10552

Poster Session

Training oncologists (Oncs) to conduct better informed discussions with African American (AA) cancer (CA) patients (pts) about tumor genomic profiling (TGP): Results of a randomized pilot trial of gene pilot pro (GPP). *First Author: Michael J. Hall, Fox Chase Cancer Center, Philadelphia, PA*

Background: Molecular characterization of tumors to guide therapy choices using next-generation sequencing-based TGP has become standard practice for pts w/ multiple CA types. AAs are more likely to have negative attitudes towards genetics, rooted in concerns about privacy, cost and discrimination, and higher mistrust of medical institutions. Oncs are poorly prepared for informed discussions w/CA pts about secondary hereditary risks of TGP and often fail to have these conversations despite 2015 ASCO guidelines benchmarking this standard, and further are poorly informed of the potential challenges of discussing TGP and germline risk w/their AA CA pts. **Methods:** Formative work included 1-on-1 interviews (n = 10) to assess oncs' perceptions of TGP use and discussions w/AA CA pts, and a national survey (n = 50) to assess TGP practice patterns, communication of hereditary risk, and challenges encountered in AAs. Interviews/survey data and advisory board input informed development of GPP, a 12 min online training video to improve Oncs' awareness of ASCO guidelines, confidence and preparation to have TGP discussions w/pts, and improve awareness of barriers to TGP unique to AA CA pts. The control consisted of 10 slides with information about TGP drawn from industry/academic websites and the 2015 ASCO guidelines. Participants (n = 63) completed baseline (100%), post-intervention (100%), and 1-month (95%) follow-up surveys. The study was approved by the Fox Chase Cancer Center IRB 18-8006. **Results:** Oncs were recruited by email and randomized to view GPP or control material. The majority were age 40-49 (38%), 71% male, 44% White, w/mean 15 yrs in practice; 85% reported none or only informal training to communicate TGP risks/results to pts. GPP produced a durable increase in recognition of 4 core ASCO guideline elements (20% baseline, 67% post, 63% 1 month). At 1-month follow-up, GPP significantly improved recognition of barriers specific to AA CA pts related to TGP and hereditary risk ($p = 0.001$) and promoted greater preparedness to support TGP discussions w/AA pts including preparedness to identify ($p < 0.01$) and understand ($p < 0.01$) issues that matter most to their AA pts. 1-month confidence to conduct difficult discussions related to genetic mistrust ($p = 0.004$) and TGP cost ($p = 0.003$) was better preserved after viewing GPP compared to control. Among Oncs viewing GPP, 90% agreed/strongly agreed that GPP helped them "better understand how to address concerns my AA pts may have about TGP" and 97% definitely/probably would recommend GPP to other Oncs. **Conclusions:** GPP significantly improved Oncs' awareness of barriers related to TGP communication in AA CA pts, improved preparedness to facilitate informed decision-making, and supported sustained confidence to lead difficult discussions. Research Sponsor: American Cancer Society.

10553

Poster Session

Integrated clinical, pathologic, and genetic data in a racially diverse hereditary breast cancer cohort. *First Author: Kenna Noel Koehler, Vanderbilt University Medical Center, Nashville, TN*

Background: Hereditary breast cancers (HBC) represent 5-10% of breast cancer, predominantly due to pathogenic/likely pathogenic (P/LP) variants in the *BRCA1* and *BRCA2* genes and other high (e.g., *PALB2*) and moderate (e.g., *ATM* and *CHEK2*) penetrance genes. There remains a paucity of data evaluating the role of germline-somatic interactions and possible confounders on breast cancer outcomes. Furthermore, current knowledge about HBC is predominantly defined in the context of European ancestry. We sought to characterize differences in clinicopathological features and somatic mutations across P/LP variants in a racially diverse HBC cohort. **Methods:** Among females with breast cancer and a confirmed P/LP variant in *BRCA1*, *BRCA2*, *PALB2*, *CHEK2*, and/or *ATM* currently enrolled through existing Vanderbilt-based studies (ICARE: Inherited Cancer Registry and BEST: Black Women: Etiology and Survival of Triple Negative Breast Cancers (TNBC)), we abstracted data from medical records and performed tumor sequencing using the Tempus xT assay (a 596-gene DNA next-generation sequencing panel and whole-transcriptome RNA sequencing). Interim differences in clinicopathological features were analyzed using Pearson's chi-square test and the frequency of somatic mutations reported by gene. **Results:** To date, we have data from 91 females with breast cancer (77% White and 23% Black) and a P/LP variant (36 *BRCA1*, 27 *BRCA2*, 13 *PALB2*, 11 *CHEK2* and 4 *ATM*). The median age at diagnosis was 44 (38-50), 85% had localized breast cancer (Stage I-II), and 69% had Grade 3 tumors. Significantly more Black participants were *BRCA1* carriers ($p = 0.008$), with no significant racial differences observed in other genes. There were significant differences in IHC subtype by gene ($p < 0.001$); with higher frequency of TNBC in *BRCA1* carriers (64%) whereas *BRCA2*, *PALB2*, *CHEK2*, and *ATM* carriers were more likely to have HR+, HER2- breast cancer (67%, 54%, 73%, 75%, respectively). Of the 85% who received chemotherapy, significantly higher rates were observed in *BRCA1* carriers ($p = 0.02$). Most participants opted to proceed with a risk-reducing mastectomy (69%) with no difference across genes ($p = 0.91$). Higher rates of somatic *TP53* mutations were observed among *BRCA1*, *BRCA2*, *PALB2* carriers (89%, 56%, 46%) but not as frequent among *ATM* (25%) and *CHEK2* (9%) carriers. **Conclusions:** These preliminary results show that among a diverse cohort of females with HBC, *BRCA1* mutations were overrepresented among Black females and those with TNBC. *BRCA1*, *BRCA2*, and *PALB2* carriers had a higher prevalence of somatic *TP53* mutations, which are typically associated with more aggressive tumor biology and worse survival outcomes. Current efforts underway include full genomic and transcriptomic analysis, through which we will be able to improve our understanding of breast cancer clinicopathological characteristics and survival outcomes among a diverse cohort of females with HBC. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology; Breast Cancer Research Foundation.

10554

Poster Session

African American women who carry the *BRCA1/2* mutation: Clinical characteristics and prevention strategies. *First Author: Ujjwal Karki, Corewell Health William Beaumont University Hospital, Royal Oak, MI*

Background: Carriers of pathogenic variants (PV) in *BRCA1/2* have an increased risk of breast, ovarian, and other cancers. The clinical characteristics and uptake of risk-reducing interventions in African American (AA) women with *BRCA1/2* PVs are less well studied. **Methods:** After IRB approval, we performed a retrospective chart review on African American women seen at Nancy and James Grosfeld Cancer Genetics Center at Beaumont Health from January 1, 2006, to December 31, 2021, who tested positive for a *BRCA 1/2* mutation. We analyzed demographics, cancer characteristics, outcomes, and prevention strategies. **Results:** Of 238 African American (AA) women who underwent genetic testing, 69 patients (29%) were identified to be a carrier of *BRCA1/2* PVs or likely pathogenic variants (LPVs). The median age at testing was 49 years (range: 24-87). Forty-six women (67%) had a cancer diagnosis, with a median age at diagnosis of 52 years. Four women had two, and one had three cancers, for a total of 52 cancers. Breast cancer was the most common type of cancer (40; 77%), with a median age at diagnosis of 48 years (range 24-73) and a majority (26; 65%) being *BRCA2* carriers. Most were invasive ductal carcinoma (87.8%), high-grade (80%), ER-positive (52%), PR-negative (68%), HER2-negative (94%) and stage I or II disease (63%). Fifteen (38%) were triple-negative. Most patients (87%) received adjuvant systemic chemotherapy or endocrine therapy, 31% received neoadjuvant chemotherapy, and 39% received adjuvant radiation. The 3- and 5-year survival was 94% and 91%, respectively, with a median follow-up of 103 months. Three patients (all *BRCA2* carriers) developed contralateral breast cancer (median time to recurrence: 201 months); 3 (all *BRCA2*) developed local recurrence (median time to recurrence: 60 months); and 4 (2 *BRCA1*, 2 *BRCA2*) developed metastatic recurrence (median time to recurrence: 34 months). Other cancers observed were ovarian ($n = 6$; 4 *BRCA2*, 2 *BRCA1*), uterine (2), lung (2), kidney (1), and glioblastoma (1). Compared to AA carriers without cancer, those with cancer were more likely to undergo risk-reducing mastectomy (RRM; 68% vs. 23%) and risk-reducing salpingo-oophorectomy (RRSO; 72% vs. 55%). In the non-cancer group, significantly fewer patients elected RRM (23%) compared to RRSO (55%). **Conclusions:** Our study outlines the characteristics of AA women who carry *BRCA1/2* PVs, revealing that most had high-grade invasive ductal breast cancer with excellent survival. Patients without a cancer diagnosis were less likely to undergo risk-reducing surgery, highlighting the importance of effective counseling focusing on primary prevention in these high-risk patients. Further research is needed to better characterize cancer risk and address potential barriers to uptake of risk-reducing interventions in this population. Research Sponsor: None.

10555

Poster Session

Racial disparities in aging-related comorbidity among breast cancer survivors. *First Author: Kirsten Nguyen, Vanderbilt University School of Medicine, Nashville, TN*

Background: Black breast cancer (BC) patients have a higher mortality rate than their white counterparts, potentially due to age acceleration caused by cancer and its treatments. However, epidemiological evidence is limited. **Methods:** Our study includes 1885 BC patients and 1224 cancer-free women (controls) recruited at Vanderbilt University Medical Center from 2004 to 2021. Patient demographics and aging-related outcomes were extracted from the tumor registry or electronic health records. Aging-related outcomes included 28 comorbidities and the Charlson Comorbidity Index (CCI) at baseline (biopsy) and follow-up (latest clinical visit). The associations of BC status with CCI and specific comorbidities were evaluated by linear and logistic regression models, respectively. The associations of race with aging-related outcomes were evaluated among cases. All analyses were adjusted for age, and follow-up outcomes were adjusted for baseline information. **Results:** The median follow-up time is 10 years. BC patients had a higher mean CCI at baseline (1.32 vs 0.59, $p < 0.01$) and follow-up (beta=1.04, 95% CI=0.94-1.14) than controls. Results from individual comorbidities showed that BC survivors had a higher risk of developing cardiovascular disease, liver disease, hypertension, hyperlipidemia, gastroesophageal reflux disease (GERD), and depression. Among BC patients, Black women were diagnosed at a younger age (52.0 vs 55.8, $p < 0.01$), but had a higher baseline and follow-up CCI than Whites. Black BC survivors were more likely to develop peptic ulcer disease, diabetes, second malignancy, hypertension, and GERD than White BC survivors, even after adjustment for baseline comorbidities. Research Sponsor: MMC, VICC, and TSU: Partners in Eliminating Cancer Disparities Grant (U54CA163072); Vanderbilt-Ingram Cancer Center SPOR in Breast Cancer (P50CA098131).

Aging-related outcomes among breast cancer patients by race.

	N	Charlson Comorbidity Index ¹ Beta (95% CI)		Peptic ulcer disease	Diabetes	Second malignancy	Hypertension	GERD
		Baseline	Follow-up					
Total	1885							
Non-Hispanic White	1622	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Non-Hispanic Black	159	0.55* (0.30, 0.81)	0.77* (0.37, 1.16)	2.34* (1.46, 3.62)	3.25* (2.15, 4.83)	1.63* (1.16, 2.25)	1.68* (1.15, 2.41)	1.77* (1.26, 2.46)
Hispanic	21	0.46 (-0.26, 1.18)	-0.44 (-1.56, 0.68)	-	0.46 (0.03, 2.27)	0.61 (0.14, 1.81)	0.41 (0.02, 2.01)	1.60 (0.60, 3.90)
Asian	25	-0.13 (-0.77, 0.50)	-0.35 (-1.34, 0.63)	1.77 (0.42, 5.15)	1.62 (0.47, 4.29)	0.64 (0.19, 1.66)	1.15 (0.45, 2.66)	1.19 (0.05, 2.65)
Other	58	-0.54* (-0.10, -0.97)	-1.44* (-2.17, -0.71)	0.56 (0.09, 1.82)	0.19 (0.01, 0.86)	0.29 (0.09, 0.72)	0.45 (0.11, 1.26)	0.19 (0.06, 0.52)

¹Linear regression models; ²Logistic regression models. Models were adjusted for age and additionally for baseline information for follow-up outcomes.
* $p < 0.05$.

10557

Poster Session

Prevalence of and racial/ethnic distribution of full-body skin examination among sexual and gender minority patients. *First Author: Jincong Q. Freeman, Department of Public Health Sciences, The University of Chicago, Chicago, IL*

Background: Skin cancer disproportionately affects sexual and gender minorities in the United States. A full-body skin examination (FBSE) can help detect early signs of skin cancer and is an important prevention method. However, there are no national guidelines of routine FBSE for skin cancer. Further, data on FBSE participation among lesbian, gay, bisexual, transgender, and/or queer (LGBTQ+) patients are lacking, and little is known about the racial/ethnic distribution of FBSE in this patient population. **Methods:** Cross-sectional survey data on FBSE participation and key characteristics were collected from patients who were recruited at clinics and community centers or via social media from August 2022 to January 2023. Eligibility criteria included being at least 18 years old and self-identifying as LGBTQ+. Receipt of an FBSE, assessed by asking patients whether they had ever received an FBSE in the past, was dichotomized as yes and no. Descriptive statistics, i.e., mean (SD) and count (%), were calculated, with distribution comparisons using Student's t, Pearson's Chi-square, or Fisher's exact tests as appropriate. **Results:** A total of 124 LGBTQ+ patients responded to the survey. The mean age was 32.4 (SD = 12.1) years. Overall, 41.5% of the patients reported ever having received an FBSE in the past. By race/ethnicity, 62.5% of Non-Hispanic Black patients reported ever having received an FBSE, followed by 52.1% of Non-Hispanic White, 28.6% of Hispanic or Latino, 28.6% of multiple races, and 10.5% of Asian ($p=0.005$). By gender identity, 61.5% of transgender male patients reported receipt of an FBSE in the past, followed by 57.1% of transgender female, 39.3% of cisgender female, 35.4% of cisgender male, and 35.0% of genderqueer, non-binary, or gender non-conforming. Comparing patients who reported ever having received an FBSE, those who did not were more likely to not be employed (47.9% vs. 26.0%, $p=0.046$), to be on Medicaid (18.5% vs. 6.1%, $p=0.074$), to not have visited a dermatologist in the past (41.7% vs. 7.8%, $p<0.001$), and to not have been told at an increased risk for skin cancer (87.3% vs. 43.2%, $p<0.001$). No significant differences in educational attainment or sexual orientation were observed between patients who reported ever having received an FBSE and those who did not. **Conclusions:** The prevalence of FBSE was higher among Non-Hispanic Black or Non-Hispanic White LGBTQ+ patients than among those who are Hispanic or Latino, multiracial, or Asian. In addition, our findings suggest that low socioeconomic status and health care utilization may influence FBSE access or participation in LGBTQ+ patients. Strategies for improving equitable access to FBSE among LGBTQ+ patients, particularly among those with ethnic minority background or low socioeconomic status and health care utilization, may be needed. Research Sponsor: Susan G. Komen Breast Cancer Foundation.

10559

Poster Session

Vitamin D deficiency as a risk factor for breast cancer development. *First Author: James David Mackey, Alara Medical Group, Dallas, TX*

Background: Previous studies and meta-analyses have suggested that women with low levels of vitamin D may be at increased risk of breast cancer development and recurrence. The relationship is suspected to be inverse, nonlinear, and predominantly present in postmenopausal women. The purpose of this study was to use the TriNetX platform to determine the magnitude of breast cancer risk increase for women with significant vitamin D deficiency and evaluate the significance of menopause on vitamin D-associated breast cancer risk. **Methods:** The TriNetX platform was used to generate patient cohorts via International Classification of Disease-10 (ICD-10) codes. All patients were females over 40, had no prior history of breast cancer (C50), and had been diagnosed with menopause (Z78.0). One cohort had less than 20 ng/mL of vitamin D while the other had greater than 30 ng/mL. The cohorts were balanced for age, race, and ethnicity, resulting in 73,659 patients in each arm. They were then evaluated for the future development of breast cancer (C50). Two additional cohorts were created of premenopausal patients aged 40-55 using the same vitamin D parameters and cohort balancing. **Results:** Postmenopausal women with vitamin D levels below 20 ng/mL had a 45% greater risk of developing breast cancer (risk ratio 1.45, 95% CI (1.38, 1.52), p -value <0.0001). (Table) Deficient premenopausal women were also found to be at significantly increased risk although the absolute risk difference was small (relative risk 1.18, 95% CI (1.10, 1.27), p -value <0.0001). **Conclusions:** These results confirm and also quantify the previously-suspected increased breast cancer risk for women who are deficient in vitamin D. The impact of low vitamin D levels on breast cancer risk in premenopausal patients was statistically significant but small in magnitude, while postmenopausal women were found to have approximately 45% higher risk as compared to women who were not deficient. Vitamin D supplementation for all deficient postmenopausal women should be considered. Research Sponsor: None.

New breast cancer incidence rates by vitamin D subgroup.

Cohort	Patients	New Breast Cancers	Risk %
Postmenopausal 0-20 ng/mL	73,659	3,944	5.35
Postmenopausal $\geq$ 30 ng/mL	73,659	2,717	3.69
Premenopausal 0-20 ng/mL	141,421	1,640	1.16
Premenopausal $\geq$ 30 ng/mL	141,421	1,386	0.98

10558

Poster Session

Melanoma literacy and predictors for skin self-examination in three western U.S. states: A population-based survey. *First Author: Jacob Nelson, Oregon Health & Science University, Portland, OR*

Background: Melanoma is a leading cause of skin cancer deaths, despite being easily treated when detected early. The objective of this study is to investigate the relationship between melanoma knowledge and beliefs, and the performance of skin self-examination (SSE) in three US states with high incidence rates of melanoma. Understanding the barriers to behaviors such as SSE can aid in the development of interventions aimed at increasing the frequency of early detection and reducing melanoma-related deaths. **Methods:** A total of 15,000 surveys were distributed to households in the states of Oregon, Washington, and Utah using a stratified two-stage sampling design. The survey responses were weighted to resemble the gender and age distributions of the US census. Rural areas were oversampled to ensure sufficient representation. The first objective of this study was to assess melanoma literacy, including knowledge about melanoma risks, attitudes, and preventive behaviors. Our second objective was to investigate the relationship between self-reported SSE and melanoma literacy, self-efficacy, and belief in the benefits of performing SSE. **Results:** Among 2,326 respondents, characteristics were similar across states (weighted by census-based population percentages), including demographics, baseline knowledge, performance of SSE, and self-efficacy in performing SSE. Rural respondents had a higher frequency of personal history of melanoma (16.2%) compared to urban respondents (9.9%). Only 21.2% of the respondents demonstrated high knowledge of melanoma. 62.8% of respondents reported having performed a SSE at some point in their lives, with only 24.6% of respondents having done so in the past 2 months. Most respondents (84.8%) believed in the effectiveness of SSE in detecting skin cancer, but only 38.3% and 7.3% reported being "fairly" or "very" confident in performing SSE, respectively. The performance of SSE was most strongly correlated with higher melanoma knowledge, higher self-efficacy, and a personal history of melanoma. **Conclusions:** The results of the survey indicate that melanoma literacy among respondents in 3 high-risk Western states is limited. A higher level of literacy was associated with a higher likelihood of reported early detection behaviors. This study provides a baseline assessment and serves as a foundation for the development of public health campaigns aimed at promoting prevention and early detection of this deadly cancer. Research Sponsor: Knight Cancer Institute.

10560

Poster Session

A nationwide population based primary CNS lymphoma (PCNSL) analysis: Do Hispanics have better outcomes? *First Author: Ysaith Orellana, Ohio University Heritage College of Osteopathic Medicine, Cincinnati, OH*

Background: Over the last decade, overall survival (OS) of PCNSL patients has increased from 12.5 months to 26 months (N. Oncol, PMID 30418592). One study examined the incidence of PCNSL in the Hispanic (HI) population in Texas (Cureus, PMID: 33042676), but a national study is needed to understand ethnic disparities, as many HI face barriers to health care access (Natl Cancer Inst Monogr. PMIDL 8562207). This study aims to understand demographics, treatment patterns, and outcomes of HI and Non-Hispanic (NH) patients with PCNSL nationally. **Methods:** Data analyzed on PCNSL patients in the United States (US) was reported to the Surveillance, Epidemiology, End Results (SEER) 18 database between 2000 and 2018. Racial groups analyzed included NH whites, HI whites, Blacks, and Asian/Pacific Islanders (PI). Patient characteristics, age-adjusted incidence rate, and survival rate were compared across ethnic groups (HI vs. NH). Stratification by age, gender, and stage at diagnosis was considered. Data was stratified using Kaplan-Meier and Cox regression analyses to compare OS between HI and NH. Multivariate analysis and propensity score matching was performed with adjustment for age, stage, and B-symptoms. **Results:** Of 5819 PCNSL patients, 15% were HI, and 85% NH. 57% were male compared to 51% of NH. As compared to NH at diagnosis, HI patients were younger, 59 years vs. 66 years ($p<0.001$); the majority of HI (42%) were diagnosed in the age bracket of 60-80y ($p<0.001$). Approximately 30% of HI were diagnosed in 2015-2018, while most of NH (29%) were diagnosed in 2010-2014 ($p=0.054$). With 52% of HI being diagnosed at $<60y$, only 32% in NH. As for race, most of HI and NH were White (97% vs. 79%), followed by Black (1% vs. 8%). On survival analysis, the survival probability at 2, 5, and 10y of HI vs. NH were (0.507 vs. 0.441), (0.395 vs. 0.322), and (0.237 vs. 0.225), respectively. The median survival time was 2.1y for HI vs. 1.2y for NH. There was an OS difference favoring HI ($p=0.0009$). On multivariate analysis, when adjusted for age, patients with PCNSL between 60-80y and above have 3.4 times more likely to die from disease after diagnosis with HR 3.4 (95% CI: 2.9-4) and 1.7 (95% CI: 1.6-1.9). **Conclusions:** Our study demonstrates statistically longer median survival and OS favoring the HI population. The younger age of diagnosis in HI patients could be a factor in their survival probability for PCNSL, given that both HI and NH received similar treatment and had a similar staging. However, additional studies would be needed to validate this observation and determine other biological or socioeconomic factors that may play a role. Research Sponsor: None.

Survival analysis.

		Hispanics (HI)	Non-Hispanics (NH)
2 years	N-Risk	359	1859
	N Event	412	2646
	Survival	0.507	0.441
5 years	CI	[0.473, 0.542]	[0.426, 0.455]
	N-Risk	175	974
	N Event	66	437
10 years	Survival	0.394	0.322
	CI	[0.359, 0.432]	[0.308, 0.336]
	N-Risk	49	370
	N Event	48	231
	Survival	0.237	0.225
	CI	[0.199, 0.284]	[0.21, 0.24]

10561

Poster Session

Elevated cancer risk among individuals with combinations of cancer-related risk factors: A large claims database analysis. *First Author: Ze Cong, GRAIL, LLC, a subsidiary of Illumina, Inc., currently held separate from Illumina, Inc., under the terms of the Interim Measures Order of the European Commission dated 29 October 2021, Menlo Park, CA*

Background: Besides age, many risk factors have been associated with elevated cancer risk. Understanding cancer incidence rates among patients with single or multiple risk factors can help inform cancer prevention and detection efforts. **Methods:** A retrospective observational analysis was conducted on individuals aged 50-79 in 2020 using Optum's de-identified Clinformatics Data Mart Database which includes Medicare Advantage (MA) (vast majority aged 65+) and commercially insured members (mostly below 65 and employed). Patients with no prior cancer diagnosis (continuously enrolled with no cancer claims for one year) and with cancer risk factors were identified using ICD-10-CM and CPT-4 codes, including autoimmune-related chronic inflammation (diabetes, inflammatory bowel disease, asthma, or rheumatoid arthritis) (INFLAM AUTO); non-autoimmune related chronic inflammation (fatty liver disease, obesity, or cirrhosis/chronic hepatitis B/C) (INFLAM NONAUTO); immunodeficiency (primary or secondary immunodeficiency, HIV, or status post organ transplant); and smoking. Cancer incidence rate ratios (IRR) were calculated by comparing one-year cancer incidence rate among the groups with risk factors versus the general population by insurance type (IRR>1 means elevated risk of cancer). Groups with evidence of any risk factor and combinations of risk factors were assessed. Statistical significance of IRRs was evaluated using logistic regression models adjusting for demographic characteristics. **Results:** Cancer incidence rates of 1.12% and 2.11% were observed among the approximately 1.3 and 2.4 million general population aged 50-79 in commercial and MA plans, respectively. Enrollees with any of the risk factors or combinations analyzed had statistically significantly elevated risk of cancer (IRRs>1.00, p<0.05). Commercially insured groups with highest risk included transplant (IRR=7.68, prevalence=0.02%), immunodeficient and smokers (IRR=3.66, prevalence=0.16%), cirrhosis/chronic hepatitis B/C (IRR=2.61, prevalence=0.41%), INFLAM AUTO and smokers (IRR=2.43, prevalence=3.56%), and smoker (IRR=2.33, prevalence=11.11%). Results in MA were generally consistent with the commercial plan (Table). **Conclusions:** Patients in both commercial and MA plans with any risk factor experienced significantly elevated cancer risk. Cancer prevention and screening strategies can be informed by risk levels among different patient subgroups to optimize resource allocation. Research Sponsor: GRAIL, LLC, a subsidiary of Illumina, Inc. currently held separate from Illumina, Inc. under the terms of the Interim Measures Order of the European Commission dated 29 October 2021.

Prevalence and cancer iRRs by risk factor group (selected).				
	Commercial		MA	
	IRR	Prevalence (%)	IRR	Prevalence (%)
Smoker	2.33	11.11	1.95	37.87
Fatty liver disease	2.30	2.92	1.84	3.47
Cirrhosis/Hepatitis B/C	2.61	0.41	2.01	1.66
Transplant	7.68	0.02	3.24	0.02
INFLAM AUTO AND Smoker	2.43	3.56	1.95	9.50
INFLAM NONAUTO AND Smoker	2.31	3.56	1.87	6.77
Immunodeficiency AND Smoker	3.66	0.16	2.19	0.41

10563

Poster Session

Assessing disparities in lung cancer screening eligibility among high-risk individuals. *First Author: Abdi Gudina, University of Rochester Medical Center, Rochester, NY*

Background: Low-dose computerized tomography (LDCT) scanning confers a 20% reduction in lung cancer mortality by diagnosing the disease at earlier, more treatable stages. Racial/ethnic minorities have historically been less likely to be eligible for lung cancer screening. In 2021, the U.S. Preventive Services Task Force (USPSTF) updated its 2013 guideline for lung cancer screening eligibility by reducing the minimum age (55 to 50) and decreasing the cumulative number of cigarette pack-years smoked (30 to 20). The purpose of this study was to assess if the updated guideline will mitigate disparities in lung cancer screening eligibility among high-risk individuals. **Methods:** Data were obtained from the Behavioral Risk Factor Surveillance System (2017-2019), a population-based survey administered annually by the Centers for Disease Control and Prevention. Only subjects with complete information on the variables used to determine eligibility (age, smoking status, age at first start smoking, age at last smoked, average number of cigarettes smoked each day) (n = 793,537) were included in the final analysis. Logistic regression was used to model the association between predictors and 2021 vs. 2013 lung cancer screening eligibility. **Results:** Based on the 2013 guideline, Non-Hispanic Blacks (OR: 0.34; 95%CI: 0.31 - 0.38), Hispanics (OR: 0.12; 95%CI: 0.10 - 0.14), and other racial/ethnic minorities (OR: 0.59; 95%CI: 0.54 - 0.64) were less likely to be eligible for lung cancer screening than Non-Hispanic Whites. Using the 2021 guideline, Non-Hispanic Blacks (OR: 0.45; 95%CI: 0.42 - 0.49), Hispanics (OR: 0.15; 95%CI: 0.13 - 0.16), and other racial/ethnic minorities (OR: 0.63; 95%CI: 0.58 - 0.67) remain less likely to be eligible for lung cancer screening than Non-Hispanic Whites. **Conclusions:** The 2021 guideline slightly reduces racial/ethnic disparities in lung cancer screening eligibility. Further efforts should be made to develop a guideline that better addresses disparities in lung cancer screening eligibility to reduce lung cancer deaths in racial minorities. Research Sponsor: NCI T32.

10562

Poster Session

Modeling genetic testing (GT) attitudes in a socio-demographically diverse cohort of patients (pts) with cancer: The importance of race/ethnicity and medical mistrust (MM). *First Author: Michael J. Hall, Fox Chase Cancer Center, Philadelphia, PA*

Background: Germline GT and tumor genomics are relevant to the care of nearly every cancer pt. These tests inform treatment planning by NGS-based tumor genomic profiling (TGP) and hereditary risk assessment. Socioeconomic and race-based disparities in GT are well-known, but the impact of growing MM, fueled by political polarization and social unrest due to overt and institutional racism, has been less studied. In previous research of African American (AA) cancer pts, we identified a consistent association of high levels of MM with negative attitudes toward GT. To inform development of an intervention to support informed decisions about GT in cancer pts, we further characterized the relationship of MM to GT attitudes. **Methods:** Pts from two Fox Chase Cancer Center (FCCC) sites were recruited (6/2022-12/2022) to complete a cross-sectional survey (n=105, Burholme campus; n=95, Temple University Hospital). A stratified purposive sampling method was employed. Data on pt demographics and disease factors were collected. MM was queried with two validated measures: LaVeist MM Index (MMI: range 0-10, measures healthcare/institution MM) and Thompson Group Based MM Scale (GBMMS: range 1-5, measures race/ethnicity specific MM; suspicion, discrimination, and lack of support subscales). Attitudes toward GT (GTpros=6 items/GTcons=11 items) were measured w/a validated scale (Morren: range 0-10) plus 4 items developed by our team. The study was approved by the FCCC IRB 22-8003. **Results:** Median age of pts was 62 yrs (range 25-91); 62% were female, 47% AA, 15% Hispanic, 42% married, 47% ≤high school grad, 52% had household income ≤\$50K/yr. Mean GBMMS was 2.11 (SD 0.80) and mean MMI was 4.63 (SD 1.54). Mean of GTpros was 8.77 (SD 1.68); GTcons 4.16 (SD 2.32). MM was associated with race/ethnicity by GBMMS (p<0.001) and MMI (p<0.04), as were GBMMS subscales (suspicion, discrimination, lack of support, all p<0.001). Race/ethnicity was not associated w/GTpros (p=0.59) but was w/GTcons (p<0.001). In univariate models both GTpros and GTcons were associated with GBMMS (p=0.005 and p<0.001, respectively) and MMI (p=0.002 and p<0.001, respectively). In a multivariable model examining GTcons, GBMMS score remained significant (p<0.001) even when controlling for race (p<0.01) and an interaction btw race*-mistrust. A similar model showed MMI score also remained significant (p=0.04) when controlling for race and interaction effects. Only the GBMMS suspicion subscale remained significant (p<0.02) in a model with both race and an interaction term. **Conclusions:** MM is markedly more common among racial/ethnic minority cancer pts, but the relationship btw MM and GT attitudes is only partially rooted in race/ethnicity. Oncologists considering germline GT or tumor genomics for pts, and efforts to support informed decision-making, must consider the pervasiveness of MM. Research Sponsor: U.S. National Institutes of Health; ECOG ACRIN.

10565

Poster Session

Patient-level factors associated with the use of active surveillance: The talking about prostate cancer cohort. *First Author: Nita Mukand, Department of Epidemiology and Biostatistics, University of California San Francisco, San Francisco, CA*

Background: Talking About Prostate Cancer is a population-based cohort study on multilevel determinants of active surveillance (AS) and patient reported outcomes in a racially and ethnically diverse population of men with low-risk prostate cancer. The study includes qualitative one-on-one interviews with patients and physicians, and quantitative cross-sectional provider and longitudinal (baseline and 12-month follow-up) patient surveys to address gaps in the literature regarding patient-level factors associated with AS, particularly among understudied populations including Asian American and Hispanic patients, we assessed socio-demographic characteristics associated with receipt of AS. **Methods:** Men aged 40-79 diagnosed with low-risk prostate cancer from May 2018 through March 2022 were identified within 12 months of diagnosis from the population-based Greater Bay Area Cancer Registry. To expand recruitment, men were also identified from the cancer registries covering the rest of California. To ensure sufficient representation of diverse racial and ethnic groups, 20% of non-Hispanic White men were sampled, while all Asian American and Pacific Islander, Black, and Hispanic men were invited to participate. Univariable and multivariable logistic regression were used to estimate the odds ratios (OR), adjusted odds ratios (aOR), and 95% confidence intervals (CI), of receiving AS. Potential predictors included year of diagnosis, age, health insurance, usual source of care, race and ethnicity, educational attainment, employment, nativity, and language preference. **Results:** Among 500 men with low-risk prostate cancer, 27% went on AS, 30% underwent surgery, radiation, hormonal treatment, cryotherapy, and/or high-intensity focused ultrasound, and 43% had not yet made a treatment decision at baseline. Among those who had made a treatment decision at baseline (N = 287), 27% of Hispanic men received AS, which was the lowest proportion among the racial and ethnic groups (Black 28%; Asian 47%; White 59%). A higher proportion of coupled men (29%) received AS compared to single men (15%). Less than half of men with less than a high school education received AS. Compared to men with a high school education or less, men with a bachelor's degree had an aOR of 2.91 (95% CI 1.10 - 8.42) and men with a graduate degree had an aOR of 4.37 (95% CI 1.50-12.76) of receiving AS. A significantly lower odds of AS was identified among Black (aOR 0.26; 95% CI 0.11-0.64) and Hispanic men (aOR 0.35; 95% CI 0.15 - 0.81) compared to non-Hispanic White men. **Conclusions:** We identified several significant socio-demographic differences between patients who received definitive treatment versus AS in this cohort, including race and ethnicity and educational attainment. Further study of these domains in larger, diverse samples will elucidate the strength of these associations within racial and ethnic groups. Research Sponsor: U.S. National Institutes of Health.

10566

Poster Session

Colorectal cancer and digital/live screening navigation: Promoting prevention through personalized recommendations and access. *First Author: Kim Newcomer, Colorectal Cancer Alliance, Washington, DC*

Background: This project evaluates the effectiveness of an advocacy organization-led digital and live navigation framework aimed at colorectal cancer (CRC) screening completion. The Colorectal Cancer Alliance's screening quiz guides patients to a clinically valid, personalized CRC screening recommendation with a handoff to live navigation for those at risk. The framework utilizes digital innovation, targeted awareness, and financial support to support populations experiencing the greatest disparities and increase screening intention, behavior, and further health equity in colorectal cancer. This simple intervention is critical due to existing research consistently indicating on-time screening for CRC leads to favorable outcomes. **Methods:** In July 2022, the Alliance launched an enhanced quiz to improve the CRC screening navigation experience and increase engagement. The new survey instrument was restructured to streamline time to completion while preserving clinically accurate risk stratification. The follow-up navigation protocol was reordered from digital-first to live-first to leverage high-touch strategies earlier in the screening journey and dynamic content was added to the recommendation page to create a more personalized resource. The Alliance also deployed social media and influencer campaigns to increase outreach to at-risk communities. **Results:** The enhanced quiz delivered over 8,300 CRC screening recommendations and improved the average monthly completion rate (33%) and contact capture rate (14.4%) compared to the previous quiz in 2022 (24%; 8%). The median age of respondents was 55, and 37.2% of the respondents were between the ages of 45 and 64. Of the respondents, 26.7% were male and 73.3% were female. The majority were White (77.1%), 7.3% identified as Black/African American, 5.5% were Hispanic or Latino, and 3% were Asian. Most respondents were symptomatic (67.8%) but 8.1% were asymptomatic high-risk. Respondents (1,078) were triaged to live Alliance patient navigation. **Conclusions:** This digital and live navigation framework may serve as a strong solution in driving colorectal cancer screening and supporting shared-decision making conversations compared to other available interventions. The framework provides users with robust access to live navigation, educational resources, and support services for CRC screening and diagnosis. The Alliance is uniquely positioned to utilize its communications channels, social media and influencer campaigns to reach at-risk communities with credibility. Data attributed to specific campaigns are still being analyzed, and the Alliance will continue to optimize its navigation protocol and awareness efforts as quality improvement processes allow for a deeper understanding of more inclusive and impactful navigation experiences to close screening gaps among at-risk populations. Research Sponsor: None.

10568

Poster Session

Navigation program for LDCT lung cancer screening implementation: A quality initiative. *First Author: Jasmine Shrestha, Mercy Clinic, Fort Smith, AR*

Background: Lung cancer remains the leading cause of cancer-related death worldwide. Despite recommendations from experts, the lung cancer screening has not been well adopted in practice. **Methods:** We started a pilot program in our cancer center in collaboration with Pulmonary medicine in November 2021 as we identified that the rates of Low Dose CT scan (LDCT) are meager in our community. Two areas that needed attention were identified. The first was the need for shared decision-making by the primary care physician (PCP) before ordering LDCT. The second was the follow-up for patients with positive lung nodules. A lung nodule patient navigator was assigned exclusively for this initiative. Reports were obtained from EPIC every month to identify patients who fit the criteria. PCPs of the respective patients were then reminded to discuss LDCT in the upcoming visit. The lung nodule navigator then followed the ordering and test results of LDCT. A dedicated lung nodule conference discussed all patients with positive lung nodules. Follow-up interventions included referrals to pulmonology, interventional radiology, or further imaging with PET scan. Per guidelines, patients who did not need acute intervention were kept on track for their follow-up CT as recommended. **Results:** We reviewed our baseline performance in LDCT from January to June 2021. The total screening included 271(32%) patients compared to 836 eligible patients who fit the criteria. From January 2022 to June 2022, out of 749 eligible patients who were expected to meet their PCP, 574(76%) patients received LDCT. Of the patients screened, 436(75%) had their baseline CT chest, with the remaining patients having follow-up CT. Fifteen patients had findings needing immediate intervention. **Conclusions:** The USPSTF has updated its annual lung cancer screening guidelines with LDCT for adults aged 50 to 80 years who have a 20-pack-year smoking history and current smoker or have quit within the past 15 years. With our approach, the screening rates have more than doubled compared to previous year. LDCT does carry certain risks, including false positive results and unnecessary biopsies; hence shared decision-making is needed before ordering the test. We identified the shared decision process as the rate limiting step across our institution. Our contact with PCP was a significant intervention that improved the screening. The second obstacle was the follow-up for positive LDCT, and we alleviated it with the multidisciplinary lung nodule conference. This process is undoubtedly difficult to achieve without a lung nodule navigator. Each hospital system is unique and has various difficulties implementing screening guidelines. We show that, with the help of a lung nodule navigator, the rates of lung cancer screening can be significantly increased. Research Sponsor: None.

10567

Poster Session

The impact of extending CRC screening to the older population: Results from CRC-AIM microsimulation model. *First Author: Derek W. Ebner, Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN*

Background: Average-risk screening for colorectal cancer (CRC) is effective and recommended. The U.S. Preventive Services Task Force issued grade A and B recommendations for screening ages 50-75 and 45-49, respectively, however the recommendation for the older population (ages 76-85) is grade C (moderate certainty that the net benefit is small). With emerging blood-based CRC screening, we evaluated the benefits of screening the older population with continued multi-target stool DNA (mt-sDNA) or FIT strategies and/or with a modality shift to blood-based tests after age 75. **Methods:** Using the validated CRC-AIM microsimulation model, triennial mt-sDNA and annual FIT screening (ages 45-75) followed by four strategies for ages 76-85 (no screening, continued mt-sDNA/FIT, or a modality shift to blood-based screening using either CMS criteria [CMS] or recently reported blood test data from the ECLIPSE study¹ [BT; Guardant Health, Inc.]) were considered. For CMS criteria and BT, CRC sensitivity were set at 74% and 83%; and adenoma sensitivity was set to 20%, and 13%; and CRC specificity was set to 90% for both tests. Real-world (RWE) adherence for initial screening was set to 80% (CMS, BT), 65.6% (mt-sDNA), and 42.6% (FIT). Adherence for follow-up colonoscopy was set to 72.1% (mt-sDNA, CMS, BT) and 46.0% (FIT). **Results:** Screening among the population aged 45-85 resulted in 281 life years gained (LYG) with continued mt-sDNA as compared to 193 with continued FIT. Furthermore, mt-sDNA reduced CRC mortality by 70% as compared to 49% by FIT (Table). When screening modality was shifted to CMS (76-85 year olds), mt-sDNA/CMS resulted in 279 LYG as compared to 196 for FIT/CMS. CRC incidence was reduced by 59% (mt-sDNA/CMS) as compared to 38% (FIT/CMS), and mortality declined by 69% (mt-sDNA/CMS) as compared to 51% (FIT/CMS). Reductions in disease burden were lower when modality was switched to BT after age 75 due to reduced test performance. **Conclusions:** Extending CRC screening to the older population with continued mt-sDNA demonstrated the best health outcomes compared to other modalities. A modality shift after age 75 to blood-based testing resulted in greater LYG as compared to no screening, with performance at CMS criteria yielding better results than BT. Therefore, despite inferior performance, blood-based tests may offer a CRC screening option for older patients who are unable to complete stool testing. Research Sponsor: Exact Sciences Corporation.

Outcomes for patients by screening modality.

Modality (Ages 45-75)	Modality (Ages 76-85)	LYG*	Incidence Reduction	Mortality Reduction
mt-sDNA	No screening	270	57%	65%
mt-sDNA	mt-sDNA	281	60%	70%
mt-sDNA	CMS Blood	279	59%	69%
mt-sDNA	BT	279	58%	69%
FIT	No screening	180	35%	43%
FIT	FIT	193	37%	49%
FIT	CMS Blood	196	38%	51%
FIT	BT	195	36%	50%

LYG: life-years gained; COL: colonoscopy; CMS Blood: Center for Medicare Services recommended blood-test; BT: trial performance blood-based test. *Per 1000 individuals¹ ECLIPSE study.

10569

Poster Session

The probability of lung cancer in patients with incidentally detected pulmonary nodules detected via low-dose computed tomography screening in China. *First Author: Guo Lan-Wei, The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, Zhengzhou, China*

Background: Low dose computed tomography (LDCT) screening has been proven to be effective in reducing lung cancer mortality, but the ensuing high false-positive and overdiagnosis rates shackle the effectiveness of lung cancer screening (LCS) in China. Nodule malignancy prediction models may be an applicable solution. **Methods:** We developed and internally validated the model using data from the ongoing Henan province Cancer Screening Program in Urban China (CanSPUC). From 2013 to 2021, 23031 heavy smokers underwent baseline screening with LDCT; 2553 participants were diagnosed with pulmonary nodules. Detailed questionnaire, physical assessment and follow-up were completed for all participants. We then externally validated the model using the National Lung Screening Trial (NLST) dataset consisting of 10485 lung nodules in 4660 participants. Multivariable Cox proportional risk regression models were used. Data analysis was performed from July 1, 2022, through December 31, 2022. **Results:** A total of 111 and 1089 lung cancer cases with a median follow-up duration of 3.7 years occurred in the Henan CanSPUC and NLST study, respectively. Age, gender, physical activity, consumption of pickled food, history of silicosis or pneumoconiosis, nodule type, size, calcification, and pleural retraction sign were included into the model. The AUC (95% CI) of the model for 5-year lung cancer risk was 0.857 (0.801, 0.914) and 0.847 (0.829, 0.881) in the training set and validation set, respectively. Compared with Mayo model, VA model, PKU model, and Brock model, the Henan CanSPUC model yield statistically better discriminatory performance (all *P* values < 0.05). The model calibrated well across the deciles of predicted risk in both the overall population and all subgroups. **Conclusions:** The model developed and validated in this study may be used to estimate the probability of lung cancer in nodules detected at baseline LDCT, allowing more efficient risk-adapted follow-up in population-based LCS programs. Research Sponsor: None.

10570

Poster Session

10571

Poster Session

LungFlag, a machine-learning (ML) personalized tool for assessing lung cancer risk in a community setting, to evaluate performance in flagging non-small cell lung cancer (NSCLC) regardless of sex or race. *First Author: David Morgenstern, Roche Diagnostics, Indianapolis, IN*

Background: Application of ML-based risk prediction models to lung cancer screening cohorts have been shown to increase screening efficiency. However, ML-based models may be vulnerable to sexual and racial bias arising from historical bias in health care access as well as biased training data. Demonstrating fairness in the predictions of ML-based models is a prerequisite to their acceptance by clinicians and patients. We assessed the clinical performance of LungFlag based on sex and race, two key demographic subgroups at risk for disparate outcomes due to bias. **Methods:** The LungFlag machine learning model is a retrospectively validated ML model intended to identify individuals who are at elevated risk for lung cancer and should be counseled regarding lung cancer screening. LungFlag uses existing routine outpatient lab measurements, smoking history, comorbidities, and demographic data to flag high-risk individuals. We compare performance of LungFlag between sexes and between races and calculate the sensitivity at the overall positivity rate of 3%. We chose a case-control design based on a large US-based community and outpatient dataset including 39,135 case patients with NSCLC and 212,454 contemporaneous NSCLC-free controls. We included ever-smokers, ages 45-80, with available lab measurements from 3-12 months before diagnosis, and minimal follow-up of 24 months. Sub-populations with less than 1% representation from the total population were excluded. **Results:** The comparison between the sub-populations presented by sensitivity and specificity indexes is detailed in the table. No statistically significant difference was demonstrated in the sensitivity of the model to flag individuals that were diagnosed with NSCLC on multiple sub-populations. **Conclusions:** The LungFlag model demonstrated fairness with respect to sex and race based on similar clinical sensitivity in a large, community-based retrospective dataset. Further assessment in prospective studies and in additional racial sub-populations is recommended to support this conclusion. Research Sponsor: Roche Diagnostics.

Demographic Parameter	Sub-Population	N Cases	N Controls	Specificity @ 3% Positivity Rate (95% CI)	Sensitivity @ 3% Positivity Rate (95% CI)	Odds Ratio @ 3% Positivity Rate (95% CI)
Sex	Female	19,555	112,720	97.2 [97.1 - 97.3]	23.1 [22.6 - 23.7]	10.4 [9.8 - 11.2]
	Male	19,580	99,734	96.8 [96.7 - 96.9]	23.4 [22.8 - 24.0]	9.2 [8.7 - 9.9]
Race	White	33,724	179,387	96.9 [96.8 - 97.0]	23.5 [23.1 - 24.0]	9.6 [9.1 - 10.2]
	Black	4,058	19,554	97.1 [96.8 - 97.3]	23.7 [22.5 - 25.0]	10.4 [8.8 - 12.0]

10573

Poster Session

Rates of routine cancer screening compared with pre-pandemic levels. *First Author: Allison H Oakes, Trilliant Health, Brentwood, TN*

Background: The COVID-19 pandemic caused significant disruptions to health-care delivery in the US due to mandatory stay-at-home orders and patient fears about visiting healthcare facilities. A logical consequence, many forms of healthcare use, including cancer screenings, sharply decreased in early 2020. Early studies suggest that cancer screening rebounded through the summer of 2020; however, > 2 years removed from the start of the pandemic, the long-term impact of missed screenings is unknown. The objective of this study was to examine trends in breast, cervical, and colorectal cancer screening from 2017-2022. **Methods:** This cross-sectional study used the Trilliant Health national all-payer claims database to analyze calendar year quarterly medical claims from Q1 2017- Q2 2022. We limited the study sample to those aged 21-85, the guideline-concordant target populations for the screening procedures. For breast and cervical cancer, we limited our sample to women. Using Current Procedural Terminology (CPT) codes, we calculated the quarterly number of individuals, per 100,000 eligible beneficiaries, who received screening for breast cancer, cervical cancer, and colorectal cancer. Percentage change in screening tests was compared. **Results:** In total, the analysis included > 300M unique individuals. For breast cancer, the median quarterly rate of pre-pandemic screening mammography was 8013 per 100k beneficiaries, which declined to 4,884 in Q2 of 2020—a 39% decrease. Screening mammography rebounded to pre-pandemic levels by Q3 and Q4 of 2020 but declined to a median rate of 7,314 per 100,000 beneficiaries in Q2 2022, with quarterly deficits ranging from 4-16%. For cervical cancer, the median quarterly rate of pre-pandemic screening was 5,469 per 100k beneficiaries. The rate of cervical cancer screening fell to 3,550 in Q2 of 2020—a 35% decline. By Q3 2020, cervical cancer screening rebounded toward the pre-pandemic median, then progressively declined to 4,557 per 100k beneficiaries by Q2 2022. Over the same time period, colorectal cancer screening decreased from a pre-pandemic median of 3,111 per 100k beneficiaries to 1,731 in Q2 of 2020—a 44% difference. From Q3 2020 to Q1 2022, the quarterly colorectal cancer screening rate remained 10-17% below pre-pandemic levels, but returned to 3,047 per 100k in Q2 2022, only 2% below the pre-pandemic median. **Conclusions:** Across the three studied cancer types, population-based screening remains below pre-pandemic levels. In agreement with other research, we find that screening quickly rebounded following the initial stages of the pandemic; however, the longer follow-up time reveals that gaps in preventive cancer screening returned and worsened. Underutilization of recommended cancer screenings will likely result in an increase in later-stage initial diagnoses and excess mortality from cancer in the future. Research Sponsor: Trilliant Health.

Assessing the risk of gastrointestinal cancers among cannabis users compared to nicotine users. *First Author: Shanawar Ali Waris, West Virginia University School of Medicine, Morgantown, WV*

Background: Exposure to nicotine is a well-studied preventable cause of numerous malignancies, while the association of cannabis use with the development of cancer is not clear. Cannabis contains both carcinogens as well as compounds with anti-tumor activity, which inhibit chronic inflammation. The aim of this study is to assess the risk of gastrointestinal malignancy in cannabis users compared to nicotine users. **Methods:** A retrospective cohort study was conducted using TriNetX, a federated database of ~100 million patient records. Adult patients (≥18 years) were queried by ICD-10 coding to find variables of interest. Two groups were created: one group with a history of only cannabis use and the other with a history of only nicotine use. Then lifetime risk of nine different gastrointestinal cancers were assessed and compared between the two groups. 1:1 propensity score matching was conducted, adjusting for comorbidities and demographics, to calculate adjusted risk ratios (aRR) with 95% Confidence Interval for the comparative analysis. **Results:** A matched cohort of 413,628 patients revealed that cannabis only patients had a significantly lower lifetime risk of developing esophageal cancer (aRR[95%CI]): (0.456 [0.364,0.572]), gastric cancer (0.492[0.41, 0.60]), pancreatic cancer (0.547 [0.47,0.64]), liver & intrahepatic bile ducts cancer: (0.728[0.70,0.75]), colon cancer (0.351[0.32,0.38]), rectosigmoid cancer (0.699[0.59,0.83]), and rectal cancer (0.563[0.46,0.68]). No significant differences were seen for small intestinal cancer (1.21[0.88,1.6]) and anal cancer (0.87[0.67,1.14]). **Conclusions:** The results of this study suggest that the lifetime risk of developing numerous gastrointestinal malignancies is lower in cannabis users when compared to nicotine users. It is not clear if this relative risk reduction is due to the beneficial effects of cannabis or a lack of nicotine consumption and its associated effect on carcinogenesis. Long-term studies following cannabis users may provide a better understanding of the association of cannabis use with the risk of developing various malignancies. Additionally, the quantity of exposure to cannabis and its association with the risk of cancer should be further investigated. Research Sponsor: None.

	Unadjusted Risk Ratio [95% CI]	Adjusted Risk Ratio [95% CI]
Esophageal Cancer	0.204[0.17,0.25]	0.456[0.364,0.572]
Gastric Cancer	0.278[0.23,0.33]	0.492[0.41, 0.60]
Pancreatic Cancer	0.269[0.24,0.30]	0.547[0.47,0.64]
Liver & Intrahepatic Bile Duct Cancer	0.531[0.52,0.54]	0.728[0.70,0.75]
Small Intestinal Cancer	0.522[0.42,0.64]	1.21[0.88,1.6]
Colon Cancer	0.214[0.19,0.23]	0.351[0.32,0.38]
Rectosigmoid Cancer	0.336[0.29,0.38]	0.699[0.59,0.83]
Rectal Cancer	0.286[0.24,0.33]	0.563[0.46,0.68]
Anal Cancer	0.409[0.33,0.50]	0.87[0.67,1.14]

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Poster Session

Incidence, landscape and survival outcome of de novo malignancy after double lung transplantation. *First Author: Liam II-Young Chung, Northwestern University Feinberg School of Medicine, Chicago, IL*

Background: Organ transplant recipients are at greater risk of developing malignancies due to their immunosuppressive management. However, the incidence of post-transplant malignancy after double lung transplantation (DLT) has not been studied. This study investigated the incidence, trends, and most common types of post-transplant malignancy following DLT. **Methods:** Data extracted from the Organ Procurement Transplantation Network (OPTN) registry after DLT for non-cancerous disease. We evaluated the incidence of post-transplant malignancy, and assessed the annual and cumulative risk of each malignancy after DLT. And the overall survival (OS) of recipients with or without post-transplant malignancy was analyzed by Kaplan-Meire survival method. **Results:** A total of 23,935 cases were identified and analyzed from the OPTN database (13,768; 57.5% male, 10,167; 42.5% female). 5,629 cases (23.5%) were found to have post-transplant malignancy and 18,306 cases (76.5%) had no post-transplant malignancy. Among patients with post-transplant malignancy 3,785 (67.2%) were male and 1844 (32.8%) were female. Those with post-transplant malignancy had a longer OS compared to those without post-transplant malignancy (P < 0.001). While the median OS was 97.2 months and 5-year survival rate was 83.6% in recipients with post-transplant malignancy, the median OS was 36.7 months and 5-year survival rate was 67.3% in For those without post-transplant malignancy. The risk for post-transplant malignancy was greatest during the first 3-5 years post-transplantation. The most common types of post-transplant malignancies were squamous cell skin cancer (n = 2711, 48.2%), basal cell skin cancer (n = 965, 17.1%), lymphoma (n = 570, 10.1%), lung cancer (n = 187, 3.3%), colorectal cancer (n = 184, 3.3%). **Conclusions:** The lifetime incidence of post-transplant malignancy following DLT was identified to be 20.1% and those with post-transplant malignancy had a longer OS compared to those without post-transplant malignancy. Further studies are needed to investigate the underlying mechanism for the increased risk of malignancy following DLT and its association with OS. Research Sponsor: None.

10575

Poster Session

Enhancing lung cancer screening through 'Saved by the Scan': Lessons from a multipronged public service advertising program. *First Author: Shreyas S Bellur, Miami Cancer Institute, Baptist Health South Florida, Miami, FL*

Background: Lung cancer screening rates remain low across the US in populations recommended for screening by low-dose CT (LDCT). Screening rates further declined during the COVID-19 pandemic, particularly in high-risk populations including racial and ethnic minorities. The American Lung Association (ALA) launched a nationwide public service advertising (PSA) program called 'Saved by the Scan' to enhance lung cancer screening rates, for which Baptist Health South Florida (BHSF) became the first healthcare system partner. The following work describes this major PSA effort in South Florida to enhance lung cancer screening, and the lessons learned thereof. **Methods:** A multipronged, institutionally-driven public awareness program, in collaboration with ALA, was initiated in 2021 by BHSF, the largest healthcare organization in the region, and was targeted towards South Florida residents. This innovative multimedia effort used traditional communication modalities, including newspapers, billboards, etc., along with digital modalities, including email and social media, to increase lung cancer screening awareness in both English and Spanish in a locally-adapted manner. Key performance indicators (KPIs), reach, and impact of the program were tracked. The most successful components, as per KPIs, were identified. Deidentified data of screening LDCT done at BHSF was reviewed to determine all individuals screened during 2019-2021 and descriptive statistics were calculated. **Results:** 4619 individuals from South Florida were screened at BHSF from 2019-2021, 1498 were in 2019, 1193 in 2020, and 1928 in 2021. Screening fell by 20.3% in 2020, likely due to the pandemic, and rose by 61.6% in 2021, helped by the program. Overall, a 21.9% increase from pre-COVID screening rates was seen. In 2022, the total reach of traditional media was estimated to be 4,607,273 individuals. Out of 133,554 emails sent, 36,877 (27.2%) were opened, with a click-through rate of 6.4%. Out of 1,768,438 digital impressions, 16,791 (0.9%) had links clicked. The total number of conversions from digital media was estimated to be 337 individuals with 232 (68.9%) from emails and 105 (31.1%) from social media. **Conclusions:** Lung cancer screening can be successfully boosted through large organizational efforts, particularly those targeted to needs of the local population. Digital media approaches for improving public health have seemingly low conversion rates but their large outreach provides a high impact. Efforts are warranted to enroll more healthcare systems and scale the program nationwide. Research Sponsor: None.

10577

Poster Session

Patient navigation for lung cancer screening in an urban safety-net system: A pragmatic randomized clinical trial. *First Author: Sheena Bhalla, University of Texas Southwestern Medical Center, Dallas, TX*

Background: Although low-dose computed tomography (LDCT)-based lung cancer screening (LCS) can decrease lung cancer mortality in high-risk individuals, it may be a complex and time-intensive process that poses challenges to patients, particularly those from minority, under- and uninsured populations. We conducted a pragmatic randomized controlled trial of telephone-based navigation for LCS within an integrated, urban safety-net healthcare system (Parkland Health, Dallas, Texas). **Methods:** Patients eligible for LCS based on United States Preventive Services Task Force 2013 Guidelines were randomized (1:1) to usual care with or without phone-based navigation. Following a structured protocol, navigators made systemic contact with patients to provide appointment reminders, share information and resources, assess barriers to LCS, and address smoking cessation. The primary endpoint was completion of the first three consecutive steps (eg, 3 annual LDCTs or LDCT, other imaging, biopsy) in a patient's LCS process. We also explored differences in completion of LCS steps in navigation and usual care groups according to patient characteristics using chi-square test. **Results:** Patients (n=447) were randomized to phone-based navigation (n=225) or usual care (n=222) between February 2017 and February 2019. Mean patient age was 62 years, 46% were female, and 69% were racial-ethnic minorities. There was no significant difference in completion of the first three steps of the LCS algorithm (12 vs. 9%; $P=0.3$) between arms. Completion of LCS steps was not impacted by navigation among different subgroups, including age (<65 vs. ≥65 years), gender (male vs. female), race/ethnicity (non-hispanic white vs. racial minorities), and comorbidity status (Charlson Comorbidity Index <5 vs. ≥5). A key reason for step non-completion was lack of order placement. In the navigation arm, 368 of expected 675 steps (55%) were ordered, and in the usual care arm, 344 of expected 666 steps (52%) were ordered. Despite low three-step completion rates overall, the majority (>75%) of LCS algorithm steps were completed when ordered by their clinical team (Table). In exploratory univariable analysis, completion rates for ordered steps were 86% for navigation and 79% for usual care ($P=0.03$). **Conclusions:** In this study, lack of order placement was a key reason for incomplete LCS steps. When orders were placed, navigated patients had higher rates of completion. Clinical team education and enhanced EHR processes to simplify order placement, coupled with patient navigation, may increase LCS uptake and completion in safety-net healthcare systems. Clinical trial information: NCT02758054. Research Sponsor: Cancer Prevention Research Institute of Texas.

Status of LCS steps	Steps ordered in the navigation cohort (%) n=368	Steps ordered in the usual care cohort (%) n=344	P value
Completed	315 (86)	273 (79)	0.03
Not completed	53 (14)	71 (21)	

10576

Poster Session

A multivariate analysis of low-dose CT lung cancer screening in a Michigan community hospital network. *First Author: Jason Law, Michigan State University, Lansing, MI*

Background: Lung cancer is the leading cause of cancer deaths in the United States. The USPSTF recommended screening for lung cancer with low-dose chest computer tomography (LDCT) in 2013. This was based on the National Lung Screening Trial (NLST) which showed a 20% relative reduction in mortality from LDCT compared with chest radiography in high-risk individuals. The major NLST eligibility criteria were age 55-74, a 30 + pack year smoking history and current smoking status or having quit in the last 15 years. The impact of other risk factors on screening results besides inclusion criteria is unknown. We sought to identify other factors for the risk of lung cancer detection in screened individuals. **Methods:** This was a retrospective cohort study employing a Michigan based McLaren Hospital Network Lung Cancer Screening Program (LCSPP) database from 2015-2022. Participant eligibility in screening was the USPSTF criteria except for an age range of 50-80. Analyses were stratified by BMI, smoking pack-years, insurance status, smoking status, sex, other CT findings, pre- vs. during COVID pandemic (before and after January 2020). Multivariate logistic regression analysis was used for odds ratios (OR) with 95% confidence intervals (CI) as estimates of the relative risk of an elevated Lung-RADS category ≥3 (high risk of detecting lung cancer). **Results:** A total of 2638 subjects, 49.91% females, 50.09% males, mean BMI 29.50 ± 7.17 (SD), pack-years 44.52 ± 18.29, Medicaid 6.66%, Medicare 32.01%, Private Insurance 57.62%, Self-pay/unknown 3.71%. Current smoker 65.49%, Former smoker 34.51%, other CT findings 51.99%, pre-COVID 46.08%, during COVID pandemic 53.92%. Lung-RADS category 0 (0.04%), 1 (35.33%), 2, (50.61%), 3 (6.56%), 4a (4.85%), 4b (1.55%), 4x (1.06%). A statistically significant association with a Lung-RADS category ≥3 was found with lower BMI, OR=0.980 (95% CI, 0.969-0.991), $p=0.0005$, and female gender, OR=1.232 (95% CI, 1.039-1.462), $p=0.0166$ (Table). **Conclusions:** In our study cohort a lower-than-average BMI and also female gender were statistically correlated with an elevated Lung-RADS category ≥3. These findings might be incorporated into a risk stratification model, however further larger studies are needed to validate our findings. Research Sponsor: None.

Multivariate logistic regression predicting Lung-RADS ≥3 among all patients (n=2,638). Odds Ratio Estimates				
Effect	Point Estimate	95% Wald Confidence Limits		P-values
BMI, below vs above mean	0.980	0.969	0.991	0.0005
Smoking pack-years	0.999	0.995	1.004	0.7867
Insurance, Medicare vs Medicaid	1.016	0.721	1.434	0.9258
Insurance, Private vs Medicaid	1.167	0.837	1.627	0.3633
Insurance, Unknown/Self-pay vs Medicaid	0.862	0.515	1.444	0.5738
Smoking status, Current vs Former	1.178	0.993	1.397	0.0602
Sex, Female vs Male	1.232	1.039	1.462	0.0166
Other CT findings, No vs Yes	1.375	0.962	1.965	0.0802
After Jan 2020 vs Before Jan 2020	1.413	0.980	2.038	0.0643

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Poster Session

Long-term clinical and psychosocial outcomes of surveillance in Li Fraumeni syndrome. *First Author: Milita Zaheed, Garvan Institute of Medical Research, Darlinghurst, Australia*

Background: Li Fraumeni Syndrome (LFS) is a high penetrance multi-organ cancer predisposition syndrome, associated with a significant lifetime risk of developing cancer. The Surveillance study in Multi-Organ Cancer prone syndromes (SMOC+) is investigating the utility of annual surveillance, with inclusion of whole-body magnetic resonance imaging (WBMRI), for hereditary cancer syndromes without well-established risk management strategies. Here we report the long-term clinical and psychosocial outcome of surveillance in participants with LFS. **Methods:** Multimodality surveillance in this multi-centre, prospective, longitudinal, observational study for adult participants with LFS included annual clinic review and examination, WBMRI, breast MRI (MRIB), full blood count, prostate specific antigen; 2-5 yearly gastro-intestinal endoscopy and faecal occult blood test in intervening years. Quantitative psychometric evaluations were requested at regular intervals each year using Hospital Anxiety and Depression Scale (HADS), the Impact of Events scale anchored to cancer (IES-C), and the Impact of Events scale MRI (IES-MRI). **Results:** From July 2013 to December 2021, 132 (67% female) participants were enrolled at a median age of 36 (range 18-69) years. There were 116 prior diagnoses of neoplasms among 68 (52%) participants, including 27 (20%) with multiple primaries. At a median follow up of 4 years, 46 new primary malignancies were diagnosed in 30 (23%) individuals, with median age at diagnosis of 43 (range 24-71 years). Four (3%) individuals developed recurrence of a prior malignancy. The malignancies were detected as a result of WBMRI (27), MRIB (7), gastroscopy (1), colonoscopy (1) and clinical review and examination (17). The most frequent new primaries were leiomyosarcoma and breast cancer (Table). Overall, 22 (17%) are not currently participating due to cancer related death (10), active cancer (6) or other life events (6). At 4 years after enrollment, 94, 80 and 50 participants completed at least one HADS (463 unique observations), IES-C (362 unique observations), and IES-MRI (268 unique observations) questionnaire, respectively. Controlling for demographic and cancer history variables, there was no evidence of changes in overall anxiety or depression ($p=0.2$), nor in degrees of distress associated with cancer ($p=0.06$) or WBMRI ($p=0.6$) over time. **Conclusions:** In LFS, annual surveillance with WBMRI is feasible and well tolerated, with no difference in distress experienced in the longer term. Over 80% of participants continue to engage with surveillance. The majority of cancer-affected individuals were able to resume surveillance after management of early disease. Research Sponsor: NSW Office of Health and Medical Research; Australian Federal Government.

Distribution of malignancies.	New Primary		Recurrence
Leiomyosarcoma	8		1
Breast cancer	7		1
Brain tumours (excluding glioma)	3		1
Glioma	3		0
Lung*	3		0
Melanoma	3		0
Prostate*	3		0
Chondrosarcoma	2		0
Liposarcoma	2		0
Other	12		1

*Adenocarcinoma.

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Poster Session

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Poster Session

Effect of colorectal cancer screening on 1-year mortality and medical costs: Real-world evidence from the largest commercial medical claims database in the US. *First Author: Chi Mai Nguyen, Department of Biostatistics and Health Data Science, Indiana University School of Medicine, Indianapolis, IN*

Background: Colorectal cancer (CRC) is the third leading cause of cancer-related deaths in the United States with increasing trends in both mortality and incidence in individuals under age 50. Whether CRC screening reduces mortality recently becomes controversial in some observational studies due to a lack of data and a possibility of screenings confounded with social determinants of health (SDoH) and patient characteristics that were not properly addressed. **Methods:** We used the Optum's de-identified Clinformatics Data Mart Database that provides information of healthcare plan, major SDoH, the CRC diagnosis, treatments, medical service and prescription charges, and survival data since 2007 for over 75 million patients to re-examine benefits of CRC screenings. Our CRC study cohort (N=99,704) included persons first diagnosed with CRC between 2010 – 2020, with 3-year pre-diagnosis continuing insurance coverage to identify pre-diagnosis screening, and 1-year follow-up to identify death and associated costs. Primary outcomes are 1-year mortality, the post-diagnosis medical and prescription cost increments, and health plan change after CRC diagnosis. Augmented inverse probability weighting (AIPW) models were employed to estimate the benefits of CRC screening, adjusting the probabilities of pre-diagnosis screenings due to insurance cover types (commercial/employer, Medicare advantage, and dual Medicare-Medicaid or low-income subsidy (LIS) covers), and healthcare plans (pre-paid, only-in-network, pay-less in-network, and fee-for-service plans), ages, sex, race, residential states, and calendar year. **Results:** In the study cohort, 37.8% have pre-diagnosis screening records, 18% died within 1 year. Women, persons under age 45, and persons with dual covers were more present in the non-screening group than the screening one. CRC screening was associated with a significant reduction of one-year mortality after adjusting for age, sex, race, health plans, and other factors (death rates in the non-screening group vs the screening one were 23% vs 12%, adjusted OR = 0.57, 95%CI = 0.55 - 0.59). Persons with no screening records experienced higher one-year medical cost increases than those who had pre-diagnosis screenings (17.8% vs 14.8%). No significant difference in health plan changes and/or disruption among the two groups was obvious for persons having either dual- or commercial-cover beneficiaries, yet the screenings slightly induced more these plan changes in the Medicare advantage beneficiaries (OR = 1.06, 95%CI = 1.01 - 1.11). **Conclusions:** The real-world evidence from the US largest medical claims database suggested that, after adjusting for the screening probability due to healthcare plans and other confounders, CRC screening dramatically reduced one-year death risk, and slightly eased the 1-year financial burdens after CRC diagnosis. Research Sponsor: None.

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Poster Session

The role of molecular biomarker CDKN-2A in early diagnosis of colorectal cancer. *First Author: Yakov Ten, National Cancer Center of Uzbekistan, Tashkent, Uzbekistan*

Background: Polyps are considered as obligate precancerous disease. The percentage of malignization ranges from 20% in single polyps to 95% in diffuse polyposis. Current research examines the results of the early diagnosis of colon cancer by using the biomarker CDKN2A for development of molecular-biological methods of prognostication. The correlation with the molecular-biological indicators were studied. It is also planned to develop an effective system for development prognostication of CRC and the formation of "risk groups" for evidence-based counselling for families which are highly predisposed to colorectal cancer. **Methods:** Investigations were carried out in 30 patients during the period 2016-2022, the study included patients with single polyps, multiple polyps, polyposis of the colon, as well as patients without a history of either familial or sporadic cancer. 12 patients had multiple polyps, 9 polyposis and 9 single colon polyps. The levels of methylation of the gene CDKN2A were determined in 10 patients. The material for the isolation of DNA was a serum obtained from venous blood, and biopsy material. DNA extraction was held according to standards. After the conversion of DNA methyl-specific PCR was done. **Results:** Among 30 patients with polyps and polyposis of the colon, serum gene CDKN2A methylated DNA was detected in 10 patients. In 4 patients malignization of the polyp was determined. If patients without malignization surgical intervention was limited with resection of the intestine without lymph dissection. In 20 patients the test result was negative. We did not perform surgical intervention to these patients and they were sent to dynamic observation. Thus, the diagnostic efficacy of detecting colorectal cancer in early diagnosis of by means of methylated DNA of the gene CDKN2A was - 33.3%. **Conclusions:** If there is a positive test for methylation of the CDKN2A-gene, the risk of colorectal cancer is considered very high and these patients underwent surgical treatment. Application of the molecular biological marker CDKN2A may be an effective method in early diagnosis of malignization of polyps. Research Sponsor: None.

Colorectal cancer screening with blood-based tests: Estimated impact of a 1-, 2-, or 3-year screening interval compared with annual FIT and triennial mt-sDNA strategies. *First Author: A. Mark Fendrick, University of Michigan, Ann Arbor, MI*

Background: Blood-based tests are an emerging option for non-invasive colorectal cancer (CRC) screening for which the Centers for Medicare & Medicaid Services (CMS) has proposed coverage every 3 years for average-risk individuals. Analyses with the CRC-AIM microsimulation model demonstrated that triennial screening with blood-based tests with CMS minimum performance often yields inferior outcomes to stool-based CRC screening (fecal immunochemical test [FIT] and multi-target stool DNA [mt-sDNA]). CRC-AIM was used to explore the impact of blood-based screening intervals, using reported performance characteristics from the ECLIPSE study (Guardant Health, Inc.)¹, on estimated clinical outcomes vs FIT and mt-sDNA screening. **Methods:** Outcomes were simulated for average-risk individuals screened between ages 45-75 years. Intervals were set at 1, 2, or 3 years for blood-based, 3 years for mt-sDNA and annually for FIT screening. The blood-based test was modeled at 83% CRC sensitivity, 13% advanced adenoma sensitivity, and 90% specificity. Perfect adherence (100%) was modeled for blood-based tests and real-world adherence rates used for CRC initial screening tests (mt-sDNA=65.6%; FIT=42.6%) and follow-up colonoscopy (mt-sDNA=72.1%; FIT=46.0%). Primary outcomes were life-years gained (LYG) and colonoscopies (COL) per 1000 individuals for blood-based screening compared to mt-sDNA and FIT. As a secondary analysis, estimates were generated with perfect (100%) adherence assumed for initial screening and follow-up colonoscopy for mt-sDNA and FIT as well. **Results:** Blood-based testing at a 3-year interval with 100% adherence led to 11% fewer LYG than mt-sDNA at RWE adherence (240 vs 270, respectively), and 9% more COL (1402/1000 vs 1288/1000). Meanwhile, blood-based testing at a 1-year interval and perfect adherence (best case scenario) resulted in the lowest LYG per COL ratio across all scenarios (16% more LYG and 87% more COL compared to mt-sDNA at RWE adherence). Blood-based test results showed similar trends when compared to FIT. **Conclusions:** Outcomes for blood-based screening every 3 years based on reported test performance characteristics and unrealistic perfect adherence demonstrate fewer LYG as compared to either mt-sDNA or FIT. When compared to real-world adherence for mt-sDNA and FIT, blood-based tests with 1- and 2-year intervals and perfect adherence had higher LYG with the tradeoff of a greater number of diagnostic colonoscopies. Research Sponsor: Exact Sciences Corporation.

LYG and COL per 1,000 patients by screening modality, interval, and adherence (RWE and perfect).					
Modality	Interval	LYG (RWE)	Number of COL (RWE)	LYG (perfect)	Number of COL (perfect)
FIT	1	179	699	326	1,668
mt-sDNA	3	270	1,288	319	1,695
Blood test	1	-	-	314	2,408
Blood test	2	-	-	273	1,771
Blood test	3	-	-	240	1,402

LYG: life-years gained; RWE: real-world evidence; COL: colonoscopy. ¹ ECLIPSE study.

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Poster Session

Does adherence to cancer prevention guidelines before diagnosis associate with improved cancer survival? *First Author: Evan W. Davis, Roswell Park Comprehensive Cancer Center, Buffalo, NY*

Background: The American Institute for Cancer Research and American Cancer Society regularly publish cancer prevention recommendations for decreasing cancer risk. Which lifestyles, or whether they work together to impact cancer survival is not well established. We examined associations of adherence to cancer prevention recommendations with mortality in 5,766 patients enrolled in the Data Bank and BioRepository at Roswell Park. **Methods:** Patients were newly diagnosed between 2003 and 2016 with a variety of pathologically confirmed invasive malignancies. Detailed epidemiological data including lifestyles one year prior to diagnosis were linked with Tumor Registry data. The primary analytic exposure was a composite Lifestyle Index Score (LIS) created in accordance with previously published standardization guidance; the primary analytic outcome was all-cause mortality. The LIS comprised seven lifestyles including: physical activity (PA); body mass index (BMI); fruit and vegetable (FV) intake; red and processed meat (RPM) intake; sugar sweetened beverage (SSB) consumption; alcohol consumption; and smoking status. Kaplan Meier analyses were used to compare survival experience according to LIS tertiles. Multivariable Cox proportional hazard models adjusted for age, tumor type, stage, and sex were used to estimate the associations of the LIS and each lifestyle factor with mortality in the overall study population and according to tumor stage. **Results:** During follow-up through April 2022, we observed 2,316 deaths (median follow-up 6.9 years). Patients reporting strongest adherence to prevention recommendations (highest LIS tertile) had significantly improved survival compared to patients with the lowest LIS (93.0 vs. 75.0 months, respectively; log-rank $p < 0.0001$). In multivariable analyses, the highest versus lowest LIS tertile was associated with a 17% reduction in mortality in the overall study population (HR = 0.83, 95% CI: 0.74-0.93). Significant mortality reductions were observed in patients diagnosed with both early- and late-stage disease (HR = 0.73, 95% CI: 0.59-0.90 and HR = 0.85, 95% CI: 0.73-0.99, respectively). Being a never smoker (HR = 0.54, 95% CI: 0.47-0.62), meeting the PA Guidelines (HR = 0.74, 95% CI: 0.66-0.83), and highest FV intake (HR = 0.82, 95% CI: 0.73-0.91) were the only independent factors associated with significant reductions in mortality. **Conclusions:** Strongest adherence to the cancer prevention recommendations before diagnosis was associated with significant reductions in mortality. These findings provide additional evidence that modifiable lifestyle factors can impact cancer survival, even among patients diagnosed with advanced-stage disease. Confirmatory studies examining post-diagnosis lifestyles are needed so that lifestyle assessment tools, education, and intervention can be clinically leveraged to improve patient outcomes. Research Sponsor: U.S. National Institutes of Health.

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Poster Session

Genetic testing into survivorship after diagnosis of breast cancer. *First Author: Steven Katz, University of Michigan Medical School, Ann Arbor, MI*

Background: Support for universal genetic testing after diagnosis of breast cancer is growing because of concerns that targeted guidelines fail to identify all patients who could benefit from genetic risk evaluation (GRE). Little is known about use of genetic testing in survivors of breast cancer over time. **Methods:** Women who were diagnosed with breast cancer in 2014-15 and reported to the SEER registries of Georgia and Los Angeles County completed a baseline survey about 9 months after diagnosis (N=2502). We performed a follow-up survey (FUPs) about 6 years after diagnosis among survivors (N=2347), of whom 1423 responded (60% response rate). We asked women about their receipt of clinical germline genetic testing and results, communication with relatives about cancer genetic testing, and use of direct-to-consumer testing (DTCT) after diagnosis. We categorized women into indications (yes/no) for GRE based on National Comprehensive Cancer Network guidelines at time of diagnosis (GRE indication baseline) and at the time of the follow-up survey (GRE indication FUPs only). **Results:** We present results for a preliminary sample (N=1272). About half of the respondents (44.6%) had indications for GRE over the study period; 28.0% at baseline; and an additional 16.6% at time of the follow-up survey (FUPs only). The Table below shows patient-reported testing at FUPs by GRE indication category (baseline, FUPs only, no indication). About two thirds of those with a baseline indication for GRE received genetic testing over the observation period: 66.5% vs 43.9% with indication at FUPs only vs 35.0% of those with no indication (p<.001). A substantial proportion of those who reported testing received the test during the survivorship period (1 to 6 years post-diagnosis): approximately one-third of those with baseline indications vs over half of those with GRE indication at FUPs only. Testers with a pathogenic variant result (n=59) were much more likely to have talked to most or all of their first-degree adult relatives about genetic testing than those with a variant of unknown significance (n=40) or a negative finding (n=382): 64.3% vs 35.0% and 37.1%, respectively (p<.001). Overall, there was very little interest in DTCT for cancer risk: 5.0% researched DTCT online somewhat to a lot; and only 3.5% had DTCT. **Conclusions:** The proportion of patients with indications for GRE after diagnosis of breast cancer markedly increases into survivorship but many patients do not receive genetic testing. Lack of survivor interest in DTCT for cancer risk is reassuring that patients are not substituting DTCT for clinical testing. Research Sponsor: American Cancer Society.

Patient-reported receipt of germline genetic testing at FUPs by GRE indication.

Date of genetic test (reported on FUPs)	GRE Indication Category(%)		
	At baseline n=356	On FUPs only n=211	No indication n=705
Ever received	66.5	43.9	35.0
Within past 2 years	9.0	12.7	9.5
2-5 years ago	13.1	11.2	5.5
>5 years ago	44.4	20.0	20.0
Never received	33.5	56.1	65.0

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Poster Session

Twenty-one gene recurrence scores in individuals with breast cancer associated with CHEK2 and ATM germline pathogenic variants. *First Author: Payal Deepak Shah, University of Pennsylvania, Philadelphia, PA*

Background: The 21-gene recurrence score assay (Oncotype DX, Genomic Health Inc., CA) is prognostic, quantifies predicted benefit of adjuvant chemotherapy, and informs clinical decisions for patients with early-stage, hormone receptor-positive (HR+) breast cancer (BC). Differences in Oncotype recurrence scores (RS) in individuals with and without *BRCA1* and *BRCA2* pathogenic variants (PV) have been demonstrated, but the results of this assay in patients with BC and germline *CHEK2* or *ATM* PV have not previously been described. This is of particular relevance as *CHEK2* BC have been associated with a worse prognosis. **Methods:** Prospective Registry of MultiPlex Testing (PROMPT) is an online research registry for individuals who have had multigene panel testing for inherited cancer susceptibility. We retrospectively evaluated Oncotype DX recurrence scores from PROMPT participants (pts) with PV or likely PV in *CHEK2* or *ATM*. Mood's median tests were used to compare median RS, and Yates corrected Chi-square tests were used to compare RS distributions between carriers and a genetically unselected reference population. **Results:** Oncotype DX reports were reviewed for 75 pts with 77 BC (n = 50 pts with *CHEK2* PV with 51 BC; n = 24 with *ATM* PV; n = 1 with *CHEK2* and *ATM* PV with 2 BC). Among *CHEK2* carriers, median RS was 17 (range 2-43) overall, 17 (2-36) for pts < age 50, and 18.5 (8-43) for pts ≥ age 50 (p-value 0.47), with distributions not significantly different than reference (< 50, p = 0.70; ≥ 50, p = 0.93). Ten pts had low penetrance *CHEK2* alleles (p.S428F or p.L157T) with median RS 16 (9-28) compared to 18 (2-43) in those with other *CHEK2* alleles (p = 0.35). Among *ATM* carriers, median RS was 17 (1-35) overall, 17 (1-35) for pts < age 50, and 16 (11-32) for pts ≥ age 50 (p = 0.51), with distributions also not significantly different (< 50, p = 0.78; ≥ 50, p = 0.79). **Conclusions:** Unlike data seen in BC associated with *BRCA1* and *BRCA2*, Oncotype DX RS in individuals with *CHEK2* and *ATM*-associated BC are similar to the published genetically unselected commercial database median RS of 16, with no clear difference based on penetrance of *CHEK2* allele. Proportions of patients < 50 and ≥ 50 with *CHEK2* and *ATM* PV with RS within the range for chemoendocrine therapy consideration are also similar to the historical reference. The inferior prognosis that has been suggested in *CHEK2* BC is not reflected in Oncotype DX RS. Research Sponsor: None.

Gene	CHEK2 (n = 51 BC) + CHEK2 & ATM (n = 2 BC)		ATM (n = 24)		Genetically unselected reference* (n = 799,986)	
	< 50 (n = 27 BC)	≥ 50 (n = 26 BC)	< 50 (n = 13)	≥ 50 (n = 11)	< 50 (n = 163,912)	≥ 50 (n = 636,074)
RS, median (range)	17 (2-36)	18.5 (8-43)	17 (1-35)	16 (11-32)	n/a	n/a
RS < 16 (n, %)	11 (41)	5 (38)	5 (38)	5 (45)	75,727 (46.2)	—
RS ≥ 16 (n, %)	16 (59)	—	8 (62)	—	88,020 (53.7)	—
RS < 26 (n, %)	—	21 (81)	—	9 (82)	—	529,850 (83.3)
RS ≥ 26 (n, %)	—	5 (19)	—	2 (18)	—	106,224 (16.7)

*Jakubowski et al., J Surg Oncol 2020. PMID 3249731.

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Poster Session

Women with pathogenic variants in moderate penetrance breast cancer genes: How frequently do they meet high penetrance genetic testing criteria? *First Author: Nicole Casasanta, Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY*

Background: 5-10% of breast cancers are associated with germline pathogenic variants in breast cancer predisposition genes. 2-5% of these variants are in moderate penetrance (MP) genes, conferring a relative risk to develop breast cancer of 2-5. Various personal history (PH) and family history (FH)-based criteria for testing high penetrance genes, such as *BRCA1* and *BRCA2*, have been proposed, but it is unknown to what extent women with pathogenic variants in MP genes may meet such criteria. We evaluated PH and FH of cancer among women with pathogenic variants in MP genes in a diverse and unselected patient cohort in New York City to determine how often they met well-established genetic testing criteria from the National Comprehensive Cancer Network (NCCN). **Methods:** Exome sequence data from ~16,000 female BioMe Biobank participants were evaluated for expected pathogenic (per ClinVar, or predicted loss-of-function) variants in *ATM*, *BARD1*, *BRIP1*, *CHEK2*, *NF1*, *PALB2*, *RAD51C*, and *RAD51D*. We extracted demographic information, PH and FH of breast, ovarian, and/or pancreatic cancer, and PH and FH of genetic testing from participant questionnaires and electronic medical record review. We then determined which participants met current NCCN criteria (version 1.2023) for high penetrance breast, ovarian, and pancreatic cancer genetic testing. **Results:** We identified 252 women with expected pathogenic variants in MP genes: 105 *CHEK2*, 58 *ATM*, 35 *BRIP1*, 24 *PALB2*, 9 *BARD1*, 8 *NF1*, 8 *RAD51D*, and 5 *RAD51C*. 30% met NCCN criteria, including 30% of those with *CHEK2* variants, 36% *ATM*, 14% *BRIP1*, 33% *PALB2*, and 30% with variants in *BARD1*, *NF1*, *RAD51D*, or *RAD51C*. 36% of those who met NCCN criteria had previously undergone clinical genetic testing. 29 of 33 (88%) women with a PH of breast cancer and 52 of 81 (64%) women with a FH of breast cancer met criteria. **Conclusions:** Current genetic testing criteria focus on identifying individuals harboring pathogenic variants in high penetrance cancer genes. However, in our study, a substantial portion of women with a pathogenic variant in a MP breast cancer gene also met such criteria, particularly when PH or FH of breast cancer were present. Only a third of those who met NCCN criteria had undergone clinical genetic testing. These findings suggest that the majority of women with genetic risk for breast cancer may be missed in clinical practice. Studies have shown that most physicians would change management strategies for patients with pathogenic variants, including variants in MP genes. As our understanding of genetic risk for breast cancer continues to evolve, we must explore strategies to improve identification and management of individuals with variants in MP breast cancer genes. Research Sponsor: None.

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Poster Session

Analysis of ATM germline mutations in solid tumors from Chinese patients. *First Author: Tao Fu, China-Japan Friendship Hospital, Beijing, China*

Background: Ataxia-telangiectasia mutated (ATM) is a tumor suppressor genes and plays an important role in the repair of DNA double-strand breaks (DSBs). Germ-line mutations of ATM gene result in the well-characterized ataxia telangiectasia syndrome, which manifests with an increased cancer predisposition, including a 20% to 30% lifetime risk of lymphoid, gastric, breast, central nervous system, skin, and other cancers. Novel therapies are in development that may improve the response to therapy of patients with ATM-deficient cancers including targeted therapy and immunotherapy. Nevertheless, the knowledge of incidence of ATM germline mutations in solid tumor remains poorly understood. **Methods:** We identified 19248 malignant solid tumors patients without selecting age or family history in a retrospective cohort. The pathogenicity of germline mutations was categorized based on American College of Medical Genetics and Genomics (ACMG) guidelines. The patients were divided into two groups, P/ LP group (with pathogenic or likely-pathogenic mutations), and Non-P/LP group (neither pathogenic nor likely-pathogenic mutation). **Results:** In 19248 patients with pan-cancer, 76 patients were found 76 heterozygous pathogenic or likely pathogenic germline mutations in ATM gene and the mutation frequency was 0.39%. Among these 76 carriers, 71 (93.4%) carried frameshift, nonsense or splice mutations (33 for frameshift, 21 for missense and 17 for splice mutations). 4 carried missense mutations and 1 carried intron mutations. Eliminated a few types of cancers that had a smaller number (less than 50), the higher frequency of mutations contained cancers were pancreatic cancer (1.0%, 7/692), breast cancer (0.71%, 3/423), gastric cancer (0.6%, 7/1094). The median age of group P/LP and non-P/LP group was 64 and 63 in pancreatic cancer, 62 and 53 in breast cancer and 62 and 61 in gastric cancer. The three genes with the most somatic mutations were TP53, MUC16 and KRAS in P/LP group and were TP53, MUC16 and EGFR in non-P/LP group. There was no significant difference in mutation frequency of the four genes. The media TMB in P/LP group and non-P/LP group were 3.55 and 2.84 respectively and there was no statistical difference. In P/LP group, only one patients is high microsatellite instability who carried a MLH1 and a ATM pathogenic mutation. **Conclusions:** This was the first report of the incidence of ATM germline mutations in Chinese solid tumors which expanded the understanding of ATM and provided a direction for clinical trial design of novel therapies. The relationship between germline mutations and cancer susceptibility will be studied in the future. Research Sponsor: None.

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Poster Session

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Poster Session

Characteristics and clinical outcome of BRCA germline mutation carriers with advanced breast cancer treated with PARP (poly ADP-ribose polymerase) inhibitors: A single institution experience. *First Author: Fatma Nihan Akkoc Mustafayev, University of Texas, MD Anderson Cancer Center, Houston, TX*

Background: About 5-10% of breast cancers (BC) are related to germline BRCA 1/2 pathogenic variants (PV). Several studies have demonstrated the effectiveness of PARP inhibitors (PARPi) in this population. However, BC patients with BRCA PVs remain a challenge to treat. In this report, we aim to characterize the clinical characteristics and outcome of a single institution cohort of advanced BC patients with a BRCA PV and who received PARPi therapy. **Methods:** Patients with BRCA 1/2 germline PVs who presented to the University of Texas MD Anderson Cancer Center Breast Medical Oncology clinics and were treated with PARPi between 2008-2022 as part of their treatment for metastatic or recurrent disease were included in the analysis. Variables included in this analysis included age at diagnosis, family history of BC and ovarian cancer, treatment details, tumor characteristics including histological type, receptor status and clinical outcome. Descriptive statistics, the Kaplan-Meier method, and The Cox proportional hazards regression model were used to report patient characteristics and outcomes. Progression free survival (PFS) was defined as the time from treatment initiation of PARPi to disease progression or death. Overall survival (OS) was defined as the time from treatment initiation of PARPi to death of any cause. **Results:** One hundred and seven patients were treated with PARPi. Median age at diagnosis was 38 years (23-73). Forty-eight (44.9%) and 59 (55.1%) patients had BRCA1 and BRCA2 mutations, respectively. Ninety-seven (90.7%) had invasive ductal carcinoma and 42 (39.3%) had triple negative BC. Nineteen (17.8%) patients were de novo metastatic BC (Stage IV). Sixty-two (57.9%) patients received one or more prior lines of chemotherapy before being treated with PARPi; 24 (22.4%) patients received prior platinum. In 91 patients evaluable for clinical response, the overall response rate (ORR) was 59.4% and the duration of response (DoR) was 7 months (2.1-96.2). In platinum-naïve patients ORR was 70.4% and DoR 7.4 months (2.1-96.2). Median PFS was 8.9 months (95% CI 6.3-10.3) and median OS 25.8 mo (95% CI 18.3-30.9). In univariate analysis, first-line PARPi use (p = 0.0274) and no previous use of platinum (p = 0.0121) were statistically significant for better PFS. Hormone receptor positive BC (p = 0.0105) was statistically significant for better OS. **Conclusions:** In this real-world single institution cohort of advanced BC patients with BRCA germline PVs who were treated with PARPi, the ORR and outcome of patients is similar to those reported in the previous clinical trials. Platinum naïve and patients who received PARPi as 1st line therapy had a better ORR. Further studies of predictive markers of response and resistance as well as sequencing with platinum are needed to optimize the use of PARPi in this patient population. Research Sponsor: Donor funds.

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Poster Session

Investigation of cancer predisposition in Fanconi anemia heterozygotes: A DiscovEHR cohort population study. *First Author: Joseph Deng, National Cancer Institute, Rockville, MD*

Background: Fanconi anemia (FA) is a cancer predisposition syndrome caused by biallelic pathogenic variants in one of 22 genes involved in DNA intrastrand crosslink repair. 20 of these genes have an autosomal recessive inheritance pattern. Of the FA genes, 5 (*BRCA1*, *BRCA2*, *BRIP1*, *PALB2*, *RAD51C*) are known cancer predisposition genes (CPG) when inherited in monoallelic autosomal dominant manner, though the heterozygous predisposition status of the remaining 15 remains unclear. Large population-level exome sequencing projects with linked health records such as the DiscovEHR cohort serve as promising tools to establish sufficient power to investigate all FA genes. Quantifying cancer risk is important for the counseling and surveillance of FA heterozygotes, especially with the ever-increasing use of genetic testing identifying these individuals. **Methods:** 170,503 individuals enrolled in the DiscovEHR Cohort were analyzed for pathogenic/likely pathogenic variants in 22 FA genes and identified 5834 subjects, the case group. ICD10 phenotype classifications for these subjects were curated to Phecodes and ICD-O-3 Site Recodes for two control arms of analysis. The first control arm included all DiscovEHR subjects excluding the case group and those with a variant of uncertain significance in the genes of interest with a deleterious in-silico score. The second control arm included individuals from the Surveillance, Epidemiology, and End Results (SEER) database. Phecode analysis yielded odds ratios adjusted for age, sex, race, smoking status, and BMI. SEER analysis yielded Standardized Incidence Ratio scores adjusted for age, sex, and birth cohort. When both arms of the analysis were completed Phecodes and SEER analyses were matched and positive signals for cancer risk were defined by statistically significant ratios in both. **Results:** The 5 known CPGs demonstrated multiple signals for cancer predisposition as expected (p < 0.0001). Results for *FANCA* (p = 0.4231) and *FANCC* (p = 0.8142) heterozygotes validated recent results from our group showing no increased risk of cancer in relatives of FA patients with these genotypes. Ten other FA genes also showed no increased risk of cancer. 3 genes suggested a possible increased risk of specific cancers in heterozygotes and are currently being evaluated in a second large population exome cohort to validate these findings. **Conclusions:** This is the largest study to date on the cancer predisposition risk in Fanconi anemia heterozygotes. We have confirmed the known risk in 5 well-described CPGs and the lack of risk amongst *FANCA* and *FANCC* heterozygotes, the most common in population. Further analysis via an additional large population cohort is underway to validate any possible novel cancer predispositions in 3 genes. For the remaining FA genes, this population analysis supports previous literature on known CPGs and the lack of cancer predisposition in most FA genes. Research Sponsor: U.S. National Institutes of Health.

Comprehensive analysis of patients with cancer with a positive CHEK2 test: Are we getting closer to a genotype/phenotype correlation? *First Author: Ana Frago, Instituto Português de Oncologia de Lisboa, Francisco Gentil, Lisboa, Portugal*

Background: The *CHEK2* gene encodes a protein kinase that acts as a tumor suppressor with an important role in DNA damage repair. This gene is included in most hereditary breast, ovarian and prostate cancer panels, but the clinical actionability of *CHEK2* pathogenic/likely pathogenic variants (PVs) may be challenging. Indeed, decisions concerning clinical surveillance and/or risk reducing procedures as well as screening for multiple associated cancer risks are not consensual. Our objective was to identify a potential genotype/phenotype association regarding *CHEK2* PV identified in our population. **Methods:** Study group included all patients (pts) who tested positive for *CHEK2* PVs between July 2000 and June 2022; control group included pts without PVs after multigene panel testing (wt) between January 2020 and June 2022. PVs were categorized as: truncating (includes nonsense, frameshift, splice site variants, gross deletions and duplications) and not truncating (missense and in-frame deletions). Clinical characteristics from both groups included gender, personal and family cancer history and tumor characteristics. **Results:** From 8604 pts tested, we identified 101 *CHEK2* and 1506 wt pts. *CHEK2* pts were mainly women (95; 92%) and Portuguese (94; 93.1%). All non-Portuguese pts had Eastern Europe ancestry. *CHEK2* pts were either heterozygous (94;93%), homozygous (3; 3%) or had digenic inheritance (4; 6%: both a *CHEK2* and a *BRCA1/2* PV). Compared to wt pts, heterozygous *CHEK2* pts were younger at 1st cancer diagnosis (44.5 yrs vs 47 yrs) and had more multiple primary cancers (OR: 1.8; p: 0.02). *CHEK2* breast cancer was mostly but not exclusively estrogen receptor positive (69/78; 88,4%) and Her2 negative (54/69; 78%). Two BC cases had triple negative phenotype. The most frequent PVs detected were c.349A > G (25 pts), c.1100del (24 pts) and c.319+2T > A (20 pts). Considering heterozygous PVs, 57 were truncating and 37 non-truncating, with c. 1100del and c.349A > G being the most frequent, in each group, respectively. For truncating versus non-truncating PVs there was no difference in phenotype regarding breast (OR: 0.69; p: 0.15), CRC (OR: 0.94; p: 0.91), gastric (OR: 0.76; p: 0.65), thyroid (OR: 1.3; p: 0.69) and kidney cancer (OR: 0.36; p: 0.27). Further stratification of PVs according to cancer type revealed a correlation of CRC with c.1100del (OR: 4.57; p: 0.0025) and c.349A > G (OR: 5.49; p: 0.0003), while gastric, kidney and thyroid cancers correlated with c.349A > G (OR: 5.8; p: 0.0069), c.1100del (OR: 26.86; p: 0.02) and c.319+2T > A (OR: 3.31; p: 0.05) PVs, respectively. **Conclusions:** This analysis suggests a potential genotype-phenotype correlation regarding *CHEK2* pathogenic variants, regardless of its truncating potential. The study of clinical outcomes will further contribute to determine how this information may influence the clinical and risk management of *CHEK2* pts and their families. Research Sponsor: None.

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Poster Session

Rates of potentially actionable germline variants in homologous recombination repair genes in a large international cohort outside of the United States. *First Author: Sarah M. Nielsen, Invitae, San Francisco, CA*

Background: Identification of pathogenic germline variants (PGVs) in homologous recombination repair (HRR) genes among patients (pts) with breast (BC), ovarian (OC), pancreatic (PaC), and prostate cancer (PrC) is critical to determine potential eligibility for targeted therapies such as PARP inhibitors (PARPi). It is important to evaluate the frequency and patterns of PGVs across different regions of the World to help inform the counseling of pts and implementation of precision medicine. **Methods:** A retrospective analysis of pts with BC, OC, PaC, and/or PrC cancer undergoing GGT through a single laboratory was conducted. The location of the ordering provider determined the assigned region, which included: Asia-Pacific (APAC), Latin America (LATAM), Middle East and African (MEA), and United Kingdom and Europe (UEKU). Analyses were limited to pts tested for PARPi-eligible (in the US) HRR genes and PGV analysis to the 10 most frequent genes for that cancer type. Descriptive statistics and Chi square with Yates correction were utilized. Significance was set at p<0.05. **Results:** The cohort consisted of 40,539 pts with an average age at testing of 51 years, the majority of whom had BC (81%) (Table). The median number of genes tested ranged from 14-85 (Table). *BRCA1* and *BRCA2* were the most frequent genes with PGVs (3,358 pts, 8%). LATAM BC pts had significantly higher rates of *BRCA1/2* PGVs (10%) than the other 3 regions (p<0.0007). OC *BRCA1/2* rates were high, and statistically similar, across regions (15-17%, p>0.08). Rates of *BRCA1/2* and *PALB2* in PaC pts did not differ between regions (4-7%, p>0.08), nor did rates of *BRCA1/2*, *CHEK2*, *ATM*, and *PALB2* in PrC pts (7-11%, p>0.16) (Table). In sum, 3,434 pts (9% of those tested for the eligible genes) had PGVs in the above PARPi-eligible HRR genes. A notable limitation is that pts were ascertained by cancer type but information on other PARPi eligibility, namely metastatic/advanced disease, was not available. **Conclusions:** 1 in 12 pts were found to carry PARPi-eligible PGVs across the 4 cancer types and regions analyzed. Knowledge of these PGVs can help inform public health policies, current and future treatment strategies, and identify at-risk family members. In some countries, GGT may represent a more cost-effective and accessible pathway to targeted therapies compared to tumor profiling due to ease of sample collection and lower cost of testing. Research Sponsor: Invitae Corporation.

Pts with PARPi-eligible PGVs by region and cancer type.

Region	Median # of genes tested				Pts tested for PARPi-eligible genes				% pts with PARPi-eligible PGVs*			
	BC	OC	PaC	PrC	BC	OC	PaC	PrC	BC	OC	PaC	PrC
APAC	48	49	50	50	7257	1622	568	533	9	15	4	7
LATAM	84	84	85	85	12202	1319	818	547	10	17	5	8
MEA	85	85	85	85	10410	1135	732	880	7	15	4	7
UEKU	14	48	30	19	2961	174	137	107	7	17	7	10

*BC and OC=BRCA1/2; PaC=BRCA1/2, PALB2; PrC=ATM, BRCA1/2, CHEK2, PALB2.

10591

Poster Session

Implementation of universal pan-cancer germline genetic testing in an Arab population: The Jordanian exploratory cancer genetics (Jo-ECAG) study. *First Author: Hikmat Abdel-Razeq, King Hussein Cancer Center, Amman, Jordan*

Background: Germline genetic testing (GGT) has a significant impact on cancer care. While universal testing has been selectively implemented in the U.S., less is known about adoption of this approach in other ethnic groups. This study reports on GGT results among newly diagnosed cancer patients (pts) in Jordan. **Methods:** Jo-ECAG was a prospective study of newly diagnosed cancer pts between April 2021 and September 2022 who underwent 84 gene GGT. Patients were classified based on the 2020 National Comprehensive Cancer Network (NCCN) GGT criteria as meeting (in criteria, IC) or not meeting criteria (out of criteria, OOC). Demographics and clinical history were clinician-provided. Pts who were carriers for autosomal recessive conditions were excluded from pathogenic germline variant (PGV) count. Differences in proportions were determined using two-tailed Fisher's exact test and the significance was set at $p \leq 0.05$. **Results:** The cohort consisted of 3,313 Arabic cancer pts, predominantly female (69.8%), with a median age of 54 at testing. Breast was the most commonly diagnosed cancer (50.4%), followed by colorectal (14.9%) and prostate (14.3%). 52% of pts tested were guidelines-based (IC). 460 PGVs were identified in 426 (12.9%) pts. PGVs were most commonly identified in *APC* (predominantly 11307K variant, 144 pts, 4.4%), *BRCA2* (72, 2.2%), *BRCA1* (36, 1.1%), *CHEK2* (26, 0.8%) and *ATM* (25, 0.8%). While IC pts were more likely than OOC pts to have a PGV (15.7% vs 9.8%, $p < 0.0001$), 156 (36.6%) pts with PGVs were OOC. 232 (54.5%) pts had PGVs in DNA damage response and repair/homologous recombination repair (DDR/HRR) genes, including 61 (26.3%) OOC pts. 3,602 variants of uncertain significance (VUS) were identified in 2,199 (66.4%) pts with 1,868 of these pts having only VUS results (56.4%), but the frequency in the latter group was not different between IC and OOC pts ($p = 0.42$). **Conclusions:** Universal GGT of all new cancer pts was successfully implemented and led to actionable findings that would have been missed with guidelines-based testing. With the exception of an overrepresentation of *APC* 11307K variants, PGV rates were similar to Western ethnic groups. Over half of pts had PGVs in DDR/HRR genes that confer potential eligibility for targeted therapies and/or clinical trials. While VUS rates were high, they were similar between IC and OOC pts. Additional efforts to sequence underrepresented populations and develop variant interpretation methods agnostic to ancestry may help to mitigate these disparities. Research Sponsor: Invitae; King Hussein Cancer Center.

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Poster Session

A pan-cancer statistical study of microsatellite instability and Lynch syndrome-associated mismatch repair genes germline mutations. *First Author: Huiya Cao, HaploX biotechnology Co., Ltd., Shenzhen, Guangdong, China*

Background: Lynch Syndrome (LS), known as hereditary nonpolyposis colorectal cancer (HNPCC1), is caused by germline mutations in the mismatch repair (MMR) genes (*MLH1*, *MSH2*, *PMS2*, *MSH6*), or epigenetic silencing of *MSH2* which caused by deletion of 3-prime exons of the *EPCAM* gene and intergenic regions directly upstream of the *MSH2* gene. DNA mismatches commonly occur in regions of repetitive nucleotide sequences called microsatellites, and the status of microsatellite instability (MSI) is the key feature in LS-associated cancers. Although there are sporadic reports of MSI and LS in certain cohorts, the real-world status of MSI in large pan-cancer cohort remains to be analyzed. **Methods:** We retrospectively reviewed all 18189 solid tumor patients from August 1, 2020 to February 5, 2023 from HaploX Genomic Sequencing Center and analyzed their germline mutations in MMR genes (*MLH1*, *MSH2*, *PMS2*, *MSH6* and *EPCAM*). MSI status was determined using Sanger sequencing or Next-generation sequencing, with tumor MSI status classified as microsatellite instability-high (MSI-H), or microsatellite-stable (MSS). **Results:** LS-associated germline mutations were detected in 0.313% ($n = 57$) of patients, and 75.4% ($n = 43$) of patients were identified as MSI-H, and 24.6% ($n = 14$) of patients were MSS. The patients were grouped into CRC/EC group (colorectal cancer and endometrial cancer) and non-CRC/EC (lung cancer, central nervous system tumor, gastric cancer, esophageal cancer, hepatological cancer, pancreatic adenocarcinoma, small bowel carcinoma, kidney cancer, etc.). Among MSI-H patients, the CRC/EC group accounted for 90.7% ($n = 39$) and the non-CRC/EC group accounted for 9.3% ($n = 4$). In MSS patients, the CRC/EC patients accounted for 35.7% ($n = 5$), and the non-CRC/EC patients accounted for 60% ($n = 9$). Among patients with MSI-H, the most frequently mutated gene was *MSH6* ($n = 9$): *MSH6* (NM_000179) c.3261dup (p.F1088Lfs*5) mutation was detected in 4 patients, of which 2 patients were paternal and both were diagnosed as colorectal cancer; *MSH6* c.718C > T (p.R240*) mutation was detected in 2 patients with available MMR IHC results, and one of them was *MSH6* negative in IHC staining. **Conclusions:** Traditionally, a family history of colorectal cancer or endometrial cancers was the primary clinical feature to diagnose Lynch syndrome. Once it was recognized that Lynch-associated CRCs were microsatellite unstable, tumor testing became an additional tool for identification of Lynch syndrome. Some previous studies also reported Lynch syndrome mutations, primarily *MSH6* and *PMS2*, were present in a few MSS patients. Thus, MSI status or family history as diagnostic factor alone may result in Lynch syndrome under-recognized, and additional NGS test on MMR genes should facilitate more accurate diagnosis. Research Sponsor: None.

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Poster Session

Real life use of biomarkers of homologous recombination deficiency (HRD) status beyond BRCA to predict the effectiveness of PARP inhibitors in ovarian cancer patients. *First Author: Lorena Inconvaia, Department of Surgical, Oncological, and Oral Sciences, Section of Medical Oncology, University of Palermo, Palermo, Italy*

Background: Testing for *BRCA* mutations (BRCAm) and genomic instability can identify epithelial ovarian cancer (OC) patients most likely to benefit from PARP-inhibitors (PARPi). However, current biomarkers of non-*BRCA* Homologous Recombination Repair (HRR) mutations are insufficient for guiding use of PARPi in the clinic. Despite non-*BRCA* HRR pathway gene mutations are rare, these patients may benefit from PARPi. Furthermore, recent preclinical findings showed that sensitivity to PARPi could be associated also with mutations in mismatch repair (MMR) genes, although sensitivity in the clinic is not proven. **Methods:** We report our real-life experience to assess the HRD status beyond *BRCAm* in newly-diagnosed OC patients, with the use of HRR gene panel and HRD genomic instability tests. After primary diagnosis, tumor and germline *BRCA* (gBRCA) status were assessed and, if *BRCA* WT, tumor HRR deficiency status were centrally determined by myChoiceCDx (Myriad) assay. NGS panel evaluating 20 MMR and HRR-genes beyond *BRCA1/2* was proposed to patients with significant personal and/or family history of cancer, resulted negative to gBRCA testing. **Results:** From January 2017 to January 2023, 540 unselected epithelial OC patients, aged 27 to 81, were tested for tumor and gBRCA status; 109 were carriers of germline pathogenic or likely pathogenic variants (PVs) in *BRCA1/2* genes (20.2%): 72 in *BRCA1* (66.1%) and 37 in *BRCA2* gene (33.9%). Additional 19 patients showed somatic PVs confined to tumor samples (3.5%). In the population of 70 *BRCA* WT patients tested by multigene panel testing, 14 germline PVs in HRR-associated (7.1%) or MMR-associated genes (12.8%) were found, including 5 in *MUTYH* (35.7%), 2 in *ATM* (14.3%), 2 in *MLH1* (14.3%), 2 in *PMS2* (14.3%), 1 in *RAD51C* (7.14%), 1 in *RAD51D* (7.14%), and 1 in *CHEK2* gene (7.14%). Out of 72 samples analyzed by HRD genomic instability test, 23 cases were identified as HRD positive (31.9%), with a median GIS score of 65.5 (44-83). Median GIS were 35 (1-72) in the 6 cases of non-*BRCA* mutated tumors (8.3%), 40 (4-82) in the 17 tumor with non-*BRCA* variant of uncertain significance (VUS) (23.6%), and 27 (2-83) in the WT samples. Median GIS were significantly higher in tumors with PVs/VUS of *RAD51* than *BRIP1* (55.5 vs 35). **Conclusions:** HRRm gene panel and HRD genomic instability tests are not interchangeable to study HRR deficiency beyond *BRCAm*. HRD genomic instability test is effective to identify patients most likely to gain benefit from PARPi, but not for predicting familial risk of cancer. In our population, NGS panel evaluating HRR genes, beyond *BRCA1/2*, improved the detection rate of HRRm by 7%, with additional finding of MMR germline mutations, and important clinical implications for family members. Prospective data are expected to evaluate the effectiveness of PARPi in these population. Research Sponsor: None.

10594

Poster Session

Hereditary breast and ovarian cancer syndrome: A misnomer? *First Author: Jessica M. Weiss, New York Medical College, Valhalla, NY*

Background: Germline pathogenic gene variants (PGV) in homologous recombination deficiency (HRD) genes are traditionally associated with breast, ovarian, pancreatic, prostate and melanoma skin cancer. Recent evidence suggests other cancers may also be associated with these genes. We analyzed the prevalence of somatic HRD mutations in common, traditionally non-hereditary breast and ovarian cancer (HBOC) associated incident cancers in the US. **Methods:** Data were collected from the American Association for Cancer Research's (AACR) Project Genomics Evidence Neoplasia Information Exchange (GENIE) database version 13.0 via cBioPortal (<http://genie.cbioportal.org>). This is a publicly available, multi-institutional database of next-generation sequencing (NGS) genomic profiles of tumor samples. The database was queried for all cancers with at least 20,000 incident cases in 2022, as reported by the American Cancer Society, excluding well established HBOC associated cancers – breast, ovarian, prostate, pancreatic, melanoma. Frequencies of somatic PGVs were reported for nine HRD genes currently included in National Comprehensive Cancer Network (NCCN) management guidelines for HBOC: *ATM*, *BARD1*, *BRCA1*, *BRCA2*, *BRIP1*, *CHEK2*, *PALB2*, *RAD51C* and *RAD51D*. **Results:** A total of 78,285 tumor samples across 12 cancer types were included. At least 1 somatic HRD was found in 6.8% of all included tumors. At least 1 HRD PGV was most common in: Uterine Cancer (694/5,760, 12.1%), Non-Melanoma Skin Cancer (1271/2,09, 10.5%), Bladder Cancer (462/4,605, 10.0%), Colorectal Cancer (1306/14,625, 8.9%) Non-Hodgkin's Lymphoma (5/58, 8.6%), Esophagogastric Cancer (356/4,649, 7.7%), Hepatobiliary Cancer (219/3,325, 6.6%), Lung Cancer (1,480/23,621, 6.3%), Kidney Cancer (113/2,564, 4.4%), Brain Cancer (420/10,206, 4.1%), Thyroid Cancer (89/2,246, 4.0%) and Leukemia (80/5,417, 1.5%). The most common PGVs across all cancer types were *BRCA1/2* and *ATM* (Table). **Conclusions:** A pan-cancer analysis using NGS data demonstrates a substantial rate of somatic HRD PGVs in common, traditionally non-HBOC associated cancers in the US. These data raise the possibility that germline pathogenic variants in HRD genes could be associated with several more cancers than currently known, underscoring the need for studies evaluating risks of the aforementioned cancers in germline PGV carriers. Additionally, these findings present opportunities for trials evaluating the efficacy of HRD-targeting therapies in these cancers. Research Sponsor: None.

Cancer Type	Mutation frequency of <i>BRCA1/2</i>	Mutation frequency of <i>ATM</i>	Mutation frequency of other included HRD genes
Bladder	3.4%	4.3%	3.3%
Brain	1.3%	1.7%	1.8%
Colorectal	4.1%	4.7%	3.3%
Esophagogastric	3.3%	3.4%	2.2%
Hepatobiliary	2.5%	2.9%	1.7%
Kidney	1.0%	2.1%	1.6%
Leukemia	0.4%	0.6%	0.7%
Lung Cancer	2.1%	3.2%	2.0%
Non-Hodgkin's Lymphoma	0%	5.2%	3.6%
Non-Melanoma Skin	4.8%	3.0%	3.9%
Thyroid	1.2%	2.0%	1.1%
Uterine	5.3%	6.3%	4.1%

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Poster Session

10596

Poster Session

Effect of somatic-germline genomic integration on the contribution of pathogenic germline genetic variants (gPV) to colorectal cancer (CRC) carcinogenesis. *First Author: Emily Harrold, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Approximately 14% of CRC patients harbor a germline pathogenic variant (gPV) in a cancer susceptibility gene. As gPV prevalence alone is insufficient evidence for cancer causation, we performed an integrated germline and somatic genomic analysis to discover the extent to which gPVs may be driving CRC carcinogenesis. **Methods:** Using the MSKCC IMPACT dataset, we identified all patients with CRC who had undergone targeted tumor-normal sequencing (NCT01775072) inclusive of up to 90-genes assessed for germline variants. gPV in tested genes were categorized according to known association with CRC susceptibility and penetrance level. For example, high/moderate penetrance CRC-risk genes included: *APC, MLH1, MSH2, MSH6, PMS2, EPCAM*, biallelic *MUTYH, SMAD4, STK11, BMPR1A, PTEN, POLD1, POLE, TP53*. Low-penetrance CRC-risk genes included: monoallelic *MUTYH, APC I1307K, CHEK2, BLM*. In patients with a gPV, biallelic inactivation at the implicated germline region was inferred based on loss of heterozygosity (LOH) or somatic pathogenic alteration in the tumor. **Results:** Of 3988 CRC patients, 16.3% (650/3988) harbored at least one gPV (65 patients: 2 gPVs; 3 patients: 3 gPVs). Among a total of 721 gPVs encompassing 55 genes (252 high-penetrance, 118 moderate-penetrance, 351 low/recessive/uncertain-penetrance), overall biallelic inactivation was observed in 41%. In patients with gPVs associated with high/moderate penetrance CRC-risk genes, biallelic inactivation in tumors was present in 70%, while in patients with gPVs in high/moderate penetrance non-CRC genes this was 24% ($p < 0.0001$). When assessed according to age at CRC diagnosis, biallelic inactivation in high/moderate penetrance CRC-risk genes was higher in patients diagnosed at age < 35 than in patients age > 50 ($p = 0.003$); no such difference was observed in high/moderate penetrance non-CRC-risk genes. Among non-CRC-risk genes, in the high/moderate penetrance HRD genes, biallelic loss in the tumor was seen in 29% gATM, 54% gBRCA1, 22% gBRCA2, 30% gBRIP1, and 40% of gRAD51C/D positive patients. There was no difference in the rate of biallelic loss by age in patients with gPVs in HRD genes. Biallelic inactivation in tumors in patients with low-penetrance CRC-risk gPVs was 40% versus 14% in patients with low-penetrance non-CRC gPVs ($p < 0.0001$). **Conclusions:** Germline-somatic integration implicated nearly half of all identified gPVs in CRC carcinogenesis. While the highest rate of biallelic inactivation was seen in high/moderate penetrance CRC-risk genes, biallelic inactivation in non-CRC genes, such as the HRD genes, warrants further assessment to discern the contribution of these gPVs to CRC carcinogenesis. Our findings may have implications for novel treatment strategies exploiting these pathways. Research Sponsor: MSKCC Center Core grant (P30 CA008748), the Molecular Diagnostics Service in the Department of Pathology, and the Marie-Josée and Henry R. Kravis Center for Molecular Oncology.

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Poster Session

A randomized controlled trial evaluating pretest cancer genetics educational video or in-person genetic counseling. *First Author: Yanin Chavarri Guerra, Instituto Nacional de Ciencias Medicas y Nutrición Salvador Zubirán, Mexico City, DF, Mexico*

Background: Cancer genetic testing indications are rapidly expanding to determine treatment eligibility for patients with cancer, to identify individual cancer risk as well as to select family members at higher cancer risk when a pathogenic variant (PV) has been identified in the family. Currently, international guidelines recommend that all candidates for genetic testing should have genetic counseling to make an informed decision for genetic testing. However, with the increased demand for genetic testing, innovative ways to deliver pretest information are needed, especially in limited resource settings, where genetic cancer professionals' availability is scarce. **Methods:** This is a non-inferiority trial comparing a pretest educational video to in-person genetic counseling. Participants referred for genetic cancer risk assessment at the *Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán* in Mexico City were enrolled if they met international cancer genetic testing criteria and did not previously have genetic testing and/or counseling. The primary outcome was the uptake of genetic testing. Secondary outcomes included changes in genetic cancer knowledge, anxiety, and satisfaction using validated tools. **Results:** A total of 250 participants were included: 124 were randomized to the in-person genetic counseling arm and 126 to the educational video arm. Mean age was 47.9 years (SD 12.7), 86.4% were women, 37.2% had high-school or less and 86.4% had personal history of cancer (70% breast cancer). Overall, test acceptance was 100% in both arms. Cancer genetics knowledge improved in both groups: in-person from .53 to .74 (diff .20; 95%CI .24-.26; $p < 0.05$) and video from .51 to .68 (diff .16; 95%CI .20-.12; $p < 0.05$). However, the in-person arm had a higher post counseling knowledge score ($p 0.001$). 43.5% and 42% of participants in the in-person and video arms had moderate-severe baseline anxiety. After intervention, both groups had a decrease in anxiety score: in-person from 5.2 to 4.7 (diff .58; 95%CI .09-1.08; $p 0.01$) and video from 4.9 to 4.1 (diff .75; 95%CI 0.42-1.08; $p < 0.05$). Both groups were satisfied with genetic services (97.5% and 92.5%, respectively; $p 0.34$). **Conclusions:** A pretest educational video was non-inferior regarding genetic testing acceptance. It was also associated with improved genetic cancer knowledge and decreased anxiety levels. These results support the use of educational videos before genetic testing where in-person genetic counseling availability is limited. Clinical trial information: pending. Research Sponsor: None.

Cost-effectiveness analyses of population-based multi-gene testing for the prevention of breast and ovarian cancer in the United States. *First Author: Fangjian Guo, University of Texas Medical Branch, Galveston, TX*

Background: The current method of testing for BRCA gene mutations, which is based on family history, often fails to identify many carriers. With the advancement of next-generation sequencing technologies, which have significantly lowered the cost of genetic testing and sequencing, population-based testing has been proposed. We evaluated the cost-effectiveness of population-based multi-gene testing as a means of preventing breast and ovarian cancer. **Methods:** We developed a microsimulation model to assess the cost-effectiveness of multi-gene testing (BRCA1/BRCA2/PALB2) for all women aged 30-35 years compared to the current standard of care that is family history-based. We selected these genes for analyses as they are most prevalent high penetrance genes. We assumed a test uptake rate of 70%. Carriers of pathogenic variants who were not affected by cancer were offered interventions, such as MRI/mammography, chemoprevention, or risk-reducing mastectomy and risk-reducing salpingo-oophorectomy (RRSO), to reduce the risk of breast and ovarian cancer. We incorporated excess coronary heart disease (CHD) deaths from premenopausal RRSO. Our main outcome measure was the incremental cost-effectiveness ratio (ICER)(i.e., cost per-quality-adjusted life year (QALY) gained), with the commonly used societal willingness to pay of \$100,000/QALY in the US as the C-E threshold. We ran 500 simulations on 1,000,000 women, employing a lifetime time horizon and payer perspective, and adjusted the cost to 2022 US dollar. We also used probabilistic sensitivity analyses to evaluate model uncertainty. **Results:** In the base case, population-based multi-gene testing is more cost-effective compared to family-history based testing, with an ICER of \$41,306/QALY (95%CI \$35,630-\$48,441/QALY). This new testing method is able to prevent an additional 1,369 cases of breast cancer and 807 cases of ovarian cancer, but it will also result in 8 excess heart-disease deaths per million women. The probabilistic sensitivity analyses show that the probability that population-based multi-gene testing is cost-effective is 100% for all the simulations. When the cost of the test exceeds \$1,100 population-based multi-gene testing becomes economically inefficient (ICER \$10,0886/QALY). **Conclusions:** Population-based multi-gene testing is a more cost-effective option for the prevention of breast cancer and ovarian cancer when compared to current family-history-based testing methods. Research Sponsor: U.S. National Institutes of Health.

10598

Poster Session

Technology-enhanced acceleration of germline evaluation for therapy (TARGET): Results of a randomized controlled trial of a pretest patient-driven webtool vs. genetic counseling for prostate cancer germline testing. *First Author: Veda N. Giri, Yale Cancer Center, Yale School of Medicine, New Haven, CT*

Background: Germline genetic testing is important for prostate cancer management, clinical trial eligibility and hereditary cancer risk assessment. Despite this, genetic testing is underutilized and there is a shortage of genetic counselors. To address these gaps, we designed a webtool to provide patient-driven genetic education and conducted a randomized non-inferiority trial to compare it with traditional pre-test genetic counseling. **Methods:** TARGET is a multi-center randomized controlled trial comparing standard pre-test genetic counseling versus web-based genetic education (intervention) (NCT04447703). The study protocol was previously published (PMID 35710085). Briefly, patients with prostate cancer who met criteria for germline testing (based on tumor features, ancestry or family history) were randomized to pre-test genetic education through genetic counseling vs a 9-module webtool created by the study team and Prostate Cancer Foundation. The primary endpoint was non-inferiority in reducing decisional conflict between the webtool and genetic counseling by a margin of 4 (set in advance) on the validated Decision Conflict Scale. Analysis of covariance was used to compare decisional conflict between groups. All participants opting for testing received a 51-gene Invitae panel, with results delivered to the patient and their provider. **Results:** 346 patients with prostate cancer with a mean age of 63.7 years were randomized to genetic counseling (n=174) or web-based genetic education (n=172). Compared to baseline, there were reductions in decisional conflict in both arms following pre-test genetic education (Table). Adjusting for study site and baseline decisional conflict, the test of non-inferiority in reducing decisional conflict between arms was statistically significant (difference = -0.04, 95% CI: -∞ to 1.95, $p < 0.001$). Overall 265 (76.6%) participants underwent genetic testing, including 146 (83.9%) in the genetic counseling and 119 (69.2%) in webtool arm, with the following results: negative (49.4%), variant of uncertain significance (35.5%) and pathogenic variant (15.1%). **Conclusions:** Delivery of pre-test genetic education through a webtool was non-inferior to genetic counseling in reducing decisional conflict. These results support a new standard of care for the use of patient-driven digital webtools for expanding access to pretest genetic education and informed decision-making for prostate cancer genetic testing. Clinical trial information: NCT04447703. Research Sponsor: Prostate Cancer Foundation.

Decisional conflict (*higher score: greater decisional conflict).			
	Total Mean (sd)	Genetic Counseling Mean (sd)	Web Based Genetic Education Mean (sd)
Baseline	36.73 (12.99)	36.69 (12.84)	36.77 (13.19)
After Pre-Test Education	28 (10.78)	28.06 (11.17)	27.93 (10.37)
*Mean Difference	-8.16 (13.13)	-8.21 (13.34)	-8.11 (12.93)

10599

Poster Session

Evaluating interventions to increase the uptake of NCCN genetic counseling recommendations. *First Author: Sophie Stempel, Rush University Medical Center, Chicago, IL*

Background: Genetic counseling for hereditary breast cancer remains underutilized despite increased access. The lack of identification and/or referral of high-risk women for genetic counseling is the major contributor to the poor uptake. A cancer risk assessment program (CRA) utilizing NCCN guidelines was implemented in our breast imaging department to identify women at increased risk for breast cancer. We analyzed the impact of informing all women who get a screening mammogram of their genetic mutation risk and the effect of nurse navigation on increasing the subsequent uptake of genetic counseling. **Methods:** To assess the effectiveness of these interventions, data from July 2021 to January 2022 was extracted from the EMR and grouped into cohorts based on nurse navigation contact and the completion of genetic counseling. A chi-squared analysis was performed to determine the significance of the results. **Results:** A total of 22,915 patients participated in the CRA program during the study period. 2,671 (11.7%) patients qualified for genetic counseling based on NCCN guidelines. 414 (15.5%) of these patients completed a genetic counseling appointment. 298 of these patients received genetic testing (72%) and 18 (4.3%) had a pathogenic mutation found. The nurse navigator was able to reach 1,288 (48%) of the 2,671 patients (Cohort A). Of these patients, 324 (25.2%) completed genetic counseling appointments compared to 90 of the 1,383 (6.5%) patients who were not contacted by the nurse navigator (Cohort B). Statistical analysis determined there was a significant difference in uptake of genetic counseling between Cohort A and Cohort B ($p < .0001$). **Conclusions:** The implementation of the CRA program at the breast imaging center uncovered many patients who qualified for genetic counseling and testing based on NCCN guidelines. Genetic counseling uptake is significantly increased in patients who are reached by a Nurse Navigator. These interventions allowed for the discovery of unsuspected deleterious genetic mutations which require more aggressive screening to allow for the early detection of breast cancer and better overall prognosis. Research Sponsor: This research was supported by a generous gift from a donor, Sheli Rosenberg.

Genetic counseling uptake between nurse navigation cohort and control.

	Total N=2,671	Percent of Population	Completed Genetic Counseling N=414	Percent of Com- pleted appt.
Patients who talked to the Nurse Navigator (Cohort A)	1,288	48.22%	324	25.16%
Patients who did not talk to Nurse Navigator (Cohort B)	1,383	51.78%	90	6.51%

10601

Poster Session

Genetic testing outcomes and pathogenic germline mutation prevalence in renal cell carcinoma. *First Author: Charles B Nguyen, Rogel Comprehensive Cancer Center, University of Michigan, Ann Arbor, MI*

Background: Germline mutations have been observed in renal cell carcinoma (RCC) with varying frequencies reported from 5% to 18% of patients. Due to the prevalence of germline mutations, current guidelines by the National Comprehensive Cancer Network (NCCN) recommend genetic testing for patients with RCC and high-risk factors such as young age, bilateral or multifocal tumors, family history of RCC, as well as certain RCC histologies. However, the germline mutational landscape in RCC has not been fully characterized. Here, we report the genetic testing results and clinicopathologic factors of patients with RCC who were referred for germline testing. **Methods:** All patients with a diagnosis code of kidney cancer and referred to the Cancer Genetics clinic at the University of Michigan between 2004 and 2022 were identified. Patients were excluded if they had erroneous RCC diagnosis codes, no history of RCC diagnosis, known familial/hereditary mutation or syndrome, or did not undergo germline testing. Genetic testing outcomes, germline mutation frequency, and clinical factors were obtained through chart review and analyzed using descriptive statistics. **Results:** A total of 322 patients with a history of RCC and referred for genetic testing were identified. The median age at diagnosis in all patients was 47 (interquartile range: 38-58). Males accounted for 56.8% of the cohort. Most patients (62.4%) had clear cell histology at initial diagnosis, whereas 30.7% had non-clear cell histology. The majority of patients (61.5%) were diagnosed at stage 1. Bilateral and multifocal tumors at diagnosis accounted for 18.9% and 12.7%, respectively. Pathogenic or likely pathogenic variants (P/LP) were identified in 43 patients (13.4%); 225 patients had negative germline testing (69.9%); 54 patients (16.8%) had a variant of unknown significance (VUS). The most frequently mutated RCC-associated genes were *FLCN* (n=10, 3.1%), *SDHA/B/D* (n=7, 2.2%), *VHL* (n=4, 1.2%), *MLH1* (n=3, 0.9%), and *FH* (n=2, 0.6%). Common mutations in other cancer-related genes were *CHEK2* (n=4, 1.2%), *ATM* (n=2, 0.6%), and *RAD50* (n=2, 0.6%). Most patients (81.4%) with a P/LP test result had at least 1 of the following: diagnosis age $\leq$ 46 years, bilateral or multifocal tumors, or at least 1 first-degree relative with RCC. Out of the patients with a P/LP result, 18 patients (39.1%) had a potentially actionable mutation. **Conclusions:** Among patients with RCC who were unselected for a known familial/hereditary predisposition, P/LP variants were present in 13.4% which is consistent with previous studies. The prevalence of *FLCN* mutations was higher in our cohort (3.1%) compared to prior observations. Most patients with a P/LP variant met the NCCN criteria for genetic testing. Future studies should optimize the current genetic testing criteria to identify a broader group of patients who may have germline mutations given potential cascade testing and therapeutic implications. Research Sponsor: None.

10600

Poster Session

Scalable new model of genomic care delivery: Assessing psychological outcomes. *First Author: Stacy W. Gray, City of Hope, Duarte, CA*

Background: Germline testing (GT) use is on the rise given testing implications for identifying cancer susceptibility and therapeutically actionable alterations. Scalable models of care that emphasize post-test, as opposed to pre-test, genetic counseling are needed to meet demand. However, little is known about the psychological impact (PI) of test result disclosure in such models. **Methods:** The enterprise-wide City of Hope INSPIRE study offers all consented patients GT for cancer susceptibility (155 genes) and actionable disorders (59 genes). In 2022, we surveyed a sub-set of English-speaking participants ~1 month following test result disclosure. We evaluated PI using the Feelings about Genomic Testing Results (FACToR) measure (distress/ uncertainty subscales 0-12; positive subscale 0-16) and explored associations between patient characteristics, GT results and PI. **Results:** Of 1000 patients surveyed, 615 completed at least one of the FACToR questions. Participants were mostly white (n=463, 75%) or Asian (n=12, 2%) and female (n=419, 68%) with a mean age of 62 yrs. 357 (61%) had a cancer diagnosis and most opted for both GT panels (97%). Eighteen percent had a pathogenic/likely pathogenic variant (PV/LPV) in an autosomal dominant condition, 8% were carriers for an autosomal recessive condition, 53% had at least one variant of unknown significance (VUS) and 21% had negative results. Most patients (n=583, 95%) had low levels of distress with a mean score of 1.67 (SD 2.31). Out of the 30 (5%) patients with higher levels of distress (score >7), results were similar for patients with and without cancer (5% and 4% respectively). Of the 30 patients with higher distress, 67% had a P/LPV variant (13 with and 7 without cancer). Patients also had low levels of uncertainty with a mean score of 2.22 (SD 2.61) and 93% (n=569) scored <7 . For those who scored higher on uncertainty (n=44, 7%), most people had cancer and a VUS (n=16, 36%), followed by cancer and LPV/PV (n=10, 23%) followed by patient without cancer with a VUS (n=6, 14%). Finally, 56% (n=44) had high positivity scores (9-16); mean 9.18 (SD 4.31). Fifty-six percent of patients felt a "good/great deal" happy about their GT and 54% were a good/great deal relieved about their results. **Conclusions:** After implementing an enterprise-wide germline testing program with an emphasis on robust post-test genetic counseling, we found very little evidence of post-disclosure distress or uncertainty. Similar to prior studies, we found that a small proportion of patients may be more vulnerable to negative PI. More work is needed to prospectively identify at risk patients to provide support to this population as we continue to develop safe, effective, and scalable models of care. Research Sponsor: None.

10602

Poster Session

Clinical utility of reporting research genetic predisposition testing results to Total Cancer Care participants. *First Author: Megan Leigh Hutchcraft, University of Kentucky Markey Cancer Center, Lexington, KY*

Background: The American College of Medical Genetics and Genomics (ACMG) has identified genes with highly penetrant phenotypes with treatment, prevention, or early disease identification strategies called secondary findings (SF) genes. ACMG recommends clinical laboratories report pathogenic/likely pathogenic (P/LP) SF variants identified during genomic testing. Cancer patients may undergo germline sequencing as part of research studies that can identify valuable SF variants. The objective of this institutional sub-study is to evaluate the feasibility of using ACMG SF genes to assess hereditary disease risk in a cancer population undergoing research sequencing. **Methods:** Between June 2017 and January 2021, patients unselected for family history, disease site, or stage enrolled in the prospective, observational Total Cancer Care study. Patients underwent research-grade germline whole exome sequencing, with bioinformatic analysis in a CLIA certified laboratory to identify P/LP variants in any ACMG SF v2.0 genes. P/LP variants were reported to treating oncologists with recommendations for genetic counseling referral. We assessed if patients with P/LP variants met NCCN guideline-directed germline testing criteria to quantify benefit from reporting research results. **Results:** We enrolled 786 patients, which included those with gynecologic (182, 23%), colorectal (124, 16%), lung/bronchus (83, 11%), and head/neck (82, 10%) cancers. The median age was 61 (IQR 52-68) years, 57% were female, 96% were non-Hispanic White, 51% had stage III/IV disease, and 64% resided in an Appalachian community. We identified 57 patients (7%) with cancer predisposition and 14 (2%) with other hereditary disease variants. 2021 NCCN guideline-directed testing would have missed 59% (42/71) of these patients. Incremental high penetrance cancer gene variants included: *BRCA1* – endometrial cancer (n = 1); *BRCA2* – cholangiocarcinoma (n = 1), colon neuroendocrine tumor (n = 1), and lung (n = 2), endometrial (n = 1), and non-epithelial ovarian (n = 1) cancers; *MSH6* – duodenal cancer (n = 1); *SDHAF2* – non-melanoma skin cancer (n = 1); *SDHB* – head/neck cancer (n = 1); and *TP53* – CNS tumor (n = 1) and head/neck cancer (n = 1). We identified patients at risk for other hereditary diseases including hypertrophic/dilated cardiomyopathy (n = 1), malignant hyperthermia (n = 3), arrhythmogenic right ventricular cardiomyopathy (n = 1), Romano-Ward long QT / Brugada syndromes (n = 4), familial hypercholesterolemia (n = 4), and ornithine transcarbamylase deficiency (n = 1). **Conclusions:** Reporting germline variants identified during research sequencing is feasible and can benefit cancer patients and their relatives. Though not traditionally assessed, non-cancer predisposition genetic variants may have important intervention opportunities and unexpected patterns may have oncologic implications that require further study. Research Sponsor: U.S. National Institutes of Health.

10603

Poster Session

Healthcare utilization among individuals diagnosed with lynch syndrome through a universal germline genetic testing program. *First Author: Heather Hampel, City of Hope, Duarte, CA*

Background: Most individuals with Lynch syndrome (LS) are unaware of their risk. Criteria-based testing will not close this gap as it fails to identify ~50% of mutation carriers. Universal germline testing (GT) for in oncology stands to identify more mutation carriers and advance cancer control. However, the clinical utility of universal germline testing is unknown. **Methods:** The enterprise-wide City of Hope INSPIRE study offers all consented patients GT for cancer susceptibility (155 genes) and actionable disorders (59 genes). We used an informatics approach to evaluate healthcare utilization for patients found to have *MLH1*, *MSH2*, *MSH6*, *PMS2* or *EPCAM* mutations. We queried codified data elements in our electronic data warehouse before and after GT (post testing interval: 1-29 months). We binned care as possibly related/ not related to HBOC based on NCCN guidelines. **Results:** Of 10,814 patients who had GT, 80 (0.74%) had a pathogenic/ likely pathogenic mutation in either *MLH1*, *MSH2*, *MSH6*, *PMS2* or a 3' deletion of *EPCAM*. The demographic distribution of LS patients was: white (n = 51, 64%), Asian (n = 13, 16%), Hispanic (n = 19, 24%); female (n = 51, 64%); the mean age was 54 yrs. Eighty-six percent (n = 69) had cancer, including 45% with cancers associated with LS (colorectal 17%, endometrial 7%, ovarian 6%, esophageal/stomach 5%, bladder/urinary tract 5%, and prostate 5%) and 41% with cancers that are not associated with LS. Fifty-two percent of all LS patients had procedures, imaging, and/or therapy potentially related to their LS diagnosis. As expected, utilization of colonoscopy, EGD, MRCP/EUS, transvaginal ultrasound, and hysterectomy with bilateral salpingo-oophorectomy (HSO) occurred both before and after testing for the cancer cohort, with the majority of utilization occurring after testing likely related to their Lynch syndrome diagnosis. Twelve (17%) cancer patients with Lynch syndrome received Immune Checkpoint Inhibitor therapies. In the unaffected cohort, rates of utilization were higher prior to testing for transvaginal ultrasound possibly because 2% underwent a HSO after their diagnosis and no longer required endometrial surveillance. Rates of colonoscopy, EGD, and HSO were all higher after GT. **Conclusions:** We found high levels of relevant healthcare utilization for Lynch syndrome gene mutation carriers in the context of universal GT. However, this initial informatics approach is limited because key information on prior GT and motivations for surgery (e.g., therapeutic vs prophylactic HSO) are not adequately captured in codified data. Codified EHR queries will need to be augmented by text mining and/or manual chart review to fully capture care and assess the clinical utility of system-wide genetic care delivery interventions. Research Sponsor: None.

10605

Poster Session

Validation of a guidelines-based brief patient-administered digital tool to assess the need for germline genetic testing. *First Author: Callan Russell, Northside Hospital, Atlanta, GA*

Background: Scalable and reliable approaches are needed to assist non-genetics clinicians in assessing whether a patient meets criteria for germline genetic testing. Insurance coverage of genetic testing often depends on such assessments. RISE Risk Assessment Module: Hereditary Cancer is a brief patient-administered digital tool designed for this purpose. The tool's assessment is based on personal and family history and is informed by national guidelines. The aim of this study was to assess the clinical validity of this digital tool by evaluating its agreement with assessments made by genetic counselors. **Methods:** We performed a chart review of cases from a telehealth genetic counseling practice seen July to October 2020. Extracted history was entered into the tool by the research team to model how a patient would complete the digital tool. The tool's assessment of whether the patient met criteria for genetic testing was compared to the assessment of the genetic counselor who saw the patient. To further validate the tool, a subset of cases were analyzed for agreement between the tool and research team on which specific history-based rules in the tool's algorithm applied for a given case. **Results:** The majority (121/152; 80%) of cases were female and the mean age was 52.3 (SD 15.9). Just over half of cases (85/152; 56%) had a personal history of cancer, including breast (27/85; 32%), colon (15/85; 18%), prostate (10/85; 12%), endometrial (12/85; 14%), and ovarian (7/85; 8%). 100/152 (66%) of cases met criteria for genetic testing. In 146/152 (96%) cases there was agreement between the assessments made by the tool and the genetic counselor regarding whether the patient met criteria for germline genetic testing. Nearly all disagreement (4/6; 67%) resulted from history intentionally left out of the tool as patients can rarely report them (aspects of tumor pathology 3/4; risk of having a pathogenic variant based on predictive models 1/4). For a subset of cases (62/152) we compared the tool and research team's assessments of which aspects of the patient's personal and family history met criteria for genetic testing. This was done by looking at which rules in the tool's algorithm were triggered by the patient's history. There was complete agreement between the tool and research team on which rules should be triggered. Completion of the tool took a mean of 3.3 minutes. **Conclusions:** The high level of agreement between the digital tool and genetic counselors supports RISE Risk Assessment Module: Hereditary Cancer as a clinically valid method of identifying individuals in need of evaluation for hereditary cancer predisposition. Complete agreement on which history-based rules applied in these cases further supports the clinical validity of the tool. Our results also suggest that the tool's assessment can be delivered in under 5 minutes, which is critical to feasibility and scalability of the digital tool. Research Sponsor: Genome Medical.

10604

Poster Session

Healthcare utilization among individuals diagnosed with hereditary breast-ovarian cancer syndrome through a universal germline genetic testing program. *First Author: Stacy W. Gray, City of Hope Comprehensive Cancer Center, Duarte, CA*

Background: Most individuals with Hereditary Breast-Ovarian Cancer Syndrome (HBOC) are unaware of their risk. Criteria-based testing will not close this gap as it fails to identify ~50% of mutation carriers. Universal germline testing (GT) in oncology stands to identify more mutation carriers and advance cancer control. However, the clinical utility of universal germline testing is unknown. **Methods:** The City of Hope INSPIRE study offers all consented patients GT for cancer susceptibility (155 genes) and actionable disorders (59 genes). We used an informatics approach to evaluate healthcare utilization for patients found to have *BRCA1/BRCA2* mutations. We queried codified data in our electronic data warehouse before and after GT (post testing interval: 1-29 months). We binned care as possibly related/ not related to HBOC based on NCCN guidelines. **Results:** Of 10,814 patients who had GT, 217 (2%) had a pathogenic/ likely pathogenic mutation in either *BRCA1* or *BRCA2*. The demographic distribution of mutation carriers was: white (n = 162, 75%), Asian (n = 28, 13%), Hispanic (n = 65, 30%); female (n = 184, 85%); the mean age was 54 yrs. Eighty-four percent (n = 182) had cancer, including 64% with cancers associated with HBOC (breast 40%, ovarian 13%, pancreatic 3%, 5% prostate, and 0.5% melanoma) and 18% with cancers that are not associated with HBOC. Eighty-three percent of patients had procedures, imaging, and/or therapy potentially related to the *BRCA* mutation. Eighty-six percent of cancer patients had potentially related care. As expected, use of breast MRI, mammography, MRCP, mastectomy, and bilateral salpingo-oophorectomy (BSO) occurred both before and after testing, with most utilization occurring prior to GT and likely related to cancer staging and treatment. The exception was MRCP which occurred more often following GT (0.6% before vs 1.2% after). Fifty-one (28%) cancer patients received PARP inhibitors. In the unaffected cohort, 67% of patients received possibly related care. Use of mammography was higher prior to GT (7% vs 2%). Consistent with the fact that some unaffected patients were likely known mutation carriers prior to consent, mastectomy was higher prior to GT (5% vs 0%) and BSO was equivalent before and after GT (1.8%). Use of breast MRI (9% vs 15%), MRCP (1.8% vs 3%) and transvaginal US (5% vs 7%) were all higher after GT. **Conclusions:** We found high levels of relevant healthcare utilization for *BRCA* mutation carriers in the context of universal GT. However, this initial informatics approach is limited because key information on prior GT and motivations for surgery (e.g., therapeutic vs prophylactic mastectomy) are not adequately captured in codified data. Codified EHR queries will need to be augmented by text mining and/or manual chart review to fully capture care and assess the clinical utility of system-wide genetic care delivery interventions. Research Sponsor: None.

10606

Poster Session

A comprehensive analysis of clinical characterization in 149 Chinese patients with Lynch syndrome. *First Author: Junqiong Lin, Second Affiliated Hospital of Guangdong Medical University, Zhanjiang, China*

Background: Lynch syndrome (LS) caused by germline pathogenic variants (PVs) in mismatch repair (MMR) genes, which increased risk of malignancy in different organs. LS-related tumors included colorectal, endometrial, gastric, ovarian, pancreas, urinary system, biliary tract, central nervous system, skin and small intestinal carcinomas (CRC, EC, GC, OC, PC, UST, BTC, CNST, SC, SIC). As sequencing technology becomes more economical and widespread, more MMR PVs were detected in LS-unrelated tumors. The aim of this study was to explore the clinical characterization in Chinese real-world LS solid tumor. **Methods:** We applied next-generation sequencing (NGS) screening to detect the germline mutation in MMR (include *MLH1*, *MSH2*, *MSH6*, *PMS2*), tumor mutation burden (TMB) and microsatellite instability (MSI) in Chinese solid tumor patients (pts). In the cohort, lung cancer (LC) was the most common cancer type, followed by CNST, CRC, hepatic carcinoma (HC). **Results:** 149 LS pts were observed in our cohort, among which 81.2% (121/149) carried LS-related tumors (44 CRC, 47 CNST, 9 EC, 9 BTC, 4 UST, 3 OC, 2 GC, 2 SC, 1 SIC), 18.8% (28/149) carried with LS-unrelated tumors (18 LC, 5 HC, 3 sarcoma, 1 ampullary carcinoma, 1 peritoneal cancer), and the age showed no significant difference between LS-related tumors and LS-unrelated tumors (average age: 48 vs 53, $p=0.08$). The distribution of MMR PVs were as follows: *MLH1* (37, 24.8%), *MSH2* (46, 30.9%), *MSH6* (34, 22.8%), *PMS2* (32, 21.5%), and comparative analysis showed that LS-related tumors tended to carry *MLH1* and *MSH2* PVs (60.3%, 73/121), while LS-unrelated tumors tended to carry *MSH6* and *PMS2* PVs (67.9%, 19/28) ($p<0.05$). 46.3% LS pts had MSI-H, concentrated in *MLH1* or *MSH2* PVs carriers. MSI-H showed a higher detection rate in LS-related tumors other than LS-unrelated tumors (56.1% vs 3.6%, $p<0.005$). Among LS-related tumors, the top 3 prevalence of MSI-H were CRC (93.2%, 41/44), BTC (55.6%, 5/9) and EC (44.4%, 4/9), which were lower in CNST (31.9%, 15/47). In addition, we found that the rate of TMB-H in LS-related tumors was also higher than LS-unrelated tumors ($p<0.001$). **Conclusions:** In our dates, 18.8% (28/149) LS pts carried with LS-unrelated tumors, which emphasized the importance of germline genetic assessment for LS in pan-cancer. In addition, MSI-H, TMB-H and MMR PVs distributions were significantly different in LS-related tumors and LS-unrelated tumors. The differences about LS clinical characterization associated with MMR genes require further study. Research Sponsor: None.

10607

Poster Session

Using patient-reported outcomes to assess the impact of germline genetic testing on prostate cancer patients. *First Author: Sarah M. Nielsen, Invitae, San Francisco, CA*

Background: Germline genetic testing (GGT) affords prostate cancer (PCa) patients (pts) opportunities for targeted therapies, prevention and cascade testing. Patient-reported outcomes (PRO) can evaluate physician effectiveness in promoting patient test comprehension and clinical decision making, which are critical to realize the benefits of GGT. PROs from a large PCa GGT study among urologists were analyzed. **Methods:** A prospective study enrolled unselected PCa pts from 15 primarily community urology practices. Pts underwent 84-gene GGT, with PROs collected via electronic or paper surveys >1-month post GGT. Differences in proportions were determined using two-tailed Fisher's exact test and significance was set at <0.05. **Results:** PROs were completed by 561/982 (57%) pts (85% white, 82% non-metastatic, median age at testing 70 years). 59 (11%) pts had positive results, 247 (44%) negative and 255 (46%) variants of uncertain significance (VUS). 72% accurately recalled their result (range, 50% [VUS]-93% [negative]). 66% of positive pts, 80% negative and 54% VUS correctly understood if their result was associated with cancer risk or not. 72% of positive pts had or planned to complete ≥1 physician recommendations, significantly more than negative or VUS pts (Table). Most pts reported that their test result reduced their concerns (40%) or did not impact their level of concern (52%) regarding their PCa diagnosis, treatment or followup. 19% of positive pts reported increased concern. **Conclusions:** GGT for PCa was deployed without causing undue concern and resulted in adherence to physician recommendations. Still, there is room for improvement in how test results (especially VUS) and recommendations are communicated to pts. Research Sponsor: Invitae Corp.

Uptake of physician recommendations among PCa position.

Recommendation	Total (n=561)	%*	Positive (n=59)	%*	Negative (n=247)	%*	VUS (n=255)	%*
No response	25	5	2	3	11	5	12	5
No additional recommendations made by physician	228	43	10	18	127	63	91	36
See a genetic counselor to further understand my test results	62	20	10	21	19	9	33	22
New treatment plan	72	23	9	19	26	13	37	2
New follow up plan	31	10	3	6	15	7	13	9
Meet with a specialist to follow up on non-PCa concerns	23	8	4	9	8	4	11	7
Recommend family members be tested and/or see genetic counselor	70	23	25	53	19	9	26	17
Completed or plan to complete ≥1 of the above recommendations	172	56	34	72 [^]	56	28	82	54 [^]

* Denominator excludes pts from rows 1 and 2. [^] Significant difference between positive and negative/VUS pts and between VUS and negative pts.

10609

Poster Session

Prospective prevalence estimation of BRCA1, BRCA2, and other germline mutations associated with hereditary pancreatic cancer (HPC) using a comprehensive gene panel in an unselected cohort of Mexican patients with pancreatic ductal adenocarcinoma (PDAC). *First Author: Vanessa Rosas Camargo, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico*

Background: Prevalence of pathogenic or likely pathogenic germline variants (PGVs) in patients with PDAC varies across populations. There is limited information on the prevalence of PGVs among Mexican patients with PDAC. We prospectively tested an unselected cohort of newly diagnosed PDAC patients using a comprehensive gene panel in order to estimate the prevalence of BRCA1/2, and other germline mutations associated with HPC. **Methods:** The protocol was approved by the ethics committee at each institution: INCMNSZ, INCAN, and CM ABC Observatorio. Key inclusion criteria: age > 18 years and PDAC diagnosed within 6 months of inclusion. Patients were enrolled consecutively, regardless of age, personal or family history of cancer, known hereditary cancer syndrome, or stage of the disease. Written informed consent was obtained before any procedure. Clinical variables including family history of cancer were collected. We used the 84-gene Invitae Multi-Cancer Panel. Genetic testing had no cost for patients. Patient characteristics and family history were summarized using descriptive statistics (IBM SPSS Statistics Version 25). The trial was registered on Clinical Trials (NCT05305001). **Results:** From August 2020 to June 2022, 119 patients with newly diagnosed PDAC were identified. Of these, 107 patients were included: 58% women, median age was 63 y/o, clinical stages at diagnosis were: I (24%), II (22%), III (6%), and IV (48%). All patients had Hispanic ancestry except one (Ashkenazi Jewish). Only 7.5% (n = 8) had a personal history of other cancer, mainly breast cancer (N = 3); 62% had a family history of any cancer, while 47.6% had a first-degree relative (FDR) with any cancer. 11% (n = 12) had family history of pancreatic cancer (PC), and 9% (n = 10) had an FDR with PC. Five patients met clinical criteria for hereditary cancer syndrome: familial pancreatic cancer (4) and Lynch syndrome (1). PGVs were identified in 17.8% (n = 19) of patients. The prevalence of PGVs in genes associated with autosomal dominant risk of PC was 11.2%: *CDKN2A* (5.6%), *ATM* (3.7%), *BRCA2* (0.93%), and *MSH6* (0.93%). Two patients had a PGV associated with autosomal dominant predisposition to other cancers (*CHEK2* and *NF1*). Six patients (5.6%) had PGVs associated with autosomal recessive predisposition to rare syndromes with increased cancer risk other than PDAC (*MUTYH*, *RECQL4*, *FH* and *WRN*). Variants of uncertain significance were present in 42% of patients. **Conclusions:** In Mexican patients with PDAC, the prevalence of PGVs on BRCA1/2 is < 1%. The prevalence of PGVs in other susceptibility genes is 11%. Our results support the role of universal germline testing in Mexican patients with PDAC using a comprehensive gene panel. Selective testing for BRCA1/2 is discouraged. Research Sponsor: Externally Sponsored Scientific Research Program by AstraZeneca.

10608

Poster Session

Somatic profiling guides germline genetic testing in patients with mutations in cancer predisposition genes. *First Author: Sourat Darabi, Hoag Family Cancer Institute, Newport Beach, CA*

Background: 15% of patients with advanced cancer have an inherited predisposition to cancer. Over a third of patients carrying a pathogenic germline variant would not qualify for genetic testing based on current National Comprehensive Cancer Network genetic testing guidelines. Supplementing the current practice of somatic sequencing with germline testing would improve treatment decisions and be informative of the risk of developing subsequent cancers in the individual. It may also extend the benefits of high-risk screening programs to family members. Offering genetic testing to patients with the highest likelihood of carrying a germline mutation is preferable to unselected sequencing given the current environment. **Methods:** We developed a list of genes to help identify patients whose somatic mutations were more likely to be found in the germline as well. We classified these genes into 3 tiers based on the likelihood of germline pathogenicity. All somatic sequencing panel results were reviewed based on the IRB-approved protocol for our designated Tier One genes (*ATM*, *BAP1*, *BMPR1A*, *BRCA1*, *BRCA2*, *BRIP1*, *MSH2*, *MSH6*, *MUTYH*, *MYH11*, *PALB2*, *RUNX1*, *SDHAF2*, *SDHB*, *SDHC*, and known founder mutations in additional genes). Treating physicians for patients whose tumors harbored a mutation in one of these genes were contacted and, if they agreed, patients were offered participation in this ongoing study. Enrolled patients had genetic counseling and testing for a multi-gene panel at no cost to them. **Results:** We reviewed 3621 somatic test results, and 339 (9.4%) patients were eligible for the study. 34 (10.03%) eligible patients were enrolled, and 33 (9.73%) completed testing. Of these, 16 had positive germline results (48.5%, though they may not all be in the originally identified genes), 8 had a variant of uncertain significance (24.2%), and 9 had negative testing (27.3%). Some patients were not referred by their treating physicians based on their own clinical assessment. Others were hesitant to enroll due to concerns about the privacy of genetic information. Other confounding factors may have affected our accrual, including the pandemic. **Conclusions:** Implementing a somatic profiling-based screening program to identify inherited cancer predisposition syndromes is feasible in patients who may not meet current germline genetic testing guidelines. Our study showed 9.73% of eligible patients underwent genetic counseling and testing, and an inherited predisposition to cancer was confirmed in almost 50% of these patients. In addition, family members were offered cascade testing. Germline genetic evaluation remains underutilized even when payor constraints are removed as a barrier. To increase the identification of patients with inherited predispositions to cancer other barriers such as a lack of referrals by treating oncologists need to be overcome. Research Sponsor: None.

10610

Poster Session

Cancer risk and characteristics in older female BRCA1/2 mutation carriers. *First Author: Bipin Ghimire, Corewell Health William Beaumont University Hospital, Royal Oak, MI*

Background: Cancer risk and characteristics in older females with *BRCA1/2* mutations are less well studied, and the role of risk-reducing strategies in this population remains unclear. **Methods:** From a database of 1070 female carriers of *BRCA1/2* pathogenic (PV) or likely pathogenic variants (LPV) seen at Nancy and James Grosfeld Cancer Genetics Center in Beaumont Health from January 2006 to December 2021, we identified 283 females who lived to age 65 or older. We analyzed cancer risk and clinical characteristics, focusing on females with cancer diagnosed at age 65 or older. **Results:** Of the 283 *BRCA1/2* carriers, 229 (81%) had a cancer diagnosis, out of which 84 (37%) were diagnosed at age 65 or older. Of all the breast cancer diagnoses (n = 173), 45 (26%) were diagnosed at age 65 or older. Among these 45 patients, median age at diagnosis was 69 years (65-87); majority were *BRCA2* carriers (62%), with invasive ductal carcinoma (80%), ER-positive (58%), PR-negative (55%), HER2-negative (97%), high grade (55%) and had stage I or II disease (78%). Fifteen patients (38%) were triple-negative. A minority (32%) received adjuvant chemotherapy, 43% received adjuvant endocrine therapy, and 54% received adjuvant radiation. During a median follow-up of 205 months for all breast cancers (n = 173), there were 52 recurrences, 28 of these (54%) were diagnosed at age 65 or older, of which 13 were contralateral (median time to recurrence: 140 months); 5 were local/regional (median time: 186 months) and 10 were metastatic (median time: 76 months). Ten of the 13 contralateral recurrences (77%) were in *BRCA1* carriers. Of the ovarian cancer diagnoses (n = 69), 27 (39%) were diagnosed at age 65 or older. Among these 27 patients, median age at diagnosis was 71 years (65-87); majority were *BRCA2* carriers (74%), had serous carcinoma (84%), with stage III or IV disease (96%). Of all ovarian cancers (n = 69), there were 15 recurrences (22%), 9 of them (60%) were diagnosed at age 65 or older. Of the 8 pancreatic cancers, 6 were diagnosed at age 65 or older. Of the 283 *BRCA1/2* carriers, 249 still had at least one breast at the time of genetic testing, and 34% elected for risk-reducing mastectomy (RRM). Of the 177 patients with intact ovaries, 71% opted for risk-reducing salpingo-oophorectomy (RRSO). Compared to *BRCA* carriers with cancer diagnosed under age 65, a smaller proportion of those diagnosed at age 65 or older opted to undergo RRM (26% vs. 40%) or RRSO (67% vs. 78%). **Conclusions:** Our study reveals that female *BRCA1/2* mutation carriers over age 65 continue to retain a significant risk of cancer, including breast, contralateral breast, ovarian, and pancreatic cancer. This finding supports the importance of continued high-risk surveillance and risk-reducing interventions in this growing demographic. Further studies are needed to better define the cancer risks and optimal management of older females with *BRCA1/2* mutations. Research Sponsor: None.

10611

Poster Session

Beyond the standards: The impact of provider collaboration on referrals to genetic counseling. *First Author: Eric S Fowler, City of Hope Atlanta, Chicago and Phoenix, Zion, IL*

Background: The Commission on Cancer standards require institutions to monitor genetic assessment for a selected cancer site, providing an opportunity to increase referrals to genetic counseling. Genetic counseling, risk assessment, and testing improve patient care, outcomes, and facilitate cascade testing in families. This study investigated how collaboration with referring providers through education, feedback, and ongoing communication impacted referrals to genetic counseling. **Methods:** Study participants included new patients with colorectal cancer (CRC) diagnosed under age 50 presenting to our institution from July 2021 to September 2022. Patients were excluded if they did not return after initial visits. Baseline and intervention time periods were compared. Interventions to increase referrals included communication with the medical staff through memoranda co-authored by genetic counselors and physician champions, presentations by genetic counselors at tumor board, medical oncology, cancer committee meetings, and emails providing quarterly and final outcomes. Descriptive statistics were utilized to review categorical data, with baseline and intervention referral rates compared with the Pearson Chi-Square Test. **Results:** 133 patients met referral criteria with ages at diagnosis ranging from 19-49 years old. Mean (and median) patient ages were comparable between baseline and intervention study periods: 42.5 (45) and 43.0 (45), respectively. In the baseline period, 10/32 (31.3%) patients were referred to genetic counseling. In the intervention period, 58/101 (57.4%) patients were referred to genetic counseling representing a 26.1% increase over baseline. The Pearson Chi-Square Test yielded a p-value of 0.01. Referral rates varied by quarter (collaboration/education began in mid-Q2): Q1 - 26.7%, Q2 - 45.8%, Q3 - 77.8%, Q4 - 60.0%, and Q5 - 34.4%. **Conclusions:** Collaboration and communication with referring providers resulted in statistically and clinically significant increases in referrals to genetic counseling. The increase in referrals was most pronounced immediately after collaboration began and declined by the last quarter. This study highlights the importance of genetics educational initiatives and ongoing communication in the oncology setting, and the need for alternative and more sustainable strategies to maintain and increase referrals to genetic counseling. Referrals to genetic counseling facilitate the provision of cancer screening guidelines for patients and their families, based on genetic test results and personal/family histories, and reinforce the importance of cascade testing where appropriate. Research Sponsor: None.

Genetics referrals: New patients with CRC < 50.				
		Baseline	Intervention	Total
n (%)	Not Referred	22 (68.7)	43 (42.6)	62 (46.6)
	Referred	10 (31.3)	58 (57.4)	71* (53.4)
	Total	32 (100.0)	101 (100.0)	133 (100.0)

*Three baseline patients were referred during intervention

10613

Poster Session

Impact of early testing and analysis of germline genetic mutation patterns in patients with breast cancer: A single institution experience. *First Author: Aswanth Reddy, Mercy Clinic Oncology, Fort Smith, AR*

Background: Approximately 3% of patients with breast cancer have a pathogenic or likely pathogenic variant (mutation) in a high-risk breast cancer gene, such as BRCA1, BRCA2 and PALB2, which increases breast cancer risk more than fourfold. Approximately 3% have a germline mutation in a moderate-penetrance breast cancer gene, such as ATM or CHEK2, which confers a two- to threefold increased risk of breast cancer. **Methods:** In 2020 we started offering germline genetic testing to all newly diagnosed breast cancer patients at the time of diagnosis irrespective of their family history. Our objectives included the following: Prevalence of mutations in breast cancer patients treated at our institution. Germline mutations in patients with Ductal carcinoma in situ (DCIS). To identify if early universal germline testing affected the surgical modality. **Results:** A total of 525 patients were seen in the oncology clinic from January 2020 to December 2022 with a breast cancer diagnosis. The median age of diagnosis is 66 (32-91) years. Invasive ductal cancer (IDC 66 %) was the most common subtype, followed by DCIS (18%) (Table 1). Most patients had estrogen-positive cancer (82% vs. 18%), and approximately 13% had HER2-positive disease (61% HER2 low). Mutation in CHEK2 (9 patients) was our cohort's most common pathogenic mutation, followed by BRCA1 (6 patients) and MUYTH (6 patients) genes. Predominant germline mutations were identified in patients with IDC, followed by DCIS. One patient with a pure mucinous subtype had a germline pathogenic mutation (RECQL4 gene). We identified a higher percentage of pathogenic breast cancer-related mutations in patients above 60 years (63% vs. 37%) and all CHEK2 mutations were in patients above 60. Out of 41 patients with pathogenic mutations, 17 underwent a partial mastectomy, 12 had a bilateral mastectomy, and two had a unilateral mastectomy. All patients with BRCA1/2 mutation chose bilateral mastectomy, and all patients with a CHEK2 mutation underwent a partial mastectomy. Several variants of unknown significance (VUS) mutations were identified, and they followed a similar pattern, being more common in patients with IDC. VUS mutations in the ATM gene were the most reported abnormality. **Conclusions:** Pathogenic mutation in the CHEK2 gene is more prevalent, and we hypothesize that this finding could be related to the demographic population treated in our institution. Also, CHEK2 mutation was only identified in patients older than 60, which argues for more testing in patients in this age group. Approximately 9% of all IDC patients had a germline mutation compared to 4.2 % in patients with DCIS. Our review identifies that patients with BRCA1/2 mutations tend to undergo prophylactic mastectomy, and early testing likely impacted this decision. From our study, we believe that germline genetic testing should be offered to all breast cancer patients. Research Sponsor: None.

10612

Poster Session

Digital cancer genetic risk assessment in a gynecologic oncology clinic. *First Author: Emily M Webster, Weill Cornell Medicine, New York, NY*

Background: Population-based screening for hereditary cancer syndromes and referral of those who screen positive for genetic testing is a cost effective, evidence-based national health priority. However, under-recognition of hereditary cancer syndromes remains a critical concern, with fewer than 20% of individuals with Hereditary Breast and Ovarian Cancer Syndrome and Lynch Syndrome identified. Here, we evaluate the Ambry Genetics Comprehensive, Assessment, Risk, and Education (CARE) Program, a risk-stratification tool to assess eligibility for National Comprehensive Cancer Network (NCCN) genetic testing criteria and lifetime risk for breast cancer based on the Tyrer-Cuzick (version 8.0) risk algorithm. **Methods:** Between November 2022 and February 2023, new patients in a gynecologic oncology clinic were prompted by text message to complete CARE prior to their appointment. Those using CARE then completed a System Usability Scale (SUS), a validated 10-item questionnaire for the assessment of perceived usability. **Results:** Sixty patients presented for a new patient gynecologic oncology appointment and were prompted to complete CARE. The median patient age was 55 years (interquartile range, 40-68). The patients self-identified as Non-Hispanic White (44, 73%), Non-Hispanic Black (5, 8%), Asian (5, 8%), Hispanic (3, 5%), other (2, 3%), and unknown (1, 2%). All identified as female. Forty-three patients (72%) completed CARE. Among CARE users, 11 (26%) were identified as meeting criteria for genetic testing; of these, 9 (82%) proceeded with point-of-care same day genetic testing. Nine (21%) patients were eligible for enhanced breast cancer screening based on an estimated lifetime breast cancer risk of 20% or greater; of these, 100% were referred for high-risk breast screening. There were no patient demographics associated with completion of CARE. Forty-one patients (72%) completed the SUS survey; the median SUS score was 80 (interquartile range, 60-92.5), which corresponded to 85-89th percentile and a letter grade of A-. **Conclusions:** Implementation of a digital tool for cancer genetic risk assessment identified a quarter of patients to be eligible for genetic testing, among whom 82% completed same-day genetic testing. Additionally, the tool was reviewed favorably by patient users. Large randomized controlled trials of health information technology tools are needed to move closer to the goal of population-based hereditary cancer risk assessment. Research Sponsor: None.

10614

Poster Session

Therapeutic applications of germline testing for cancer predisposition genes in Asia in the real world. *First Author: Seng Wee Cheo, Department of Haematology-Oncology, National University Cancer Institute, Singapore, Singapore*

Background: Germline genetic testing is traditionally done in patients suspected with hereditary cancer syndrome for enhanced cancer surveillance and/or prevention. In recent years, germline genetic testing is increasingly performed for therapeutic indication, given the approval of PARP inhibitor in advanced cancer patients with germline BRCA1/2 or other homologous recombination repair (HRR) gene mutations, and immunotherapy for patients with mismatch repair gene mutations. We evaluated the clinical utility of actionable (treatable) pathogenic germline mutations (PGM) in a tertiary cancer center in Asia. **Methods:** We conducted a retrospective review of cancer patients who underwent germline genetic testing at the National University Cancer Institute, Singapore, Cancer Genetics Clinic. The primary objectives were to determine the prevalence of potentially actionable PGM in cancer predisposition genes and their therapeutic applications, with focus on BRCA, HRR and mismatch repair genes. **Results:** From 2000 till 2022, 1154 cancer patients underwent germline genetic testing, with the majority (81.9%) tested with multi-gene panels comprising 9-134 genes. 93% (n = 1069) fulfilled conventional criteria for genetic testing; 7% (n = 81) were tested specifically for treatment decisions. 411 (35.6%) patients tested positive for a PGM, of which 334 (81%) were potentially actionable. BRCA1/2 mutations accounted for 62.3% of actionable mutations, followed by mismatch repair (18%; MLH1 8.7%, MSH2 6%, MSH6 2.1%, PMS2 1.2%), and other HRR genes (19.7%: RAD51 6.3%, ATM 4.8%, PALB2 3%, BRIP1 2.4%, others 3.3%). Among patients with BRCA/HRR gene mutations, breast (60%) and ovarian cancer (26.7%) were the commonest primary cancer. 152 germline positive patients have advanced cancers, and 79 (52%) patients received germline directed therapies (PARP inhibitor: n = 75; immunotherapy: n = 4). Median duration of immunotherapy in the 4 mismatch repair gene carriers was 20.5 months (range 5-40). Among germline BRCA/HRR mutation carriers with advanced cancer who were treated with PARP inhibitor, ovarian cancer was the commonest (n = 49), followed by breast (n = 14) then prostate (n = 6). Median PARP inhibitor treatment duration was 8 months (range 1-76). Among germline BRCA/HRR mutation carriers who received platinum-based chemotherapy, pathological complete response rate in the neoadjuvant setting was 53% (n = 17 breast cancers; TNBC [n = 11], other subtypes [n = 6]) and objective response rate was > 80% in the advanced setting (n = 71; ovarian = 51, breast = 9, others = 11). **Conclusions:** About one-third of cancer patients tested in a high risk Cancer Genetics Clinic in a tertiary cancer centre in Asia carry PGM, of which ~80% are potentially actionable. > 50% advanced cancer patients with actionable PGM received germline directed therapies, confirming the clinical utility of germline testing in the real world. Research Sponsor: None.

10615

Poster Session

Utility of multi-gene panel-based germline analysis following genomic profiling and cascade testing in advanced solid tumors: An initial report of the BRANCH study. *First Author: Takeshi Kuwata, National Cancer Center Hospital East, Kashiwa-Shi, Japan*

Background: Genetic testing for pathogenic germline variants (PGVs) is performed to identify hereditary cancer syndromes (HCS) and to evaluate the application of targeted therapies in clinical oncology. Multi-gene panels (MGPs) have become popular for identifying HCS; however, their clinical utility in therapeutic applications and confirmatory germline testing for presumed PGVs and in cascade testing are not well established. **Methods:** BRANCH [UMIN000046085] is a multicenter clinical study to confirm PGVs in: i) patients with advanced solid tumors in whom a presumed PGV has been detected by comprehensive genomic profiling (CGP) (cohort A); ii) patients who received a germline BRCA (gBRCA) test (cohort D); and iii) first-degree relatives of patients with PGVs identified in this study (cohort C). PGVs were examined in 35 HCS genes using an MGP combined with digital multiple-ligation-dependent probe amplification. **Results:** MGP results were available for 75 patients in cohort A and 83 in cohort D (3 February 2023). The most common cancer in cohort A was colorectal cancer (13%) followed by ovarian (12%) and breast (11%) cancers. Of 103 tested presumed PGVs, 46 (45%) were confirmed as PGVs, with the highest germline conversion rates in *BRCA1* (8/8, 100%), followed by *PALB2* (5/6, 83%) and *BRCA2* (15/19, 79%) among the genes tested in ≥ 3 patients. In tissue-based CGP, true PGVs had a higher variant allelic frequency (median 55.7% [range, 31.9–96.8]) than non-PGVs (37.0% [9.3–86.9]). In cohort D, 61 (74%) patients had breast cancer, including one with both breast and ovarian cancers. All BRCA PGVs identified by gBRCA test were identified by MGP in 28 BRCA-positive patients. Intriguingly, among 55 patients (66%) in whom no BRCA PGV was detected by gBRCA test, non-BRCA PGVs were identified in 6 (11%) patients (2 *PALB2* and 1 each of *ATM*, *CHEK2*, *MSH2* [large deletion], and *TP53*). Thirty relatives in 18 pedigrees received MGP-based cascade testing in cohort C. The most frequent target genes were *BRCA2* followed by *BRCA1* and *PALB2*. The same PGVs as the probands were confirmed in 11 (37%) individuals and novel PGVs were identified in 2 (7%) relatives, leading to double PGVs in homologous recombination genes (*PALB2+BRCA2* and *BRCA2+ATM*), respectively. **Conclusions:** MGP successfully determined germline variants among presumed PGVs identified by CGP in patients with advanced solid tumors, and detected non-BRCA PGVs in 10% of gBRCA-negative patients. Furthermore, MGP-based cascade testing has the potential to identify other PGVs in addition to those detected in the probands. Clinical trial information: UMIN000046085. Research Sponsor: FALCO biosystems Ltd.; The National Cancer Center Research and Development Fund; Grant-in-Aid for Scientific Research (KAKENHI).

10617

Poster Session

Eliminating barriers to uptake of germline genetic testing for patients with advanced cancer: The GTAC study. *First Author: Kara K. Landry, University of Vermont Larner College of Medicine, Burlington, VT*

Background: Identification of pathogenic germline variants (PGVs) is important in guiding treatment decisions, cancer screening and testing of family members. While genetic testing indications expand, barriers to testing still exist. Streamlined processes for genetic testing are needed. Our study assessed the feasibility of a novel approach in which patients with cancer underwent genetic testing first with genetic counseling after for only those with a PGV. **Methods:** This was an IRB approved study of patients with metastatic solid tumors within < 1 year of diagnosis. Participants were referred by their oncologist and underwent germline testing with an 84-cancer gene panel after signing informed consent. Results were called to patients by a research coordinator if testing was negative and by a genetic counselor if found to have a variant of uncertain significance. Patients with a pathogenic germline variant (PGV) were called by the genetic counselor and scheduled to meet with the genetics team for full counseling. All patients received a letter documenting results and implications. Patient and provider satisfaction surveys were administered in follow-up. **Results:** 125 patients were eligible and 91 enrolled. Reasons for lack of participation included: early death or decline in health (n = 11, 32.4%). The mean age of patients was 66 (SD 12.6). 60 (65.9%) were male and 43 (47.3%) resided in a rural area. Cancer types represented included: GI (n = 27, 16.5%), lung (n = 22, 13.4%), prostate (n = 19), and renal (n = 4). A PGV was identified in 13 (14.8%) participants. 10 (76.9%) had follow up with a genetic counselor, 2 (15.4%) declined and 1 (7.7%) died prior to being seen. PGVs identified include: *MUTYH* (n = 5), *MITF* (n = 2), *CHEK2* (n = 2), *WRN* (n = 1), *RAD51D* (n = 1), *CDH1* (n = 1), *NTHL1* (n = 1). 74 (81.3%) participants completed the survey. The vast majority appreciated having undergone testing (n = 70, 94.6%) and having testing incorporated into an existing appointment (n = 69, 93.2%). 61 (82.4%) participants felt confident in their understanding of the results. All providers (n = 16, 100%) were satisfied with this testing process and most (n = 15, 93.8%) felt that genetic test results were obtained in a timelier fashion and reported interest in continuing this testing process. 5 (38.5%) patients with PGVs had a first degree relative undergo cascade testing within 6 months of results. **Conclusions:** We show that this paradigm shifting process of testing first and counseling after is feasible and acceptable for cancer patients with high rates of cascade testing. Patients and providers report high satisfaction with this process. This process removes known barriers to testing, such as extra clinic visits and time delays to testing. Further use of this process will require delivering education to patients prior to testing and ensuring that providers are comfortable ordering testing. Research Sponsor: UVM Cancer Center at the University of Vermont Medical Center.

10616

Poster Session

A population-based study of BRCA breast cancer incidence and prognosis in the Italian Emilia Romagna region: The MUTina study. *First Author: Laura Cortesi, Department of Oncology and Haematology, University Hospital Modena, Modena, Italy*

Background: In Italy, about 3% of all breast cancer (BC) are related to BRCA1 and BRCA2 gene mutations. In the Emilia Romagna Region, a unique hub and spoke model was adopted for select and follow people at risk, starting from the Regional Screening Programs, General Practitioners and specialists, covering all the area. This study was designed to uniformly identify and treat BRCA1/2 related BC. Characteristics and outcome of tumors detected by this protocol will be presented. **Methods:** In this multicenter-retrospective study, seven out of nine provinces collected data about BRCA-related BC identified in the Emilia-Romagna region. Patients and tumors characteristics, surgical information, treatment modalities for early (neoadjuvant or adjuvant therapies) and advanced disease, type of relapse (local/distant), second primary tumors occurrence, surgical preventive strategies (bilateral mastectomy, oophorectomy), gene testing data, disease free survival (DFS) and overall survival (OS) were registered. Comparisons between BRCA1 and BRCA2 tumors were performed. **Results:** Since 2000 to 2011, 284 BC were registered (171 BRCA1, 110 BRCA2 and 3 BRCA1 and BRCA2 mutated) with a median age at onset of 42 years. BRCA1-related tumors were mostly triple negative BC (TNBC) compared to BRCA2 ones. The diagnosis was at stage I in 52.3% of cases, being 59.7% BRCA1 and 39% BRCA2 (P = 0.0015). BRCA2 patients, compared to BRCA1, received more frequent up-front surgery (85% vs. 74.9%, P = 0.049) and less chemotherapy (34.1% vs 65.9%, P = 0.004). After a median 12-years follow-up period, 136 patients (47.9%) developed an ipsilateral/local or systemic recurrence or contralateral second BC. BRCA1 developed more local recurrences, compared to BRCA2 that had more distant relapses (P = 0.013). Median OS was not reached in the whole population, with 80.3% of patients alive at the analysis cut-off. Among the two populations, there was a benefit trend for BRCA1 patients (P = 0.071), mostly for those who received chemotherapy (P = 0.0036), contralateral mastectomy (P = 0.0001) and oophorectomy (P < 0.0001). Finally, 25.7% of patients developed a second tumor, excluding BC, mostly ovarian cancer. **Conclusions:** Although BRCA1-related BCs show more aggressive characteristics than BRCA2 BC, the early diagnosis due to our regional surveillance program, leads to a trend for better outcome, even if not statistically significant. The BRCA1 highest rate of recurrence reflects the tendency to local rather than distant relapse. Furthermore, the BRCA deficiency appears to be a predictor of chemosensitivity. Finally bilateral mastectomy and oophorectomy seem to be associated to better outcome. In conclusions, our data support the using of an intensive screening associated to maximal surgery and chemotherapy when BC arises in BRCA carriers, to overcome the unfavorable tumors characteristics of these patients. Research Sponsor: Rotary District 2072.

10618

Poster Session

Geographical impact on prostate cancer genetic testing eligibility: A preliminary study from an academic cancer center. *First Author: Samantha Beck, University of Utah, Salt Lake City, UT*

Background: Germline testing (GT) for prostate cancer (PCa) helps to determine treatment selection and other cancer risk, which guides screening recommendations. Patients with PCa that is high risk group by NCCN and greater stage should receive genetic counseling (GC) referral. There is limited data on differences in genetic services given the rurality of PCa patients. This study aims to determine the geographical distribution of PCa patients meeting GC referral and GT criteria. **Methods:** A retrospective analysis evaluated data from electronic medical records of PCa patients at an NCI-designated cancer research facility. Data was abstracted from new PCa patients seen in 2019 and 2021, years before and after the COVID-19 pandemic. Data includes demographic information, cancer staging, and pathology results. Regions of urbanicity, urban and non-urban (rural/frontier), were categorized through zip codes and defined by Utah Department of Health and Human Services. Criteria for GT followed NCCN guidelines (v.1.2023). Statistical methods for descriptive and comparative analysis done using Chisquare, Fisher's exact, and Mann Whitney tests in R*Stats to compare 2019 and 2021 cohorts. **Results:** Out of 525 PCa patients' initial treatment at HCI in 2019 (n = 346) and 2021, (n = 179) 94% self-reported as White (p = 0.164) with a median age of 66 (p = 0.690) and 51% being employed (p = 0.396) at time of first treatment. Of these, 414 (79%) were from an urban area and 111 (21%) from a non-urban area (p = 0.883). The cohort was primarily from 2019 (66%), with 274 (79%) and 72 (21%) of the PCa patients living in urban and non-urban areas, respectively. In 2021 (34%), 140 (78%) and 39 (35%) patients were from urban and non-urban areas. Criteria for GT were met in 37% (n = 196) of PCa patients (p = 0.595). Regions were independently compared by race, age, employment, and year. No statistical difference across all variables was found (p > 0.05). Geographical regions did not impact GT eligibility. **Conclusions:** This preliminary study shows that geographical region does not impact GT eligibility in PCa patients seen at HCI during 2019 and 2021. The years analyzed is a proxy for differences in aggressiveness by rurality. The results show 37% of the PCa patients met criteria for GT. No significant differences were identified by geographical region, race, age, employment, or the year of initial treatment. Further research is being conducted to determine if access to PCa GC uptake is impacted by geography and differing service delivery models after criteria for GT has been met. Research Sponsor: University of Utah Graduate Program of Genetic Counseling.

10619

Poster Session

Perceived mental and physical health in patients with common cancers: A study using the PROMIS framework in All of Us database. *First Author: Rajaa Mohamed Salih, Harlem Hospital Center, New York, NY*

Background: The self-perception of one's mental and physical health (MH and PH) is of utmost importance for individuals diagnosed with cancer. This study focuses on the assessment of self-perceived mental and physical health (MH and PH) in individuals diagnosed with cancer. The Patient-Reported Outcomes Measurement Information System (PROMIS) framework is used to measure health outcomes, with PROMIS-PH measuring physical well-being and PROMIS-MH measuring mental health status. The study aims to evaluate self-reported mental and physical health of individuals with common cancers in the All of Us database, which includes over 414,000 participants in the US who have completed PROMIS-PH and PROMIS-MH surveys. **Methods:** We included participants from All of Us dataset version 6, which includes survey data collected between May 6, 2018 and January 1, 2022 who had available electronic health records data (N = 258,188). From the survey data, we calculated PROMIS-PH and PROMIS-MH score in participants with diagnosis code (ICD9/ICD10) of any cancers (N = 36377), breast (N = 5172), prostate (N = 5234), colon (N = 2366), and lung cancer (N = 2338). The study compared scores each cancer groups using Wilcoxon rank sum test, with a significance level of $P < 0.05$. Analysis was performed in the web-based platform Jupyter Notebook using programming language R. **Results:** The study calculated PROMIS-MH and PROMIS-PH scores based on two questions, with response options valued from 1 to 5. The higher the score, the higher the level of perceived mental and physical health. Results showed that the mean PROMIS-MH score for all cancers was 7.38, with the highest score of 7.67 in prostate cancer and the lowest score of 7.10 in lung cancer. The mean PROMIS-PH score for all cancers was 7.31, with the highest score of 7.62 in prostate cancer and the lowest score of 6.71 in lung cancer. Prostate cancer group showed the highest PROMIS-PH and PROMIS-MH scores among the four cancer groups ($P < 0.05$), while participants with lung cancer reported the lowest PROMIS-PH and PROMIS-MH scores ($P < 0.05$). Additionally, breast cancer had higher PROMIS-MH and PROMIS-PH scores compared to all cancers ($P < 0.05$), while lung cancer had lower PROMIS-MH and PROMIS-PH scores ($P < 0.05$). There was no significant difference in PROMIS-MH score between all cancers and colon cancer. **Conclusions:** These results suggest that individuals with lung cancer may have a lower level of perceived mental and physical health compared to those with other cancers. Further research is needed to understand the underlying causes of these differences and to evaluate the effectiveness of interventions aimed at improving the well-being of individuals with cancer. Research Sponsor: None.

10621

Poster Session

Clinical and social importance of follow-up assessment of family members of patients with BRCA mutations. *First Author: Ivana Lucia de Oliveira Nascimento, Oncoclinicas - Grupo Oncoclinicas, Salvador, Brazil*

Background: The identification of *BRCA1* and *BRCA2* genes mutations are of paramount importance in the treatment and follow-up of hereditary cancer patients. When a pathogenic variant (PV) is identified in one of these genes, the surveillance for new primary tumors becomes individualized. When a pathogenic mutation is identified other family members may also be at high risk for developing tumors. Then the investigation should become familiar. **Methods:** This study reports the experience of a public oncogenetics service with the identification and follow-up of relatives of patients with *BRCA* mutations. Of the 1505 patients registered, 773 are probands, of which 71 had a mutation in one of the *BRCA* genes. A total of 503 family members were evaluated, with an average of 13 relatives per proband. **Results:** Of the 353 relatives with a *BRCA1* mutation, 132 had the familial mutation, and only 18 had cancer diagnosis. The mean age of the evaluated family members was 37 years, lower than the mean age at diagnosis of the probands, which was approximately 41 years, two founder mutations in *BRCA1* (NM_007300.4:c.3331_3334del and NM_007300.4:c.211A > G) were more recurrent among index cases, which is associated with the ancestral background of the local population. For the *BRCA2* gene, 148 family members were evaluated, of which 77 had a mutation and 23 had a previous cancer diagnosis. The mean age of family members evaluated for *BRCA2* mutation was 43 years, similar to the mean age at diagnosis of the proband: 41 years. The NM_000059.4:c.1389_1390del and NM_000059.4:c.7124T > G variants was the most frequent in *BRCA2*. **Conclusions:** This data reinforces the importance of genetic counseling and testing of family members when a pathogenic variant is identified in a cancer patient. It is clear that early initiation of surveillance protocols, with screening and prophylactic surgeries are very effective tools for those high risk patients, they just have to be early diagnosed with the PV to benefit from this strategies. In addition, this assessment helps in understanding the mutational profile of the population in order to improve the planning of services in oncogenetics. Research Sponsor: CNPq and Federal University of Bahia-Brazil; Laboratory of Immunology and Molecular Biology of UFBA.

10620

Poster Session

Spectrum of germline pathogenic variants among patients with cancer in Mexico. *First Author: Jose Luis Rodriguez Olivares, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, México, Mexico*

Background: Up to 10% of patients with cancer harbor pathogenic germline variants (PVs) in one or more cancer susceptibility genes. Genetic cancer risk assessment (GCRA) is an important tool for the management of patients with cancer. It allows the identification of candidates for structured screening protocols, risk reduction strategies, targeted therapies and cascade testing. Knowledge about the prevalence and spectrum of PVs is limited among underrepresented populations. We studied the prevalence of germline PVs in a cohort of Mexican patients with cancer. **Methods:** Between April 2017 and September 2022, patients with diagnosis of cancer who met clinical criteria for GCRA according to international guidelines (NCCN) and were enrolled in the international Clinical Cancer Genomics Community Research Network (CCGCRN) registry at Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán were included. Cancer risk counseling and germline multi-gene panel testing were performed. Post-test counseling and cascade testing with known PV analysis was offered. **Results:** 1322 patients met inclusion criteria (probands n = 1027, relatives n = 295). Among the probands, 72.4% (744/1027) were women, median age at cancer diagnosis was 48.2 years (range 1-88) and 9.8% (n = 101) had more than one primary tumor. 14.5% (149/1027) of probands had a positive result in which 152 PV were identified (*BRCA1* n = 39, *BRCA2* n = 33, *ATM* n = 11, *CHEK2* n = 11, *MLH1* n = 11, *TP53* n = 7, *PALB2* n = 7, *NF1* n = 6, *MSH2* n = 5, *MSH6* n = 3, *PTEN* n = 3, *APC* n = 2, *BRIP1* n = 2, *CDH1* n = 2, *RB1* n = 2 and 1 PV in the genes: *CDKN2A*, *MAX*, *MUTYH*, *NBN*, *PTCH1*, *RAD50*, *SDHA* and *SDHB*). The frequency of PV according to cancer diagnosis was: breast 15.5% (82/527), prostate 2% (4/198), ovarian 15.6% (12/77), colorectal 26.6% (16/60) and pancreatic 11.9% (5/42). The frequency of recurrent, potentially founder PVs in their respective genes was as follows: *BRCA1* del(exons9-12) 30.7% (12/39) and *CHEK2* c.707T > C 81.8% (9/11). Among the relatives referred for cascade testing the frequency of PV was 40% (118/295), 18.6% (55/295) had personal history of cancer with a median age at diagnosis of 47 years. **Conclusions:** Our results show a wide spectrum and a variable frequency of PVs among one of the largest examined cohorts of Mexican patients with cancer, with a high frequency of PVs among cases of breast, ovarian, and colorectal cancer. In contrast to reports from other populations, there was very low frequency of PVs among patients with prostate cancer. The outcomes of this study add to our understanding of the genetic epidemiology of cancer in the Mexican population, and support creating GCRA programs to improve access to multi-gene panel testing among underrepresented patients in limited resource settings. Research Sponsor: U.S. National Institutes of Health.

10622

Poster Session

A scalable approach to democratizing cancer risk stratification: One health-care system's approach using a patient-facing digital platform. *First Author: Heather Fecteau, Ambry Genetics Corporation, Aliso Viejo, CA*

Background: Access to genetic testing and risk stratification is primarily gated by referrals from non-genetics providers for patients who meet testing criteria. The majority of Americans seek care at community hospitals that are closer to home; community hospitals are faced with the challenge of how to democratize access to precision oncology and cancer prevention. Research has shown that the establishment of such protocols is challenging, requiring organizational buy-in, capital, resources, and the involvement of multiple levels of clinical and nonclinical stakeholders. Here we highlight Sarah Cannon, the Cancer Institute of HCA Healthcare, and their programmatic approach to risk stratification using a digital platform offered universally to all patients undergoing screening mammography. **Methods:** From February to November in 2022, fourteen sites were assessed to have appropriate provider and facility capabilities to support the implement the CARE program. The web-based risk-stratification tool is sent to individuals before standard ambulatory appointments to assess their lifetime risk for breast cancer based on the Tyrer-Cuzick (version 8.0) risk algorithm and National Comprehensive Cancer Network (NCCN) genetic testing criteria. Testing criteria included hereditary breast, ovarian, pancreatic, and prostate cancers, Lynch syndrome, and familial adenomatous polyposis (FAP). Retrospective data was pulled from patients seen between February 2022 through January 2023. The outcome measures included percentage of individuals who completed the risk-assessment, met genetic testing criteria, pursued germline genetic testing, received a positive germline result, and/or had a breast cancer risk $\geq 20\%$. **Results:** During the 10 months at the 14 community hospitals a total of 25,671 individuals were invited for risk assessment through the CARE program; 19,277 (75.1%) individuals completed assessment. Overall, 5,070 (26.3%) met genetic testing criteria and 1,536 individuals had a $\geq 20\%$ lifetime risk of breast cancer, for a total of 34% of patients identified as elevated risk. 23.4% (1,187) of those meeting criteria opted to proceed with germline genetic testing. An additional 126 individuals who did not meet criteria pursued genetic testing. Of the 1,313 completed genetic tests, 96 (7%) had positive genetic test results. Fifty-four of 96 (56%) positive results had an impact on medical management and cancer prevention. **Conclusions:** Sarah Cannon and HCA Healthcare have successfully begun implementing a comprehensive, digital risk stratification program in the community hospital setting to provide standardized access to genomic testing and risk stratification. By identifying patients with an elevated risk for cancer, the potential for increased early cancer detection and precision oncology can be observed in a scalable and sustainable program. Research Sponsor: None.

10623

Poster Session

Impact of risk-reducing mastectomy on quality of life of women with Li-Fraumeni syndrome. *First Author: Natalia Polidoro, Sirio Libanês Hospital, Sao Paulo, Brazil*

Background: Risk-reducing mastectomy (RRM) is a common strategy for managing breast cancer (BC) risk in women with Li-Fraumeni syndrome (LFS). Data on uptake and health-related quality of life (HRQoL) in LFS are limited and often extrapolated from *BRCA* scenario, despite the lack of evidence on survival benefits in LFS. This study evaluated RRM uptake and its impact on HRQoL in women with LFS. **Methods:** TP53 PV female carriers from a Brazilian LFS cohort from January 2012 to December 2022 were eligible. After informed consent, 90 women reported oncological status, uptake of RRM, and completed BREAST-Q questionnaire. Scores were compared among different BC risk management strategies and minimal important difference (MID) of ≥ 4 was described. Multivariable analyses were performed to identify surgical factors related to HRQoL outcomes. **Results:** 71.7% (n=33) of women diagnosed with unilateral BC (n=46) underwent contralateral risk-reducing mastectomy (CRRM) at a median age of 39 years. Among unaffected BC women (n=44), 36.3% underwent bilateral risk-reducing mastectomy (BRRM) at a median age of 36 years. CRRM was associated with lower scores for psychosocial (64[±19] vs 93[±21], $p=.05$) and physical well-being (72[±16] vs 92[±18], $p=.001$). BRRM women had lower physical well-being scores (72[±19] vs 92[±13], $p=.003$). MID associated with worst HRQoL outcomes were seen in all four domains on CRRM women and on satisfaction with breasts and physical well-being of BRRM patients (table). Nipple-sparing mastectomy (NSM) presented better psychosocial (74[±20] vs 52[±19], $p=.04$) and sexual well-being (60[±20] vs 46[±20], $p=.05$) when compared to skin-sparing mastectomy (SSM) on CRRM patients and with higher sexual well-being (60[±20] vs 46[±20], $p=.05$) on BRRM patients. Women with BRRM > 2 years had better physical well-being (83[±14] vs 56 [±12], $p<.001$). There were no significant differences in scores of women with age ≥ 35 years at the time of BRRM, although MID ≥ 4 was observed on psychosocial and sexual well-being and satisfaction with breasts: -23.0, -14.4, and -20.0, respectively. **Conclusions:** We observed high rates of RRM in LFS women and those were associated with worse outcomes on breast HRQoL in comparison to surveillance. The potential benefits and harms of RRM should be carefully discussed with patients before performing it, especially in LFS women where the survival benefits of these interventions remain uncertain. Research Sponsor: None.

Mean scores by BC risk strategy.

	Affected by BC (n=46)				Unaffected by BC (n=44)					
	Mean (SD)			p	Mean (SD)			p		
	CRRM	No CRRM	MID ≥ 4 MID*		BRRM	No BRRM	MID ≥ 4 MID*			
Psychosocial	64.0 (±20)	93 (±21)	0.05	-29	81.8	64.0 (±23)	64 (±23)	0.94	0.0	43.7
Sexual	52.4 (±20)	66.3 (±21)	0.08	-14	75.0	61.3 (±20)	59.3 (±16)	0.73	2.0	50
Satisfaction with breasts	58.9 (±17)	65.6 (±21)	0.27	-7	54.5	56 (±21)	71 (±26)	0.24	-15	62.5
Physical chest	72 (±16)	92 (±19)	<0.01	-20	90.9	72 (±19)	92 (±14)	<0.01	-20	75

* % of RRM patients with MID ≥ 4 from the surveillance group.

10625

Poster Session

Risk of death among lung cancer patients before and during the COVID-19 pandemic. *First Author: Teddy Tai Loy Lee, The University of Hong Kong, Hong Kong, Hong Kong*

Background: The survival of lung cancer patients in Hong Kong before and during the COVID-19 pandemic is poorly understood. **Methods:** Patients diagnosed with lung cancer from January 1 2010 to October 31 2022 were recruited from all 43 public hospitals in Hong Kong. Patients who died on the day of cancer diagnosis were excluded. Patients between 2020-2022 (pandemic) were matched with patients diagnosed between 2010-2019 (pre-pandemic) using 1:1 propensity score matching, based on demographics and comorbidities such as age, sex, and Charlson Comorbidity Index (CCI), to study survival before and during the pandemic. The outcomes were 1-year and 6-month all-cause mortality. In subgroup analysis, patients were categorized into 12 groups, from 2010 to 2022, based on the year of first diagnosis of lung cancer to investigate yearly changes in mortality. Patients with confirmed diagnosis of COVID-19 infection were also analyzed. **Results:** A total of 42102 lung cancer patients (66.0% male, age 72±12 years (median±SD), CCI 7.00±2.42) were recruited from 2010 to 2021 with 1-year follow up. Only 36 patients were confirmed COVID-19 positive. The matched cohort consisted of 4958 pandemic patients (68.6% male, age 72±12 years, CCI 8.00±2.43) and 4958 pre-pandemic patients (67.7% male, age 73±12 years, CCI 7.53±2.48). 2782 (56.1%) and 3846 (77.6%) pandemic patients died within 6 months and 1 year respectively, compared to 2338 (47.2%) and 3194 (64.4%) pre-pandemic patients. In subgroup analysis by year of lung cancer diagnosis, patients diagnosed in 2021 had highest risk of 1-year mortality (85.1%). There was no significant difference in mortality between patients with and without confirmed COVID-19 positivity. The cohort of 2022 lung cancer patients, with higher COVID-19 positivity, was still undergoing follow-up and will be included in the analysis at the time of presentation. **Conclusions:** Lung patients diagnosed during the COVID-19 pandemic are associated with higher risk of death within the first year compared to that of pre-pandemic patients, and is likely not associated with COVID-19 positivity. Research Sponsor: None.

Covariate balance after propensity score matching.

Characteristics	Pre-COVID period (N=4958)	COVID Era (N=4958)
Male, N (%)	3358 (67.7)	3401 (68.6)
Baseline age, years, Median(SD)	73.25 (11.69)	72.24 (11.93)
Charlson Comorbidity Index, Median(SD)	8.00 (2.48)	8.00 (2.43)
Hypertension, N (%)	1882 (38.0)	1894 (38.0)
Atrial fibrillation, N (%)	238 (4.8)	239 (4.8)
Heart failure, N (%)	186 (3.8)	190 (3.8)
Diabetes mellitus, N (%)	922 (18.6)	894 (18.0)
Chronic kidney disease, N (%)	118 (2.4)	125 (2.5)
Ischemic stroke, N (%)	175 (3.5)	169 (3.4)
Peripheral vascular disease, N (%)	41 (0.8)	34 (0.7)
Intracranial hemorrhage, N (%)	57 (1.1)	53 (1.1)
Hemiplegia, N (%)	20 (0.4)	22 (0.4)
Rheumatic disease, N (%)	28 (0.6)	28 (0.6)
Peptic ulcer, N (%)	57 (1.1)	53 (1.1)
1-year mortality, N (%)	3194 (64.4)	3846 (77.6)
6-month mortality, N (%)	2338 (47.2)	2782 (56.1)

10624

Poster Session

Newly diagnosed lung cancer in hospitalized patients during the COVID-19 pandemic: How well are LDCTs utilized? *First Author: Jonathan Assis, HCA Florida Brandon Hospital, Brandon, FL*

Background: Medicare covers the cost of lung cancer screening in individuals aged 50-77 years with a high-risk smoking history. The COVID-19 pandemic caused a decrease in outpatient visits and cancer screenings. The objective of this study was to provide a comparison between the multitude of lung cancer diagnoses upon presentation to the hospital predating and during the COVID-19 pandemic in patients with varying insurance types. **Methods:** We retrospectively reviewed fifteen hospitals in West Florida with newly diagnosed lung cancer during the pre-pandemic period from March 2019-August 2020 and the pandemic period from March 2020- August 2021. These patients were split into subcategories based on insurance type: private medical insurance; Medicare; Medicaid; no insurance; and other. The chi-square test was used for statistical analysis. **Results:** A total of 1409 inpatients, 676 during the pre-pandemic and 733 during the pandemic, were identified with a new diagnosis of lung cancer upon presentation to the hospital. 74% of the pandemic population and 77% of the pre-pandemic population were patients insured with Medicare. Hospitals without LDCT screening programs were found to have 317 lung cancer diagnoses during the pre-pandemic period and 292 during the pandemic period. Hospitals with LDCT screening programs were found to have 359 lung cancer diagnoses during the pre-pandemic period and 441 during the pandemic period. Chi-square tests comparing pre-pandemic to pandemic did not show a p-value of statistical significance. **Conclusions:** A substantial number of patients with Medicare were newly diagnosed with lung cancer during the pre-pandemic and pandemic periods compared to patients with other insurance types. Although Medicare provides LDCT screening for lung cancer in high-risk populations at no out-of-pocket cost, about 75% of West Florida's patients were diagnosed with lung-cancer upon presentation to the hospital. Hospitals with LDCT screening programs had an increase in cancer diagnoses during the pandemic, consistent with prior research data. Instead, the pandemic did not seem to affect hospitals without LDCT screening programs. We need to address the barriers in implementation of LDCT hospital-based screening programs to increase early diagnoses and decrease hospitalization diagnoses, leading to improved lung cancer mortality. Research Sponsor: None.

Frequency of patients with newly diagnosed lung cancer based on insurance type.

Insurance Type	Private	Medicare	Medicaid	No Insurance	Other
Pandemic (N= 733)					
Frequency, N	71	565	39	8	50
Frequency Percent out of Pandemic (N=733), %	9.69	77.08	5.32	1.09	6.82
Frequency Percent out of Total (N=1409), %	5.04	40.10	2.77	0.57	3.55
Pre-Pandemic (N=676)					
Frequency, N	75	501	39	9	52
Frequency Percent out of Pre-Pandemic (N=676), %	11.09	74.11	5.77	1.33	7.69
Frequency Percent out of Total (N=1409), %	5.32	35.56	2.77	0.64	3.69

10626

Poster Session

Immunogenicity after COVID-19 vaccination in patients with solid tumor and hospital staff: A prospective single-center observational study. *First Author: Yuki Katsuya, Department of Experimental Therapeutics, National Cancer Center Hospital, Tokyo, Japan*

Background: Patients with tumor are at high risk of severe COVID-19, and vaccination against SARS-CoV-2 is recommended. Impact of cancer treatment on immunogenicity has not been evaluated well. **Methods:** This prospective study was conducted to assess the seroconversion rate of SARS-CoV-2 vaccines among patients with cancer and hospital staff. Further, we focused on the difference among cancer treatment regimens. SARS-CoV-2 spike protein-specific IgG (S-IgG) were evaluated before the first vaccination, 1-3 months, 4-6 months, and 7-12 months after the second vaccination, and 1-3 months after the third vaccination. The primary endpoint was seroconversion rate measured 1-3 months after the second vaccination. **Results:** From April 2021 to November 2021, consent was obtained from 629 cancer patients and 210 hospital staff. Excluding missing data and withdrawal of consent, 590 cancer patients and 183 hospital staff without complications was analyzed. At 1-3 months after the second vaccination, S-IgG antibody concentration higher than the cut-off value (20 BAU/mL) was found in 96.1% (567/590) patients with cancer and 100% (183/183) of the healthy controls (p = 0.0024). At 4-6 months after second vaccination, S-IgG antibody concentration higher than the cut-off value was found in 93.1% (461/495) patients with cancer and 100% (170/170) of the healthy controls (p < 0.0001). The significant difference in seroconversion rate between the two groups persisted even after 7-12 months. Patients undergoing treatment regimens such as platinum combination therapy (median: 423.7, 95% CI: 264.2-767.0, p = 0.003) and alkylating agent (median: 57.5, 95% CI: 5.4-748, p < 0.0001) among cytotoxic drugs, and PARP inhibitor (median: 264, 95% CI: 43-690.4, p = 0.0004), mTOR inhibitor (median: 227.4, 95% CI: 5.7-323.4, p = 0.0036), BCR-ABL inhibitor among drugs (median: 124.4, 95% CI: 0.0-288.9, p = 0.005) among target molecule drugs showed lower antibody titer compared to the no-treatment patients with cancer group. **Conclusions:** SARS-CoV-2 vaccine immunogenicity was low among patients with cancer compared to healthy control. Also, several treatment regimens were found to negatively impact immune response. Clinical trial information: UMIN000049403, UMIN000049430. Research Sponsor: Sysmex.

Patient	cut off value	pre	1-3m after 2nd shot	4-6m after 2nd shot	7-12m after 2nd shot, before 3rd shot	1-3m after 3rd shot
S-IgG	20 BAU/ml	8/537 (1.4%)	567/590 (96.1%)	461/495 (93.1%)	169/179 (94.4%)	149/153 (97.3%)
S-IgG median (95% CI)		0.0 (0.0-0.0)	761.8 (681.2-864.3)	198.3 (176.6-226.9)	230 (167.8-262.9)	3536 (2930-4672)
N-IgG	10 SU/ml	7/537 (1.3%)	6/590 (1.0%)	4/495 (0.8%)	3/179 (1.6%)	4/153 (2.6%)
N-IgG median (95% CI)		0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)
S-IgM	20 SU/ml	25/37 (0.0%)	191/590 (32.2%)	12/495 (2.4%)	1/179 (0.5%)	9/153 (5.8%)
S-IgM median (95% CI)		0.6 (0.0-0.6)	9.8 (8.6-12.0)	1.4 (1.2-1.6)	1.4 (1.0-1.8)	2.7 (1.9-3.9)

10627

Poster Session

AI to characterize patients with lung or ovarian cancer and those with cachexia for discovery of undiagnosed, misdiagnosed, and miscoded patients at scale in a privacy-preserving manner. *First Author: Yike Guo, Imperial College London, London, United Kingdom*

Background: Discovering undiagnosed, misdiagnosed or miscoded patients is critical to ensure suitability for clinical care pathways and for maximizing clinical trial recruitment. Meta-data (e.g. ICD) and generic NLP based approaches fall short due to: lack of scalability, significant miscoding of patient records and searching a pre-empted list of features without understanding their context or relationships between them. This study addresses these limitations through the application of Pangaea's novel AI product (PIES) to characterize patients, which has discovered 4x more undiagnosed, misdiagnosed and miscoded patients in a scalable and privacy-preserving manner. **Methods:** PIES was configured on 235 clinically validated lung, ovarian and cachectic cancer patient records from secondary care. First, PIES determines all concepts which are reflected in a patient's record based on a medical knowledge base. Second, PIES determines key clinical features and actionable relationships between them which help stratify the target patient population. Third, the findings from steps 1 and 2, are validated by clinicians and all feedback is used to refine these steps and evolve the results through a continuous loop. Following these, PIES's characterization of the target patient population is applied across clinically validated datasets for evaluation and then across multiple healthcare systems behind their firewalls to ensure scalability and privacy compliance. **Results:** Applied to a dataset of 100 clinically validated patients, ICD codes correctly discovers 48 lung cancer patients and misses 18 patients (i.e. who had a diagnosis of lung cancer but were miscoded). By contrast, PIES discovers 63 lung cancer patients and misses only 3 patients. Similarly, ICD codes correctly discovers 36 ovarian cancer patients and misses 16 patients in a dataset of 100 clinically validated patients. PIES correctly discovers all 52 ovarian cancer patients. Separately, in a dataset of 235 clinically validated patients, ICD codes correctly discovers 39 cachectic cancer patients and misses 122 patients. By contrast, PIES discovers 146 cachectic cancer patients and misses only 15 patients. **Conclusions:** Pangaea's AI-driven product for characterizing patients discovered 48% more lung cancer patients, 62% more ovarian cancer patients and 276% more cachectic cancer patients for screening, compared to ICD codes. This includes undiagnosed and misdiagnosed patients. Pangaea's product platform permits the evolution of knowledge for characterizing different target patient populations through its application across multiple healthcare systems, without the need to move or touch the data, thereby ensuring scalability in a privacy compliant manner. Research Sponsor: None.

10629

Poster Session

Inverse association of post-transplant malignancy and graft failure on survival outcome following double lung transplantation. *First Author: Jeeyeon Lee, Northwestern Memorial Hospital, Chicago*

Background: Graft failure (GF) and post-transplant malignancy (PTM) are common causes of death in lung transplantation. Immunosuppression to prevent graft failure is known to lead to de novo malignancies after solid organ transplantation. Here, we assess the relationship between graft failure and de novo malignancies after double lung transplantation (DLT). **Methods:** Data extracted from the Organ Procurement Transplantation Network (OPTN) registry were analyzed. DLT cases for non-cancerous diseases were selected. We evaluated the overall survival (OS) of recipients with or without PTM (PTM+ or PTM-), and that of recipients with or without GF (GF+ or GF-) after DLT. The association between GF and PTM was investigated. **Results:** Among 23,935 DLT recipients, there were 5,629 cases (23.5%) of PTM+ and 18,306 cases (76.5%) of PTM -, and 2,316 cases (9.7%) of GF+ and 21,619 cases (90.3%) of GF- following DLT. Among GF+ cases, the prevalence of acute, hyperacute, and chronic rejection after DLT was 1,962 cases (84.7%). The OS in recipients with GF+ was worse than that in recipients with GF- (p < 0.001). However, inversely, the OS in recipients with PTM+ was better than that of recipients with PTM- (p < 0.001). When patients were categorized into four categories by each factor (GF-, GF+, PTM+, PTM-), the GF rate was lower in recipients with PTM+ than in those with PTM- [GF+/PTM+ (n = 368, 1.5%) versus GF+/PTM- (n = 1,948, 8.1%)] (p < 0.001), and the PTM+ rate was higher in recipients with GF- than in those with GF+ [GF-/PTM+ (n = 5,261, 22.0%) versus GF+/PTM+ (n = 368, 1.5%)] (p < 0.001). And the GF-/PTM+ group showed the best prognosis with 97.3 months of median OS, and the GF+/PTM- group showed the worst prognosis with 36.8 months of median OS (p < 0.001). **Conclusions:** Recipients who developed PTM following DLT had longer OS compared with those who did not. And the GF rate was significantly lower in recipients with PTM compared to those without PTM. Further research is needed to investigate the underlying mechanism of the inverse association between PTM and GF in DLT recipients. Research Sponsor: None.

10628

Poster Session

Learned lessons from a US-wide outreach program to broaden enrollment to the PROMISE Registry, a prostate cancer genetic registry. *First Author: Channing Judith Paller, The Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, Baltimore, MD*

Background: Updates to NCCN genetic testing recommendations and approved PARPI treatments for prostate cancer (PCa) patients (pts) have clarified the need for genetic registries to identify pts for novel treatments and understand real-world effects of targeted therapies. PROMISE (NCT04995198) is a US prospective genetic registry that has deployed an outreach program to broaden enrollment beyond the usual approach of academic medical centers as recruitment sites. PROMISE aims to create a PCa genetic registry by enrolling and screening 5,000 PCa pts via germline testing to identify 500 for long-term follow-up with germline mutations in genes of interest. **Methods:** The outreach program was initiated in May 2021 alongside enrollment. The program aims to supplement ongoing recruitment at 23 institutions by broadening enrollment to include populations and areas not served by academic medical centers. Direct-to-pt outreach was prioritized via partnerships with PCa advocacy organizations with groups and geographic areas with high prevalence of PCa. Online activities include webinars, interviews, podcasts, articles, partner email blasts, and newsletters. In-person activities include tabling and presentation at patient- and provider-facing conferences, and tabling at pt walks. Letters were sent introducing PROMISE through the Maryland Cancer Registry to individuals with PCa. A dedicated team including marketing, partnerships and engagement, and website SEO specialists support the program. Funding for the outreach program is provided by the study funder, Advancing Clinical Trials (ACT). **Results:** As of January 2023, study accrual is 54% ahead of initial projections. 2,178 have been enrolled and 219 are eligible for long-term follow-up across 48 states, with most enrollment occurring on the east and west coasts. Race/ethnicity distribution is as follows: American Indian or Alaska Native 0.4%, Asian 2.0%, Black 3.9%, Hispanic 1.8%, Native Hawaiian or Pacific Islander 0.1%, White 76.4%, unknown 0.4%, and no response provided 16.3%. **Conclusions:** Traditional recruitment efforts by academic medical centers, when supplemented with direct-to-pt outreach yields increased enrollment. Effective components include 1) partnerships with PCa advocacy organizations, 2) communication from PIs, Investigators, and other medical professionals via webinars and interviews with clinically relevant topics and Q&A, and 3) varied methods of outreach. While the program has led to high accrual, distribution of enrolled participants supports findings from other genetic and genomic registries indicating that increasing diversity continues to be a challenge. Moving forward, we will continue to work with outreach partners to find well-targeted, efficient ways to reach PCa patients with attention to increasing participant diversity. Clinical trial information: NCT04995198. Research Sponsor: Advancing Cancer Treatment, Inc.; Partial support by a grant (W81XWH-18-2-0060, W81XWH-17-2-0043) from the Department of Defense.

10630

Poster Session

Prevalence of pathogenic germline variants in a cohort of patients with early onset non-small cell lung cancer (EOLUNG). *First Author: Maria Jove, Catalan Institute of Oncology, Hospital Duran i Reynals, IDIBELL. Medical Oncology, Hospitalet, Spain*

Background: Patients with early onset lung cancer might be more likely to carry pathogenic (or likely-pathogenic) germline variants (PGV) in genes associated with cancer predisposition. However, germline testing is not recommended in this population. We designed this study to determine the prevalence of PGVs in patients with early onset lung cancer. **Methods:** This prospective, multicenter cohort study assessed PGV in patients younger than 51 years diagnosed with non-small cell lung cancer (NSCLC) in 3 sites at the Catalan Institute of Oncology between June 2018 to May 2022. Genomic DNA was sequenced using a custom-designed NGS panel covering 164 cancer-predisposing genes and results were discussed in a multidisciplinary tumor board. **Results:** 138 patients were included. Median age was 45.5 (28-50) years; 49% were females; 79% were ever-smokers with a median packs-year of 24 and median age of tobacco initiation of 16 years old. Most patients had non-squamous histology (88%) and had stage IV (62%) at diagnosis. Somatic oncogenic drivers were found in 74 patients (54%): *EGFR* 27 (20%), *ALK* 22 (16%); *KRAS* 20 (14%); *RET* 3 (2%); *ROS1* 1 (1%); *BRAF* *V600E* 1 (1%). Only 4% had past personal history of cancer and 50% had family history of cancer in a first-degree relative, being lung and breast cancer the most common tumors. Overall, 20 patients (14%) carried PGVs involving 12 genes associated with cancer predisposition: *PARK2* (n=4); *SBDS* (n=3); *NBN* (n=2); *ATM* (n=2); *TSC1* (n=2) and *BLM*, *FANCA*, *MCPH1*, *PMS2*, *POLH*, *SDHA*, *RECQL4* (n=1, each). Four patients (3%) fulfilled criteria to be referred to genetic counseling clinic. There were no significant differences in clinical and molecular characteristics among patients with PGVs compared to their counterparts (Table). **Conclusions:** In this prospective cohort, 14% of patients with early onset NSCLC harbored germline PGVs. As clinicopathological and genomic features were not associated with PGVs, germline testing might be considered in addition to comprehensive genomic characterization of tumor tissue in young patients with NSCLC. However, only a minority of PGVs were deemed clinically actionable. Research Sponsor: Spanish Lung Cancer Group, Spanish Society of Medical Oncology.

Summary of epidemiological, clinicopathological and molecular features by PGV status.			
	No PGV (n = 118)	PGV (n = 20)	p-value
Age groups, n (%)			1.0
≤ 40 years	25 (21%)	4 (20%)	
> 40 years	93 (79%)	16 (80%)	
Gender, n (%)			0.702
Male	62 (53%)	9 (45%)	
Female	56 (47%)	11 (55%)	
Smoking history, n (%)			0.953
Never-smokers	25 (21%)	4 (20%)	
Former smokers	63 (53%)	10 (50%)	
Current smokers	30 (26%)	6 (30%)	
Personal history of cancer, n (%)			0.137
No	115 (97%)	18 (90%)	
Yes	3 (3%)	2 (10%)	
First degree family history of cancer, n (%)			0.754
No	56 (48%)	11 (55%)	
Yes	60 (52%)	9 (45%)	
Stage, n (%)			0.182
I-III	46 (39%)	7 (35%)	
IV	72 (61%)	13 (65%)	
Histology, n (%)			0.925
Non-squamous carcinoma	105 (89%)	17 (85%)	
Squamous cell carcinoma	13 (11%)	3 (15%)	
Actionable driver, n (%)			1.0
No	64 (58%)	12 (60%)	
Yes	46 (42%)	8 (40%)	

10631

Poster Session

Validation of a breast cancer polygenic risk score in 15,490 Brazilians using exome sequencing. *First Author: Flavia Eichemberger Rius, Mendelics, São Paulo, Brazil*

Background: Brazil has a highly admixed population with significant Southern European, African and Native American genetic ancestries. Approximately 75% of the population has two or more continental ancestries. Therefore, breast cancer polygenic risk scores (PRS) developed in predominantly European populations requires validation in the Brazilian population. Compared with genotyping arrays and whole genome sequencing, affordable and scalable whole exome sequencing (WES) allows genotyping of both rare and common variants in the targeted regions and imputation of common variants not directly captured. In this study we validate a previously developed 3820-variant PRS using WES in 15,490 Brazilians. **Methods:** The cohort consisted of 6,362 women with a history of breast cancer (mean age 49.6, stdev 11.6) and 9,128 unphenotyped adults as controls (mean age 41.6, stdev 13.3). WES were performed on germline DNA and variants were called and curated. Imputation was done using the 1000 Genomes Phase 3 reference panel for variants falling outside the WES captured regions. After excluding subjects with known pathogenic or likely pathogenic variants in *BRCA1*, *BRCA2*, *PALB2*, *PTEN*, or *TP53*, and first or second-degree relatives of the probands, 14,577 individuals remained in the final analysis (5,730 cases and 8,847 controls). We restricted PRS calculation to 2,893 of the original 3,820 variants with an estimated global imputation accuracy of 96%. Odds ratios (OR) were adjusted using the top 10 principal components. **Results:** The breast cancer PRS showed a highly significant correlation with cancer risk (p-value = 7.1e-81, OR = 1.43, 95% confidence interval (CI) = 1.38-1.48 per PRS standard deviation). Compared with women in the middle deciles, those in the highest 10% had an OR of 1.93, while those in the lowest 10% had an OR of 0.52 (Table). **Conclusions:** In this study we show that WES can capture 76% of the variants included in a previously developed and validated breast cancer PRS, and the calculated PRS is correlated with breast cancer risk in the admixed Brazilian population. This opens the door for clinical studies into the application of PRS in Brazil, particularly in women without mutations in breast cancer high-penetrance genes. In addition, our WES-based PRS strategy can be quickly, affordably, and seamlessly adopted by labs that already offer Hereditary Breast Cancer panels that use WES as a backbone. Research Sponsor: Mendelics.

Breast cancer odds ratio per PRS decile.

Decile (%)	OR (95% CI)	p-value
0-10	0.52 (0.44 - 0.60)	3.4e-18
11-20	0.72 (0.62 - 0.83)	6.7e-06
21-30	0.76 (0.66 - 0.88)	1.4e-04
31-40	0.91 (0.79 - 1.05)	0.19
41-50	1.18 (1.03 - 1.35)	0.018
51-60	1.29 (1.12 - 1.48)	2.9e-04
61-70	1.46 (1.28 - 1.68)	4.0e-08
71-80	1.93 (1.69 - 2.21)	2.2e-21

10632

Poster Session

Overall and non-lung cancer incidence in the national lung screening trial (NLST) as indicators of potential for multi-cancer screening. *First Author: Ellen T. Chang, GRAIL, LLC, a subsidiary of Illumina, Inc., currently held separate from Illumina, Inc., under the terms of the Interim Measures Order of the European Commission dated 29 October 2021, Menlo Park, CA*

Background: Single-cancer screening strategies address only one component of the overall population cancer burden. Even high-risk populations in single-cancer screening trials experience a considerable burden of other cancer incidence; therefore, we assessed non-lung cancer incidence in the NLST to evaluate the proportion of un-screened cancers. **Methods:** The NLST was a randomized controlled trial of screening for lung cancer in adults aged 55–74 years with ≥30 pack-years of smoking history, enrolled in 2002–2004 and actively followed through 2009. Incident cancers were identified via participant questionnaires, death certificates, and direct notifications, and confirmed by medical record abstraction. The present analysis includes first invasive primary cancers diagnosed after study randomization. Non-lung cancer incidence was similar between the two trial arms, which were therefore combined for analysis. **Results:** Among 53 229 subjects (median follow-up 6.5 years), the incidence of any first primary cancer was 1941 per 100 000 person-years, of which 1327 per 100 000 (68%) was non-lung cancer. Non-lung cancer incidence rates exceeded that for lung cancer in all 5-year age categories (especially at younger ages) and all quintiles of smoking pack-years (especially with fewer pack-years). After lung cancer, the most common cancers were other leading cancer types in the general US population, as well as other smoking-related cancers (Table). No recommended population-based screens exist for 54% of observed cancer cases (3332 of 6142, excluding lung, colon/rectum, female breast, and cervix). **Conclusions:** In the NLST, only 32% of first primary cancer incidence was lung; non-lung cancer comprised 68%, and most cases were cancer types with no generally recommended screening strategy. Even in a high-risk population, a single-cancer screening test misses most cancers, illustrating the value of multi-cancer screening tests that can detect a broad spectrum of cancers and, therefore, have the potential to address a currently inaccessible portion of cancer morbidity and mortality. Research Sponsor: GRAIL, LLC, a subsidiary of Illumina, Inc., currently held separate from Illumina, Inc., under the terms of the Interim Measures Order of the European Commission dated 29 October 2021.

Cases and crude incidence rates (per 100 000) of first primary invasive cancers after randomization in the NLST.					
Primary site	n	Incidence rate	Primary site (cont. 1)	n	Incidence rate
Total	6142	1941.5	Lymphoma	200	63.2
Non-lung	4197	1326.7	Kidney*	182	57.5
Lung*	1945	614.8	Pancreas*	148	46.8
Prostate	1353	427.7	Melanoma	118	37.3
Breast	524	165.6	Esophagus*	93	29.4
Colon/rectum*	343	108.4	Stomach*	66	20.9
Urinary bladder*	241	76.2	Soft tissue including heart	22	7.0
Head/neck*	236	74.6	Anal	11	3.5
Other	217	68.6	Gallbladder	9	2.8
			Cervix*	5	1.6

*Smoking-related cancers

10633

Poster Session

Implementing a germline testing program using fingernail specimens for patients with hematologic malignancies and initial clinical findings. *First Author: Michael Francis Walsh, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: About 5-20% of hematologic malignancies (HM) occur in the setting of a genetic cancer predisposition syndrome. Additionally, overt constitutional syndromes involving multiple systems may also predispose to HM. The spectrum of cancer predisposition in patients with HM has been limited partially due to the difficulty of germline sample ascertainment from patients with liquid tumors as skin biopsies and fibroblast cultures are often required for testing. **Methods:** Hematologic malignancy patients enrolled in Memorial Sloan Kettering Cancer Center's institutional 12-245 study who were having somatic testing performed on their tumor were given the option to consent to germline testing using fingernail specimens. The validated germline assay using nails as a sample type was approved as a clinical test by the New York State Department of Health. Samples were analyzed using a custom panel consisting of 82 cancer predisposition genes. Single nucleotides, insertions/deletions, and copy number variants were detected using our analytic pipeline and analyzed according to ACMG criteria for pathogenicity. Only pathogenic and likely pathogenic germline variants (gPV) were returned. **Results:** Among 86 HM patients (acute myeloid leukemia, n = 19; myelodysplastic syndrome, n = 16; acute B lymphoblastic leukemia, n = 9; acute T-cell leukemia, n = 4; mixed phenotypic acute leukemia, n = 1; chronic lymphocytic leukemia, n = 7; hairy cell leukemia, n = 1; chronic myeloid leukemia, n = 4; chronic myelomonocytic leukemia, n = 1, non-Hodgkin lymphoma, n = 12; Hodgkin lymphoma, n = 8; and multiple myeloma, n = 4), gPV were detected in 16% (14/86). Heterozygous gPV identified in high/moderate penetrant genes included 2 *BRCA1*, 2 *ATM*, 1 *PALB2*, and 3 *CHEK2*. Monoallelic carriers for homozygous disease included 2 *MUTYH* and 1 *MSH3*. Biallelic gPV were identified in 3 patients (1 *FANCA*, 1 *ATM*, 1 *MSH6*); the patients with Fanconi anemia (age 25) manifesting with MDS and constitutional mismatch repair deficiency (age 13) presenting with T-cell lymphoblastic lymphoma had not been previously diagnosed with these conditions and did not have obvious clinical features outside of their cancer diagnosis. In all 3 patients, identification of an autosomal recessive syndrome impacted therapeutic planning. **Conclusions:** Our study demonstrates the feasibility of utilizing nails, a non-contaminated germline sample source, for HM predisposition with a significant proportion of pediatric and adult HM patients identified to harbor gPV in a cancer predisposition gene. Autosomal recessive diseases should be considered not only in pediatrics but also adult patients and requires confirmation of allele segregation in parents. Our data also demonstrate the importance of gPV in HM for therapeutic planning. Research Sponsor: Niehaus Center for Inherited Cancer Genomics; V Foundation.

10634

Poster Session

Correlation of unobserved incidence of cancer in earlier stages with the observed incidence. *First Author: Jagpreet Chhatwal, Massachusetts General Hospital, Harvard Medical School, Boston, MA*

Background: Population-level cancer registries report observed (screening or clinically detected) incident cancer cases. However, the underlying true cancer incidence may be higher than observed. We estimate the unobserved cancer incidence by stage for eight different cancers. **Methods:** Using the CDC's National Program of Cancer Registries (NPCR) and the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) combined incidence databases, we first estimated observed incidence rates by cancer type and stage. Newly observed cancers in later stages must have existed at a previous point in time at an earlier stage (and age). Considering that, we used backward induction approach to estimate the unobserved incidence rate of cancer. We also accounted for mortality from competing factors before cancer was detected. Cancer progression between stages was defined by dwell times, which were synthesized in an ensemble approach from published literature and empirical estimates. We estimated unobserved annual incidence cases in early-stage (stages I and II) for the age 50+ population and compared them with observed incidence cases for each cancer type between 2015-2019. **Results:** The below table shows the annual unobserved and total (unobserved plus observed) cancer incidence by stage for the eight most prevalent cancers. We estimated that the top three cancers with the highest proportion of unobserved early-stage annual incident cases were lung (157,400 cancers unobserved out of 226,400 total), with 70% unobserved; pancreatic (34,700 annual unobserved out of 52,500 total), with 66% unobserved, and non-Hodgkin's lymphoma (46,400 unobserved out of 73,600 total), with 78% unobserved. In contrast, the cancers with the lowest proportion of unobserved early-stage incident cases were breast (29,100/203,400 [14%]), urinary bladder (27,000/81,800 [33%]), and prostate (110,600/258,900 [43%]). Cancers with a high screening rate have lower unobserved early stage incidence than cancers with a low screening rate or without a screening test. **Conclusions:** We estimated a large undiagnosed incidence of cancer in early stages. This represents an opportunity for novel early detection technologies to detect cancer in earlier stages. Research Sponsor: Exact Sciences Corporation.

Cancer	Stage I-II Unobserved/Total (%)	Screening Test Available	National Annual Screening Rate in Eligible Population
Lung	157,400/226,400 (70%)	For high-risk smokers only	0.2% ¹
Pancreatic	34,700/52,500 (66%)	No	-
Non-Hodgkin's Lymphoma	46,400/73,600 (63%)	No	-
Head and Neck	27,400/47,200 (58%)	No	-
Colorectal (colonoscopy)	71,300/136,900 (52%)	Yes	8.8% ¹
Prostate	110,600/258,900 (43%)	Yes	39% ²
Urinary Bladder	27,000/81,800 (33%)	Yes	-
Breast	29,100/203,400 (14%)	No	48.1% ¹

¹NORC at the University of Chicago. (2022). Source <https://cancerdetection.norc.org/>

²CDC, National Center for Health Statistics, National Health Interview Survey, 2005-2018.

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Poster Session

TPS10636

Poster Session

Pre-diagnosis dietary patterns and risk of multiple myeloma in the NIH-AARP cohort. *First Author: Richa Parikh, Department of Hematology/Oncology, Karmanos Cancer Institute, Wayne State University, Detroit, MI*

Background: Despite patient interest in knowing whether diet is linked to multiple myeloma (MM), there is limited research on dietary patterns and MM risk (Malik et al. BCJ 2022). Two studies have assessed this risk, albeit with a small number of MM cases. The EPIC-Oxford cohort and Oxford Vegetarian study (65 MM cases) showed that fish eaters, vegetarians and vegans had significantly reduced MM risk compared to meat eaters (Key et al. AJCN 2014). The Nurses' Health Study and Health Professionals Follow-up Study (478 MM cases) showed a significantly increased MM risk in men with Empirical Dietary Inflammatory Pattern (Lee et al. JNCI Can Spectr 2019). To our knowledge, this is the largest epidemiologic study to date assessing pre-diagnosis dietary patterns and MM risk. **Methods:** The NIH-AARP Diet and Health study is a prospective cohort of 567,169 persons who completed a food frequency questionnaire in 1995-1996 and were followed until December 2011. Healthy Eating Index-2015 (HEI-2015), Healthy Diet Score (HDS), alternate Mediterranean Diet (aMED) and healthful Plant-based Diet Index (hPDI) scores were calculated using *a priori* defined methods and grouped into quartiles, with higher scores reflecting healthier eating patterns. We prospectively evaluated the association between pre-diagnosis dietary patterns and MM incidence in this cohort. Hazard ratios (HR) and 95% confidence intervals (95%CI) were estimated using multivariate Cox proportional hazards models adjusted for age at study entry, sex, race, body mass index, education, and total energy intake (by residual method). Sensitivity analysis was conducted to assess reverse causality by excluding MM cases diagnosed within one year of follow-up. **Results:** Among 392,589 participants (after exclusions), a total of 1,366 MM cases (59% males; 92% non-Hispanic whites) were identified during the follow-up period. Analysis revealed a significant association between hPDI scores and reduced MM risk (highest vs lowest quartile, HR 0.85; 95%CI 0.73-1.0; p=0.043) (Table). In sensitivity analysis (1,302 MM cases), the association was no longer significant (HR 0.87; 95%CI 0.74-1.03; p 0.09) but trended in the same direction. This may be due to small sample size, given MM is a rare disease. HEI-2015, HDS and aMED scores were not associated with MM risk. **Conclusions:** A healthful plant-based diet was associated with reduced MM risk in the NIH-AARP cohort. These results will help oncologists and patients make informed choices about their diet. Research Sponsor: U.S. National Institutes of Health; MSK Paul Calabresi Career Development Award for Clinical Oncology K12CA184746, Paula and Rodger Riney Foundation, Allen Foundation Inc, Parker Institute for Cancer Immunotherapy at MSK, HealthTree Foundation, International Myeloma Society.

Cox multivariate analysis for dietary score quartiles and MM risk.					
Quartiles	Q1	Q2	Q3	Q4	p-value
HEI-2015	1.00	1.15 (0.99, 1.34)	1.01 (0.87, 1.18)	1.01 (0.87, 1.19)	0.2055
HDS	1.00	0.95 (0.81, 1.10)	0.88 (0.76, 1.03)	0.92 (0.79, 1.07)	0.4537
aMED	1.00	1.02 (0.89, 1.18)	1.0 (0.87, 1.16)	0.92 (0.79, 1.07)	0.5942
hPDI	1.00	1.02 (0.88, 1.17)	1.05 (0.9, 1.23)	0.85 (0.73, 1.00)	0.0429*

Hazard Ratio (95%CI) *Statistically significant.

TPS10637

Poster Session

Characterization of pre-malignant lesions in patients with pediatric neurofibromatosis type 1 using a novel whole-body magnetic resonance imaging technique. *First Author: Nicole M. Baca, Cedars-Sinai Medical Center Medical Pediatric Hematology/Oncology, West Hollywood, CA*

Background: Neurofibromatosis Type 1 (NF-1) patients can develop benign tumors, plexiform neuromas (PN), that may transform into malignant peripheral nerve sheath tumors (MPNST)(Tucker, et al. 2009). MPNST are rare, but in NF1, the lifetime incidence is 8-13% and MPSTs present at younger ages(Miettinen, et al. 2017). MPNST are aggressive tumors requiring full resection for best outcomes (Mautner, et al. 2008). Emerging data suggests whole-body MRI (WB-MRI) can identify NF patients with higher PN tumor burden and maybe at risk of developing MPNST. We have created a rapid, motion-robust quantitative WB-MRI technique that is likely suitable for pediatric patients. High-resolution multiparametric tissue mapping, including T1, T2, and ADC (apparent diffusion coefficient), are acquired concurrently in a single scan, as shown in prior studies (Christodoulou, et al. 2018, Ma, et al. 2020, Nguyen, et al. 2016, Wang, et al. 2020). This project will evaluate the feasibility and reproducibility of novel WB-MRI for the characterization of pre-malignant lesions in NF-1 patients. **Methods:** Trial Design: Pilot study of novel WB-MRI technique in pediatric NF-1 patients with a goal of 15 patients between the ages of 5-17 years. Trial MRI scans are performed at baseline, 1 month, and then 12 months (+/-3 months). A clinical 3T MR scanner (Siemens MAGNETOM Vida) performs a head-to-knee WB-MRI in 70 minutes. Signal-to-noise ratio (SNR) and imaging quality scores will be evaluated. The lesion volume and mean T1/T2/ADC are measured for each lesion on the corresponding quantitative maps based on manual ROI's (regions of interest). To assess scan-rescan reproducibility, image quality metrics (SNR and quality score), lesion identification, and lesion characteristics (T1, T2, and ADC) will be compared between the baseline and the 1-month scan using a Bland-Altman analysis and Schuirman's equivalence. The coefficient of variation (CV = 100 [SD/mean] %) values for each of the quantitative values will be calculated. To evaluate for lesion characterization, changes in the mean in each MRI quantitative metrics (T1, T2, and ADC) will be measured for each lesion on the baseline and 12-month visit. Spaghetti plots will be used to visualize the change over time, and the difference in mean will be tested using an appropriate parametric or nonparametric test depending on the results of tests on normality and homoscedasticity. Intervention: WB-MRI at baseline, 1 month, and 12 months (+/-3 months) Eligibility: 5 to 17 years old not requiring sedation; Clinically or molecularly diagnosed NF-1 including mosaic/segmental subjects; Not Eligible: allergy to animal dander, animal-instigated asthma, pregnant, breastfeeding, or have intrauterine device; Current Enrollment (February 2023): 5 subjects (One unable to finish a non-sedated MRI). Clinical trial information: NCT04763109. Research Sponsor: Cedars-Sinai Cancer Pilot Project Committee 2020 Developmental Funds for Investigator Initiated Trials (IIT) Award.

Metformin for chemoprevention of lung cancer in high-risk overweight or obese individuals. *First Author: Isra Nour, Northwestern University, Chicago, IL*

Background: Lung cancer is the most common cause of cancer-related deaths in the United States, with tobacco smoking being the most important risk factor. However, ~60% of individuals at a high risk for lung cancer or with early-stage lung cancer are either overweight or obese. Preliminary studies suggest that the diabetes drug metformin improves survival in high BMI lung cancer patients and inhibits lung cancer progression in preclinical models, likely through its effects on the obesity-triggered changes to the immune microenvironment of the lung, particularly, the regulatory T cells (Tregs) in the airway. Given the known dysregulation of Tregs in obesity and the importance of Tregs in lung carcinogenesis, we hypothesize that metformin therapy will reprogram the immune defense of obesity in directions that are consistent with the control of nascent lung tumor development. While more generalized lung cancer prevention approaches have to date shown limited effectiveness, the targeting of a specific subset of individuals at high risk for lung cancer provides a precision prevention approach, which is likely to be more effective. **Methods:** This is an open-label, randomized, wait-list control trial, where 50 non-diabetic obese/overweight former smokers with over 20 pack year smoking history and PLCOm2012 Lung Cancer Risk Prediction score above 1.34% will be enrolled. They will be equally randomized to either oral metformin or no treatment for 26 weeks followed by partial crossover, whereby no-treatment subjects will receive metformin for 26 weeks. The open-label, wait-list control design allows inclusion of a control group to assess stability of the primary biomarker in an untreated population while retaining the statistical power of 40 metformin-treated subjects (assuming 20% subject attrition) and will aid accrual since all trial participants will be treated. Treatment regimen is one daily dose of metformin at 500 mg for 1 week followed by 1000 mg for the second week and 2000 mg thereafter for a total of 24 weeks. Sampling for endpoint assessment include bronchoscopy with biopsy and bronchoalveolar lavage (BAL) and blood collection before and after completion of metformin treatment. The primary endpoint is to evaluate the effect of metformin treatment on the expression of PD-1, an immune checkpoint factor, on BAL Tregs. The secondary endpoints include stability of BAL Treg PD-1 expression over time and the impact of metformin on circulating immune cells. Trial sites include Roswell Park Comprehensive Cancer Center, the Rocky Mountain Regional Veterans Affairs Medical Center, and University of British Columbia, Vancouver. Since the trial opened to accrual in March 2022, 77 patients have been pre-screened and 19 were consented. Among them, 10 participants have been enrolled and randomized, 5 in each arm. We expect to complete accrual by April 2024. Clinical trial information: NCT04931017. Research Sponsor: U.S. National Institutes of Health.

TPS10638

Poster Session

Connecting Black families in Houston, Texas, to hereditary cancer genetic counseling, genetic testing, and cascade testing by using a simple cancer genetic risk assessment and telegenetics. *First Author: Darya Aleksandrova Kizub, Division of Cancer Medicine, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Hereditary breast and colorectal cancers accounts for 5-10% of all cases, but less than half of all eligible patients undergo NCCN guideline-concordant screening. This proportion is even lower among Black patients, who have a higher breast cancer and colorectal incidence and mortality. Recruitment through community organizations has been shown to identify patients who are eligible for genetic testing but have not been offered it by their doctor. Our one-page cancer genetic risk assessment (CGRA) and telegenetics were previously shown to improve adherence to genetic testing guidelines for hereditary breast and ovarian cancer. Our objective is to identify adults eligible for hereditary breast and colorectal cancer syndromes genetic testing using trusted community organizations that serve the Black community as entry points, reach them with our tailored program, and measure impact. **Methods:** In this prospective single-arm trial, adults of > 18 years old who self-identify as Black or African American are recruited during events put together by community organizations in Houston, Texas. The CGRA was modified to encompass hereditary breast and colorectal cancer syndromes based on NCCN guidelines. To improve convenience, eligible participants can be consented and fill out the CGRA in-person or via QR code link using a smart phone. Study team members attend community events and are also available via phone to help with informed consent, CGRA, etc. Those at high risk for hereditary breast and colorectal cancer syndromes are provided with educational materials and can be sent the saliva-based kit or complete it on-site. When results of genetic testing include a pathogenic mutation (PV) or variant of uncertain significance, individuals receive telegenetic counseling and risk reduction resources, including about cascade genetic testing. Others are notified of negative results. The program includes education for interested community organization members about importance of genetic testing. The program is projected to reach 1,000 participants with 300 completing genetic testing and identification of 11 PV. The study is overseen by a Community Advisory Board. Impact will be evaluated via a multiple methods design using the Reach, Effectiveness, Adoption, Implementation, Maintenance (RE-AIM) Qualitative Evaluation for Systematic Translation (QuEST) framework six months after program start. Quantitative data will be analyzed using descriptive statistics and standard tests of association. Data collected via semi-structured interviews with participants and program implementers will be audio-recorded, transcribed, double-coded, and analyzed via thematic analysis. Enrollment started December of 2022. 15 participants patients enrolled during two community events. Clinical trial information: NCT05694559. Research Sponsor: Susan G. Komen.

11000Clinical Science Symposium

Differential burnout by race, sex, and sexual orientation in academic oncology. *First Author: Bismarck Odei, University of Utah, Salt Lake City, UT*

Background: Burnout is a concern in medicine with negative effects on physician wellbeing, workforce retention, and patient outcomes. Research has shown that rising burnout can lead to medical errors, lower patient satisfaction, and decreased professional work effort. The presence of burnout in oncology is well documented, however it is unclear if burnout affects all groups equally in academic oncology. **Methods:** We obtained national faculty data from the Association of American Medical Colleges StandPoint Faculty Engagement Survey, conducted 2017-2020 (overall response rate 64%). Burnout was considered any response endorsing at least "one or more symptoms of burnout". Self-reported workplace culture was assessed for key factors: collegiality, diversity, faculty wellness, and recruitment/retention of underrepresented in medicine (UiM) faculty. Faculty demographics included age, sex, race/ethnicity, sexual orientation (heterosexual, bisexual, lesbian/gay), rank, degree, and any department or institutional leadership role. Multivariate analysis (MVA) identified factors associated with faculty burnout. **Results:** A total of 724 academic oncologists were identified. Most were male (58%) and identified as heterosexual (95%). Race/ethnicity were mostly White (65%), with 29% Asian, 2% Black, and 3% Hispanic/Latino; 7% were considered UiM. Most (53%) were senior faculty; 37% had a leadership role. Overall, 22% reported burnout. Self-identified lesbian/gay/bisexual faculty had the highest rate of burnout (43% vs 21%, $p = 0.0005$) followed by female faculty (31% vs 16% men, $p = < 0.0001$). Asian faculty had the lowest burnout rates (12%) followed by White and Hispanic (both 26%), Black (33%), and multi-racial physicians (50%, $p = 0.003$ for comparisons). Pooled UiM had numerically higher burnout but this was not statistically significant (30% vs 22%, $p = NS$). On MVA, lesbian/gay/bisexual (OR = 3.56, 95%CI 1.55-8.18, $p = 0.003$) and female (OR = 2.32, 95%CI 1.51-3.56, $p < 0.0001$) faculty had increased odds of burnout. Most agreed that their institution cultivates collegiality (80%), diversity (73%), and faculty wellness (53%); men were more likely to endorse positive diversity (77% vs 68% women, $p = 0.004$). Most agreed their institution was successful in recruiting (63%) and retaining (58%) UiM faculty, however non-UiM were more likely to agree with this for recruitment (64% vs 46% UiM, $p = 0.01$) and retention (50% vs 42% UiM, $p = 0.01$). **Conclusions:** Nearly 1 in 4 oncologists report burnout with self-identified female and lesbian/gay/bisexual faculty at the highest risk. Additionally, in general, men and non-UiM faculty were more likely to feel their workplace culture was favorable. Urgent and tailored interventions at the institutional and departmental level will be critical to address both drivers of faculty burnout and the impact of burnout on attrition and career trajectory for marginalized and minoritized groups. Research Sponsor: None.

11002Clinical Science Symposium

Diversity, equity, and inclusion (DEI) and health equity (HE) education in hematology/oncology (HO) fellowship: A longitudinal curriculum. *First Author: Norin Ansari, Yale Cancer Center, Yale School of Medicine, New Haven, CT*

Background: The medical workforce remains markedly less diverse than the patients we care for, and outcomes disparities persist. This highlights the need for DEI efforts and HE education. In 2021, we implemented a DEI curriculum in the HO fellowship at Yale Cancer Center (YCC) and found improvements in our fellows' upstander responses. We present an assessment 1 year after initiation of this series and we share our longitudinal 3-year DEI/HE curriculum and other institutional steps taken to improve equity. **Methods:** An anonymous survey assessing DEI/HE needs, experiences with and comfort level addressing discrimination, and preferences for curriculum was emailed to all YCC HO fellows. 1st year fellows had no formal DEI education prior to the survey. Senior fellows had completed 1 year of the fellowship's DEI series. **Results:** 23 fellows (79%) responded, including 8 1st year and 13 senior fellows (2 unknown). Most fellows had experienced (78%) or witnessed (87%) some form of discrimination. Notably, 1st year fellows felt under-equipped to navigate bias and microaggressions compared to senior fellows. 1st year fellows reported a mean confidence score of 2.5/5 navigating these events when experienced personally and 2.9/5 when directed at others, compared to senior fellows (mean confidence scores 3 and 3.2 respectively). Fellowship DEI education was perceived as important (mean 8.6/10). When asked which DEI/HE topics they would be interested in learning about, the most popular choices among the 23 fellows were cancer treatment and outcomes disparities (78%) and bystander training (70%). They indicated lectures from field experts (65%), affinity groups (57%), small group discussions (52%), and advocacy education (52%) would be useful to them. The chief fellows convened a series of discussions with faculty and field experts, which led to creation of a 3-year longitudinal DEI/HE curriculum. This includes an annual cancer disparities lecture and bystander training session, and 2-4 rotating lectures per year covering implicit bias training, issues of race, gender, LGBTQIA+, disability, and religion in the workforce and in patients' experiences, pay and promotion disparities, and financial toxicity for patients. YCC and fellowship leadership have also implemented a DEI lecture series, increased recruitment of under-represented in medicine (URiM) physicians, established an URiM mentorship group and a diversity enhancement program for rotations for URiM medical students, and encouraged community engagement. **Conclusions:** DEI/HE education at all levels is essential for fostering equity in the workplace and patient care. Implementation of a longitudinal curriculum in parallel with other YCC initiatives has improved fellows' confidence in navigating bias and microaggressions. This curriculum can serve as a guide for other programs developing DEI/HE education. Research Sponsor: None.

11001Clinical Science Symposium

The ticking "biological clock": Reproductive assistance, costs, and elective fertility preservation in female oncologists and trainees. *First Author: Emily MacDuffie, University of Pennsylvania, Philadelphia, PA*

Background: Women in medicine are often in training during their peak fertility years. Many women defer childbearing until after training due to career concerns; in consequence, female physicians experience a higher rate of infertility than the general population. Experiences of infertility among female physicians and attitudes towards fertility preservation have not been well described. **Methods:** A novel 39 question survey was designed after comprehensive literature review to collect cross-sectional data on attitudes toward family planning and utilization of assisted reproductive technology (ART) among self-identified US female oncologists of all career levels. Descriptive statistics summarized frequencies of responses. **Results:** A total of 1005 responses were collected from female oncologists, of which 811 (81%) were attending/practicing physicians and 194 (19%) were trainees (192 residents/fellows and 2 medical students). 32% reported experiencing infertility. Of these 318 women, 9% reported no out-of-pocket expenses for ART while 39% spent more than \$10,000 and 20% spent $\geq$ \$30,000. Side effects from infertility treatment required missing work for 22% and another 25% suffered mental health concerns related to infertility. Elective cryopreservation of eggs or embryos was reported by 6% of attendings and 4% of trainees. Among the 25 attendings who reported plans/desire to undergo fertility preservation in the future, most (76%) were unsure of feasibility. This was similarly reported in 72% of the 32 trainees with plans/desire to pursue fertility preservation. More trainees than practicing physicians (73% vs 65%) felt that fertility preservation should be discussed during medical training. Similarly, more trainees than attendings (58% vs 47%) felt that fertility concerns have a negative influence of their decision on when to start a family. While only 5% of all respondents reported using fertility preservation, an additional 6% were planning/considering using it and 21% felt that it would have benefitted them had it been available and affordable during training. Of the group that felt it would have been beneficial, 52% had experienced infertility. **Conclusions:** A third of surveyed female oncologists report experiencing infertility. Those that seek reproductive assistance can incur significant out of pocket costs with treatment related effects that can disrupt work or cause mental health concerns. Although fertility preservation was used by very few, one in five felt it could have been helpful to them if it was available and affordable. These results underscore the need to better support women in medicine to reduce the impact of infertility for female oncologists. Research Sponsor: None.

11003Poster Discussion Session

Workplace sexual harassment in academic oncology. *First Author: Divya Yerramilli, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Research has shown workplace sexual harassment (WSH) is a pervasive problem in academia, affecting recruitment, retention & career advancement of women faculty. This study examines WSH in academic oncology faculty in a national survey. **Methods:** We obtained data from the Association of American Medical Colleges StandPoint Faculty Engagement Survey between 2020-22 representing a national sample of academic faculty from 25 medical schools (overall response rate (RR) 58%). WSH was considered specific "unwanted behavior" by coworkers that occurred at least once in the past year. Reporting questions were asked on a 5-point Likert Scale from Strongly Disagree to Strongly Agree, with 6th option "I Don't Know." Responses were grouped as Agree/Strongly Agree vs all others. Chi-square tested for differences by gender and race/ethnicity. **Results:** 807/1,287 oncologists participated in the survey (RR 63%), and 91% (731) answered the WSH questions. Most self-identified as men (58%) and only 8% identified as underrepresented race/ethnicity (URiM). See Table for findings. In oncology, women experienced any WSH at higher rates than men (33.1% vs 10.3%, $p=0.001$). The most common was derogatory comments due to gender. Regardless of gender, most knew how to report WSH incidents, but men were more likely to feel safe reporting. While 64.9% of men felt confident that their medical school would resolve WSH incident(s) effectively, only 48.7% of women did. Positive perceptions of reporting decrease among those who reported harassment. URiM faculty (35.6% vs.18.5%, $p=0.001$) were more likely than non-URiM faculty to experience at least one of the five harassment behaviors, although this was limited by small sample. **Conclusions:** In academic oncology, women and URiM experience workplace sexual harassment more often than men and non-URiM. Less than half of women felt confident that reporting an incident would lead to effective resolution. Urgent intervention is needed to combat the negative force of sexual harassment on workforce equity. Research Sponsor: Cancer Center Support Grant from the National Cancer Institute (P30 CA008748).

	Men	Women	
In thinking about unwanted behaviors over the past 12 months, how often did a school of medicine faculty member or staff member (including supervisors)...			
Tell sexist stories/jokes	8.1% (34/422)	17.3% (53/306)	$p<0.001$
Make offensive remarks about appearance, body, sexual activities	2.4% (10/421)	7.8% (24/306)	$p=0.001$
Refer to your gender in offensive, insulting, or vulgar terms	2.6% (11/421)	11.9% (36/303)	$p<0.001$
Put you down or acted in a condescending way due to gender	2.4% (10/419)	25.2% (77/305)	$p<0.001$
Overall Rate of Harassment	10.3%	33.1%	$p=.001$
If I experienced sexual harassment... Agree/Strongly Agree			
I would feel safe reporting the incident(s)	81.3% (343/422)	68.7% (211/307)	$p<0.001$
I know to whom I can report the incident(s)	77.7% (328/422)	71.7% (218/304)	$p=.121$
I feel confident the incident(s) would be resolved effectively	64.9% (271/417)	48.7% (149/306)	$p<0.001$

11004

Poster Discussion Session

Should I stay, or should I go? Factors associated with intent to leave academic oncology. *First Author: Ana I. Velazquez Manana, University of California San Francisco, San Francisco, CA*

Background: Physicians who are female and/or belong to racial/ethnic groups underrepresented in medicine (UIM) face disparities in salary, promotion, and leadership opportunities in academic oncology. Also, growing rates of burnout, increasing burden of documentation/administrative tasks, and lack of adequate supportive staff represent threats to workforce retention, particularly for female and racial minority subgroups. We evaluated the prevalence and factors associated with likelihood of leaving their specific academic institution in a national sample. **Methods:** We obtained national faculty data from the AAMC's StandPoint Faculty Engagement Survey, conducted between 2017-2020 with 25 U.S. medical schools. Chi-squared and Fisher's exact tests were used to determine differences in likelihood of leaving their institution within 1-2 years by sex and UIM status. Multivariate analyses (MVA) examined the associations between likelihood of leaving their institution and self-reported sex, year born, sexual orientation, UIM race/ethnicity, degree, academic rank, and administrative role. **Results:** We identified 724 oncology faculty at academic institutions (overall response rate 64%). Slightly less than half of oncologists self-identified as female (42%, n = 303) and only 7% (n = 47) as UIM. When asked about the likelihood of leaving their current institution, 22% (n = 152/687) of oncologists reported being at least somewhat likely to leave within the next 1-2 years. Notably, 26% of female oncologists reported they were likely to leave, compared to 19% of males (p = 0.022); no differences were observed by UIM status (p = 0.714). MVA identified sex as associated with likelihood of leaving; females had 78% higher odds of leaving their institution within 1-2 years (aOR 1.78; 95% CI, 1.13-2.79). Among those likely to leave, 46% (n = 72/157) reported intent to leave academic medicine completely; rates were similar across sex and UIM groups (p = 0.746). When evaluating workplace experience, most oncologists (86%, n = 621) felt respected in their workplace. Among those reporting feelings of disrespect in the workplace, 16% of female oncology faculty felt disrespected due to their gender (n = 47), compared to 0% of male oncologists. A small number of faculty reported disrespect due to age (n = 26), race/ethnicity (n = 11), sexual orientation (n = 2), marital status (n = 10), or religion (n = 7). Females endorsed greater feelings of disrespect in all categories other than religion. **Conclusions:** Female oncologists are almost twice as likely to state they are likely to leave their academic institutions within 1-2 years; this aligns with published data on attrition of female faculty in academic medicine. Our findings confirm the persistence of these trends in the modern era and stress the urgency of improving workplace experience, culture, and supports in order to preserve and enhance the diversity of faculty in academic oncology. Research Sponsor: None.

11006

Poster Discussion Session

A multifaceted approach to wellness in a hematology/oncology fellowship program. *First Author: Thejal Srikumar, Yale New Haven Hospital, New Haven, CT*

Background: Burnout is widespread among physician trainees and is a growing problem despite increasing awareness. We describe multiple efforts in a single institution's Hematology/Oncology (HO) fellowship program to help support trainees' wellness. **Methods:** A needs assessment was conducted to identify wellness topics and programming important to fellows. Anonymous surveys were distributed to all fellows in Yale's HO fellowship program at the start of the academic year. Three senior fellows reviewed the results and, with the support of core faculty, designed initiatives to address top priorities. The interventions included off-campus debrief sessions for fellows only, Schwartz Rounds-style discussions during weekday didactic slots, faculty-led didactics on Imposter Syndrome and Perfectionism, and several off-campus, after-hours social activities. A follow-up survey was conducted six months after the initial survey (mid-academic year) to garner feedback. **Results:** Of the 23 fellows who were sent the initial survey, 17 responded (73.9%). The most requested discussion topics were Perfectionism Traps, Imposter Syndrome, Achieving Happiness/Defining Success at Work, and Myths About Work/Life Balance. Most fellows (76.5%) responded that they would attend off-site debrief sessions if offered. In response to the initial survey, several initiatives were undertaken as described in Methods. The mid-year survey was completed by 16 of 23 fellows (69.6%). Of these 16 respondents, attendance was as follows: 31.3% for after-hours debrief sessions, 75% for Schwartz Rounds-style discussion, 75% for Imposter Syndrome and Perfectionism lecture, and 75% for at least one social activity. The majority of fellows who attended these events reported them to be helpful (range 75-100%). Themes identified from written comments included universal appreciation for wellness programming efforts and a desire for more sessions for group reflection. One fellow noted these activities were "helpful for wellness and fostering a pleasant work environment." Other fellows noted the Imposter Syndrome discussion "should be mandatory" and "would be helpful earlier in the year." Several fellows expressed their wellness was linked to clinical workload, and one fellow noted sessions outside of regular work hours are difficult to attend. **Conclusions:** Structured needs assessment and implementation of wellness programming in a HO training program appeared to be beneficial to the majority of fellows. To our knowledge, this is the first description of comprehensive fellow-directed wellness initiatives in HO training. Continued efforts must be made to better support fellows, including options in location, timing, faculty presence, and optimizing work responsibilities and expectations. Further study is necessary to quantify the impact of these initiatives and to tailor the most effective approach to fellows' wellness. Research Sponsor: None.

11005

Poster Discussion Session

Hematology/oncology program director perspectives on recruitment and inclusion of a diverse workforce. *First Author: Ana I. Velazquez Manana, University of California San Francisco, San Francisco, CA*

Background: Despite progress in the enrollment of underrepresented in medicine (UIM) individuals in medical schools, hematology/oncology (HO) remains one of the least diverse medical subspecialties. We evaluated current recruitment efforts and barriers to the inclusion of UIM individuals in HO fellowship programs. **Methods:** We conducted a national online survey of program directors (PDs) and associate PDs (reported in aggregate as PDs) of adult and pediatric HO fellowships. Each PD received a unique survey link via email and 4 email reminders over the 8-week study period. Interim results at 4-weeks are presented and summarized with descriptive statistics. **Results:** At a pre-defined interim time point of 4 weeks, 78 HO PDs participated (18% response rate) and 69 completed the survey (88% completion rate). Most self-identified as women (57%, n = 38) and White (55%, n = 37), were affiliated with an academic program (79%, n = 53), and led an adult HO fellowship (73%, n = 49). Most PDs reported under or no representation of UIM faculty in their divisions; 9% (n = 6) self-identified as UIM. PDs reported their HO fellowships matched a median of 3 UIM fellows over the last 5 years (IQR 2-5 over 5 years); 46% (n = 32) reported UIM recruitment was unchanged and 4% (n = 3) decreased during this period. About half of PDs (51%, n = 35), matched a UIM candidate in the 2023 match. Of the 21% (n = 14) of PDs whose programs had no UIM fellows, 0% matched a UIM applicant in the 2023 match. 52% (n = 36) of PDs endorsed an inability to match UIM applicants despite consistently ranking them highly. PDs perceive the top 3 barriers to UIM recruitment as: low number of UIM applicants (53%, n = 41), geographic program location (50%, n = 39), and lack of diverse faculty/fellows in their program (42%, n = 31). 10% (n = 7) also reported meeting resistance about DEI initiatives. While 53% (n = 41) of PDs believe fellow demographics should reflect the local population, 23% (n = 16) don't know how to increase diversity and 11% (n = 8) do not believe their program's diversity needs to increase. In answers to open ended questions, some PDs expressed disagreement with the definition of UIM and reported a perceived limited number of qualified UIM applicants. Almost all institutions provide DEI training (96%, n = 72) for faculty and most PDs believe it has improved recruitment and inclusion of diverse individuals (52% and 65%, respectively). Yet, 34% (n = 23) agree that UIM fellows in their program are treated differently because of their race/ethnicity and 22% (n = 15) agree that UIM fellows reported their identity or background to be respected by faculty, peers, and staff. **Conclusions:** Historically and currently excluded populations remain underrepresented in the HO workforce. PDs face multiple barriers to the recruitment of diverse fellows, including differing views on the definition of UIM and perception of the value of diversity in the physician workforce. Research Sponsor: None.

11007

Poster Discussion Session

Remote delivery of a mindfulness-based intervention to decrease stress levels and promote coping among health-care workers during the COVID-19 pandemic. *First Author: Joelle Antoine Helou, Department of Oncology, Western University, London, ON, Canada*

Background: The COVID-19 pandemic has caused significant stress amongst everyone around the world. Healthcare workers (HCW) in particular, experience substantial stress in these challenging environments. In an effort to find supportive interventions for radiation oncology providers, while respecting the requirements of physical distancing, we proposed the remote delivery of a mindfulness-based intervention (MBI). The primary aim of this study is to determine the association of this intervention with a reduction of perceived stress. Secondary aims are to evaluate the impact on coping and burnout amongst HCW in the Radiation Program (RP). **Methods:** This is a single-centre, single-arm, pilot study. All HCW associated with the RP were eligible. This was a voluntary effort. The intervention - manualized, mindfulness-based group for HCW, entitled Mindfulness-Based Resilience and Well-Being Training, consisted of four 1-hour sessions per week for 4 weeks. From Nov 2020 to Dec 2021, 6 consecutive closed groups MBI were delivered remotely using Zoom. Each group consisted of 5-12 participants and one professional with a background in mindfulness facilitation. The Perceived Stress Scale (PSS), The Maslach Burnout Inventory and the BriefCOPE questionnaire were collected pre-intervention, and at 1, 4 and 12 weeks post-intervention. Linear mixed effect models with a random intercept to account for the repeated measures were used to assess the change of outcomes over time. **Results:** Amongst 43 HCWs who expressed initial interest, 33 completed the study. At 1-, 4- and 12-weeks post-intervention 25, 24 and 21 participants provided completed questionnaires respectively. Time constraint was the main reason for withdrawal and missing data. There was a significant decrease in perceived stress at week 1, 4 and 12 when compared to baseline [mean baseline PSS score: 22.5 (SD = 4.6), week 1: 18.4 (4.9), p = 0.002, week 4: 16.8 (6.5), p < 0.001, week 12: 16.3 (6.8), p < 0.001]. Overall, 7 (21%) participants reported high PSS (27-40) at baseline while none reported high levels at 1 and 12 weeks. Problem focused coping (p = 0.02), and active coping (p = 0.009) were significantly higher at 1 week but not at 4 and 12 weeks. **Conclusions:** The remote delivery of a MBI is feasible and effective to reduce perceived stress levels and to promote coping across HCWs. These findings need to be validated in a larger cohort. Time was a major constraint preventing the participation of interested HCWs. It would be extremely valuable for departments to support such interventions and programs to help HCWs cultivate skills to meet the demands related to working in healthcare environments throughout and beyond this crisis. Research Sponsor: internal departmental funds.

11008

Poster Discussion Session

Tumor board tuesday and awareness of novel therapies and toxicities in solid tumor oncology. *First Author: Johnathan Ebben, University of Wisconsin Hospitals and Clinics, Madison, WI*

Background: Social media platforms, including Twitter, offer novel tools to accelerate discussion and learning that crosses national borders, flattens hierarchies, and enables collaborations not previously possible. Here, we report on a new initiative, Tumor Board Tuesday (TBT), which facilitates the presentation of cases with active discussion from thousands of stakeholders across the oncology community, highlighting new practice changes and precision oncology strategies. Herein, we sought to evaluate 1) the nature of participation by individuals and groups, as well as their scope of participation in TBT; 2) the impact of participation in TBT, including new collaborations forged, practice changes, increased knowledge of the use of novel agents, and their associate toxicities, as well as emerging clinical trials available to patients. **Methods:** TBT performed a survey designed to assess the demographics, experience, and opinions of platform users. This survey was collated with voluntary pre/post TBT presentation knowledge checks to assess knowledge acquisition. **Results:** Based on the survey of TBT participants (n = 38), participant gender is roughly balanced (48.4% women, 48.4% men; 3.2% prefer not to answer). 83.6% of respondents reside in the United States, 8% in Brazil, 5.4% in India, and 3% in Ireland. Interestingly, the majority of respondents identified Twitter as their primary source for oncologic and practice changing updates. Among self-identified oncologists, 12.9% identified as senior members of the field, 51.6% as mid-career, 16.1% as early career, and 12.9% as fellows/trainees. Despite the wide variation in career stage, 81.1% of respondents noted that they had become aware of a new treatment option or modality through TBT participation, which caused 78.4% to change or re-think their treatment approach. In addition, 75.7% of respondents noted that TBT had helped them to become more aware of novel agent toxicities, and 78.4% became aware of a clinical trial option because of TBT participation. Finally, 78.4% of respondents identified TBT as a tool that had helped grow professional connections and networks. On average, there were 56 respondents to knowledge-based questions within each TBT presentation. Analysis of responses to pre and post TBT questions focused on breast, GU, and pulmonary malignancies revealed a 12%, 13%, and 6% respective increase in correct answer choices. **Conclusions:** Social media, specifically, the use of the TBT platform engages oncology professionals across the career spectrum, enhances learning about novel therapies and corresponding toxicities, and broadens professional connections. Research Sponsor: None.

11010

Poster Discussion Session

Quality and accessibility of liquid biopsy information: An analysis of online content. *First Author: Henry Kazunaru Litt, University of California, San Francisco, San Francisco, CA*

Background: Circulating tumor DNA assays, also known as liquid biopsies, are increasingly used by oncologists to evaluate residual disease, cancer genomic composition, resistance mechanisms, and guide therapy selection. Since patients often use the internet as a source of medical information, we evaluated the quality, accessibility, and understandability of publicly available online information on liquid biopsies. **Methods:** We performed a cross-sectional study of 100 videos and 100 webpages that resulted from the search of "liquid biopsy" on a commonly used search engine (Google) and social network (YouTube). Videos over 5 min, scientific articles, and non-English content were excluded. Videos were evaluated for content, intended audience, and perceived sex and race/ethnicity of speakers. Two independent reviewers evaluated understandability and quality of health information using two validated tools for consumer health information (PEMAT, DISCERN). Any disagreements were resolved by a 3rd independent reviewer. Webpages were evaluated for accessibility (use of visual aids, other languages), quality of information (authors, citations, indications, limitations, cost), reading level, and presence of commercial bias. Reading level was evaluated using the validated Flesch-Kincaid (FK), Gunning Fog (GF), and SMOG indices. Data was summarized with descriptive statistics. **Results:** We reviewed 100 videos, with 190 median views per video (IQR: 75-719). Most videos were intended for a scientific audience (72%) and lacked diversity of speakers. The majority of featured speakers were perceived as male (65%) and non-Hispanic white (72%). Overall, liquid biopsy videos were complex and low quality. Only 9% of videos were understandable and 8% presented moderate to high quality health information. Furthermore, we reviewed 100 webpages about liquid biopsies; key characteristics are summarized in the table. About a third of webpages included indications (36%) and limitations (35%) of liquid biopsies. Webpages had a median text reading level of 14.1 (IQR: 12.1-15.8), 16.4 (IQR: 14.4-18.6), and 15.9 (IQR: 13.9-16.9) based on FK, GF, and SMOG indices, respectively. Only 2 websites had one index reading level of 8th grade or lower as recommended by the NIH and CDC. **Conclusions:** Online content about liquid biopsies is complex and requires education levels exceeding the reading level of the general US population. Extensive shortcomings in sources of unbiased and understandable information for patients with cancer exist. As novel diagnostic technologies and treatments emerge, efforts should be made to develop understandable, unbiased, and high-quality information resources for patients with cancer. Characteristics of liquid biopsy webpages. Research Sponsor: None.

Characteristics	%
Commercial bias	61
- Brand	50
- Company website	29
Liquid biopsy cost	16
Visual aids	20
Multiple languages	5
Author names	42
Citations	29
Publication date	57

11009

Poster Discussion Session

Assessment of YouTube as an information source for immune checkpoint inhibitors (ICIs). *First Author: Tulika Garg, Government Medical College and Hospital, Chandigarh, India*

Background: YouTube is an open-access source of information. With more than 2.5 billion users, it can play a pivotal role in educating or misinforming cancer patients. ICI has changed the treatment paradigm for cancer over the past decade. There is scarce data to evaluate the quality of information on ICI uploaded on YouTube. We aim to assess the quality and engagement parameters of the 100 most viewed videos on YouTube focusing on ICI. **Methods:** A systematic search was conducted on YouTube using the search terms ("Immunotherapy AND Cancer"; "Immune Checkpoint Inhibitors AND Cancer"). The 100 most viewed English videos were selected. We utilized the already validated PEMAT¹ and DISCERN² tools to assess the quality of these videos on ICI. Additionally, we looked at the number of views, comments, and likes. Descriptive statistics and Pearson correlation tests were performed using R studio v2022.12.0-353. **Results:** The videos in our study had up to 42 million views (median views: 17,617). These videos were categorized by sources; academic (54%), media (31%), and industry (15%). The mean DISCERN score for the videos was 43.4. Only 22% videos were in the good or excellent category. Most videos (53%) discussed the benefits of ICI, whereas only 29% discussed the adverse effects of ICI. Shared decision-making was promoted by 34% of videos, and only 6.7% of videos summarized the information at the end, based on the DISCERN criteria. The medical terminologies were defined by 48.5% of videos, and 31% were broken into short sections with informative headers per PEMAT understandability criteria. There was no significant association between the video source and video engagement parameters, including likes, views, and comments. However, a trend towards an increased number of likes (r=-0.195, p=0.04) and comments (r=-0.213, p=0.03) was noticed with lower DISCERN scores (poor quality videos). **Conclusions:** The majority of YouTube videos are focused on the benefits of ICI. They are less likely to discuss the adverse effects or shared decision-making. In summary, YouTube videos contain biased information on ICI. Further efforts from academic institutions are needed to improve the quality and engagement of these videos. 1. Shoemaker SJ et al. The Patient Education Materials Assessment Tool (PEMAT) and User's Guide; 2. Charnock D et al. DISCERN: an instrument for judging the quality of written consumer health information on treatment choices. J Epidemiol Community Health. 1999. Pearson correlation coefficient (r) between quality assessment scores and video variables. Research Sponsor: None.

Video variables	DISCERN
Likes	r=-0.195, p=0.04
Video length	r=0.104, p=0.29
Comments	r=-0.213, p=0.030
Views	r=-0.101, p=0.30

11011

Poster Discussion Session

Defining the educational needs for a community-based hematology/oncology career: A national needs assessment. *First Author: Shubham Agrawal, Mercy Catholic Medical Center, Darby*

Background: Fellowship training is largely rooted in academic medical centers, though many graduates will ultimately pursue careers in community-based settings. We initiated a national survey of hematologists/oncologists practicing in community or academic-community hybrid settings to understand providers' educational needs. We hypothesized that the current model of fellowship training is not optimized for those pursuing community-based hematology/oncology careers. **Methods:** An electronic questionnaire was developed surveying current attitudes and practices of community-based hematologists/oncologists. Survey participants from across the United States were contacted via professional organizations. We primarily assessed whether survey participants received any specific training during fellowship for community-based practice. Participants were also surveyed regarding whether such training may have affected their preparation. Relative risk (RR) and 95% confidence intervals (CI) were calculated using modified Poisson regression with robust error variance adjusted for: time in clinical practice (< 10 years), size of graduating fellowship training program (> 5), board certification (hematology and oncology vs. either), and training program geographic location (by region) to identify factors associated with receiving community oncology-specific training. **Results:** Of the preliminary cohort of 120 participants from across 25 states, 66% were male, 69% identified as White, and 69% had been in practice for > 10 years. Less than half (43.2%, binomial 95% CI 34.6%-52.2%) received any training for a career in a community-based setting. Participants identified rotations in community settings (48%), direct mentorship from community-based physicians (41%), and longitudinal clinic in a community setting (39%) as experiences that would have been valuable. Specific curricula of interest included: medical operations and administration (67%), health policy (38%), and quality improvement (30%). Respondents in clinical practice for < 10 years were more likely to have received any community oncology-specific training (RR 2.02, 95% CI 1.10-3.72); other factors were not significantly associated with the primary outcome (P > 0.05). **Conclusions:** National trends indicate a growing need for hematology/oncology graduates in community-based settings. Our study demonstrates substantial unmet needs as they relate to training fellows destined for careers in community-based practice. Prospective design of clinical training and curricula emphasizing longitudinal exposures to and key aspects of health care delivery in the community setting are paramount to achieving optimal, goal-concordant hematology and oncology training. Research Sponsor: None.

11012

Poster Discussion Session

Integration of clinical trial development in hematology and oncology fellowship training: Washington university school of medicine experience. *First Author: Christine Auberle, Washington University School of Medicine in St. Louis, St. Louis, MO*

Background: Education in clinical trial design and development is highly variable among Hematology and Medical oncology fellowship programs. The Clinical Trial Development (CTD) program at Washington University in St. Louis (WUSM) is an experiential learning curriculum designed to provide a structured and personalized education to fellows about clinical investigation in Hematology and Oncology. We describe the results of the CTD program and its impact on subsequent academic faculty appointments. **Methods:** The CTD program was initiated at WUSM in 2002 as a hands-on learning experience for Hematology and Oncology fellows in the design, implementation, evaluation, and publication of clinical trials. Each fellow was required to identify a mentor in their first year of training and propose at least one CTD project, determined as a prospective investigator-initiated clinical trial involving human subjects or materials. Outcome data were collected from an internal registry of fellow CTD projects, Clinical Trials Management System (OnCore), PubMed, ClinicalTrials.gov and e-mail inquiries to fellows and mentors. Descriptive statistics were collected for the characteristics of CTD projects, including the phase of study, site (single center or multicenter), disease subtype, projects that received IRB approval, and projects that resulted in publication. Logistic regression and odds ratios (OR) were also used to assess the association between these characteristics and academic faculty appointments. **Results:** We included 118 fellows who began fellowship from 2002 to 2021 for this analysis with 16 still in training. Many trials were phase I/II (n = 53; 45%), phase I (n = 34; 29%) and phase II trials (n = 17; 14%) and most trials were single center studies (n = 93; 79%). Disease types of the investigations were evenly distributed between Oncology (n = 60, 51%) or Hematology (n = 58, 49%). Most fellows were successful in obtaining IRB approval for their CTD project (n = 93, 79%) and approximately two thirds of those with IRB approval went on to publish their results in peer-reviewed journals (n = 60, 65%). Forty-five percent of fellows who published their CTD projects were first authors (n = 27) and 38% published in journals with an impact factor of greater than 10. Among the graduating fellows, two-thirds (n = 67, 66%) secured an academic faculty appointment. Fellows with IRB approved CTD projects had significantly higher odds of obtaining an academic faculty appointment (OR 4.96, 95% CI 1.54-15.98, p < 0.05). **Conclusions:** The CTD program is a well-established clinical investigation program for fellows with a track record of success and impact on subsequent academic faculty appointments. The CTD program is a model that other fellowship programs can emulate for education related to clinical trials. Research Sponsor: Washington University in St. Louis.

11014

Poster Discussion Session

Innovating the hematology/oncology (H/O) curriculum for internal medicine (IM) residents: A modified flipped classroom (FC) approach. *First Author: Parva Kiran Bhatt, Tufts Medical Center Hematology-Oncology Fellowship, Boston, MA*

Background: Nationally, a framework for H/O education for IM residents that is simultaneously clinically relevant, concordant with the ABIM Blueprint, and efficient in delivery is lacking at the graduate medical education (GME) level. At our institution, based on feedback from our residents we recognized an opportunity to innovate the H/O curriculum through active learning approaches to better meet the needs of our residents. **Methods:** Adopting the Kern Model of curriculum development, a needs assessment was performed to gauge resident opinions on the current H/O didactics and towards active learning approaches. Survey results informed the development of 4 FC modules, meant to seamlessly integrate into the existing didactics of morning report (MR) and noon conference (NC). Each module consisted of a video on a cancer type viewed during MR, case-based activity during NC, and an instructor's guide. Following the Kirkpatrick model, resident opinions were assessed via surveys and feedback sessions. Pre/post-tests at 3 time points were used to assess learning. Standardized patient encounters (SPEs) with clinical competency scoring scales were developed to assess clinical reasoning skills. **Results:** 43% of residents (33/76) completed the needs assessment. A majority of respondents (82%) indicated the existing H/O didactics did not provide enough foundational knowledge. 87% of residents indicated a need for more active learning and 72% expressed interest in a FC approach. 43% (33/76) of residents attended ≥1 session (NC or MR). Post-intervention, 81% of residents strongly agreed the FC modules were relevant to clinical practice and board exams. 93% of residents strongly or somewhat agreed it was feasible and manageable to incorporate the FC format. Pre/post-test results showed statistically significant improvement in scores from before to after viewing the MR video (1-way ANOVA, p<0.011) with a medium effect size of 0.11. Significant change was not seen when the same test was taken after the case-based NC activity (p=1). Clinical competency scores from SPEs of full-participant residents were significantly higher compared to residents who did not participate in a FC module (t-test, mean 8.4 vs. 6.2/10, p<0.001). **Conclusions:** Our pilot H/O FC curriculum was overwhelmingly viewed as favorable and reported as clinically relevant, feasible, and manageable by our residents. Pre/post test results suggest that viewing the pre-session video during MR resulted in significant learning as compared to attending the case-based session during NC. Superior performance on SPEs by residents attending in full as compared to non-participants provides strong evidence supporting our modified FC approach in improving clinical reasoning skills. Overall, our study supports a broader application of our innovative FC model into existing traditional lecture-based resident H/O curricula. Research Sponsor: None.

11013

Poster Discussion Session

Novel curriculum for training in medical cannabis in oncologic populations for oncology trainees. *First Author: Rushad Patell, Beth Israel Deaconess Medical Center, Boston, MA*

Background: There is continued uptake in the use of medical cannabis (MC) among patients with cancer. Our group previously conducted a national study that showed that while a majority of oncology fellows discussed MC with patients, very few feel well informed in doing so. We hypothesized that an evidence-based curriculum on the use of MC for oncology trainees is feasible to develop and would be effective in improving confidence to discuss MC with patients. **Methods:** A multidisciplinary expert team designed an evidence-based educational curriculum in 5 modules specifically for MC in oncology populations that included pharmacology/history, symptom management, cancer-directed effects, toxicities and practical/logistic concerns. The curriculum was piloted as a one-hour webinar at three US hematology oncology fellowship training programs in 2022-2023. Anonymous incentivized survey instruments that were designed to assess self-perceived knowledge, attitudes and behaviors pertaining to MC (on a 5-point Likert scale; strongly agree to strongly disagree) were distributed anonymously via email at the pilot (t = 0) and immediately after (t + 7 days); additional delayed surveys (t+90 days) are in progress. **Results:** Of 35 eligible trainees, 31 completed the pre-training surveys (88.6%), and 26 (74.3%) completed the post-training surveys. Most trainees indicated that the curriculum is helpful (88.5%, 95% CI: 69.8-97.6) and that they would recommend it to their colleagues (80.8%, 95% CI: 60.6-93.4). Following the webinar, there was significant improvement in self-reported comfort with discussing MC for symptom management (3.2% vs. 92.3%, P < 0.001), risks of MC (9.7% vs. 76.9%, P < 0.001) and modes of MC use (16.1 vs. 80.8%, P < 0.001). The majority of participants (80.0%, 95% CI: 59.3-93.2) reported that they were more likely to initiate conversations about MC with their patients after attending the webinar. **Conclusions:** In this multi-center study, we demonstrate that it is feasible to develop and deliver a fellow-focused, evidence-based curriculum for MC use in patients with cancer. The webinar was well received and demonstrated significant improvement in fellow-reported attitudes surrounding MC efficacy, risks, and modes of use. Further work to assess durability of the curriculum on knowledge, attitudes, and behaviors is ongoing. Research Sponsor: None.

11015

Poster Session

Creating an infrastructure to address physician and advanced practice provider burnout at a complex community cancer care delivery system. *First Author: Alison Tray, Hartford HealthCare, Hartford, CT*

Background: Oncology clinicians are at risk for developing burnout due to work-related factors such as high acuity patients, long work hours, limited autonomy, administrative and documentation demands (Copur, 2019; Eelen et al, 2014). The COVID-19 Pandemic has intensified burnout due to rapid and multiple changes in clinical practice, lack of fulfillment, and heightened moral distress and personal challenges (Hlubocky et al 2021). As a multi-center community cancer care system, an infrastructure was created and operationalized to address the work-related factors contributing to burnout. The purpose of the project was improved identification and prioritization of clinician (physician and APP) needs with subsequent targeted intervention. **Methods:** To measure success, a partnership with the American Medical Association (AMA) was formed to deploy the Mini-Z burnout survey. The survey was administered on July 2-August 20, 2021 to all Medical Oncology physicians and Advanced Practice Providers (APPs), n = 60. The survey was re-deployed from July 13-September 2nd, 2022. Data was collated by the AMA and presented back to executive leadership. Through this survey and follow up focus groups, it was identified that physicians tended to struggle more with the EHR and inability to disconnect from work compared to APPs. Our APPs identified several areas of opportunity including onboarding/orientation, mentorship/professional development, pay and scope of practice. An EHR Well-being Committee was established to evaluate EPIC signal reports to address both system and individual clinician needs. To address APP needs, key factors were addressed in the realm of professional development/orientation, compensation and scope of practice. This was approached with the goal of short-term gains and long-term sustainability. **Results:** The results indicated a 23.8% improvement in job satisfaction, 4.9% improvement in job stress, and 26.3% improvement in employment outlook. A decrease was also noted in EHR time outside of work (4.5%) and burnout (16.1%). All areas of improvement met or exceeded national benchmarks. Analysis of these results indicate statistical significance for job satisfaction (p = 0.028, CI 2.8-40.4%) and employment outlook (p = 0.033, CI 2.4-45.8%). Results that indicated improvement but were not statistically significant were job stress (p = 0.688, CI 17.6-27.4%), burnout (p = 0.191, CI 7.4-37.5%) and EHR time outside of work (p = 0.806). **Conclusions:** While the survey data does not account for clinician turnover between 2021 and 2022, initial review indicates a positive impact on job satisfaction and employment outlook which may be an early indication of improved colleague appreciation. Further study, post-pandemic is needed to evaluate effectiveness of care team efficiency and ongoing work to streamline EHR usage. Research Sponsor: None.

Addressing resiliency and burnout: A quantitative needs assessment of oncology physician assistants (PAs). *First Author: Eric Daniel Tetzlaff, Fox Chase Cancer Center, Philadelphia, PA*

Background: Significant progress has been made in understanding the factors associated with oncology (onc) PA burnout. However, little is known about what PAs need to mitigate burnout, the availability of resources, and barriers to interventions. **Methods:** A national survey of onc PAs was conducted in 2022. PAs completed a quantitative needs assessment to determine the importance of and their perceived skills in topics of self-care, clinical care, and professional development. For importance, “high importance” included ratings of ‘Essential’ or ‘Very Important’; for perceived skill, “high skill” included ratings of ‘Excellent’ or ‘Good’. Engagement with employee assistance programs (EAPs) was examined. Resiliency & Burnout were assessed using the Connor-Davidson Resilience Scale & the Maslach Burnout Inventory. **Results:** PAs (n = 171) were mostly practicing in medical oncology (66%) and outpatient (66%). The high importance topics most often identified were dealing with difficult patients (93%), dealing with difficult providers (89%), delivering bad news (88%) and coping with death / patient suffering and personal grief (86%). Topics less often reported as high importance included opportunities to be a mentor (61%), professional coaching (59%) and mindfulness skills (53%). PAs frequently reported high skills in dealing with difficult patients (75%), delivering bad news (72%), and resiliency skills (59%). Fewer PAs reported high skills for debriefing following significant events (49%) and mindfulness skills (42%). Burnout (BO) rates were higher for those with lower perceived skills in resiliency (p = 0.03) and dealing with difficult providers and staff (p = 0.03) but did not differ based on importance of any topics. Resiliency significantly increased with increasing levels of reported importance for the mindfulness skills training, cognitive skills training, and debriefing after significant events topics. Resiliency significantly increased with increased levels of perceived skill for all topics explored. Common barriers to well-being EAP participation were lack of time (58%) and concerns about confidentiality and stigma (26%). For PAs with concerns about stigma, resiliency scores were lower (6.4 vs 7.0; p < 0.001) and BO rates were higher (73% vs 47%; p = 0.005). **Conclusions:** Perceived deficiencies in resiliency training and managing difficult work relationships correlate with higher rates of burnout in onc PAs. Barriers to participation in EAPs, which may help address these deficits, are common and when present are associated with an alarming rate of burnout and lower resiliency. Cultural change in medicine is needed to reduce perceived and experienced stigmatizing experiences to address burnout. These findings suggest that burnout interventions which focus on building resiliency and managing work relationships are crucial and may be best implemented outside of the workplace. Research Sponsor: Association of PAs in Oncology.

11018 **Poster Session**
Characterizing imposter syndrome among oncologists on social media. *First Author: Eleonora Teplinsky, Valley Health System, Paramus, NJ*

Background: Imposter syndrome (IS) is defined as an inability to believe that one's success is deserved. It is commonly encountered by physicians, with cited statistics ranging from 22% to 98%, is associated with negative mental health impacts and can be harmful to one's wellbeing. Given increasing SM use in hematology/oncology (H/O), we aimed to evaluate the effect of SM on IS among oncology trainees and oncologists. **Methods:** An anonymous online survey was distributed to oncology trainees and oncologists through SM platforms (Twitter, Facebook (FB), Instagram (IG)) and e-mail. Questions included demographics, current SM use, a novel scale for IS on SM (Table), Young Imposter Syndrome (YIS) Scale (a validated IS instrument) & assessment of mental health impacts of SM. **Results:** Out of 195 respondents, 103 answered all questions; median age 40y (27-65), 81% female. 21% were trainees and 36%, 30%, and 12% were early, mid and late-career faculty, respectively. Specialties included: adult H/O (72%), gynecologic oncology (11.3%), radiation oncology (10.5%), surgical oncology (4.1%), and pediatric H/O (1.5%). Twitter was the most commonly used SM platform (68%) followed by FB (36%) & IG (20%). 26% utilized professional SM 0-1 times/week while 28% did so daily. 97/157 (62%) noted positive mental health impacts from SM. 41% felt anxious, lonely or depressed due to SM. 19.7% have experienced SM harassment or cyberbullying. More than 50% of respondents met criteria on the YIS and IS scale; indeed, the YIS and IS on SM Scales were significantly correlated with each other (r = 0.57, p < 0.001, N = 103). The presence of IS on SM was associated with gender but not race/ethnicity or career stage. 59% of females versus 28% of males met criteria for IS (p = 0.02). The presence of IS on SM was significantly associated with self-perceived IS in professional settings (p < 0.001), but not in personal settings (p = 0.21). **Conclusions:** Many oncology professionals experienced IS while interacting on SM, but also note a positive mental health impact with SM use. The presence of IS on SM correlated with results on the YIS Scale, suggesting a novel assessment method, but further validation is needed. Future efforts to combat IS on SM while enhancing positive aspects of medical SM are warranted. Research Sponsor: None.

IS on SM for medical professionals scale (Thermometer 1-10); 10=always/significant impact; 0=never/no impact.
How often do you feel insecure posting about a medical topic on SM?
How often do you feel like you aren't qualified to comment on medical topics on SM despite having appropriate training?
How often are you fearful of joining in medical conversations on SM due to concerns about misspeaking?
How often do you feel insecure on SM due to comparing yourself with topic/disease experts in your field?
Do you feel better or worse after logging off of SM?
How does the number of followers you have on SM impact your mental health?
How does the number of likes or shares on your SM posts impact your mental health?

The implementation of a self-care tool for patients that may reduce clinician burden. *First Author: Jenny Wei, Department of Medicine, The Permanente Medical Group, San Francisco, CA*

Background: Addressing the side effects and concerns of patients is paramount during cancer treatment. At this time, this significant workload often involves active management by oncology clinicians which may exacerbate clinician burnout. However, minor side effects and routine concerns may be managed by patients themselves. While there are valuable resources available online including Cancer.net by the American Society of Clinical Oncology (ASCO), patients may benefit from a targeted and personalized approach. Herein, we developed a novel online patient self-assessment and self-care tool within Kaiser Permanente Northern California (KPNC), an integrated healthcare system caring for about 4.5 million patients, that aims to help patients with cancer address routine concerns, enabling them to participate in targeted self-management. **Methods:** Under the novel 4R Oncology model (Right Info / Right Care / Right Patient / Right Time), the self-care tool was implemented to promote patient self-management and improve team-based care and was further developed into a web-based intervention by KPNC. Patients with specific minor concerns were directed to Cancer.net webpages that described how these concerns could be self-addressed. We assessed pageview (a page loaded within a browser) data from May 2021 to December 2022. Main topics were Managing Side Effects and Concerns Related to Your Cancer Treatment, Nutrition Concerns, Emotional or Practical Concerns, Additional Resources and COVID-19 information. If patients were unable to address their concerns with the self-care tool, they were instructed to contact their care team for follow-up. **Results:** Within the 20-month study period, there were 4,991 total pageviews of the self-care tool. The most pageviews in one month were 501 in November 2022 and the least were 93 in December 2021. Pageviews increased over time with most months in 2022 reaching over 200 pageviews compared to only half of months in 2021 surpassing 200 pageviews. The most frequent pageviews were diarrhea (124), nutrition (124), sleep (101), use of herbs or supplements (100) and nausea or vomiting (98). While there were many topics available on the website, the most viewed pages involved gastrointestinal concerns. The least viewed included Life Care Planning/Advance Health Care Directive (6) and Chemobrain (8). **Conclusions:** Examination of pageview data from a self-assessment and self-care tool targeting patients with cancer within an integrated healthcare system reveals substantial interest in self-management. While it is unclear whether patients find the self-care tool's information useful currently, further research is underway using patient surveys to evaluate its utility. Implementation of helpful information can empower visitors to be aware of their options and engage in self-management of routine conditions, which in turn can optimize their health while decreasing oncology clinician burnout. Research Sponsor: None.

11019 **Poster Session**
Impact and engagement of a virtual platform to provide equitable oncology education globally. *First Author: Yan Leyfman, Icahn School of Medicine at Mount Sinai South Nassau, Oceanside, NY*

Background: Social media has emerged as a powerful outlet for the dissemination of medical information, especially in resource-limited regions, due to its mass global reach. However, misinformation has presented an unexpected detriment to public health on a global scale. To address this, *MedNews Week (MNW)*, a free, virtual educational platform streamed on most social media platforms was developed to provide global oncology education through biweekly programming. Its leading show, *Keynote Conference*, features live virtual presentations from oncology's premier global leaders discussing the latest developments in the field before a mainstream global audience. The aim of this study was to assess the worldwide reach and impact of this cost-free, virtual oncology education platform. **Methods:** From January 2022 to February 2023, *MNW* hosted 33 global leaders as Keynote Speakers discussing the latest developments in oncology. Viewership, impressions, and outreach data were collected from *MNW's* social media accounts and Tweepmaps. Data was analyzed to assess *MNW's* global reach and engagement and stratified based on engagement sentiment, gender, age group, and occupation. **Results:** During this period, *MNW* produced a healthcare social grasp score of 64% and generated over 64,000 Twitter impressions engaging 1.9 million viewers over 13 months in the US, UK, Ireland, India, France, and 16 lower socioeconomic (SE) countries and 99 cities. Most of the followers were from non-healthcare fields with more males than females (Table). Those who engaged conveyed positive sentiments (64%) contributing to a viewership increase from 47,589 (6 months) to 61,539 (1 year), where 60% of the audience was found to originate from lower SE regions globally. **Conclusions:** *MNW* has demonstrated an ability to attract and sustain a diverse, global, growing mainstream audience. Given *MNW's* continued growth, it provides a proof-of-concept model to engage and disseminate medical information to mainstream audiences. The platform's ability to showcase global leaders to mainstream audiences gratuitously, especially in lower SE regions that have been historically underserved, offers a practical approach to combat educational inequity. Consequently, such a platform has demonstrated great potential to positively impact global oncology education. Demographics of *MedNews Week's* audience. Research Sponsor: None.

Followers	n (%)
Age group	
10 to 23 years	47 (4.58%)
> 24 years	979 (95.42%)
Gender	
Male	990 (47.96%)
Female	854 (41.37%)
Occupation	
Healthcare	887 (42.99%)
Non-healthcare	1176 (57%)

11020

Poster Session

Reliability of audiovisual information on lung cancer from cancer organizations. First Author: Hardik Dand, Swedish Hospital, Chicago, IL

Background: In the US, lung cancer is the leading cause of cancer death and second most common cancer. YouTube (YT), a social media platform with billions of users, can improve knowledge but also disseminate inaccurate information. Research has shown YT plays a key role in public health. This study assesses the reliability of YT videos about lung cancer using its own algorithm compared to videos from three cancer organizations. **Methods:** We searched “lung cancer” on YT and selected 8 videos with the most views. Then, “lung” was searched from YT profiles of American Cancer Society (ACS), National Cancer Institute (NCI), and National Comprehensive Cancer Network (NCCN). Criteria required videos to be less than 10 minutes and have “lung” in the description. Videos were excluded if not in English, older than 15 years, patient stories, or sponsored by pharmaceutical entities. The videos were graded by 3 independent medicine residents using the validated methods of Patient Education Materials Assessment Tool Understandability and Actionability (PU and PA) and Journal of the American Medical Association (JAMA) scoring. Higher percentages of PU and PA represented more understandable and actionable material. Higher JAMA score (up to 4) indicated better quality of information. Descriptive statistics and non-parametric Kruskal-Wallis tests were done. **Results:** A total of 36 videos were identified. PU mean was 74.2% (SD 21.4) in YT compared to 62.4% (SD 15.2), 53.1% (SD 28), and 58.8% (SD 13.9) for ACS, NCI, and NCCN respectively. PA mean was 46.6% (SD 46.8) for YT compared to 12.9% (SD 31.7), 38.9% (SD 53.6), and 8.2% (SD 21.2) for ACS, NCI, and NCCN respectively. A statistically significant higher median actionability score can be seen in YT. The JAMA average was 1.9 (SD 0.2) for YT compared to 2.1 (SD 0.1), 2.3 (SD 0.6), and 2.0 (SD 0) for ACS, NCI, and NCCN respectively. While a statistically significantly higher median JAMA score is seen in NCI videos, no meaningful difference can be extrapolated given all average scores of roughly 2. **Conclusions:** YT produced videos of higher understandability and actionability compared to videos from cancer organizations. As patients continue to rely on social media for information, trusted cancer sources should develop more reliable material for improved patient education. Comparison of scores from averages of 3 reviewers. Research Sponsor: None.

	YT (N=8)	ACS (N=6)	NCI (N=3)	NCCN (N=19)	Total (N=36)	p value
PU						
Mean % (SD)	74.2 (21.4)	62.4 (15.2)	53.1 (28)	58.8 (13.9)	62.4 (17.8)	
Median % (Q1, Q3)	80.1 (69.8, 85.6)	62.7 (54.2, 64.1)	45.9 (37.7, 64.9)	55.5 (51.9, 66.9)	61.1 (50.6, 78.6)	0.315
PA						
Mean % (SD)	46.6 (46.8)	12.9 (31.7)	38.9 (53.6)	8.2 (21.2)	20.1 (35.4)	
Median % (Q1, Q3)	41.8 (0.0, 91.8)	0.0 (0.0, 0.0)	16.7 (8.3, 58.3)	0.0 (0.0, 0.0)	0.0 (0.0, 18.0)	0.031*
JAMA						
Mean (SD)	1.9 (0.2)	2.1 (0.1)	2.3 (0.6)	2.0 (0.0)	2.0 (0.2)	
Median (Q1, Q3)	2.0 (1.9, 2.0)	2.0 (2.0, 2.0)	2.0 (2.0, 2.5)	2.0 (2.0, 2.0)	2.0 (2.0, 2.0)	0.032*

*Statistically significant.

11022

Poster Session

The impact of physician gender on patient satisfaction in an academic hematology/oncology practice. First Author: Alaina Marie Turchi, Indiana University, Indianapolis, IN

Background: Gender disparities continue to remain under addressed in medicine. While prevalent in many forms, patient bias and perceptions toward their healthcare team can impact patient compliance and care. Health systems often gauge patient satisfaction with physicians and post these ratings online. It is possible that gender biases affect patient satisfaction scores and evaluations. Here, we assess the impact of physician gender on patient satisfaction scores and comments in an academic hematology/oncology practice. **Methods:** A retrospective mixed-method analysis was conducted from patient satisfaction scores and comments obtained between January and June of 2021. Patients were asked a series of three questions about their care. Patients' response to the question, “How likely would you be to recommend this providers office to friends and family?”, was analyzed on a score of 0-10, with 10 being extremely likely and 0 being not at all likely. Patients were then asked for the primary reason for their scoring, in an open-ended format. Mixed-gender codified data was quantified from de-identified, de-gendered patient comments. To identify the differences in patient perception between male and female physicians, we specifically examined the data of positive and negative impressions of variables including professional behaviors, expertise, kindness, compassion, and interactions with ancillary staff amongst providers. **Results:** Patient satisfaction scores from 199 unique patients were reviewed; 140 (70.4%) were about male-identifying physicians while 59 (29.6%) were related to female-identifying physicians. The mean satisfaction score was 9.95 ± 0.29 for female physicians and 9.64 ± 1.38 for male physicians ($p = 0.011$). Of patients responding, 76 (38%) were male and 123 (63%) were female. Female physicians scored higher than male physicians for both male and female patients (10.0 ± 0 versus 9.65 ± 1.37 ($p = 0.011$) and 9.77 ± 0.60 versus 9.62 ± 1.40 ($p = 0.011$), respectively). Kindness and compassion were mentioned in 36% and 42% of all female physician scores, respectively, and in 29% and 33% of all male physician scores; these did not reach statistical significance ($p = 0.587$ and $p = 0.257$). 21% of all male physician scores positively mentioned physician expertise, compared to 15% of female physician scores; this also did not reach statistical significance ($p = 0.434$). **Conclusions:** Female physicians had a higher mean satisfaction score in patient evaluations than their male counterparts by both male and female patients. Numerically, more patient comments about female physicians mentioned kindness or compassion, while fewer mentioned expertise. This early work will be expanded to a larger dataset of evaluations in addition to further exploration of how female and male oncology providers are perceived by patients in multiple other categories. Research Sponsor: None.

11021

Poster Session

How reliable are post-mastectomy breast reconstruction videos on YouTube? First Author: Nina Morena, McGill University, Montreal, QC, Canada

Background: Social media are a significant source of information for young women with breast cancer (YWBC) undergoing post-mastectomy breast reconstruction (PMBR). The emphasis on visual storytelling and building community in online spaces renders YouTube (YT) to be a common platform for discussions of BR. This study aims to assess the quality of YT videos about PMBR, identify themes related to the PMBR experience, and quantify perceptions of BR as an option PM. **Methods:** YT was searched incognito with terms “young women breast cancer reconstruction” in 08/2022, in order from most to least viewed. Title, upload date, length, poster identity, number of likes and comments were collected. The Patient Education Materials Assessment Tool for audiovisual materials (PEMAT A/V) evaluated understandability and actionability. DISCERN assessed quality and reliability. Presence of sponsorship, intended audience, patient and healthcare professional narratives, and perceptions of PMBR were collected. Reviewers noted whether PMBR was shown and how. Themes were collected inductively and deductively for thematic analysis. **Results:** 193 videos were identified. Mean video length was 14.6 minutes (SD 20.0 min). 87.1% included sponsorships. 95.9% of videos were posted by an organization. 60.6% were information-based; 45.6% experience-based. Mean PEMAT scores for understandability and actionability were 71.3% (SD 13.4) and 35.7% (SD 41.8), respectively. Mean DISCERN was 2.6/5 (SD 1.2). Patient narrative was present in 52.6% and healthcare professionals' in 68.4%. PMBR was visually presented 22.8% of the time. 13.5% of videos explicitly recommended PMBR. 2.6% explicitly discouraged it. Patients (77.7%) represent the majority of the intended audience. Most common deductively identified themes included treatment (87.1%), family relationship (17.1%), motherhood (15.5%), fertility (11.9%). Inductively identified subthemes included differentiating between various options for PMBR surgery, BRCA genetic testing, psychosocial effects of breast cancer and PMBR, and recovery from surgery. **Conclusions:** YT is a platform wherein various PMBR options are widely discussed and explained. PMBR videos are highly understandable but have moderate levels of actionability, quality, and reliability. Videos are highly sponsored, demonstrating significant institutional bias. Themes are overwhelmingly treatment and surgery-based. Personal themes were present but not dominant. Distribution of PEMAT and DISCERN scores. Research Sponsor: Nina Morena is supported by funding from the Social Sciences and Humanities Research Council and the Fonds de Recherche du Québec – Société et Culture.

Tool	Value	Mean	SD	Min	Max	Median
PEMAT Understandability	Total points (numerator)	7.4	1.5	2.0	11.0	7.0
	Total possible points (denominator)	10.4	0.9	7.0	12.0	10.0
	Score (%)	71.3	13.4	22.2	100.0	72.7
PEMAT Actionability	Total points (numerator)	1.1	1.3	0.0	4.0	0.0
	Total possible points (denominator)	3.1	0.3	3.0	4.0	0.0
	Score (%)	35.7	41.8	0.0	100.0	0.0
DISCERN	Total points	41.8	12.5	17.0	74.0	42.0
	Average on 5	2.6	1.2	1.0	5.0	3.0

11023

Poster Session

A review of diversity, equity, and inclusion (DEI) efforts by medical oncology journals. First Author: Inas Abuali, Massachusetts General Hospital, Boston, MA

Background: In recent years, there has been a growing awareness of the ongoing structural inequities impacting all facets of academic medicine. Efforts are underway to adopt an intentional and systemic approach to meaningful incorporation of DEI in academia. Here, we review the ongoing efforts by scientific peer-reviewed journals to ensure an equitable publication process, and an inclusive and diverse participation and distribution of oncological research. **Methods:** Medical oncology journals with the highest impact factor were identified using the SCImago Journal Rank (SJR), a publicly available portal that includes the journals and country scientific indicators developed from the information contained in the Scopus database. 39 Journals in the first ranking quartile (Q1) with the highest impact were identified to have an SJR >2. An online review of journal websites' content was performed between Jan 8th – Feb 8th, 2023, to extract the data available in the accompanying table. **Results:** 38.5% of journals include a DEI statement on their website. One journal has a dedicated editorial director of equity. Three journals (8%) have a specific online DEI corner highlighting related articles and initiatives. 20% of the journals publicly outlined specific DEI policies, such as formalizing the process for assessment and reporting, and identifying and inviting peer reviewers with DEI expertise. Finally, 20% of journals published limited specific metrics assessing the impact of their DEI efforts, such as data regarding the primary corresponding authors at country and region level in the last five years, and the gender diversity of their editorial boards. **Conclusions:** Our study highlights the limited publicly available data online regarding ongoing DEI initiatives and dedicated editorial positions in high impact medical oncology journals. It is imperative that we aim for greater intentionality and transparency about such efforts, with reporting of clear and specific impact metrics. In addition, these efforts cannot be performative and must foster a more equitable scholarly publication process, promote accountability, and assist in formulating best practices. Our analysis suggests a clear unmet need and represents a call to action. High impact oncology journals have an opportunity to set the tone for the entire oncology medical community. Research Sponsor: None.

	Number of Journals
DEI statement available online	15/39 (38.5%)
Has a dedicated DEI editor/ associate editor	1/39 (2.5%)
Dedicated online DEI corner	3/39 (8%)
Specific DEI policies outlined	8/39 (20%)
Specific metrics and impact of DEI initiatives	8/39 (20%)

11025

Poster Session

Bringing the teaching close to home: Implementation of a near-peer model for an introductory hematology-oncology fellowship lecture series. *First Author: Jonathan L Berry, Beth Israel Deaconess Medical Center, Boston, MA*

Background: Hematology/oncology fellowship has a steep learning curve. Foundational knowledge at the start of fellowship is essential, given limited exposure to key disease-specific concepts in prior training. We have previously employed an expert faculty-led "introductory boot camp" during the first 2 months of fellowship training. Trainees provided feedback that this was not best meeting fellows' needs. We hypothesized that a near-peer teaching model, led by senior fellows, would better align lecture content and scope with the needs of new fellows and improve senior fellows' mastery of clinical knowledge and comfort with teaching skills. **Methods:** Using a constructivist theory of learning, we selected the most relevant topics from the curriculum and assigned each senior fellow 1-2 hour-long sessions on clinical areas of interest, paired with expert faculty. A one-hour workshop on lecturing techniques and instructional design was held for all senior fellows. Educational sessions led by senior fellows and expert faculty occurred July-September 2022 in a hybrid format. An IRB-exempt anonymous survey was sent to participating fellows and faculty regarding effectiveness of the educational sessions and the process of preparing to lead sessions. **Results:** 15 of 17 fellows (88%) and 12 of 15 faculty (80%) completed the survey. Overall, 71% (95% CI 33-82) of fellows and 75% (95% CI 43-95%) of faculty felt the new series was taught at an appropriate level for new fellows. All fellow respondents felt the approach was helpful for clinical practice and board preparation. All participating senior fellows felt equipped to teach and that the exercise improved confidence in the content and their teaching skills. No fellows proposed a return to the prior model, and 80% of faculty felt the near-peer approach should be continued in future years. Qualitative analysis of narrative responses identified several strengths, including emphasis on focused, introductory frameworks and the generation of living resources for future reference. Areas identified for future improvement include providing more guidance and structure for pre-lecture faculty-fellow preparations. **Conclusions:** A near-peer model of introductory lectures is feasible to implement, produces improved satisfaction with the curriculum, and can be a means of presenting foundational content in hematology and oncology concordant with the learners' needs. This method has important implications for developing learner-concordant, expert-driven curricula in large and rapidly changing content areas within hematology/oncology. Research Sponsor: None.

11027

Poster Session

Utility of a novel trainee-level hematology/oncology podcast in graduate medical education. *First Author: Ronak Mistry, Vanderbilt University Medical Center, Nashville, TN*

Background: Despite the popularity of podcasts in medical education, there are a limited number of trainee-level hematology/oncology (H/O) podcasts. We created & implemented a novel H/O podcast curriculum to address this barrier. Here, we evaluated the utility of this podcast for H/O fellows & internal medicine (IM) residents on H/O rotations. **Methods:** We included IM residents & H/O fellows at Vanderbilt University Medical Center in the 2022-2023 academic year. Each IM resident starting on a H/O inpatient rotation received an email prior to their rotation with list of recommended episodes. H/O fellows were encouraged to listen to episodes at their discretion. We developed anonymous surveys using a 5-point Likert scale (1, "strongly disagree" to 5, "strongly agree") to understand how the podcast helped prepare them clinically & if H/O podcasts were effective educational tools. **Results:** A total of 20 trainees completed the survey including 7 residents (35%) & 13 fellows (65%). All post-graduate years were represented. Results of the survey are presented in the table. Most felt the podcast material helped with inpatient rotations & consults, was clinically relevant, & helped with clinical decision-making with a mean score of 4.76, 4.79, and 4.50, respectively. Respondents agreed the fundamentals of H/O are amenable to a podcast platform & are likely to continue to use podcasts as learning tools in H/O with a mean score of 4.68 and 4.40, respectively. When restricting to the fellow cohort, the majority felt that the podcast material helped them prepare for their clinic patients with a mean score of 4.62. Most found the podcast convenient & the most common activities while listening to our podcast were driving (70%), doing chores (35%), exercising (25%), and eating (25%). **Conclusions:** H/O fellows & IM residents found the trainee-level podcast curriculum clinically relevant and helped with clinical decision making. The respondents also all agreed or strongly agreed that podcasts are an effective medium to teach hematology/oncology. Our successfully piloted podcast curriculum can be adapted to other training programs to improve foundational knowledge in oncology. Research Sponsor: None.

Responses to survey.

Question	Strongly Disagree (1) (no., %)	Disagree (2) (no., %)	Somewhat Agree (3) (no., %)	Agree (4) (no., %)	Strongly Agree (5) (no., %)	N/A (no., %)	Mean (no.)	Total (no.)
The material helped with inpatient rotations/ consults.	0	0	2 (10%)	5 (25%)	11 (55%)	2 (10%)	4.76	20
Fellows: The material helped prepare for clinic patients.	0	0	1 (7.69%)	3 (23.08%)	9 (69.23%)	0	4.62	13
The material was clinically relevant.	0	0	0	4 (20%)	15 (75%)	1	4.79	20
The material helped with clinical decision-making.	0	0	2 (10%)	5 (25%)	11 (55%)	2 (10%)	4.50	20
Fundamentals of H/O are amenable to a podcast as a teaching platform.	0	0	0	6 (30%)	13 (65%)	1	4.68	20
I am likely to continue to use podcasts as a learning tool.	0	0	2 (10%)	8 (40%)	10 (50%)	0	4.40	20

11026

Poster Session

Fellow-led didactics in a hematology/oncology fellowship program. *First Author: Rajat Thawani, Medical Oncology, Oregon Health & Science University, Portland, OR*

Background: The pandemic in 2020 made us used to virtual learning, but as we recover from the pandemic, we are forced to rethink how we deliver education to trainees in medicine. The pandemic has led to a significantly decreased attention span and face to face interactions, in addition to an increased screen time. In our program, this led to us noting a lower engagement in the fellowship didactics as we recovered from the pandemic. This forced us to rethink how the Oregon Health & Science University (OHSU) hematology and oncology fellowship delivers educational content. After interviewing all stakeholders, we moved to an in-person fellow led didactic approach, under the mentorship of a faculty expert who helps trainees design content and is present for discussion. The rationale behind this approach was to boost peer-to-peer learning, supply relevant content and increase engagement. The fellows and faculty were provided guidelines about length of talk, presentation of data and use of interactive tools. **Methods:** After 6 months of introducing fellow led didactics, we surveyed all fellows and select faculty who were mentors on more than one occasion about their opinion. A survey link was sent to all 12 fellows and 18 faculty members who regularly took part in fellowship didactics. **Results:** All 12 fellows responded to the survey. On a Likert scale of 1-5, they scored improvement in knowledge at 4.58 (0.64) and rated both the content and presenter at 4.25 (0.43). A third felt that this way of delivering didactics was a lot better and the rest felt it was a little better. On the negative side, they felt that they were spending more time preparing content (40% spent 7-9 hours a month) but were optimistic about lesser commitment next year as we bank the PowerPoint presentations. Nine of the 18 (50%) invited faculty responded to the survey, and on a scale of 1-5, they rated their improvement of knowledge as 4.44 (0.68). They scored the content and presenter at 4.44 (0.5) and 4.56 (0.68) respectively. 88.9% felt that the didactics were either a little or a lot better, and 11.1% felt them to be the same. On average, they spent less time on the content than they did if they were presenting. **Conclusions:** Overall, both faculty and fellows felt that this method of delivering didactics in a hematology oncology fellowship program was more effective. The fellows felt that they needed to put in extra hours for preparation, but this will probably go down as they build on earlier presentations. Research Sponsor: None.

11028

Poster Session

Teaching how to navigate difficult conversations: A combined palliative care-oncology didactic simulation intervention for hematology/oncology fellows. *First Author: Megan Dupuis, Vanderbilt University Medical Center, Nashville, TN*

Background: ASCO strongly endorses the integration of palliative care to improve patient outcomes and support patients in their cancer trajectories. Developing core palliative care skills for trainees is therefore essential, with few ACGME approved pilot programs offering combined fellowship training. Our institution's Heme/Onc fellows reported a need for additional education in leading difficult conversations. **Methods:** We piloted a didactic simulation (sim) session for each fellowship class, led by a faculty member who is dual board-certified in Medical Oncology and Hospice/Palliative Medicine. Trainees received a lecture on validated communication tools and oncology-specific language to help navigate difficult conversations. Trainees then role-played in small groups using sample cases, with Heme/Onc faculty supervision and real-time feedback, followed by class reflection. Pre- and post-sim surveys were electronically administered to assess knowledge of communication tools and comfort in discussing difficult topics. Comfort questions were scored on a 5-point Likert Scale, using student t-tests to detect differences pre- and post-sim, and ANOVA to compare responses among classes. **Results:** A total of 16/21 (76.2%) fellows completed both pre- and post-sim surveys. Knowledge of communication tools increased from 21.9% pre-sim to 79.7% post-sim. Comfort significantly increased for explaining palliative-intent chemotherapy, hospice, and discussing an uncertain prognosis (Table). There was a significant difference among classes pre-sim for addressing negative emotions (mean comfort level: 1st years 2.8, 2nd years 3.4, 3rd years 3.83; p=0.046) and for discussing an uncertain prognosis (mean comfort level: 1st years 2.6, 2nd years 3.6, 3rd years 3.83; p=0.043); however, these interclass discrepancies were eliminated post-sim. Overall, fellows reported that the sim sessions were effective for developing their knowledge and comfort in having difficult conversations. **Conclusions:** A novel sim intervention led by a physician who is dual board-certified in palliative care and medical oncology improves trainee competency with navigating difficult conversations. Analysis of the intervention's durability of response and iterative refinement of its curriculum are ongoing. Research Sponsor: None.

Comfort with cancer communication topics.

	Pre-sim Mean	Post-sim Mean	P-value
I am comfortable...			
telling a patient bad news, such as having progression on a scan.	3.92	4.18	0.216
explaining palliative-intent chemotherapy.	4.13	4.63	0.003
explaining the role of hospice.	3.94	4.31	0.029
asking a patient about code status.	4.13	4.25	0.592
responding to negative patient emotions such as sadness or anger.	3.34	3.81	0.082
discussing prognosis when the outcome is predictable.	3.87	4.31	0.052
discussing prognosis when the outcome is uncertain.	3.34	4.06	0.020

11029

Poster Session

Hematology and oncology fellow education about sexual and reproductive health: A survey of program directors in the United States. *First Author: Jennifer B. Reese, Fox Chase Cancer Center, Philadelphia, PA*

Background: Sexual and reproductive health (SRH) concerns are important areas of health and quality of life for patients with cancer that should be included in routine cancer care, according to clinical guidelines. Yet, oncologists often hesitate to raise SRH with their patients due to lack of training. We conducted a national survey of hematology/oncology fellowship program directors (PDs) in the U.S. to understand the state of current fellowship education on three key SRH subjects: fertility, sexual health, and safe sex practices. We assessed rates of provision of formal/informal instruction and endorsement of barriers to formal instruction. **Methods:** A 13-item survey of education on fertility, sexual health, and safe sex practices in adult hematology/oncology programs was sent to all PDs in the U.S. via an online link or paper survey. PD's received a \$5 gift card for participating. Descriptive statistics and McNemar tests were used. **Results:** One hundred-twelve PDs responded to the survey (63% response rate). Of these, 75% of PDs reported their programs offered >1 hour of formal instruction on fertility, 42% on sexual health, and 31% on safe sex practices; formal instruction was more common for fertility than either other subject (p 's < .001). Male and female fertility preservation was addressed in 62% and 59% of programs, respectively. Cancer-related sexual side effects for women and men were covered in less than one-quarter of programs (23% and 20%, respectively). Regarding informal instruction, > 73% of programs reported using clinical experience to train fellows in SRH; other informal instruction methods (i.e., case-based methods, webinars, journal clubs, grand rounds) were less common. Lack of experts/resources was the most widely endorsed barrier to providing education about fertility (55%), sexual health (75%), and safe sex practices (69%) and was more widely endorsed for sexual health and safe sex practices compared to fertility (p 's < .01). Lack of space in the curriculum and the topic not being required were also commonly endorsed barriers. **Conclusions:** Data from this national survey of fellowship program directors show that training in SRH is rare, particularly for sexual health. Barriers to training, especially difficulties in finding content experts, may be leading to a heavy reliance on informal methods of instruction, which are both variable and incomplete. Concerted efforts to integrate SRH into fellowship training, including novel educational curricula, are needed if SRH is to be addressed in routine cancer care. Research Sponsor: U.S. National Institutes of Health.

11031

Poster Session

The brown university cancer prevention and survivorship curriculum: A case study on program development in an internal medicine residency. *First Author: Elizabeth Francis, Brown University/Lifespan Hospitals, Providence, RI*

Background: Advances in screening, early detection, and treatment have increased the number of cancer survivors. Cancer survivors have a unique set of medical, psychosocial, physical, and financial challenges. Though it is critical for provider teams to be attuned and equipped to address these issues, we identified two training programs in this discipline. Medical residency clinical education does not fully explore the role of cancer preventative services and survivorship experiences available to patients and their families. We developed an elective at Alpert Medical School at Brown University/Lifespan Internal Medicine Residency Program (Brown) to improve medicine residents' knowledge and clinical skills on different aspects of the cancer control continuum, with a focus on prevention, early detection, survivorship and surveillance. **Methods:** In 2020, a team of Brown internal medicine (IM) residents, faculty and one hematology oncology (heme/onc) fellow examined the existing cancer prevention and survivorship infrastructure, identified key faculty and clinics, and examined existing programs at peer institutions. A needs assessment was completed by Brown IM residents and heme/onc fellows. We then designed the Cancer Prevention & Survivorship Elective, an innovative and novel educational elective for medical residents to promote interest, awareness, and understanding of cancer prevention and survivorship. The 6 module one month elective features didactics and clinical experiences offered via a live and independent study fashion. The elective brought together 27 disciplines, 64 faculty lecturers from 10 peer institutions across the United States and included 20 unique clinics. Residents completed anonymous pre- and post-course surveys to measure their understanding and degree of confidence in different aspects of cancer prevention and survivorship, not limited to surveillance, health disparities and global perspective, primary and secondary prevention, late and long-term effects, and quality of life. **Results:** In January 2023, ten residents, ranging from first- to third-year IM and medicine-pediatrics, participated in the live elective. Two IM residents have registered to complete the elective via independent study in 2023. To date, the Cancer Prevention and Survivorship Elective has improved IM residents' confidence, comfort and clinical skills in treating patients along the cancer care continuum. **Conclusions:** This curricula serves as an example for inter-institutional collaboration, and highlights the need for a multidisciplinary approach when caring for patients at high-risk of developing cancer and surviving cancer. Research Sponsor: Brown University Star Grant.

11030

Poster Session

Recommendations for medical cannabis use in cancer patients by US oncology fellows and the impact of receiving prior training. *First Author: Kian Tehranchi, Beth Israel Deaconess Medical Center, Boston, MA*

Background: Despite the rising use of medical cannabis, limited evidence informs the safety and efficacy of cannabis use in cancer patients. A national survey of oncology fellows found that fellows felt insufficiently informed to make clinical recommendations about cannabis. In this secondary analysis of that survey, we aimed to measure how frequently trainees recommend cannabis and determine factors that influence this practice. Given the lack of evidence, we hypothesized that fellows who had been trained in medical cannabis use would be less likely to recommend cannabis to their patients. **Methods:** An online survey assessing trainee practices on medical cannabis was sent to 155 oncology fellowship program directors between January - March 2021 and directors were asked to distribute it to their fellows. The primary outcome was the number of times oncology fellows recommended cannabis in the prior year. Log-binomial regression was used to calculate risk ratios (RR) and 95% confidence intervals (CI) to evaluate whether the number of cannabis recommendations varied by participant age, gender, legality of cannabis in the state of practice, and prior training in medical cannabis. **Results:** Nationally, 40 programs from 25 states participated, with 189 of 462 trainees across these programs responding (40% response rate). Twenty-two percent (95% binomial CI: 16.3-29.0%) of participants reported recommending medical cannabis to >5 patients in the past year. Twenty-four percent (95% binomial CI: 18.4-30.5%) of participants had prior training in medical cannabis. Among participant characteristics, only prior training in medical cannabis was associated with recommending cannabis to >5 patients (RR: 2.42; 95% CI: 1.39-4.20). **Conclusions:** Despite limited evidence to support medical cannabis use among cancer patients, one in five oncology fellows participating in our study recommended it to >5 patients in the past year. Prior training was associated with doubling of rates of recommending medical cannabis in this group. It is thus of critical importance that fellowship training on this subject reflects best available evidence to guide trainees in well-informed decision-making. Factors associated with trainees recommending medical cannabis to >5 patients. Research Sponsor: None.

Predictor	Unadjusted RR (95% CI)	Adjusted* RR (95% CI)
Birth year		
1975-1984	1.84 (0.67-5.10)	-
1985-1989	1.66 (0.78-3.55)	-
1990-1994	1.00	-
Legal status in state of practice		
Comprehensive medicinal and recreational	1.00	1.00
Comprehensive medicinal only	1.08 (0.59-1.96)	1.05 (0.60-1.85)
Allows products with low THC/high CBD	0.64 (0.25-1.62)	0.89 (0.34-2.32)
Prior training in medical cannabis	2.60 (1.54-4.40)	2.42 (1.39-4.20)

*Adjusted for medical school graduation year, legal status in state of practice, and prior training in medical cannabis.

11032

Poster Session

Mapping objectives of a new interprofessional morbidity and mortality conference to ACGME core competencies in hematology/oncology. *First Author: Aditya Sharma, Dartmouth-Hitchcock Medical Center, Lebanon, NH*

Background: Safety and quality improvement requirements are a part of the core competencies for ACGME-accredited hematology/oncology fellowships. The morbidity and mortality conference (MM) is a tool that has been used to identify safety issues and areas for improvement. The traditional format primarily includes an audience of clinicians. We sought to develop an interactive, interprofessional MM (i-MM), including institutional leadership, physicians, fellows, residents, advanced practice providers, nursing, and pharmacy, while meeting the ACGME Core competencies for Patient Safety and Quality Improvement in Hematology and Medical Oncology. **Methods:** A pilot i-MM was designed to create an enriching, interprofessional discussion regarding patient safety and quality improvement. We implemented a Plan-Do-Study-Act (PDSA) design to create the i-MM model that map to the core competencies. The first session was focused on two mortality events in immunocompromised hosts that triggered the sepsis bundle, one of which was due to toxic megacolon. The i-MM objectives were aligned with ACGME hematology/oncology fellowship requirements of quality and safety. The effectiveness of the pilot session was gauged via an anonymous post-session survey using a 4-point Likert scale. **Results:** A total of 32 people attended the pilot i-MM, including quality and safety leaders, faculty, fellows, medical residents, pharmacy, and nursing. A total of 10 participants across professions completed the post-i-MM survey. The survey demonstrated an average of 3.8/4 for all interprofessional educational goals, which included demonstration of mutual respect between healthcare professionals, engaging in effective interprofessional communication, and working within an interprofessional team. Content-specific aspects of the survey were rated with an average effectiveness of 3.60/4. Feedback on the survey recommended limiting i-MM to one case presentation instead of multiple. During the debrief session, it was reported that several nurses felt the moderated session was "inclusive and empowering". **Conclusions:** The i-MM was an effective approach to meeting ACGME requirements for safety and quality learning objectives while creating an inclusive environment for all team members. Future PDSA cycles will continue to map i-MM learning objectives to ACGME hematology/oncology fellowship program core competencies in Section VI.A.1 and the section on Professionalism. Core competency mapping will guide future presentations that address issues on quality, safety, and health care disparities. Specific presenters and moderators from different professions will be chosen to lead each i-MM, with the goal of examining each case from different perspectives to provide a holistic interprofessional view of delivering quality medical care to patients. Research Sponsor: None.

11033

Poster Session

The cognitive load of inpatient consults involving immune-related adverse events. *First Author: Sam Brondfield, University of California, San Francisco, San Francisco, CA*

Background: Immune-related adverse events (irAE) requiring hospitalization involve complex, multidisciplinary management. Expertise in oncology and/or the affected organ(s) may be required in the form of inpatient consults. Trainees (fellows and residents) often provide such consults. irAE consults may be rich learning opportunities, but it is unclear whether the cognitive load, or mental effort, required for these complex cases may overwhelm trainees and impair learning. To investigate the cognitive load of irAE consults, we surveyed trainees who had recently completed an irAE consult and compared the results to a control dataset. **Methods:** Between October 2021 and January 2023, we identified patients hospitalized due to irAEs at the University of California, San Francisco by reviewing patient lists (oncology consults and hospital medicine admissions) daily. We emailed the published Consult Cognitive Load (CCL) survey to any residents or fellows who had signed initial consult notes in the charts of identified patients. The CCL uses 4-point scales to measure three types of cognitive load related to one consult: intrinsic load (IL) related to the consult task itself, extraneous load (EL) related to distractions during the consult, and germane load (GL), the mental effort left over for learning after IL and EL are accounted for. IL, EL, and GL scores range from 4 to 16. Using two-tailed t tests, we compared mean IL, EL, GL, and total cognitive load (the sum of IL, EL, and GL) between the irAE group and a control group of fellows and residents who performed a variety of consults at five University of California hospitals during a 2018-2019 study (n = 142). Detecting a difference of 0.5 with a variance of 0.5 (calculated for the control group), 80% power, and 95% confidence required an irAE group sample size of 18. **Results:** Of 36 trainees contacted for the irAE group, 18 completed the CCL (50% response rate, 61% fellows, 39% residents). The irAE group and the control group (80% fellows, 17% residents, 3% not reported) spanned multiple specialties. Total cognitive load (p = 0.49) and IL (p = 0.95) did not differ. EL was significantly lower (8.4 vs 10.3, p = 0.002) and GL higher (11.9 vs 10.8, p = 0.04) in the irAE group. **Conclusions:** Trainees experienced similar cognitive load when performing irAE consults as compared to other consults, but the sources of cognitive load differed. Trainees performing irAE consults expended less mental effort on distractions (EL) and more on learning (GL) as compared to other consults. The consult task itself (IL) imposed a similar amount of cognitive load whether or not it was an irAE consult. Complex irAE cases did not overwhelm trainees or preclude learning; rather, trainees performing irAE consults exhibited a sharpened focus on the task at hand and extracted more learning than trainees performing other consults. Educators should foster trainee exposure to inpatient irAE consults to promote worthwhile learning. Research Sponsor: UCSF RAP Grant.

11035

Poster Session

Multimodality, online oncology learning resources: Meeting residents where they are—A pilot to create a new oncology curriculum. *First Author: Jennifer King, Indiana University Simon Comprehensive Cancer Center, Indianapolis, IN*

Background: The Accreditation Council for Graduate Medical Education (ACGME) requires internal medicine residents to have access to different medical subspecialties, including hematology/oncology. While inpatient rotations in hematology/oncology have been associated with a decreased interest in a career in oncology, dedicated educational sessions have been shown to improve residents' interest in the field. In recognition of different learning styles and modalities and the need for asynchronous delivery, we aimed to build an effective curriculum for oncology learners using interactive, multimodality, online learning tools and resources. **Methods:** Using the Canvas online learning management system, individual learning modules covering major cancer types were created. Each learning module consisted of a pre-survey assessing the learners' evaluation of their own knowledge and comfort with the topic, a brief audio or video file covering high-yield information about the cancer type, interactive case-based questions reviewing and reinforcing the information, and a post-survey assessing the change in the learners' evaluation of their knowledge and comfort in clinical application of the information. The pre- and post-surveys were rated on a 5-point Likert scale. Median values and interquartile ranges are reported. A one-sided t-test was used to compare responses. **Results:** Two fully completed learning modules have been created. The lung cancer module included a high-yield, 10-minute voice-over PowerPoint presentation followed by interactive, case-based questions. The breast cancer module used a high-yield, 10-minute podcast with an accompanying handout for notes followed by case-based interactive questions. Seven learners have completed both pre- and post-survey responses for comparison. Two were completed by PGY1, 4 by PGY2, and 1 by a PGY3 resident. Median rating of the learners' knowledge of the specific cancer type increased from 2- Fair (1.5) on the pre-survey to 3- Neutral (1) after completing the learning module (p = 0.001). 100% of learners agreed or strongly agreed that their knowledge increased after completing the module. All 7 residents felt more comfortable with their clinical application of the cancer topic material after completing the module, median 2(1) on pre-survey vs. 3(0.5) on post-survey; p = 0.0004. **Conclusions:** The creation of online, multimodality learning resources has resulted in improvements in learners' perceived knowledge and comfort with clinical application of oncology topics. Using learning science principles, this pilot project serves as the foundation for further innovative and interactive educational resources and modules created for oncology learners. Research Sponsor: None.

11034

Poster Session

The impact of oncology hospitalist utilization on resident education. *First Author: Sunil Mahesh Bhatt, Yale University, New Haven, CT*

Background: In multiple U.S. cancer centers, dedicated hospitalists provide inpatient care to admitted patients as medical oncologists focus increasingly on outpatient care. Hospitalist integration is most common in medical oncology. Despite increasing prevalence of this model, little is known about the impact of oncology hospitalists on medical education. **Methods:** Beginning 6/26/21, an oncology hospitalist service was established at Yale-New Haven Hospital's Smilow Cancer Center. In the first year of the program, the Hospitalist Service (HS) provided a dedicated oncology hospitalist as the attending of record on one of two inpatient teaching services. The hospitalist was supported by a consulting medical oncologist. The traditional service (TS), led by a rotating board-certified medical oncologist, remained unchanged. The study interval was the first 11 months of the program, 6/26/21-5/28/22. Residents were randomly assigned to either the HS or TS. A two-week period in January was excluded due to hospitalist redeployment during the COVID-19 Omicron surge. At the conclusion of the study, a survey was distributed to residents to evaluate the educational experience on TS and HS. Questions using five-point Likert scales were used to elicit information on the quality and content of formal teaching, goals of care discussions and mentorship. The Yale University IRB considered this study to be Quality Improvement and required no further action. The Mann-Whitney U test was used to assess for differences between the two groups with a p-value of < 0.05 indicating statistical significance. **Results:** Out of 84 eligible residents, 36 (43%) responded including 19 interns (53%), 11 second years (31%) and 6 third years (17%). There were 15 responses (42%) following an HS rotation and 18 following a TS rotation (50%). Three individuals (8%) did not complete the entire survey and were excluded. All residents rotating on HS reported that their attending was easily accessible by phone compared with only 69% of those on TS (p = 0.11). Sixty-nine percent of residents on HS compared to 73% on TS noted having adequate opportunities to lead GOC discussions (p = 0.87). Fifty-four percent of residents on HS felt they had sufficient support during family meetings compared to 69% on TS (p = 0.98). Compared with only 8% on HS, 22% of residents on TS felt there were sufficient opportunities for oncology-specific professional mentorship (p = 0.64). Satisfaction with the amount of informal teaching did not differ significantly between the teams (p = 0.62). Altogether, 87% of residents reported that the total amount of teaching led to insufficient time for patient care. **Conclusions:** This survey suggests hospitalists provide greater accessibility at the cost of decreased specialty-specific mentorship in oncology. Further work is needed to better understand challenges and opportunities surrounding oncology hospitalist integration in academic medicine. Research Sponsor: None.

11036

Poster Session

Efficacy of a hematology/oncology podcast curriculum at a community-based internal medicine program. *First Author: Madeline Campbell Fitzpatrick, University of Tennessee, Nashville, TN*

Background: Medical podcasts have gained increasing popularity; however, there is limited evidence regarding their utility as an effective learning resource in Graduate Medical Education. Community-based internal medicine (IM) residents often have less exposure and education in hematology and oncology. To address this barrier, we developed a novel trainee-level hematology/oncology podcast curriculum to improve foundational knowledge for IM residents. **Methods:** A hematology/oncology podcast curriculum was implemented for IM residents at a community-based residency program in the 2022-2023 academic year. We developed ten episodes regarding workup and management of cytopenias, oncologic emergencies, and hematologic emergencies. We distributed anonymous pre- and post-intervention surveys to understand the impact of the podcast curriculum on a 5-point Likert scale on residents' self-perception of their knowledge. Two sample paired t-test was used to compare mean differences in surveys. **Results:** A total of 17/27 residents (63%) completed the pre-intervention survey, and 9/27 residents (33%) completed the post survey. The pre-survey was more heavily weighted towards residents earlier in their training with 53% PGY1s, 29% PGY2s, and 18% PGY3s. With 5 being entirely comfortable, there was a statistically significant increase in mean comfort level in the workup and management of various cytopenias (2.65 to 4.0, p < 0.01) and the management of oncologic emergencies (2.29 to 4.2, p < 0.01). Comfort level in the management of hematologic emergencies numerically improved from 3.35 to 3.57 but was not statistically significant. Most residents (90%) agreed or strongly agreed that the fundamentals of hematology/oncology were amenable to a podcast platform. Many residents found this modality convenient and performed other activities while listening to the podcast including driving (82%) and exercising (55%). The majority of residents who completed the post-survey (64%) reported that they will continue to use podcasts to supplement their medical education. **Conclusions:** Community-based IM residents' comfort with the field of hematology/oncology improved following the medical podcast educational intervention. Residents found the learning platform amenable to the fundamentals of hematology/oncology and will continue to utilize medical podcasts to supplement their education. Our successfully piloted podcast curriculum can be adapted to other IM programs to improve foundational knowledge in hematology/oncology. Research Sponsor: None.

11037

Poster Session

Effects of a focused one-day interactive session on oncology research on medical students' interest in and understanding of oncology research. *First Author: Jawad Alrawabdeh, University of Jordan, Amman, Jordan*

Background: Literacy and proficiency in medical research are crucial for the development of modern-day physicians. The need to equip future doctors with sufficient research skills is particularly important in oncology research, as cancer is the second leading cause of death in Jordan and the first worldwide. With the support of the University of Jordan ASCO-OSIG, we explored the efficacy of an interactive research intervention in highlighting the foundations of cancer clinical, basic, and translational research among undergraduate medical students. **Methods:** We designed and implemented a one-day educational program about all types of cancer research: clinical, basic, and translational. To evaluate the impact of this ASCO-OSIG initiative, students were asked to voluntarily fill surveys before and after the event. Medical students in both their pre-clinical and clinical training were invited to attend the event. Prominent researchers and experts from multiple tertiary cancer centers in Jordan presented 50min lectures on the foundations of clinical, basic, and translational oncology research. **Results:** A total of 111 participants filled the pre and post surveys, of which ASCO-OSIG members comprised 28.8% of the sample. Approximately 51.4% of participants were pre-clinical students and 48.2% were in their clinical years. About half of our cohort (50.2%) have previously engaged in research projects with only 10.2% of participants have been involved in oncology research. The event was effective in promoting participants' understanding and familiarity of the fundamentals of clinical (p-value < 0.001), translational (p-value < 0.001), and basic oncology research (p-value < 0.001). Most students were satisfied with the event; with 55% and 32.4% of students reporting being very satisfied and extremely satisfied with the event, respectively. Moreover, 83.8% of participants felt that oncology research was easier to get into after the event. About 96% of students reported that they would recommend this event to a colleague. **Conclusions:** We demonstrated that a focused one-day cancer research conference had improved medical students' understanding towards oncology research. Due to its design simplicity, other global ASCO-OSIG coordinators could implement the model within their respective institutions. Future efforts should expand on the available research initiatives and include other medical schools worldwide. Research Sponsor: None.

11039

Poster Session

A pilot curriculum to transition from 2D to 3D image-guided brachytherapy: A preliminary needs assessment. *First Author: Joy Ogunmuyiwa, New York Presbyterian Brooklyn Methodist Hospital, Brooklyn, NY*

Background: Gynecologic cancers are one of the leading causes of death globally with a disproportionate burden of disease found in low to middle income countries (LMIC). Brachytherapy is often a necessary component in treatment management as it can deliver a high dose of radiation to the tumor while employing a steep dose fall off that spares the adjacent organs at risk. With 3D image guided brachytherapy (3D-IGBT), treatment planning utilizes volumetric images with the target volume and organs at risk contoured, reducing toxicity and improving outcomes when compared to 2D planar imaging. Despite this advantage, only a limited number of LMIC centers perform 3D-IGBT. Transitioning to 3D-IGBT requires considerable planning, resources, and training. The development of a multidisciplinary, computer-based training program to facilitate the transition to 3D-IGBT was identified as a priority of multiple Radiation Oncology departments in Nigeria. The aim of this preliminary needs assessment was to identify the necessary resources and anticipated barriers to development of a pilot training curriculum for the transition to 3D-IGBT. **Methods:** An anonymous, 16-question online survey was distributed to clinicians, physicists, radiation therapists, and staff within a Radiation Oncology department of a teaching hospital in Lagos, Nigeria. **Results:** In January 2023, 53 respondents completed the survey. Of the respondents, 36.5% were female and 63.5% were male. The average age was 37.5 (SD = 7.8). Clinical experience ranged from < 5 years (52.6%), 6-10 years (9.4%), to > 10 years (30.2%). Respondents included radiation therapists (28.8%), clinicians (27%), nurses (23.1%), and physicists (15.4%). Multiple barriers to implementation of 3D-IGBT were identified including lack of training (79.2%) or experience (58.5%), lack of financial investment (50.9%), and anticipated repair/replacement of equipment (41.5%). A majority of respondents identified staff training/education (66%) as critical to delivering 3D-IGBT. When asked about the curriculum components needed, most respondents believed that it should include plan review (96.2%), contour review (94.3%), and peer review of clinical cases (92.5%). **Conclusions:** Various areas of potential need were identified through this preliminary needs assessment, most notably, staff training. These findings suggest that there is an unmet need to further develop and implement a structured didactic and skills-based curriculum to transition from 2D to 3D-IGBT at these institutions. Identified focus areas including contour, peer, and plan review will help guide the refinement of this curriculum. These findings are an important first step in delivery of safe and efficacious 3D-IGBT in an LMIC. Research Sponsor: None.

11038

Poster Session

Early introduction to clinical radiation oncology through a self-directed competency-based medical student curriculum. *First Author: Cheryl Claunch, Baylor College of Medicine, Houston, TX*

Background: Specialty training is not traditionally incorporated into standard medical education and there is a deficiency in exposure to Radiation Oncology for "last minute" interested candidates, particularly from underrepresented backgrounds. Therefore, we implemented MERA0-200, an introductory 2-week in-person and virtual medical education curriculum without clinical prerequisites to facilitate early introduction to the field of Radiation Oncology and report its effect on student comfort and familiarity with radiation planning and contouring. **Methods:** Clinical students were enrolled in a 2-week elective without clinical prerequisites that integrated both clinical activities and self-directed learning through virtual contouring modules. The virtual curriculum was designed around three modules available on EduCase. A survey was conducted after completion of the modules that solicited self-identifying information and to assess their efficacy in increasing understanding of basic contouring skills. Paired t-tests were used to compare pre- and post-elective assessment results. **Results:** Twenty-three total students have completed MERA0-200 from Fall 2020 to Spring 2023. Of those, 15 submitted the survey. Eight (53%) students did not answer self-identifying information such as gender, race, ethnicity, or country of origin. Four (27%) students identified as Asian and 3 (20%) as white. No students identified as Hispanic, Latino or Spanish origin. Seven (46%) students identified as having USA as country of origin. Seven (47%) students reported interest in radiation oncology, medical oncology or surgical oncology. Three (20%) students were MS2, 7 (47%) were MS3, and 5 (33%) were MS4. Overall, there was a significant increase in comfort level using radiation planning software (p = 1.1e-4) as well as ability to find relevant contouring references (p = 4.2e-5). Knowledge of the anatomy and contouring principles also improved for the three modules: eye and brain (p = 2.8e-7), high grade glioma (3.2e-6), and head and neck nodal stations (4.5e-6). CNS module difficulty on a scale of 1-10 had a median difficulty score of 7 (range 3-8) and head and neck module difficulty was a median of 7 (range 3-10). **Conclusions:** Implementation of MERA0-200 improved medical student exposure to the field of Radiation Oncology and improved medical student comfort and familiarity with radiation planning and across all disease sites covered. More outreach work needs to be done to facilitate inclusion of minority student populations and students from underrepresented backgrounds. Early introduction at the medical student level could be a pathway to improve disparity in the field of Radiation Oncology. Research Sponsor: None.

11040

Poster Session

Web-based patient educational material on chimeric antigen receptor T-cell therapy: Quantitative assessment of readability. *First Author: Rahul Kumar Thakur, Jacobi Medical Center/Albert Einstein College of Medicine, Bronx, NY*

Background: Chimeric antigen receptor (CAR) T-cell therapy is another paradigm-shifting advancement for hematologic malignancies, creating unprecedented treatment options. However, there is still a lack of knowledge and understanding among patients regarding this novel therapy. Most patients turn to online resources, ranging from social media to federal websites, to gather health information to supplement decision-making. Given that the average American adult reads between the sixth- and eighth-grade levels, national organizations recommend that patient resources be written at the sixth-grade level or below. The purpose of this study was to evaluate web-based patient educational material on CAR-T cell therapy resources using measures of readability and compare it to national guidelines. **Methods:** Online patient information on CAR-T cell therapy from the top 20 U.S. Cancer center as per US news ranking was collected. We analyzed the content by six of the most common readability tests- Flesch Reading Ease score (FRE), Gunning Fog (GF), Flesch-Kincaid Grade Level (FKGL), Coleman-Liau Index (CLI), Simple Measure of Gobbledygook (SMOG) Index, and the Automated Readability Index (ARI). The text from each article was carefully reviewed and analyzed using the software Readable, and the readability scores with standard deviation (SD) were obtained. **Results:** The mean score FRE score was 48.5 (SD: 6.7), which corresponds to college level and is difficult to read. The mean GF score was 8.7(SD: 1.5), which represents the writing of an 8th grader. The FKGL score was 8.6 (SD: 1.1), which represents a level of 8th grade or above. The mean CLI score was 11.5(SD: 1.3), which is the text level for high school juniors. The mean SMOG index was 10.9 (SD: 1), which is the level of a 12th grader. The ARI score was 7.8 (SD: 1.3), indicating a 7th-grade level. **Conclusions:** Overall, web-based CAR-T cell therapy patient educational materials scored poorly and does not meet the national recommendations. Authors of patient resources should incorporate readability criteria and prompt a revision or creation of new educational materials including videos and audio to support general patient understanding. By making CAR-T therapy information easily understandable, internet users can be better informed about their treatment decisions. Research Sponsor: None.

11041

Poster Session

Empowering self-advocacy for breast health: A successful educational campaign on breast cancer risk and screening recommendations. *First Author: Matthew Culbert, Department of Radiation Oncology, University of Florida College of Medicine, Gainesville, FL*

Background: The purpose was to develop and distribute an educational campaign on breast cancer risk and screening recommendations to empower women, men, and transgender individuals to take charge of their breast health. Identifying individuals at high risk for developing breast cancer through educational campaigns can lead to earlier detection and improved health outcomes. It was hypothesized that the development of a multi-platform educational campaign including televised ads, website, and mobile applications (apps), would result in a broad reach and accessibility of breast cancer risk and screening recommendations. **Methods:** The campaign ran from 10/1/22 – 12/2/22 and included a variety of mediums, such as televised ads, website, and mobile apps for iOS and Android devices, all of which were available in English and Spanish. An educational video series was developed to raise awareness about the updated guidelines for breast cancer screening from the American College of Radiology (ACR). Videos focused on the importance of screening for women with a high risk of breast cancer and transgender individuals taking hormone therapy. To complement the televised video, case-based teaching illustrations were created for the website and apps. Resources included screening recommendations, local resources for breast cancer screening and foundations for financial assistance. These materials could be accessed at the website <https://myriskbreastcancer.com>. The website and mobile apps featured a risk calculator developed using the GAIL model from SAS, coded in the Dart programming language to ensure compatibility and all user inputs were stored in a secure Firebase database. To reach a wider audience, responsive social media ads were developed and distributed through targeted Google Ads campaign. Analytics were collected and analyzed using Google Analytics and user inputs from the mobile application to assess the campaign's effectiveness. **Results:** Televised ads reached a total of 673,920 impressions over 142 educational video sessions. Google display ads had 152,672 impressions and 462 click-throughs with an audience of 49.2% female and 50.8% male. The mobile application was downloaded 2,030 times on iOS and 722 times on Android, and installed in 131 countries. The website saw 930 impressions and 637 users completed the online calculator, with 72 identified as high risk at time of initial data collection on 12/1/22. **Conclusions:** The educational campaign was successful in reaching > 500,000 impressions within two months of release, sharing knowledge about breast cancer risk and screening recommendations across all gender types. Use of multiple platforms, including television, social media, and mobile apps, allowed for broad reach and accessibility nationally and internationally, including the identification of 72 individuals at high risk for developing breast cancer. Research Sponsor: Florida Breast Cancer Foundation.

11042

Poster Session

Clinicians' experiences with patients with cancer or their families who endorse medical misinformation. *First Author: Amitabha Palmer, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Medical misinformation causes delays in cancer care, forgoing of treatment, economic harms, potentially toxic effects, and harmful medical interactions with standard curative treatments. Previous literature has examined patients' traits and beliefs. However, effectively caring for patients with cancer who endorse medical misinformation also requires better understanding the experiences, competencies, and concerns of the clinicians who treat them. We conducted an IRB approved study of physicians and advanced practice providers at a large cancer center. **Methods:** We surveyed clinicians about following themes: i) prevalence of misinformation, ii) attitudes towards patients endorsing misinformation, iii) strategies and competence, iv) resources to help them successfully address patients. **Results:** 87 clinicians responded to the survey. The median response was 15% of patients endorse claims that are false or misleading about standard-of-care cancer treatments and 20% endorse claims that overstate the benefits or understate the risks of unconventional treatments. The most common misinformation concerned herbs and supplements. Clinicians ranked provides hope and poor medical literacy as the top reasons for why their patients endorse medical misinformation followed by distrust in conventional medicine, cultural factors, and religiosity. The primary attitude clinicians project to patients when they request unconventional treatments was Openness/Equanimity (75.6%), Curiosity (43.9%), Skepticism (18.3%), Disdain/Disappointment (0, 0.0%), Other (6.1%). The primary internal attitude clinicians experienced in these situations was Openness/Equanimity (25.6%), Skepticism (57.3%), Curiosity (40.2%), Disdain/Disappointment (22.0%), Other (6, 7.3%). When asked if they'd be open to a patient using a harmless unconventional treatment that had no evidence of therapeutic benefit, 17.1% said yes, 17.1% said no, and 65.9% said it depends. Correcting misinformation is difficult: 38.2% report success rates below 60% for correcting misinformation and 68.5% report success rates below 80%. Several factors contributed to low success: Only 26% said that they have enough time to adequately address patients who endorse misinformation. Moreover, 46.9% report insufficient resources, 65% claim insufficient training, and 51.3% claim insufficient institutional support. **Conclusions:** Many cancer care providers feel insufficiently trained and supported to address patients who endorse medical misinformation. Cancer care institutions must develop training and resources to help clinicians effectively address patients who endorse misinformation about their care. Research Sponsor: None.

11500

Oral Abstract Session

Efficacy and safety of nivolumab and trabectedin in pretreated patients with advanced soft tissue sarcomas (STS): Results of a phase II trial of the German Interdisciplinary Sarcoma Group (GISG-15, NitraSarc). *First Author: Peter Reichardt, HELIOS Klinikum Berlin-Buch, Klinik für Interdisziplinäre Onkologie, Sarkomzentrum Berlin-Brandenburg, Berlin, Germany*

Background: Programmed death-1 (PD-1) inhibitors alone have modest activity in the treatment of most STS. A possible synergistic effect of combined trabectedin with PD-1 inhibitor nivolumab has been previously reported. Herein we evaluated the efficacy and safety of trabectedin plus nivolumab as a second-line treatment of patients with anthracycline-pretreated metastatic or inoperable STS. **Methods:** The prospective, explorative, two-group, non-randomized phase II NITraSarc trial enrolled patients with advanced lipo- or leiomyosarcomas (Group A; GA) or with non-L-sarcomas (Group B; GB). Patients were initially treated with 3 cycles of trabectedin 1.5 mg/m², followed by the combination of trabectedin 1.5 mg/m² plus nivolumab 240 mg in a so-called "late combination cohort" (LCC) for up to 16 cycles. After positive results of a preplanned interim analysis, patients received the combination therapy already starting from Cycle 2 in an "early combination cohort" (ECC). Primary efficacy endpoint was progression-free survival rate after 6 months (PFSR6) according to RECIST v.1.1. A central pathological assessment (CPA) was done from tumor specimen from all patients. Updated results according to cpa are presented. **Results:** A total of 92 patients were recruited in the trial: 43 patients in GA and 49 in GB. In GA, 28 patients (63%) had leiomyosarcoma and 15 (37%) had liposarcoma. Most common sarcoma types in GB were pleomorphic (n = 12), spindle cell (n = 11), fibromyxoid (n = 6), synovial (n = 5) and epithelial (n = 4) sarcoma. After median follow up of 16.6 months, overall PFSR6 as per CPA in GA was 47.6% (60% in LCC vs 36.4% in ECC) and 14.6% in GB. Median PFS was numerically higher in GA compared to GB (5.5 vs 2.3 months) and even longer in LCC vs ECC (9.8 vs 4.4 months). Median overall survival was more than three times longer in GA vs GB (18.7 vs 5.6 months) and, again, longer in LCC vs ECC (24.6 vs 13.9 months). Safety of trabectedin and nivolumab was consistent with the safety profiles of each drug alone with no relevant new findings for the combination or between LCC and ECC. **Conclusions:** Our study confirms the activity of trabectedin plus nivolumab, particularly in patients with lipo- or leiomyosarcomas. There is a significant difference between ECC and LCC in terms of PFSR6, PFS and OS. The results in patients with non-L-sarcomas do not justify further investigation of this combination. Clinical trial information: NCT03590210. Research Sponsor: University Medicine Greifswald, Germany; PharmaMar, Bristol-Myers Squibb.

11502

Oral Abstract Session

ImmunoSarc2: A Spanish Sarcoma Group (GEIS) phase Ib trial of doxorubicin and dacarbazine plus nivolumab in first line treatment of advanced leiomyosarcoma. *First Author: Javier Martin Broto, Medical Oncology Department, Fundacion Jimenez Diaz University Hospital, Madrid, Spain, Institute of Biomedicine of Seville, University of Seville, Seville, Spain*

Background: The immunogenic death caused by certain chemotherapy agents consists of molecular changes in tumor dying cells that stimulate immunogenicity and enhance antitumor effects. Doxorubicin is one validated drug related to immunogenic death, mainly through calreticulin membrane translocation that elicits immunogenic signals as phagocytosis by dendritic cells. Doxorubicin plus pembrolizumab was explored in a phase I/II trial treating patients with metastatic/unresectable sarcomas, achieving 22% PR, 59% SD, and 19% PD, with mPFS of 8.1 months superior to historical controls. We hypothesized that the addition of an anti-PD1 (nivolumab) would increase the antitumor activity of commonly used upfront polychemotherapy in leiomyosarcoma (LMS) of doxorubicin plus dacarbazine. We present here the phase Ib, cohort 7b of ImmunoSarc2 trial. **Methods:** Adult patients (pts), with ECOG 0-1, naïve of previous anthracycline-containing treatments and with centrally confirmed diagnosis of advanced/metastatic leiomyosarcoma (LMS) were eligible. Initial dose level 0 (LO) was defined as doxorubicin (DOX) 75 mg/m²/d 20 min on D1 followed by dacarbazine (DAC) 400 mg/m²/d 60 min on D1 and 2, plus nivolumab (NIV) 360 mg on D2 after DAC Q3W with GCSF support. This combo would be given up to 6 courses of 21-day cycles, followed by 1-year NIV maintenance. A -1 dose level (L-1) was defined with the same regimen but with NIV 240 mg. A classic 3+3 phase 1 design was used to determine the MTD based on DLTs (main endpoint) observed during the first 21-day cycle. The cohort was foreseen to be extended with the RP2D up to 20 evaluable patients. Secondary endpoints included ORR and safety profile among others. **Results:** Between January 2022 and February 2023, 20 pts (M/F 6/14), ECOG 0/1 (15/5), with median age 54 years (31-72) were enrolled. All patients were treated with the initial LO scheme and no DLTs were observed being LO the RP2D. Grade 3-4 toxicities were neutropenia (20%), anemia (10%), febrile neutropenia, asthenia, and GGT increased (5% each). Four pts are not evaluable for efficacy (1 due to uncompliant dosing and 3 for not reaching the first tumor assessment yet). Of 16 efficacy-evaluable pts, RECIST ORR according to local clinical site assessment was 9 PR (56.2%), 6 SD (37.5%), and 1 PD (6.3%) (2 SD cases had tumor size reductions > 20%). Five pts ended treatment due to progression (4 radiological, 1 clinical) and 15 pts remain under the trial therapy. mPFS for evaluable patients was 8.67 months (95% CI: 7.96-9.37) with a median follow-up of 8 months (2-12). **Conclusions:** DOX 75 mg/m²/d on D1 followed by DAC 400 mg/m²/d on D1 and 2, plus NIV 360 mg on D2 after DAC Q3W, followed by 1-year NIV maintenance is a feasible and well-tolerated scheme. Clinical activity is encouraging improving historical efficacy outcomes in first line of advanced LMS, which deserves further testing in phase II trials. Clinical trial information: NCT03277924. Research Sponsor: Drug supply, shipping and insurances were provided by BMS and Pfizer. Operational expenses were in charge of GEIS group.

11501

Oral Abstract Session

A single-arm, open-label phase 2 trial of doxorubicin plus zalifrelimab, a CTLA-4 inhibitor, with balstilimab, a PD-1 inhibitor, in patients with advanced/metastatic soft tissue sarcomas. *First Author: Breelyn A. Wilky, University of Colorado Anschutz Medical Campus, Aurora, CO*

Background: Doxorubicin (DOX) is the standard of care for unresectable soft tissue sarcomas (STS). DOX induces immunogenic cell death in numerous preclinical models. Immune checkpoint inhibitors (ICIs) including antibodies (ab) to PD-1 and CTLA-4 have shown modest activity, but most STS are immune "cold" tumors and do not respond. We hypothesized that concurrent DOX would improve immunogenicity of STS and boost efficacy of ICIs, including anti-CTLA-4 ab zalifrelimab (ZAL) and anti-PD-1 ab balstilimab (BAL). **Methods:** We conducted a single arm Phase 2 trial of combination DOX/ZAL/BAL for patients (pts) with advanced/metastatic STS in the 1st/2nd treatment lines without prior DOX or ICI (NCT04028063). The study was a Simon minimax 2-stage design to accrue 28 pts evaluable for primary endpoint of progression-free survival rate at 6 months (PFS_{6mo}) by RECIST 1.1. We aimed to improve PFS_{6mo} by 20% with DOX/ZAL/BAL over null rate of 43.4% based on average PFS of 2 prior DOX monotherapy trials. Secondary endpoints were objective response rate (ORR), disease control rate (DCR), overall survival (OS), duration of response (DOR), and adverse events (AEs). All pts received up to 6 DOX cycles with concurrent ZAL/BAL; pts on stage 1 began DOX at cycle 2 with ZAL/BAL at cycle 1, pts on stage 2 began DOX/ZAL/BAL at cycle 1. Imaging was obtained prior to the first dose of DOX (baseline), and then every 6 weeks (wks) to 6 mo, and thereafter every 9 wks. Tumor biopsies/peripheral blood were obtained at baseline, on-treatment, and progression for immune profiling. **Results:** 35 patients were accrued as of 1/25/23. 25 pts are currently evaluable for primary endpoint of PFS_{6mo} and 28 for efficacy (at least one post-treatment scan). PFS_{6mo} is estimated at 52% (95%CI 31-72), with mPFS of 25.6 wks (24.0-44.9). ORR was 36% (19-56), and DCR was 86% (67-96). Median DOR was 12.8 wks (range 6-105). Most pts with PR who progressed did so on BAL after DOX completion. Responses were observed in pts with intimal sarcoma, angiosarcoma, MPNST, LPS, LMS, endometrial stromal sarcoma, UPS, and sclerosing epithelioid fibrosarcoma. Improved outcomes were observed in stage 1 pts compared to stage 2 pts, including PFS_{6mo} (56.3% v. 25.0%), mPFS (31.7 v. 25.3 wks), ORR (56% v. 8.3%), and DCR (94% v. 75%). Toxicity was as expected with grade 3/4 TRAEs in 48% of 31 evaluable pts, primarily DOX-related hematologic AEs, and immune-related AEs requiring steroids in 19% of pts. **Conclusions:** Combination DOX/BAL/ZAL led to meaningful efficacy, including favorable PFS_{6mo} and responses in several STS subtypes unlikely to respond to DOX or ICI monotherapy. Further investigation is required to determine if the stage 1 priming dose of ZAL/BAL prior to DOX improved clinical outcomes. An ongoing cohort is exploring a next-generation CTLA-4 inhibitor, botensilimab in combination with DOX +/- BAL. Clinical trial information: NCT04028063. Research Sponsor: Agenus Bio; Cancer League of Colorado; University of Colorado Cancer Center.

11503

Oral Abstract Session

A multicenter phase II study of cabozantinib + nivolumab for patients (pts) with advanced angiosarcoma (AS) previously treated with a taxane (Alliance A091902). *First Author: Juneko E. Grilley-Olson, Duke Cancer Institute, Duke University, Durham, NC*

Background: Collectively, sarcomas have demonstrated less benefit from immunotherapy than many other cancers. Pts with AS have limited options, particularly after taxane chemotherapy. Although AS is a vascular malignancy, anti-VEGF therapies have minimal monotherapy clinical activity. Some cutaneous AS have a high UV damage signature, but other AS often do not. Cabozantinib (C) is a multitargeted inhibitor that may alter PD-1 expression in regulatory T cells, promoting an immune permissive environment when combined with nivolumab (N), a fully human anti PD-1 MAB. We hypothesize that the combination of C+N will be an effective therapy in AS, across AS subtypes. **Methods:** This open-label multi-arm study enrolled pts with locally advanced/metastatic AS. Arm 3, reported here, enrolled pts who had received a taxane for AS (including adjuvant) prior to study enrollment. Pts were not restricted on number of prior lines, but prior anti-VEGF and immunotherapies were not allowed. Eligible pts received C (40 mg po daily) with N (480 mg IV every 4 wks). Treatment was permitted beyond progressive disease (PD) in the 1st 12 wks (4 wk confirmatory scan), but PD response was censored at 12 wks. The Simon 2-stage design (null and alternative overall response rate (ORR) were 10% and 35%, respectively) required ≥1 confirmed response in 9 pts in the 1st stage, and >4 of 18 pts (91.4% power, alpha 0.095) for the primary endpoint. Secondary endpoints were adverse events (AEs), progression free, overall survival (PFS, OS), and pt-reported outcomes (PRO). **Results:** 21 eligible pts [median age 66 yrs (32-92), 10 female] received ≥1 dose of C+N. Primary disease sites: 12 cutaneous (scalp/face), 1 liver, 2 breast, 6 other. All pts received prior taxanes (11/21 = 52% as adjuvant therapy) and 5/21 (24%) had also received prior anthracycline (all relapsed AS). Primary endpoint: 13 of the first 18 evaluable patients (72%) experienced objective response (OR, 95%CI: 47%-90%). After a median follow-up of 11.2 mo, 13 of 21 pts achieved OR (11 partial response, 2 complete), for ORR 62% (95%CI: 38-82%). Responses were seen in pts with primary cutaneous disease 7/12 (58%) and noncutaneous disease 6/9 (67%). Median PFS was 9.6 mo (5.3-NR), and OS 20.5 mo (14.4-NR). Off treatment reasons include: progressive disease (14), comorbid condition unrelated to AS or study (1); 6 pts remain on study. Grade (G) 3 hypertension was the only possibly treatment related AE (TRAE) occurring in 310%. No G 4/5 TRAE were reported. **Conclusions:** C + N demonstrated significant antitumor activity in taxane-pretreated AS and was well tolerated without new safety concerns. Activity of the combination was seen across AS subtypes. PRO and exploratory analyses are ongoing. Support: U10CA180821, U10CA180882, U24 CA196171, U10CA180820; <https://acknowledgments.alliancefound.org>. U10CA180868; U10CA180888. NCT04339738. Clinical trial information: NCT04339738. Research Sponsor: U.S. National Institutes of Health.

LBA11504

Oral Abstract Session

Randomized phase II trial of cabozantinib combined with PD-1 and CTLA-4 inhibition versus cabozantinib in metastatic soft tissue sarcoma. *First Author: Brian Andrew Van Tine, Washington University Siteman Cancer Center, St. Louis, MO*

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2023, issue of the *Journal of Clinical Oncology*.

11505

Oral Abstract Session

A phase II study of cabozantinib and temozolomide in patients with unresectable or metastatic leiomyosarcoma and other soft tissue sarcomas. *First Author: Mark Agulnik, City of Hope Comprehensive Cancer Center, Duarte, CA*

Background: Potentiation of chemotherapy, without increased toxicity, to improve outcome is an area of interest. Preclinical and clinical evidence shows simultaneous utilization of antiangiogenic agents and chemotherapy have a synergistic effect. We hypothesized that the dual targeting of VEGF and c-MET pathways with cabozantinib (CAB) would result in clinical benefit for patients with soft tissue sarcoma (STS) when combined with temozolomide (TMZ), an alkylating agent. Utilization of CAB/TMZ is anticipated to produce a synergistic antitumor effect worthwhile to explore in STS. **Methods:** A multicenter phase II study of CAB/TMZ in patients with unresectable/metastatic leiomyosarcoma (LMS) and other STS was conducted by the Midwest Sarcoma Trials Partnership. Age ≥ 18 , adequate performance status, organ function, measurable disease (RECIST 1.1), and 0-5 prior chemotherapy regimens were required. CAB 40 mg PO daily plus TMZ 150-200 mg/m² PO 1-5 days were given in 28-day cycles until disease progression or unacceptable toxicity. Patients enrolled in 2 cohorts: 1. Uterine and non-uterine LMS 2. Other STS. The first 14 subjects to be enrolled in the study in either cohort served as a safety lead in. The primary endpoint was progression-free rate (PFR) at 12 weeks for cohort 1. Secondary endpoints include overall response rate (ORR), clinical benefit rate, median progression-free survival (PFS), overall survival, and safety and tolerability. The exploratory endpoint was to estimate the correlation of PFR and OS to expression levels of VEGF, amongst others. A Simon 2-stage design was used. **Results:** A total of 42 patients were enrolled in Cohort 1, and 30 in Cohort 2, across 5 sites. For Cohort 1, median age was 59 years (range 35-86), 85.7% were non-Hispanic, 73.8% were female, 61.9% had ECOG of 0. The PFR at 12 weeks was 45.9% (for 37 evaluable patient) with a median PFS of 6.4 months (95% CI 4.6-6.7). Five PR were observed for an ORR of 13.5%. For Cohort 2, median age was 63 (20-86), 83.3% were non-Hispanic, 36.7% were female, 53.3% had ECOG of 0. The PFR at 12 weeks was 50% (for 28 evaluable patients) with a median PFS of 3.2 months (95% CI 1.4-4.6). One PR was observed. Reported grade 3-4 adverse events attributed to one or both intervention drugs affecting $\geq 10\%$ of patients (n = 70) included hypertension (10%), decreased neutrophils (18.7%), decreased platelets (31%). **Conclusions:** The combination therapy of CAB/TMZ in patients with unresectable or metastatic LMS exceeded its primary endpoint with a PFR at 12 weeks $> 39\%$. The PFS of 6.4 months in Cohort 1 exceeds rates achieved with second line tyrosine kinase inhibitors (TKIs) and alkylators in LMS patients. Treatment was feasible and did not reveal any previously unreported toxicities. The combination with CAB with TMZ demonstrated meaningful clinical benefit and is worth further exploration in LMS. Clinical trial information: NCT04200443. Research Sponsor: Exelixis.

11506

Oral Abstract Session

A phase III randomized trial of neo-adjuvant chemotherapy in high-risk soft tissue sarcoma (ISG-STIS 1001): Feasibility and activity of concurrent chemotherapy and radiation therapy. *First Author: Elena Palassini, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy*

Background: The ISG-STIS 1001 was an international, randomized, phase III, clinical trial for localized, high-risk, soft tissue sarcoma comparing neoadjuvant chemotherapy (ChT) with a standard regimen of epirubicin plus ifosfamide (EI) versus an histology-tailored regimen (HT) in five histologic types, within the context of an integrated multimodality strategy. In addition, in this study, a parallel group of patients (pts) was not randomized but just registered and treated with EI. Radiation-therapy (RT) could be delivered either pre-operatively (concurrent to ChT) or post-operatively, according to clinical judgement. Final results of ISG-STIS 1001, published in 2020, showed a benefit in favor of EI, in terms of overall survival, in comparison to HT. Herein, we analyzed tolerability and activity of ChT with EI either in the standard arm of the trial or in the parallel group, whether alone and concurrent to RT. **Methods:** The EI regimen was made up of epirubicin 120 mg/m² plus ifosfamide 9 g/m². RT was delivered at a dose of 44-50 Gy pre-operatively or 60-66 Gy post-operatively. In the current analysis, toxicities related to EI were analyzed separately in the group receiving concurrent pre-operative ChT and RT and in the group treated with pre-operative ChT alone and receiving RT post-operatively. Surgical complications and radiological response according to RECIST were analyzed in the above mentioned two groups. Data on ChT dose-intensity will be provided. **Results:** Among the 548 pts (287 randomized and 261 registered) included in the ISG-STIS 1001, 289 pts were considered for the current analyses (111 pts randomized in the EI arm and 178 pts just registered). 146 pts were treated with pre-operative RT and 143 with post-operative RT. In regard to toxicities, no statistically significant differences were found between pts treated with pre-operative concurrent ChT and RT and pts treated with pre-operative ChT alone. When surgical post-operative complications were considered, a higher number of wound dehiscence (9% vs 3.5%, respectively, p = 0.053) and seroma (10.5% vs 3%, respectively, p = 0.009) were observed in pts treated with pre-operative concurrent ChT and RT compared to pts treated with pre-operative ChT alone. Finally, a statistically significant association between RECIST response and pre-operative RT was found (p = 0.041), RECIST partial responses (PR) being 19% and 10% in pts receiving concurrent pre-operative ChT plus RT and in pts treated with pre-operative ChT alone, respectively. **Conclusions:** The concurrent administration of EI and RT was confirmed to be feasible and safe, resulting in an increased number of PR. Also given the final results of this randomized trial, favoring the EI arm, this combination may help when tumors are of borderline resectability or function preservation is a goal. Research Sponsor: None.

11507

Oral Abstract Session

Efficacy of combination lurbinectedin (LURBI) + doxorubicin (DOX) from the phase 1B soft-tissue sarcoma (STS) lead-in to a randomized phase 2 trial in leiomyosarcoma (LMS). *First Author: Gregory Michael Cote, MGH Cancer Center, Boston, MA*

Background: Single agent or combination chemotherapy, typically Dox- or gemcitabine-based, are standard 1st- and 2nd-line therapies in patients (pts) with metastatic LMS; however, objective response rates (ORR), progression-free, and overall survival (PFS/OS) remain inadequate. Lurbi (PharmaMar S.A. / Jazz Pharmaceuticals) binds to DNA inhibiting transcription and inducing double strand breaks leading to apoptosis and delaying S/G2 progression. In a prior pilot study, we showed Lurbi+Dox is well-tolerated, with signs of activity, particularly in LMS. We designed this phase 1b to optimize dosing to lead into a randomized (1:1) phase 2 trial of Dox+Lurbi in anthracycline-naïve LMS. Herein we provide updated efficacy and tolerability data for this Phase 1b cohort. **Methods:** Pts > 18 yrs with locally advanced/metastatic, unresectable non-GIST STS (Phase 1b only) w/o prior anthracycline or Lurbi/trabectedin, ECOG PS < 3 , RECIST 1.1 measurable, and normal organ function were eligible. The phase 1b followed a 3+3 design. Dosing included fixed Lurbi (3.2 mg/m² d1) with two Dox dose levels (DL; DL1: 25 mg/m² d1; DL2 25 mg/m² d1+8). All pts received GCSF prophylaxis. Tumor assessments were every 2 cycles. DL1 was chosen as RP2D and the phase 2 trial began accrual in Aug 2022 aiming to enroll 50 LMS pts randomized 1:1 (stratified by uterine LMS [uLMS]) v. other LMS) with PFS as primary endpoint. Pts progressing on Dox are allowed to cross to Lurbi monotherapy. **Results:** 10 patients were enrolled in Phase 1b. Histologies included 5 LMS (4 uLMS) and 1 each of myxofibrosarcoma (myxFS), undifferentiated pleomorphic sarcoma (UPS), dedifferentiated liposarcoma (DDLPS), endometrial stromal sarcoma (ESS), and solitary fibrous tumor (SFT). With a median follow-up of 344 days, 5/10 pts remain on treatment with median PFS of 357 days (95%CI 175-ND). 6 pts demonstrated partial response (PR; 5 confirmed), 3 with stable disease (SD), and 1 with progressive disease (PD, Table). Median time to PR was 81 days (range 46-207). Duration of response was over 132 days in all responders with 3 still on treatment. Treatment-related AEs were typical for Dox/Lurbi, including nausea, fatigue, and reversible LFT elevations/cytopenias. Updated safety and response data will be provided at the time of the meeting. **Conclusions:** Lurbi+Dox is well-tolerated with efficacy in STS including 6/10 pts achieving PR, 9/10 pts staying on treatment for > 120 d, and 6/10 pts > 200 d. The randomized phase 2 study is currently enrolling. Clinical trial information: NCT05099666. Research Sponsor: Jazz Pharmaceuticals.

Histology	# Prior Systemic Therapies	RECIST 1.1 Best Response / %	Duration of Response (days)	Time on Treatment (days)	Treatment Ongoing
uLMS	0	PR -69	140	224	Y
myxFS	1	PR -66	132	175	
UPS	0	PR -61	279	357	
LMS	0	PR -50	133	269	Y
uLMS	1	PR -43	136	182	
DDLPS	0	PR -41	*	207	Y
uLMS	1	SD -12		361	Y
ESS	1	SD -9		312	Y
SFT	1	SD 5		124	
uLMS	0	PD 52		42	

*PR on 1/30/2023 assessment; duration pending follow-up scans.

11508

Oral Abstract Session

Safety and clinical activity of TTI-621 in combination with doxorubicin in patients with unresectable or metastatic high-grade leiomyosarcoma: Results from the low-dose expansion cohort. *First Author: Sujana Movva, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: TTI-621 is a recombinant fusion protein combining the Fc region of human IgG1 with a fragment of human SIRP α , designed as a decoy receptor for CD47 on tumor cells to interrupt CD47-SIRP α signaling and promote macrophage-mediated phagocytosis of tumor cells as well as activation of NK cells. Preclinical studies suggest TTI-621 may enhance the response to doxorubicin in macrophage-rich tumors that express CD47, such as leiomyosarcoma (LMS). A phase 1/2 dose escalation study with high- and low-dose expansion cohorts evaluating TTI-621 + doxorubicin in patients (pts) with advanced LMS is ongoing (NCT04996004); results from the low-dose expansion cohort are presented. **Methods:** This open-label study enrolled anthracycline-naïve pts aged ≥ 18 y with evaluable unresectable or metastatic high-grade LMS and ≤ 1 prior line of therapy for advanced disease. Pts in the low-dose expansion cohort received TTI-621 0.2 mg/kg on Days 1 and 8 in combination with doxorubicin 75 mg/m² on Day 1 of 21-day cycles for a maximum 6 cycles, followed by TTI-621 monotherapy on Days 1 and 15 of 28-day cycles until objective disease progression. Primary objectives for the expansion phase were evaluation of safety and investigation of clinical activity via assessment of overall response and clinical benefit rates as defined by RECIST v1.1 criteria. **Results:** At data cut-off (Oct 3, 2022), 23 pts were evaluable for safety and 20 for clinical response. In the safety population, 39% had received prior treatment for advanced disease. Two pts (9%) experienced Grade ≥ 3 AE assessed as related to TTI-621 treatment: pancreatitis (n = 1, 4%) and platelet count decreased (n = 1, 4%). Seven pts (30%) experienced Grade ≥ 3 AE related to the combination of TTI-621 and doxorubicin, including two pts (9%) each with platelet count decreased and white blood cell count decreased and three pts (13%) with neutrophil count decreased. Grade ≥ 3 doxorubicin-related AEs were more common (n = 17, 74%); most frequent were neutrophil count decreased (n = 8; 35%), white blood cell count decreased (n = 7; 30%), and neutropenia (n = 6; 26%). One pt experienced an infusion-related reaction (Grade 1 chills) assessed as related to TTI-621. No pts attained complete response, but one pt had a complete resolution of all target lesions. Five pts (25%) attained partial response for an overall response rate of 25%; 11 pts (55%) attained stable disease for a disease control rate of 80%. **Conclusions:** Addition of TTI-621 to doxorubicin showed promising clinical activity and a favorable safety profile among pts with advanced LMS, including those with prolonged exposure to TTI-621 (> 360 d). Clinical trial information: NCT04996004. Research Sponsor: Pfizer.

11510

Clinical Science Symposium

The clinical value of tumor-informed minimal residual disease detection in sarcoma. *First Author: Yiwei Fu, Department of Musculoskeletal Oncology, the First Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China*

Background: The high recurrence and metastasis rates lead to poor survival of patients with sarcoma. At present, circulating tumor DNA-based minimal residual disease (MRD) has been studied in various solid tumors and proved to be valuable in guiding treatment and predicting recurrence, but its application in sarcomas is rarely reported. **Methods:** Tumor tissue samples were used for whole exome sequencing (WES) and clonal mutations were selected for the customized MRD panel. Blood samples were collected for MRD detection. Experiments were conducted at Origimed, a College of American Pathologists accredited and Clinical Laboratory Improvement Amendments certified laboratory. **Results:** A total of 84 sarcoma patients including 47 bone tumor (BT), 32 soft-tissue sarcoma (STS), and 5 undifferentiated small round cell sarcoma (USRCS) patients were enrolled. Patients consisted of 49 (58.3%) males and 35 (41.7%) females, with a median age of 23 years old (1-85 years old). Based on WES, we found that 64% (49/36/77/15) of the mutated genes were unique to each patient, and 70.4% (859/1220) of selected tumor-informed single nucleotide variants (SNV) were variants with unknown significance, suggesting that tumor-informed MRD is superior to panel-based MRD in sarcomas. In this cohort, 78.6% (66/84) of patients successfully constructed MRD panels, including 85.1% (40/47) of BT patients, 75% (24/32) of STS patients, and 40% (2/5) of USRCS patients. The main reason for failure was the scarcity of SNVs detected. Preoperative MRD detection was performed on 6 cases and revealed a positive rate of 100%. MRD detection was performed twice on 2 patients during preoperative neoadjuvant therapy. For the patient with constant allele frequencies detected throughout the treatment course, imaging showed tumor enlargement; While for another patient with a trend of reduction in allelic frequency, imaging showed tumor shrinkage and necrotic tumor tissue was observed in surgery one month later. These two patients had not recurred after surgery at the time of analysis. Post-surgery MRD detection was performed on 27 patients, of which 1 STS and 7 BTs were positive (30%, 8/27). Three of them confirmed recurrence by imaging at 12, 30, and 101 days after detection of positive MRD, respectively. However, there were still no imaging recurrence in the other patients so far, including the 5 remaining patients with positive MRD and 19 patients with negative MRD. Follow-up is still ongoing. **Conclusions:** MRD tests had been successfully performed in most of the sarcoma patients. Due to the heterogeneity of sarcomas, about 64% of mutated genes of sarcomas are unique individually, which may be more suitable for monitoring with tumor-informed MRD panel. Tumor-informed MRD could be used to predict the efficacy of preoperative neoadjuvant therapy and discover recurrence earlier than imaging in sarcoma. Research Sponsor: None.

11509

Clinical Science Symposium

Molecular residual disease (MRD) detection using bespoke circulating tumor DNA (ctDNA) assays in localized soft tissue sarcoma (STS). *First Author: Abdulazeez Salawu, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada*

Background: Surgery and (neo)adjuvant radiotherapy (RT) are the mainstay curative treatments for localized STS. Despite treatment, up to 50% of STS patients experience metastatic relapse, and routine use of adjuvant systemic therapy (AST) remains controversial. The presence of ctDNA following curative-intent treatment of STS is a potential biomarker for MRD and may identify patients who are likely to benefit from AST. Given the genomic heterogeneity of STS, a histology-agnostic approach to ctDNA detection in this population is desirable. **Methods:** Patients (pts) with localized, high risk (size ≥ 5 cm, grade ≥ 2) STS were enrolled prior to (neo) adjuvant RT and surgery. Pts who received (neo)adjuvant systemic treatment were excluded. Blood samples for ctDNA analysis were collected at diagnosis, post-RT, post-surgery and every 3 months for up to 2 years. Whole exome sequencing (WES) of archival tumor and matched normal were carried out to identify patient-specific, somatic, single nucleotide variants. Personalized and tumor-informed, multiplex PCR next generation sequencing-based ctDNA (Signatera) assays were then developed to track ctDNA in serially collected plasma samples. ctDNA levels were expressed as mean tumor molecules per milliliter (MTM/ml) of plasma. Radiologic surveillance was performed every 3 months following surgery. The primary endpoint was a ctDNA detection rate of >70% at diagnosis. Secondary endpoints included MRD detection after local therapy and correlation of ctDNA levels with disease relapse. **Results:** A total of 140 plasma samples from 22 pts [18 male and 4 female; median age: 65 years, range: 30 – 84] were obtained. RT was preoperative in 19/22 pts. Of the 22 tumor samples, 20 had adequate tissue quality for WES to enable ctDNA assay design. Tumor histologic subtypes included undifferentiated pleomorphic sarcoma (n = 6), myxofibrosarcoma (n = 5), and liposarcoma (n = 9). A median of 7 plasma samples per patient (range: 2 – 10) were analyzed. ctDNA was detected in 80% of pts (16/20) at diagnosis, with median ctDNA level of 3.4 MTM/mL (range: 0.2 – 1393.9). Of these 16 pts, 15 (94%) became ctDNA negative at the immediate post-surgical timepoint. In addition, ctDNA was detected in 4 pts (80%) prior to or around radiologic relapse with a median lead time of 92 days. **Conclusions:** Personalized, tumor-informed ctDNA assays can detect MRD after definitive local therapy and/or prior to radiologic recurrence in patients with localized high-risk STS. As such, serial ctDNA monitoring provides prognostic value and may further identify patients that will benefit from AST treatment. Additional studies evaluating ctDNA as a predictive biomarker for AST benefit are ongoing. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology; Natera.

11511

Clinical Science Symposium

Histopathological response (HR) after neoadjuvant chemotherapy (ChT) for high-risk soft tissue sarcomas (STS): A planned analysis of the ISG-STIS-1001 trial. *First Author: Sandro Pasquali, Molecular Pharmacology, Department of Experimental Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Milano, Italy*

Background: HR after neoadjuvant ChT for high-risk STS has not been prospectively characterized and the prognostic implications remain unclear. This planned analysis of the ISG-STIS-1001 trial, which compared neoadjuvant anthracycline plus ifosfamide (AI) and a histology-tailored (HT) ChT, was aimed at characterizing HR after neoadjuvant ChT and investigating association with the risk of recurrence. **Methods:** Patients registered in the ISG-STIS-1001 study (ID: NCT01710176) were included if they had the per-protocol assessment of HR in surgical specimens. The following morphological post-treatment changes were considered: residual stainable tumor cells, necrosis, hemorrhage, sclerosis, sclerothyalinosis, and fibrohistiocytic reaction with haemosiderin. Pathologists at each study site analyzed and expressed each of these changes as a rate within each tumor. Disease-free survival (DFS), which was the trial primary end-point, was the outcome variable. **Results:** HR was assessed in 201 of 287 randomized patients (47 had re-excision, 7 did not have surgery, and 32 were not evaluable after wide excision), who were followed up for a median of 89 months (IQR 75-102 months). Presence (>1%) of stainable tumor cells (N=194, 96%) was not associated with DFS (HR=1.47, 95%CI 0.36-5.98, P= 0.591). Conversely, presence (≥ 1) of necrosis (N=169, 84%) was associated with shorter DFS (HR=3.11, 95%CI 1.36-7.14, P=0.007) and sclerothyalinosis >20% (N=42, 21%) was associated with a lower risk of recurrence (HR=0.51, 95%CI 0.28-0.94, P=0.031). These findings were confirmed when patients who had preoperative radiotherapy (N=32) were excluded. In patients randomized to AI with tumors evaluable for HR (N=98), sclerothyalinosis >20% (N=24, 24.5%) maintained the association with a lower risk of recurrence (HR=0.24, 95%CI 0.09 – 0.67, P=0.007). Finally, the prognostic value of necrosis and sclerothyalinosis for DFS held also when patients registered in the study (187/361 evaluable for HR) were selected in addition to randomized patients. **Conclusions:** This is the first study that prospectively evaluated HR after neoadjuvant ChT in high-risk STS. Previous classifications of HR were based on expert consensus and had limited prognostic relevance. In this study residual stainable tumor cells, which is often considered the most relevant post-treatment change, did not stratify patient risk, while sclerothyalinosis (>20%) singled out patients with the best outcome after neoadjuvant ChT. Clinical trial information: NCT01710176. Research Sponsor: Partially funded through a European Union grant (EUROSARC FP7 278472; A.G.) and PharmaMar (A.G.). The French sites were supported by awards to J.-Y.B. from NETSARC, LYRICAN (INCA-DGOS-INSERM 12563) and DEPGYN (RHU4).

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Clinical Science Symposium

Deep learning with whole slides images to predict histological response to neoadjuvant chemotherapy in patients with resectable high grade soft-tissue sarcomas: A multicenter study. *First Author: Benjamin Adjadj, OWKIN, Paris, France*

Background: Two recent randomized trials have confirmed the potential benefit of neoadjuvant anthracycline-based chemotherapy in patients with high-grade soft-tissue sarcomas (STS) (Issels et al 2018, Gronchi et al 2017). However, as for adjuvant chemotherapy, the main issue with neoadjuvant treatment of STS patients is the identification of predictive factors of response to chemotherapy that could avoid for a majority of patients ineffective and potentially toxic treatment with impaired quality of life. Histological response, defined as the percentage of stainable tumor cells on the surgical specimen, has been shown to be a reliable surrogate for metastasis-free survival and overall survival in bone but also in soft-tissue sarcomas (Crombe et al JCO Clin Inf 2021). Developing a tool to help medical oncologists predict the potential benefit of neoadjuvant chemotherapy prior to starting the treatment would be of great value for precision medicine in sarcomas. To address this need, we propose a deep learning-based approach to predict histological response to neoadjuvant chemotherapy patients from routine histological whole slide images sampled at diagnosis. **Methods:** A cohort of 220 patients with high grade limb and trunk wall STS enrolled in the NEOSARCOMICS study (NCT02789384, sponsor: Institut Bergonié, Bordeaux, France) was used to train a model to predict the binarized histological response from diagnostic biopsies. Responders are defined by a histological response inferior or equal to 10%. Digitized hematoxylin/eosin slides were preprocessed to segment the tissue and decompose the image into patches of smaller resolution. Features were extracted from each patch using a Vision Transformer pretrained in a self-supervised fashion on histology slides. A Multiple Instance Learning model was trained on the resulting features to compute a prediction at the patient level. The algorithm was trained and validated through a 5-fold, 5-repeat cross-validation scheme. Finally, external validation is performed on an unseen cohort from Centre Léon Bérard to assess the robustness of the model. **Results:** To predict histological response to neoadjuvant chemotherapy, a model using only diagnostic biopsies achieved an AUC of 0.69 (95% confidence interval, 0.60-0.76). External validation is ongoing and shows promising preliminary results with an AUC of 0.67 (95% confidence interval with bootstrapping, 0.45-0.89). **Conclusions:** This multi-center study demonstrates that deep-learning models can accurately predict the histological response to neoadjuvant chemotherapy from routine histological whole slide images sampled at diagnosis. This model could be used as a pre-screening tool to improve patient selection for neoadjuvant chemotherapy in STS. Research Sponsor: OWKIN.

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Poster Discussion Session

Tumor volume and T2 hyperintensity changes from DeFi: A phase 3, randomized, controlled trial of niraparic acid in patients with desmoid tumors. *First Author: Thierry Alcindor, McGill University Health Center, Montréal, QC, Canada*

Background: MRI tumor volume or T2 signal intensity changes may represent novel imaging techniques that could have a prognostic or predictive value for assessing response in desmoid tumors (DT). For example, hyperintense areas on T2-weighted images have been associated with active fibroblastic proliferation and ≥90% hyperintensity is associated with DT disease progression, whereas iso- or hypo-intense areas are associated with inactive sites of disease. In DeFi (NCT03785964), the novel gamma secretase inhibitor niraparic acid (n=70 patients) significantly improved the primary endpoint of PFS compared with placebo (n=72 patients; hazard ratio, 0.29 [95% CI, 0.15, 0.55; $P < 0.001$]) and significantly improved the secondary endpoint of ORR per blinded, independent central review (41% vs 8%; $P < 0.001$). Complete responses were achieved in 7% with niraparic acid and 0% with placebo. Here, we present an exploratory analysis of MRI tumor volume and T2 signal intensity changes in DeFi. **Methods:** Eligible adults had histologically confirmed DT that had progressed ≥20% per RECIST v1.1 within 12 months of screening. Patients were randomized 1:1 to receive niraparic acid 150 mg or placebo twice daily taken continuously in 28-day cycles. Volumetric MRI and T2 hyperintensity of the largest target tumor were evaluated at screening and every 6 cycles during the double-blind phase. MRI T2 signal intensity is represented as the ratio of hyperintensity in total tumor volume to muscle background. A blinded, independent, central radiologist reviewed all MRI scans. **Results:** Niraparic acid treatment led to more substantial reductions versus placebo in tumor volume and T2 hyperintensity ratio (Table). At baseline, similar proportions of patients in each arm had a T2 hyperintensity ratio ≥90% (95% vs 97%). This ratio changed from ≥90% at baseline to <90% at any time after baseline in 34% of patients in the niraparic acid arm and 15% of those on placebo. **Conclusions:** In DeFi, niraparic acid demonstrated substantial reduction of tumor volume and T2 hyperintensity of the largest target tumors by MRI compared with placebo in adults with DT. These results are consistent with the significant improvement in ORR achieved with niraparic acid. These data suggest that volumetric MRI and T2 hyperintensity might provide additional information in the evaluation of treatment response in DT. The prognostic or predictive value of these imaging techniques in DT should be further studied. Clinical trial information: NCT03785964. Research Sponsor: SpringWorks Therapeutics.

MRI tumor volume and T2 hyperintensity of the largest tumor.

Best % change from baseline at any time post-treatment	Median	Interquartile range (Q1, Q3)	Range (min, max)	P value
Tumor volume				
Niraparic acid (n=61)	-58.9	-84.7, -8.9	-100.0, 172.5	$P < 0.0001$
Placebo (n=61)	13.8	-26.1, 58.6	-97.8, 339.0	
T2 hyperintensity ratio				
Niraparic acid (n=53)	-55.1	-73.5, -20.8	-100.0, 517.2	$P = 0.0001$
Placebo (n=60)	-19.8	-42.9, 6.2	-88.6, 441.7	

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Poster Discussion Session

Impact of pregnancy in women with desmoid fibromatosis: An international retrospective observational study. *First Author: Marco Fiore, Sarcoma Service, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy*

Background: Desmoid fibromatosis (DF) often occurs during pregnancy/peripartum. Guidance for planning new pregnancies during active surveillance or following DF resection has been limited. Thus, we sought to evaluate outcomes and decision making in the peripartum. **Methods:** Women of child-bearing age with DF diagnosed between 2000 and 2020 were interviewed about procreation decisions, in a multicenter retrospective observational study (NCT05284305). Pregnancies simultaneous or after diagnosis were analyzed. Primary outcome was DF progression/recurrence within 1 yr postpartum. Secondary outcomes were spontaneous regression, switch to active treatment, and obstetric risks. To estimate probability of progression, a random intercept logistic model was fit to account for correlation of progression in multiple pregnancies in the same patient. **Results:** Of 483 pts interviewed, 120 (24.8%) postponed, 32 (6.6%) interrupted, and/or 232 (48%) avoided pregnancy (in 93.3%, 50%, and 72.9% of cases because of DF), respectively. 147 pregnancies in 131 pts were concurrent with or after diagnosis: 26 (17.7%, Group A) concurrent with diagnosis, 48 (32.7%, B) after DF resection, and 73 (49.7%, C) with DF on surveillance. Estimated probability of progression was 12.0% (CI 2.0 – 48.4) during pregnancy and 15.8% (5.6 – 37.5) postpartum; for pregnancies after diagnosis (Groups B and C), these rates were 5.1% (0.4 – 40.0) and 9.0% (1.8 – 35.0). On multivariate analysis, age at pregnancy and size of primary DF were significant risk factors for progression (Table). Estimated probability of spontaneous regression was 3.6% (CI 0.2–40.7) during pregnancy and 7.1% (CI 0.3 – 67.2) postpartum. 7/38 (18.4%) spontaneously regressed after pregnancy-related PD, 4/23 (17.4%) in Groups B and C. Treatment for progression was needed in 9/79 (11.4%) postpartum, in 4/63 (6.3%) in Groups B and C. Obstetric complications were comparable to population data in developed countries. **Conclusions:** After DF diagnosis, pregnancy is safe with a risk of progression of 5% during pregnancy and 9% postpartum. Treatment is needed in only 6%. Spontaneous regression is less common but occurs even after initial progression. Patients decision making about procreation appeared to be influenced by their DF diagnosis. This study supports counseling that fertility options should be fully explored with expert guidance as intervention rates are low. Research Sponsor: None.

Multivariable logistic model for progression of disease.

	OR	Lower 0.95	Upper 0.95	p-value
Age at pregnancy 38 vs 31	18.66	2.99	116.51	0.0017
Size 7 vs 3 cm	3.10	1.34	7.19	0.0084
Nr. of previous pregnancies 2 vs 0	1.56	0.28	8.67	0.6098
Pregnancy type				0.1853
A vs C	5.40	0.83	35.11	
B vs C	0.00	0.00	>10000	
Site				0.4915
Extremity vs Abdominal wall	0.92	0.11	7.69	
Intrabdominal vs Abdominal wall	11.07	0.11	1070.71	
Other vs Abdominal wall	0.27	0.02	3.44	
Hormonal stimulation before pregnancy Yes vs No	6.06	0.62	59.02	0.1209

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Poster Discussion Session

RINGSIDE phase 2/3 trial of AL102 for treatment of desmoid tumors (DT): Phase 2 results. *First Author: Mrinal M. Gounder, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: For patients with desmoid tumors (DT, aggressive fibromatosis), systemic therapy that results in tumor regression, symptom improvement and durable tolerability is needed. Gamma secretase inhibitors (GSIs) have demonstrated antitumor activity against DT. AL102 is a potent, orally available, selective GSI under investigation for treatment of DT. **Methods:** RINGSIDE (AL-DES-01) is a Phase 2/3 study for patients with progressing DT. In the open-label Phase 2 study (Part A), adults with progressing DT (≥10% unidimensional growth within 18 months or DT-related pain requiring non-opioid medication) were randomized to three dosing regimens: 1.2 mg QD, 2 mg intermittent BIW (2 days on 5 days off), or 4 mg intermittent BIW. Patients who complete Phase 2 roll over into an open-label extension (OLE). RINGSIDE Phase 3 (Part B) is a double-blind, placebo-controlled study evaluating the chosen dose regimen from Phase 2 (1.2 mg once daily) utilizing PFS as the primary endpoint. We report updated efficacy and safety results from RINGSIDE Phase 2. **Results:** Enrollment of all 42 patients into Phase 2 was completed as of March 2022. As of January 3, 2023, median time on study was 10.5 months (range 0.8 – 14.7) and 30 patients (71.4%) were still on study, 10 (23.8%) of whom rolled over to the OLE. Mean age was 39.9 years, 73.8% were women and 69% had received prior desmoid cancer therapy. The best response in the evaluable population as assessed by blinded independent central review (BICR) was partial response (PR) in 6/12 patients (50%) for 1.2 mg QD, 3/13 patients (23.1%) for 4 mg BIW, and 5/11 patients (45.5%) for 2 mg BIW. Disease control rate was 100%, 91%, and 97% in these groups, respectively. A consistent pattern of deeper, more rapid and maintained response was observed with 1.2 mg QD. Median volume change (BICR) from baseline was -51.9% for 1.2 mg QD, -9.5% for 4 mg BIW, and -15.2% for 2 mg BIW at Week 16 and -76.4%, -35.5%, and -51.2%, respectively, at Week 28. Similar patterns were observed for % changes from baseline in T2 signal intensity, suggesting reduction of tumor cellularity. Consistent with the mechanism of action of GSIs, the five most common Grade 1-2 treatment-emergent adverse events (TEAEs) were diarrhea, nausea, fatigue, alopecia, and dry skin. Grade 3 drug-related TEAEs were reported in 26.2% of patients across all tested doses. There were no Grade 4, Grade 5, or serious TEAEs related to AL102 per investigator assessment. There were no new safety signals. **Conclusions:** In this Phase 2 study, AL102 was safe and generally well tolerated across all tested doses. The safety profile was consistent with the GSI class of drugs. Tumor response, volume reduction and T2 signal reduction were observed earlier in the 1.2 mg QD group, with deeper and maintained treatment responses. This dose was selected for study in RINGSIDE Phase 3, which is currently enrolling in multiple countries. Clinical trial information: NCT04871282. Research Sponsor: Ayala Pharmaceuticals.

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Poster Discussion Session

A phase II basket trial of dual anti-CTLA-4 and anti-PD-1 blockade in rare tumors (DART) SWOG S1609: The desmoid tumors (cohort 27). *First Author: Young Kwang Chae, Northwestern University, Chicago, IL*

Background: Dual inhibition with Anti-PD-1 and anti-CTLA4 checkpoint inhibitors is efficacious in many malignancies, but their potential role in numerous rare solid cancers is yet to be established. Desmoid tumors (DT; fibromatosis) are rare tumors of the soft tissue, and the mainstay of treatment is surgery (Richard Riedel, 2022). The utility of immunotherapy in this group of patients has not been explored. This study presents the first results of ipilimumab and nivolumab used in the DT cohort (#27) of the SWOG S1609 Dual Anti-CTLA-4 & Anti-PD-1 blockade in Rare Tumors (DART) trial. **Methods:** DART is a prospective, open-label, multicenter/multi-cohort phase 2 clinical trial of ipilimumab (1mg/kg intravenously every 6 weeks) plus nivolumab (240mg intravenously every 2 weeks). The primary endpoint includes objective response rate (ORR) (RECIST v1.1) (confirmed complete (CR) and partial responses (PR)). Secondary endpoints include progression-free survival (PFS), overall survival (OS), stable disease (SD) > 6 months, and toxicity. **Results:** Sixteen evaluable patients (median age 37) with desmoid tumors were analyzed. Location of the tumors are: 8, abdomen; 3, lower limb; 2, upper limb; 2, pelvis; and 1, neck. ORR was 18.8% with 3 patients attaining PR: 40% regression with ongoing duration of response (DoR) at over 30+ months; 83% regression (PFS 16 months); and 71% regression (PFS of 8.4 months). Of note, 3 patients had SD (3/16, 18.8%) with some shrinkage of the tumors and a durable response; 23% regression with PFS of 1820+ days; 6% regression with PFS of 902 days; 1% regression with PFS of 1147+ days. Overall clinical benefit rate (CBR; no progression > 6 months) was 62.5%. The median PFS was 17.9 months, 6-month PFS 69%, 1-year PFS 62%. All patients were alive at 1 years; median OS was not assessable as 14 patients are showing ongoing survival. The most common adverse events were fatigue (43.8%, n = 7), nausea (37.5%, n = 6), hypothyroidism (31.3%, n = 5), diarrhea, hyperthyroidism, headache, and adrenal insufficiency (25%, n = 4 each). There were 8 incidents (50%) of grade 3-4 adverse events. 7 adverse events led to discontinuation. There were no grade 5 adverse events. **Conclusions:** Ipilimumab plus nivolumab in treatment of desmoid tumors resulted in an ORR of 18.8% and CBR of 62.5% with durable responses seen. This is the first prospective study demonstrating efficacy of the combination in this rare disease. Correlative studies to determine response and resistance markers are ongoing. Expanded prospective studies in desmoid tumors are needed. Clinical trial information: NCT02834013. Research Sponsor: U.S. National Institutes of Health; Bristol-Myers Squibb.

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Poster Discussion Session

Interim results of a phase II trial of first line retifanlimab (R) plus gemcitabine and docetaxel (GD) in patients (pts) with advanced soft tissue sarcoma (STS). *First Author: Evan Rosenbaum, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: GD is an alternative to doxorubicin in the front line setting in advanced STS. In the Phase I portion of this study, the PD-1 antibody R, plus GD, was generally well tolerated. We hypothesized that R+GD would be more effective than historical controls treated with GD alone. **Methods:** This is an ongoing open-label single-center study of R+GD in pts with treatment-naïve unresectable or metastatic high-grade STS. G (900 mg/m²) is administered on days 1 and 8 and D (75 mg/m²) on day 8, in 21-day cycles. R (375 mg flat dose) is administered on day 1 starting in cycle 2 and continued as monotherapy 'maintenance' after completion of 6 cycles of GD. Up to fifty pts can accrue into five histology-specific cohorts of 10 pts each. The primary endpoint is to estimate the progression-free survival (PFS) rate at 24 weeks. Secondary endpoints included safety, best overall response rate (RR) by RECIST 1.1, disease control rate (DCR), and duration of response (DOR). Subgroup analyses to evaluate all endpoints within each histology-specific cohort are preplanned. An early stopping rule for excessive toxicity will halt accrual if a prespecified severe adverse event rate is surpassed. **Results:** As of January 11, 2023, 43 pts were enrolled and treated with R+GD. The leiomyosarcoma (LMS), undifferentiated pleomorphic sarcoma (UPS)/myxofibrosarcoma (MFS), dedifferentiated liposarcoma (DDLPS), and other STS cohorts (n = 10 pts each) were fully accrued. Three of 10 angiosarcoma (AS) pts were enrolled. Median age was 59.5 (range 21 – 81) and 27 (63%) were male. Two DDLPS patients were not yet evaluable for response. Of 41 evaluable pts, the best overall RR was 22% (95% confidence interval [CI]) 11 – 38). Confirmed responses were seen in UPS/MFS (n = 4), LMS (2), AS (2), and follicular dendritic cell sarcoma (1). Three pts (LMS, ossifying fibromyxoid tumor, AS) had an unconfirmed PR, for a best RR of 29% (95% CI 16 – 46). Median PFS was 32.7 weeks (95% CI 26.4 – not estimable [NE]) and median DOR was 24 weeks (95% CI 15 – NE). Safety was evaluated in all 43 pts and the early stopping rule was not triggered. Eighteen (42%) pts had at least one Grade (Gr) 3 or 4 treatment-related adverse event (TRAE). The most common (> 5%) were anemia (16%), neutropenia (9%), febrile neutropenia (7%), lung infection (7%), and leukopenia (7%). Seven pts (16%) had pneumonitis: one Gr 1, four Gr 2, and two Gr 3. Six pts (14%) stopped treatment due to toxicity, including five with pneumonitis. **Conclusions:** The median PFS of R+GD appears promising compared to historical controls, although the primary endpoint analysis is pending completion of accrual. There was a higher incidence of pneumonitis with the combination compared to GD alone. Future studies of this combination will need to carefully consider the benefits and risks after the final efficacy and safety analyses are performed. Clinical trial information: NCT04577014. Research Sponsor: Incyte Corporation.

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Poster Discussion Session

A pilot study of lenvatinib plus pembrolizumab in patients with advanced sarcoma. *First Author: Sujana Movva, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: New treatment options are needed for sarcomas. Lenvatinib (L) is an oral, multi-tyrosine kinase inhibitor with significant inhibitory activity against VEGF receptor (VEGFR) 1-3, FGF receptor (FGFR) 1-3, KIT, platelet-derived growth factor receptor (PDGFR) alpha/beta, and RET. Experimental models suggest that L can favorably alter the tumor immune environment, and the combination of L and pembrolizumab (P) has proven to be synergistic and effective across multiple solid tumor types, providing rationale for this study. **Methods:** This is a pilot study evaluating the efficacy of L and P in select sarcomas. Patients who had at least 1 prior regimen but ≤ 3 were enrolled into one of five cohorts (n = 10 each): A: leiomyosarcoma (LMS); B: undifferentiated pleomorphic sarcoma (UPS); C: angiosarcoma and epithelioid hemangioendothelioma (EHE); D: synovial sarcoma (SS) and malignant peripheral nerve sheath tumor (MPNST); and E: osteosarcoma (OS) and chondrosarcoma (CS). Patients were treated with an initial 2-week run-in of L 20 mg orally daily. Subsequently, P was administered at 200 mg IV every 21 days. The primary endpoint for each cohort was the best objective response rate (ORR) documented by RECIST v1.1 by 27 weeks. The combination was considered worthy of further study if 2 or more responses were observed in a cohort. Secondary endpoints included progression-free survival (PFS), overall survival, duration of response, and safety of the combination. Archival tissue and on-treatment biopsies were collected. **Results:** As of January 31st, 2023, cohorts A, D and E have completed accrual. The best response in the LMS cohort was stable disease (SD). In cohort D there were 3 partial responses (PR): 2 SS; 1 radiation associated high grade MPNST. In cohort E one of 6 patients with OS had a PR. To date, of the 6 patients with angiosarcoma, there was 1 PR in a patient with adrenal primary that occurred after the prespecified 27-week timepoint. One of 5 evaluable patients in Cohort B had a PR. Among the 44 patients evaluable for safety, most common AEs were hypertension (56.8%), diarrhea (45.5%), proteinuria (45.5%), fatigue (40.9%), headache (36.4%) and nausea (36.4%). Most common ≥ grade 3 AEs were hypertension (13.6%), dyspnea (6.8%), non-cardiac chest pain (6.8%), syncope (6.8%). **Conclusions:** A signal of activity was noted in this pilot study for patients with OS, MPNST, angiosarcoma and SS. In the LMS cohort, there were no responses, and PFS was poor. Enrollment to cohorts B and C is ongoing. Clinical trial information: NCT04784247. Research Sponsor: Parker Institute for Cancer Immunotherapy, Sarcoma Foundation of America, Witherwax Fund, Linn Fund, EHE Foundation.

Cohort	Subtype	Evaluable Disease (N)	Median Age, range	% Female	Best ORR at 27 weeks, % (N)	Median PFS (weeks), (95% CI)
A	LMS	10	50 (34-70)	90	SD: 60% (6)	17.9 (6.6-23)
B	UPS	5	55 (29-72)	40	PR: 20% (1)	25.3(8.3-38)
C	Angiosarcoma	6	64 (30-74)	62.5	SD: 60% (3)	40.9 (7.1-61.3)
D	EHE SS MPNST	2 6 3	36(25-71)	44.4	PR: 33.3% (3, SSx 1, MPNST x 1)	32 (4.3-51.1)
E	OS CS	6 4	33 (18-61)	10	SD: 44.4% (4) PR: 10% (1, OS) SD: 70% (7)	20.7 (8-NR)

*1 PR after 27 weeks in a pt with angiosarcoma.

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Poster Discussion Session

SARC037: Results of phase I study of trabectedin given as a 1-hour (h) infusion in combination with low dose irinotecan in relapsed/refractory Ewing sarcoma (ES). *First Author: Patrick Grohar, Children's Hospital of Philadelphia, Philadelphia, PA*

Background: Recurrent ES carries a poor prognosis, and systemic therapies have limited efficacy. Preclinical models suggested that trabectedin (T) could achieve serum concentrations high enough to suppress the dominant oncogene of ES (i.e. EWS::FLI1 transcription factor), and that this effect is sustained by subsequent administration of low dose irinotecan (I). We conducted a phase I study of T+I in patients (pts) with ES. **Methods:** This multicenter dose escalation study employed a standard 3+3 design. T was given as a 1-h infusion on day (D)1 with low dose I intravenously on D2 and 4 of a 21D cycle. Dose limiting toxicities (DLTs) were evaluated in cycle one. Eligibility required confirmed EWS::FLI1 fusion transcript, age ≥10 years, ECOG performance status ≤2, adequate organ function and willing to have a research biopsy if safely accessible. Primary objectives were to determine the recommended dose (RD) and safety of T+I. Secondary objectives comprised efficacy of T+I and avidity of ES for 3'-Deoxy-3'-¹⁸F Fluorothymidine (¹⁸F-FLT) PET. **Results:** 20 pts enrolled from 1/2021-12/2022 across 5 sites, 5F/15M, median age 18 years (range 10-59). Pts had received a median of 4 (range 2-9) prior therapy lines including irinotecan in 60% of pts. Grade (G) 3/4 treatment-emergent adverse events (TEAEs) occurring in ≥10% of pts were: elevated ALT/AST, elevated creatinine phosphokinase, febrile neutropenia, anemia, lymphopenia, neutropenia, and thrombocytopenia. There were 2 G5 respiratory TEAEs. ¹⁸F-FLT PET scans were obtained in 5 pts. ES tumors were ¹⁸F-FLT PET avid. Dose level (DL)2 was the RD. At DL 2 and above, there were 4 PRs, 6 SD in 14 evaluable pts (Table). **Conclusions:** T+I can be safely administered to heavily pretreated pts with ES, demonstrating activity at the RD with 3 PRs (n=5 evaluable). The ¹⁸F-FLT PET may be useful to understand patterns of disease progression in ES. Correlative studies will be critical to understanding the mechanism of drug activity. Given the clinical benefit seen with T+I at RD, a phase II portion in pts with ES ≥6 years old is actively accruing. Clinical trial information: NCT04067115. Research Sponsor: U.S. National Institutes of Health; 1 Million 4 Anna; Janssen Pharmaceuticals.

Dose Level	No. Pts treated	DLTs observed	Best Response (No. of evaluable pts)
1: T=0.8 mg/m ² I=25 mg/m ²	4	-	3 PD (3)
2: T=1.0 mg/m ² I=25 mg/m ²	6	-	3 PR, 1 SD, 1 PD (5)
3: T=1.1 mg/m ² I = 25 mg/m ²	4	G4 Neutropenia G3 Thrombosis	1 PR, 1 SD, 1 PD (3)
4: T=1.0 mg/m ² I = 30 mg/m ²	6	G2 Joint Infection G3 Fatigue	4 SD, 2 PD (6)

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Poster Discussion Session

SELISARC: A Spanish Sarcoma Group (GEIS) phase I/II trial of selinexor plus gemcitabine in selected sarcoma subtypes—Results of the phase I part. *First Author: Javier Martin Broto, Fundacion Jimenez Diaz University Hospital and Health Research Institute-Fundación Jiménez Díaz University Hospital, Autonomous University of Madrid (IIS-FJD, UAM), Madrid, Spain*

Background: Selinexor (KPT-330) (S), a small-molecule inhibitor of the nuclear export mediator exportin-1 (XPO-1), is able to reduce mRNA and protein expression of DNA damage repair (DDR) gene products, being synergistic with DNA damage agents as gemcitabine (G) in preclinical experiments. We hypothesized that selinexor would have a synergistic effect with gemcitabine in selected sarcoma patients (pts). **Methods:** Adult progressing pts, ECOG 0-1, with up to 2 previous systemic therapies for advanced disease (localized unresectable/metastatic) with centrally confirmed diagnosis of undifferentiated pleomorphic sarcoma (UPS), leiomyosarcoma (LMS), alveolar soft part sarcoma (ASPS), or osteosarcoma (OS) were eligible. S (days 1, 8, 15) and G (days 1, 8) were given in four dose levels, L1: S 60 mg + G 1,000 mg/m² 30 min, L2: S 60 mg + G 1,000 mg/m² (10 mg/m²/min), L3: S 60 mg + G 1,200 mg/m² (10 mg/m²/min), and L4: S 80 mg + G 1,200 mg/m² (10 mg/m²/min). A L1 level was defined with S 60 mg + G 800 mg/m² (30 min). A classic 3+3 design was used to determine the RP2D based on DLTs observed during the first 21-day cycle. *In vitro* research was performed in LMS and OS cell lines to test the synergy of the combination (MTS and flow cytometry assays). **Results:** Between November 2020 and June 2022, 17 pts (M/F 9/8), ECOG 0/1 (14/3), median age 50 years (22-71) were recruited. The median of previous lines was 1 (1-2). Diagnosis was: 9 LMS (52.9%), 6 OS (35.3%), 1 ASPS and 1 synovial sarcoma (SS) (5.9%). Three pts were treated in each of the first 3 levels and 8 pts in L4 (2 pts were not evaluable for DLT due to improper dosing). Only one DLT was observed in L4 (G4 thrombocytopenia) and this level was selected as RP2D. G3/4 toxicity: Neutropenia (52.9%), thrombocytopenia (41.2%), febrile neutropenia (11.8%), anemia, nausea, asthenia, vomiting, alopecia, and lipase increased (5.9% each). There were 3 RECIST PR, 7 SD, and 7 PD. Median PFS for LMS was 7 months (95% CI: 3-11). No relevant clinical activity was observed in OS. *In vitro* cell viability studies shown that S+G was synergistic in the majority of LMS cell lines tested (combination index of 0.789 for CP0024, 0.791 for SK-UT-1, 0.604 for AA and 1.186 for IEC005). However, our results indicated antagonism of S+G in OS cell lines, with values for the combination index of 1.67 for MG63, 1.54 for SAOS2 and 1.23 for U2OS. Apoptosis assays by flow cytometry confirmed these observations in LMS and OS cells. **Conclusions:** At the RP2D, S 80 mg + G 1,200 mg/m² (10 mg/m²/min) is a feasible scheme with manageable toxicity. S+G has shown promising clinical activity for LMS, which warrants further investigation in a phase II. Preclinical studies shown the synergy and the antagonism of S+G in LMS and OS, respectively. Clinical trial information: NCT04595994. Research Sponsor: Spanish Group for Research in Sarcoma; Karyopharm.

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Poster Discussion Session

Multi-omic characterization of gastrointestinal stromal tumor (GIST) in a large real-world patient cohort. *First Author: Jonathan C. Trent, Sylvester Comprehensive Cancer Center, University of Miami Miller School of Medicine, Miami, FL*

Background: Molecular knowledge of GIST is limited due to its rarity, few genes have been identified as relevant determinants of outcomes, tumor evolution and therapeutic targets. Therefore, we aimed to dissect the GIST molecular landscape in the largest series of real-world patients reported to date. **Methods:** 946 GIST patient samples (536 localized, 369 metastatic, 41 unknown) underwent next-gen sequencing of DNA (592-gene, N = 495; whole exome, N = 451) and RNA (whole transcriptome, N = 592) at Caris Life Sciences (Phoenix, AZ). Gene expression signatures of proliferation (Cristescu, 2021), cell cycle activation (CINSARC; Chibon, 2010), inflammation (T-cell inflamed; Ayers, 2017) and tumor microenvironments (MCP-counter; Becht, 2016) were examined. Statistical significance tested by χ^2 , Fisher's exact, or Mann-Whitney U as appropriate. **Results:** GIST samples were comprised of 80% (N = 758) *KIT*mut, 8.1% (N = 77) *PDGFR*mut, and 11.7% (N = 111) *KIT*/*PDGFR* wild-type (WT), with 14.8% (N = 140) samples harboring a secondary *KIT* variant suggestive of TKI resistance. Overall median TMB was 2 mutations/MB (range 0-13). WT GIST were identified with mutations in *NF1* (33.7%), DNA repair genes (16.7%), *SDHX* (8.2%), *BRAF* (6.3%), and *PTEN* (1.9%), along with *NTRK3* fusions (3.1%). Primary *KIT* variants occurred in exons 11 (83.5%), 9 (13.9%), and 13 (2.6%), and secondary *KIT* variants (14.6% of total *KIT* mutations) were distributed across the ATP binding pocket (36.8%) and activation loop (63.2%). Primary *PDGFR* mutations were in exons 18 (62.4%), 12 (11.0%), 14 (4.6%) and other (16.5%). *KIT*/*PDGFR*mut GIST infrequently harbored *RB1*, *TP53*, *SETD2*, *ARID1A*, *PIK3CA*, *PTEN*, *TSC1*, *BRCA1*, or *CHEK2* co-mutations (1-5% each). Copy number amplification (≥ 6 copies) was overall uncommon ($\leq 2\%$ for all genes). Proliferation and cell cycle activation signatures were higher in *KIT* exon 11 indels v. missense mut (1.2-fold, $p < 0.05$) and *KIT* resistant v. *KIT* primary (1.2-fold, $p < 0.05$), but not in *KIT* exon 11 557/558 v. others, nor between *KIT* v. *PDGFR* v. WT subgroups. Deletion of tumor progression genes *MAX* (40.0%), *CDKN2A* (32.3%), and *DEPDC5* (33.9%) was associated with increased proliferative gene expression (1.2-, 1.3-, and 1.2-fold, $p < 0.05$ each), while *MDM2* deletion (52.5%) was not (1.1-fold, $p = 0.37$). Compared to *KIT*mut and WT GIST, *PDGFR*mut had increased abundance of several immune cell populations (range 1.2-3.7-fold, $p < 0.05$), along with enhanced inflammation signatures (1.1- and 1.2-fold, $p < 0.05$). **Conclusions:** This series provides unprecedented resolution of *KIT*/*PDGFR*mut GIST with features of clinical aggressiveness associated with *KIT* exon 11 indels and resistance mutations, illustrating a specific cytogenetic genotype with more aggressive growth and malignant behavior. Identification of less common molecular alterations that drive kinase activation and impaired DNA damage repair warrant further investigation. Research Sponsor: Caris Lifesciences.

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Poster Discussion Session

A phase I study of nanoparticle albumin-bound sirolimus (NAB-S) combined with pazopanib (PAZO) in patients with advanced soft tissue sarcoma (STS). *First Author: Lee D. Cranmer, University of Washington, Fred Hutchinson Cancer Center, Seattle, WA*

Background: NAB-S (ABI-009, nab-rapamycin) is approved for treatment of adults with unresectable or metastatic perivascular epithelioid cell tumors. Albumin binding improves sirolimus solubility and may target it to tumoral cells. mTOR inhibition may enhance PAZO activity directly and by overcoming resistance. We assess feasibility and safety of the combination. **Methods:** Eligible patients (≥ 18 y) had: advanced, unresectable, non-adipocytic STS progressing after 1-5 prior therapies; adequate end-organ function; ECOG performance status 0-1; measurable target lesions (RECIST v1.1); and no prior mTOR or angiogenesis inhibitor treatment. The study was conducted according to a 3+3 design. Initial cohorts received 800 or 400 mg PAZO daily and 60, 45 or 30 mg/m² of NAB-S on days 1 and 8 on a 21-day cycle. Subsequently, NAB-S was administered only on day 1 based on preliminary analysis of adverse events (AEs) and pharmacokinetics (PK). Primary endpoint was determination of maximally tolerated dose (MTD). Dose-limiting toxicities (DLT) were grade 3-5 adverse events (AE) during the first cycle not due to PAZO. Secondary endpoints included AE characterization (CTCAE v5.0), descriptive evaluation of responses and their duration, and correlative/PK studies. **Results:** 19 patients were treated; initially, 13 received NAB-S on days 1 and 8. DLT included thrombocytopenia (TCP, n = 7), decreased WBC/neutrophils (n = 2), increased lipase (n = 1), and proteinuria (n = 1). Due to overlapping AEs or possible NAB-S/PAZO interaction, further cohorts received 400 mg PAZO daily and either 30 or 45 mg/m² NAB-S (n = 6). There were no DLTs in the 30 mg/m² cohort (n = 3). In the 45 mg/m² cohort, 2 out of 3 patients had TCP meeting DLT definition. Grade 3-4 AEs in more than 10% included: TCP (58%), neutropenia (11%), leukopenia (11%), lymphopenia (11%), and diarrhea (11%). Any grade AEs in $> 50\%$ included: TCP (74%), mucositis (63%), fatigue (58%), and acneiform rash (53%). There was no grade 5 AEs. Of 19 treated, 11 (58%) discontinued due to disease progression, 3 (16%) due to AE (TCP-2, transaminitis-1), and 1 (5%) due to death from disease. Four (21%) remain on study as of 2/2023. 18 were evaluable for best response: 3 partial responses (PR; leiomyosarcoma, solitary fibrous tumor, spindle cell sarcoma), 13 stable disease (SD), 2 progressive disease. Clinical Benefit Rates (CBR = PR+SD) at 3 and 6 months were 72% (13/18) and 59% (10/17). Among the leiomyosarcoma subset, CBR at 3 and 6 months were 90% (9/10) and 80% (8/10). Correlative and pharmacokinetic results will be presented. **Conclusions:** Thrombocytopenia was the most prominent DLT when studying the NAB-S/PAZO combination. 3 patients out of 19 discontinued therapy due to AEs; the remainder continued therapy after adjustment. MTD and RP2D is NAB-S 30 mg/m² day 1 and PAZO 400 mg days 1-21. Preliminary evidence of activity of the combination was observed. Clinical trial information: NCT03660930. Research Sponsor: Aadi Bioscience.

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Poster Discussion Session

Clinical efficacy of avapritinib in gastrointestinal stromal tumors (GIST) with different *KIT* genotypes: Post hoc analysis of the phase 1 NAVIGATOR and phase 1/2 CS3007-101 trials. *First Author: Michael C. Heinrich, Portland VA Health Care System and OHSU Knight Cancer Institute, Portland, OR*

Background: Avapritinib, a novel *KIT*/platelet-derived growth factor receptor α (*PDGFR*) kinase inhibitor, is approved in patients (pts) with GIST harboring *PDGFR* activation loop (AL) exon 18 mutations, based on unprecedented clinical antitumor activity. Despite available treatments, there remains a great unmet medical need for pts with *KIT*-AL-mutant GIST receiving 2nd-line (2L) standard of care (SOC) sunitinib, and pts with primary *KIT* exon 9 (*KIT* 9)-mutant GIST receiving 4th-line (4L) SOC ripretinib. This post hoc analysis assessed the clinical benefit of avapritinib in pts with *KIT* mutations, especially with AL exons 17 and 18, or primary *KIT* 9 mutations. **Methods:** Tumor tissue and liquid biopsy samples were collected and analyzed to determine baseline mutational status. *KIT* molecular subgroups and outcomes were determined in pts with primary *KIT* mutations treated with oral avapritinib 300 mg once daily (starting dose) enrolled in the phase 1 NAVIGATOR (NCT02508532) and phase 1/2 (China bridging) trials (NCT04254939, CS3007-101). Pts with *PDGFR* mutations and *PDGFR*-*KIT* co-mutations were excluded. Progression-free survival (PFS) and objective response rate (ORR) were compared using Cox and logistic regression, respectively. **Results:** A total of 160 pts with *KIT*-mutant GIST were evaluated (NAVIGATOR, n = 131; CS3007-101, n = 29). At data cutoff (NAVIGATOR: March 31, 2021; CS3007-101: June 30, 2021), median follow-up duration was 22.0 months (95% CI 18.3-27.4). *KIT*-AL mutations were more frequently detected (n = 74, 46.3%) than *KIT*ATP-binding pocket (ABP) mutations (n = 34, 21.3%). Sixty pts (37.5%) had *KIT*-AL mutations without *KIT*-ABP mutations (AL^{pos}ABP^{neg} group); the remaining 100 pts were designated as *KIT* OTHERS. Across all lines of therapy, the adjusted (inverse probability weighting of baseline characteristics) median PFS (mPFS) was longer for the AL^{pos}ABP^{neg} group than for the *KIT* OTHERS group (9.1 vs 3.4 months; HR 0.47, 95% CI 0.32-0.68; $P < 0.0001$), and the ORR was higher (31.4% vs 12.1%; odds ratio 3.31, 95% CI 1.44-7.58; $P = 0.0047$). mPFS and ORR in the *KIT*AL^{pos}ABP^{neg} group were 19.3 months and 38.5%, respectively, in the 2L setting (n = 13) and 11.0 months and 36.4%, respectively, in Chinese pts (3-9 lines, n = 11). In pts with *KIT* 9 mutations in the 4L (n = 14) and > 4 L settings (n = 19), mPFS was 5.6 and 3.7 months, respectively. **Conclusions:** This post hoc analysis demonstrated significantly more robust avapritinib antitumor activity in pts with *KIT* AL^{pos}ABP^{neg} GIST versus pts with other *KIT* mutation profiles. The results suggest that avapritinib could confer meaningful clinical benefit in pts with GIST and specific *KIT* mutation types, especially *KIT*-AL or *KIT* 9 mutations. Avapritinib might be a potential 2L option for pts with *KIT*AL^{pos}ABP^{neg} GIST, and in later lines of therapy for pts with AL^{pos}ABP^{neg} or *KIT* 9 mutation profiles. Clinical trial information: NCT02508532, NCT04254939. Research Sponsor: CStone Pharmaceuticals.

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Poster Discussion Session

Overall survival and long-term safety in patients with advanced gastrointestinal stromal tumor previously treated with imatinib: Updated analyses from INTRIGUE. *First Author: Robin Lewis Jones, Sarcoma Unit, The Royal Marsden NHS Foundation Trust and Institute of Cancer Research, London, United Kingdom*

Background: Ripretinib is a switch-control tyrosine kinase inhibitor approved for patients (pts) with gastrointestinal stromal tumor (GIST) who received prior treatment with ≥ 3 kinase inhibitors, including imatinib. Sunitinib is approved for advanced GIST after imatinib failure. In the first interim analysis (IA) for overall survival (OS) in the INTRIGUE trial, data were immature (OS event rate, 22.3%), and median OS was not reached in either arm for the *KIT* exon 11 intent-to-treat (ITT) and all-patient (AP) ITT populations (S Bauer, et al. *J Clin Oncol*. 2022). Additionally, ripretinib had a more favorable safety profile with fewer grade 3/4 treatment-emergent adverse events (TEAEs) than sunitinib. Here, we present the second IA of OS and updated safety from INTRIGUE. **Methods:** INTRIGUE is a global, open-label, phase 3 study that enrolled adult pts with advanced GIST who had disease progression on or intolerance to imatinib (NCT03673501). Randomization was 1:1 to ripretinib 150 mg once daily (QD) or sunitinib 50 mg QD (4 wks on/2 wks off) and was stratified by *KIT* mutational status and imatinib intolerance. OS was a key secondary endpoint; data cutoff for the second IA was Sept 1, 2022. **Results:** Of 453 pts in the AP ITT population, 444 received treatment; 51 remain on treatment (33/223 [14.8%] with ripretinib and 18/221 [8.1%] with sunitinib). Common reasons for treatment discontinuation were progressive disease (PD) assessed by independent radiologic review (55.4%), PD assessed by investigator (10.6%), clinical PD (5.9%), withdrawal of consent (5.4%), and adverse event (AE; 4.5%); fewer pts discontinued due to an AE for ripretinib vs sunitinib (2.7% vs 6.3%). Following study treatment discontinuation, 58 pts (25.6%) from the sunitinib arm received ripretinib; 139 pts (61.5%) from the ripretinib arm later received sunitinib. There were 185 OS events (40.8%) in the AP ITT population; median duration of follow-up was 28.7 and 28.5 months for ripretinib and sunitinib, respectively. OS was similar with ripretinib vs sunitinib in the AP ITT (median 35.5 vs 30.9 months; HR 0.88, 95% CI 0.66 to 1.18; nominal $P=0.39$) and *KIT* exon 11 ITT populations (median 34.0 vs 31.5 months; HR 1.05, 95% CI 0.75 to 1.48; nominal $P=0.77$). The updated safety profile was consistent with the primary analysis; fewer pts had grade 3/4 TEAEs with ripretinib vs sunitinib (95 [42.6%] vs 149 [67.4%]). Dose interruptions and reductions were lower with ripretinib vs sunitinib. The median (range) treatment duration was 7.9 (0.2–38.2) months for ripretinib and 6.5 (0.2–38.3) months for sunitinib. **Conclusions:** In the second IA from INTRIGUE, OS was similar between treatment arms. The safety profile remained consistent with additional data, and results demonstrate favorable safety with ripretinib in pts with advanced GIST previously treated with imatinib. Clinical trial information: NCT03673501. Research Sponsor: Deciphera Pharmaceuticals, LLC.

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Poster Session

Camrelizumab in combination with doxorubicin, cisplatin, ifosfamide, and methotrexate as neoadjuvant therapy for osteosarcoma: A single-arm, exploratory phase II trial. *First Author: Qinglian Tang, Sun Yat-Sen University Cancer Center, Guangzhou, China*

Background: Tumor necrosis rate after neoadjuvant therapy is one of the strongest predictors of long-term outcome for patients with osteosarcoma. Patients with good response (tumor necrosis rate $\geq 90\%$) have a substantially better survival than those with poor response (tumor necrosis rate $< 90\%$), with 5-year overall survival of 75–80% and 55–65%, respectively. However, treatments for osteosarcoma have not yet shown much progress since the introduction of perioperative chemotherapy in 1970s. New neoadjuvant combinations are required to explore for osteosarcoma. **Methods:** In this phase II trial (NCT04294511), patients aged 14–65 years with histopathologically confirmed osteosarcoma and Eastern Cooperative Oncology Group performance status of 0–1 received three 21-day cycles of neoadjuvant regimen (camrelizumab 200 mg on day 1 of each cycle; doxorubicin 37.5 mg/m² or liposomal doxorubicin 25 mg/m² on days 1–2 of cycles 1 and 3; cisplatin 100 mg/m² on day 2 of cycles 1 and 3; methotrexate 8–12 g/m² on day 12 of cycle 1; and ifosfamide 3 g/m² on days 1–4 of cycle 2). Surgery was scheduled 12–14 days after neoadjuvant therapy. Two weeks after surgery, patients received 6 cycles of adjuvant therapy (camrelizumab 200 mg on day 1 of each cycle; doxorubicin 37.5 mg/m² or liposomal doxorubicin 25 mg/m² on days 9–10 of cycles 1, 3, and 5; cisplatin 100 mg/m² on day 10 of cycles 1, 3, and 5; methotrexate 8–12 g/m² on day 2 of cycles 1, 3, and 5; and ifosfamide 3 g/m² on days 1–4 of cycles 2, 4, and 6). The primary endpoint was good response (tumor necrosis rate $\geq 90\%$) rate after neoadjuvant therapy. **Results:** A total of 86 patients were screened and 75 patients signed informed consent from December 2019 to June 2022. By the data cutoff date on December, 2022, 8 patients did not complete neoadjuvant therapy and 2 patients refused surgery. 65 patients completed neoadjuvant therapy, one patient had disease progression before surgery, 64 received surgical resection and adjuvant therapy, and 44 completed adjuvant therapy. Thirty-one (48.4%, 95%CI: 36.6%–60.4%) of 64 patients showed good response. The most common grade 3–4 adverse events were decreased platelet count (44.0%), decreased white blood cell (37.3%), decreased neutrophil count (29.3%), oral mucositis (14.7%), increased alanine aminotransferase (12.0%), and increased aspartate aminotransferase (10.7%). **Conclusions:** Camrelizumab combined with doxorubicin, cisplatin, methotrexate and ifosfamide in the perioperative treatment of osteosarcoma patients were safe and tolerable. Postoperative good response rate was similar to previously reported results. Survival follow-up is still ongoing to analyze the effect of perioperative immunotherapy combined with chemotherapy on long-term outcomes of patients with osteosarcoma. Clinical trial information: NCT04294511. Research Sponsor: None.

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Poster Session

Two schedules of vincristine, irinotecan and temozolomide (VIT) for patients with relapsed or refractory Ewing sarcoma: A randomized controlled phase 2 trial. *First Author: Jie Xu, Peking University People's Hospital, Beijing, China*

Background: Vincristine, irinotecan and temozolomide (VIT) has provided an effective regimen in relapsed or refractory Ewing sarcoma patients. Optimal dose schedule of VIT is still undefined. **Methods:** We did this phase 2 randomized controlled trial and included patients with relapsed or refractory Ewing sarcoma. They were randomly assigned (1:1) by random number table method to either shorter dx5 schedule (Irinotecan 50mg/m²/d D₁₋₅, Vincristine 1.4mg/m² D₁) or protracted dx5x2 schedule (Irinotecan 20mg/m²/d D_{1-5,8-12}, Vincristine 1.4mg/m² D_{1,8}) together with a fixed dose of temozolomide (100mg/m²/d D₁₋₅) in both groups. Patients were treated every 3 weeks till progression or unacceptable toxic effects for up to eight cycles. The primary endpoint was objective response rate at 12 weeks (ORR_{12w}). The secondary endpoint was progression-free survival (PFS), overall survival (OS) and safety. The study was powered to detect a 30% improvement in the response rate from 20% of dx5 schedule to 50% of dx5x2 schedule ($\alpha=0.1$, $1-\beta=0.9$, one-sided test favoring dx5x2 schedule since the only difference of clinical importance was an improved response with the inconvenient schedule of dx5x2). A sample size of 30 patients per group (60 randomly assigned patients) was required to detect a significant improvement in ORR_{12w}. **Results:** Between May 21, 2020, and August 8, 2022, 24 patients were randomly assigned to dx5 schedule while 22 to dx5x2 schedule, respectively. Median follow-up was 10.7 months (IQR 9.7–13.9) in the dx5 group and 8.3 months (IQR 4.4–15.3) in the dx5x2 group. ORR_{12w} was lower in dx5 group than in dx5x2 group (5 [20.8%] of 24 patients vs 12 [54.5%] of 22; $p=0.019$). There was no significant difference in PFS between the two groups (median PFS 2.3 months [95% CI 0.0–4.7] in dx5 group vs 4.3 months [2.7–6.0] in dx5x2 group; hazard ratio [HR] 0.956 [95% CI 0.84–1.09]; $p=0.434$). Also, there was no significant difference in OS (median OS 14.8 months [95% CI 12.0–17.6] vs 12.8 months [95% CI 6.9–18.7]; HR 0.957 [95% CI 0.81–1.12]; $p=0.594$). Patients in dx5 schedule reported more grade 3 and 4 adverse events (AEs) than dx5x2 schedule, including diarrhea/abdominal pain (23 [23.7%] of 97 courses vs 8 [8.4%] of 95 courses, $p=0.005$), vomiting/nausea (6 [6.2%] vs 1 [1.1%], $p=0.035$). Other common grade 3 and 4 AE ($> 5\%$) were similar between two schedules ($p > 0.05$), including fatigue (24 [24.7%] vs 14 [14.7%]), leukopenia (6 [6.2%] vs 8 [8.4%]), neutropenia (5 [5.2%] vs 8 [8.4%]), and anemia (5 [5.2%] vs 7 [7.4%]). Unfortunately, the isolation policy of COVID-19 significantly restricted the speed of recruiting and the sponsor stopped following support to our study. **Conclusions:** Protracted dx5x2 VIT schedule showed superior efficacy and favorable tolerability compared with the shorter dx5 VIT schedule in patients with relapsed or refractory Ewing sarcoma. Clinical trial information: NCT03359005. Research Sponsor: This work was funded by Project (RDX2019-09) supported by Peking University People's Hospital Scientific Research Development Funds.

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Poster Session

PEPN1924, a phase 2 study of trastuzumab deruxtecan (DS-8201a, T-DXd) in adolescents and young adults with recurrent HER2+ osteosarcoma: A children's oncology group pediatric early-phase clinical Trial Network study. *First Author: Damon R. Reed, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL*

Background: Overall survival for patients (pts) with recurrent, unresectable osteosarcoma (OS) remains poor, and event free survival (EFS) based on historical benchmarks has been used to determine efficacy of investigational agents. HER2, a transmembrane receptor with kinase activity involved in cell signaling through the RAS pathway, is expressed in OS. T-DXd is a HER2 targeting antibody linked to DXd with preclinical in vitro studies demonstrating activity in OS correlating with the presence of HER2 expression. We report results of a Phase 2 study of T-DXd in adolescents and young adults with HER2 positive relapsed, unresectable OS. **Methods:** Pts (12–39 yrs) with relapsed, unresectable OS were eligible for screening. The most recent available tissue sample was centrally evaluated for HER2 expression by immunohistochemistry. Pts with greater than 10% of OS cells with cytoplasmic or membranous HER2 expression of any intensity were eligible to receive T-DXd at 5.4mg/kg IV every 3 wks for up to 2 yrs. The proportion of pts with an EFS at 24 wks was the primary endpoint estimated using a 9+15 Simon's optimal two-stage design assuming an unacceptable response rate of 12%, acceptable response rate of 40%, 5% type 1 error, and 90% power. **Results:** 50 pts were screened for HER2, and 41 samples met the membranous or cytoplasmic HER2 expression inclusion criteria. A single pt had an assay failure and 8 pts had tumor samples with less than 10% HER2+ cells. Nine eligible pts were enrolled (7 male) between April 15th and November 11th of 2021 and received T-DXd. 2 pts were < 18 yrs old and the median age was 19.3 years. Seven pts received 2 cycles and had progressive disease (PD) at the first evaluation. A single pt withdrew consent before the first evaluation. The final pt was event free at wk 24, meeting the protocol specified criteria for a response. With a single pt having more than 24 wks of stable disease (SD) of the 9 planned in the first stage, this study did not meet criteria to progress to stage 2. The estimated response rate is 11.1% (1-sided 95% CI LB: 0.6%). The single responder with SD for 12 cycles had 15% HER2 positive OS cells and the remaining pts had 30–100% HER2 staining. A single cycle 1 DLT of thrombocytopenia (GR4) was observed. No unexpected or at least possibly or greater related AE's were observed. Grade 3–4 at least possibly related AE's occurred in 3 of 9 patients and included nausea, vomiting, tumor hemorrhage, cytopenias ($n=3$), wound infection, and hypertension. **Conclusions:** T-DXd did not demonstrate sufficient response to expand enrollment to the planned second stage in pts with OS. None of the pts had significant HER2 membranous staining which may account for the limited efficacy. No new toxicities were observed. Further correlative studies including PK, anti-T-DXd analyses and circulating tumor DNA are ongoing. Clinical trial information: NCT04616560. Research Sponsor: U.S. National Institutes of Health.

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Poster Session

Variations in the approach to lung metastases in osteosarcoma among pediatric and adult patients. *First Author: Victoria A Wytiacz, Department of Internal Medicine, University of Michigan, Rogel Cancer Center, Ann Arbor, MI*

Background: Osteosarcoma (OS) is most common in the pediatric (ped) and young adult population but can occur at any age. Amongst other factors, older age confers a worse prognosis, and it is uncertain whether this is due to inherent biologic differences or treatment approaches. Lung-only metastases (mets) is common, and metastasectomy is performed frequently to improve overall survival. Little is known about the differences in lung-only metastatic OS and approaches to metastasectomies between ped and adult populations. **Methods:** A single-institution retrospective chart review using a free-text search engine and keywords "osteosarcoma, "lung mets" and "pulmonary mets", generated 206 patients(pts) diagnosed from 2006-2021. Eligible pts had a diagnosis of lung-only metastatic disease, resection performed at the institution and at least one year of follow-up data. Data was analyzed in two cohorts based on age at OS diagnosis: ped (age<18) and adult (age > 18 years), as well as with age as a continuous predictor. **Results:** Fifty pts (27F/23M) with lung only mets were eligible for analysis with a median follow up of 10.4 years. Median age was 23 yrs (range 6-77); 20 pts (40%) were ≤18 years old; 31 pts (16 ped, 15 adult) had an extremity primary site. Rates of metachronous (67% vs 60%) and bilateral (50% vs 40%) lung mets were similar in ped vs. adult pts, respectively. The median number of lung mets was 2 (range 1 to > 25) with 50% of patients (35) having 2-6 metastases (8 ped, 20 adult). The median size of lung metastasis was 1.2 cm (range 0.1-4.0 cm). 15 ped pts (75%) underwent metastasectomy, compared to 19 adult (63.3%) (OR 1.74, p = 0.39). Probability of metastasectomy decreased with age when used as a continuous predictor (p = 0.11). Ped pts were more likely to have an open procedure as compared to thoracoscopic (OR 12.75, p < 0.01). There was no significant difference in relapse-free survival between ped and adult pts who underwent metastasectomy (p = 0.84). Median overall survival following lung metastasis detection was 5.8 years for ped pts compared to 3 years for adult pts (p = 0.15 from Cox model). **Conclusions:** Multiple tumor and patient-specific factors affect the decision to undergo metastasectomy in lung-only OS. In our single-center study we learned that timing, pattern, and number of lung mets in ped vs. adult pts were similar, but younger pts were more likely to undergo an open procedure. Our data trended towards a lower chance of undergoing metastasectomy with older age. Larger studies are required to further understand decision-making and therapeutic outcome and a randomized study of open vs. thoracoscopic metastasectomy for lung-only OS mets is underway. In this small study, many patients with lung-only metastatic OS had long-term survival. We showed that relapse-free survival post-metastasectomy was similar in ped and adult patients. Research Sponsor: None.

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Poster Session

ALMB-0168, a novel Cx43 hemichannel agonist monoclonal antibody, for metastatic or unresectable osteosarcoma after standard chemotherapy: A multicenter, open-label, single-arm, phase 1 study. *First Author: Jingnan Shen, Department of Musculoskeletal Oncology, the First Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China*

Background: The treatment of metastatic or unresectable osteosarcoma after standard chemotherapy remains a significant clinical challenge. Connexin 43 (Cx43) hemichannel has been suggested to be a key regulator of bone homeostasis and represents a new target for bone and breast cancer. ALMB-0168, a first-in-class therapeutic antibody agonist for Cx43 hemichannel, has been shown to suppress the growth and migration of osteosarcoma and breast cancer bone metastases in preclinical studies. **Methods:** Patients ≥16 years with histologically confirmed osteosarcoma who progressed after standard chemotherapy were eligible. This study consists of accelerated titration followed by a 3+3 design with 7 planned ALMB-0168 dose levels (1, 3, 6, 12, 18, 24, and 30 mg/kg) administered intravenously once every 3 weeks and then dose expansion at the potential recommended phase 2 dose (RP2D). Primary endpoints are safety and tolerability. Adverse events are rated according to the NCI CTCAE v5.0. Key secondary endpoints are overall response rate (ORR) and disease control rate (DCR) assessed using RECIST v1.1. **Results:** As of August 21, 2022, 14 patients (10 males, 4 females) with median age 27.5 years (range 16-38 years) were enrolled; ECOG PS was 0 in 7 patients (50.0%), 1 in 6 patients (42.9%) and 2 in 1 patient (7.1%). 5 patients received ≥2 prior lines of therapy. Six dose levels (1-24 mg/kg) have been completed in this ongoing study with no dose-limiting toxicities reported. Treatment related adverse events (TRAEs) of any grade occurred in 10 (71.4%) patients and were Grade 3 in 1 patient (infectious pneumonia); no events were Grade 4 or 5. Common TRAEs (> 10%) were proteinuria (21.4%), anemia (21.4%), hematuria (14.3%), and increased aspartate aminotransferase (14.3%). No Cx43-related cardiac events or severe hepatic events were observed. A total of 13 patients were evaluable for response. ORR was 15.4% (2/13, 95% CI: 1.9-45.5%), including 2 partial responses (PR), 1 patient each at 6 mg/kg and 18 mg/kg. The patient at 6 mg/kg, who had ≥3 prior lines of therapy and lung metastases, achieved durable disease control with stable disease (SD) for 33 weeks followed by PR for 8+ weeks (at the time of analysis). The DCR was 53.8% (7/13, 95% CI: 25.1-80.8%) with 2 PRs and 5 SDs. **Conclusions:** ALMB-0168 demonstrated encouraging efficacy and tolerable safety in patients with metastatic or unresectable osteosarcoma after standard chemotherapy in a phase 1 dose-escalation trial. Dose escalation is ongoing and dose expansion will start at the potential RP2D levels. Clinical trial information: NCT04886765. Research Sponsor: Alimab Therapeutics (Shanghai) Inc.

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Poster Session

Evaluation of local control strategies on patterns of treatment failure in patients with localized ewing sarcoma treated on AEWS1031: A report from the children's oncology group. *First Author: Safia K. Ahmed, Mayo Clinic Arizona, Phoenix, AZ*

Background: To evaluate clinical characteristics and patterns of treatment failure in patients with localized Ewing sarcoma (ES) treated on AEWS1031 according to local control (LC) strategies, tumor size, and tumor site. **Methods:** AEWS1031 was a phase 3 randomized trial comparing two interval compressed chemotherapy regimens. Patients who completed LC on AEWS1031 were analyzed. LC was with surgery alone (S), definitive radiation therapy (RT), or surgery plus radiation (S+RT), and determined by the treating investigator. Local failure (LF) and distant failure (DF) were defined as recurrence at primary tumor site or distant site, respectively. Fine and Gray method was used to estimate cumulative incidence of LF and DF from time LC was completed. P-values were calculated using logrank or Gray's test, as appropriate. A two-sided p-value of ≤0.05 was considered significant. **Results:** 588 patients completed LC. Median age at enrollment was 13.0 years (range: 0.6-33.9 years). Tumor sites were categorized as extremity (230; 39%), axial (142; 24%), extraosseous (110; 19%), and pelvis (106; 18%). At diagnosis, tumor volume (TV) was ≥200 mL in 170 patients (31%) and maximum tumor dimension (MTD) was ≥8 cm in 289 patients (52%). LC was with S in 320 patients (54%), RT in 160 (27%), and S+RT in 108 (18%). Eight patients received pre-operative RT. Fifty-three patients (13.1%) who received S+RT had an R1 resection. LC with S was more likely for extremity (58%), RT for pelvis (38%) and S+RT for axial (36%) and extraosseous (34%) primary tumors (p < 0.01). With median follow up of 67.6 months from LC, the 5-year cumulative incidences of LF and DF for the entire cohort were 6.0% (95% CI, 4.3-8.3%) and 11.0% (95% CI, 8.6-13.9%), respectively. Eleven patients experienced simultaneous LF and DF. LF incidence was 5.0% for S, 8.4% for RT, and 5.6% for S+RT (p=0.47). DF incidence was 11.8% for S, 6.4% for RT, and 15.1% for S+RT (p=0.16). LF incidence by tumor site was 3.6% for extremity, 8.7% for pelvis, 7.3% for axial, and 6.8% for extraosseous (p=0.08). LF incidence was higher for primary tumors ≥200 mL (11.3%) compared to tumors < 200 mL (3.9%; p<0.01) and for tumors ≥8 cm (7.8%) compared to tumors < 8 cm (4.4%; p=0.02). Tumor size was associated with a higher LF incidence for S and RT, but not for S+RT (Table). LF incidence was 4.0% for R0, 7.5% for R1 with RT, and 16.7% for R1 without RT (p=0.02). **Conclusions:** We report the lowest LF incidence to date for prospective ES trials conducted. Both larger TV and MTD were associated with higher LF. Future investigations will aim to evaluate the impact of chemotherapy dose-intensity on LC and identify risk-stratification variables for improved LC. Five-year LF incidence by LC and tumor size. Clinical trial information: NCT01231906. Research Sponsor: U.S. National Institutes of Health.

	< 200 mL	≥ 200 mL	p	< 8 cm	≥ 8 cm	p
Surgery	2.6%	12.1%	<0.01	4.0%	6.5%	0.06
RT	6.8%	14.3%	0.07	5.1%	12.9%	0.06
S+RT	3.5%	7.1%	0.42	4.8%	5.2%	0.91

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Poster Session

ETCTN/NCI 10330: A phase 2 study of belinostat with SGI-110 (guadecitabine) or ASTX727 (decitabine/cedazuridine) for the treatment of unresectable and metastatic conventional chondrosarcoma. *First Author: Kristine Peregrino Lacuna, Columbia University Irving Medical Center, New York, NY*

Background: Conventional chondrosarcoma (cCS) is the 2nd most common primary bone tumor and is resistant to chemotherapy and radiation. *IDH1/2* mutations (m) occur in 50% of cCS. Both *IDHm* and wild-type (wt) cCS harbor epigenetic dysregulation. In preclinical models of *IDHm* and wt cCS, combination treatment with HDAC and DNMT inhibitors (i) suppressed growth *in vitro* and *in vivo* by reversing the hypermethylated state and inducing tumor suppressors, interferon response genes and apoptosis (Sheikh T, Schwartz G. Mol Cancer Ther 2021;20). **Methods:** NCI 10330 is a single-arm, multicenter, phase 2 study evaluating the HDACi belinostat (B) with the DNMTi SGI-110 (S) or ASTX727 (A). A replaced S due to drug availability (pts were replaced). Pts had advanced cCS, ECOG PS ≤ 2 and could be treatment naïve. Progression was required for grade 1 cCS. Pts received B 1000mg/m² IV + S 45mg/m² SC both days 1-5 or B (same dosing) + A (cedazuridine 100mg/decitabine 35mg) PO both days 1-5, in 28-day cycles. 1° endpoint was objective response. A Simon 2-stage design was used. If ≥ 2/13 responses occurred in stage 1, the study would proceed to full accrual. Design had 85% power with α = 0.05 to test ORR 8% vs 28%. 2° endpoints included safety, PFS and OS. A safety lead-in was performed. Paired biopsies were collected. **Results:** Stage 1 is complete. 19 pts were treated: 6 on B+S and 13 on B+A. Median age was 50 and 67 years, respectively. All pts had prior surgery. 17% (B+S) and 38% (B+A) had prior radiation. 33% (B+S) and 55% (B+A) were *IDHm*. 67% (B+S) and 75% (B+A) were histologic grade ≥ 2. There were no objective responses. Best response (at 8 weeks) was stable disease (SD) in 4/6 pts (67%) on B+S and 6/10 pts (60%) on B+A. mPFS was 4.2 mos (95% CI 1.97-NR) for B+S and 3.8 mos (95% CI 2.17-NR) for B+A. mOS has not been reached. For B+A, mPFS for *IDHm* vs wt pts was 4.7 and 3.1 mos, respectively (p=0.21). One pt with *IDHm* grade 2 cCS who progressed on FT-2102 (*IDH1*) remains on B+A > 1 year. There were no DLTs during either safety lead-in. Grade 3/4 treatment-related adverse events (TRAEs) occurred in 17% (B+S) and 69% (B+A). For B+A, the most common grade 3/4 TRAE was neutropenia (54%) and the most common all-grade TRAEs were nausea (69%), leukopenia (61%), neutropenia (54%), anemia (46%) and fatigue (46%). Paired tumor biopsies are being evaluated with whole exome sequencing, RNAseq, methylation array and multiplex IHC with results forthcoming. **Conclusions:** Combination HDACi + DNMTi was well-tolerated in advanced cCS. There were no objective responses; however, a subset of pts experienced prolonged SD with a trend towards improved mPFS in *IDHm* pts. Correlative work is ongoing with a focus on differential effects on *IDHm* tumors and whether modulation of the immune microenvironment might support combinations with immunotherapy. Support: UM1CA186689. Clinical trial information: NCT04340843. Research Sponsor: U.S. National Institutes of Health.

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Poster Session

Phase I study of the mutant *IDH1* inhibitor ivosidenib: Long-term safety and clinical activity in patients with conventional chondrosarcoma. *First Author: William D. Tap, Memorial Sloan Kettering Cancer Center, Weill Cornell Medical College, New York, NY*

Background: Chondrosarcomas (CS) are rare primary bone malignancies for which there are no approved systemic therapies. 85% of CS are the conventional subtype. Mutations in the isocitrate dehydrogenase 1 (*IDH1*) gene occur in ~50% of conventional CS. In a phase 1 study in patients (pts) with *IDH1*-mutated advanced solid tumors, ivosidenib (IVO), an oral potent inhibitor of mutant *IDH1*, demonstrated manageable toxicity (without dose-limiting toxicities), suppression of the oncometabolite 2-hydroxyglutarate at dose levels ≥ 300 mg/day, and disease control in pts with conventional CS. We report long-term safety, tolerability and efficacy of IVO in pts with conventional CS. **Methods:** In this phase I multicenter open-label dose-escalation and expansion study, IVO was administered orally (100 mg twice/day [BID] to 1200 mg once/day [QD]) in continuous 28-day cycles. Primary outcome was safety and tolerability; secondary outcomes included clinical activity (objective response rates [ORR, defined as complete response (CR) + partial response (PR)], stable disease [SD] and progression-free survival [PFS]). Adverse events (AEs) were assessed every visit and reported per the Common Terminology Criteria for Adverse Events (CTCAE version 4.03). Responses were assessed every other cycle using Response Evaluation Criteria in Solid Tumors (RECIST version 1.1). **Results:** 13 pts with advanced conventional CS were included in this analysis (data cut off 15 September 2022; women, n = 4; median age 54.0; AJCC tumor grade I [n = 2], II [n = 8], III [n = 1], unknown [n = 2]; 6 had received prior systemic therapy; received 100 mg IVO BID [n = 1], 400 mg QD [n = 1], 500 mg QD [n = 7], 800 mg QD [n = 2], and 1200 mg QD [n = 2]). Median treatment duration was 11.3 months (range: 0.5-92.6 months). Four pts (30.8%) have continued therapy for > 6 years (two of which were treated for > 7 years). Median relative dose intensity was 100%. The most frequent treatment emergent AEs (in > 4 pts; mostly grade 1/2) were diarrhea (n = 5) and nausea (n = 5). Six pts experienced grade ≥ 3 AEs. Three pts experienced serious AEs (none considered related to treatment). There were no discontinuations, dose reductions or deaths due to AEs. The ORR was 23.1%. Median duration of response was 42.5 months (range: 25.8-51.8 months). One pt with a base of the skull lesion achieved a CR (1200 mg IVO QD); two achieved PR (one 500 mg and one 1200 mg IVO QD); seven had SD (five received ≥ 500 mg IVO QD) and two had PD (both received ≥ 500 mg IVO QD). All responses occurred after > 2 years on treatment. Median PFS was 7.4 months (95% CI: 2.0-61.3). **Conclusions:** In pts with *IDH1* mutated advanced conventional CS, IVO demonstrates manageable toxicity and durable disease control including long-term responses, extending several years for a proportion of pts. Future studies are warranted to better understand the efficacy of IVO in pts with advanced conventional CS. Clinical trial information: NCT02703994. Research Sponsor: This study was supported by Agios Pharmaceuticals, Inc. Servier Pharmaceuticals LLC has completed the acquisition of Agios' oncology business.

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Poster Session

Prolonged 14-day continuous infusion of high-dose ifosfamide (14IFO) for relapsed/refractory high-grade osteosarcoma (R/R HOS): A retrospective multicenter cohort study. *First Author: Elisa Tirtel, Pediatric Onco-Hematology, Regina Margherita Children's Hospital, AOU Città della Salute e della Scienza, University of Torino, Torino, Italy*

Background: The prognosis of patients (pts) with relapsed/refractory (R/R) High-Grade Osteosarcoma (HOS) remains dismal without an agreement on systemic therapy. The use of 14IFO with an external pump in outpatient setting (1g/sqm/day x 14 days every 21) in R/R HOS pts is limited. This is the first retrospective cohort study focused on 14IFO activity and toxicity in this setting (NCT04651569). **Methods:** Five Centers of the Italian Association of Pediatric Onco-Hematology and Italian Sarcoma Group participated to the study. Primary aim is to investigate 14IFO activity in pts with R/R HOS younger than 40 years. Secondary aim is to evaluate toxicity, according to CTCAE v.5, and clinical benefit. Progression Free Survival (PFS) and Overall Survival (OS) analysis are performed using the Kaplan Meier method with 95% confidence interval (CI). **Results:** Between 2012 and 2021, 26 R/R HOS pts were treated with 14IFO (median follow-up: 17.5 months, range: 4.6 – 83 months). Median age is 19 years at the beginning of 14IFO; eleven pts (42%) are ≤ 18 years. Three pts (12%) have a localized HOS, twelve pts (46%) have pulmonary disease only and eleven pts (42%) have a pluri-metastatic HOS. Eleven pts (42%) have a relapsed HOS with a median disease-free interval (DFI) of 13 months before 14IFO, the remaining (58%) have a refractory disease to two or more treatments. Overall, thirteen pts (50%) receive 14IFO as second line therapy and fifteen pts (57%) are pre-treated with ifosfamide in first line. Disease Control Rate is 57.5% (5 Partial Response + 10 Stable Disease). Seven pts (27%) receive a local treatment after 14IFO (5 surgery, 1 Radiotherapy (RT), 1 Carbon Ion RT). The median PFS is 4.1 months (95% CI 2.13, 7.37). 6-month and 1-year PFS are 38% (95% CI 24-63) and 8% (95% CI 2-29), respectively. The median OS is 13.7 months (95% CI 10.6 – 23.7). 1-year and 2-year OS are 51% (95% CI 35-75) and 22% (95% CI 9.5-49), respectively. Relapsed pts have both longer median PFS and OS compared to pts with a refractory disease [PFS: 7.33 months vs 2.13 months (p = 0.02); OS: 19.4 months vs 10.7 months (p = 0.1)]. Sixteen pts (61%) receive at least 4 cycles and an amount of 101 cycles are evaluated for toxicity. Grade 4 hematological toxicity is reported in 15 cycles (14.8%) as follows: i) white-blood cell decrease in 6 cycles (6%); ii) neutropenia in 7 cycles (7%); iii) thrombocytopenia in 2 cycles (2%). One patient has one episode of febrile neutropenia. No grade 3-4 non hematological toxicities are reported. **Conclusions:** This trial shows a non inferiority activity of 14IFO compared to other treatments in this setting, despite the small number of pts. Therefore, 14IFO should be considered as a treatment option in R/R HOS, especially for its well tolerated toxicity profile and the home-administration that improve patient's quality of life and it could significantly reduce cancer care cost. Clinical trial information: NCT04651569. Research Sponsor: None.

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Poster Session

A phase 2 study of an anti-PD-L1 antibody (atezolizumab) in dedifferentiated chondrosarcoma. *First Author: Mohamad Adham Salkeni, Developmental Therapeutics Clinic, Division of Cancer Treatment and Diagnosis, National Cancer Institute, National Institutes of Health, Bethesda, MD*

Background: Chondrosarcoma (CS) is one of the most common bone malignancies in adults. Contrary to the indolent nature of low-grade CS, the dedifferentiated subtype (dCS), representing 5-10% of all CS, is known for aggressive behavior, high risk of relapse following resection, and poor prognosis. Expression of PD-L1 has been demonstrated in dCS samples and correlated with high numbers of tumor-infiltrating lymphocytes (Kostine, et al., Mod Pathol, 2016). Response to anti-PD1 therapy has not been evaluated prospectively. We report here the outcomes of a dCS cohort treated with the anti-PD-L1 agent, atezolizumab (atezo). **Methods:** Patients (pts) 2 years of age or older received intravenous atezolizumab 1200 mg (15 mg/kg with a 1200 mg cap in pediatric pts) once every 21 days. Prior immune checkpoint inhibitor therapy was not allowed. Primary objective was response rate (ORR). Imaging was carried out at the end of cycle 3 and then every two cycles; responses were evaluated per RECIST 1.1. The study employed a Simon two-stage design. If no responses were observed within 9 months of the ninth patient being enrolled, the cohort was to be terminated early. Research biopsies for immuno-pharmacodynamic (IO-PD) studies were collected at baseline, prior to C3D1, and optionally at progression. **Results:** Nine pts were enrolled to the dCS cohort. Three pts were female, 8 pts were White (1 unknown), all had an ECOG performance score ≤ 1 , and their median age was 63 years (range, 53-85). Primary disease sites were pelvis (2); sternum (2); femur, hip, chest, scapula, and lung (1 each). Median duration of treatment for all pts was 9 weeks. Seven pts were evaluated for response, of whom 3 (42.9%) were documented to have stable disease (SD) as best response, lasting a median of 25.9 weeks (range, 15-38.3 weeks). Four pts had a best response of disease progression. Two pts died prior to first response assessment. No RECIST objective responses were observed; the cohort was closed due to futility. Reasons for treatment discontinuation included progression (n = 6), death (1, respiratory failure unrelated to treatment), withdrawal of consent (1), and SARS-CoV-2 infection (1). Treatment-related adverse events (TrAE), grades 1-3, occurred in 7 pts (78%). Grade 3 TrAEs occurred in 2 pts (22%), included infusion reaction, myonecrosis, and anemia. IO-PD studies are ongoing to elucidate changes within the tumor microenvironment. **Conclusions:** Though objective response was not seen, atezo showed stabilization of disease in 1/3 of the patients with this aggressive tumor. IO-PD results will be critical to identify determinants of atezolizumab resistance within this dCS cohort and to identify possible partners for combination therapy. Funded by NCI Contract No. HHSN2612015000031. This project was also supported in with funding and drug supply from Genentech Inc (a member of the Roche group). Clinical trial information: NCT04458922. Research Sponsor: U.S. National Institutes of Health.

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Poster Session

Survival outcomes in pediatric patients with metastatic Ewing sarcoma who achieve a rapid complete response of pulmonary metastases. *First Author: Audra J Reiter, Ann & Robert H. Lurie Children's Hospital, Chicago, IL*

Background: Twenty-five percent of patients with Ewing Sarcoma (EWS) have metastatic disease at diagnosis, most commonly in the lungs. Our objectives were to compare overall (OS) and pulmonary disease-free survival (PDFS) between patients with metastatic EWS at diagnosis who achieve rapid complete response (RCR), defined as radiographic resolution of all pulmonary nodules at the end of induction chemotherapy, and those with residual pulmonary nodules after induction chemotherapy (non-RCR). **Methods:** This multi-center, retrospective cohort study included children under 20 years of age with metastatic EWS treated from 2007-2020 at 19 institutions participating in the Pediatric Surgical Oncology Research Collaborative. Chi-square tests were conducted for differences among groups, and p < 0.05 was considered significant. Kaplan-Meier curves were generated for OS and PDFS. Cox regression was performed for OS, controlling for whole lung irradiation (WLI), extrapulmonary metastases, and age. **Results:** Among 153 patients with metastatic EWS at diagnosis, 61 (40%) achieved RCR, and 87 (57%) did not (5 unknown). The median number of pulmonary nodules was 3.5 in the RCR vs 5 in the non-RCR groups (p = 0.02), while bilateral disease was present in 44 (72%) RCR vs 75 (86%) non-RCR patients (p = 0.03). Pulmonary relapse occurred in 58 (38%) patients, including 18 (29%) in the RCR and 36 (41%) in the non-RCR groups (p = 0.14). Factors associated with pulmonary relapse in the univariate analysis include median age [15 years (IQR: 12-17) with pulmonary relapse vs 12 years (IQR: 9-16) without (p = 0.03)] and extrapulmonary metastases at diagnosis [24 (41%) patients with pulmonary relapse vs 26 (27%) patients without pulmonary relapse (p = 0.05)]. WLI was performed in 100 patients and was not associated with a reduction in pulmonary relapse (p = 0.93). Complete surgical clearance of pulmonary disease was attempted in 29 (19%) patients, including 17 of the patients who met the criteria for RCR. On Kaplan-Meier analyses, 5-year PDFS did not significantly differ based on RCR (67%) vs. non-RCR (53%, p = 0.13), or WLI (61%) vs. no WLI (54%, p = 0.32). However, 5-year OS did vary significantly between patients with RCR and WLI (85%), RCR without WLI (55%), non-RCR with WLI (60%), and non-RCR without WLI (25%; p < 0.01). In Cox regression analysis, RCR was associated with improved OS after controlling for WLI, extrapulmonary metastases, and patient age (HR 0.51, p = 0.03). **Conclusions:** Patients with EWS who had pulmonary metastases at diagnosis had improved OS if they achieved RCR and received WLI, despite having no significant differences in rates of pulmonary relapse. Further research is needed to determine whether clearance of pulmonary disease achieved through surgical metastasectomy provides a comparable survival benefit and if any subsets of patients have a reduced risk of pulmonary relapse after resection. Research Sponsor: None.

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Poster Session

Outcomes in patients with advanced gastrointestinal stromal tumor who did not have baseline ctDNA detected in the INTRIGUE study. *First Author: Jonathan C. Trent, Sylvester Comprehensive Cancer Center, University of Miami Health System, Miami, FL*

Background: Ripretinib is a switch-control tyrosine kinase inhibitor approved for patients (pts) with gastrointestinal stromal tumor (GIST) who received prior treatment with ≥ 3 kinase inhibitors, including imatinib. Exploratory baseline circulating tumor DNA (ctDNA) next-generation sequencing (NGS) analysis from INTRIGUE showed pts with second-line advanced GIST with primary *KIT* exon 11 mutations and secondary resistance mutations exclusively in *KIT* exons 17/18 derived clinical benefit from ripretinib but not sunitinib (Bauer S et al. *J Clin Oncol*. 2023; Abs 397784). Outcomes in pts with advanced GIST with ctDNA not detected (ctDNA-ND) had not been evaluated. Here, we present exploratory data from INTRIGUE in pts who had baseline ctDNA-ND vs ctDNA detected (ctDNA-D). **Methods:** INTRIGUE is an open-label, phase 3 study that enrolled pts with advanced GIST who had disease progression on or intolerance to imatinib (NCT03673501). Pts were randomized 1:1 to ripretinib 150 mg once daily (QD) or sunitinib 50 mg QD (4 wks on/2 wks off) and stratified by mutation according to local pathology report. Baseline peripheral whole blood was analyzed by Guardant360, a 74-gene ctDNA NGS-based assay. Pts with ctDNA-D had ≥ 1 somatic alteration in the 74 genes analyzed. **Results:** Pts with ctDNA-ND (82/362, 22.7%) were younger (median: 55.5 vs 62.0 years) and had smaller sums of longest diameters of target lesions (median [range]: 57.6 [11–459] vs 108.8 [15–418] mm) vs ctDNA-D (280/362, 77.3%). Progression-free survival (PFS) was longer in pts with ctDNA-ND vs ctDNA-D and numerically higher with ripretinib vs sunitinib in pts with ctDNA-ND (Table). Pts with ctDNA-ND categorized as not having a *KIT* exon 9 mutation at randomization (*KIT* exon 11, other *KIT*/PDGFRA, or *KIT*/PDGFRA wild-type; n = 71) had longer PFS with ripretinib vs sunitinib (median not estimable [NE] vs 11 months; HR = 0.56; 95% CI 0.28 to 1.12). Objective response rate (ORR) and overall survival (OS) were higher with ctDNA-ND vs ctDNA-D. Safety was similar between groups and consistent with the primary analysis. **Conclusions:** Pts with ctDNA-ND had better efficacy outcomes vs pts with ctDNA-D in both treatment arms; PFS was numerically higher with ripretinib vs sunitinib in pts with ctDNA-ND. Although little is known about the biology driving ctDNA in GIST, these data suggest pts may have improved outcomes and different treatment sensitivity based on ctDNA detectability. Clinical trial information: NCT03673501. Research Sponsor: Deciphera Pharmaceuticals, LLC.

Outcomes by ctDNA detection.

	ctDNA-ND R vs S	ctDNA-D R vs S
Pts, n	40 vs 42	135 vs 145
mPFS, ^a months	16.6 vs 11.0	6.8 vs 6.9
HR (CI)	0.73 (0.39 to 1.39)	1.23 (0.92 to 1.64)
ORR, %	25.0 vs 26.2	19.3 vs 15.9
Response difference, % (CI)	-1.2 (-19.6 to 17.5)	3.4 (-5.5 to 12.4)
mOS, ^b months	NE vs NE	27.7 vs 29.5
HR (CI)	0.84 (0.25 to 2.75)	1.05 (0.75 to 1.47)

Data cutoff: ^aSept 1, 2021; ^bSept 1, 2022. CI, 95% confidence interval; HR, hazard ratio; m, median; R, ripretinib; S, sunitinib.

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Poster Session

Combination targeted therapy with avapritinib and sunitinib in patients with refractory gastrointestinal stromal tumors after failure of standard treatments: A small prospective pilot study. *First Author: Yanzhe Xia, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China*

Background: There is currently no standard treatment after ripretinib beyond the fourth-line setting for refractory gastrointestinal stromal tumors (GISTs). A combination of tyrosine kinase inhibitors (TKIs) is rational to be potentially effective after failure of standard therapies. The objective of this study was to explore the efficacy and safety of avapritinib plus sunitinib in refractory GISTs. **Methods:** This was a prospective cohort study in part of a real-world trial (NCT05461664) exploring avapritinib in GIST patients (pts) after failure of standard treatments. Participants received avapritinib 100–200 mg once a day (QD) combined with sunitinib 25–37.5 mg QD continuously in 28-day cycles until disease progression (PD) or discontinuation from January 2022 to January 2023. Clinical outcomes including objective response rate (ORR), survival and safety were assessed. **Results:** A total of 11 pts with a median age of 57 years were enrolled. Median follow-up duration was 4.1 months (range, 1.4–12.8 months). Median sum of target lesions was 28.2 cm (range, 6.6–47.0 cm). Four pts had primary *KIT* exon 11 mutation, 6 had exon 9 and one had exon 17, secondary mutation *KIT* exon 13 was in 2 pts, exon 14 in one, exon 16 in 2 and exon 17 in 7 pts. Seven pts received more than 4 lines of prior TKIs, three received 3 and one had 2 lines of prior TKIs. One patient (9.1%) achieved partial response (PR) with 48.7% lesion length reduction, 9 (81.8%) had stable disease (SD) with 8 out of 9 pts achieving tumor shrinkage (median sum of lesion reduction of 20.8% [range, 9.8–27.3%]), and one (9.1%) had PD according to mRECIST1.1. Eight pts (72.8%) achieved PR, one (9.1%) had SD, and 2 (18.2%) had PD according to the Choi criteria. Until last follow-up, 4 pts progressed, one withdrew from the study and one discontinued treatment after surgery. Five pts were still receiving treatment, one exceeded 1 year with 26.3% lesion reduction in the seventh line setting. Progression-free survival and overall survival results were immature. ORR and lesion reduction trended favorably in those with *KIT* activation loop (AL) mutations, but this was not statistically significant. The dose of avapritinib (100–150 mg/d) and sunitinib (25–37.5 mg/d) could be tolerated. Common adverse events (AEs) were anemia, leukopenia, diarrhea, fatigue, periorbital and face edema, and memory impairment. Common grade ≥ 3 AEs included anemia (54.5%), leukopenia (36.4%), diarrhea (36.4%), tumor hemorrhage (27.3%) and gastrointestinal hemorrhage (18.2%). **Conclusions:** The preliminary results from this study demonstrated meaningful clinical benefit with avapritinib plus sunitinib, achieving significant lesion reduction in refractory GISTs, especially those with *KIT*/AL secondary mutations. Further studies are warranted to determine the optimal dosing regimen of two targeted drugs. Clinical trial information: NCT05461664. Research Sponsor: None.

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Poster Session

Safety, pharmacokinetics (PK), and clinical activity of bezucastatinib + sunitinib in previously-treated gastrointestinal stromal tumor (GIST): Results from part 1 of the phase 3 Peak study. *First Author: William D. Tap, Memorial Sloan Kettering Cancer Center, Weill Cornell Medical College, New York, NY*

Background: Patients with GIST often relapse after first line therapy with imatinib due to secondary resistance mutations in *KIT*. As the *KIT* mutation targeting profiles of bezucastatinib (type I TKI) and sunitinib are distinct and complementary, when combined they inhibit a broad spectrum of secondary *KIT* mutations. In a prior Phase 1b/2a study (NCT02401815), the combination of the original formulation (Form. A) of bezucastatinib + sunitinib had an acceptable safety profile and was associated with clinical activity at the RP2D (Wagner, JAMA Oncol 2021;7(9):1343-50). An optimized formulation (Form. B) of bezucastatinib with improved bioavailability was developed to reduce pill burden for GIST pts. PK and safety results from the Part 1a lead-in of Peak (NCT05208047) have been previously presented (Wagner, CTOS 2022, P320). Herein we intend to report comprehensive clinical results from Part 1a including duration of therapy, initial response assessment and updated safety. **Methods:** Peak, a randomized Phase 3, open-label study, aims to evaluate efficacy and safety of bezucastatinib + sunitinib vs sunitinib in pts with imatinib-resistant or intolerant GIST. In Part 1a of the 3-part study, bezucastatinib (Form. B) dosing was escalated in serial cohorts based on PK results until the target exposure, comparable to those achieved at the RP2D established in the Phase 1b/2a study, was achieved. Key inclusion: adult with locally advanced, metastatic and/or unresectable GIST, ≥ 1 measurable lesion according to modified RECIST v1.1, and ECOG PS 0 to 2. **Results:** Part 1a enrolled 19 pts. Five pts (Cohort 1) received the starting dose of once daily (QD) bezucastatinib 300 mg+ sunitinib 37.5 mg; dose was escalated to 600 mg with 14 pts receiving bezucastatinib 600 mg + sunitinib 37.5 mg. Median age - 60 yrs (range: 42-77); 68% male; 95% ECOG PS 0-1; 95% metastatic and 5% locally advanced. As of Sept 2022 data cutoff, the median (range) treatment duration was 6 weeks (3.1, 23.9). Due to AEs, one pt required dose reduction of bezucastatinib (Gr 3 diarrhea) and 1 pt discontinued (Gr 2 rash). The majority of TEAEs were low grade, with no $\geq$ Gr4. Most common TRAEs were diarrhea (37%), neutropenia (37%), ALT (32%) and AST (26%) increases. One pt experienced SAEs of Gr 2 neutropenia and pyrexia and Gr 3 thrombocytopenia. Steady state exposure in pts receiving QD doses of bezucastatinib 600 mg + sunitinib 37.5 mg in this study were similar to that at the RP2D established in the prior Phase 1b/2a study. **Conclusions:** Initial data from Peak shows an encouraging safety and tolerability profile with no unique safety signals when compared to the known safety profile for sunitinib monotherapy. A dose of bezucastatinib 600 mg QD + sunitinib 37.5 mg QD was confirmed for use in Peak study Part 2, for which enrollment is ongoing. Updated data from Part 1a, including response data, will be presented. Clinical trial information: NCT05208047. Research Sponsor: Cogent Biosciences.

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Poster Session

Fluorine-18 fluorodeoxyglucose (¹⁸FDG)-uptake assessment of PDGFRA mutant gastrointestinal stromal tumors (GIST): A retrospective multicenter Italian study. *First Author: Maria Concetta Nigro, Oncology Unit, Department of Medical and Surgical Sciences (DIMEC), University of Bologna, Bologna, Italy*

Background: D842V PDGFRA mutation identifies a molecular subtype of GIST, primarily resistant to imatinib and characterized by higher indolent behavior and a prominent immune profile. Although functional imaging with ¹⁸FDG-PET plays a proven role in GIST, especially in early assessment tumor response, less is known about ¹⁸FDG-uptake according to the GIST molecular subtypes. Taking into account of clinical and molecular features of D842V mutant GIST, we assumed that this subset of GIST could also have a different ¹⁸FDG-uptake. Therefore, the aim of the present study has been to investigate the degree of FDG uptake of PDGFRA mutant GIST, focusing on D842V ones, in order to better define the role of functional imaging in this rare and peculiar subset of GIST. **Methods:** Patients with PDGFRA mutant GIST underwent ¹⁸FDG-PET were retrospectively included from seven GIST Italian reference centers. Data on maximum standardized uptake (SUVmax) value of primary tumor or metastatic disease were collected. **Results:** 71 patients have been included: 37 (55.1%) with D842V PDGFRA mutant GIST (group A) and 34 (47.9%) with PDGFRA non-D842V mutant GIST (group B). Additionally, 30 patients with exon 11 *KIT* mutant GIST have been included, as control (group C). SUVmax values were obtained from primary tumor and metastatic lesions in 55 (54.4%) and 46 (45.6%) patients, respectively. Considering the whole population of 101 patients, the global median SUVmax was 3.7 (IQR 0-9.1), while the median SUVmax for group A, B, and C was 0, 3.6, and 10.4, respectively. The median SUVmax of PDGFRA mutant GIST was significantly lower than the median value of exon 11 *KIT* mutant GIST (p < 0.001). Notably, median ¹⁸FDG-uptake was significantly lower in D842V PDGFRA mutant GIST compared to PDGFRA non-D842V mutant ones (p = 0.021). **Conclusions:** PDGFRA D842V-mutant GIST present an overall lower ¹⁸FDG uptake compared to other GIST subgroups. This feature could be related to their specific molecular background and is consistent with their higher tendency to an indolent behavior. Therefore, the role of functional imaging with ¹⁸FDG-PET in this subset of GIST is limited. Finally, the prognostic value of the ¹⁸FDG-uptake degree within all PDGFRA mutant GIST will be investigated in the future. Research Sponsor: None.

11540

Poster Session

Antitumor activity of olverembatinib (HQP1351) in patients (pts) with tyrosine kinase inhibitor (TKI)-resistant succinate dehydrogenase (SDH)-deficient gastrointestinal stromal tumor (GIST). *First Author: Haibo Qiu, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University Cancer Center, Sun Yat-sen University, Guangzhou, China*

Background: Treatment of pts with GIST has been transformed by TKIs. However, treatment resistance is a challenge in managing locally advanced or metastatic disease. Pts with SDH-deficient GIST typically present with multifocal and multinodular disease that is insensitive to most TKIs. Olverembatinib is an investigational novel, potent, orally active third-generation TKI with promising activity against GIST in multiple preclinical models. **Methods:** The aim of this study was to evaluate the safety and efficacy (per RECIST v1.1) of olverembatinib in pts with TKI-resistant metastatic SDH-deficient GISTs (confirmed by immunohistochemistry). Olverembatinib was administered orally once every other day (QOD) in 28-day cycles. **Results:** As of January 15, 2023, 20 pts with SDH-deficient GIST had received ≥ 1 dose of olverembatinib (median age, 30 [14-56] years), and 19 had received 1 to TKIs (50% of pts ≥ 3 ; Table). The dose range of olverembatinib was 20 to 50 mg (50 mg cohort [n = 6]; 40 mg [n = 8]; 30 mg [n = 6]). The median (range) treatment duration was 7.8 (1.81-42.3) months. A total of 5 of 20 pts experienced partial response (PR) as the best response. Of 16 evaluable pts treated with > 4 cycles of olverembatinib, the clinical benefit rate (CBR; complete response + PR + stable disease > 4 cycles) was 93.8% (15/16); the longest treatment duration was 42 months. All pts experienced treatment-emergent adverse events (AEs; most, grade 1 or 2); 2 pts experienced grade 3 AEs; the only hematologic AE with an incidence rate $\geq 20\%$ was anemia (55%). A total of 15 (75%) pts experienced treatment-related AEs (grade 3 neutropenia [n = 1]). No treatment-related serious AEs were reported. **Conclusions:** Olverembatinib was well tolerated up to 50 mg QOD and showed antitumor activity in pts with TKI-resistant, SDH-deficient GIST. A total of 5 PRs were reported among 20 evaluable pts and 15 SDs among 16 pts treated for ≥ 4 cycles (98.3% CBR). These promising findings warrant further investigation. Internal study identifier: HQP1351SJ003. Clinical trial registration: NCT03594422. Research Sponsor: Ascentage Pharma Group.

Baseline characteristics.	
Characteristics	No.
Median age (range), y	30 (14-56)
Male, no. (%)	6 (30)
Primary tumor site, no. (%)	
Stomach	20 (100)
Prior TKI, no. (%)	
0	1 (5)
1	6 (30)
2	3 (15)
≥ 3	10 (50)

11542

Poster Session

Longitudinal follow-up and outcomes of pediatric and adult patients with SDH-deficient GIST. *First Author: Urania Dagalakis, Pediatric Oncology Branch, Center for Cancer Research, Bethesda, MD*

Background: Gastrointestinal stromal tumor (GIST) are gastrointestinal non-epithelial neoplasms most commonly driven by somatic mutations in *KIT* or *PDGFRA*. Approximately ten percent of GIST are due to germline mutations in *SDHx* or epigenetic loss of expression of *SDHC*. While *KIT* and *PDGFRA* driven GIST respond to treatment with tyrosine kinase inhibitors, effective systemic therapies for SDH-deficient GIST have not yet been identified. SDH-deficient GIST are indolent tumors that typically progress slowly over time. A better understanding of the natural history of patients with these neoplasms is critical to identify effective treatments and improve patient care. A cohort of patients with SDH-deficient GIST is followed at the NIH Clinical Center and through the NIH Pediatric and Wild-type GIST Clinic. The aim of this study is to characterize the long-term outcome of this cohort of patients. **Methods:** Data from patients with SDH-deficient GIST enrolled in a study Natural History and Biospecimen Acquisition for Children and Adults with Rare Solid Tumors (NCT03739827) from January 2019 through January 2023 at the NIH were evaluated. In addition to review of medical records and imaging, when available, tumors were characterized by sequencing of *SDH* genes. Germline analysis of *SDH* genes was offered to consenting patients and families. **Results:** Clinical information and specimens were collected from 77 GIST patients (median age at diagnosis 21.5, [range 7-57] years; 72.7% (56) female, 21.3% (21) male) were classified by molecular subtypes: 33.8% SDHC epimutation, 28.6% SDHA, 22.1% SDHB, 14.3% SDHC and 1.3% SDHD. Median age at presentation of SDHC epimutation was younger (14.5 years, range: 8-56) when compared to SDHA (27.5 years, range: 7-55), SDHB (22 years, range: 8-54), SDHC (18 years, range: 10-57) and SDHD (39 years, N = 1). Most commonly, patients had at least one surgery (55.8%) while a lower proportion had four or more (7.8%). Primary tumors occurred in the stomach with 26% having metastases at presentation the most common location being the liver (10.4%). Overall, 64.9% of patients were treated with imatinib, 39% were treated with sunitinib and 15.6% received other additional systemic therapies. Within the cohort there were 13% of patients with paragangliomas and 6.5% with chondromas while only 9.1% had a family history of GIST. **Conclusions:** Longitudinal follow-up of an SDH-deficient GIST patient cohort will allow for better understanding of the natural history including treatment history and survival of patients with this rare disease and will help to optimize strategies for treatment and follow-up of these patients. Research Sponsor: U.S. National Institutes of Health.

11541

Poster Session

Clinical utility of liquid-based comprehensive genomic profiling (CGP) in gastrointestinal stromal tumors (GIST). *First Author: Lindsey Hildebrand, Boston Medical Center, Boston, MA*

Background: GIST is the most common mesenchymal cancer of the digestive tract. Beyond surgery, treatment for GIST focuses largely on tyrosine kinase inhibitors (TKI), whose selection and potential resistance depend on select mutations. We present the molecular landscape of GIST utilizing tissue and liquid biopsies with emphasis on the clinical utility of liquid biopsy in advanced GIST. **Methods:** Liquid (FoundationOne Liquid CDx [F1LCDx]) and tissue (FoundationOne CDx) CGP was performed by hybrid capture, targeted NGS at Foundation Medicine Inc. Tissue and liquid samples from 2,198 and 147 patients, respectively, were analyzed. A cohort of 27 paired tissue and liquid samples were also evaluated. The levels of circulating tumor DNA (ctDNA) in liquid biopsies was quantified by tumor fraction (TF), with a TF algorithm incorporating aneuploidy, variant allele frequency, and canonical alterations detected on F1LCDx. **Results:** Tissue CGP (n = 2,198) revealed the following prevalence of primary driver alterations: *KIT* (77%), *PDGFRA* (8%), *NF1* (6%), *SDHAB/C/D* (SDHx, 3%) and *BRAF* (1%). Rates of molecular markers previously associated with worse prognosis included: *CDKN2A* (29%), *RB1* (9%), *TP53* (6%) and *SETD2* (4%). 7% of cases had no reportable known pathogenic alterations in canonical GIST genes (wild-type GIST), while 2% of cases had a mutation in more than one driver. In a cohort of 147 liquid biopsies, TF was $< 1\%$ in 68.0%, 1-10% in 18.4%, $> 10\%$ in 13.6% of samples. In samples with elevated TF ($> 10\%$), the prevalence of targetable driver alterations in *KIT* (89%), *PDGFRA* (4%), *NF1* (4%) and *BRAF* (4%) was comparable to the tissue prevalence. In liquid, 58% (39/67) of samples with a *KIT*-driver mutation had a co-occurring imatinib-resistant *KIT* alteration. In addition, 4/147 patients (3%) were predicted to harbor a germline *KIT* mutation, including one patient (0.6%) with a potential imatinib-resistant *KIT* D820G germline mutation and another with clinical suspicion of germline *KIT* L576P mutation due to the presence of multiple primary GISTs, hyperplasia of myenteric plexus and dysplastic skin nevi. In paired tissue/liquid samples, liquid detected 2/2 driver mutations found in tissue when liquid TF was $> 10\%$, and 5/6 in specimens with TF $> 1\%$. In the overall cohort, the relative prevalence of *KIT* exon 9 and 11 driver alterations was comparable in tissue vs liquid, while imatinib-resistance *KIT* exon 13 and 17 mutations were enriched in liquid samples. **Conclusions:** Known driver and TKI-resistant mutations of both somatic and potential germline origin are identified in peripheral blood ctDNA of GIST patients. Liquid biopsy shows high concordance to tissue in identifying driver mutations in the presence of elevated TF and may exhibit TKI-resistant specific alterations. This study indicates that liquid biopsy may be useful in the molecular classification of GIST during the medical management of advanced GIST patients. Research Sponsor: Foundation Medicine, Inc.

11543

Poster Session

Efficacy and safety of ripretinib in Chinese patients with advanced gastrointestinal stromal tumors (GIST) as ≥ 4 th line therapy: Long-term update from a single-arm, phase 2 trial. *First Author: Jian Li, Peking University Cancer Hospital & Institute, Beijing, China*

Background: In INVICTUS study (NCT03353753), ripretinib as ≥ 4 th line (4L) GIST therapy significantly improved median progression-free survival (mPFS) versus placebo (hazard ratio 0.15, 95% confidence interval [CI] 0.09-0.25; mPFS 6.3 vs 1.0 months) with a satisfactory safety profile. In the primary analysis (data cut-off: 26 Feb 2021) of the bridging study (NCT04282980) of INVICTUS, ripretinib as ≥ 4 L therapy showed consistent efficacy and safety profiles in Chinese GIST patients to those in INVICTUS, with mPFS of 7.2 months and objective response rate (ORR) of 18.4% (7/38 patients). The overall survival (OS) data was immature at the primary analysis. Here we report the long-term updates of this bridging study. **Methods:** Patients received ripretinib 150 mg once daily continuously in 28-day cycles until progressive disease or other protocol-specified events for treatment discontinuation. The primary endpoint was progression-free survival (PFS) by independent radiologic review (IRR) using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 GIST-Specific Standard. Secondary endpoints included ORR by IRR, time to best response (TBR), duration of response (DOR), OS and safety. Adverse events were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events v4.03. **Results:** Overall, 39 patients were enrolled. Thirty-eight patients received continuous ripretinib treatment and were included in the efficacy analysis set. All 39 patients received at least one dose of ripretinib and were included in the safety set. The updated data cut-off was 23 Aug 2022. The overall median follow-up (90% CI) was 23.00 (11.99, 24.87) months. In the efficacy analysis set, mPFS (90% CI) by IRR was 6.44 (2.89, 8.31) months and ORR was 21.1% (8/38 patients). Median TBR and median DOR for the 8 patients with confirmed partial response were 2.25 and 8.57 months, respectively. The median OS (95% CI) in the efficacy analysis set was 25.56 (11.73, not evaluable) months. In the safety set, 20.5% of patients experienced ≥ 1 grade 3/4 treatment-related treatment-emergent adverse events (TRAEs). Compared to the primary analysis, the increase in TRAEs and new TRAEs leading to dose modification were minimal after 18 months of additional follow-up. **Conclusions:** After long-term follow-up, the more mature results continued to support the clinically meaningful benefit in PFS and also demonstrated clinically meaningful benefit in OS in Chinese ≥ 4 L GIST patients, while the safety profile remained satisfactory. Clinical trial information: NCT04282980. Research Sponsor: Zai Lab (Shanghai) Co., Ltd.

11544

Poster Session

Exploratory novel biomarker and resistance mechanism of milademetan, an MDM2 inhibitor, in amplified MDM2 intimal sarcoma from an open-label phase 1b/2 trial (NCC1806/MK004). *First Author: Takafumi Koyama, Department of Experimental Therapeutics, National Cancer Center Hospital, Tokyo, Japan*

Background: Amplified *Murine double minute 2 (MDM2)* is found in > 70% of intimal sarcoma, known as one of the ultra-rare sarcomas. Milademetan (DS3032, RAIN-32) is a novel, specific, small-molecule MDM2 inhibitor that disrupts MDM2 and the tumor suppressor protein p53 interactions in tumor cells. We conducted a phase 1b/2 trial (Trial registration No: JMA-IA00402) in patients with amplified *MDM2* wild-type *TP53* intimal sarcoma as a sub-study under the nationwide large registry for rare cancers in Japan (MASTERKEY Project). Eleven patients were enrolled, and ten were included in the efficacy analysis. Two (20%) patients had durable responses for > 15 months. Milademetan provided clinical benefits in patients with amplified *MDM2* intimal sarcoma. Predictive biomarkers other than amplified *MDM2* and acquired resistance mechanisms for milademetan are unknown. **Methods:** Whole-exome and RNA sequencing analyses of pre-treatment tissue samples were conducted to identify determinants of response. Genomic alterations were analyzed for 10 patients, and gene expression was analyzed for 9 patients using their pre-treatment tissue samples. Targeted sequencing of cell-free DNA (cfDNA) samples (liquid biopsy) was also conducted sequentially at three points [before treatment with milademetan (baseline), at Cycle 2 Day1, and at the time of disease progression] to identify determinants of response and resistance. **Results:** From whole-exome and RNA sequencing analyses of pre-treatment tissue samples, we could not find any molecular pathways associated with the anti-tumor activity of milademetan. Focusing on 8 genes (*CDK4*, *CDKN2A*, *CDKN2B*, *EGFR*, *ERBB3*, *MDM2*, *PDGFRA*, *TP53*) known to be frequently altered in intimal sarcoma and 10 genes (*AKT1*, *ATM*, *BBC3*, *CDKN1A*, *CDKN1C*, *CHEK2*, *MDM4*, *PMAIP1*, *PPM1D*, *TP53*) reported to be associated with MDM2 inhibitor responses; we found that anti-tumor activity correlated with amplified *TP53* (p -value = 0.028) and negatively with *CDKN2A* loss (p -value = 0.071). Eight of the 10 patients had their cfDNA collected sequentially at baseline, at Cycle 2 Day1 and disease progression; however, one did not consent to the exploratory analysis study using cfDNA, and one had cfDNA collected at baseline but not at disease progression due to ongoing treatment. Of the eight patients, *TP53* mutations in cfDNA were detected in one and five patients at baseline and disease progression, respectively. The cfDNA allele frequency of *TP53* mutations increased with disease progression. **Conclusions:** *CDKN2A* loss and amplified *TP53* could be associated with the anti-tumor activity of milademetan in patients with amplified MDM2 intimal sarcoma. Acquired *TP53* mutations were detected in sequential liquid biopsies as loss-of-function mutations, and these *TP53* mutations might compromise the anti-tumor activity. Clinical trial information: JMA-IA00402. Research Sponsor: None.

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Poster Session

Alternative splicing (AS) regulation as a novel therapeutic target in soft-tissue sarcoma (STS). *First Author: David Silva Moura, Health Research Institute-Fundación Jiménez Díaz University Hospital, Autonomous University of Madrid (IIS-FJD, UAM), Madrid, Spain*

Background: There is an urgent clinical need to identify novel treatments for advanced STS, since all the clinical trials testing chemotherapy combinations have failed to improve survival compared to doxorubicin (dox) alone. AS deregulation has been associated with cancer initiation, progression and resistance to therapy. This deregulation can occur due to mutations or imbalanced expression or activity of splicing factors (SF). The alteration SF can alter thousands of pre-mRNAs, increasing cellular complexity and facilitating tumour progression. CDC-like kinases (CLK) that phosphorylate serine-arginine-rich SF (SRSFs), are key regulators of AS. SM09419 is an oral pan CLK/DYRK inhibitor that has been shown to inhibit SRSF phosphorylation, selectively modify spliceosome activity and decrease tumour growth by multiple mechanisms including the downregulation of Wnt/ β -catenin signalling, a pathway that we reported to be important in sarcoma. **Methods:** A panel of 9 STS cell lines, including LMS (CPO024, IEC005, AA, SK-UT-1), LPS (93T449), synovial sarcoma (MCP037) and UPS (MCP016, MCP021, MCP025) were used to analyse the effect of SM09419 (provided by Biosplice) or PRI-724 (Wnt/ β -catenin inhibitor) on cell viability (MTS assays). TOP flash β -catenin/TCF-responsive reporter assay was performed to evaluate the inhibition of the Wnt/ β -catenin pathway in response to SM09419. *In vivo* experiments tested the combination of SM09419 (25mg/kg 5 days on and 2 off, for 21 days cycle) plus IP dox (5mg/kg once a week for 21 days cycle) in LMS (IEC005) and synovial sarcoma (FJD-SS-001) PDX models. **Results:** Our results showed that SM09419 had superior activity in STS cells compared to specific Wnt/ β -catenin inhibitors with IC_{50} values starting at 29.8 nM in SK-UT-1 cell line, whereas PRI-724 IC_{50} values were clearly higher, starting from 5.18 μ M in 93T449 cells. SM09419 treatment significantly inhibited the transcriptional activity of β -catenin by 40% in the MCP021 cells, demonstrating the regulatory activity of AS inhibitors on this pathway. *In vivo* studies confirmed the higher efficacy of SM09419 in monotherapy compared to dox, in inhibiting tumour growth ($p < 0.05$), which was potentiated when combined with dox. The combination was increasingly active in synovial sarcoma with tumour regressions in 3 out of 4 mice, including one complete response. Treatment schedule was adapted to a single IP administration of dox (5mg/kg) and 5 administrations of SM09419 (25mg/kg), to improve the tolerability of the combination. **Conclusions:** The effects of pan CLK/DYRK inhibition on growth and survival of STS cancer cell lines and PDX models, indicate that can STS may be therapeutically addressed with these AS-modulators. The combination of SM09419 with dox was active in STS preclinical models known for their resilience toward treatment. Based on these results, the exploration of such combinations in clinical trials is warranted. Research Sponsor: Foundation AECC - GEACC19007MA.

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Poster Session

Large versus limited molecular profiling panel screening program in patients with metastatic sarcoma: An exploratory subgroup analysis from the Profiler 02 trial. *First Author: Mehdi Brahmi, Centre Léon-Bérard, Lyon, France*

Background: Profiler 02 (NCT03163732) is a multicentre, randomized molecular screening clinical trial aiming to evaluate the feasibility and the benefit of a large NGS (Next-generation sequencing) panel (FoundationOne Medicine NGS panel or FOne, 324 cancer-related genes) compared to a limited one (Control panel or CTRL, 87 cancer-related genes) in terms of clinical, quality of life and health economic outcomes. We present here the results of the patients with advanced/metastatic sarcoma included in the Profiler 02 trial. **Methods:** Patients (pts) were enrolled during their first-line of standard therapy for an advanced sarcoma. All sarcomas diagnosis were performed within the RRePS network (French pathology network of reference for sarcomas) and a central pathological review confirmed if quality and quantity of material were acceptable for molecular analysis. Patients were randomized within the two study arms (FOne versus CTRL) and DNA was analysed using both panels. The primary objective of the study was to compare the proportion of patients for whom a genomically driven recommended therapy (RT) could be initiated based on the FOne versus CTRL panels. A dedicated Molecular Tumour Board (MTB) reviewed tumour genomics data of both panels independently to propose a RT. **Results:** From January 2018 to July 2019, 39 pts with sarcoma (20F, 19M), with a median age of 54 years [21-81], were randomized between FOne Arm (17 pts) and CTRL Arm (22 pts). Pathological subtypes per arm are presented in the table. Overall, 19 pts (49%) had at least one genomically driven RT, 11 according to both panels and 8 according to FOne panel exclusively (McNemar's test, $p=0.01$). Main RT were CDK4/6 inhibitors ($n=5$), PI3K/AKT/mTOR inhibitors ($n=4$), and immunotherapy ($n=4$). After the MBT, a RT was initiated for seven patients, four according to FOne panel only and three according to both panels. Importantly, a complete response was observed for a metastatic MPNST (Malignant Peripheral Nerve Sheath Tumor) with a high tumour mutational burden (TMB) detected by the FOne panel (37 mutations per megabase) and treated with durvalumab (anti-PDL1) + tremelimumab (anti-CTLA4). **Conclusions:** Although from an exploratory subgroup analysis, these results suggest that a large molecular profiling panel including TMB (FOne panel) might increase the number of RT and the number of sarcoma patients treated. Studies of precision medicine in rare cancers such as sarcomas are feasible, this approach could benefit to patients. Clinical trial information: NCT03163732. Research Sponsor: LYRICAN (INCA-DGOS-Inserm_12563), NetSARC (INCA & DGOS), InterSARC (INCA), LabEx DEVweCAN (ANR-10-LABX 0061), PIA Institut Convergence Francois Rabelais PLAScan (PLAScan, 17-CONV-0002) and EURACAN (EC 739521); ARC, La Ligue contre le Cancer; Roche.

Pathological subtypes distribution.

Pathological subtype	N	FOne Arm	CTRL Arm
Leiomyosarcoma	14	8	6
Undifferentiated pleomorphic sarcoma	9	4	5
Rhabdomyosarcoma	3	1	2
MPNST	3	0	0
Osteosarcoma	3	3	0
Malignant phyllode tumor	2	0	2
Extraskeletal myxoid chondrosarcoma	1	1	0
Synovial Sarcoma	1	0	1
Myxofibrosarcoma	1	0	1
Angiosarcoma	1	0	1
CIC-rearranged sarcoma	1	1	0
Total	39	17	22

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Poster Session

Novel genomic alterations and transcriptomic-based tumor microenvironment classification of sarcoma and their impact on treatment decision making. *First Author: Irina Zhuk, BostonGene, Corp., Waltham, MA*

Background: Sarcomas are rare tumors of mesenchymal origin, with over 50 different histological sarcoma subtypes. The heterogeneous molecular and immunologic characteristics of sarcomas present many challenges for diagnostics and treatment plans. We aim to provide a more comprehensive molecular testing and immune profiling of sarcoma patients. **Methods:** The cohort consisted of samples from 200 patients diagnosed with sarcomas. WES and whole transcriptome analysis were performed on all samples. Tumor Portrait test identified genomic alterations of sarcomas and classified tumor microenvironment (TME) subtypes. The actual response to immune checkpoint inhibitor (ICI) treatment was determined using RECIST criteria and compared to response predictions by the Tumor Portrait test. **Results:** Across sarcoma subtypes, the most common mutations were in tumor suppressors including *TP53*, *RB1*, *CDKN2A*, and *TSC1/2*. We report fusions in 20.5% of cases, with commonly described diagnostic fusions accounting for 34/41 cases. In one case, the detection of the *ZC3H7B-BCOR* fusion suggested a change in diagnosis from uterine leiomyosarcoma to endometrial stromal sarcoma. Several previously unreported fusions were detected, including potentially targetable (*ARID1A-NUDC*, *MICAL3-MAPK*) and prognostic (*YWHE-CIC*) fusions. DNA damage response related genes were mutated in 12% of cases. Other less commonly detected targetable alterations were found in the following genes: *MDM2*, *CDK4*, *SMARCB1*, *NF1*, *PIK3CA*, *NTRK1-3*, *FGFR1-4*. Transcriptomic-based TME classification found that 52% of patients had an Immune-Enriched (IE) TME, with 26.5% and 25.5% grouped in the IE-Fibrotic and IE-non-Fibrotic subtype, respectively, which we previously showed is associated with good response to ICI treatment. In contrast, 48% of the patients presented with a Fibrotic (F, 30%) or Desert (D, 18%) subtype, are predicted to have a poor response to ICI treatment. Our classification of sarcomas based on TME subtypes conforms well with predicted responses of tumors to ICI therapy found in previous reports. Soft-tissue angiosarcomas, undifferentiated pleomorphic sarcoma, and myxofibrosarcomas presented TMEs of the IE subtype in 75% of cases, significantly more compared to 34% of the bone neoplasm cases, which are known for their favorable and unfavorable response to ICI therapy, respectively (Chi-squared test, $p = 0.001$). In retrospective chart review, we had response data on 24 patients who received ICI treatment. The disease control rate, defined as CR+PR+SD as best response, was significantly higher in the IE subtype compared to the F/D subtype (85.7% vs 20%, Chi-squared test, $p < 0.003$). **Conclusions:** Together, our findings identify actionable and diagnostic alterations in diverse mesenchymal tumors and suggest that ICI treatment may be beneficial in immune-enriched sarcomas. Research Sponsor: BostonGene Corporation.

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Poster Session

Next generation sequencing reveals targetable mutations in multiple sarcoma histologies. *First Author: Rodney Dixon Dorand, Vanderbilt-Ingram Cancer Center, Nashville, TN*

Background: Sarcomas are a rare and heterogeneous group of cancers that arise from bone or soft tissue, and two thirds have poorly defined mutational profiles. Given their rarity, few comprehensive studies have fully characterized mutations and gene expression across sarcoma histologies correlated with clinical outcomes. Further studies are needed to determine the presence of targetable mutations that may improve patient outcomes. In this study, we explored the genomic landscape and clinical actionability of sarcoma mutations from patients enrolled in our CAUSAL (Cohort to Augment the Understanding of Sarcoma survivorship Across the Lifespan) study. **Methods:** Between 04/01/2022 and 01/01/2023, 481 participants, treated from 2012 – present with multiple sarcoma histologies were enrolled on CAUSAL. Next Generation Sequencing (NGS) was performed on primary or metastatic tumors from 76 patients to determine DNA mutations within a 648 gene panel. Whole transcriptome RNA sequencing (seq) provided expression profiles and RNA fusion products. Further analysis was performed using principal components analysis of RNA seq data to explore correlates amongst sarcoma subtypes. Tumor mutations were queried in ClinVar for relevance to known variants and were assigned to tiers I-IV based on the ESMO scale for clinical actionability of molecular targets (ESCAT). Tier I mutations have drug-mutation matched evidence of actionability while tier IV have only pre-clinical evidence. **Results:** NGS has been completed on 76 tumor samples. Sequenced tumors represented 19 histologies, with the most common ones as follows: undifferentiated pleomorphic sarcoma (15.8%), liposarcoma (9.2%), gastrointestinal stromal tumor (9.2%), osteosarcoma (7.9%), and leiomyosarcoma (7.9%). Of 76 patients, 66 (87%) had at least one mutation detected with an mean frequency of 2.74. *TP53* (20/66), *RBI* (14/66), and *ATRX* (9/66) were most commonly mutated genes. Mean (std) tumor mutation burden (TMB) was 3.4 m/MB (3.5m/MB) and one tumor had TMB of 25.3 m/MB. Of the 76 samples, 68 had RNA expression and fusion data available, of which 42 (62%) had anomalous expression changes and 11 had RNA fusions. The most overexpressed genes were *NY-ESO-1* (13), *LAGE-1* (9), and *RET* (7); the most under-expressed genes were *SMARCB1* (9) and *MGMT* (6). 30.2% (23 of 76) of patients had potentially actionable DNA mutations, 9 had ESCAT tier I DNA mutations, 3 had tier II, 10 had tier III, and 1 had tier IV. 29.4% (20/68) of patients had potential targets based on RNA expression. 51.3% (39/76) patients had either a potential DNA or RNA target, and 6.6% (5/76) had multiple RNA or DNA targets. **Conclusions:** NGS revealed potentially actionable targets in over half of sarcoma patients based on ESCAT criteria. With ongoing accrual and sequencing of additional tumor specimens future analysis of CAUSAL will focus on assessing the correlation between targetable mutations and clinical outcomes. Research Sponsor: U.S. National Institutes of Health.

11551

Poster Session

Aristolochic acid (AA) exposure and telomere maintenance mechanism in liver angiosarcoma (AS). *First Author: Tom Wei-Wu Chen, Department of Oncology, National Taiwan University Hospital, Taipei, Taiwan*

Background: Liver AS has a grave prognosis and our previous study (Chen TW et al. Cancer 2022) showed that the incidence of liver AS is higher in Asia. We aimed to investigate the etiology of liver AS and its molecular characteristics. **Methods:** We performed whole exome (WES) and transcriptome sequencing (RNA-seq) of AS (liver 10, scalp 5, breast 2, trunk 1, heart 1) and hepatocellular carcinoma (HCC, 9) from National Taiwan University Hospital (NTUH) and re-analyzed WES & RNA-seq of AS from the Count Me In Project (CMI, 46). Somatic mutations and copy number alternation were called by Mutect2 and Sequenza from tumor-normal matched WES. Non-negative matrix factorization was used to determine mutational signature profiles and the contributions of each signature to each sample. Telomere length was estimated using TelSeq. **Results:** We identified four single-base-substitution (SBS) signatures using somatic mutations from 74 (AS/HCC 65/9) WES data. The dominated signature in liver AS had exceptionally high cosine similarity (93.08%) with COSMIC SBS22 (ver 3.2), which is related to AA exposure. The AA-mutation signature contributed significantly (adjusted $p < 0.01$) to the DNA mutations in 70% (7/10), 0% (0/9), 7% (3/46), and 56% (5/9) of liver AS (NTUH), nonliver AS (NTUH), CMI AS, and HCC (NTUH), respectively. *TP53* (60% vs 22% vs 32%) and *ATRX* (40% vs 0% vs 11%) mutations were more common in liver than nonliver AS (NTUH) or CMI, while *KDR* mutation rates were similar (30% vs 44% vs 22%). Among *TP53* mutations from liver AS with AA signature, 86% (6/7) showed the typical A:T > T:A mutation caused explicitly by AA-induced DNA damage. In liver vs nonliver AS, the median number of mutations and neoantigen burdens were 6.55 vs 0.98 ($p = 0.0076$) and 1572 vs 544 ($p = 0.095$), respectively. Although liver AS and HCC were highly associated with AA-mutation signature, liver AS had significantly longer telomeres in terms of tumor/normal telomere ratio (median 1.27 vs 1.16, $p = 0.0009$) but a significantly lower telomerase enzyme activity ($p = 0.016$). We did not find an association between *ATRX* mutation, or its mRNA expression level, with the extended telomere length in liver AS. Compared to nonliver AS, the activity of the telomere replication molecule *BUB1* was significantly higher in liver AS ($p = 0.0029$). **Conclusions:** Our study is the first to connect AA exposure to the etiology of liver AS. The high mutation rate and distinct telomere maintenance mechanism of liver AS provides insights into future treatments. Research Sponsor: National Taiwan University Hospital; Good Liver Foundation.

11549

Poster Session

Loss of the DNA repair gene RNase H2 and a unique subset of DDR-deficient leiomyosarcomas. *First Author: Michael Nakazawa, University of Texas MD Anderson Cancer Center Hematology/Oncology Fellowship, Houston, TX*

Background: Targeting the DNA damage response (DDR)/Homologous Recombination (HR) pathway is an emerging therapeutic approach for leiomyosarcoma (LMS). Loss of RNase H2 decreases DNA repair via the Non-Homologous End-Joining (NHEJ) pathway, leading to increased double stranded breaks, replication stress, and increased cell death. Therefore, we developed an assay to screen for RNase H2 loss in STS patient samples to determine its prevalence and prognostic significance, particularly in LMS patients. **Methods:** *RNASEH2B* homozygous deletion (HomDel) calls from TCGA samples were based on the Allele-Specific Copy number Analysis of Tumors (ASCAT2) algorithm. Immunohistochemistry (IHC) of RNase H2 was performed on tissue microarrays (TMAs) of uterine (U-LMS) and soft tissue (ST-LMS) leiomyosarcoma samples from MD Anderson Cancer Center (MDACC) using a selective antibody developed by Repare Therapeutics. RNase H2 loss was defined as $\leq 10\%$ cells without nuclear IHC staining and scored by experienced pathologists in 2 separate cohorts. Genomic analysis was performed using SNIpDx™, a targeted-NGS assay designed to detect allelic loss of function in select DDR related genes and whole genome sequencing (WGS). MDACC TMA samples were clinically annotated by retrospective review. **Results:** Using TCGA data, *RNASEH2B* HomDels were seen in 6% (5/80) of all LMS cases, with a higher proportion in U-LMS (15%; 4/27) as compared to ST-LMS (2%; 1/53). In a pan-tumor TMA, RNase H2 loss by IHC was found in 3.8% (32/843) of samples overall, and in 10% (9/88) of LMS samples. This proportion of RNase H2 loss was higher in a larger MDACC LMS cohort, where negative staining of RNase H2 was found in 30% (33/110) of U-LMS and 38% (39/102) of ST-LMS cases. 30 MDACC LMS cases (15 U-LMS and 15 ST-LMS) were analyzed for *RNASEH2B* HomDels by SNIpDx. In U-LMS, *RNASEH2B* HomDels were detected in 64% (7/11) of RNase H2 IHC loss cases vs. 0% (0/3) in RNase H2 IHC intact cases. No *RNASEH2B* HomDels were detected in ST-LMS cases (10 IHC loss, 5 intact). The median overall survival (mOS) of MDACC U-LMS patients ($n = 109$) was 4.3 years. No significant mOS difference was seen in RNase H2 IHC intact cases versus loss (mOS 4.4 v 3.3 years, $p = 0.54$). In a separate cohort, 45 U-LMS samples were screened by IHC; 22% (10/45) had RNase H2 loss. *RNASEH2B* HomDels were detected in 70% (7/10) of RNase H2 IHC loss cases using SNIpDx and confirmed using WGS. In contrast, *RNASEH2B* HomDels were detected in 3% (1/33) of RNase H2 IHC intact cases. In the combined U-LMS cohort with IHC and SNIpDx results ($n = 71$), the diagnostic accuracy, sensitivity and specificity of RNase H2 IHC for detecting *RNASEH2B* HomDels was 76%, 93% and 71% respectively. **Conclusions:** RNase H2 loss via *RNASEH2B* HomDels is prevalent in U-LMS and is unique from other DDR pathway alterations. RNase H2 IHC is an effective screening tool and is being developed for future clinical trials targeting DDR in LMS. Research Sponsor: Repare Therapeutics.

11552

Poster Session

Phase 1 trial of avelumab with hypofractionated thoracic radiation therapy (HT-RT) in patients with metastatic soft-tissue sarcomas (mSTS). *First Author: Shane H Zaidi, Royal Marsden Hospital, London, United Kingdom*

Background: Combining HT-RT with anti PD-L1 therapy may enhance local and distant tumour control in mSTS. This was a Phase 1 trial to evaluate the safety, tolerability, and efficacy of avelumab in patients with mSTS. **Methods:** This was a single centre phase 1 trial of avelumab with HT-RT in patients with mSTS (NCT03602833). Patients > 18 years with at least 2 pulmonary metastases, ECOG performance status 0-1 were eligible between Oct 2018-Apr 22. Patients received HT-RT (36 Gy in 12 fractions), with concurrent intravenous avelumab (10 mg/kg q14d) until disease progression. The primary end point was safety of avelumab with HT-RT. Secondary endpoints included local control rate at 3 months. Dose limiting Toxicity (DLT) assessed from start of HT-RT and avelumab up to Cycle 7 avelumab and defined as: $\geq$ G2 pneumonitis, $\geq$ G2 myelitis, $\geq$ G3 non-haem toxicity, $\geq$ any other G4 and/or HT-RT interruption > 5 days. Response was evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST). **Results:** 12 patients were treated in this trial. Histological subtypes: leiomyosarcoma ($n = 2$), undifferentiated pleomorphic sarcoma ($n = 2$), and spindle cell sarcoma ($n = 2$). The median age was 57.5 (37-68) years, 7 were female (58%). All patients had lung metastases. 1 previously received SBRT to the lung, and 5 (42%) patients had received prior systemic treatment. 12 patients received at least one cycle of avelumab, median 9 (range: 1-37), and treatment was discontinued in 11 (92%) patients; 10 (83%) stopping for progressive disease, 1 (8%) patient for G4 immune-mediated hepatitis after DLT period and 1 patient completed and continues on compassionate-use avelumab. Eleven (92%) completed radiotherapy (36 Gy, 12 fractions). No DLTs or treatment-related deaths were observed. HT-RT toxicity: 3 G2 acute (1 oesophagitis, 2 skin) noted up to 11 weeks. 13 G1 late toxicities (5 pneumonitis, 5 skin, 1 cardiac, 1 myelitis, 1 oesophagitis) reported. Avelumab toxicities: 2 G3 (1 ALT rise, 1 viral infection) and 3 G4 (1 AST rise, 1 hepatitis, 1 sepsis) reported after DLT observation period. The median follow-up was 21.8 (range 3.2-31.9) months with a 3-month local control rate of 50% (95% CI, 21%-74%). RECIST responses at 3 months were 0 CR, 1 (8%) PR, 5 (42%) SD and 5 (42%) PD. **Conclusions:** Avelumab in combination with thoracic radiotherapy was safe with encouraging anti-tumour activity in patients with metastatic soft-tissue sarcomas. Additional molecular biomarker analyses are in progress. Clinical trial information: NCT03602833. Research Sponsor: Merck Serono Ltd. (CrossRef Funder ID: 10.13039/100009945); Royal Marsden/ Institute of Cancer Research London BRC.

11553

Poster Session

Efficacy and safety of anlotinib combined with anthracycline and ifosfamide followed by anlotinib maintenance in advanced soft tissue sarcoma: A single-arm, phase 2 trial. *First Author: Zengjun Liu, Rare tumors Department, Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, Huaiyin District Jinan, China*

Background: Anthracycline plus ifosfamide is the standard first line treatment regime for advanced soft tissue sarcoma (STS). Anlotinib, a multikinase angiogenesis inhibitor, has evolved as a standard second line treatment option in Chinese advanced STS patients. This study was performed to evaluate the efficacy and safety of anlotinib combined with anthracycline and ifosfamide followed by anlotinib maintenance in the first line treatment of patients with advanced STS. **Methods:** This prospective, open-label, single-arm, phase 2 trial was conducted in Shandong Cancer Hospital and Institute (ChiCTR2100054711). The key inclusion criteria included: (a) age was 18-70 years; (b) ECOG performance state of 0-1; (c) histologically confirmed high-grade STS; (d) unresectable or metastatic STS; (e) previously untreated, and sensitive to chemotherapy; (f) having measurable lesions according to RECIST 1.1. All patients received up to 6 cycles of anlotinib (12 mg QD on day1-14, 21 days per cycle) combined with anthracycline (epirubicin 40mg/m²/d on day 1-2, 21 days per cycle; or liposomal doxorubicin 30mg/m²/d on day 1, 21 days per cycle) and ifosfamide (2g/m²/d on day 1-3, 21 days per cycle) followed by anlotinib maintenance until disease progression, unacceptable toxicity or death. Pegylated recombinant human granulocyte colony-stimulating factor was administered following chemotherapy. The primary endpoint was objective response rate (ORR). The secondary endpoints included progression-free survival (PFS), overall survival (OS), and adverse effect (AE). **Results:** From December 2021 to December 2022, 31 patients (median [range] age, 53 [18-69] years; 20 [64.5%] male) were enrolled. 29 were evaluable for objective response, and the ORR and DCR were 31.03% (95%CI, 17.28-49.23%) and 82.76% (95%CI, 65.45-92.4%), respectively. With a median follow-up duration of 6.3 months (range, 0.8-14.0), the median PFS for all 31 patients was 6.9 months (95% CI, 2.62-11.17). The median OS was not reached. Treatment-related AEs of any grade occurred in all patients. The most common AEs included nausea/vomiting (88.46%), anemia (23.08%), leukopenia (19.23%), venous thrombosis (15.38%), hand-foot syndrome (11.54%) and elevated alanine aminotransferase or aspartate aminotransferase (11.54%). The most frequent $\geq$ grade 3 AEs were leukopenia (11.54%) and thrombocytopenia (7.69%). 2 serious AEs (1 left heart failure and 1 intestinal obstruction) were recorded. No treatment-related death occurred. **Conclusions:** This study suggested that anlotinib combined with anthracycline and ifosfamide followed by anlotinib maintenance demonstrated encouraging efficacy with a manageable safety profile in the first line treatment of patients with advanced STS. Clinical trial information: ChiCTR2100054711. Research Sponsor: Beijing Lize Charity Foundation.

11555

Poster Session

Results of SOC-2082 phase 2 study using metronomic gemcitabine, doxorubicin and docetaxel plus nivolumab as second/third-line therapy for advanced sarcoma. *First Author: Nadezhda Omelchenko, Sarcoma Oncology Research Center, Santa Monica, CA*

Background: Metronomic dosing of gemcitabine, doxorubicin and docetaxel causes less severe side effects than standard chemotherapy for advanced sarcoma. The addition of nivolumab to this regimen has potential to have synergistic effects and improve treatment outcomes. **Methods:** Primary objective: To assess progression-free survival (PFS); Secondary objectives: (1) To evaluate best overall response during treatment period confirmed in a 6-week follow-up, (2) PFS rate at 6 and 9 months, (3) Overall survival (OS) rate at 6, 12 months, and (4) Incidence of treatment-related adverse events (TRAEs). Inclusion criteria: Previously treated male and female subjects, $\geq$ 18 years of age, pathologically confirmed diagnosis of locally advanced, unresectable, or metastatic sarcoma, measurable disease by RECIST v1.1, and acceptable hematologic and organ functions. Exclusion Criteria: History of autoimmune disorder. Treatment schedule: Metronomic doses of gemcitabine (600 mg/m² max:1000 mg), doxorubicin (18 mg/m²; max: 32 mg), docetaxel (25 mg/m²; max:42 mg) on Day 1 and Day 8, and nivolumab (240 mg) on Day 1 only. Repeat treatment cycles are continued every three weeks if the toxicity grade is $\leq$ 1. **Results:** This report on the modified intent-to-treat population (n=59). This population completed at least one treatment cycle and had a follow-up CT or MRI scan at week 6. Best Overall Response = 8 PR, 44 SD, 7 PD. The disease control rate (CR+PR+SD) was 88.1%. Median PFS was 5.1 (95% CI: 2.837-7.363) months; 6 month PFS rate 52.5%. Median OS, 15.3 (95% CI: 5.48-25.12) months, with 6-month OS 88%. Safety analysis: Grade 3/4 TRAEs include fatigue (n=18), nausea (n=13), neutropenia (n=10), thrombocytopenia (n=9), anemia (n=9), diarrhea (n=1). There were no unexpected adverse events. **Conclusions:** Taken together, the data suggests that nivolumab in combination with metronomic doses of gemcitabine, doxorubicin and docetaxel (1) may have synergistic activity, and (2) by indirect comparison, may be as effective as standard first line therapy for advanced sarcoma with manageable toxicity. Clinical trial information: NCT04535713. Research Sponsor: None.

11554

Poster Session

A phase Ia/Ib, dose-escalation/expansion study of the MDM2-p53 antagonist BI 907828 in patients (pts) with solid tumors: Safety and efficacy in patients with dedifferentiated liposarcoma (DDLPS). *First Author: Patricia LoRusso, Yale University School of Medicine, Yale Cancer Center, New Haven, CT*

Background: Inactivation of p53 is a key mechanism which promotes tumor survival and proliferation. p53 inactivation can be due to mutations in *TP53* or downregulation of wild-type (wt) p53 by the key negative regulator mouse double-minute 2 (MDM2). BI 907828 is a highly potent MDM2-p53 antagonist which has demonstrated preclinical antitumor activity, particularly in *TP53*-wt *MDM2*-amplified DDLPS models. In this phase I study (NCT03449381), BI 907828 monotherapy is being evaluated in pts with advanced solid tumors, including DDLPS. During dose escalation (phase Ia), BI 907828 had a manageable safety profile and the selected recommended dose for expansion (RDE) was 45 mg q3w. Here we report safety data in all pts who received the RDE of 45 mg q3w and present efficacy data in the subgroup of pts with DDLPS. **Methods:** In Phase Ia, pts received one of two BI 907828 dosing schedules: Arm A, day 1 of 21-day cycles (q3w); Arm B, days 1 and 8 of 28-day cycles. During Phase Ib (dose expansion), pts were enrolled to Cohort 1 (*TP53*wt, *MDM2*-amplified sarcoma) or Cohort 2 (other *TP53*wt, *MDM2*-amplified solid tumors). Here we focus on Cohort 1 (received BI 907828 45 mg q3w). The primary endpoint (phase Ib) was progression-free survival (PFS). Secondary endpoints/objectives included overall response rate (ORR) and grade $\geq$ 3 treatment-related AEs (TRAEs). **Results:** As of December 22, 2022, a total of 137 pts had been enrolled; 72 (52.6%) were male, 77 (56.2%)/59 (43.1%) had ECOG PS 0/1, and the median number of prior systemic therapies was 2 (range, 0-11). In the 73 pts who received the RDE of 45 mg q3w, the most common any-grade TRAEs were nausea (74.0%) and fatigue (61.6%). 33 (45.2%) pts had grade $\geq$ 3 TRAEs; the most common were thrombocytopenia (23.3%), neutropenia (21.9%), anemia (11.0%), and leukopenia (11.0%). 22 (30.1%) pts had TRAEs leading to dose reductions and 6 (8.2%) had TRAEs leading to treatment discontinuation. 20 pts (27.4%) had serious AEs; the most common were nausea, pulmonary embolism (each 4.1%), sepsis, small intestine obstruction, vomiting, thrombocytopenia, and pyrexia (each 2.7%). 50/73 pts who received 45 mg q3w had advanced DDLPS; all had *MDM2*-amplified disease. Of the 42 evaluable DDLPS pts, 8 achieved a confirmed PR (ORR 19.0%; locally assessed) and a further 29 achieved a best response of stable disease (including 2 with unconfirmed PR), giving a disease control rate of 88.1%. Preliminary median PFS was 8.1 months. **Conclusions:** BI 907828 demonstrated a manageable safety profile overall and encouraging preliminary efficacy was seen in pts with advanced *MDM2*-amplified DDLPS; Phase Ib is ongoing. BI 907828 is also being evaluated versus doxorubicin as first-line treatment for pts with advanced DDLPS in the ongoing Phase II/III Brightline-1 study (NCT05218499), for which the FDA has granted a Fast Track Designation. Clinical trial information: NCT03449381. Research Sponsor: Boehringer Ingelheim.

11556

Poster Session

Interim results of a phase 2 study using talimogene laherparepvec, nivolumab, and trabectedin for advanced leiomyosarcoma. *First Author: Neal Shiv Chawla, City of Hope Comprehensive Cancer Center, Duarte, CA*

Background: Intratumoral injection of Talimogene Laherparepvec (TVEC) has a local oncolytic effect and evokes a cytotoxic immune response. The combination of Trabectedin (T) and Nivolumab (N) is a safe and effective therapy in soft tissue sarcoma (STS). This study aims to determine the safety and efficacy of adding TVEC to the combination of T and N in advanced leiomyosarcoma (LMS). **Methods:** Objectives: Primary: To assess progression-free survival (PFS). Secondary: (1) To evaluate the best overall response, (2) PFS rate at 6 and 9 months, (3) Overall survival (OS) rate at 6, 9, and 12 months, (4) Incidence of conversion from unresectable to the resectable tumor, and (5) Incidence of treatment-related adverse events (TRAEs). Patients and Methods: Eligible patients included patients $\geq$ 18 years of age with locally advanced unresectable or metastatic LMS, measurable disease by RECIST v1.1, and at least one accessible tumor for TVEC intratumoral injection. N (3 mg/kg q2 weeks), T (1.2 mg/m² q3 weeks), and TVEC (1x10⁸ PFU/ml q 2 weeks depending on tumor size) were administered. A starting dose of TVEC (1x10⁶ PFU/ml) was initially given, followed by a total dose of 1x10⁸ PFU/ml q 2 weeks depending on tumor size) three weeks later. **Results:** Efficacy: Per protocol, there were 11 evaluable subjects (Modified Intention to Treat [mITT] patients who had completed at least one treatment cycle and had a follow-up CT scan). The median number of prior lines of therapy was 4 (range 1-8). Confirmed Best Overall Response (BOR) by RECIST v1.1 = 2 PR, 9 SD (BOR Rate 18.2%). The disease control rate (PR+SD) at week 6 was 100%. The median PFS was 7 months (range: 3-18); 6-month PFS rate, 55%; median OS 18.2 months (range: 4- 32); 6-month OS rate, 91%. There was no conversion from unresectable to resectable tumor. Response was not related to PD-L1 positivity but both patients with PR were ER+/PR+ and had uterine LMS. There were 15 evaluable subjects for OS analysis under the Intention-to-Treat (ITT) population who received at least one dose of study drug. The median OS was 12 (range 0-32) months; 6-month OS rate, 60%. Safety: Eight of 15 (53.3%) patients experienced at least one $\geq$ Grade 3 treatment-related adverse event (TRAE). Grade 3 TRAEs include anemia (n=3), thrombocytopenia (n=2), neutropenia (n=1), increased ALT (n=1), increased GGT (n=1), decreased LVEF (n=1), myalgia (n=1). Grade 4 TRAE include thrombocytopenia (n=1). The TRAEs were related to Trabectedin use. No new safety signals noted in this study. **Conclusions:** These results suggest that (1) By indirect comparison, the combination regimen using Talimogene laherparepvec, Nivolumab & Trabectedin may be more effective as second/third-line/fourth therapy for advanced leiomyosarcoma with manageable toxicity (Trabectedin alone for LMS= 4.3 mos; Dacarbazine alone = 1.6 mos; Demetri 2015), and (2) The best responders are patients with HR+ uterine LMS. Clinical trial information: NCT03886311. Research Sponsor: Amgen.

11557

Poster Session

Metronomic dosing of selinexor in select soft tissue sarcomas (STS). *First Author: Aisha Alshibany, Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada*

Background: Selinexor (S) is a first-in-class, oral, selective inhibitor of nuclear export (SINE). S has a demonstrated anti-tumor activity in STS. However, the use of S can be associated with toxicities, such as nausea, anorexia and fatigue. A modified dosing schedule may improve the tolerability of S without compromising its efficacy. **Methods:** We evaluated S when given metronomically in patients (pts) with advanced metastatic leiomyosarcoma, endometrial stromal sarcoma, and malignant peripheral nerve sheath tumors. S was administered daily for 4-days in a row followed by 3-days break, repeated weekly in a 28-days cycle. Dose levels (DL) were escalated using a 3+3 design to determine maximum tolerated dose. DL included 2.5mg (DL1), 5mg (DL2), 7.5mg (DL3), 10 mg (DL4), 12.5 mg (DL5), 15 mg (DL6) and 17.5 mg (DL7). S was administered until unacceptable toxicities or disease progression. Imaging was performed every 8 weeks. Primary objectives were safety and tolerability as well as the determination of the recommended phase II dose. Secondary objectives were anti-tumor activity, toxicity profile, and pharmacokinetics (PK) profile. **Results:** Twenty-five pts (22 females/3 males, median age 59 years [range 35-84]) were enrolled at different DL (3, 3, 4, 6, 6, 3 pts at DL1 to DL6 respectively). The most common adverse events (AE) of any grade were constipation (n = 11, 50%), nausea (n = 11, 50%), and dysgeusia (n = 10, 45%). Eight (36%) pts experienced G3/4 AE while on trial; most were hematological toxicities seen in 3 (14%) pts (anemia, neutropenia, and leukopenia, n = 1 each). Non-hematological G3/4 AE were seen in 5 (23%) pts (Including: colonic obstruction, atrial fibrillation, and spinal cord compression, n = 1 each). Two Dose limiting toxicities were experienced, at DL4 (thrombocytopenia) and DL5 (transaminitis). Twenty-two pts were evaluable for response; 10 (45%) pts had stable disease (SD) as best response. Eight pts with SD had disease stability of > 4 months. Twelve pts (55%) had progressive disease. Median progression-free survival was 2.4 months (95% CI 1.7-5.3 months). PK data is awaiting final analysis. **Conclusions:** Metronomic S demonstrated tolerability in selected sarcoma pts. Signs of potential clinical benefit was seen in the form of SD. Further data comparison with historical controls and PK analysis are needed to put this finding into perspective. Clinical trial information: NCT04811196. Research Sponsor: University Health Network, Toronto.

11559

Poster Session

Efficacy and safety profile of pimicotinib (ABSK021) in tenosynovial giant cell tumor (TGCT): Phase 1b update. *First Author: Hairong Xu, Department of Orthopaedic Oncology Surgery, Beijing Ji Shui Tan Hospital, Peking University, Beijing, China*

Background: TGCT is a rare type of locally aggressive neoplasm that is mainly caused by overexpression of colony-stimulating factor 1 (CSF1) gene. Pimicotinib is an oral, highly potent, and selective small-molecule antagonist of CSF-1R with minimum inhibition of c-Kit and PDGFR, and has been granted Breakthrough Therapy Designation for TGCT by FDA in Jan 2023. Here, we report the updates from 50 mg QD cohort as well as the preliminary data from 25 mg QD cohort in TGCT pts. **Methods:** The study (NCT04192344) is to evaluate the safety and preliminary antitumor activity of Pimicotinib at 50 mg QD and 25 mg QD in TGCT pts not amenable to surgical resection. **Results:** As of December 31, 2022, 49 TGCT pts were enrolled, including 37 pts treated with 50 mg QD and 12 pts with 25 mg QD. Median age was 39 y (range: 19-76) and 40.8% were male. The tumor location was mainly in knee (53.1%), hip (18.4%) or ankle (12.2%). Thirty-one pts received at least one prior surgery, and 1 pt received prior exploratory systemic therapy (Anlotinib). Median treatment duration was 7.9 mos (range: 0.4-12.5), and 89.8% remained on treatment. The ORR was 77.4% (24/31, including 2 CR) in 50 mg QD and 40% (4/10, including 1 CR) in 25 mg QD by IRC based on RECIST 1.1. Most responses were achieved within 25 wks and median DOR in both cohorts was not reached. Average improvement of flexion range of knee at wk 13 from baseline was 30.2 degrees (n = 13, range: 2, 105) in 50 mg QD and 4.8 degrees (n = 5, range: -12, 24) in 25 mg QD. Proportion of responders based on BPI-30 at wk 25 was 66.7% (16/24) in 50 mg QD and 60% (3/5) in 25 mg QD, along with a similar trend of stiffness. Most TEAEs were Gr 1 or 2. Four Gr 3/4 TEAEs were reported (2 drug-related), including 1 Gr 3 serious TEAE. Most common TEAEs (≥20%) include LDH increase (75.5%), CPK increase (67.3%), α-HBDH increase (63.3%), AST increase (42.9%), amylase increase (26.5%), ALT increase (24.5%), pruritus (20.4%) and rash (20.4%). No hair color changes or serious liver injuries were reported. CPK and transaminase elevations were asymptomatic, on-target and quickly recovered after drug interruptions. Under steady-state, 50 mg QD resulted in ~ 2-fold higher C_{max} and C_{trough} compared to 25 mg QD, in sync with findings from escalation phase. Significant PD changes were observed in both cohorts, such as increase in plasma CSF-1 levels, decrease in non-classical monocytes and C-terminal telopeptide (CTX). Changes from baselines in both CSF-1 and CTx showed a correlation with pimicotinib plasma concentrations. **Conclusions:** Pimicotinib has demonstrated a significant antitumor activity, favorable safety, and PK profiles at both 50 mg QD and 25 mg QD with no apparent hepatotoxicity. The changes in PD biomarkers indicate significant CSF-1R inhibition in TGCT pts. Updated data from 50 mg QD cohort showed higher ORR and continuous improvement over a longer treatment time, which supports the further evaluation of Pimicotinib in a phase 3 study. Clinical trial information: NCT04192344. Research Sponsor: Abbisko Therapeutics Co, Ltd.

11558

Poster Session

Results from phase I/II study of NY-ESO-1-specific TCR gene-transduced T cell therapy (TBI-1301, mipetresgene autoleucel) in patients with advanced synovial sarcoma. *First Author: Akira Kawai, Department of Musculoskeletal Oncology, National Cancer Center Hospital, Tokyo, Japan*

Background: Synovial sarcoma is one of malignant soft tissue tumors with a poor prognosis. A cancer-testis antigen NY-ESO-1 is expressed in the tumors of 50-80% synovial sarcoma patients. The purpose of this study was to evaluate the safety and the efficacy of gene engineered autologous T cell product with NY-ESO-1 siTCR retroviral vector which expressed affinity-enhanced NY-ESO-1-specific TCR and siRNA to silence endogenous TCR (TBI-1301). **Methods:** This was an open label phase I/II study to evaluate safety, appearance of replication competent retrovirus (RCR), appearance of clonality, *in vivo* cell kinetics and clinical responses. TBI-1301 were manufactured from each subject's leucocytes stimulated with anti-CD3 antibody and Retronectin and transduced with NY-ESO-1 siTCR retroviral vector. TBI-1301 was infused at split dose of 5×10^9 cells following cyclophosphamide treatment at 750 mg/m² for two days to HLA-A*02:01 or HLA-A*02:06 positive subjects with synovial sarcoma expressing NY-ESO-1, which were surgically unresectable and refractory to anthracycline therapy. **Results:** Eight subjects were enrolled and treated with TBI-1301. The objective response rate was 50.0% with best overall partial response in 4 of 8 subjects according to RECIST v1.1/irRECIST and the median overall survival was 650 days. Cytokine release syndrome (CRS) occurred in 50.0% (4/8) and consisted of 1 subject with grade 1 CRS and 3 subjects with grade 2 CRS. All subjects who developed CRS recovered with prespecified treatment, in which 2 subjects were treated with symptomatic therapy, 1 subject was treated with tocilizumab and 1 subject was treated with both tocilizumab and corticosteroid. No subjects had immune effector cell-associated neurotoxicity syndrome (ICANS). RCR and clonal dominance were not detected in any subjects throughout the study period. **Conclusions:** Adoptive immunotherapy with TBI-1301 to selectively target NY-ESO-1 positive tumors will become a promising treatment for advanced or recurrent synovial sarcoma with acceptable toxicity. Clinical trial information: NCT03250325. Research Sponsor: Takara Bio Inc.

11560

Poster Session

Evaluation of hyperprogression in patients with sarcoma treated with targeted therapy and/or immunotherapy in early-phase clinical trials. *First Author: Aisha Alshibany, Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada*

Background: Hyper-progressive disease (HPD) is an adverse outcome with acceleration of tumor growth, often accompanied by clinical deterioration. This phenomenon is described with immunotherapy (IT) but its incidence in sarcoma and/or in the context of targeted therapy (TT) remains unknown. Tumor growth rate (TGR) allows for dynamic evaluation of tumor volume change over time and may complement RECIST. We evaluated HPD in sarcoma patients (pts) treated in early-phase trials by assessing TGR and describing their subsequent clinical outcomes. **Methods:** We retrospectively reviewed medical records from advanced soft tissue sarcoma (STS) pts enrolled in early phase trials at the Princess Margaret Cancer Centre between January 2012 and December 2022. TGR was calculated based on tumor measurements taken at pre-baseline, baseline, and on-treatment CT scans. We used the Champiat formula (Clin Cancer Res 2017) to calculate TGR ratio. Primary objective was to describe the incidence of HPD, defined as a TGR ratio of > 50%. Secondary objective was to investigate the correlation between HPD with progression-free survival (PFS) and overall survival (OS). **Results:** We identified a total of 192 pts involved in STS early phase trials from 2012-2022. Most common histology was leiomyosarcoma seen in 72 pts. Eighty-four pts (43.8%) received TT, 75 (39%) pts received IT-based, and the rest had combined TT/IT regimens (n = 33, 17.2%). The incidence of HPD was 6.8% (n = 13), including IT-based (n = 9) and non-IT-based (n = 4) regimens. HPD was associated with a worse PFS, and OS compared to non-HPD pts (median PFS 1.6m vs 4.6m HR: 5.5, 95%CI 2.8-10.6, P < 0.001; median OS 5.5 vs 16.1 months; HR: 3.7, 95%CI: 2.0-7.1, P < 0.001). On multivariable analysis, only IT was significantly associated with HPD (OR 3.9, 95%CI: 1.1-13, P = 0.021). There was no association between HPD and new lesions or sarcoma histology subtype. **Conclusions:** HPD occurs in a small subset of sarcoma patients undergoing clinical trials with TT or IT. Exploring TGR provides clinically meaningful data as it pertains to HPD as it predicts OS and PFS in sarcoma patients undergoing early-phase clinical trials. Research Sponsor: None.

11561

Poster Session

Novel MRI scoring system to assess osseous malignancy in patients with soft tissue sarcoma following radiotherapy. *First Author: Gayathri Vijayakumar, Rush University Medical Center, Chicago, IL*

Background: Although radiotherapy is an important component of STS management, radiation induced changes such as radiation osteitis are commonly identified on magnetic resonance imaging (MRI). These imaging findings may be concerning for malignancy and sometimes require biopsy for investigation. This study proposes a novel MRI scoring system to assess osseous lesions and predict potential for malignancy based on MRI score in STS patients who received radiotherapy. **Methods:** The MRI score consisted of 3 parameters: morphology, signal intensity, and progression. Interobserver reliability between the total score of MRI examinations scored by two senior musculoskeletal radiologists were analyzed with Cohen's kappa coefficient. Receiver operating curve (ROC) analysis was performed to determine a predictive MRI score for malignancy. **Results:** 156 MRI's from 30 STS patients who received radiotherapy were retrospectively reviewed. Two (6.7%) patients developed regional osseous metastasis identified on MRI. The kappa coefficient of the scoring system was 0.785 demonstrating substantial interobserver agreement ($p < 0.001$). ROC analysis demonstrated that the optimal cut-off value for malignant lesion on MRI was 5.5 (area under the curve 0.998 [95% CI 0.993-1.000] $p < 0.001$). **Conclusions:** This novel MRI scoring system recommends lesions with a score of six and above to be biopsied to distinguish if malignancy is present. We believe this scoring system can be utilized by multidisciplinary care teams to guide clinical recommendations for patients with STS and MRI findings concerning for malignancy versus radiation induced changes. Research Sponsor: None.

Supple score-MRI scoring system.

	-1	0	1	2	3
Morphology	N/A	Serpiginous or linear abnormality; Diffuse normal marrow signal; Hyperintense T1 and Hypointense T2FS/STIR	Diffuse/patchy signal abnormality on T2FS/STIR with ill-defined edges Hyperintense on T2FS/STIR, Iso to hyperintense on T1	Focal signal abnormality on T2FS/STIR with ill-defined edges Hyperintense on T2FS/STIR, Hypointense on T1	Focal nodular or ovoid signal abnormality on T2FS/STIR
Signal Intensity	N/A				N/A
Progression	Decreased signal abnormality	N/A; Stable	New signal abnormality	Interval growth of the signal abnormality	N/A

11562

Poster Session

The SPEARHEAD-1 trial of afamitresgene autoleucel (afami-cel [formerly ADP-A2M4]): Analysis of overall survival in advanced synovial sarcoma. *First Author: Brian Andrew Van Tine, Washington University School of Medicine, St. Louis, MO*

Background: Afami-cel is an autologous, T-cell receptor (TCR) T-cell therapy to treat human leukocyte antigen (HLA) A*02-eligible patients (pts) with advanced solid tumors positive for the cancer testis antigen melanoma-associated antigen A4 (MAGE-A4). The efficacy and safety of afami-cel in pretreated pts with advanced/metastatic synovial sarcoma or myxoid/round cell liposarcoma are being evaluated in the Phase 2, two-cohort, open-label, SPEARHEAD-1 (NCT04044768) trial. Here we report interim overall survival (OS) data in the pts with advanced synovial sarcoma in Cohort 1. **Methods:** Pts who were HLA-A*02 positive with advanced synovial sarcoma (with evidence of clinical/radiological progression) positive for MAGE-A4 received afami-cel after lymphodepleting chemotherapy containing fludarabine and cyclophosphamide. The primary endpoint was overall response rate per RECIST v1.1 by independent review. Secondary endpoints included OS and progression-free survival (PFS), estimated utilizing the Kaplan-Meier method. **Results:** As of August 29, 2022, 44 pts with synovial sarcoma received afami-cel ($2.68-9.99 \times 10^9$ transduced T-cells) in Cohort 1. The median age was 41 years (range: 19-73 years), 50% of pts were female, 89% of pts were white, 96% of pts were typed as HLA-A*02:01P, and median tumor MAGE-A4 expression H-score was 257 (132-300). Pts were heavily pre-treated with a median of 3 prior lines of therapy (range: 1-12). The median follow-up time at the data cut-off was 20.8 months. Median PFS was 3.8 months (95% CI: 2.8, 5.8) and 4.1 months (95% CI: 2.8, 6.9) by independent and investigator review, respectively. Median OS by independent review was 15.4 months (95% CI: 10.9, not estimable) with 52% of pts censored at the data cut-off. The 12-month OS probability was 60% and 24-month OS probability was 40%. Twenty-one pts received additional therapy during long term follow up (systemic therapy, $n = 20$; radiation, $n = 6$; other, $n = 4$). In the 17 pts who had a RECIST response by independent review, the median OS was not reached, the 12-month OS probability was 90%, and 24-month OS probability was 60%. **Conclusions:** Pts with advanced synovial sarcoma treated with afami-cel in SPEARHEAD-1 had encouraging survival, especially those pts with a RECIST response. Clinical trial information: NCT04044768. Research Sponsor: This study was sponsored by Adaptimmune. Writing/editorial support was provided by Excel Scientific Solutions and was funded by Adaptimmune.

11562

Poster Session

HH2853, an EZH1/2 inhibitor, in patients with epithelioid sarcoma: Preliminary results from the phase 1 part of a first-in-human phase I/II study. *First Author: Zhengfu Fan, Peking University Cancer Hospital and Institute, Beijing, China*

Background: Epithelioid sarcoma (ES) is a rare and aggressive subtype of soft-tissue sarcoma. Over 90% of tumors have lost INI1 expression, leading to oncogenic dependence on the transcriptional repressor EZH2. Tazemetostat (an EZH2 inhibitor) has been approved by FDA for clinical use in ES. HH2853 is a novel selective EZH1/2 dual inhibitor, which has demonstrated superior anti-tumor efficacy to tazemetostat in INI1-loss preclinical models. **Methods:** This is a first-in-human, open-label, multicenter, Phase (Ph) I/II study in patients (pts) with relapsed/refractory non-Hodgkin lymphomas or advanced solid tumors. Ph I is composed of two parts: dose escalation and dose extension part. Local pathologically documented, advanced recurrent or metastatic ES pts who received prior systemic anti-tumor therapies or have no standard therapy are eligible. HH2853 was administered orally twice daily (BID) on a continuous 28-day treatment cycle. Safety and clinical activity of HH2853 were assessed in pts with ES from the Ph I part. **Results:** Between Dec 2, 2021 and Nov 7, 2022, 32 pts with pre-treated ES were enrolled to three dose levels (400, 600, and 800 mg BID) from 4 sites in China. Median prior lines of therapy was two. 12 (37.5%) pts received ≥ 3 lines of prior therapies. 30 (93.8%) pts had documented loss of INI1 expression by local immunohistochemical analysis. There were 18 (56.3%) pts with proximal subtype. As of Jan 4, 2023, at a median treatment duration of 124 days, the most common treatment-related adverse events (TRAE) were diarrhea (59.4%), blood bilirubin increased (43.8%), white blood cell count (WBC) decreased (34.4%), rash (31.3%), anemia (25.0%), hypokalemia (21.9%), and platelet count (PLT) decreased (21.9%). TRAEs of $\geq$ Grade 3 included diarrhea, WBC decreased, anemia, hypokalemia, and neutrophil count decreased (6.2%, each), and blood bilirubin increased, PLT decreased, blood creatine phosphokinase increased, and hyperglycemia (3.1%, each). TRAEs leading to dose interruption or reduction were reported in 21.9% and 12.5% pts, respectively. No TRAE led to dose discontinuation or death. Tumor responses were observed from 400 to 800 mg BID. Overall response rate (ORR) was 15.6% (5/32) per investigator assessment according to RECIST 1.1. Three pts had unconfirmed response waiting to be confirmed at the next scheduled assessment, expecting to bring the total ORR to 25% [95% CI 11.5 - 43.4]. Median time to response was 1.9 months. One patient with complete response (CR) has responded for 222 days from the initial response. Disease control rate (DCR) (DCR = CR + partial response + stable disease at 6 weeks) was 78.1% [95% CI 60-90.7]. **Conclusions:** HH2853 showed an acceptable safety profile and promising anti-tumor activity in heavily pretreated ES pts with a wide therapeutic window, providing evidence for further investigation. Clinical trial information: NCT04390737. Research Sponsor: Haihe Biopharma Co., Ltd., Shanghai, China.

11564

Poster Session

Impact of nirogacestat on pain, a key symptom in patients with desmoid tumors (DT): Results from the phase 3 DeFi study. *First Author: Winette T.A. Van Der Graaf, Department of Medical Oncology, Netherlands Cancer Institute, Amsterdam, Netherlands*

Background: Pain reduction is a key treatment goal in DT (aggressive fibromatosis): 60% of patients (pts) experience chronic pain. In the phase 3 DeFi trial, nirogacestat (NIRO; $n = 70$) significantly improved progression-free survival compared with placebo (PBO; $n = 72$) in pts with progressing DT (HR: 0.29 [95% CI, 0.15-0.55]; $P < 0.001$). Also as previously reported, NIRO significantly reduced pain severity by 1.50 points (on a 10-point scale) compared with PBO at cycle 10 (28-day cycles; $P < 0.001$) per the prespecified secondary endpoint of "worst pain" from the Brief Pain Inventory Short Form (BPI-SF). Additional aspects of pain were collected in DeFi to further characterize treatment impact and consistency across multiple pain assessment tools. **Methods:** In DeFi, pts completed 3 prespecified pain assessment tools through end of treatment: BPI-SF (worst pain), Gounder/Desmoid Tumor Research Foundation Desmoid Symptom Scale (GODDESS-DTSS pain scale: worst pain, dull pain, shooting pain), European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire (QLQ-C30 pain scale: pain, pain interference with daily activities). Change from baseline (BL) in pain scores was compared between arms; analyses included mixed models for repeated measures to compare change from BL and stratified Cochran-Mantel-Haenszel to compare proportions of pts with clinically meaningful pain reduction (defined using prespecified thresholds) at cycle 10. Cycle 10 was preselected to allow adequate time for a treatment effect to be observed. **Results:** Statistically significant and clinically meaningful pain reductions were observed with NIRO compared with PBO at cycle 10 across all assessment tools; statistically significant differences between arms occurred as early as cycle 2 and were sustained throughout treatment. At cycle 10, NIRO reduced mean BL pain per GODDESS-DTSS (0-10 range) by 1.78 points (SE = 0.26) and PBO increased pain by 0.32 points (SE = 0.27; $P < 0.001$). At cycle 10, NIRO reduced mean BL pain per QLQ-C30 (0-100 range) by 22.05 points (SE = 3.38) and PBO increased pain by 7.19 points (SE = 3.64; $P < 0.001$). Clinically meaningful pain reduction (by ≥ 2.0 points) per BPI-SF worst pain (0-10 range) was achieved by 72% of pts with NIRO vs 29% of pts with PBO at cycle 10 ($P < 0.001$). Per GODDESS-DTSS, clinically meaningful pain reduction (by ≥ 1.9 points) was achieved by 62% of pts with NIRO vs 19% of pts with PBO at cycle 10 ($P = 0.002$). **Conclusions:** Rapid, sustained, and consistent reductions in different aspects of pain were observed with NIRO compared with PBO across multiple assessment tools in pts with DT. Furthermore, a significantly greater proportion of pts achieved clinically meaningful reductions in pain with NIRO than with PBO. As pain is the most commonly reported symptom, pain reduction should be a key clinical trial endpoint and a key treatment goal in DT. Clinical trial information: NCT03785964. Research Sponsor: Spring-Works Therapeutics, Inc.

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Poster Session

A phase II trial with safety lead-in to evaluate the addition of sotigalimab, a CD40 agonistic monoclonal antibody, to standard-of-care doxorubicin for the treatment of advanced sarcoma. *First Author: Sminu (Sam) Bose, Columbia University Irving Medical Center, New York, NY*

Background: Immune checkpoint inhibitors have limited efficacy in soft tissue sarcoma (STS) due to insufficient T-cell activation and infiltration by immunosuppressive macrophages. Sotigalimab (S), a high-affinity humanized monoclonal antibody for CD40, promotes antigen presentation, stimulates T-cell responses, and reprograms immunosuppressive macrophages. Preclinical studies with CD40 agonists revealed efficacy in immune “cold” tumor types and synergy with chemotherapy. Standard first-line doxorubicin (D) provides objective response rate (ORR) < 15% and median progression free survival (mPFS) of 4–6 mos in advanced STS. We therefore conducted this first-in-human study of D+S in STS. **Methods:** An open-label, single-arm, multi-center, phase 2 study evaluated D+S in advanced STS. Pts had ECOG PS ≤ 1 and any number of prior lines (but were anthracycline-naïve). The study initially enrolled all STS subtypes (except KS and GIST) but was amended in 12/2020 to limit enrollment to dedifferentiated liposarcoma (DDLPS), leiomyosarcoma (LMS), and undifferentiated pleomorphic sarcoma (UPS). Pts received D 75 mg/m² IV D1 + S 0.3 mg/kg IV D1 for eight 21-day cycles, followed by S monotherapy. A safety lead-in was performed (first 6 patients). Primary endpoint was ORR. Secondary endpoints included PFS and safety. A Simon two-stage design was used. If ≥ 7/32 responded overall, the treatment would be considered promising (85% power, α = 0.05). A subset of patients underwent paired tumor biopsies. **Results:** 32 pts have enrolled (median age 62; 10 LMS, 10 UPS, 9 DDLPS, 3 other). 4 pts remain on treatment with median follow-up of 2.8 mos (1 UPS pt has not reached first imaging). D (75 mg/m²) + S (0.3 mg/kg) was safe and tolerable without dose limiting toxicity. Overall ORR was 16% (5/31). Objective responses occurred in UPS (2), LMS (1), other LPS (1), and epithelioid hemangioendothelioma (1). Overall mPFS was 7.5 mos (95% CI 5.6–14.9 mos) and PFS rate at 6 and 12-mos was 55% and 31%, respectively. mPFS by STS subtype was 11.9 mos (95% CI: 10.3–NE) for DDLPS, 7.5 mos (95% CI: 1.4–NE) for UPS and 5.6 mos (95% CI: 1.3–NE) for LMS. Overall, 17/31 (55%) pts experienced grade 3 or 4 adverse events (AEs): most commonly, neutropenia (32%), febrile neutropenia (19%), and anemia (16%). 16% of pts experienced cytokine release (all low-grade). Correlative analysis of biopsies with high-definition spatial proteomics is ongoing. **Conclusions:** D (75 mg/m²) + S (0.3 mg/kg) every 21 days is safe and tolerable in STS. Final analysis of the primary endpoint awaits further follow-up on recently enrolled patients. Subtype-specific analysis suggests improvement in median PFS for DDLPS over historical controls: 11.9 mos vs 4 mos (Stacchiotti S. Ann Oncol 2020; Livingston M. Sci Rep 2017). An expansion of the DDLPS cohort is planned. Clinical trial information: NCT03719430. Research Sponsor: Apexigen, Inc.

11567

Poster Session

Immune correlates of outcome in patients with leiomyosarcoma (LMS) treated with durvalumab plus olaparib or cediranib: Transcriptome analysis from the DAPPER study. *First Author: Abdulazeez Salawu, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada*

Background: Immune checkpoint blockade (ICB) as monotherapy has not shown clinical benefit in non-inflamed (cold) tumors such as LMS. Combining ICB with angiogenesis, or poly-ADP ribose polymerase (PARP) inhibitors may increase tumor immunogenicity by altering the immune cell composition of the tumor microenvironment (TME). In the DAPPER trial [NCT03851614], advanced LMS pts were randomized to receive ICB (Durvalumab 1500mg IV q4w) with either angiogenesis (Cediranib 20mg qd PO on 5 days/week) or PARP inhibition (Olaparib 300mg bid PO) until unacceptable toxicity or disease progression (Ayodele et al, *J Clin Oncol*, 2021). Here, we present the results of transcriptomic and immune biomarker analyses of patients (pts) in the whole cohort. **Methods:** Radiologic responses were assessed using RECISTv1.1 and survival analysis performed by Kaplan-Meier method. Transcriptome analysis by RNAseq was performed on fresh tumor biopsies obtained from all pts at screening. Relative fractions of 22 immune cell subsets in the TME were inferred from gene-expression profiles using CIBERSORT v1.06. Gene set variation analysis (GSVA) to identify transcriptomic signatures associated with progression-free (PFS) or overall survival (OS) benefit was performed using GSVA R package v1.42. For comparison with an independent cohort, GSVA was also performed using transcriptome data from LMS pts (n = 104) in the cancer genome atlas (TCGA) dataset. **Results:** Among 28 response-evaluable pts, 1 (3.6%) had partial response; 10 (35.7%) had stable disease (SD); and 17 (60.7%) had progressive disease. Median PFS and OS were 2.8 months (95% CI, 2.8–5.4) and 14.6 months (95% CI 10.7–NR), respectively. RNAseq data of adequate quality was available for 17 pts. Using the median CIBERSORT score as cut-off, pts with high M1 macrophage levels at baseline had significantly longer OS (p = 0.0019). High M1/M2 macrophage ratio score was also associated with longer OS (p = 0.05). GSVA identified 7 immune- and angiogenesis-related signatures that were associated with significantly longer OS. After false discovery rate correction, 1 signature comprising genes reflective of high overall B-cell activity remained significant. No transcriptomic signatures were associated with OS in the TCGA LMS cohort where pts did not receive ICB. **Conclusions:** Transcriptomic analysis shows that macrophage presence in the TME is associated with longer OS. Association of the B-cell activity signature with longer OS in LMS pts on the DAPPER trial, but not in the ICB treatment-naïve TCGA cohort suggests that high B-cell activity may identify pts who are more likely to have favorable outcomes with ICB and supports previous reports in sarcoma (Petitprez et al, *Nature*, 2020). Our results support ongoing further evaluation and integration of these biomarkers in LMS. Clinical trial information: NCT03851614. Research Sponsor: University Health Network; AstraZeneca.

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Poster Session

A phase II clinical trial of chidamide in combination with toripalimab in patients with advanced soft tissue sarcoma. *First Author: Xing Zhang, Department of Medical Melanoma and Sarcoma, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University, Guangzhou, China*

Background: Chidamide is an oral subtype-selective histone deacetylase inhibitor which is effective on the patients with hematological tumors and reported to enhance the efficacy of checkpoint blockade therapies and regulate the host immune response. Here, we report preliminary results of Chidamide in combination with Toripalimab in soft tissue sarcoma (STS) patients. **Methods:** An open, single arm, phase II study of Chidamide with Toripalimab in patients with advanced soft tissue sarcoma after failure of standard treatment was conducted. Eligible patients could have any number of prior therapies, excluding HDAC inhibitors and immune checkpoint inhibitors treatment. All patients received Chidamide orally at 30mg twice weekly in combination with intravenous Toripalimab 240mg every 21 days until progression or unaccepted toxicity. The primary endpoint was RECIST1.1 objective response rate (ORR). The secondary endpoint included progression free survival (PFS), overall survival (OS), disease control rate (DCR) and safety. **Results:** Forty-six patients with advanced soft tissue sarcoma were enrolled. The median age of the patients was 47 years and the median prior lines of therapy were 3. The main subtypes included leiomyosarcoma (30.4%), well/differentiated liposarcoma (30%), myxoid/round cell liposarcoma (7%), undifferentiated sarcoma (9%), and osteosarcoma (7%). Treatment was well tolerated with the most common adverse events mainly in grade I and grade II, including thrombocytopenia (43.5%), nausea (28.3%), neutropenia (23.9%), fatigue (17.4%) and hypothyroidism (15.2%). Among 46 efficacy-evaluable patients, the overall response rate and disease control rate were 23.9% and 80.4%, respectively. The median time to an initial response was 3 months (range, 2 to 14), and the 3-mon and 6-mon progression-free survival rate were 92.7% and 58.9%, respectively. **Conclusions:** Chidamide with Toripalimab every 21 days was well tolerated and showed promising efficacy in patients with advanced STS. Clinical trial information: NCT04025931. Research Sponsor: Shenzhen Chipscreen Biosciences Co., Ltd. and Shanghai Junshi Biosciences Co., Ltd.

11568

Poster Session

Intratumoral INT230-6 (cisplatin, vinblastine, shao) alone or with ipilimumab prolonged survival with favorable safety in adults with refractory sarcomas. *First Author: Christian Frederick Meyer, Johns Hopkins Hospital, Baltimore, MD*

Background: Sarcomas are a rare and diverse group of solid tumors from mesenchymal cells; chemotherapy provides limited benefit for metastatic disease. INT230-6 is a novel formulation of cisplatin (CIS), vinblastine (VIN) and a tissue dispersion enhancer (SHAO) designed for intratumoral (IT) delivery. The drug diffuses into cancer cells, causes apoptosis and recruits dendritic and T-cells to the tumor. Adding ipilimumab (IPI) appears to improve INT230-6 responses in models and clinically. The study evaluated INT230-6 for safety and efficacy alone and with intravenous (IV) IPI. Previously reported results showed INT230-6 alone induced tumor regression, T-cell influx and abscopal effects in uninjected lesions^{1,2}. **Methods:** IT-01 is an open-label phase 1/2 study in adults with locally advanced, unresectable or metastatic solid tumors, including sarcoma. INT230-6 dose was set by tumor diameter or volume. INT230-6 was dosed IT Q2W for up to 5 doses alone or with IPI at 3mg/kg Q3 weeks for 4 doses. Maintenance INT230-6 dosing was Q9W. **Results:** The study enrolled 29 sarcoma patients with 11 subtypes (mainly leiomyosarcoma, liposarcoma, pleomorphic, chondrosarcoma and chordoma). The maximum INT230-6 dose at a single visit was 175 mL (87.5 mg of CIS, 17.5 mg VIN) in 1 or more tumors, an amount that exceeds an IV dose of VIN or CIS. PK analysis shows that >95% of VIN stays in the tumor. The >20% treatment-related adverse events (TRAEs) in evaluable monotherapy patients (n=15) were localized pain (80%), nausea (40%), fatigue (33%), decreased appetite (27%), and vomiting (20%). The >20% TRAEs in evaluable IPI/INT230-6 patients (n=14) were fatigue (39%), localized pain (39%), nausea (31%), pruritus (23%), rash (23%) and vomiting. G3 TRAEs occurred in 20% and 7% of patients in the INT230-6 and combination arms respectively with no grade 4 or 5 events in either arm. RECIST metrics are confounded by IT injections due to the large volume of highly retained INT230-6 and the influx of immune infiltrates. Analysis of median overall survival (mOS) for INT230-6 alone (n=15) was 649 days. For INT230-6 dosed at a volume/total tumor burden (TTB) ratio of ≥40%, the mOS was 715 days. The mOS of the combination has not been reached with over 1 year of median follow-up. OS data compare favorably to a synthetic control (mOS of 205 days) based on historical data³. The hazard ratios of INT230-6 alone or with IPI for OS to the synthetic control were 0.446 and 0.270, p-values <0.01. **Conclusions:** INT230-6 dosed IT alone or with IPI was well-tolerated in diverse sarcomas. INT230-6 use was associated with immune infiltration and favorable mOS as compared to a synthetic control, particularly when ≥40% of the TTB was injected. A randomized phase 3 trial vs. SOC in selected sarcoma subtypes with an OS endpoint is planned. References: 1. Oncoimmunology. 2019 Jul 16;8(10). 2. ASCO 6/2022. 3. Sci Rep. 2016;6:35448. Clinical trial information: NCT03058289. Research Sponsor: Intensity Therapeutics.

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Poster Session

Phase I/II study to evaluate penpulimab combined with anlotinib and epirubicin in the first-line treatment of soft tissue sarcoma: Updated. *First Author: Yuhong Zhou, Liver Cancer Institute, Zhongshan Hospital, Fudan University, Shanghai, China*

Background: Anthracycline-based chemotherapy regimens are the cornerstone of first-line treatment of recurrent/metastatic unresectable soft tissue sarcoma(STS), while the efficacy was not satisfactory (the median PFS: 4-8 months). Anti-angiogenesis TKI hypothetically can improve the efficacy of chemotherapy by remodeling the immunosuppressive TME. We conducted this trial to explore the safety and efficacy of PD-1 antibody Penpulimab(P) plus anlotinib(A) and epirubicin(E) in the first-line treatment of STS. The results of the phase I study were reported (2022 ESMO). We updated the latest efficacy and safety data. **Methods:** This ongoing phase I/II, open-label trial (ChiCTR2100048014) enrolled patients (pts) aged 16-75 years old with pathologically confirmed metastatic or unresectable locally advanced STS. Pathologic types are moderately sensitive or above to anthracycline chemotherapy. Pts who met the inclusion criteria were treated with phase I dose results (E 60 mg/m² + A 10 mg and P 200 mg ; E: IV, D1-3, Q3W, A: PO, QD, D1-14, Q3W, P: IV, Q3W) for a total of 6 treatment cycles (3 weeks each). A+P was maintained for 2 years until progressive disease or unacceptable toxicity. The primary endpoint was PFS(progression-free survival) and secondary endpoints were ORR(objective response rate), DCR(disease control), OS(overall survival), 2-year OS and PFSR at 3 and 6 months. The response to treatment was evaluated according to RECIST version 1.1. In addition, adverse events were evaluated by CTCAE v5.0. **Results:** From September 2021 to December 2022, 32 pts (14 males and 18 females) were enrolled with the median age is 53.5 (range 29-73) years old. Pathological types included liposarcoma (DDLPS 14, PLS 1, n = 15), undifferentiated sarcoma (n = 4), leiomyosarcoma (n = 5), angiosarcoma (n = 3), fibrosarcoma (n = 2), and others (n = 3). At the data cut off date on December 20, 2022, Median follow-up time was 3.5 months (range 0.03-15.38), Median PFS was 10.55 months [95%CI 4.60, 14.59]. Median OS was not reached. The PFS at 3 months and 6 months was 86.76%, 68.16%, respectively, and the OS at 12 months was 92.64%. 24 pts were eligible for the evaluation of tumor response, the objective response rate (ORR) was 12.50% (4/24) and the disease control rate (DCR) was 68.75% (14/24). The incidence of treatment-related adverse events of grade 3 was 31.25%, with a higher incidence of hypertriglyceridemia (9.38%), Neutrophil count decreased (6.25%), palmar-plantar erythrodysesthesia syndrome (6.25%), febrile neutropenia (6.25%), respectively. The incidence of Severity Adverse Event was 12.5%. 50 pts are expected to be enrolled in the study, and the data will be mature after the follow-up is completed. **Conclusions:** Penpulimab(P) plus anlotinib(A) and epirubicin(E) has shown encouraging activity as first-line treatment for STS, which significantly prolong the PFS with well tolerance. Clinical trial information: ChiCTR2100048014. Research Sponsor: None.

11571

Poster Session

Trabectedin (T) versus adriamycin plus dacarbazine (A-DA) in advanced solitary fibrous tumor (SFT): Results from a phase II randomised clinical study (STRADA). *First Author: Silvia Stacchiotti, IRCCS Foundation National Cancer Institute, Milan, Italy*

Background: T and A-DA showed antitumor activity in a PDX model of dedifferentiated-SFT (D-SFT) and a few cases of activity in advanced SFT pts have been reported. The efficacy of these agents in advanced typical- (T-) malignant- (M-) SFT is unclear. A phase 2 randomised (R) study was conducted within the Italian Sarcoma Group (ISG) to investigate the activity of T and A-DA in advanced T-, M- and D-SFT (Clin-Gov: NCT03023124). **Methods:** An Italian, multicentre, investigator-initiated prospective open-label, R, non-comparative, phase 2 trial was started in July 2017 involving 6 ISG sites, to evaluate the activity of front-line T (1,5-1,3 mg/sqm at investigator's discretion, day 1 every 3 wks; arm A) vs A-DA (A 75 mg/sqm day 1 + DA 400 mg/sqm days 1,2 every 3 wks; arm B) in > 18 years-old pts with advanced SFT (T-SFT, M-SFT, D-SFT) until progression or limiting toxicity; in arm B, a maximum number of 6 cycles was foreseen, given the constrain of the maximum tolerated dose of A. Eligible pts had to show RECIST progression in the 6 mos prior to study entry. Centralized pathologic and radiologic review was performed. Pts were randomly assigned to Arm A or Arm B (1:1 ratio), with cross over in case of progression (PD) or unacceptable toxicity prior to the completion of the 6 cycles (arm B in case of randomization to arm A and vice versa). An interim analysis was pre-planned after reaching 10 evaluable pts in each arm, and at least 1 response in arm A was required to continue the study. Primary end-point was the overall response rate (ORR) by RECIST; secondary end-points ORR by Choi, progression-free survival (PFS), overall survival (OS). **Results:** Enrollment for the interim analysis was completed in September 2022. 30 pts were screened and 23 were enrolled (7 screening failure): T-SFT = 7, M-SFT = 14, D-SFT = 2. All pts were naïve; 3 pts are ongoing, 20 completed their treatment (12 = PD, 8 = other). All pts were evaluable for RECIST. No responses by RECIST were seen in each arm (ORR 0%), while stable disease (SD) and PD were 9 (45%) and 1 (5%) in arm A and 8 (40%) and 2 (10%) in arm B, respectively. At a 15.9-mo (I.Q. range 11.3-29.0) m-FU, m-PFS by RECIST was 9.2 (2.7-not assessable) mos in arm A and 8.0 (1.1-not assessable) mos in Arm B, with 29.6% progression-free pts at 1 year in arm A and 18.7% in arm B. Median OS was 34.3 (9.3-not assessable) mos in arm A, 31.5 (4.2-31.5) mos in arm B. **Conclusions:** No responses were seen neither to T nor to A-DA across all SFT subtypes; therefore, the study was closed to enrolment for T-SFT and M-SFT after the interim analysis. Noteworthy, both T and A-DA stabilised the disease in about 40% of previously progressive pts, and nearly 30% of pts treated with T were free from progression at 1 year. On the other hand, no conclusion can be drawn yet on the activity of T/A-DA in this SFT subtype, since D-SFT cases who entered the study were only 2 and the enrolment of D-SFT is still ongoing. Clinical trial information: NCT03023124. Research Sponsor: Pharmamar.

11570

Poster Session

A phase II study of talimogene laherparepvec (T-VEC) and pembrolizumab in patients with advanced sarcoma: Results of expansion cohorts. *First Author: Ciara Marie Kelly, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: The open-label, single-center phase II study of T-VEC and pembrolizumab in patients with advanced sarcoma met its primary endpoint and demonstrated a best objective response rate of 30% at 24 weeks per RECIST v1.1 (Kelly CM, et al, Jama Oncology, 2020). Responses were seen in undifferentiated pleomorphic sarcoma (UPS), myxofibrosarcoma (MFS), epithelioid sarcoma (ES), cutaneous angiosarcoma (AS), and undifferentiated sarcoma not otherwise specified. Here, we report the efficacy observed in three histology specific expansion cohorts: 1) UPS/MFS, 2) cutaneous AS and 3) ES. **Methods:** Patients refractory to ≥ 1 prior line of systemic therapy or declined standard of care systemic therapy received pembrolizumab intravenously and intratumoral T-VEC injections on day 1 of a 21-day cycle. The primary endpoint was best objective response (ORR, complete and partial responses per RECIST v 1.1) by 24 weeks estimated for each subtype-specific cohort. Secondary objectives included: adverse events (AEs, TRAEs), median PFS and correlatives. **Results:** Twenty-one patients enrolled in the expansion cohorts: median age 72 years (range: 39-85), male 57%, ≥ 1 prior line of therapy (43%). Treatment was well tolerated in twenty patients; one patient discontinued study therapy due to grade 3 immune mediated hepatitis. Nineteen patients were evaluable for efficacy (one patient withdrew from the study and another discontinued treatment before week 24). Subtype specific best ORR by 24 weeks per RECIST v 1.1: UPS/MFS – 11% (n = 1/9)[95% CI: 0.0-0.48]; AS – 43% (n = 3/7)[95% CI: 0.1-0.82]; ES – 0% (n = 0/3). The best ORR overall for the AS cohort was 71% (n = 5/7)[95% CI: 0.03-0.95]. Median PFS (weeks) was 14.9 [CI: 7-11] for UPS/MFS and 54 [95% CI: 3- not reached] for AS (Table). **Conclusions:** TVEC and pembrolizumab demonstrated acceptable safety and promising anti-tumor activity in cutaneous AS (head & neck (n = 4) and Stewart-Treves syndrome involving the upper extremity (n = 1)). Five AS patients experienced a partial response with durable disease control, remaining on study for 1-2 years or more. Two delayed responses were observed in the AS cohort after the pre-specified 24-week criteria. One AS responder progressed on immune checkpoint inhibition prior to study entry. Correlative analyses are ongoing. Clinical trial information: NCT03069378. Research Sponsor: Merck and Amgen; Cycle for Survival; from NIH/NCI Cancer Center Support Grant p30 CA008748; Angiosarcoma Awareness, Inc foundation provided funding for travel reimbursement for angiosarcoma participants in the expansion cohort.

	UPS/MFS (n = 10*)	Cut. AS (n = 8*)	ES (N = 3)
Median Age (range)[years]	69 (48-81)	80 (72-85)	63 (39-70)
Prior treatment (%)			
≤ 2 regimens	7 (70)	4 (50)	2 (66.6)
≥ 3 regimens	3 (30)	4 (50)	1 (33.3)
Prior immunotherapy (%)	2 (20)	1 (12.5)	0 (0)
≥ Grade 3 TRAE (%)	0 (0)	1 (hepatitis) (12.5%)	0 (0)
Best ORR at 24 weeks n (%) [CI]	1 (11) [0.0-0.48]	3 (43) [0.1-0.82]	0 (0)
Best ORR overall n (%)	1 (11)	5 (71)	0 (0)
Clinical benefit rate (%)	6 (67)	5 (71)	1 (33.3)
Median PFS (weeks)	14.9 (CI: 7-110)	54 (CI: 3- NR)	—

*One patient was evaluable for toxicity but not evaluable for efficacy because they came off study prior to week 24.

11572

Poster Session

Efficacy of eribulin administered in combination with an immune checkpoint inhibitor (ICI) and anlotinib as salvage treatment for patients (pts) with advanced adult soft tissue sarcoma (STS). *First Author: Xi Guo, Department of Medical Oncology, Zhongshan Hospital, Fudan University, Shanghai, China*

Background: Eribulin combined with a multi-targeted antiangiogenic tyrosine kinase inhibitor has shown efficacy in STS. ICIs have also exhibited improved survival in some STS subtypes. We investigated the efficacy and safety of triple combination therapy with eribulin, an ICI and anlotinib in the treatment of advanced STS in an adult Chinese population. **Methods:** This study retrospectively analyzed data from patients diagnosed with advanced STS who received combination therapy with eribulin, an ICI and anlotinib at the Department of Oncology, Zhongshan Hospital affiliated to Fudan University. The primary endpoint was progression-free survival (PFS). Secondary endpoints included objective response rate (ORR) by RECIST v1.1, disease control rate (DCR), and treatment-related adverse events (TRAEs) by CTCAE v5.0. **Results:** Medical records from 32 pts treated between August 15, 2020 and January 31, 2023 were included; the median age was 56 years, 71.8% (23/32) were female, 75.0% (24/32) had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1, and 25.0% (8/32) had an ECOG PS of 2. Pts had received a median of 2 (range 0-6) prior regimens and the median follow-up was 4.1 months. Among the patients, 50.0% (16/32) had liposarcomas (including 1 with pleomorphic liposarcoma and 15 with dedifferentiated liposarcoma [DDLPS]), 31.3% (10/32) had leiomyosarcomas (LMS), 3 had undifferentiated pleomorphic sarcoma (UPS), and 1 each had angiosarcoma, rhabdomyosarcoma and desmoplastic small round cell tumor. In a preliminary analysis, 29 pts were evaluable for clinical activity; partial responses (PRs) were achieved in 3 pts (2 DDLPS, 1 UPS), the ORR and DCR were 10.3% (3/29) and 62.1% (18/29) respectively, and the median PFS was 5.7 months (95% CI 2.7-9.8). Of the 15 pts with DDLPS (median 1 prior line of therapy; median follow-up 6.3 months), 13 were evaluable for clinical activity; a PR was achieved by 15.4% (2/13), the DCR was 61.5% (8/13), the median PFS was 9.8 months (95% CI 1.8-28.5) and treatment was ongoing in 46.7% of pts (n = 7). Among the 9 evaluable pts with LMS, 0 achieved a PR, the DCR was 44.4% (4/9), median PFS was 3.9 months and 3 pts were still receiving treatment. In the overall cohort (n = 32), TRAEs of any grade occurred in 56.3% of pts (n = 18), the most common were myelosuppression (28.1%), fatigue (15.6%), fever (12.5%) and rash (12.5%). Grade 3/4 TRAEs occurred in 12.5% of pts, with no grade 5 events. **Conclusions:** This study demonstrates the potential efficacy of combination therapy with eribulin, an ICI and anlotinib in patients with advanced STS, especially in those with the DDLPS subtype. Our data suggest that this combination has good tolerability and a prospective trial is warranted. Clinical trial information: ChiCTR2100053594. Research Sponsor: None.

11573

Poster Session

Trabectedin failure-free survival (TFFS) after resuming trabectedin (T) in advanced myxoid liposarcoma (MLPS) patients. *First Author: Chiara Fabroni, Italian National Cancer Institute, Milan, Italy*

Background: To explore the time to trabectedin failure-free survival after resumption of T in advanced MLPS patients who were stable or responding to T at the time of discontinuation. **Methods:** We retrospectively collected the cases of all patients with advanced MLPS treated with T at our institution from September 2002, highlighting those who were free from progression (according to RECIST) after 6 cycles of T. Trabectedin failure-free survival (TFFS) was defined as time from the first cycle of T to progression (PD) or death, whichever occurred first. Survival analyses were performed using the Kaplan-Meier method. **Results:** Since September 2002, 75 patients with recurrent myxoid liposarcoma received T at our institution. A total of 56 patients were free from progression (according to RECIST) after 6 cycles of T and were included in this analysis. Among them, 25/56 (45%) interrupted their treatment in absence of progression, while 31/56 (55%) patients received T until progression of disease. In the former group, 11/25 had surgery of their residual disease, 3/25 received radiotherapy, 5/25 interrupted T for toxicity and 6/25 patients shared the decision to stop with the clinician. Among patients who received surgery, 2/11 had monofocal disease (longest diameter < or = 5cm), 4/11 had monofocal disease (longest diameter between 10-18 cm) and 5/11 had plurifocal disease. The interruption of T in these 25 patients occurred after a median of 12 cycles (interquartile range = 9-14). Median TFFS was 43.4 months (95%CI 38.7-NA). In the concurrent group of patients who received T continuously, the median TFFS was 14.2 months (95% CI: 10.8-21.9). **Conclusions:** While the longer TFFS of patients undergoing discontinuation cannot be compared with the shorter of those who did not interrupt, the former group being biased favorably (feasibility and exploitation of surgery, other likely determinants of physician's decision to stop), we speculate that there may be a subgroup of selected patients with advanced myxoid liposarcoma primarily responding to T, who could benefit from a "stop and go" policy, thus prolonging the overall time interval within which T remains active. Prospective studies in selected subgroups of MLPS patients on optimization of treatment strategy with T are worthwhile. Research Sponsor: None.

11575

Poster Session

Risk stratification tools to help decide on adjuvant chemotherapy usage in resected soft tissue sarcomas: A 10 year review of an Irish sarcoma centre experience. *First Author: Catherine Weadick, Department of Medical Oncology, Cork University Hospital, Cork, Ireland*

Background: Soft tissue sarcoma (STS) is comprised of 80 pathologic subtypes based on a combination of distinctive morphological, immunohistochemical and molecular features. Adult-type soft tissue and visceral sarcomas are rare, with an estimated incidence of 4-5/100,000/year in Europe. The National Comprehensive Cancer Network (NCCN) guidelines recommend consideration of neo-adjuvant or adjuvant systemic treatment in resectable stage III (high grade tumours which are >5cm) and also in those who need to undergo an amputation or radical resection with adverse functional outcomes. The Sarcuator risk prediction tool has identified a threshold of risk above which the administration of chemotherapy may provide an overall survival benefit. This can be applied to the most common histologic subtypes. Patients affected by these subtypes and with a 10-year predicted OS likelihood <60% are considered as high risk and therefore, should be considered for adjuvant chemotherapy. Alternatively, tumours considered at high risk of recurrence based on size >5cm and high grade histology, may benefit from adjuvant chemotherapy. Therefore, the aim of this project is to review the outcomes of resected extremity/trunk soft tissue sarcoma and assess the prognostic accuracy of these risk prediction methods. **Methods:** All new patients with resected STS discussed in the STS MDT in Cork University Hospital between Jan 2012 – Dec 2021 were identified. The histology and imaging of the identified patients were reviewed. Data regarding demographics, histology, treatment and outcomes was collected. Risk assessment using AJCC and Sarcuator score was done on all patients with an extremity or trunk sarcoma. Overall survival was recorded and assessed including Kaplan Meier method for time to event analysis. **Results:** 200 patients were identified as having an STS resected - 134 of these were located on the trunk or extremities representing 24 different histological subtypes. Sarcuator score was calculated for 60 of these (well differentiated liposarcomas, desmoid tumours, and dermatofibrosarcoma protuberans were excluded). 3 patients received adjuvant chemotherapy and 4 patient neoadjuvant chemotherapy. Overall survival data is presented below. **Conclusions:** Our cohort is representative of the broad histological subtypes expected in sarcoma. Sarcuator score results correlate with international outcomes, with higher scores associated with increased mortality. In our cohort, sarcuator score was more predictive of outcome than tumour grade/size alone. Research Sponsor: None.

Sarcuator score – risk assessment	No. patients	No. of deaths	5 yr OS rate (n = 30)
High risk	19	8 (42.1%)	60.2%
Low risk	41	6 (14.6%)	87.1%
AJCC staging - risk assessment	No. patients	No. of deaths	5 yr OS rate (n = 30)
High risk	25	8 (32%)	67.6%
Low risk	35	6 (17%)	86.3%

11574

Poster Session

Outcome of patients (PTS) with advanced epithelioid hemangioendothelioma (EHE) after failure on sirolimus (S). *First Author: Claudia Giani, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy*

Background: EHE is an ultra-rare sarcoma, showing a highly variable clinical behavior, from indolent to very aggressive. Systemic agents available for treatment of sarcoma have marginal activity in EHE. S showed antitumor effect in PDX models and pts affected by advanced EHE. However, clinical data on S in EHE are only retrospective and uncontrolled. This makes it difficult to interpret if the median progression-free survival (m-PFS) of 13 mos and the m-overall survival (m-OS) of 18.8 mos observed in the 38 progressive pts included in the largest series available (Stacchiotti et al, doi:10.1002/cncr.33247) were attributable to the antitumor effect of S or to EHE natural history. To fill this gap, we reviewed the outcome of pts included in this series who went off S. **Methods:** Clinical data of all EHE pts included in the above-mentioned retrospective study and treated with S for advanced disease between 2010 and 2019 were reviewed, focusing on pts who discontinued S for any reason. Progression was retrospectively categorized by RECIST 1.1 progressive disease (PD) and as "clinical progression" (CP), CP being defined as worsening of systemic symptoms and/or serosal effusion without criteria for RECIST PD. Survival analyses were performed by Kaplan-Meier method. OS was defined as the time from S start until death or last follow-up (FU), post-discontinuation OS (pOS) as the time from S discontinuation until death or last FU, post-discontinuation PFS (pPFS) as the time from S discontinuation until first evidence of progression (PD or CP) or death, post-re-challenge PFS (pR-PFS) as the time from S re-challenge until first evidence of progression (PD or CP) or death. **Results:** Of the 38 pts, 24 stopped S and were included in this analysis (median age = 47 yrs; serosal effusion yes/no = 9/15; S discontinuation due to: RECIST PD = 12, CP = 3, toxicity = 7; other = 2). After S discontinuation all pts had an event (PD or CP or death), and 13/24 (54%) pts did not receive further treatments, while 11/24 (46%) started again a systemic treatment. In particular, 6/24 (25%) restarted S (all after interval progression, PD or CP) with a new stable disease in 5/6 cases. At last FU, 6/24 (25%) pts were alive, 18/24 (75%) dead. At 62.2-mo m-FU (IQR 46-124), m-OS was 14.3 mos (95% CI, 7.3-21.2). Overall m-pPFS was 3.02 mos (95% CI, 1.6-4.4), m-pOS was 7.15 mos (95% CI, 4.4-9.9). m-pPFS of pts who discontinued S without evidence of progression (PD or CP) was also 3.02 mos (95% CI, 2.9-3.1). m-PFS following the re-challenge of S (m-pR-PFS) was unreached; 1 pt died following PD after 19 mos, 1 pt was alive and showed CP at 40 mos, 4 were alive and progression-free after 27, 31, 55, 94 mos. **Conclusions:** In our study the outcome of EHE pts who discontinued S was poor, with a m-pPFS of 3 mos and a m-pOS of 7 mos. However, pts who discontinued S for reasons other than progression benefited from S re-challenge, suggesting that in advanced EHE there is a subset of long-responders to S. Research Sponsor: None.

11577

Poster Session

Clinical implications of recurring mutations in myxoid liposarcoma (MLS). *First Author: Prapassorn Thirasastr, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: MLS is a subset of liposarcoma characterized by a translocation, t(12;16), FUS-DDIT3 or less frequently t(12;22), EWSR1-DDIT3. Additional mutations have been reported in *TERT* promoter, *PIK3CA*, and *PTEN* and some were associated with the more aggressive round cell phenotype. Our study aimed at analyzing the clinical significance of these recurring mutations. **Methods:** MLS patients (pt) with available next-generation sequencing (NGS) data (any clinical grade) between Jan 2014 to Oct 2022 were included. Baseline characteristics, chemotherapy (CMT) response (partial response [PR] and stable disease [SD]), and survival were collected for doxorubicin-ifosfamide (AI), doxorubicin-dacarbazine (ADIC), trabectedin (T), and eribulin (E). Binary logistic regression was used to evaluate mutations associated with response. Cox proportional-hazard regression was used to investigate associations of variables with progression-free survival (PFS) and overall survival (OS). The Kaplan-Meier method was used to estimate survival and log-rank tests were used to compare survival between groups. **Results:** Of 18 MLS pt included, median age at diagnosis was 42 years (R 30-65). Majority were male (12/18, 67%), had localized disease at diagnosis (13/18, 72%), and had lower extremities as primary location (10/18, 56%). Eight (44%) had round-cell > 5% and 15 (83%) had primary tumor > 5 cm. Somatic mutations were reported in 15 pt (83%); the most common were *TERT* promoter (61%), *PTEN* (28%), *PIK3CA* (22%), and *TP53* (17%). None showed significant association with clinical factors (age, sex, size, stage, round cell > 5%, primary location). Forty-eight records (18 AI, 6 ADIC, 19 T, and 5 E; 3 pt received AI and T twice for different recurrences), were evaluated for PFS and 47 records had response data available. For AI, ADIC, T, and E, PR rate was 39% (7/18), 17% (1/6), 32% (6/19), and 40% (2/5), while clinical benefit (CBR: PR + SD ≥ 3 mo) was 67% (12/18), 50% (3/6), 63% (12/19), and 80% (4/5), respectively. PR or CBR were not associated with the common mutations for any regimen. Median follow up (FU) from start of CMT was 4 mo (R 0.5-31). PFS (95%CI) was 11 (6.7- Not Reached [NR]), 1.2 (1.1-NR), 23 (6.3-NR), and 8 (1.3-NR) mo for AI, ADIC, T, and E, respectively. *PIK3CA*m (n = 15) was associated with improved PFS with CMT (PFS [95%CI]: *PIK3CA*w 7.8 [6.3-11.2] vs. *PIK3CA*m 23 mo [1.3-NR]; multivariate hazard ratio [HR] 0.23, p = 0.036, adjusted by gender and ADIC regimen). This appeared to be mainly driven by the *PIK3CA*m/*TERT*wt (n = 8, HR 0.07, p = 0.006). For T, *PIK3CA*m/*TERT*m (n = 3) showed a trend for lower PFS (1.3 mo) in contrast to other groups (23 mo). **Conclusions:** *TERT* promoter mutation was the most frequent mutation but was not associated with outcome in our small series. *PIK3CA*m suggested PFS benefit from CMT while, on the contrary, dual *PIK3CA*m/*TERT*m showed a trend towards shorter PFS with T. The predictive and prognostic role of these mutations in MLS warrant further study. Research Sponsor: None.

11578

Poster Session

DKC expression by RNAseq as a potential biomarker of gemcitabine response in sarcoma. *First Author: David A. Liebner, The Ohio State University, Columbus, OH*

Background: Deoxycytidine kinase (DKC) is responsible for activation of gemcitabine by phosphorylation of gemcitabine to its monophosphate form. Studies have suggested that DKC expression may be correlated to response to gemcitabine in various solid tumors, and that downregulation of DKC may be at least partly responsible for gemcitabine-resistance *in vitro*. However, the significance of DKC expression in sarcomas as a biomarker of response to gemcitabine remains poorly characterized. **Methods:** Participants enrolled in the prospective Electronic Health Record (EHR)-Based Comprehensive Bone and Soft Tumor Registry (NCT02677961) at The Ohio State James Cancer Center who had received gemcitabine-based chemotherapy for the treatment of bone and soft tissue sarcoma were eligible for this study. A total of 179 patients were identified who had received at least one cycle of gemcitabine-based chemotherapy, between January 1st, 2014, to December 31st, 2022. Whole exome RNAseq expression data was available for 36 of these patients who had received gemcitabine-based chemotherapy in the setting of active disease. **Results:** Of the 36 patients included in this study, 22 were female and 14 were male. Nine different main disease types were identified in the patient subset. These include angiosarcoma (8), chondrosarcoma (1), leiomyosarcoma (16), liposarcoma (3), malignant peripheral nerve sheath tumor (1), myxofibrosarcoma (2), osteosarcoma (2), undifferentiated pleomorphic sarcoma (3), and undifferentiated spindle cell sarcoma (1). The median time to treatment discontinuation (TTD) among all patients was 178 days. Among DKC low-expressors (n = 16), the median TTD was 86 days; among high-expressors (n = 16), the median TTD was not reached. Differences between groups did not reach statistical significance (HR = 0.55, p = 0.14). **Conclusions:** DKC expression by clinical RNAseq is a potential biomarker of gemcitabine-response in sarcoma, but larger studies are necessary to evaluate the potential clinical significance and possible role of DKC expression in identifying patients most likely to benefit from gemcitabine-based chemotherapy. Research Sponsor: Ohio State University, Division of Medical Oncology Research Award.

TPS11579

Poster Session

AOST2031: An in-progress COG phase 3 randomized controlled trial comparing open vs thoracoscopic management of pulmonary metastases in patients with osteosarcoma. *First Author: John J Doski, University of Texas Health Sciences Center at San Antonio, San Antonio, TX*

Background: Pulmonary metastasectomy is considered a necessary component of curative therapy in pulmonary metastatic osteosarcoma, however the optimal surgical approach is unknown. Two approaches include open surgery (OSY) including thoracotomy or sternotomy and minimally invasive surgery (MSY) by thoracoscopy. No randomized trial has been completed comparing these approaches in patients with osteosarcoma, however randomized controlled trials in other cancers have not identified superior outcomes in patients undergoing OSY. OSY allows for direct palpation of all lung surfaces and more pulmonary metastatic nodules can be identified during OSY compared to the number predicted by pre-operative imaging. MSY offers the benefit of faster patient recovery, improved quality of life and potential for equivalent surgical control of relevant metastatic disease. Given wide variability in surgical approach and willingness of both surgical oncology and patient advocacy communities to participate in a randomized trial, AOST2031 was developed to address this clinical equipoise. **Methods:** Eligibility for AOST2031 includes patients < 50 yrs with a histological diagnosis of osteosarcoma and evidence of pulmonary metastases at initial diagnosis or at first recurrence. Patients must have oligometastatic lung metastasis considered resectable by either OSY or MSY, with rapid central review of chest CT images to confirm eligibility. Systemic therapy considered equivalent to methotrexate, cisplatin and doxorubicin is required to be ongoing in newly diagnosed and completed in patients with recurrence. Exclusion criteria include unresectable primary disease, metastatic disease requiring anatomic lung resection, pleural or mediastinal lesions or pleural effusions, progression while receiving initial therapy, extra-pulmonary metastases and prior chest surgery for pulmonary metastases. Patients are randomized 1:1 to either OSY or MSY, with randomization stratified by disease status and risk. The primary outcome is thoracic event free survival, defined as intrathoracic tumor recurrence or death that results from the procedure or a complication related to the procedure. Two-hundred and twenty-five eligible patients are anticipated to answer the primary objective. Secondary objectives include event free, overall survival and . Exploratory objectives include surgical complication rates, patterns of recurrence, use of surgical localization techniques, comparison of CT findings to pathology of resected specimens, and patient reported outcomes. Biologic objectives include the collection of metastatic tissues to facilitate the study of metastatic disease and serial blood samples for future tumor profiling, germline and circulating tumor DNA studies. AOST2031 opened to enrollment at NCTN sites in February 2022. Clinical trial information: NCT05235165. Research Sponsor: U.S. National Institutes of Health.

TPS11580

Poster Session

A randomized, open-label, phase 2 study evaluating abemaciclib in combination with irinotecan and temozolomide in participants with relapsed or refractory Ewing sarcoma. *First Author: Gertjan VAN HAL, Eli Lilly and Company, Indianapolis, IN*

Background: Ewing's sarcoma (ES) is the second most common malignant bone tumor affecting children and young adults. Patients with relapsed disease have a poor prognosis and need effective therapies. *EWS-FLI1*, the most common ES fusion gene (90-95% of cases), is an oncogenic transcription factor that downregulates intrinsic cyclin-dependent kinase (CDK) inhibitors, *CDKN1A* and *CDKN1C*, which promote cell cycle arrest and upregulates *CDK4*, which drives entry into the cell cycle. This provides a biological rationale for the clinical evaluation of CDK4/6 inhibitors in ES. Abemaciclib is a selective CDK4/6 inhibitor approved for the treatment of breast cancer. It is approximately 14 times more potent against CDK4/cyclin D1 than CDK6/cyclin D3 in enzymatic assays and has the advantage of continuous dosing schedule without breaks for neutrophil recovery. Abemaciclib is currently also in clinical development for paediatric patients with relapse/refractory solid tumors in combination with irinotecan and temozolomide (JPCS study, NCT04238819). This study, NCT05440786, will evaluate the potential benefit of adding abemaciclib to irinotecan plus temozolomide for the treatment of relapsed/refractory ES. **Methods:** This randomized, open-label, Phase 2 study is part of the CAMPFIRE master protocol. It is enrolling paediatric and young adult patients (1-39 years) with relapsed/refractory ES or ES-like tumors. Approximately 45 patients will be randomized 2:1 between 2 arms: irinotecan and temozolomide with or without abemaciclib. Stratification factors include age, pulmonary/non-pulmonary site of metastases, and time to recurrence from initial diagnosis. Patients will receive irinotecan (50 mg/m²/day intravenously) and temozolomide (100 mg/m²/day orally) on days 1-5. Abemaciclib will be administered orally twice-daily on a continuous 21-day cycle. The abemaciclib dose will be 55mg/m² BID for patients < 18 years and 100mg BID for those ≥ 18 years. Besides 25 and 50mg tablets, abemaciclib will be available as 2.5mg granules allowing administration of doses as low as 10mg to patients with a body surface area lower than 0.2m². Treatment continues until disease progression or other discontinuation criteria are met. The primary endpoint is progression-free survival (PFS) determined by a blinded independent review committee using Response Evaluation Criteria in Solid Tumors, Version 1.1. Key secondary endpoints include overall survival, objective response rate, duration of response, disease control rate, PFS determined by investigator assessment, safety, and pharmacokinetics. Additional analysis includes exploratory biomarker testing. This study is open and actively enrolling in Australia, Europe, Japan, and United States. Clinical trial information: NCT05440786. Research Sponsor: Eli Lilly and Company.

TPS11581

Poster Session

ENLIGHTEN-01: A phase 1 study of fluorescein-specific (FITC-E2)-CAR T cells in combination with folate-fluorescein (UB-TT170) for osteosarcoma. *First Author: Catherine Michelle Albert, Seattle Children's Research Institute, Seattle, WA*

Background: Outcomes for relapsed osteosarcoma (OS) remain poor and there are no systemic therapies that have been shown to provide a survival benefit. Chimeric Antigen Receptor (CAR) T cell immunotherapy involves the adoptive transfer of T-lymphocytes that have been engineered to recognize tumor-specific antigens, resulting in targeted lysis of malignant cells. Folate receptors (FR) are membrane-bound surface proteins that bind folates with high affinity. FRs are overexpressed in OS and have very limited expression in normal tissue. UB-TT170 (Umoja Biopharma) is a small molecule bispecific "adapter" consisting of folate conjugated to fluorescein (FL). It penetrates tumors in minutes and is retained for long periods of time due to high affinity for the FR, while unbound UB-TT170 rapidly clears from the blood and from FR- tissues. We hypothesize that administration of fixed dosing anti-FL(FITC-E2) CAR T cells followed by escalating doses of UB-TT170 will deliver personalized immunotherapy to OS patients. In addition, this approach offers an attractive safety mechanism since administration of NaFL should reverse CAR T cell reactivity. **Methods:** We designed a Phase I study for young adult (15-30 yr) patients with recurrent/refractory OS to examine the safety and feasibility of administering autologous, peripheral blood-derived T cells that have been genetically modified to express a 2nd generation FL-specific CAR in combination with intra-subject dose escalation of UB-TT170. The primary objective is to identify a recommended dose escalation sequence of UB-TT170 to move forward in clinical development. A 3+3 design will be used to investigate 3 possible dosing sequences. The trial opened in July 2022. As of January 5, 2023, 5 subjects have enrolled and one subject has been treated on dose regimen 1. T cell products have been successfully manufactured for all enrolled subjects. The trial remains open to enrollment. Clinical trial information: NCT05312411. Research Sponsor: Umoja Pharma; Seattle Children's Therapeutics.

TPS11582

Poster Session

INSIGHT: A phase 3, randomized, multicenter, open-label study of ripretinib vs sunitinib in patients with advanced gastrointestinal stromal tumor previously treated with imatinib harboring *KIT* exon 11 + 17 and/or 18 mutations. First Author: Suzanne George, Dana-Farber Cancer Institute, Boston, MA

Background: Gastrointestinal stromal tumor (GIST) is the most common gastrointestinal sarcoma, with approximately 80% of cases driven by *KIT* mutations. Most patients (pts) with advanced GIST develop disease progression following first-line treatment with imatinib due to *KIT* secondary resistance mutations occurring most commonly in the ATP-binding pocket (exons 13/14) and/or activation loop (exons 17/18). Sunitinib is approved as second-line therapy for advanced GIST. Ripretinib is a switch-control tyrosine kinase inhibitor approved for pts with GIST who received prior treatment with 3 or more kinase inhibitors, including imatinib. In the phase 3 INTRIGUE study (NCT03673501) in second-line advanced GIST, ripretinib was not superior to sunitinib in terms of progression-free survival (PFS); however, a more favorable safety profile was observed with ripretinib vs sunitinib (Bauer S et al. *J Clin Oncol*. 2022). Exploratory mutational analysis from INTRIGUE using baseline circulating tumor DNA (ctDNA) demonstrated that pts harboring primary *KIT* exon 11 mutations with secondary resistance mutations exclusively in *KIT* exons 17 and/or 18 derived PFS benefit with ripretinib vs sunitinib (median, 14.2 vs 1.5 months; HR = 0.22, 95% CI 0.11 to 0.44, nominal $P < 0.0001$; Bauer S et al. *J Clin Oncol*. 2023; abstract 397784). Here, we describe a planned phase 3 study for pts with advanced GIST previously treated with imatinib harboring *KIT* exon 11 + 17 and/or 18 mutations. **Methods:** INSIGHT is a phase 3, randomized, open-label study that aims to evaluate the efficacy of ripretinib vs sunitinib in pts with advanced GIST previously treated with imatinib and who harbor *KIT* exon 11 + 17 and/or 18 mutations. Eligible pts must be ≥ 18 years old with histologically confirmed GIST and co-occurring *KIT* exon 11 + 17 and/or 18 mutations confirmed by ctDNA analysis. Pts must also have advanced disease with ≥ 1 measurable lesion per modified Response Evaluation Criteria in Solid Tumors (mRECIST) v1.1, radiologic progression on imatinib, and an Eastern Cooperative Oncology Group Performance Status ≤ 2 . Key exclusion criteria include a *KIT* exon 9, 13, or 14 mutation via ctDNA at screening and prior treatment with another line of therapy in addition to imatinib for advanced GIST. A total of 54 pts will be randomized (2:1) to receive ripretinib 150 mg once daily (QD; continuous) or sunitinib 50 mg QD (4 weeks on/2 weeks off) in 6-week cycles. The primary endpoint is PFS by independent radiologic review (IRR) per mRECIST v1.1; key secondary endpoints are objective response rate by IRR using mRECIST v1.1 and overall survival. Safety and patient-reported outcome measures will also be assessed. Pts randomized to the sunitinib arm may cross over to the ripretinib arm upon disease progression. Clinical trial information: NCT05734105. Research Sponsor: Deciphera Pharmaceuticals, LLC.

TPS11584

Poster Session

Alliance A092104: A randomized phase 2/3 study of olaparib plus temozolomide versus investigator's choice for the treatment of patients with advanced uterine leiomyosarcoma after progression on prior chemotherapy. First Author: Kristine Peregrino Lacuna, Columbia University Irving Medical Center, New York, NY

Background: Uterine leiomyosarcoma (uLMS) is an aggressive sarcoma subtype with frequent metastatic relapse. Advanced uLMS is treated with gemcitabine/docetaxel or anthracycline-based regimens. After failure of initial chemotherapy, remaining options provide limited benefit (trabectedin: objective response rate (ORR) 11%, median progression-free survival (mPFS) 4.0 months (mo); pazopanib: ORR 11%, mPFS 3.0 mo; dacarbazine: ORR 9%, mPFS 1.5 mo). 18-23% of uLMS harbor deleterious alterations in homologous recombination (HR) DNA repair genes. HR-deficient cancers are unable to effectively repair double-stranded DNA breaks and may be sensitive to poly ADP-ribose polymerase (PARP) inhibitor-based strategies. In preclinical studies, the combination of temozolomide (T), an alkylating agent, and olaparib (O), a PARP inhibitor, markedly suppressed proliferation of uLMS models. Among 22 uLMS patients with median 3 prior lines, O+T demonstrated mPFS 6.9 mo and ORR 27% (Ingham M. et al. ASCO 2021: #11506). In correlative analysis, alterations in HR genes including *PALB2* and *RAD51B* or absence of *RAD51* foci formation by a functional assay were observed in patients with prolonged PFS (Bose S. et al. ASCO 2022: #11509). Based on these results, we designed a randomized phase 2/3 study to further evaluate O+T in advanced, pretreated uLMS. **Methods:** Alliance for Clinical Trials in Oncology A092104 is a randomized, open-label phase 2/3 clinical trial of O+T versus investigator's choice in advanced uLMS. Eligible patients have ECOG performance status ≤ 2 , progression on ≥ 2 prior treatment lines and measurable disease. Patients are randomized 1:1 to receive T 75 mg/m² orally daily + O 200 mg orally twice daily on days 1-7 in 21-day cycles (Arm 1) or investigator's choice of trabectedin 1.5 mg/m² over 24 hours every 21 days or pazopanib 400-600 mg orally daily (Arm 2). For phase 2, the primary endpoint is PFS. The design evaluates for an improvement in PFS from 4 mo to 8 mo, requires 70 patients, and yields 90% power and 1-sided alpha 0.10. If phase 2 is positive, phase 3 will enroll. For phase 3, the primary endpoint is overall survival (OS). The design evaluates for an improvement in OS from 13 mo to 23 mo, requires 165 patients (including 70 from phase 2) and yields 90% power with 1-sided alpha 0.025. Secondary endpoints include ORR, duration of response, safety and patient-reported outcomes. Archival tissue will be collected and evaluated with a *RAD51* foci formation assay. Genomic sequencing results will be obtained where available. The study opened to accrual in 1/2023. Support: U10CA180821, U10CA180882, U24 CA196171; <https://acknowledgments.alliancefound.org>. Clinical trial information: NCT05633381. Research Sponsor: U.S. National Institutes of Health.

TPS11583

Poster Session

ENVASARC: A pivotal trial of envafolelimab and envafolelimab in combination with ipilimumab in patients with advanced or metastatic undifferentiated pleomorphic sarcoma or myxofibrosarcoma who have progressed on prior chemotherapy. First Author: Richard F. Riedel, Duke Cancer Institute, Duke University Medical Center, Durham, NC

Background: Metastatic undifferentiated pleomorphic sarcoma (UPS) and the genetically related myxofibrosarcoma (MFS) are soft tissue sarcoma (STS) subtypes with poor prognoses. While responses to first-line chemotherapy can approach 20%, efficacy remains limited in the 2nd-line setting and beyond. Pazopanib, the only FDA approved treatment in the refractory setting, has demonstrated an objective response rate (ORR) of 4%. Envafolelimab is a single domain PD-L1 antibody administered by rapid subcutaneous (SQ) injection that is approved for the treatment of microsatellite instability-high (MSI-H) cancer in China. The activity of envafolelimab appears to be similar to other PD-1 antibodies administered intravenously (i.v.). Envafolelimab demonstrated a 32% ORR in MSI-H colorectal cancer patients with progressive disease following three approved chemotherapeutics, similar to the ORR of 28% and 33% with nivolumab and pembrolizumab in these patients, respectively. The rationale for the ENVASARC is based on envafolelimab activity in STS in phase 1 trials and previously reported activity of checkpoint inhibition in UPS/MFS: single-agent pembrolizumab demonstrated a 23% ORR, while the combination of nivolumab and ipilimumab demonstrated a 29% ORR in refractory UPS/MFS. **Methods:** ENVASARC (NCT 04480502) is a pivotal multicenter (at 30 U.S. and U.K. centers) open-label, randomized, non-comparative, parallel cohort study of envafolelimab 600 mg every 3 weeks by SQ injection (n = 80) or envafolelimab 600 mg every 3 weeks by SQ injection combined with ipilimumab 1 mg/kg every 3 weeks i.v. for four doses (n = 80) in patients with locally advanced, unresectable or metastatic UPS/MFS with disease progression on one or two lines of prior therapy. The primary objective of each of parallel cohort is to demonstrate an ORR with a lower limit of the 95% confidence interval that excludes 5.0% in each cohort. If ≥ 9 responders are observed among the 80 patients enrolled in each cohort, then the lower bound of the 95% confidence interval will exclude 5.0%. Secondary endpoints include duration of response, PFS and OS. Key inclusion criteria: ≤ 2 prior lines of therapy (neoadjuvant therapy excluded), ECOG ≤ 1 . Clinical trial information: NCT04480502. Research Sponsor: TRACON Pharmaceuticals.

TPS11585

Poster Session

A phase 2, open-label, adaptive, dose-ranging study with long-term extension to evaluate the safety, tolerability, efficacy, and pharmacokinetics of intra-articular AMB-05X injections in patients with tenosynovial giant cell tumor. First Author: Hans Gelderblom, LUMC Leids Universitair Medisch Centrum, Leiden, Netherlands

Background: CSF1R is a clinically validated target for Tenosynovial Giant Cell Tumor (TGCT). CSF1 is overexpressed in TGCT and, via action at the colony-stimulating factor 1 receptor (CSF1R), leads to the proliferation of synovial-like mononuclear cells and recruitment of multinucleated giant cells, foam cells, siderophages, and inflammatory cells, which compose the bulk of the neoplasm. Although non-metastatic in nature, TGCT can develop into locally destructive lesions that cause significant local tissue injury, loss of joint function, and impaired quality of life. When complete resection is achievable without significant morbidity, the standard of care for patients with TGCT is surgical resection. Recurrence after surgery occurs in up to 30% of patients with localized TGCT and 83% of patients with diffuse TGCT (Mastboom 2019, Patel 2017). Repeat surgeries may be necessary but often leads to further morbidity, complications, and reduced function of affected joints. A safe, effective, and convenient pharmacotherapy is a desirable addition to the therapeutic armamentarium for TGCT. AMB-05X is a potent and selective anti-CSF1R monoclonal antibody in development for local treatment of TGCT. Intra-articular (IA) injection of AMB-05X enables high drug concentration at the tumor site while minimizing systemic exposure and toxicity. A proof-of-concept study of IA AMB-05X for TGCT found clinically meaningful improvement in objective response rate, functional (pain, stiffness, range of motion) and quality of life measures after 12 weeks of therapy with no serious and a low number of adverse events associated with targeting CSF1R. This phase 2 study aims to establish the optimal dosing regimen and local administration of AMB-05X and confirm the efficacy and safety of 24 weeks and longer treatment. **Methods:** AMB-051-07 (NCT05349643) is an open-label, multicenter, phase 2 study of AMB-05X in patients with TGCT. The trial is being conducted at multiple sites in North America, Europe, and Australia. The dosing schedule includes an injection interval of every 4 weeks and longer, including an extended dosing period. Adult patients with histologically confirmed symptomatic TGCT with one joint involvement whether surgically amenable or non-amenable with measurable disease and adequate organ function are being enrolled. After the initial cohort of patients with TGCT of the knee, other joints may be enrolled pending evaluation by the DMC. The primary study outcome measures are objective response rate (ORR) per RECIST v1.1 by central radiology review and safety. Secondary outcome measures include ORR per modified RECIST and Tumor Volume Score, duration of response, time to response, PRO/QOL (including range of motion, stiffness, pain), pharmacodynamics and pharmacokinetics. Clinical trial information: NCT05349643. Research Sponsor: AmMax Bio, Inc.

TPS11586

Poster Session

PEMBROCABOSARC: Combination of pembrolizumab and cabozantinib in patients with advanced sarcomas. *First Author: Sabrina Sellan-Albert, Institut Bergonie, Bordeaux, France*

Background: Despite optimal treatment, up to 40% of patients with sarcomas will develop locoregional and/or distant relapse and median survival in this setting is less than two years. There are very few options in the treatment of undifferentiated pleomorphic sarcomas whereas there is no specific treatment regimen established for recurrent osteosarcoma (OSS) and Ewing sarcoma (ES). Innovative strategies are therefore urgently needed in these settings. In preclinical studies, while immune checkpoint inhibitors were insufficient in controlling tumour growth, combining them with M2 macrophage or angiogenesis targeting resulted in superior tumour control (Mao et al, Clin Cancer Res 2016; Zhu et al, Cancer Res 2014). Combining both antiangiogenic and MET inhibition properties, cabozantinib has shown both preclinical and clinical activity, notably in osteosarcoma and Ewing sarcoma (Italiano et al. ESMO 2018). Interestingly, cabozantinib has also recently been shown to trigger an innate immune response in a preclinical model (Patnaik et al, Cancer Discov 2017). Altogether, these findings pave the way for studies assessing the impact of targeting angiogenesis, MET and immune response in soft-tissue and bone sarcomas. **Methods:** PEMBROCABOSARC (NCT05182164) is a multi-stratum, three single-arm phase 2, multicenter, open-label study investigating pembrolizumab combined with cabozantinib in patients with advanced selected sarcomas: undifferentiated pleomorphic sarcoma (stratum 1), osteosarcoma (stratum 2), Ewing sarcoma (stratum 3). Strata 1 and 2 will enroll ~32 patients and stratum 3 ~55 patients, respectively. Each stratum phase II will be conducted using a Simon's optimal two-stage design. Eligible and consented patients must be ECOG PS 0-1, have measurable and progressive disease according to RECIST 1.1 and have received less than 3 previous lines of systemic therapy for advanced disease and consent also to baseline and per treatment biopsies. Cabozantinib will be administered orally, once daily at a fixed dose of 40 mg, continuously. Pembrolizumab will be administered by intravenous infusion every 3 weeks on Day 1 of each cycle, at a fixed dose of 200 mg. Both treatments will start on Day 1 (of cycle 1). The primary endpoint is 6-months non progression rate as per RECIST 1.1. Secondary endpoints include adverse events (AEs)/serious AEs, best overall response, and progression-free survival. Pharmacodynamic and other biomarkers will be explored on blood and tumor tissue. The first patient received study drug on May, 31, 2022; 8 of planned 119 patients have been enrolled and 5 sites across France among the planned 10, are currently enrolling patients. Clinical trial information: NCT05182164. Research Sponsor: IPSEN PHARMA; French DGOS.

TPS11588

Poster Session

Engagement of patient participation in genomics research by the Osteosarcoma and Leiomyosarcoma Count Me In Projects of the Cancer Moonshot funded PE-CGS Network. *First Author: Suzanne George, Dana-Farber Cancer Institute, Boston, MA*

Background: Osteosarcoma (OS) and Leiomyosarcoma (LMS) are sarcomas with complex genomes for which there has been limited progress in identifying new treatments and improving outcomes. Slow progress in OS and LMS is partially due to insufficient characterization of the genomic landscape. Generating large genomic datasets in OS and LMS is challenging because of the rarity of these sarcomas and recruitment barriers such as care fragmentation between institutions and specialties. The OS and LMS Project research studies aim to: 1) establish a network of engaged pediatric and adult participants with OS and LMS who will co-create a shared database of clinical, genomic, molecular, and patient reported data to enable research; 2) define the clinicogenomic landscape of OS and LMS; and 3) optimize the approach to direct patient engagement in cancer research. **Methods:** Count Me In, a research initiative with prior success in angiosarcoma, working with patients and advocates created websites (OSProject.org and LMSProject.org) where patients register and consent to participation. Projects were launched in September, 2022. After 5 months of accrual, 306 patients age 6-79 from 149 Institutions have consented. Blood and saliva are collected from consented participants, tumor samples are obtained from pathology departments and medical records are requested from treating hospitals. WES and WGS of tumor and normal, and RNASeq of tumor is performed. ctDNA is obtained and sequenced. Results are shared with patient, advocacy, physician and research communities in several ways. Individual participants receive a shared learning report describing the somatic variants identified in their tumor from paired tumor-normal WES and are offered genetic counseling and clinical germline testing. Registered participants receive updates via email and Project websites. There are regular pre-publication data releases to the genomic data commons and to cBioPortal. A physician engagement committee meets regularly to discuss clinical insights and conundrums from shared learning reports and germline testing. Patient accrual over the next 3 years is anticipated to result in sequencing of 750 tumor-normal pairs and 500 ctDNA samples. Research Sponsor: U.S. National Institutes of Health.

TPS11587

Poster Session

SARC041: A phase 3 randomized double-blind study of abemaciclib versus placebo in patients with advanced dedifferentiated liposarcoma. *First Author: Mark Andrew Dickson, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Recurrent or metastatic dedifferentiated liposarcoma (DDLs) remains a difficult disease to treat. Available agents such as doxorubicin, eribulin, trabectedin, ifosfamide, dacarbazine, or gemcitabine-based regimens are associated with low response rates and only modest improvements in progression free or overall survival. The oncogene CDK4 is ubiquitously amplified in this disease and represents a rational therapeutic target. In single-arm phase 2 studies, treatment with selective CDK4 inhibitors resulted in clinical benefit (12-week progression-free survival (PFS) of 57% with palbociclib and 74% with abemaciclib). We hypothesize that treatment with abemaciclib will improve PFS compared to placebo in patients with recurrent or metastatic DDLs. **Methods:** This is a phase 3 randomized double-blind study of abemaciclib versus placebo. Eligible patients have recurrent or metastatic dedifferentiated liposarcoma (purely well-differentiated liposarcoma excluded), progression of disease by RECIST 1.1 in the 6 months prior to study entry, any number of prior systemic therapies, and adequate organ function and performance status. Patients are stratified by number of prior lines of therapy (0 vs 1 or more) and randomized 1:1 between abemaciclib 200 mg PO twice a day and matching placebo. Patients are followed with scans every 6 weeks (every 12w after 36w) and those with progression of disease on placebo may cross over to open label abemaciclib. The primary endpoint is PFS. Target enrollment is 108 evaluable patients which provides 80% power with two-sided 10% significance level to detect a hazard ratio of 0.6. Secondary endpoints include response rate, PFS and response rate after crossover, and overall survival. Archival tissue will be collected to explore potential biomarkers. As of Feb 1, 2023, 43 patients have been accrued at 9 participating centers. Clinical trial information: NCT04967521. Research Sponsor: Eli-Lilly.

TPS11589

Poster Session

Phase 1 dose-expansion study of oral TP-1287, a cyclin-dependent kinase 9 (CDK9) inhibitor, in patients with Ewing sarcoma (EWS). *First Author: Gregory Michael Cote, MGH Cancer Center, Boston, MA*

Background: Cyclin-dependent kinase 9 (CDK9) blockade inhibits tumor growth and progression by impairing the transcription of key oncogenes, such as myeloid cell leukemia-1 (MCL-1) and c-MYC. CDK9 overexpression has been observed in sarcoma patients (pts), and CDK9 has emerged as a potential therapeutic target in pts with sarcoma. TP-1287 is an investigational orally delivered phosphate prodrug of the CDK9 inhibitor alvocidib. In preclinical studies, TP-1287 has been shown to decrease MCL-1 expression and phosphorylation of RNA polymerase II (RPB1), and inhibit tumor growth in an Ewing sarcoma (EWS) mouse model. Phase 1 dose-escalation in solid tumors has completed and TP-1287 is being investigated in a dose expansion cohort in pts with EWS (NCT03604783). The design of the expansion part of the trial in pts with EWS is herein described. **Methods:** Up to thirty pts with EWS will be enrolled in this dose expansion cohort. Key eligibility criteria are age ≥ 18 years (≥ 12 years, if weight ≥ 40 kg); histologically confirmed locally advanced or metastatic unresectable EWS; received 1 to 5 prior lines of treatment including an anthracycline; one or more measurable tumors per the RECIST v1.1; ECOG performance status of ≤ 1 ; acceptable liver and renal function, and acceptable hematologic and coagulation status; no treatment with surgery, chemotherapy, or investigational therapy within 28 days or 5 half-lives. Eligible pts will be treated with oral TP-1287 monotherapy RP2D established from the dose escalation part (11 mg BID, continuous dosing in a 28-day treatment cycle) and will continue treatment until treatment-related adverse event or disease progression. Assessments will be performed on Day 1 and Day 15 of each cycle. Tumor response assessment will be done after Cycle 2 and at the end of every other cycle thereafter. The primary objectives are objective response rate (ORR) and clinical benefit rate (CBR); secondary objectives are median progression-free survival (PFS), PFS rate at 16-weeks and 24-weeks and safety; and exploratory objectives include evaluation of systemic exposure and pharmacodynamics. Safety data will be reviewed on an ongoing basis and a Bayesian approach will be used to assess the efficacy data. Statistical analysis for safety and efficacy parameters will be primarily descriptive in nature. EWS dose expansion cohort is currently recruiting in the United States. Clinical trial information: NCT03604783. Research Sponsor: Sumitomo Pharma Oncology.

TPS11590

Poster Session

A phase II study of palbociclib combined with retifanlimab in patients with advanced dedifferentiated liposarcoma. *First Author: Sandra P. D'Angelo, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Dedifferentiated liposarcoma (DDLPS) is characterized by near universal amplification of the cyclin-dependent kinase 4 (*CDK4*) gene. Palbociclib (P) is a selective CDK4/6 inhibitor that has demonstrated promise in phase II studies of DDLPS. Anti-PD-1 therapy has also shown signals of efficacy, with an approximate overall response rate of 10% in DDLPS patients. CDK4/6 inhibitors upregulate antigen processing and presentation, suppress regulatory T cells, and increase inflammation within the tumor microenvironment. Combined with anti-PD-1 blockade, they can induce an inflamed T cell phenotype and tumor regression in pre-clinical models. We hypothesize that P combined with the anti-PD-1 inhibitor retifanlimab (R) will be safe and tolerable and have synergistic activity leading to activation of T cells and resultant clinical responses. **Methods:** NCT04438824 is a phase II study of P plus R with a safety lead-in phase. Patients with unresectable or metastatic DDLPS who have received any number of prior therapies are eligible to enroll. On the safety lead-in phase, 6 patients received P (125 mg once daily orally for 21 days followed by 7 days off) plus R (500 mg IV flat dose), repeated in 28-day cycles. P was initiated as monotherapy two weeks prior to initiation of R. The primary endpoint of the safety lead-in was to confirm the recommended phase two dose of the combination. Accrual to the safety lead-in has been completed and a pre-planned phase II expansion portion was opened to accrual. A study amendment was passed that revised the treatment schedule on the expansion cohort to start both P and R concomitantly on day 1 of each cycle. This revised schedule was based on recent data demonstrating the superior safety of a concurrent, rather than staggered, dosing schedule. The primary endpoint of the expansion phase is to estimate the best overall response rate (ORR) by RECIST 1.1. Secondary endpoints include describing the safety and estimating clinical benefit rate, duration of response, progression-free, and overall survival. A total of 30 patients treated with the revised dosing scheme will be enrolled onto the expansion phase. Twelve patients have been enrolled to date. An ORR of 5% will be considered not promising, while an ORR of 25% will be considered promising. The null hypothesis will be rejected if 4 or more patients have a confirmed objective response to treatment. This design has a type I error rate of 0.06 and a type II error rate of 0.04. Mandatory pre- and on-treatment biopsies will be performed for correlative analyses. Clinical trial information: NCT04438824. Research Sponsor: Incyte; U.S. National Institutes of Health.

12000

Oral Abstract Session

A multicenter randomized controlled trial (RCT) for the effectiveness of comprehensive geriatric assessment (CGA) with extensive patient coaching on quality of life (QoL) in older patients with solid tumors receiving systemic therapy: G-oncoCOACH study. *First Author: Cindy Kenis, Department of General Medical Oncology and Geriatric Medicine, University Hospitals Leuven & Department of Public Health and Primary Care, Academic Centre for Nursing and Midwifery, KU Leuven - University of Leuven, Leuven, Belgium*

Background: CGA is internationally recommended in the care for older patients with cancer (e.g. ASCO). Only a few recent RCTs have examined the impact on patient's QoL. Aim of this study is to evaluate the effectiveness of CGA coordinated by a geriatric team combined with intensive patient coaching (= intervention group (IG)) versus standard of care, which is CGA coordinated by an oncology team (= control group (CG)) on QoL in older patients with solid tumors receiving systemic therapy. **Methods:** The G-oncoCOACH study was a multicenter RCT in two academic Belgian hospitals (NCT04069962). Eligibility criteria were 70+ years, solid tumor, systemic therapy with curative or non-curative intent (first/second-line), and physician-estimated life expectancy > 6 months. IG patients received CGA coordinated by the geriatric team in close collaboration with the oncology team, increasing multidisciplinary care and in combination with intensive patient coaching to increase patient compliance. This supports patient empowerment by improving self-efficacy and supporting self-management of age-related problems. It included an individual counselling session at start of systemic therapy to discuss CGA results and recommendations with the patient and to determine their priorities, followed by individual counselling organized at 2, 4, 5, 8 and 10 months. Primary endpoint was global health status (GHS) of the European Organisation for Research and Therapy of Cancer (EORTC) QoL questionnaire measured at 6 months after start of systemic therapy. Sample size calculation required > 195 included patients for primary endpoint (≥10 points QoL change at 6 months) for 80% power at 2-sided 5% significance level. After exclusion of multicollinearity, the change in QoL GHS between baseline and 6 months follow-up was analyzed with a mixed model. **Results:** From 10/2019 to 9/2021, 212 participants were enrolled (CG (n = 107); IG (n = 105)). Mean age was 76.8 years; 52.4% were female (n = 111). The 3 most common tumor types were digestive (n = 65; 30.7%), thorax (n = 44; 20.8%), and urogenital (n = 33; 15.6%). Cancer therapy was started mostly with non-curative intent. After 6 months, the difference between CG and IG in change of adjusted QoL GHS versus baseline amounted 12.8 points in favor of the IG (95%CI 6.7-18.8; p < 0.0001). This difference consisted of an improvement of 4.5 point versus baseline in the IG and decline of 8.2 points in the CG. Secondary endpoints (e.g. QoL at 3 and 12 months, patient satisfaction, severe systemic therapy-related adverse events, survival) will be presented at the meeting. **Conclusions:** CGA coordinated by a geriatric team combined with extensive patient coaching improves QoL GHS in older patients with cancer compared to CGA coordinated by an oncology team. Clinical trial information: NCT04069962. Research Sponsor: Stand Up Against Cancer.

12002

Oral Abstract Session

Results of a tailored multimodal lifestyle follow-up care program focusing on physical activity, nutritional behavior and psychological processes in adolescent and young adult cancer survivors: The CARE for CAYA multicenter, randomized clinical trial. *First Author: Simon Elmers, Hubertus Wald Tumor Center - University Cancer Center Hamburg, University Medical Center Hamburg-Eppendorf, Hamburg, Germany*

Background: The aim of the CARE for CAYA-program (CFC-P) was to implement a multimodal lifestyle program in addition to medical follow-up care for child, adolescents and young adult cancer survivors (CAYAs). **Methods:** The CFC-P was a multicenter program with an initial randomized clinical trial (RCT) comparing need-based modular interventions to usual care for CAYAs aged between 15 and 39. A comprehensive assessment (questionnaires and medical examination) was conducted to determine individual needs regarding nutrition, physical activity and psychoneurology. If "high need" was identified, CAYAs could take part in up to three modules over 12 months. In the intervention group (IG), each module included five consultations plus newsletters. The control group (CG) included one baseline counselling in each module. The primary outcome was defined as the rate of CAYAs with "high need(s)" after 12 months of intervention. Secondary outcomes included feasibility, cost-effectiveness, modular-specific endpoints, quality of life (QoL) and fatigue. **Results:** 791 CAYAs were included at 14 German CAYA survivorship clinics from December 2017 to March 2021. Most common tumor types were lymphoma 26.8% (n = 211), sarcoma 13.2% (n = 104) and leukemia 10.0% (n = 79). 58.0% (n = 457) were female, median age was 23.9 years, time since end of tumor specific therapy was < 5 years in 54.4%, > 5 years in 21.2%, > 10 years in 11.5% and > 15 years in 12.9% of patients (median: 57.0 months). 86.2% (n = 679) reported an initial "high need" in at least one module. After 52 weeks, 83.9% (n = 396) of 472 evaluable participants continued to report or developed a "high need": 59.3% (n = 235) in IG and non-randomized cohort, 28.8% (n = 114) in CG and 12.7% (n = 47) with no initial "high need". 357 participants were evaluable in the RCT (63% (n = 226) female, median age 25.0 years). 26.2% (n = 94) reported a "high need" in one, 35.7% (n = 128) in two and 37.6% (n = 135) in three modules. 271 patients could be analyzed at 52 weeks, 87.0% of IG (n = 120 of 138) and 86.5% of CG (n = 115 of 133) continued to have at least one "high need". The primary outcome did not differ significantly between groups (p = .905). However, both showed an increase of QoL and a reduction of fatigue. **Conclusions:** In the CFC-P, the feasibility of a large trial to regularly assess lifestyle habits and the psychosocial situation and determine the efficacy of a need based multimodal interventions in CAYAs was demonstrated. Although a high need for support was revealed in this population, no significant changes with the applied interventions were noted after 12 months. The obtained data will guide the development and implementation of multimodal interventions in long term follow up of CAYAs. Clinical trial information: DRKS00012504. Research Sponsor: Federal Joint Committee.

12001

Oral Abstract Session

Effect of a telephone-based weight loss intervention (WLI) on weight at 12-months in women with early breast cancer: Results from the Breast Cancer Weight Loss (BWEL) trial. *First Author: Jennifer A. Ligibel, Dana-Farber Cancer Institute, Boston, MA*

Background: Obesity is a poor prognostic factor in early breast cancer. The Breast Cancer Weight Loss (BWEL) trial (Alliance for Clinical Trials in Oncology A011401; NCT02750826) evaluates the impact of a WLI on invasive disease-free survival in breast cancer patients (pts) with a body mass index (BMI) ≥27 kg/m². Here we report the impact of the WLI on weight change. **Methods:** Eligible pts were within 14 months of diagnosis of stage 2-3 HER2-negative breast cancer, had completed chemotherapy and radiation (if administered), and were randomized 1:1 to a telephone-based WLI plus health education (HE) or an HE alone control group. The WLI was delivered by telephone-based health coaching and focused on caloric restriction and increased exercise. Height and weight were measured at baseline and 12 months. Changes in weight were compared between groups. Analysis was performed with univariable and multivariable (including arm, baseline weight, menopausal status, race/ethnicity, and hormone receptor [HR] status) regression models. A 0.05 level of significance was used. **Results:** 3181 women were randomized between 8/2016 and 2/2021. At baseline, mean BMI was 34.5 (±5.74) kg/m², mean age was 53.4 (±10.58) years, and 57% of pts were postmenopausal at the time of diagnosis. 80.3% of participants were White, 12.8% were Black, and 7.3% were Hispanic. Follow-up weight was available from 2293 pts alive and disease-free at 12 months. The WLI led to a significant decrease in weight relative to controls; pts randomized to WLI lost an average of 4.8% (±7.9) of baseline body weight at 12 months vs. 0.8% (±6.4) weight gain in controls (p<0.0001). Pts randomized to WLI experienced significant weight loss (vs controls) across demographic and tumor factors (Table). WLI effect differed significantly by menopausal status (interaction p value = 0.0057) and race/ethnicity (interaction p-value = 0.019), but not HR status (interaction p-value = 0.17). **Conclusions:** A telephone-based WLI induced significant, clinically meaningful weight loss in breast cancer pts with overweight and obesity across demographic and tumor factors. Additional tailoring of the WLI could be useful to enhance weight loss in Black and younger pts. Further follow-up of the BWEL trial will evaluate whether the WLI improves disease outcomes. Support: U10CA180821, U10CA180882, UG1CA189823; <https://acknowledgments.alliancefound.org>. Clinical trial information: NCT02750826. Research Sponsor: U.S. National Institutes of Health; Susan G. Komen Foundation, Breast Cancer Research Foundation, American Cancer Society.

% Weight Change at 12-months (SD).				
	Control (n=1173)	WLI (n=1220)	P value*	
Overall	+0.8 (6.4)	-4.8 (7.9)	P <0.0001	
Menopausal status				
Premenopausal	+1.4 (6.6)	-3.3 (7.8)	P <0.0001	
Postmenopausal	+0.5 (6.3)	-5.9 (7.8)	P <0.0001	
Race/Ethnicity				
Black	+2.1 (5.9)	-1.6 (7.1)	P <0.0001	
Hispanic	+1.0 (6.6)	-3.2 (6.3)	P <0.0001	
Non-Black/non-Hispanic	+0.7 (6.4)	-5.4 (8.0)	P <0.0001	
HR Status				
HR+	+0.8 (6.3)	-5.0 (7.5)	P <0.0001	
HR-	+1.0 (6.7)	-3.7 (8.0)	P <0.0001	

*Kruskal-Wallis test.

12003

Oral Abstract Session

Chemotherapy induced peripheral neuropathy (CIPN) due to paclitaxel versus docetaxel in patients with early-stage breast cancer receiving taxane therapy: SWOG S1714. *First Author: Meghna S. Trivedi, Columbia University, New York, NY*

Background: Paclitaxel (Pac) and docetaxel (Doc) are used to treat early-stage breast cancer (BC). CIPN due to taxane therapy can cause sensory and motor deficits. CIPN symptoms caused by Pac versus Doc are not well described. **Methods:** SWOG S1714 enrolled patients ≥ 18 years with Stage I-III primary NSCLC, BC, or ovarian cancer starting treatment with a taxane-based regimen. CIPN was assessed by the patient-reported EORTC QLQ-CIPN20 (CIPN-20) and clinician-assessed NCI-CTCAE. Assessments occurred at baseline and 4, 8, 12, and 24 weeks after registration. Increase in CIPN-20 sensory subscale score ≥ 8 points was considered clinically meaningful. Chi-square and Fisher tests were used for baseline comparisons; logistic regression was used for multivariable analyses. **Results:** Among 1336 enrolled patients, 1106 of eligible patients had a diagnosis of BC, with median age 54.8 y (range 23.9-84.2 y), 99.3% female, and 72.3% White/11.3% Black/4.6% Asian/11.1% Hispanic/Latino. Pac was administered to 615 (55.6%) and Doc to 491 (44.3%) patients. Between the Pac and Doc cohorts, there were significant baseline differences in median age, diabetes, and performance status. At 24 weeks, the proportion of patients with ≥8 point increase in CIPN-20 sensory score was lower for Doc (40.5%) vs Pac (50.2%) (odds ratio [OR] 0.64, 95% CI 0.50, 0.82; multivariable adjusted p<.001). At nearly every timepoint through 24 weeks, patients treated with Pac had more sensory and motor neuropathy as measured by both the CIPN-20 and NCI-CTCAE (Table). **Conclusions:** In this diverse cohort of patients with BC, the frequency of CIPN was higher than expected for both Pac and Doc and more severe in patients receiving Pac. These findings based on CIPN-20 can assist in treatment decision-making about taxane therapy. Long term follow up will better characterize the differences in the trajectory of CIPN between Pac and Doc. Funding: NIH/NCI/NCORP grant UG1CA189974. Clinical trial information: NCT03939481. Research Sponsor: U.S. National Institutes of Health.

	Week 8				Week 12				Week 24			
	Pac	Doc	OR (95% CI)	p value	Pac	Doc	OR (95% CI)	p value	Pac	Doc	OR (95% CI)	p value
Mean change in CIPN-20 sensory subscore (SD)	11.38 (16.19)	4.24 (12.33)		<.001	16.06 (18.41)	8.34 (15.47)		<.001	14.96 (19.28)	10.50 (17.30)		<.001
Mean change in CIPN-20 motor subscore (SD)	4.76 (12.58)	2.72 (10.13)		0.006	7.94 (14.52)	5.79 (13.01)		0.02	8.49 (14.94)	6.46 (13.97)		0.03
1+ Grade increase in CTCAE Peripheral Sensory Neuropathy	38.8%	21.4%	0.41 (0.31, 0.54)	<.001	46.8%	30.6%	0.49 (0.38, 0.63)	<.001	45.1%	35.4%	0.61 (0.48, 0.79)	<.001
1+ Grade increase in CTCAE Peripheral Motor Neuropathy	11.0%	5.8%	0.51 (0.32, 0.82)	0.005	15.9%	11.1%	0.68 (0.48, 0.98)	0.04	14.6%	11.1%	0.76 (0.53, 1.10)	0.15

Note: P-values for all comparisons derived from multivariable analyses adjusted for: age at registration, race (white/nonwhite), diabetes at registration, performance status (0 vs >0), and the baseline score.

12004

Oral Abstract Session

Phase 3 randomized placebo-controlled trial of donepezil for late cancer-related cognitive impairment in breast cancer survivors exposed to chemotherapy from the Wake Forest NCORP Research Base REMEMBER trial (WF97116). *First Author: Steve R. Rapp, Wake Forest University School of Medicine, Winston-Salem, NC*

Background: Cancer-related cognitive impairment (CRCI) is common among breast cancer survivors (BCS). Prior studies of late CRCI suggest repurposing cognitive enhancing medication may benefit survivors. The REMEMBER prospective, randomized, double-blind, placebo-controlled trial compared the efficacy of donepezil, an acetylcholine esterase inhibitor, versus placebo to reduce late CRCI among BCS previously exposed to chemotherapy. (Clinical Trials #NCT02822573). **Methods:** Women ≥ 18 years of age, with a history of breast cancer who completed ≥ 4 cycles of chemotherapy 1 to 5 years prior to enrollment, self-reported CRCI, with evidence of a memory deficit on the Hopkins Verbal Learning Test-Revised (HVLT-R) were eligible. Women were randomized to a 24-week course of donepezil (5mg/daily x 6 wk. titrated to 10mg/daily x 18 wk.) or placebo. A cognitive battery assessing memory, attention, executive function, verbal fluency, and processing speed was administered at baseline, week 12, 24 (end of intervention), and 36 (wash-out) along with patient-reported outcome measures and adverse events. There was 90% power to detect a treatment difference of 2 words for HVLT-IR (effect size=0.47) Mixed effects repeated measures analysis of covariance (RMANCOVA) models were utilized to assess treatment differences in memory (primary outcome) and other cognitive domains (secondary outcomes) with model covariates of treatment, time, time by treatment interaction, baseline outcome level, age stratification and an unstructured covariance matrix to account for within participant correlation over time. **Results:** A total of 276 patients from 87 NCORP sites (mean age=57.1yr, SD=10.5) an average of 29.6 months post-chemotherapy completion were randomized to donepezil (n=140) or placebo (n=136). The primary outcome of memory (HVLT-R total) at 24 weeks was not different between treatments (donepezil mean=25.98, placebo = 26.50, p=0.32). There were no statistically significant differences between treatments at 12, 24, or 36 weeks on attention, executive function, verbal fluency, or processing speed. Exploratory analyses additionally adjusting for education, baseline fatigue and depression as well as independent analyses considering treatment interaction with endocrine therapy and menopausal status also did not result in any differences by group for any outcomes. Twenty-five grade 3 or 4 adverse events were reported with no differences by treatment. **Conclusions:** BCS 1-5 years after completing chemotherapy, randomized to 24 weeks of a daily dose of 5-10mg of donepezil, did not perform differently at the end of treatment on tests of memory or other cognitive functions than survivors randomized to placebo. Funding: NIH/NCI 2UG1CA189824. Clinical trial information: NCT02822573. Research Sponsor: U.S. National Institutes of Health.

12006

Oral Abstract Session

Reduced symptom burden after implementation of an electronic symptom management program. *First Author: Jessica J Bian, MaineHealth Cancer Care, South Portland, ME*

Background: The SIMPRO consortium implemented an electronic patient reported outcomes (ePRO) symptom management program as part of routine clinical care for patients (pts) receiving systemic cancer therapy or surgery across six health systems including rural and community cancer centers. To evaluate impact of the Epic-integrated electronic symptom management (eSyM) program on quality of life, pre- and post-implementation surveys were sent to a subset of gastrointestinal, thoracic, and gynecologic medical oncology (MO) and surgical (Surg) patients at all sites. **Methods:** A survey assessing symptom burden, health literacy, and self-efficacy was administered to separate groups of MO and Surg pts before (Pre-Implementation) and after (Post-Implementation) eSyM deployment. A waiver of documentation of consent was obtained for participation. Questions were derived from validated instruments including PROMIS, a standardized measurement tool for patient-reported symptoms. Surveys were completed 30-90 days after surgery or start of systemic therapy. PROMIS item responses were scored individually then translated into standardized T-scores with a mean of 50 based on an established reference population. Mean T-scores for PROMIS depression, anxiety, fatigue, and pain interference were calculated. Higher T-score correlated with greater symptom burden. Comparison between groups utilized non-parametric Kruskal-Wallis testing. **Results:** The number of survey responses were 498 MO Pre-Implementation, 518 MO Post-Implementation, 566 Surg Pre-Implementation, and 507 Surg Post-Implementation. MO pts reported significantly lower PROMIS mean T-scores for depression, anxiety, fatigue, and pain interference after eSyM compared to a similar group of MO pts prior to eSyM. Surg pts reported lower T-scores for depression, anxiety, fatigue, and pain interference after eSyM compared to a similar group of Surg pts prior to eSyM, although reduction in pain interference was not statistically significant. **Conclusions:** eSyM deployment in MO was associated with a significant reduction in patient reported depression, anxiety, fatigue, and pain interference. Surgical pts after eSyM deployment reported significantly lower rates of depression, anxiety, and fatigue. External validation with PROMIS based surveys demonstrated small but meaningful benefits of ePRO symptom monitoring as part of routine clinical care across six diverse health systems. Clinical trial information: NCT03850912. Research Sponsor: U.S. National Institutes of Health.

Medical Oncology	Pre-Implementation Mean T-score	SD	Post-Implementation Mean T-score	SD	p-value
Depression	50.1	9.0	48.7	8.2	0.02
Anxiety	52.4	9.8	50.0	9.6	< 0.0001
Fatigue	57.4	10.5	55.8	9.7	0.04
Pain Interference	54.0	10.3	52.5	9.9	0.02
Surgery	Pre-Implementation Mean T-score	SD	Post-Implementation Mean T-score	SD	p-value
Depression	47.9	8.5	46.0	7.5	0.0002
Anxiety	49.9	9.3	47.4	8.8	< 0.0001
Fatigue	51.3	10.9	49.0	11.1	0.0008
Pain Interference	52.9	9.8	51.7	9.4	0.053

12005

Oral Abstract Session

Randomized double-blind, placebo-controlled study of topical diclofenac in prevention of hand-foot syndrome in patients receiving capecitabine. *First Author: AKHIL Santhosh, All India Institute of Medical Sciences, Delhi, New Delhi, India*

Background: Capecitabine induced HFS is associated with deterioration of quality of life of patients and dose of capecitabine is often reduced to manage this adverse event. Celecoxib is the only effective intervention in preventing HFS; however, its widespread use is limited due to its own safety concerns. We conducted this study to assess the efficacy of topical diclofenac in preventing capecitabine induced HFS. **Methods:** Patients with breast and gastrointestinal (GI) cancers, planned for capecitabine (monotherapy or combination) treatment were randomized in 1:1 to receive topical diclofenac or placebo gel for 4 cycles or until development of HFS, whichever was earlier. Stratified (male or female; capecitabine monotherapy or combination therapy) permuted variable size block randomization was done using a computer-generated random numbers sequence. Primary objective was to compare the incidence of grade 2 or higher HFS in diclofenac and placebo arms. Secondary objectives were incidence of any grade HFS, capecitabine dose changes due to HFS and self-reported adherence with application. **Results:** A total of 263 patients were randomized to apply topical diclofenac gel (n=130) or placebo (n=133). Baseline characteristics were similar in both the arms (Table). The incidence of grade 2 or higher HFS was 3.8% (95% CI, 1.6%-8.9%) in the diclofenac arm compared with 15.0% (95% CI, 9.9%-22.2%) in the placebo arm (P=0.003). Any grade HFS was significantly lower in the study arm compared with the placebo arm (6.1% vs 18.1%; P=0.003). A lower incidence of HFS was observed in the diclofenac arm across the subgroups (breast and GI cancers; males and females). Capecitabine dose reductions were less frequent in the diclofenac arm (3.8%) compared with the placebo arm (15%) (P=0.002). Adherence to topical treatment was similar in the diclofenac arm (96.7 +/- 19.1%) compared with the placebo arm (94.0 +/- 28.3%) (P=0.36). Other capecitabine associated adverse events, including diarrhea, mucositis, and myelosuppression were not significantly different in both the arms. **Conclusions:** Topical diclofenac is effective in preventing all grades of HFS in patients receiving capecitabine. Diclofenac application was also associated with lesser dose reductions of capecitabine. This trial establishes topical diclofenac as the new standard of care to prevent capecitabine associated HFS. Clinical trial information: CTRI/2021/01/030592. Research Sponsor: Indian Association for Supportive Care in Cancer (IASCC); Alkem Laboratories provided diclofenac gel and placebo.

	Diclofenac (n=130)	Placebo (n=133)
Characteristic		
Median age (IQR)	47 (39-58)	47 (38-55)
Sex		
Female	91 (70.0%)	96 (72.2%)
Males	39 (30.0%)	37 (27.8%)
Performance Status		
0-1	84 (64.6%)	80 (60.2%)
2	46 (35.4%)	53 (39.8%)
Type of therapy		
Monotherapy	56 (43.1%)	52 (39.1%)
Combination	74 (56.9%)	81 (60.9%)
Type of cancer		
Breast	77 (59.2%)	71 (53.4%)
GI	53 (40.8%)	62 (46.6%)
Outcome		
HFS		
Grade 1	3 (2.3%)	4 (3.0%)
Grade 2	2 (1.5%)	13 (9.8%)
Grade 3	3 (2.3%)	7 (5.3%)

LBA12007

Oral Abstract Session

Effectiveness of a cardiovascular health EHR application for cancer survivors in community oncology practice: Results from WF-1804CD. *First Author: Kathryn E. Weaver, Wake Forest University School of Medicine, Winston-Salem, NC*

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2023, issue of the *Journal of Clinical Oncology*.

12008

Oral Abstract Session

Telehealth-based psychological intervention for caregivers of patients with primary malignant brain tumors: A randomized controlled trial. *First Author: Deborah Anne Forst, Massachusetts General Hospital, Boston, MA*

Background: Caregivers of patients with primary malignant brain tumors (PMBT) face unique challenges caring for someone with a progressive neurological illness. In preliminary studies, we found that 50% or more of caregivers had clinically significant anxiety symptoms in the months following the patient's PMBT diagnosis. However, few interventions have been developed to specifically target anxiety symptoms in this population. **Methods:** We conducted a randomized controlled trial evaluating the efficacy of NeuroCARE, a population-specific intervention addressing anxiety in caregivers of patients receiving treatment at two academic centers. Eligible caregivers were within six months of the patient's PMBT diagnosis and had clinically significant anxiety symptoms (score ≥ 5 on the Generalized Anxiety Disorder-7 tool). Participants were randomized 1:1 to NeuroCARE or usual care. NeuroCARE consisted of six one-on-one telehealth sessions with a mental health clinician or trainee and incorporated evidence-based skills for 1) coping with worry, 2) using assertive communication techniques, 3) optimizing social support, and 4) promoting relaxation and healthy sleep. Participants completed questionnaires at baseline, 11 weeks (immediately post-intervention) and 16 weeks (1 month post-intervention). Our primary endpoint was anxiety symptoms at 11 weeks (Hospital Anxiety and Depression Scale (HADS) – Anxiety Subscale score). We also assessed depression symptoms (HADS – Depression Subscale), quality of life (QOL; Caregiver QOL survey), caregiver burden (Caregiver Reaction Assessment), self-efficacy (Lewis Cancer Self-Efficacy scale), coping (Measure of Current Status) and post-traumatic stress disorder (PTSD) symptoms (PTSD Checklist for DSM-5). We used analysis of covariance to evaluate the effect of NeuroCARE versus usual care on these outcomes. **Results:** We enrolled 120 caregivers (60 per arm, mean age = 53 years, 83% female), the majority of whom were caring for their spouse/long-term partner (70%), child (17%), or parent (7%). At 11 weeks, NeuroCARE participants reported significantly lower anxiety symptoms than those assigned to usual care (means: 8.87 vs 10.69, $p = 0.008$). NeuroCARE caregivers also reported significantly lower depression symptoms (6.08 vs 7.77, $p = 0.004$) and better self-efficacy (128.81 vs 111.17, $p < 0.001$) and coping (32.25 vs 25.65, $p < 0.001$) at 11 weeks. Study groups did not differ with respect to caregiver burden, PTSD symptoms, or QOL at 11 weeks. **Conclusions:** A population-specific telehealth-based psychological intervention (NeuroCARE) led to significantly lower anxiety and depression symptoms and better self-efficacy and coping among caregivers of patients with PMBT compared with usual supportive care. Clinical trial information: NCT04109209. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology.

12010

Clinical Science Symposium

Frailty status determined by an electronic health record embedded frailty index and hospitalization risk among older adults following the initiation of cancer chemotherapy. *First Author: Heidi D. Klepin, Wake Forest University School of Medicine, Winston-Salem, NC*

Background: Novel strategies are needed to efficiently identify older adults at high risk for hospitalization before and after chemotherapy initiation. An electronic frailty index (eFI) holds promise as a passive digital marker for frailty available to estimate risk at the point of care. The objective of this study was to evaluate the association of pre-treatment eFI with risk of hospitalization after receipt of cancer chemotherapy among older adults. **Methods:** Consecutive patients ($N = 509$ aged 65+ with newly diagnosed lung, colorectal or breast cancer treated with chemotherapy) were identified from our cancer registry between 2017 and 2020. Calculation of the eFI is automated in the EMR. It requires at least two ambulatory visits over a 2-year period and utilizes demographic information, vital signs, smoking status, ICD-10 diagnosis codes, select outpatient laboratory measurements, and functional information (if available from Medicare Annual Wellness Visits) during the 2 years prior to diagnosis. Frailty status is categorized as fit ($eFI \leq 0.10$), pre-frail ($0.10 < eFI \leq 0.21$), and frail ($eFI > 0.21$) based on the proportion of deficits present over the total number evaluated (score range 0-1). Non-calculable scores indicate insufficient historical primary care data within two year prior to cancer diagnosis. Outcomes were hospitalization at 3 and 6 months post chemotherapy initiation. Time to first hospitalization was estimated by eFI category, using Cox regression models to estimate the adjusted association between frailty status and hospitalization. **Results:** The cohort included 509 adults (median age 72.2 yrs, 55% female, 83% white, 13% black, 45.8% stage 4) with lung ($N = 312$), colorectal ($N = 111$), and breast ($N = 86$) cancers. Distribution of eFI categories at diagnosis were fit (26.3%), pre-frail (42.4%), frail (16.3%) and not calculable (14.9%). Hospitalization rates at 3 and 6 months post chemotherapy were 12.0% (fit), 29.9% (pre-frail), 46.3% (frail), 45.9% (not-calculable) and 24.4% (fit), 41.3% (pre-frail), 59.8% (frail) and 49.8% (non-calculable), respectively ($p < 0.0001$). Adjusting for age, gender, race, stage, and cancer type, the incidence of hospitalization was higher for frail (Hazard Ratio (HR) 2.96, 95% Confidence Interval (CI) 2.05, 4.27), pre-frail (HR 1.41, 95% CI 1.03, 1.94), and not calculable eFI categories (HR 2.01, 95% CI 1.33, 3.03) compared to fit patients. **Conclusions:** Over forty percent of frail older adults with lung, colorectal, or breast cancer identified by eFI were hospitalized within the first 3 months of chemotherapy initiation. The eFI can inform real-time shared treatment decision-making and identify a sub-set of patients who may benefit from care delivery interventions to decrease unplanned hospitalization and improve quality of care. Research Sponsor: U.S. National Institutes of Health.

12009

Clinical Science Symposium

Electronic frailty index predicts 30-day mortality from chemotherapy in breast, colorectal and lung cancer. *First Author: Agnieszka Michael, University of Surrey, Guildford, United Kingdom*

Background: Older and frail patients with cancer (Ca) often receive less aggressive treatment and as a result have worse survival. Current methods of assessing fitness (performance status) for intensive treatment such as chemotherapy are inadequate. The complexity of geriatric assessments, lack of training and time pressures in busy clinics, mean that better solutions are needed. A UK initiative - the electronic frailty index (eFI) - is derived from a cumulative deficit frailty model and provides a measure of frailty alongside pre-existing conditions such as issues with mobility, fractures, falls, memory, sight, hearing, anaemia, tremor, diabetes, heart, thyroid, skin, respiratory, cerebrovascular, circulation, social vulnerability, and polypharmacy (36 fields) (Clegg et al). Patients are classified into the following groups: no frailty, mild, moderate or severe frailty. We used the same methodology to investigate whether eFI predicts adverse outcomes of chemotherapy in frail patients with Ca. **Methods:** The study conducted retrospective data analysis of Ca patients treated with chemotherapy from Public Health England (PHE) Systemic Chemotherapy Dataset (SACT) years 2015-2018. Eligible patients had stage II - III breast Ca, stage III colon Ca or stage IIB-IV non-small-cell lung Ca (NSCLC). The data from SACT was linked with hospital episodes' statistics (obtained from NHS-Digital) to calculate 30-day SACT mortality, overall survival and hospital admissions. eFI was calculated from the above 35 fields; polypharmacy was not available from NHS-Digital data. **Results:** The eFI was calculated for 78799 patients: colorectal 17951, lung 22052, and breast 38796. 20388 patients were ≥ 70 y.o. and 58411 were < 70 y.o. Most patients were fit with an eFI score of 0-69% (54563), 19% (15,295) had mild frailty, 7.7% (6104)-moderate, and 3.6% (2837) had severe frailty. 4.2% (3356) of patients died within 30 days of SACT. For colorectal Ca patients the risk of dying within 30 days of SACT in patients ≥ 70 y.o. was twice that of the < 70 y.o. (OR 2.04 -CI 1.58 - 2.64); patients with mild eFI did not differ - OR: 1.07 (CI 0.78-1.45), moderate frailty: 1.6 (CI 1.1-2.33) and severe frailty: 2.13 (CI 1.34-3.39). In breast Ca patients, 30-day mortality for ≥ 70 y.o. was 6.38 times higher than for < 70 y.o. (95% CI 4.29-9.49); eFI for mild frailty - OR of 1.45 (95% CI 0.78-2.71), moderate frailty-OR of 3.5 (95%CI 1.82-6.75) and severe frailty 5.73 (95% CI 2.66-12.3). The 30-day mortality in lung cancer in ≥ 70 y.o. and < 70 y.o. did not differ with OR 0.95 (95% CI 0.88-1.03) for ≥ 70 y.o. Patients with mild frailty had OR for 30-day mortality of 1.17 (95% CI 1.07-1.28), moderate frailty-OR of 1.28 (95%CI 1.15-1.44) and severe frailty 1.48 (95% CI 1.28-1.77). **Conclusions:** The eFI closely predicts poor outcomes from SACT, particularly in early breast and colon cancer, and requires further evaluation in a prospective study. Research Sponsor: Research for Patient Benefit, National Institute of Health Research.

12011

Clinical Science Symposium

Web-based patient-reported outcome measures (PROMs) in elderly cancer patients: A French multicentric prospective feasibility trial (the FASTOCH study). *First Author: Mathilde Cancel, Department of Medical Oncology, CHU Bretonneau Centre, Tours University, Tours, France*

Background: Web-based PROMs in cancer care improve overall survival and quality of life. There is, nonetheless, no data available on this type of follow-up in the elderly population. **Methods:** From February 2021 to April 2022, 75 or more years-old patients ongoing any active anti-cancer treatment (such as chemotherapy, targeted therapy, hormonotherapy, immune therapy) were included, in six French cancer centers. Feasibility of the web-based PROMs was assessed as the part of the population included that could use the Ana-Health's web-based application "ANA" to monitor their symptoms, the others being considered as in "primary failure" due to technological barriers or refusal to participate. Among the patients that agreed to participate, we then defined as "active" those who filled at least one form during the three months follow up. We also searched for factors restraining elderly patients to use "ANA" and evaluated their satisfaction. **Results:** Overall, 473 patients were included in the study. There were 288 patients in "primary failure" (233 without Internet access, 17 not comfortable enough to use web-based PROMs, 38 refusals to participate). Among the 185 patients "willing to participate", there were 122 "active" patients and 63 "inactive" ones, leading to a 26% feasibility in intention-to-test and a 66% feasibility in per protocol analysis. Patients "willing to participate" were from higher socio-professional category ($p = 0.002$) and had a significantly higher G8 score (13.5 versus 12, $p < 0.001$), particularly when considering the autonomy ($p = 0.028$), cognitive assessment ($p = 0.003$) and general condition ($p < 0.001$) items. In the multivariate analysis, the socio-professional category and the general condition were still significantly different ($p = 0.009$ and 0.002 respectively). The only factor that remained significantly different between the "active" and "inactive" populations was the better general condition in the "active" group ($p < 0.001$). The "inactive" patients prematurely ended their participation because they lost interest in the web-based follow up significantly more than the "active" group (28 "inactive" patients, i.e. 44%, vs 5 "active" patients, i.e. 4%, $p < 0.001$). Similarly, the "active" patients were significantly more satisfied with "ANA" than the "inactive" (71% vs 29%, $p < 0.001$). **Conclusions:** Our study shows that, in the elderly population treated for a cancer, a web-based application to measure PROs is feasible, however socio-professional category, general condition and above all technological barriers are of some concern. Research Sponsor: Antenne d'Oncogériatrie - région Centre Val de Loire; Agence Régionale de Santé de la région Centre Val de Loire.

12012

Clinical Science Symposium

Cost-utility of geriatric assessment in older adults with cancer: Results from the 5C trial. *First Author: Yeva Sahakyan, University Health Network, Toronto, ON, Canada*

Background: Geriatric assessment is a guideline-recommended approach to optimize cancer management in older adults. We conducted a cost-utility analysis alongside the recently published 5C randomized controlled trial to compare geriatric assessment and management (GAM) with usual care in older adults with cancer. **Methods:** The economic evaluation was conducted from a societal perspective, using a 12-month time horizon. The 5C study enrolled patients age 65+ from 8 Canadian hospitals and randomly assigned them to receive GAM or usual care. Patients were initiating systemic therapy with curative or palliative intent. Quality-adjusted life years (QALYs) were measured using the EQ-5D-5L questionnaire. Healthcare utilization was evaluated using cost diaries and chart reviews. The primary outcome, an incremental monetary benefit (INMB), was evaluated for the full sample and for prespecified subgroups. Multiple imputation was used to account for missing data. The 95% confidence intervals (CI) were computed using bootstrapping. **Results:** The study included 350 patients, of which 173 received GAM and 177 received usual care. At 12 months, the average QALYs per patient were 0.747 and 0.753 for GAM and usual care respectively (Δ QALY = -0.006, 95%CI: -0.06 to 0.05). The total average costs per patient were \$48,397 and \$45,342 for GAM and usual care (Δ Cost = \$3,078 (95% CI: -\$5,336 to \$12,050). At a cost-effectiveness threshold of \$50,000/QALY the INMB was negative (-\$3,962; 95% CI: -\$7,117 to -\$794) meaning that GAM was not cost-effective compared to usual care. In a subgroup analysis the INMB was positive (\$4,639, 95% CI: \$61 to \$8,607) for patients treated with curative intent, and the intervention was cost effective in 78% of simulations, but remained negative (i.e. not cost-effective) for patients treated with palliative intent (INMB -\$13,307, 95% CI -\$18,063 to -\$8,264). **Conclusions:** This is the first cost-utility analysis of GAM in cancer. The findings showed that GAM was cost-effective for cancer patients treated with curative intent but not for patients with palliative intent. Although the primary results of the 5C trial were negative, extrapolating our costing data to positive GAM trials like GAIN, GAP70, and INTEGRATE will provide a more complete picture of the cost effectiveness of GAM in this setting. Clinical trial information: NCT03154671. Research Sponsor: Canadian Cancer Society.

12014

Poster Discussion Session

Fertility post immune checkpoint blockade. *First Author: Martinique Ogle, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Immune checkpoint blockade (ICB) is radically altering the treatment paradigm for a wide range of malignancies. Consequently, the proportion of ICB exposed pts will expand and the impact of ICB on fertility is of increasing importance. We sought to evaluate fertility outcomes post ICB exposure at our institution. **Methods:** Pts <45 years old post ≥ 1 cycles of ICB at MSK who consented to the MSK-IMPACT protocol (NCT01775072) were screened for eligibility (n = 537). Pts in receipt of prior cytotoxic chemotherapy or tyrosine kinase, BRAF or MEK inhibitors were excluded. 96 eligible pts were emailed a 28-question survey; 65% were followed up by phone. **Results:** 50/96 pts responded to the survey, male to female ratio was 27:23. 5 pts were excluded from final analysis due to additional systemic agent use pre-conception. Median age at ICB exposure was 35 (range 19-44). 53% (25/45) of pts received ICB in the metastatic setting. 40% (17/42) of pts received fertility counseling pre-ICB use. There was no statistically significant difference between rates of fertility counseling in metastatic vs non-metastatic settings (p = 0.14). 7 pts (14%) conceived and 2 pts (4%) are currently trying to conceive children post ICB. 4 pts (3 female, 1 male) conceived children with reproductive technology. 3/4 pts used sperm or embryos frozen prior to ICB and IVF leading to successful pregnancies, 2 of which are currently ongoing. One patient froze embryos 6 months after 2 years of PD1 inhibitor (PD1i) monotherapy and embryo implantation led to a currently ongoing pregnancy. Notably this pt developed hypothyroidism with ICB use, controlled with levothyroxine, and has remained euthyroid during pregnancy to date. 3 pts (2 female, 1 male) receiving single agent PD1i in the localized setting conceived naturally at 2 yrs, 9 months and 2 months respectively post ICB. 4/8 pregnancies are currently ongoing without reported immunological complications. 3 deliveries have resulted in 4 children (including 1 set of twins). 1 of these pts had a 1st trimester miscarriage of unclear cause followed by successful pregnancy complicated by gestational diabetes. First pregnancies occurred a median of 1 year post ICB (range 2-24 months). No autoimmune conditions in progeny were reported. **Conclusions:** Successful conception occurred both naturally and with reproductive assistance technologies post ICB. Most pts did not receive fertility counseling pre-ICB use, possibly reflective of nascent appreciation of complete and durable ICB responses. There were no definite adverse immunological complications reported in pregnancy or progeny of these pts. As ICB indications expand prospective evaluation of ICB impact on fertility in pts desirous of a family is critical and consequently we are integrating longitudinal fertility analysis in neoadjuvant ICB protocols. Research Sponsor: None.

Cancer	Colorectal	6
Melanoma	22	
Renal	9	
Other	8	
Treatment Setting	Adjuvant/Neoadjuvant	20
	Metastatic	25
ICB Agents	CTLA-4i	19
	PD-1i	49
	CTLA-4i + PD-1i	19

12013

Poster Discussion Session

Impact of immune checkpoint inhibition on ovarian reserve in patients with melanoma enrolled in the ECOG-ACRIN E1609 adjuvant trial. *First Author: Elizabeth Iannotti Buchbinder, Dana-Farber Cancer Institute, Boston, MA*

Background: Immunotherapy with immune checkpoint inhibition (ICI) is being widely adopted in the treatment of patients with a wide range of malignancies. However, we have no data on how these therapies influence fertility or ability to undergo fertility treatments after therapy. Within the melanoma community numerous women of childbearing age have been treated with ICI including ipilimumab, nivolumab and pembrolizumab. Anti-mullerian hormone (AMH) is a biomarker of ovarian reserve and a predictor of response to fertility treatments, including in vitro fertilization (IVF). In women under the age of 35 who have no reproductive pathology, AMH should be detectable and remain relatively stable over time. Above the age of 35 AMH decline accelerates as the number of eggs decreases more rapidly due to normal ovarian aging. **Methods:** Pre and post-treatment samples from women aged 20-35 whose melanoma was treated with 3 mg/kg ipilimumab (57%) or 10 mg/kg ipilimumab (43%) in the adjuvant setting on trial ECOG-ACRIN E1609 were analyzed in collaboration with the BWH Reproductive Endocrine Laboratory. Serum samples were tested for luteinizing hormone (LH), follicle stimulating hormone (FSH), estradiol, AMH and prolactin. **Results:** Samples from E1609 were available from 28 female patients with a median age of 28 (min 20, max 35). The median time between samples was 8.0 months (min 0.7, max 16.4). 53% of patients had stage IIIB melanoma, 43% stage IIIC and one patient had M1a disease. AMH, estradiol and LH significantly decreased after treatment (p < 0.001, p = 0.016, p = 0.012, respectively) (Figure 1); there was no significant difference in the level of FSH and prolactin before and after the treatment (p = 0.68, p = 0.12, respectively). The median AMH was 4.24 ng/mL in the pre-treatment group and 3.51 in the post-treatment group. **Conclusions:** In this study of young women treated with ipilimumab there was a significant decrease in AMH before and after ICI therapy suggesting that ovarian reserve and possibly female fertility may be impacted by immune checkpoint inhibition. Further investigation is needed to look at PD-1 inhibition and combination immunotherapy effects on ovarian reserve and female fertility. In addition, there is a similar need to examine ICI effects on male fertility. Research Sponsor: None.

12015

Poster Discussion Session

Effect of flibanserin on libido in women with breast cancer on adjuvant endocrine therapy. *First Author: Shari Beth Goldfarb, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Breast cancer and its treatment can cause decreased libido. This study evaluates the use of Flibanserin in women with breast cancer on endocrine therapy who are experiencing decreased libido. It is the first study evaluating Flibanserin for medically induced decreased libido. **Methods:** 37 women (mean age of 49) with stage 0-III ER+ breast cancer on endocrine therapy for at least three months were enrolled on a longitudinal IRB-approved trial from both an academic center and an alliance community site. All patients met criteria for the diagnosis of HSDD as defined by the DSM-IV and ISSWSH consensus paper. Patients took Flibanserin 100mg at bedtime for 24 weeks and were followed for 52 weeks. Patients were monitored closely with medical exams and questionnaires at baseline, weeks 4, 8, 16, 24 and 52. Feasibility and efficacy of Flibanserin was measured by patient reported validated instruments such as Female Sexual Function Index (FSFI), Pittsburg Sleep Quality Index (PSQI), PROMIS, and EQ5D. **Results:** A statistically significant improvement in the sexual domains of desire, arousal, lubrication, orgasm, satisfaction, and pain were seen as measured by the FSFI while on Flibanserin, which declined after discontinuing the medication. At baseline, patients had an average libido of 1.7, which increased to 2.8 at 24 weeks and declined to 2.5 after discontinuing treatment. Sexual confidence and satisfaction at baseline were an average of 1.2 and 1.6 respectively and increased to an average of 2.5 and 2.6 after treatment. Ability to become lubricated was 1.3 at baseline and increased to 4.4 at 24 weeks. Ability to maintain lubrication and ease of lubrication both averaged 1.6 at baseline and increased to 3.4 at week 24. Ease and frequency of climax scored an average 1.4 at baseline, then increased to 2.6 and 2.9 respectively at week 24. Patients reported less pain and distress with sexual intercourse throughout the study and an increased number of sexually satisfying events. At baseline, the average score for overall state of health was 78/100. At 24 weeks, the average score increased to 93 and declined to 82 at week 52 (after medication was discontinued). Patients slept an average of 6.7 hours per night at baseline, which increased to 7.7 hours on Flibanserin and decreased to 5.5 hours after discontinuing the medication. **Conclusions:** Our study found statistically significant improvement in the sexual domains of desire, arousal, lubrication, orgasm, satisfaction, and pain as measured by the FSFI from baseline to week 24 while on Flibanserin. It also showed improved overall health-related quality of life and sleep. Flibanserin is an effective treatment option for women with breast cancer. A larger randomized placebo-controlled study is still needed to further evaluate Flibanserin in women with breast cancer and medically induced decreased libido. Clinical trial information: NCT03707340. Research Sponsor: Sprout Pharmaceuticals.

12016

Poster Discussion Session

Long-term outcomes of adolescents and young adults with testicular germ cell tumors: A population-based retrospective matched cohort study. *First Author: Rand Ajaj, The Hospital for Sick Children Research Institute, Child Health Evaluative Sciences, Toronto, ON, Canada*

Background: Testicular germ cell tumor (TGCT) survival exceeds 90%, but survivors of adult TGCT are at risk of developing late effects. Little is known about the risk for late effects in survivors of TGCT in children, adolescents, or young adults (CAYA). **Methods:** We identified all CAYA aged 11-21 years at TGCT diagnosis in Ontario, Canada, between 1992-2021. Those with complete treatment records were matched 1:5 by birth date and postal code at diagnosis to individuals from the general population (controls). Controls' index date was defined as the diagnosis date of their survivor match. Participants were linked to health administrative databases to identify second malignant neoplasms (SMN); cardiovascular disease (CVD: congestive heart failure [CHF], myocardial infarction, coronary artery disease, pericardial disease, valvular abnormalities, arrhythmia, stroke, hypertension); renal disease (dialysis, kidney transplant); and hearing loss (physician-diagnosed hearing loss, hearing aid use). Cumulative incidences were compared between survivors and controls, and between chemotherapy and surgery treated survivors using Gray's test. Cox proportional hazard models compared the risk of late effects between survivors and controls. **Results:** 521 TGCT survivors (296 chemotherapy treated, 225 treated with surgery only) were matched to 2605 controls. Median age at diagnosis/index date was 19 years. Survivors' median follow-up time was 14.8 years (interquartile range: 10.7-21.7). Compared to controls, survivors had higher 15-year incidence and hazard ratio (HR) of all SMN (5.0% vs 0.5%; HR 8.4, $p < .0001$), non-testicular SMN (2.1% vs 0.5%; HR 3.8, $p = 0.0003$), dialysis (1.0% vs 0.04%; HR 12.4, $p = 0.003$), kidney transplant (0.4% vs 0.0%, $p = 0.002$), hearing loss (7.1% vs 3.1%; HR 1.8, $p = 0.005$), and hearing aid use (1.0% vs 0.2%; HR 4.1, $p = 0.02$). Survivors were at substantially increased risk of any CVD (8.2% vs 5.5%; HR 1.4, $p < 0.03$), CHF (1.2% vs 0.2%; HR 5.0, $p = 0.006$), arrhythmia (1.8% vs 0.5%; HR 3.4, $p = 0.002$), and stroke (0.8% vs 0.05%; HR 8.7, $p = 0.0006$) despite no anthracycline exposure. Compared to surgery only treated survivors, chemotherapy treated survivors had higher 15-year incidence of any CVD (13.1% vs 2.0%, $p < 0.0001$), CHF (2.1% vs 0.0%, $p = 0.03$), arrhythmia (3.3% vs 0.0%, $p = 0.02$), stroke (1.4% vs 0.0%, $p = 0.02$), hypertension (7.4% vs 2.0%, $p = 0.009$), and hearing loss (10.2% vs 3.0%, $p = 0.02$). **Conclusions:** Survivors of TGCT during CAYA are at considerable risk for late effects affecting multiple organ systems. In addition to previously described morbidities like hearing loss, survivors (particularly those who received chemotherapy) are at higher risk of CVD. Despite excellent rates of cure, TGCT survivors diagnosed at a young age require life-long risk-directed follow-up to maximize their long-term health. Research Sponsor: Canadian Institutes of Health Research (CIHR); The Ontario Graduate Scholarship (OGS) through the University of Toronto and the Research Training Competition (Restracomp) award through The Hospital for Sick Children.

12018

Poster Discussion Session

Predicting therapy-induced cardiomyopathy in long-term survivors of childhood cancer: A report from the St. Jude Lifetime Cohort (SJLIFE) and the Childhood Cancer Survivor Study (CCSS). *First Author: Kateryna Petrykey, St Jude Childrens Research Hospital, Memphis, TN*

Background: Cancer-therapy-induced cardiomyopathy (CCM) is the leading non-cancer cause of mortality among long-term survivors of childhood cancer, the prevalence of which increases with age. Early identification of survivors at risk provides opportunities for targeted prevention strategies. Here, we developed and validated a clinically applicable CCM prediction model based on survivor characteristics, treatment exposures and inherited genetic variation among long-term survivors of childhood cancer. **Methods:** Long-term survivors from SJLIFE (training cohort; $n = 3,350$; median age 34 years, range 8-72 years) and CCSS (validation cohort; $n = 7,008$; median age 36 years, range 11-64 years) were assessed by the five different general population polygenic risk scores (multiPRS) for dilated cardiomyopathy, hypertrophic cardiomyopathy, heart failure, ejection fraction and left ventricular end systolic volume. Multivariable logistic regression was used to predict 15-year risk of the CCM (defined as CTCAE grade ≥ 3 cardiomyopathy requiring heart failure medications or heart transplantation or leading to death). Model performance was assessed by the area under the receiver operating characteristic curve (AUC). **Results:** CCM was clinically identified in 150 (4.5%) SJLIFE and self-reported in 156 (2.1%) CCSS survivors, respectively. AUC of clinical models with attained age, sex, age at primary cancer diagnosis, cumulative anthracycline dose, mean heart radiation dose (heart RT), and genetic ancestry was 0.81 (95% CI, 0.78-0.85) in SJLIFE and 0.78 (95% CI, 0.74-0.81) in CCSS. Inclusion of cardiovascular risk factors (hypertension, dyslipidemia, and diabetes) significantly increased AUC to 0.83 (95% CI, 0.80-0.87; $P = 0.011$; SJLIFE) and 0.84 (95% CI, 0.80-0.87; $P < 0.001$; CCSS). The addition of the multiPRS further provided significant but modest increases in AUC in SJLIFE (0.84; 95% CI, 0.81-0.87; $P = 0.022$) and CCSS (0.85; 95% CI, 0.81-0.88; $P = 0.031$). In low-risk survivors (exposed to $< 100 \text{ mg/m}^2$ anthracyclines and < 15 Gray heart RT), we observed a possibly larger magnitude AUC increase after adding multiPRS, 0.73 (95% CI, 0.65-0.82) to 0.76 (95% CI, 0.68-0.83; $P = 0.11$) in SJLIFE and 0.77 (95% CI, 0.65-0.90) to 0.82 (95% CI, 0.69-0.94; $P = 0.073$) in CCSS. **Conclusions:** Inherited polygenic factors contributed significantly to improve CCM prediction over available clinical risk factors and may be of benefit to low-risk survivors for whom routine cardiac surveillance is not currently recommended. Research Sponsor: U.S. National Institutes of Health; American Lebanese Syrian Associated Charities; Cancer Center Support [CORE].

12017

Poster Discussion Session

Social determinants of health burden among adolescent and young adult cancer patients and impact on overall survival. *First Author: Elizabeth Rodriguez, McGovern Medical School, Houston, TX*

Background: The 5-year survival rates for adolescents and young adults (AYA) with cancer have steadily improved, yet disparities by race/ethnicity persist. The drivers of these disparities remain unclear. Neighborhood socioeconomic deprivation has been linked to adverse health outcomes independent of the effects of individual-level measures of social determinants of health (SDOH). We evaluated the impact of neighborhood SDOH on overall survival (OS) in a diverse AYA cancer patient population treated in a single academic setting. **Methods:** This study utilized a multi-ethnic cohort of AYA cancer survivors ($N=10,261$) diagnosed between ages 15-39 seen at MD Anderson Cancer Center between 2000 and 2016. Patient demographics, zip code at presentation, cancer characteristics, and follow-up were obtained from our institutional tumor registry. Zip codes were linked to Area Deprivation Index (ADI) values, a validated neighborhood-level SDOH measure, with higher ADI representing worse SDOH. **Results:** The cohort included 6,361 (62%) non-Hispanic White, 1,112 (10.8%) non-Hispanic Black, and 2,133 (20.8%) Hispanic AYA cancer patients, with 655 (6.4%) of other ethnicities or missing information. The mean ADI value was significantly higher ($p < 0.05$) for Black (61.7) and Hispanic (65.3) patients, compared to White (51.2) patients. Analysis of ADI by cancer type showed significant differences, mainly driven by the significantly higher ADI in patients with cervical cancer (62.3) than other cancer types. In contrast, AYA patients diagnosed with breast cancer (53.0) and CNS tumors (52.9) resided in neighborhoods with the lowest ADI values. ADI was a significant predictor of OS overall. In multivariable models that included gender, age at diagnosis, cancer diagnosis, and race/ethnicity, risk of death for AYA cancer patients residing in neighborhoods with ADI in the highest quartile was greater than that for patients in the lowest quartile (HR: 1.09, 95% CI: 1.00-1.19, $p=0.043$). **Conclusions:** Our results in this large multi-ethnic cohort indicate that non-White AYA patients with cancer more commonly live in neighborhoods associated with higher ADI compared to their White counterparts. Even when treated in the same academic setting, AYA cancer patients with higher ADI experienced worse OS across cancers. Although the magnitude of the effect was moderate, the presence of this effect within a tertiary cancer center with existing barriers to care suggests that ADI is a meaningful risk factor impacting survival. Further analysis is warranted to determine the generalizability of these findings to the patient population more broadly. However, the results provide intriguing evidence for potential interventions aimed at supporting AYA cancer patients from disadvantaged backgrounds. Research Sponsor: The University of Texas MD Anderson Cancer Center Support Grant from National Institutes of Health (P30 CA016672), The University of Texas MD Anderson Cancer Survivorship Seed Fund; Henry S. Moss Heart Trust Fund.

12019

Poster Discussion Session

Cannabis extract for secondary prevention of chemotherapy-induced nausea and vomiting: Results of a phase II/III, placebo-controlled, randomised trial. *First Author: Antony Mersiades, NHMRC Clinical Trials Centre, The University of Sydney; Northern Beaches Hospital, Sydney, NSW, Australia*

Background: The aim of this multi-centre, randomised, placebo-controlled, phase II/III trial was to determine the efficacy of adding an oral THC/CBD (tetrahydrocannabinol/cannabidiol) cannabis extract in adults who experience CINV during moderate and highly emetogenic intravenous chemotherapy regimens despite guideline-consistent anti-emetic prophylaxis. The phase II crossover component has been published (Grimson et al, AnnOnc 2020). Here we report the definitive results from the combined phase II/III components with a planned sample size of 250 patients. **Methods:** For the definitive phase III component, participants were randomised 1:1 to receive, oral THC 2.5mg/CBD 2.5mg (Tilray TN-TC11M) capsules TDS days -1 to 5, or placebo (in addition to guideline-consistent anti-emetics including rescue medications) for cycles A, B and C. Primary endpoint was the difference in gaining a 'complete response' (no emesis and no use of rescue medications) during 0-120 hours from chemotherapy for cycle A. **Results:** Complete response was achieved in 24% and 8% with THC/CBD and placebo, respectively (absolute difference 16%, P -value 0.01). The study closed early due to slow accrual without knowledge of study outcomes, with a total of 147 patients recruited 2016-22 (pilot $n=78$, definitive $n=69$). Median age was 56 years (range 25 to 80), 78% were females, 39% reported historic cannabis use, 65% were treated with curative intent. Most common regimens were doxorubicin/cyclophosphamide (AC, 31%), and fluorouracil/oxaliplatin (FOLFOX, 17%), 97% received corticosteroid & 5-HT3 antagonist, 80% received NK-1 antagonist, 10% received olanzapine. Efficacy and safety are shown in the table. No SAEs were attributed to THC/CBD. **Conclusions:** Oral THC/CBD was associated with a significant increase in the proportion of patients achieving a complete response in chemotherapy-induced nausea and vomiting and was well tolerated, representing an effective new treatment in the management of this condition. Future analyses will report quality of life and cost-effectiveness. Funding from NSW Government Dept of Health. Drug supply by Tilray. Clinical trial information: ACTRN12616001036404. Research Sponsor: NSW Health.

Efficacy and cannabinoid-related adverse events.				
Outcome	THC/CBD %	Placebo %	Difference % (95% CI)	P-value
Complete response*	24	8	16 (4, 28)	0.01
No vomiting	70	58	12 (4, 27)	0.14
No use of rescue medications	28	10	18 (6, 31)	0.01
No significant nausea (score <2)	20	7	13 (2, 24)	0.03
Cannabinoid-related adverse event	THC/CBD any grade	Placebo any grade	THC/CBD Moderate/Severe	Placebo Moderate/Severe
Sedation	54	24	18	7
Dizziness	40	14	10	0
Disorientation	17	5	3	0
Anxiety	6	8	3	1

* Complete response = no vomiting and no use of rescue medications.

12020

Poster Discussion Session

12021

Poster Discussion Session

Safety and efficacy of cannabidiol in the management of chemotherapy-induced peripheral neuropathy. *First Author: Marisa C. Weiss, Lankenau Institute for Medical Research, Wynnewood, PA*

Background: Chemotherapy-induced peripheral neuropathy (CIPN) is a common dose-limiting complication of cancer treatment that can negatively impact survival and quality of life. Cannabidiol (CBD) has been shown to attenuate CIPN in rodent models although its ability to reduce CIPN symptoms in humans is unexplored. **Methods:** A phase 3 randomized double-blind, placebo-controlled clinical trial was conducted between 6/1/2020 and 8/8/2022. Participants with nonmetastatic breast, colorectal, endometrial, and ovarian cancer (all stages) experiencing grade 2-3 CIPN (duration $\leq$ 2 years) were enrolled after completing taxane or platin-based chemotherapy. They were randomized into active and placebo groups, and followed x 16 weeks. The active group received 135 mg/day of CBD, provided as hemp-based whole plant extract in gelpcaps, while placebo consisted of coconut oil gelpcaps, delivered x 12 weeks. Participants were evaluated every 2 weeks using the EORTC QLQ-CIPN20, which assesses three categories of symptoms: sensory (numbness, tingling, pain), motor (weakness, difficulty walking), and autonomic (blurriness, hearing loss). Side effect and safety data were logged daily. **Results:** Of 230 participants with CIPN identified, 124 met eligibility, 54 consented and enrolled, and 46 completed $\geq$ 8 of the 12-week treatment phase and were included in the analysis. Mean age was 59.6 years; 89.1% were female. Of those participants, 63% had breast cancer, 19.6% colorectal, 15.2% ovarian, and 2.2% uterine. CIPN20 scores were summated and standardized. With placebo as the reference group, main effects for sensory and motor scales were adjusted for time from enrollment and baseline CIPN grade. Participants receiving CBD had greater improvement of sensory function ($p=0.048$), with reduced numbness and tingling, but without significant pain reduction ($p=.282$) or change in motor function ($p=.158$) vs placebo. No autonomic changes were observed. CBD was well tolerated without serious adverse events. **Conclusions:** CBD reduced numbness/tingling and improved sensory function vs. placebo, as assessed by the CIPN20 scale. These symptoms are among the most common and challenging symptoms of CIPN, for which there are limited available treatment options. However, CBD did not affect pain and motor function. Thus, this preliminary study provides evidence that CBD, dosed at 135 mg/day, might serve as a treatment for some CIPN symptoms without serious adverse events. Further research is needed to confirm these results and to assess the safety and efficacy of CBD combined with chemotherapy to prevent or attenuate CIPN. Such an advance could deliver a survival benefit by helping more people complete and better tolerate chemotherapy. Clinical trial information: NCT04398446. Research Sponsor: Ecofibre/Ananda Health.

	Adjusted Main Effects β (95% CI)*	P
Sensory		
CBD	-10.2 (-20.3, -0.1)	0.048
Motor		
CBD	-8.4 (-20.0, 3.3)	0.158
Tingling and Numbness		
CBD	-10.4 (-20.9, 0.02)	0.05
Pain in Hands/Feet		
CBD	-7.6 (-21.6, 6.3)	0.282

12022

Poster Discussion Session

Neurocognitive function outcomes in NRG/RTOG 0534, the SPPOINT trial. *First Author: Jeffrey Scott Wefel, MD Anderson Cancer Center, Houston, TX*

Background: RTOG 0534 established the benefit of adding of short term androgen deprivation therapy (PBRT+STADT, Arm 2) to prostate bed salvage radiotherapy (PBRT, Arm 1), and demonstrated that elective pelvic lymph node irradiation combined with STADT (PBRT+STADT+PLNRT, Arm 3) results in further reductions in progression. Longitudinal monitoring of neurocognitive function (NCF) was conducted to evaluate the hypothesis that patients treated with STADT will demonstrate greater decline in NCF compared to patients receiving PBRT alone. **Methods:** Patients were administered the Clinical Trial Battery [Hopkins Verbal Learning Test – Revised (HVLT-R), Trail Making Test (TMT), and the Controlled Oral Word Association (COWA) test] by certified test administrators at baseline, and at 6 weeks (6w), 1 year (1yr), and 5 years after the end of RT (5yr). Raw NCF tests scores were converted to standardized z-scores adjusted for age and education when necessary. Analyses included z-score change and reliable change index (RCI) determined decline compared to baseline, and longitudinal mixed effect regression models using z-scores. To control for multiplicity, $p < 0.025$ is required for statistical significance. **Results:** Among the 1716 analyzable patients, 429 consented to NCF monitoring. There were no significant differences in sociodemographic or clinical characteristics between arms. NCF test completion was 82, 76, 63 and 30% at baseline, 6w, 1yr, and 5yr, respectively. RCI-based NCF deterioration was more frequent in Arm 3 compared to Arm 1 at 6 weeks on Delayed Recall (16% vs. 7%, $p = 0.023$). Patients in Arm 3 evidenced greater z-score decline compared to patients in Arm 1 at 6w on HVLT-R Total Recall [M(SD) Z-score Δ = -0.1(1.0) vs 0.2(0.9), ($p = 0.020$)] and Delayed Recall [M(SD) Z-score Δ = -0.4(1.5) vs 0.1(1.2), ($p = 0.012$)]. Mixed effects models identified statistically significant differences in z-scores between Arm 3 and 1 at 6w on Delayed Recall [-0.541 (SE 0.178, $p = 0.002$)]. A statistically significant difference was observed between Arm 2 and 1 at 6w on TMTB [1.498 (SE 0.626, $p = 0.017$) favoring Arm 2]. Between arm differences were not seen at any other time point, or on other NCF outcomes. **Conclusions:** Compared to patients treated with PBRT alone, patients treated with PBRT+STADT+PLNRT exhibited greater worsening in episodic verbal learning and memory processes at 6 weeks after the end of RT, while patients treated with PBRT+STADT exhibited greater improvement in processing speed. The absence of long term or progressive cognitive decline associated with STADT-containing regimens is promising but limited by substantial missing data at year 5. FUNDING This project was supported by grants 10CA180868 (NRG Oncology Operations), U10CA180822 (NRG Oncology SDMC), CTEP from the National Cancer Institute (NCI). Clinical trial information: NCT00567580. Research Sponsor: U.S. National Institutes of Health.

Long term efficacy of psilocybin in patients with cancer and major depressive disorder (MDD). *First Author: Manish Agrawal, Sunstone Therapies, Rockville, MD*

Background: Up to 25% of people living with cancer have depression. Existing psychological interventions have limited efficacy in treating depression. Psilocybin, a 5-hydroxytryptaminergic psychedelic, coupled with group therapy is safe and effective in ameliorating symptoms of depression (Agrawal et al, ASCO 2022). Response to psilocybin treatment was observed in 83.3% of patients at 8 weeks, and 50% of patients showed full remission of depressive symptoms. This study evaluates the efficacy of psilocybin-assisted group therapy in relieving depression in cancer patients over 18 months. **Methods:** Adults with curable or metastatic cancer and MDD (according to DSM-5) underwent psychological assessments at baseline. They were treated with single-dose psilocybin 25 mg administered simultaneously in group cohorts of 3-4, supported with group and individual psychological therapy, and evaluated at 8 weeks and 18 months. Primary objectives were long-term effectiveness on depression and anxiety severity (as measured by change in Montgomery Asberg Depression Rating Scale [MADRS] and Hamilton Depression Rating Scale [HAM-A] scores by independent rater assessments) as well as clinical response ($\geq 50\%$ decrease in MADRS total score from baseline to 18 months) and remission (defined as patients with a MADRS total score ≤ 10 at 18 months). **Results:** Of 30 patients enrolled in the parent study, 2 died and 4 were lost to follow-up. Clinical response was demonstrated in 18/28 patients (64.2%) from baseline to 18 months follow-up (see table); 16/28 patients (57.1%) demonstrated remission of depression at 18 months. In 24 evaluable patients, continued reduction in mean depression severity scores was also demonstrated from baseline to week 8 (MADRS by 20.6 points [95% CI 23.2, 18.0, $p < 0.001$] and HAMA-A by 16.7 points [95% CI 19.7, 13.7, $p < 0.001$]) and from baseline to 18 months (MADRS by 16.7 points [95% CI 20.4, 12.9, $p < 0.001$] and HAMA-A by 14.4 points [95% CI 17.3, 11.4, $p < 0.001$]). **Conclusions:** Long-term follow-up suggests continued robust clinical response and remission from depression with a single dose of psilocybin and simultaneous psychological support in patients with cancer and MDD. These findings indicate psilocybin may play a role in treatment of depression in cancer patients, and further investigations are ongoing. Research Sponsor: Sunstone Medical, PC.

Follow-up Visit	Number of Patients	Clinical Response from Baseline	Clinical Response from Baseline Through Week 8
Week 8 (study termination)	28	22 (78.6%)	–
18 months	28	18 (64.3%)	17 (60.7%)

12023

Poster Discussion Session

Yoga vs. behavioral placebo for fatigue and quality of life among older cancer survivors. *First Author: Evelyn Arana, Wilmet Cancer Institute, University of Rochester Medical Center, Rochester, NY*

Background: Older cancer survivors consistently express the need for interventions to reduce fatigue and maintain quality of life (QOL). We previously showed that yoga, compared to standard care, effectively improved fatigue and QOL among older survivors. Whether yoga is superior to a rigorous behavioral placebo for improving fatigue and QOL in older survivors is unknown. To examine the efficacy of yoga vs a behavioral placebo for improving fatigue and QOL in older survivors. **Methods:** Older cancer survivors (age 60+) 2-60 months post-treatment were randomized to receive Yoga for Cancer Survivors (YOCAS; 75-minute sessions 2x/week for 4 weeks) or a behavioral placebo (Survivorship Health Education – SHE; 75-minute sessions 2x/week for 4 weeks). The YOCAS intervention includes breathing exercises, yoga poses, and mindfulness activities. The SHE placebo includes education based on ASCO cancer survivorship recommendations. Fatigue and QOL (i.e., overall, physical, emotional, and functional) were assessed pre- and post-intervention with the Functional Assessment for Chronic Illness Therapy-Fatigue (FACIT-F). The within-group and between-group intervention effects on fatigue were examined by 2-tailed t tests and ANCOVAs. **Results:** 173 older survivors were enrolled (91% women, mean age 67 [range=60-85], 90% White, 10% racial minority, 2.3% Hispanic, 71% breast cancer). On average, participants completed 6 in-person yoga sessions and 1 additional weekly, home-based yoga practice, for an average of 183 minutes of yoga/week with no intervention-related adverse events. There were significant between group differences on fatigue, where yoga participants reported significantly more improvement in fatigue than controls (1.6 $\pm$ 0.9, $p<0.05$). There were also significant between group differences on the emotional component of QOL, where yoga participants reported significant improvement in the emotional component of QOL but controls did not (0.8 $\pm$ 0.4, $p<0.045$). Moreover, there were statistical trends for between group differences on the physical and functional component of QOL, where yoga participants reported improvements in the physical (0.8 $\pm$ 0.4, $p<0.063$) and functional components of QOL (0.9 $\pm$ 0.5, $p<0.089$) but controls did not. There were significant between group differences on overall QOL, where yoga participants reported significant improvement in overall QOL but controls did not (3.8 $\pm$ 1.4, $p<0.007$). 94% of participants reported the intervention useful for symptom management and would recommend it to others. **Conclusions:** Results suggest that older survivors: 1) can safely utilize yoga for treating side effects, 2) experience improvements in fatigue and QOL via yoga therapy, and 3) find yoga a useful treatment for side effects and recommend it to others. Future research is needed to confirm these results and increase uptake by older, and ethnically and racially diverse survivors. Clinical trial information: NCT02613364. Research Sponsor: U.S. National Institutes of Health.

12024

Poster Discussion Session

The menopause after cancer study: A multimodal technology assisted intervention for the management of menopausal symptoms after cancer. *First Author: Fionán Donohoe, UCD Gynaecological Oncology Group, Dublin, Ireland*

Background: Vasomotor symptoms (VMS) of menopause represent a significant challenge for many patients after cancer treatment, particularly if menopausal hormone therapy (MHT) is contraindicated. **Methods:** The Menopause after Cancer (MAC) Study (NCT04766229) was a single arm phase II trial examining the impact of a composite intervention on quality of life (QoL) in women with moderate to severe VMS after cancer. The intervention consisted of: (1) use of non-hormonal pharmacotherapy to manage VMS (citalopram for predominantly daytime VMS and/or gabapentin for predominantly nocturnal VMS) (2) digital cognitive behavioural therapy for insomnia using Sleepio (BigHealth), (3) self-management strategies for VMS delivered via a mobile application called myPatientSpace and (4) nomination of an additional support person/partner. The primary outcome was cancer specific QoL assessed by the EORTC QLQ C30 version 3 at 6 months. Secondary outcomes included frequency of VMS, bother/interference of VMS (hot flush rating scale [HFRS]) and prevalence of insomnia (sleep condition indicator [SCI] ≥ 16) at 6 months. **Results:** 205 women (82% history of breast cancer) with a median age of 49 years (range 28-66) were recruited. Date of diagnosis ranged from January 2004 until January 2022, with 65% of participants diagnosed from 2019 onwards. Participants had a median of 10 hot flashes in a day (SD 9.2) and 4 night sweats each night (SD 4.9). 17.1% were prescribed citalopram, 62.8% gabapentin alone and 20.1% were prescribed both medications. 120 women completed the protocol. In the intention to treat (ITT) cohort (n = 205) mean QoL scores increased from 62.2 (SEM 1.4) at baseline to 70.4 (SEM 1.7) at 6 months (p < 0.001). In the per protocol (PP) cohort, (n = 120) mean QoL scores increased from 62 (SEM 1.7) to 70.4 (SEM 1.7) at 6 months (p < 0.001). Clinically meaningful improvements were seen across multiple domains of the EORTC QLQ C30 including cognitive function, emotional function and social functioning. Frequency of VMS decreased by 50% at 6 months in the ITT and PP cohorts. Mean HFRS scores decreased from 7.6 (SEM 0.1) to 3.4 (SEM 0.2) at 6 months (p < 0.0005) in the ITT cohort (7.5 (SEM 0.1) to 3.4 (SEM 0.2) (p < 0.001) in the PP cohort) demonstrating reduction in bother/interference of VMS. The prevalence of insomnia reduced from 92% at baseline to 38.7% at 6 months (p = 0.006) in the ITT cohort (95.2% to 38.7% in the PP cohort (p = 0.006)). Mean SCI scores increased from 8.5 (SEM 0.4) at baseline to 17.3 (SEM 0.5) at 6 months (p < 0.0005) in the ITT cohort (7.9 (SEM 0.4) to 17.3 (SEM 0.5) (p < 0.001) in the PP cohort). Significant reductions in wakefulness after sleep onset and sleep onset latency were major contributors to this improvement in insomnia symptoms. **Conclusions:** The MAC study demonstrates that improvements in QoL can be achieved using this multimodal intervention to target VMS and insomnia after cancer. Clinical trial information: NCT04766229. Research Sponsor: Irish Cancer Society.

12026

Poster Session

Interventions to improve outcomes for caregivers of patients with advanced cancer: A systematic review and meta-analysis. *First Author: Ronald Chow, Princess Margaret Cancer Centre, Toronto, ON, Canada*

Background: More than one in ten adults in the US are family caregivers, with cancer among the most common diagnoses of care recipients. Family caregivers of patients with advanced cancer often have poor quality of life (QOL) and mental health. We examined the effectiveness of interventions offering support for caregivers of patients with advanced cancer on caregiver QOL and mental health outcomes. **Methods:** We searched Ovid MEDLINE, EMBASE, Cochrane CENTRAL, and CINAHL databases from inception through 6/2021. Eligible studies reported on randomized controlled trials for adult caregivers of adult patients with advanced cancer. Meta-analysis was conducted for primary outcomes of QOL, physical well-being, mental well-being, anxiety, and depression, from baseline to follow-up of 1-3 months; secondary endpoints were these outcomes at 4-6 months and additional caregiver burden, self-efficacy, family functioning and bereavement outcomes. Random effects models were used to generate summary standardized mean differences (SMD). Meta-regression was conducted for primary outcomes that were significant for the intervention, assessing for mediation effect modification by caregiver sex and age of patient and caregiver. Type I error was 0.05. PROSPERO Registration: CRD42019136321. **Results:** Of 12,193 references identified, 56 articles reporting on 49 trials involving 8,554 caregivers were eligible for analysis; 16 (33%) targeted caregivers (mostly psychoeducational or problem-solving interventions), 19 (39%) patient-caregiver dyads (mostly counseling/therapy), and 14 (29%) patients and their families (mostly palliative care teams). At 1-3 month follow-up, interventions had a significant effect on overall QOL (SMD 0.24 (0.10 to 0.39), $I^2 = 52.0\%$), mental well-being (SMD 0.14 (0.02 to 0.25), $I^2 = 0.0\%$), anxiety (SMD 0.27 (0.06 to 0.49), $I^2 = 74.0\%$), and depression (SMD 0.34 (0.16 to 0.52), $I^2 = 64.4\%$), compared to standard care. At 1-3-month follow-up, a larger age difference (older patient and younger caregiver) was associated with a greater positive effect on QOL (p = 0.04) and depression (p = 0.02). In narrative synthesis, interventions demonstrated improvements in caregiver self-efficacy and grief. **Conclusions:** Interventions targeting caregivers, dyads, or patients and families led to improvements in caregiver QOL and mental health outcomes. These data support the routine provision of available interventions to support caregivers of patients with advanced cancer. Research Sponsor: Canadian Institutes of Health Research (grant number 152996 to C.Z.), Harold and Shirley Lederman Chair in Psychosocial Oncology and Palliative Care (C.Z.).

12025

Poster Session

A meta-analysis studying the utility of cryotherapy in the prevention of peripheral neuropathy in breast cancer patients receiving paclitaxel and nab-paclitaxel. *First Author: Prashanth Ashok Kumar, Upstate University Hospital, Syracuse, NY*

Background: Debilitating Peripheral Neuropathy (PN) caused by paclitaxel adversely impacts the quality of life in Breast Cancer (BC) patients. Cryotherapy using cooling devices during taxane infusion is a non-invasive strategy to prevent PN, but its efficacy has not been established. We hope to answer this question through our meta-analysis. **Methods:** A systematic search with keywords and controlled vocabulary encompassing BC, antineoplastics, and paclitaxel was conducted in PubMed, CINAHL, Embase, Scopus, Web of Science Collections, and CENTRAL. All databases were searched on March 7, 2022. There were no search restrictions on date, language, status, or outcomes. 405 records were identified, and duplicates were removed using EndNote 20. The remaining 372 records were imported into Covidence, and the titles and abstracts were screened independently by 2 reviewers. 22 out of 63 full texts were relevant to our question of which 14 [12 Randomized control studies and 2 retrospective studies] were included for the meta-analysis using R package meta. Only studies that analyzed cryotherapy use in BC patients who received paclitaxel or nab-paclitaxel were included. Relative risk (RR) derived from random effects model with Mantel-Haenszel method was used to compare the occurrence of PN between cryotherapy vs placebo groups. **Results:** Pooled incidence of Common Terminology Criteria for Adverse Events (CTCAE) grade ≥ 2 PN was 24.85% (81/326) in the cryotherapy arm and 42.35% (72/170) in the placebo arm. Overall RR for CTCAE grade ≥ 2 PN with cryotherapy compared to placebo was 0.45 [0.27,0.77, p = 0.0031]. RR for sensory PN was 0.19 [0.05, 0.66, p = 0.009] and for motor PN was 0.18 [0.03, 0.99, p = 0.0491]. RR for Patient Neurotoxicity Questionnaire (PNQ) score $\geq D$ which connotes severe neuropathy was 0.24 [0.09,0.62, p = 0.0035]. Cold intolerance was the predominant adverse effect at 15% (37/247). Fingernail paronychia and skin irritation were reported at 0.8% (2/247) each. 5.1% (15/294) stopped cryotherapy use prior to completion. However, this number was driven by a single study (10/16 patients stopped using cryotherapy due to cold intolerance) and 7/11 studies had no discontinuations. Visual inspection of our funnel plots revealed no publication bias. **Conclusions:** Use of cryotherapy decreased the occurrence of CTCAE grade ≥ 2 PN by 55% in BC patients getting paclitaxel or nab-paclitaxel. Occurrence of both sensory and motor PN were lower. Cold intolerance was the most frequently reported issue with its use but lead to relatively low discontinuation rates in most studies. Given the lack of any severe adverse effect, cryotherapy use must be encouraged for patients receiving paclitaxel and nab-paclitaxel. Further studies are needed establish a standardized way of applying cryotherapy in terms of the device to use, timing and other logistical factors. Research Sponsor: None.

12027

Poster Session

Use of clinical pathways to identify patients with cancer who may benefit from serious illness conversations. *First Author: Cody E Cotner, Department of Medicine, Brigham and Women's Hospital, Boston, MA*

Background: Treatment pathways are widely used to provide decision support and encourage guideline adherence. Pathways data may be used to identify patients for targeted interventions to improve cancer care. For example, pathways data may enable the identification of patients with poor prognoses for whom serious illness conversations (SICs) should be prioritized to ensure goal-concordant care. **Methods:** For patients starting new therapies at Dana-Farber, oncologists select a node in clinical pathways to indicate the line of treatment. Subspecialty oncologists identified "poor prognosis" nodes in pathways, defined as therapies for patients with expected survivals of < 12 months and for whom an SIC would be appropriate (e.g., 3rd-line treatment for metastatic colon cancer). Pathway node navigations for patients with metastatic solid tumor malignancies with poor prognosis nodes (n = 21 disease pathways) were combined with electronic medical record data to identify SIC documentation in an advance care planning module within 6 months of pathway navigation and patients' dates of death if present. For each node, we calculated the median overall survival (OS), the proportion of patients with an SIC, and the proportion of patients who died before reaching the next node. **Results:** There were 10,132 navigations for 7,031 patients (median age 67 years, 52% female, 86% White) between 8/16/2019 and 1/4/2023. With each treatment line, patients' median OS decreased and SIC rates increased (examples for 3 diseases in Table). Among patients who reached poor prognosis nodes, the median OS was 4.9 months, mean SIC rate was 43.8%, and 60.2% of patients died without reaching a subsequent node. For nodes immediately prior to poor prognosis nodes, the median OS was 7.1 months, the mean SIC rate was 25.2%, and 31.3% of patients died without reaching the next node. 46.3% of patients died without reaching a poor prognosis node. The proportion of patients having an SIC at death was 40.9% among all decedents, 50.8% for decedents reaching a poor prognosis node, and 29.3% for decedents who do not reach a poor prognosis node. **Conclusions:** Clinical pathways can be used as a scalable method to identify patients with metastatic solid tumors and poor prognoses. In our study, only half of patients who reached a poor prognosis node had an SIC before death and nearly half of decedents never reached a poor prognosis node, underscoring the importance of identifying this population to improve end-of-life care. A clinical trial using pathways to identify and deliver interventions to increase SICs is ongoing. Research Sponsor: None.

Metastatic cancer type	Line of treatment (* poor prognosis node)	Number of navigations	Median OS, months	Patients with documented SIC, %	Patients at last node, %
Colon	1	696	10.1	18	18
	2	416	8.3	25	29
	3*	286	5.4	37	41
Castrate-resistant prostate	1	167	12.2	13	18
	2	380	9.4	27	23
	3*	162	7.8	36	36
Non-small cell lung (Nonsquamous)	1	953	7.9	23	37
	2	304	4.8	33	44
	3*	218	3.9	52	60

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Poster Session

12029

Poster Session

Quality for all: Clinical trial enrollment and end-of-life care in solid and hematologic malignancies. *First Author: Melissa R Rosen, Duke University School of Medicine, Durham, NC*

Background: All patients with cancer deserve quality end-of-life (EOL) care. Despite established EOL quality metrics, many patients with cancer receive futile, aggressive EOL care with infrequent palliative care involvement and advanced care planning (ACP) documentation. Clinical trials are critical to advancing cancer care; at National Cancer Institute-designated cancer centers, ~20% of patients participate in clinical trials at some point. We aim to identify associations between trial enrollment in the last year of life (YOL) and EOL quality metrics for adults with solid or hematologic malignancies to identify opportunities to advance cancer care near death. **Methods:** This is a retrospective review of patients with solid or hematologic cancers treated at a single academic institution who died of disease between 2018 – 2022. Patients were identified using institutional registries. Inclusion criteria were ≥18 years of age with active disease at death. Outcomes include: initiation of new anti-cancer therapy, Intensive Care Unit (ICU) admission, hospitalization, or Emergency Department (ED) visit in the last 30 days of life (DOL), referral to hospice, palliative care involvement, and documentation of goals of care (GOC) and ACP paperwork. **Results:** Among 9,384 patients, 637 (6.8%) enrolled in clinical trials in the last YOL. Most common disease sites were gastrointestinal, thoracic, and genitourinary. Patients enrolled in clinical trials were more likely to initiate new anti-cancer treatments in the last 30 DOL ($p < 0.001$), less likely to be referred to palliative care ($p = 0.008$) or have GOC documentation ($p = 0.001$), and less likely to visit the ED ($p = 0.016$) or die in an inpatient setting ($p = 0.02$). No differences were noted in referrals to hospice, ICU or hospital admissions in last 30 DOL, or ACP paperwork. **Conclusions:** Enrollment in a clinical trial in the last YOL was associated with several measures of aggressive EOL care. Low rates of palliative care and hospice engagement and infrequent documentation of ACP decisions across the study population suggest opportunities for improvement for all patients, regardless of trial enrollment. Research Sponsor: None.

	Non-trial participants, N (%) (n = 8747)	Trial participants, N (%) (n = 637)	Total (n = 9384)	P-value
Last 30 DOL: New anti-cancer treatment	1226 (14)	116 (19.6)	1342 (14.4)	0.0003
Last 30 DOL: ED visit	2688 (30.7)	154 (24.2)	2842 (30.4)	0.016
Last 30 DOL: Hospital admission	2986 (34.1)	194 (30.6)	3181 (34)	0.59
Last 30 DOL: ICU admission	79 (0.9)	5 (0.8)	84 (0.9)	1.0
Palliative care referral	2438 (27.9)	146 (22.9)	2583 (27.5)	0.008
Hospice referral	2174 (24.9)	140 (22)	2314 (24.7)	0.11
Death: inpatient	1487 (17)	85 (13.3)	1572 (16.8)	0.020
Documentation of GOC	2112 (24.1)	108 (17)	2220 (23.7)	<0.001
Documentation of ACP paperwork	1317 (15.1)	98 (15.4)	1415 (15.1)	0.87

DOL, days of life; ED, emergency department; ICU, intensive care unit; GOC, goals of care; ACP, advanced care planning.

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Poster Session

End-of-life outcomes of patients with advanced cancer enrolled in palliative care. *First Author: Andrew Lynch, Kaiser Permanente Oakland Medical Center, Oakland, CA*

Background: Palliative Care (PC) integration improves end-of-life (EOL) outcomes for patients with advanced cancer. However, there is limited evidence in real world settings of the impact of PC enrollment on EOL outcomes and the presence of racial disparities in PC enrollment. We sought to understand how PC enrollment differs between certain patient demographics and whether enrollment affects EOL outcomes in a large integrated health system. **Methods:** This retrospective cross-sectional study included adults 18 years and older diagnosed with Stage IV solid cancers who died within 1 year of diagnosis at 21 cancer centers within Kaiser Permanente Northern California between 2018-2020. Demographics, clinical variables and EOL outcomes were compared by PC enrollment status. Categorical and continuous comparisons were made using Chi-squared and t-tests, respectively. **Results:** Among 3,575 patients diagnosed with stage IV solid cancers who died within 1 year of diagnosis (mean age 73.2), 52.8% were male; 8.2% were Black, 11.0% Hispanic, 12.3% Asian, and 67.7% non-Hispanic White. Most patients (93.0%) selected English as their preferred language. The most common cancer subtypes were thoracic (33.2%), upper GI (32.4%), and lower GI (10.6%). Overall, 1613 patients (45.1%) were enrolled in PC. Baseline demographics were similar between the PC and no-PC groups including gender ($p = 0.58$), race ($p = 0.32$), and preferred language ($p = 0.23$). There was a difference in mean age between groups (72.0 vs. 74.2, $p < 0.01$). Patients enrolled in PC were more likely to enroll in hospice (42.9% vs. 25.7%, $p < 0.01$, Table) and less likely to be hospitalized in the last 30 days of life (35.5% vs. 45.7%, $p < 0.01$, Table). Short hospice stays (< 3 days) were uncommon in both groups, and there was no statistically significant difference between groups (4.5% vs. 5.4%, $p = 0.49$, Table). There was no significant difference in the proportion of patients with multiple ED visits in the last 30 days of life between groups (21.0% vs. 21.8%, $p = 0.56$, Table). **Conclusions:** PC enrollment is associated with significant improvement in some EOL outcomes with higher rates of hospice enrollment and lower rates of hospitalization at the EOL. These outcomes were seen without racial disparities in PC enrollment. Future studies are needed to assess other outcomes related to goal-concordant care and to determine which patients benefit most from PC enrollment. Research Sponsor: None.

Comparison of quality EOL outcomes between those enrolled in PC and those not enrolled in PC.					
	Enrolled in PC		Not enrolled in PC		p-value
	N=1613	%	N=1962	%	
Hospice Utilization					
Enrolled in hospice	692	42.9	504	25.7	<.01
Hospice stay < 3 days	31	4.5	27	5.4	0.49
Acute Care Utilization					
> 1 ED visit last 30 DOL*	339	21.0	428	21.8	0.56
Hospitalization last 30 DOL*	572	35.5	897	45.7	<.01

*DOL = Days of Life

Trends in place of death in adolescents and young adults dying from cancer in the US, 2003-2019. *First Author: S. M. Qasim Hussaini, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins Hospital, Baltimore, MD*

Background: Adolescents and Young Adults (AYAs) face unique social challenges in navigating care at end-of-life (EOL). Place of Death (PoD) is an important determinant of patient and caregiver preference, access to home-based supportive care, and cost of caregiving at EOL. We sought to describe disparities in PoD in AYAs who died from cancer between 2003-2019. **Methods:** We used deidentified death certificate data via the CDC Wonder database. We included decedents aged 15-44 years with an underlying cause of death from cancer (through ICD codes) from 2003-2019. We stratified findings by age, race/ethnicity, sex, cancer site, and urban/rural metro status. We classified PoD as (1) medical facility (2) nursing home (3) home, or (4) hospice facility. Odds ratios (OR) for the association between PoD and geographic region were calculated using multinomial regression, adjusting for year of death. **Results:** We included 301,886 AYA deaths from cancer (53.9% female, 15.6% non-Hispanic Black, 18.4% Hispanic, 15.6% rural, 28.6% breast, 19.9% colorectal, 18.4% lung, 16.9% brain, 16.2% leukemia). From 2003-2019, deaths in a medical facility reduced from 11,579 (52.7%) to 7,952 (49.5%), home from 8,630 (39.3%) to 6032 (37.5%), and in a hospice facility increased from 152 (0.7%) to 2,245 (14.0%). Compared with older adults (>45), AYAs were 42% and 37% less likely to die at home or in a hospice facility than a medical facility. Within AYAs, similar trends were noted for Hispanic and non-Hispanic Blacks when compared to non-Hispanic Whites, and rural residents when compared to urban residents. AYAs with leukemia were most likely to die in a medical facility and least likely in hospice, brain cancer most likely to die at home or in a nursing facility, while colorectal and breast cancers had equal uptake of hospice. **Conclusions:** AYAs have lower hospice uptake at EOL with notable sociodemographic, geographic and disease-site specific variation. These data likely reflect complex treatment planning and care access/preference at EOL. Dying at home may be unattainable for AYAs, unless they are able to afford help or have family who are willing to be caregivers. Future work investigating whether the offerings of hospice meet the basic care needs of AYA with cancer at EOL is necessary. Research Sponsor: None.

Odds Ratios (OR) of dying at home or in hospice facility.		
	OR ^a (Home)	OR ^b (Hospice)
Age >45 (ref)	-	-
Age <45	0.58 [0.58, 0.58]	0.63 [0.63, 0.63]
NH-White (ref)	-	-
Hispanic	0.63 [0.61, 0.64]	0.60 [0.6, 0.61]
NH-Black	0.47 [0.46, 0.48]	0.74 [0.74, 0.74]
Rural (ref)	-	-
Urban	0.79 [0.77, 0.80]	1.68 [1.68, 1.69]
CRC (ref)	-	-
Brain	1.37 [1.34, 1.41]	1.06 [1.05, 1.08]
Breast	0.68 [0.67, 0.69]	0.74 [0.72, 0.77]
Leukemia	0.17 [0.16, 0.17]	0.13 [0.13, 0.13]
Lung	0.65 [0.63, 0.66]	0.63 [0.62, 0.64]

Odds of dying at home^a in a hospice facility^b compared to a medical facility for the subgroup of interest compared to the reference group (for example, ages > 45 v ≤ 45).

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Poster Session

Patient characteristics associated with psychosocial distress about end-of-life. *First Author: Ana Isabel Tergas, City of Hope, Duarte, CA*

Background: A cancer diagnosis and subsequent treatment can cause significant psychosocial distress, including fear about the end of life (EoL). Although distress is common, it often goes unrecognized due to the challenge of routine psychosocial distress screening. This study sought to determine patient characteristics associated with EoL-related distress. **Methods:** A validated psychosocial distress screening tool (SupportScreen) was administered to patients prior to treatment at an NCI-designated cancer center between 2009-2017. Fear about EoL was measured on a 5-point Likert scale with scores of ≥3 indicating “high” distress. Multivariable logistic regression was used to test the association between fear of EoL and patients’ characteristics (age, sex, education, household income, survey language, race/ethnicity, and cancer diagnoses). Pairwise comparisons were run for cancer types and p-values were adjusted. **Results:** A total of 4,198 patients with cancer were included. Of these, 21.5% reported high distress from fear about EoL. Most patients were women (61%) and non-Latino white (60%). The average age was 59.9 years (SD = 13.9). About 29% of the participants had household income < \$40,000. The most common cancers in this sample were breast (22%), hematological (15%), gastrointestinal (14%) and gynecological (13%). Adjusted analyses showed that being a woman (OR = 1.30, $p < 0.042$), taking the survey in Spanish (OR = 1.71, $p = 0.020$) and having a household income < \$40,000 (OR = 1.80, $p < 0.001$) were all associated with high distress for EoL. Among cancer types, lung cancer (versus breast, digestive, gynecological, hematological, and prostate cancers) was significantly linked to high distress (p -values < 0.05). Conversely, older age (OR = 0.99, $p = 0.009$) was associated with low distress. **Conclusions:** In this study, we identified patient clinical and demographic characteristics associated with high levels of distress due to fear of EoL. Patients who have lower household income, limited English proficiency, are younger, and female, as well as patients with lung cancer, may benefit from targeted screening for EoL distress, to facilitate early identification and tailored supportive care assistance. Research Sponsor: U.S. National Institutes of Health.

12032

Poster Session

Psychosocial health of patients engaging in medical aid in dying and their family members: A prospective descriptive analysis. *First Author: Chloe Turner, Texas Tech University, Lubbock, TX*

Background: Medical Aid in Dying (MAID) allows patients (pts) with a terminal illness and less than 6 months prognosis to request a prescription that will end their life. MAID is controversial; opponents argue that negative psychological health underlies the choice, and that participation adversely affects pts and FMs. This is the first study to prospectively examine psychological health of pts and Family Members (FMs) who engaged in MAID and compare this to the psychological health of pts and FMs who did not utilize MAID. **Methods:** Pts and FMs were recruited prospectively from End-of-Life Washington (largest non-profit, public MAID advocacy/assistance organization in Washington State) from September 2022-January 2023 to a self-report, longitudinal study. Pts, FMs or the dyad were enrolled. Results of this study are compared to previously published results: *means (standard deviation, SD) taken from *Singer, et al. 2021; **Frikkel, et al. 2021; ^Robinson, et al. 2016 and ~Trevino, et al. 2013. + indicates no significant difference between MAID and non-MAID subjects at $p > .05$ level. **Results:** 16% (8/51) of eligible pts and 49% (20/41) of eligible FMs were recruited. 55% (n = 11) of FMs were spouses. There was no difference in sex and subjects were mostly white (pts 87.5%; FMs 95%) with college or higher degrees (pts 62.5%; FMs 85%). Most pts reported having cancer (n = 6 [75%]; neurologic condition, n = 1 [12.5%]; cirrhosis, n = 1 [12.5%]); most FMs also reported their pt had cancer (n = 17 [85%]; neurologic condition, n = 3 [15%]). There were no differences in psychological health between terminal cancer pts and FMs who engaged in MAID and advanced cancer pts & FMs who did not (see table). **Conclusions:** In this study, FMs and pts participating in MAID appear to have rates of negative psychological states that are in the low to moderate range. These rates appear similar to pts with advanced cancer and their FMs who are not engaging in MAID. Future research should study larger, heterogeneous populations earlier in the illness trajectory. Research Sponsor: Washington State Legislature.

	MAID FMs n = 20	Non-MAID FMs	MAID Pts n = 8	Non-MAID Pts
Post-traumatic stress	.76 (.54)	1.83* (1.69)+	.45 (.35)	-
Total demoralization	-	-	11.83 (7.83)	7.64* (6.43)+
Meaning and Purpose subscale	-	-	6.83 (6.04)	3.75* (3.67)+
Distress and Coping Ability subscale	-	-	5.86 (2.54)	3.89* (3.45)+
Depression	-	-	9.53 (4.54)	8.30** (4.10)+
Pre-death grief	24.83 (5.95)	21.49* (8.47)+	29.5 (5.96)	22.34 ~(-7.15)+
Caregiver burden	15.11 (10.97)	11.86* (9.42)+	-	-

12034

Poster Session

The impact of patient age on palliative care utilization and end-of-life outcomes among patients with metastatic breast cancer. *First Author: Carley Mitchell, University Hospitals, Department of Medicine, Cleveland, OH*

Background: Among patients with advanced cancer, palliative care (PC) utilization is frequently associated with improved quality of life, less aggressive end of life (EOL) measures, and hospice enrollment at the time of death. While older age is often associated with less PC utilization. The interplay between patient age, site and timing of PC with resultant EOL trends is not well understood. We aimed to assess these variations within a single institution's metastatic breast cancer (mBC) population. **Methods:** An IRB approved retrospective study was conducted. All adult, decedent, mBC patients from 2011-2022 were analyzed. Manual chart review extracted demographic and clinical data related to diagnosis, treatment, PC utilization and death. The relationship of patient age with PC utilization (including setting and timing), aggressive EOL measures, hospice care at the time of death, and hospice duration were evaluated. Univariate analyses were conducted and factors with a significance level $p < 0.15$ were further evaluated on multivariable logistic regression. **Results:** 278 decedent mBC patients met inclusion criteria. Any form of PC interaction from date of metastatic diagnosis to date of death, and utilizing outpatient (OP) PC (i.e., only OP or OP + inpatient (IP)) during the last year of life were significantly associated with hospice enrollment at the time of death. Similarly, utilizing only OP PC (i.e., no IP) was significantly associated with a longer time on hospice care. There was a trend toward shorter hospice durations in mBC patients who received only IP PC, and patients who received any IP PC or had their first PC interaction < 4 months prior to the time of death were more likely to experience ≥ 1 aggressive EOL measure. Young adults (< 40) were significantly more likely to receive some form of PC throughout their disease course, with a trend toward receiving only IP PC. While no significant relationships were identified between age and EOL factors, there were trends toward young and middle-aged adults (40-64) receiving ≥ 1 aggressive EOL measure and less time on hospice compared to older adults (≥ 65). **Conclusions:** This study gives important insight into a breast cancer-specific female population. Results highlight the importance of PC, especially in the OP setting, and its effect on hospice enrollment prior to death. However, there appears to be an interesting dichotomy between young adults receiving more PC and worse EOL experiences compared to older adults receiving less PC and better EOL experiences. These results should guide and promote, early OP focused PC specifically for young and middle-aged adults to help improve challenging EOL transitions. Research Sponsor: None.

Variable	Odds Ratio	Univariate p-value	Multivariate p-value
Any PC			
< 40 v 40-64	9.28	0.04	0.11
< 40 v ≥ 65	10.95	0.03	
Hospice care at time of death			
Any PC v None	2.39	0.01	0.01
Any OP PC v None	2.89	0.02	0.04
≥ 3 weeks on hospice	Only OP PC v None	7.55	0.04

12033

Poster Session

Risk of malnutrition and predisposing factors among Mexican patients with advanced cancer. *First Author: Sergio Contreras, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán (Mexico), México City, Mexico*

Background: Malnutrition is a predictor of cancer survival independent of cancer site. However, routine screening for malnutrition is underutilized. Advanced cancer accounts for 60% of cancer cases in developing countries of which approximately 52 % have malnutrition. This study aimed to describe factors associated with risk of malnutrition among patients with advanced cancer. **Methods:** We conducted a cross-sectional analysis of baseline data from patients with recently diagnosed advanced cancer included in a multidisciplinary patient navigator-led supportive care program in Mexico City (Te Acompañamos). At the time of enrollment in the program, patients completed a series of questionnaires including assessments of quality of life (FACT-G), various symptoms and the validated malnutrition screening tool (MST). Clinic and demographic characteristics were obtained from the patient chart. Descriptive statistics were used for analysis and factors associated with risk of malnutrition were analyzed by bivariate testing. **Results:** Between August 2017 and December 2022, a total of 601 patients were included. Mean age was 62 years (range 18-94), 57.2% were women, 56% had gastrointestinal and 28% gynecological malignancies. 72 % screened positive for malnutrition on the MST and 49 % reported nausea on FACT-G. Patients with an ECOG performance status ≥ 3 were more likely to screen positive for malnutrition (OR 5.9 95%CI 2.5- 13) as well as those with baseline nausea (OR 2.99; 95%CI 1.9-4.7). On the other hand, patients with active chemotherapy (OR 1.4 95%CI, 1.016-1.95) and those receiving antiemetic treatment with a single medication (OR 1.63 95%CI, 1.1-2.4) were more likely to have nausea. No other clinical or demographic characteristics were significantly associated with screening positive for malnutrition or reporting nausea, including gender, age, history of smoking or alcohol abuse, type of neoplasia, or oncologic treatment. **Conclusions:** Our results show that a high proportion of patients with advanced cancer are at increased risk for malnutrition and report nausea. Poor functional status and nausea were strongly associated with a higher risk of malnutrition, while receiving insufficient antiemetic medication was associated with increased odds of nausea. This suggests that appropriate treatment of nausea and nutritional interventions should be prioritized early in the management of patients with advanced cancer regardless of the type of cancer treatment in order to avoid malnutrition and improve patient well-being. Research Sponsor: Fundación para la Salud y la Educación Dr. Salvador Zubirán.

12035

Poster Session

Falls and hospitalization during chemotherapy in older women with early breast cancer. *First Author: Jingran Ji, City of Hope, Duarte, CA*

Background: Hospitalizations are frequent, burdensome, and potentially avoidable complications of cancer treatment in older adults. While geriatric assessments can identify older patients at risk for hospitalization, the use of these assessments in clinic is limited by time and resources. Screening for falls in the past 6 months is a quick and simple question that clinicians can ask in clinic and fall history has been linked to chemo-related toxicity. Here, we hypothesized that in older adults with cancer fall history prior to chemo is associated with an increased risk of hospitalization during chemo. **Methods:** In a prospective multicenter study of 497 women age ≥ 65 with stage I-III breast cancer treated with neo/adjuvant chemo, we assessed baseline self-reported fall history in the past 6 months as a dichotomous (yes/no) and continuous variable (no. of falls). Our primary endpoint was hospitalization during chemo (yes/no, yes defined as incident hospitalization assessed from start to end of chemo and attributed to toxicity from chemo). We used multivariable logistic regression to examine the association between fall history and hospitalization during chemo, adjusting for socio-demographic and clinical covariates. **Results:** The median age was 70 (65-86), 65% had stage II/III disease, 37% had anthracycline, and 72% received primary prophylaxis with G-CSF. Of the 497 participants, 60 (12%) reported falls (median 1.0 [1-6]) at baseline, and 114 (23%) were hospitalized during chemo (median 1.0 [1-4]). The most common toxicities that resulted in hospitalization were febrile neutropenia (25%), anemia (13%), dehydration (13%), and fatigue (13%). Women who fell in the 6 months prior to chemo had greater odds (adjusted OR = 2.69, 95% CI 1.42-5.11, $p = 0.003$) of being hospitalized during chemo compared to women who did not fall. **Conclusions:** In this cohort of older women with early breast cancer, fall history prior to chemo was associated with an increased risk of hospitalization during chemo, independent of sociodemographic and clinical factors. Oncologists do not routinely assess fall history when considering chemo in older adults. Screening for falls is a quick, simple, and important indicator of vulnerability that oncologists may use to identify patients at risk for hospitalization during chemo and inform personalized, patient-partnered treatment decisions. Clinical trial information: NCT01472094. Research Sponsor: U.S. National Institutes of Health; Breast Cancer Research Foundation; Center for Cancer and Aging.

Univariate and multivariable associations between fall history and hospitalization during chemo.						
	Hospitalization during chemo		Univariate		Multivariable*	
	Yes	No	OR (95% CI)	p-value	OR (95% CI)	p-value
Falls in past 6 months	n=114	n=383	N=497			
No	90 (21%)	343 (79%)	433	1.00		1.00
Yes	23 (38%)	37 (62%)	60	2.37 (1.34-4.19)	0.003	2.69 (1.42-5.11)
Each 1-point increase in no. of falls	-	-	-	1.56 (1.15-2.09)	0.002	1.62 (1.16-2.25)

*Adjusted for age, race/ethnicity, education, BMI, no. of comorbidities, physical function, albumin, and chemo regimen.

12036

Poster Session

The association of the comorbidity polypharmacy score (CPS) with functional limitations, frailty, and mortality in older adults with gastrointestinal malignancies. *First Author: Brian Westbrook, University of Alabama at Birmingham, Birmingham, AL*

Background: Older adults share a growing burden of cancer morbidity and mortality. The presence of comorbid medical conditions and polypharmacy may present significant challenges to cancer management for older adults. Although geriatric assessment (GA) is recommended to personalize treatment for older adults with cancer, it remains underutilized in routine oncology practice, and how best to measure comorbidity and polypharmacy remain unknown. The Comorbidity Polypharmacy Score (CPS), which is the sum of the number of comorbid medical conditions and medications for a patient, has been validated in other medical fields. Here we review the association of CPS with key outcomes among older adults with gastrointestinal (GI) malignancy. **Methods:** The Cancer and Aging Resilience Evaluation (CARE) tool is a brief, patient-completed GA developed for older adults with cancer at the University of Alabama at Birmingham (UAB). For patients enrolled in the CARE registry, diagnosed with a new GI malignancy between September 2017 and April 2021, we calculated a CPS based upon the number of patient-reported medical comorbid conditions and daily medications. Patients were separated into two groups, those with CPS ≥ 15 , or high-risk, and those with CPS < 15 . Multivariable analyses were adjusted for age, sex, race, cancer type, and cancer stage, and were performed to examine the potential association between high-risk CPS and falls, functional limitations, frailty, and mortality. **Results:** 548 patients were included in this study with a mean age of 69.7 years; 44.9% female and 23.9% Black. Common GI malignancies included colorectal (30.8%), pancreatic (25.5%), hepatobiliary (17.7%), and gastroesophageal (10.8%). Patients with CPS ≥ 15 were more likely to report falls (adjusted odds ratio [aOR] 3.39, 95% CI 1.91-6.02), dependence in activities of daily living (ADL) (aOR 3.07, 95% CI 1.67-5.66) and instrumental ADL (aOR 3.81, 95% CI 2.02-7.20), and have frailty (aOR 5.17, 95% CI 2.84-9.39). There was not a statistically significant association with either six-month or twelve-month survival. **Conclusions:** CPS was associated with falls, functional limitations, and frailty, but not survival, among older adults with GI malignancies. This association highlights the potential role of CPS as an efficient screening tool for older adults with cancer who would benefit from more comprehensive comorbidity and medication review. Research Sponsor: Supported in part by the National Cancer Institute of the National Institutes of Health (K08CA234225) and the Doris Duke Charitable Foundation CARES program at UAB.

12038

Poster Session

Association of sarcopenia and treatment tolerability in older adults with advanced cancer: Secondary analysis of a nationwide NCI Community Oncology Research Program (NCORP) randomized clinical trial. *First Author: Richard Francis Dunne, Wilmot Cancer Institute, University of Rochester Medical Center, Rochester, NY*

Background: Sarcopenia (sarc) is defined by reduced muscle function paired with low muscle mass or quality. Sarc is common in older adults, but the relationship between sarc and treatment tolerability in older patients (pts) with cancer has not been established. This secondary analysis of our nationwide University of Rochester NCORP Research Base randomized trial examines whether pre-treatment sarc was associated with treatment toxicity and survival in older pts with advanced cancers. **Methods:** Pts aged 70 and older with incurable solid tumors and lymphoma initiating a new high-risk systemic treatment were enrolled in GAP70+ (NCT02054741). GAP70+ was a cluster randomized trial evaluating whether a geriatric assessment intervention can reduce cancer treatment toxicity. This secondary analysis included 161 pts with baseline computed tomography (CT) scans and physical function testing. Sarc was defined as low muscle strength (5-time Chair Stand Test > 16.7 seconds) with reduced muscle mass (BMI and sex-specific cutoffs, cm/m²) or low muscle quality (Hounsfield units [HU] average radiodensity thresholds) utilizing validated cross-sectional CT imaging metrics. Sarc was defined as severe in presence of reduced physical performance (Timed-Up-And-Go > 13.5 seconds). We evaluated if the proportion of pts experiencing any grade 3-5 toxicity in the first 3 months of treatment using Common Terminology Criteria for Adverse Events (CTCAE) V4.0 was higher in those with sarc than those without sarc. Multivariate logistic regression was used to further explore this relationship. Multivariate Cox regression analysis was performed to evaluate the association of sarc and severe sarc with 1-year survival. **Results:** Mean age of the 161 participants included in this cohort was 76.6 years and 60.9% of were male; over half had gastrointestinal (34.8%) or lung cancer (23.6%). Sarc was found in 91 of 161 (56.5%) pts; 54 had severe sarc. Pts with sarc did not experience significantly more grade 3-5 toxicity compared to those without sarc (79.1% vs. 71.4%, $p = 0.26$). However, pts with sarc experienced more grade 3-5 non-hematologic toxicity (63.7% vs. 44.3%, $p = 0.01$) on univariate and multivariate analysis (OR 2.2, CI 1.1-4.5, $p = 0.02$). The association between sarc and worse survival at 1-year was not statistically significant (OR 1.5, CI 0.9-2.4, $p = 0.13$). Those with severe sarc did demonstrate significantly worse 1-year survival on multivariate analysis (HR 1.8, CI 1.1-2.9, $p = 0.02$). **Conclusions:** Older pts with cancer and sarc were more likely to suffer serious non-hematologic toxicity from cancer treatment. Furthermore, those with severe sarc had significantly worse survival. Evaluation for sarc before initiating treatment in older adults could help oncologists identify pts at higher risk of toxicity and poor survival. Clinical trial information: NCT02054741. Research Sponsor: U.S. National Institutes of Health.

12037

Poster Session

Biologic profile to predict overall survival in non-metastatic breast cancer: A latent class analysis on aging biomarkers. *First Author: Claire Falandry, Unité d'Oncogériatrie, Centre Hospitalier Lyon Sud and CarMeN laboratory of Lyon University, Pierre-Benite, France*

Background: The aging process is heterogeneous and the result of different biological mechanisms. Blood biomarkers involved in the aging process, aside from comprehensive geriatric assessment, may help clinicians when facing equivocal therapeutic decisions, for example adjuvant treatment at high risk of toxicities. **Methods:** This study was conducted on a previously published cohort (PMID 25989735) including 162 patients aged ≥ 70 years ("Old") and 82 patients aged ≤ 60 years ("Young") with newly diagnosed non-metastatic breast cancer. Serum samples collected from all patients at breast cancer diagnosis, before any treatment were available from the extensive Leuven blood biobank. Overall survival was evaluated with October 7, 2022 as data cutoff. A panel of blood aging biomarkers attributed to inflammation: IL6, MCP1, RANTES, telomere shortening: telomeric DNA ratio T/S, telomeric dysfunction: CRAMP, chitinase activity, and anabolism : IGF1. Considering a high risk of collinearity, we performed a latent class analysis (LCA) on the whole cohort, to delineate the respective roles of inflammaging, replicative senescence and sarcopenia on patient clusters. **Results:** In univariate analysis were significantly associated with a poorer survival: high MCP1, hazard ratio (HR) = 1.57 (95%CI 1.32-1.87), high chitinase activity, HR = 1.33 (95%CI 1.12-1.57), and low IGF1, HR = 1.76 (95%CI 1.47-2.11). The biomarkers correlation matrix identified a significant correlation of Chitinase activity with MCP1, IGF1, CRAMP; of CRAMP with IL6; and IGF1 with T/S ratio. LCA identified 2 biologic profiles within the population, representing 137 (56.1%, class 1) and 107 (43.9%, class 2) patients. Class 1 was associated with a significantly poorer overall survival: HR = 3.52 (95%CI 2.28-5.45), and age-adjusted HR = 1.77 (95%CI 1.12-2.80). The best predictors for class 1 membership were low IGF1 (89%), high MCP1 (82%), high chitinase activity (79%), high IL6 (69%). Class 1 represented 77% of the "Old" and 15% of the "Young" populations. **Conclusions:** Our results delineate an unfavorable biologic profile that transcends chronological age and significantly predicts a poorer overall survival, underpinned by markers of both inflammaging, telomeric dysfunction and sarcopenia. The strong correlation between markers argues for a unique underlying biological pathway. Noteworthy, high IGF1, usually considered as a risk factor for breast cancer progression, was associated with a better prognosis. Low IGF1, high chitinase activity and high MCP1 appear as promising predictive biomarkers. Research Sponsor: Fund for Scientific Research Flanders (FWO Vlaanderen) (Hans Wildiers); La Ligue nationale Contre le Cancer (Claire Falandry).

12039

Poster Session

Defining an abnormal geriatric assessment for older adults with cancer: Which deficits matter most? *First Author: Anthony Carrozzi, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada*

Background: At present, there is no universal, objective, and evidence-based definition of what constitutes an abnormal geriatric assessment (GA) in geriatric oncology (GO). In the literature, a threshold number of abnormal GA domains (ranging from 1-4) is often used to define an abnormal GA. However, it is not well-established whether having a specific number of abnormal domains more frequently leads to treatment plan modification (TPM), a key goal of GA, or if particular domains have a greater impact on TPM. The primary objectives of this study are: (1) to determine how well the current definitions of an abnormal GA predict TPM following GA, and (2) to identify particular GA domains associated with TPM. **Methods:** A retrospective review of the GO clinic database at Princess Margaret Cancer Centre was conducted. All new patients seen in clinic from May 22, 2015 to June 10, 2022 who met the following criteria were included: (1) referred for treatment decision making, (2) received a complete GA, and (3) had a proposed oncologic treatment plan. Demographic, oncologic, and GA-domain variables were extracted. Univariate and multivariate logistic regression modelling was conducted using SPSS to determine each variable's association with TPM; age, sex, frailty (VES-13) score, and treatment intent were included in all multivariate models. Area under the curve (AUC) was calculated for each model. **Results:** The study cohort ($n = 736$) had a mean age of 80.7 years (61-100), 46.1% was female, and 78.3% had a VES-13 score indicating vulnerability. In univariate analysis, age, VES-13 score, disease stage, treatment intent, all GA domains (except Medication Optimization and Social Supports), and all threshold numbers of abnormal domains (except 1 and 7) were significantly associated (p -value < 0.050) with TPM. The best-performing threshold number of abnormal domains in univariate analysis was 4 (AUC 0.628). Overall, the best-performing multivariate model based on AUC was the model containing all 6 significant GA domains (AUC 0.710). In this model, age, treatment intent, Comorbidities, Falls Risk, and Cognition were independently associated with TPM (p -value < 0.05). The multivariate model with a threshold of 4 abnormal domains alone had an AUC of 0.689 and age, VES-13 score, treatment intent, and the threshold were independently associated with TPM. Of the models which included a single GA domain plus the threshold, the models with Comorbidities and Cognition performed best, having AUCs of 0.699 and 0.700, respectively. **Conclusions:** Overall, our results suggest that an abnormal GA (leading to TPM) may be best defined as one with abnormalities in the domains of Comorbidities, Falls Risk, and Cognition. In terms of a strictly numerical threshold, a GA may be best defined as abnormal if at least 4 GA domains are abnormal. When at least 4 GA domains are abnormal, abnormalities in Comorbidities and Cognition appear to best predict TPM. Research Sponsor: Sinai Health & University Health Network Geriatrics Summer Scholars Program.

12040

Poster Session

Associations of frailty with overall survival (OS) and functional decline among older adults with non-small-cell lung cancer (NSCLC) receiving chemotherapy, immunotherapy, and/or targeted therapy. *First Author: Howard Jinsoo Lee, University of California, San Francisco, San Francisco, CA*

Background: Among older adults with cancer receiving chemotherapy, frailty indices can predict poor outcomes including survival and toxicity. Given the increasing use of immunotherapy and targeted therapy to treat NSCLC, we assessed the prognostic importance of frailty among older adults with NSCLC receiving systemic therapy. **Methods:** This multi-site prospective cohort study enrolled adults age ≥ 65 with advanced NSCLC starting chemotherapy, immunotherapy, and/or targeted therapy with non-curative intent. Patients completed geriatric assessments pretreatment and at 1, 2, 4, and 6 months. We constructed a 47-item deficit-accumulation frailty index including pretreatment demographic, geriatric assessment, and clinical factors using established methodology. Frailty scores ranged from 0 (no frailty deficits) to 1 (all frailty deficits present). We categorized patients as robust (< 0.2), pre-frail ($0.2-0.34$), or frail (≥ 0.35). The primary outcome was OS. Secondary outcomes included treatment-related grade ≥ 3 adverse events (AE), unplanned hospitalization, and functional decline in instrumental activities of daily living (IADL). We conducted a Kaplan-Meier survival analysis to estimate OS by frailty group and Cox proportional hazards models adjusting for treatment type. We used logistic regression models to evaluate the association of frailty with secondary outcomes adjusting for treatment type. **Results:** Among 149 patients, median age was 73 (range 65-94). During the study, 32% received targeted therapy, 29% immunotherapy, 27% chemoimmunotherapy, and 12% chemotherapy. Overall 43% of patients were robust, 38% pre-frail, and 19% frail. Frailty was associated with Asian race, lower education, Medicaid insurance, and no prior NSCLC surgery. Notably, frailty was not associated with age or treatment type. Median OS was 18.7 months overall: not reached for robust patients, 8.9 months for pre-frail, and 5.6 months for frail patients. Adjusting for treatment type, pre-frail (HR 2.11, 95% CI 1.24-3.60; $p = 0.006$) and frail (HR 2.86, 95% CI 1.52-5.39; $p = 0.001$) patients had worse OS compared to robust patients. During treatment, 29% developed a grade ≥ 3 AE, 31% had an unplanned hospitalization, and 41% developed IADL decline. Pre-frail/frail patients were more likely to develop IADL decline (HR 2.18, 95% CI 1.02-4.68; $p = 0.04$) than robust patients, but there were no differences in toxicity or hospitalization. **Conclusions:** Frailty is prognostic for OS among older adults with advanced NSCLC receiving systemic therapy across treatment types and predicted IADL decline. Frailty assessment before initiation of systemic therapy may help identify older adults with advanced NSCLC at higher risk of poor outcomes to inform decision making, individualize anticipatory guidance, and optimize supportive care. Research Sponsor: U.S. National Institutes of Health.

12042

Poster Session

Exploring decisional control preferences in older patients with cancer and their caregivers. *First Author: Sofiia Hryniv, University of Rochester, Rochester, NY*

Background: Shared decision making is preferred by many patients but it is often viewed from the lens of the patient and physician dyad only. Caregivers often support cancer decision-making, although their decision control preferences are not typically considered. We explored decisional control preferences of older patients with cancer and their caregivers, and examined concordance in preferences of the dyad, as well as patient, caregiver, physician factors associated with concordance. **Methods:** We utilized data from a national geriatric assessment (GA) cluster-randomized trial (NCT 02054741; PI: Mohile; funding NCI UG1CA189961) that recruited patients aged ≥ 70 with incurable cancer, their caregivers, and oncologists. Controlled Preferences Scale (CPS) was used to assess shared decision making preferences. Both patients and caregivers were asked about the role of patients (Patient-role CPS) and caregiver (Caregiver-role CPS) in the decision making process. Patient-role CPS options were 1) doctor makes the decisions, 2) doctor makes the decisions with patient's input, 3) equally shared decision, 4) patient makes the decisions with doctor's input, 5) patient makes the decisions. Caregiver-role CPS options were 1) doctor makes the decisions, 2) patient makes the decision with doctor, 3) patient and caregiver make the decisions with doctor, 4) caregiver makes the decisions with doctor. Matching responses of the dyads for each CPS question were considered concordant. We used descriptive statistics to summarize CPS for patients and caregivers and the concordance between them. We utilized logistic regression to assess dyads' sociodemographic information, patients' GA and physicians' practice characteristics associated with patient-caregiver CPS concordance. **Results:** Enrolled dyads with completed CPS were included ($N=332$); mean age (SD) of patients and caregivers was 76.6 (5.3) and 66.6 (12.2). Women constituted 39% of patients and 76% of caregivers. Patient-role CPS for patients' (and caregivers') were 11% (6%) for doctor makes the decisions, 33% (28%) for doctor makes the decisions with patient's input, 45% (49%) for equally shared, 9% (14%) for patient makes the decisions with doctor's input, 2% (3%) for patient makes the decision. Patients' (and caregivers') answers on caregiver-role CPS were 20% (19%) for doctor makes the decisions, 18% (28%) for patient makes the decisions with doctor, 61% (52%) for patient and caregiver make the decisions with doctor and 1% (1%) for caregiver makes the decisions with doctor. Dyads concordance occurred in 46% of patient-role CPS and 54% of caregiver-role CPS, indicating moderate concordance. No baseline factors were associated in dyad concordance for either the patient-role or caregiver-role CPS. **Conclusions:** Clinicians should inquire about decisional control preferences of patients and caregivers in order to optimally support shared decision making. Clinical trial information: NCT02054741. Research Sponsor: U.S. National Institutes of Health.

12041

Poster Session

Satisfaction in older patients by geriatric assessment using a novel tablet-based questionnaire system: A cluster-randomized, phase III trial of patients with non-small-cell lung cancer (ENSURE-GA study; NEJ041/CS-Lung001). *First Author: Sayo Soda, Department of Pulmonary Medicine and Clinical Immunology, Dokkyo Medical University School of Medicine, Tochigi, Japan*

Background: To provide optimal treatment for older cancer patients, it is necessary to carry out a geriatric assessment (GA) to evaluate geriatric syndrome. However, GA is not widely performed because it requires expertise. In this ENSURE-GA study, we evaluated if providing a GA summary and recommendations for GA-guided interventions using a novel tablet-based questionnaire system improved satisfaction about communication with physicians for older patients with non-small-cell lung cancer (NSCLC). **Methods:** Patients with NSCLC who were incapable of radical treatment aged 75 or older were enrolled. All patients underwent a standardized GA using a tablet before starting treatment. Participating institutions were cluster-randomized into the intervention group and the control group. In the intervention group, GA summary and recommendations for GA-guided interventions were immediately returned to guide physicians in selecting treatments and interventions. The control group did not provide a GA summary. The primary outcomes were difference in patient satisfaction pre-treatment and percent change pre- and post-treatment according to the HCCQ questionnaire. **Results:** A total of 1,021 patients from 78 institutions in Japan were enrolled between 2019–2022. There were no differences in patient backgrounds between the intervention group and the control group: mean age 80.1 yrs. vs. 80.0 yrs.; male 64.1% vs. 66.8%; adenocarcinoma 70.4% vs. 64.8%; and performance status 0-1, 82.4% vs. 79.0%, respectively. All GA domain evaluation results, such as ADL and cognitive function, also did not differ between the two groups. Pre-treatment satisfaction scores were significantly higher in the intervention group than in the control group (29.9 vs. 29.1, $p = 0.003$). There was no significant difference in the mean percent change between the two groups (-0.13 vs. 2.38 , $p = 0.165$). **Conclusions:** Providing the oncologist with a GA summary and recommendations for GA-guided interventions improved patient satisfaction from the start of treatment. A novel system using a tablet may be effective at promoting GA more widely. Clinical trial information: UMIN0000037590. Research Sponsor: Japan Agency for Medical Research and Development.

12043

Poster Session

Association of nutrition with psychological health and quality of life among older adults with advanced cancer. *First Author: Surbhi Singhal, Stanford Hospital & Clinics, Stanford, CA*

Background: Impaired nutrition is associated with greater treatment toxicity and reduced overall survival in patients with advanced cancer. We aimed to evaluate the association of impaired nutrition with psychological health and quality of life among older adults with advanced cancer who were starting cancer treatment with palliative intent. **Methods:** This secondary analysis was performed on baseline data from a nationwide cluster randomized clinical trial (ClinicalTrials.gov identifier: NCT02107443; PI: Mohile; funding NCI UG1CA189961). Adults age ≥ 70 with advanced cancer and ≥ 1 geriatric assessment impairment were enrolled from 2014 to 2017. Patients with BMI < 21 kg/m², $> 10\%$ involuntary weight loss in the past 6 months, or Mini Nutritional Assessment Short Form (MNA-SF) score of ≤ 11 were considered to have impaired nutrition. We used separate multivariable linear regressions to evaluate the association of impaired nutrition with each measure of psychological health and quality of life, which included Geriatric Depression Scale (GDS-15, range 0-15), Generalized Anxiety Disorder-7 (GAD-7, range 0-21), NCCN Distress Thermometer (NCCN DT, range 0-10) and Functional Assessment of Cancer Therapy-General (FACT-G, range 0-108). Analyses were adjusted for baseline patient demographics, clinical characteristics, and geriatric assessment. **Results:** Among 541 patients, mean age was 77 (range 70-96) and 60% had impaired nutrition. Among the 326 patients with impaired nutrition, 95% had MNA-SF ≤ 11 , 23% had $> 10\%$ weight loss in the last six months, and 20% had BMI < 21 kg/m². Mean baseline GDS-15 was 3.1 (standard deviation [SD] 2.7), GAD-7 was 2.9 (SD 4.0), NCCN DT was 2.9 (SD 2.7), and FACT-G was 80 (SD 14). In the adjusted model, compared to those with normal nutrition, older adults with impaired nutrition had greater depression (mean 0.65 points higher on the GDS-15, $p < 0.01$) and lower quality of life (mean 6.0 points lower on the FACT-G, $p < 0.01$). There was insufficient evidence of an association between nutrition and anxiety ($\beta = 0.67$, $p = 0.06$) or distress ($\beta = 0.26$, $p = 0.28$). **Conclusions:** Recognition of malnutrition by oncology providers is crucial for older adults with advanced cancer. Impaired nutrition is associated with greater depression and lower quality of life among older adults with advanced cancer. Tailored resources to improve psychological health and quality of life are needed to support older adults with impaired nutrition receiving cancer treatment. Research Sponsor: U.S. National Institutes of Health.

12044

Poster Session

12045

Poster Session

Racial differences in muscle measures and survival among older adults with GI malignancies. *First Author: Gabriel Aleixo, Cleveland Clinic Foundation, Cleveland Heights, OH*

Background: Sarcopenia (low muscle mass) and myosteatosis (fat infiltration of muscle) can be assessed from routinely obtained Computed tomography (CT) images and are independent predictors of chemotherapy toxicities and survival among patients with gastrointestinal (GI) malignancies. However, most studies to date have consisted of predominantly white populations. Therefore, the role of sarcopenia and myosteatosis among racial minority populations is unknown. Our objective was to examine racial differences in muscle measures and their association with survival among older adults with GI malignancies. **Methods:** This is a prospective cohort study of older adults with GI cancers from the University of Alabama at Birmingham. Single slices of axial CT images from L3 segments were analyzed using Slice-O-Matic software. Skeletal muscle area (cm²) was divided by height to obtain the skeletal muscle index (SMI, cm²/m²). Skeletal muscle radiodensity (SMD) in Hounsfield units (HU) was used to approximate muscle composition. Sarcopenia (low SMI) and myosteatosis (low SMD) were defined based on standard cut-offs developed in a cohort of GI malignancies (Martin et al., JCO 2013). We compared differences in muscle measures between non-Hispanic (NH) White and NH Black participants. We utilized Cox models, separated by race, to examine the impact of muscle measures on survival. We adjusted for age, sex, education, cancer type, cancer stage, lines of therapy, and comorbidities. **Results:** Six hundred sixty patients were included, 76% NH White and 24% NH Black. The median age was 69.4 years, 35% had colorectal cancer, and 42% had stage IV disease. NH Black patients had higher SMD (41.7 vs. 38.3 HU; $p < 0.001$) and lower rates of myosteatosis (40% vs. 27%; $p = 0.04$) but similar SMI (42.3 vs. 41.1 cm²/m²) and rates of sarcopenia (58% vs. 55%). In stratified Cox models, each 5 HU unit increase in SMD was associated with reduced risk of all-cause mortality of NH black patients (HR 0.88; 95% CI 0.80-0.98 $p = 0.02$) and not in NH White patients (HR 0.95; 95% CI 0.88-1.01; $p = 0.14$). Meanwhile, each 5-unit increase in SMI was associated with improved survival in NH White patients (HR 0.91; CI 0.85-0.98; $p = 0.03$) but not in NH Black patients (HR 0.89 CI 0.78-1.03 $p = 0.13$). When using existing cut points for sarcopenia and myosteatosis, NH White patients with sarcopenia had worse survival (HR 1.42; CI 1.04-1.92; $p = 0.02$), but sarcopenia among NH black patients was not associated with worse survival (HR 1.16 95% CI 0.62-2.16 $p = 0.64$). Myosteatosis was not associated with worse survival in either NH white (HR 95%CI 0.95-1.68 $p = 0.10$) or NH black patients (HR 1.61 95%CI 0.88-2.95 $p = 0.12$). **Conclusions:** Muscle measures may differ by race and have different associations with survival by racial group. Therefore, it is essential to develop cut points for muscle measures incorporating race. Research Sponsor: U.S. National Institutes of Health; Doris Duke Charitable Foundation; CARES program at UAB.

12046

Poster Session

Association between food insecurity and frailty among older adults with gastrointestinal malignancies: The CARE Registry. *First Author: Mackenzie Elisha Fowler, University of Alabama at Birmingham, Birmingham, AL*

Background: Food insecurity is associated with higher gastrointestinal (GI) cancer mortality, but its association with frailty, a known predictor of premature mortality among older adults with cancer, is less understood. Our objective was to evaluate the association between food insecurity and frailty among older adults with GI malignancies. **Methods:** In this cross-sectional analysis, we included 424 older adults ≥ 60 y recently diagnosed with GI cancer undergoing self-reported geriatric assessment (GA) at their first pre-chemotherapy visit to the University of Alabama at Birmingham oncology clinic. Food insecurity was the exposure of interest, defined using the 2019 United States Department of Agriculture Economic Research Service (USDA ERS) Low-Income, Low-Access (LILA) measure, which classifies census tracts based on income and/or access to food stores at various distances by urban-rural status. The primary outcome was frailty measured via the CARE Frailty Index, a composite measure based on the proportion of deficits across several GA measures (44 items in total). Frailty was dichotomized as frail or robust/pre-frail. We examined the association between LILA and frailty with modified Poisson regression accounting for census tract clustering. **Results:** Median age at study participation was 69 (IQR: 64, 76), 56.6% were male, 27.2% were non-Hispanic black, 31.4% had colorectal, 28.1% had pancreatic cancer, and 71.7% presented with stage III/IV disease. LILA versus non-LILA had a higher proportion of participants who were non-Hispanic Black (52.1% vs. 11.0%, $p < 0.001$) and lower educated (high school or less: 50.6% vs. 35.0%, $p = 0.020$). After adjustment for age, race, sex, cancer type and stage, LILA was associated with 37% higher risk of frailty (RR: 1.37, 95% CI: 1.05, 1.80) versus non-LILA. Analysis of LILA sub-categories revealed that the overall effect may be driven by low income + low access at 1 mile for urban/10 miles for rural areas (RR: 1.47, 95% CI: 1.12, 1.94) and low income + low access at 0.5 mile for urban/10 miles for rural areas (RR: 1.39, 95% CI: 1.05, 1.85). Low income + low access at 1 mile for urban/20 miles for rural areas, low income + low access with a vehicle or at 20 miles, low income only, or low access only did not demonstrate a significant difference. **Conclusions:** Low income and low access to food stores is associated with higher risk of frailty among newly diagnosed older adults with GI cancers prior to systemic treatment. Intervening on food insecurity at the local level, particularly in areas with low income and low access, may be a target for improving rates of frailty among older adults with GI cancers. Future studies are needed to determine causality. Research Sponsor: U.S. National Institutes of Health; Agency for Healthcare Research and Quality.

Peaceful acceptance of illness among older adults with cancer. *First Author: Elizabeth Gilbride, University of Rochester, Rochester, NY*

Background: Greater illness acceptance is associated with lower levels of psychological distress and higher rates of completion of advance care planning in adults with advanced cancer. However, studies on factors associated with illness acceptance among older adults with advanced cancer are limited and historically have not explored its relationship with caregiver or physician characteristics, despite the important role caregivers and oncologists play in patient illness acceptance. We aimed to evaluate the associations of patient, caregiver, and physician-related factors with illness acceptance among older adults with cancer. **Methods:** We utilized data from a national geriatric assessment cluster-randomized trial (NCT 02054741; PI: Mohile; funding NCI UG1CA189961). We recruited patients aged 70 years or over with stage III or IV incurable solid tumors or lymphoma and at least one geriatric assessment domain impairment as well as their caregivers. Illness acceptance was assessed using the 5-item Peace, Equanimity, and Acceptance in the Cancer Experience (PEACE) questionnaire (range 5-20). Higher PEACE score indicates greater illness acceptance. Multiple linear regression was used to assess the associations of patient, caregiver, and physician-related variables with PEACE. Variables included patient sociodemographic factors, geriatric assessment variables, and estimated life expectancy; caregiver sociodemographic variables, anxiety, depression, and physical function; and oncologist years in practice and comfort with geriatrics. **Results:** We included 333 patient-caregiver dyads; mean age (SD) of patients and caregivers, respectively, were 76.8 (5.4) and 66.6 (12.1). Approximately 27%, 26%, and 16% of patients had lung, gastrointestinal, and genitourinary cancers, respectively. Mean PEACE score was 17.4 (2.5), indicating relatively high illness acceptance (Table). On regression analysis, patient psychological impairment domain (including both anxiety and depression) ($B = -0.89$; $p > 0.01$), patient's lower estimated life expectancy (≤ 1 vs. > 5 years, $B = 1.19$, $p = 0.02$), and lower caregiver education attainment ($\leq$ high school vs. college; $B = -0.86$; $p < 0.01$) were associated with a lower illness acceptance. No physician variables were associated with PEACE. **Conclusions:** A better understanding of illness acceptance and its associated factors can facilitate patient-caregiver dyadic interventions to improve illness acceptance. Research Sponsor: U.S. National Institutes of Health; PCORI.

PEACE questionnaire.				
	Not at all	To a slight extent	To some extent	To a large extent
To what extent are you able to accept your diagnosis of cancer?	0.3%	3.3%	25.5%	70.9%
To what extent would you say you have a sense of inner peace and harmony?	3.3%	8.1%	43.5%	45.0%
To what extent do you feel that you have made peace with your illness?	4.5%	8.7%	39.0%	47.7%
Do you feel well loved now?	0.6%	1.2%	8.1%	90.1%
To what extent do you feel a sense of inner calm and tranquility?	2.1%	9.6%	45.3%	42.9%

12047

Poster Session

Regorafenib in older adults with metastatic colorectal cancer: A multi-center, single arm phase II trial. *First Author: Nabeel Badri, Wilmot Cancer Institute, University of Rochester Medical Center, Rochester, NY*

Background: Metastatic colorectal cancer (mCRC) is a leading cause of death, particularly in older adults. Regorafenib (REGO) is an FDA-approved oral multi-kinase inhibitor for refractory mCRC based on the CORRECT trial results, but older adults were underrepresented with a median age of 61 (54–67). This study aimed to evaluate REGO safety in older adults with mCRC and assess the feasibility of using geriatric assessment (GA) to predict toxicity risk. **Methods:** 27 subjects (PTs) enrolled (median age 73, range 65-85) and started at 120mg of REGO for 21 days of a 28-day cycle with provider discretion to escalate to full dose of 160mg after cycle 1. GA was conducted at enrollment, 4 weeks later, and then every 3 months to monitor for any deterioration. GA assessed 8 geriatric domains (comorbidity, functional status, physical performance, cognition, psychological state, nutrition, medication review, and social support) using validated tools. Primary objective was to assess grade 3-5 toxicity rate, with secondary objectives evaluating REGO efficacy and exploring baseline GA and toxicity risk associations. Kaplan-Meier method was used to estimate median overall survival (OS) and progression-free survival (PFS) from date of consent. Continuous GA measures were compared using non-parametric Wilcoxon rank-sum test, and binary GA measures were compared using Fisher's exact test. **Results:** Of 27 PTs enrolled, 15 were male, 12 were female, and 19 identified as white. At baseline, 77.7% of PTs had at least 3 (1-9) GA impairments. Physical performance (80.8%), comorbidity (75%), and cognition (69.2%) were the most prevalent impaired GA domains. 40% required dose reduction by end of cycle 2, and none escalated to full dose. 55% of PTs completed cycle 3. Main reasons for drug discontinuation were disease progression (80%) and toxicity (12%). 74.1% of PTs experienced at least one treatment-related grade 3-4 toxicity. Fatigue (33%), hypertension (30%), and hand-foot syndrome (15%) were the leading grade 3-4 toxicities. Median OS was 5.6 months (95% CI: 3.6-12.2m), and median PFS was 2.8 months (95% CI: 2.5-3.4m). There was no significant difference in baseline GA measures between those who experienced toxicities and those who did not. No statistically significant toxicity risk was associated with any baseline GA impairment. The prevalence of impaired mini-nutritional assessment increased over 4 weeks (58% to 91%, $p < 0.01$), and median Short Physical Performance Battery (SPPB) scores decreased (7 to 6, $p = 0.03$). **Conclusions:** The study found that older adults with mCRC had comparable survival with REGO but experienced high toxicity. This may be ameliorated by recently published step-wise REDOS dosing method and should be considered in older adults with mCRC. The study confirms the feasibility of implementing GA within clinical trials. More data is needed on the role of GA in predicting toxicity with targeted therapies. Clinical trial information: NCT02466009. Research Sponsor: Bayer.

12048

Poster Session

An evaluation of the financial toxicity amongst older patients with cancer in India. *First Author: Anant Ramaswamy, Tata Memorial Hospital (HBNL), Mumbai, India*

Background: Financial toxicity (FT) of cancer is prevalent among older patients in high-income countries, but there is no data about the financial burden faced by older patients in India. This study aimed to explore the FT of cancer among older Indian patients. **Methods:** This was a cross-sectional observational study conducted in the geriatric oncology clinic of Tata Memorial Hospital (Mumbai, India). Patients aged 60 years and above with cancer were included. Patients and their relatives were enquired regarding their occupations, monthly income, and source of funding for cancer treatment. The modified Kuppuswamy scale was used for stratification of socio-economic status (SES). The financial burden was evaluated using the Comprehensive Score for Financial Toxicity-Functional Assessment of Chronic Illness Therapy (COST-FACIT) scale. In addition, the Consumer Financial Protection Bureau Financial Well-Being Scale and the 28th question of QORTC QLQ-C30 were used to assess the financial quality of life. **Results:** Between June 2022 and January 2023, 498 patients were included. The median age was 67 (IQR, 63-72) years, and 360 (72.3%) were male. Common malignancies included gastrointestinal (199, 40.0%), lung (169, 34.0%) and urological (63, 12.7%); 320 (64.4%) had metastatic disease. According to the modified Kuppuswamy scale, most of the participants belonged to upper-lower SES (223, 44.8%), followed by lower-middle (115, 23.1%), upper-middle (97, 19.5%), lower (59, 11.8%) and only 4 (0.8%) belonged to upper SES. The source of funding was mostly from family members (264, 53.9%), insurance (72, 14.7%), while 59 patients (12.0%) did not require external support. Sixty-one (12.4%) had to borrow money, twenty-one (4.3%) participants had taken a loan, and 13 (2.6%) had sold their assets for the purposes of treatment. Moderate-severe burden on COST-FACIT was present in 165 (33.1%), whereas 333 (66.9%) experienced no or mild burden. High FT was associated with lower socioeconomic status (OR: 4.69, 95%CI 2.47-8.91, p-value < 0.001), poor financial well-being (OR: 9.35, 95%CI 5.52-16.46, p-value < 0.001) and poor score on Financial quality of life (OR: 5.16, 95%CI 3.39-7.86, p-value < 0.001). **Conclusions:** In older Indian patients with cancer, there is a high prevalence of financial burden and is associated with poor socioeconomic status, poor financial well-being and poor financial quality of life. More than half the patients depended on their family members to meet the cost of cancer treatment. Research Sponsor: None.

12050

Poster Session

Association of emotional support with quality of life, mental health, and survival among older adults with gastrointestinal (GI) malignancies. *First Author: Daniel Clausing, University of Alabama at Birmingham, Birmingham, AL*

Background: Emotional support (ES) is the most frequently reported support need among older adults with cancer. Yet, the association of ES with cancer outcomes is largely unknown. This study examined the association of ES with health-related quality of life (HRQoL), mental health, and survival among older adults with GI malignancies. **Methods:** We included older adults (≥60y) newly diagnosed with GI cancer and undergoing a self-reported geriatric assessment (GA) at first clinic visit. Self-reported ES, measured by the Medical Outcomes Survey was the primary exposure. Outcomes included physical and mental HRQoL as measured by the Patient-Reported Outcomes Measurement Information System® (PROMIS) 10-item global assessment, anxiety and depression as measured by the PROMIS Anxiety and Depression Short Form 4a, respectively, and one-year, two-year, and overall survival. Linear regression evaluated the association between ES and t-scores of physical/mental HRQoL. Logistic regression evaluated the association of ES with anxiety and depression. Models were adjusted for age, race, sex, and cancer type/stage. Kaplan-Meier curves and log-rank tests evaluated the association between ES and survival outcomes. **Results:** Overall, 795 participants were included. The median age was 68 (IQR: 64-74) and patients were 58.0% male, and 74.6% White. The most common cancers included colorectal (37.9%) and pancreatic (30.8%), with mostly advanced staged disease (Stage III/IV: 72.1%). A majority (77.6%) had adequate ES. Patients with inadequate ES were more likely to be Black (31.5 vs. 20.8%, p=0.005), disabled (24.1 vs. 10.4%, p<0.001), and widowed/divorced (54.2 vs. 24.8%, p<0.001). After adjustment, patients with inadequate ES had lower physical and mental HRQoL t-scores (Physical β: -3.35, 95% CI: -5.25, -1.46; Mental β: -2.46, 95% CI: -4.11, -0.81) and higher odds of depression (aOR: 2.22, CI: 1.34-3.69). There was no statistically significant association with anxiety (aOR: 1.15, CI: 0.73, 1.81). No differences were observed between patients with inadequate versus adequate ES in one-year, two-year, or overall survival (Log-Rank tests: one-year, p=0.952; two-year, p=0.606; overall, p=0.584). **Conclusions:** Older adults with inadequate ES have higher odds of poor physical and mental HRQoL and depression, but no difference in survival compared to those with adequate ES. Further work is necessary to determine if interventions to improve ES also improve HRQoL and depression. Research Sponsor: U.S. National Institutes of Health; Doris Duke Charitable Foundation.

12049

Poster Session

Overall survival outcomes in older patients with metastatic breast cancer: A National Cancer Database analysis. *First Author: Rima Patel, Icahn School of Medicine at Mount Sinai, New York, NY*

Background: Over the last few decades, improvements in healthcare have increased life expectancy by nearly 10 years resulting in a rise in America's older population. As age is one of the most significant risk factors for the development of cancer, there is a projected increase in the incidence of cancer in the elderly population, with the largest absolute and relative increases in breast cancer (BC). Although treatment advances have improved outcomes for patients with metastatic breast cancer (MBC), patients in clinical trials are often younger and there is limited data for the older population. The goals of this study were to use the National Cancer Database (NCDB) to assess overall survival (OS) in older patients over 75 years of age with MBC and evaluate the impact of tumor features and demographic factors. **Methods:** Women with a diagnosis of BC at age ≥75 years and with metastases at time of initial diagnosis from 2010 to 2019 were identified from the NCDB. Patients were stratified into age subgroups of 75-79, 80-84, and ≥85 years. Chi-square tests were used to compare categorical variables. Kaplan Meier curves were used to determine OS distributions for patients by age, BC subtype and year of diagnosis. Log-rank tests and multivariable cox proportional hazards modeling was performed to assess the difference in OS by BC subtype. **Results:** Of 17,325 eligible women included in the final analysis, 39.4% were 75-79, 30.1% 80-84, and 30.4% ≥85 years of age. We observed an improvement in OS over time, with 5-year OS rates improving from 13.7% in 2010 to 15.2% in 2015, p = 0.017. Three-year OS rates were higher in patients aged 75-79 (34.2%) compared with patients aged 80-84 (28.7%) and ≥85 years (18.6%), p < 0.001. Outcomes varied by BC subtype with better prognosis in patients with hormone receptor (HR)+, HER2-negative BC (3-year OS 35.1%), followed by HR+, HER2+ (32.8%), HER2+, HR-negative (20.6%) and lastly, HR-negative, HER2-negative BC (9.7%), p < 0.001. Based on multivariable analyses, a higher comorbidity index was associated with worse outcomes (HR 1.654 [1.48-1.849], p < 0.0001). Higher income (≥\$63,000) was associated with decreased mortality (HR 0.859 [0.784-0.941], p = 0.0011) compared with lower income (< \$38,000). While the type of cancer facility (academic, community, etc) did not impact mortality, older patients living in metropolitan areas (> 1 million) had improved outcomes (HR 0.829 [0.689-0.996], p = 0.046), compared to those in rural areas. **Conclusions:** We observed a modest though significant improvement in survival outcomes over time in older patients with MBC. Prognosis was better in patients with HR+ BC compared with HR-negative, HER2+, and HR-negative, HER2-negative subtypes. However, outcomes in patients ≥85 years remain poor. Given the lack of clinical trial data in older patients with cancer, future studies should specifically focus on improving outcomes in this population. Research Sponsor: None.

12051

Poster Session

Toxicity and outcomes of ipilimumab plus nivolumab in patients 80 years and older. *First Author: Haley M Meyer, Mayo Clinic in Arizona, Phoenix, AZ*

Background: The combination of ipilimumab and nivolumab (Ipi-Nivo) is a standard of care regimen in many malignancies. However, immune-related adverse events (irAE) are common and are of great concern, especially when treating the elderly population. This subgroup of patients may be at greater risk for serious irAEs and be less able to tolerate the potential treatment side effects. We sought to retrospectively evaluate our experience treating elderly patients ≥ 80 years with Ipi-Nivo to characterize adverse events. **Methods:** A retrospective chart review of the electronic medical records of all patients treated with Ipi-Nivo at the Mayo Clinic Health System was performed. Patients with any solid tumor who received their first dose of Ipi-Nivo at the age of ≥ 80 were included. Records were analyzed for baseline characteristics, cancer type, toxicity, and response to therapy. Differences between continuous and categorical variables were assessed using the students' t-test and the chi-squared test, respectively. Overall survival (OS) was estimated using the Kaplan-Meier method. Cox proportional hazard models assessed the relative contribution of factors to survival after treatment. P values < 0.05 were considered statistically significant. All analyses were performed using SAS V.9.4. **Results:** Forty-six patients met inclusion criteria, 13 females and 33 males. Median age of first dose was 83 (Range: 80 - 94). Sixty-seven percent had an ECOG performance status (PS) 0-1 and 33% had an ECOG PS 2-3. Thirteen (28.3%) patients received 4 cycles of Ipi-Nivo. Cancers included: 18 (40%) melanomas, 10 (21%) mesothelioma, 9 (19.5%) lung cancers, and 9 (19.5%) other types. Thirty-one patients (67%) developed at least one irAE. Of the irAEs, 8 (17.4%) were grade 1, 20 (43.5%) were grade 2, 14 (30.4%) were grade 3, and 3 (6.5%) were grade 4. Systemic steroids were used in 29 (63%) patients. Twenty-six (56.5%) patients were hospitalized for any cause, and 12 (26.1%) were hospitalized due to an irAE. Of the 26 patients hospitalized during treatment, 19 (73%) died within 1 year of discharge; 11 (42%) died within < 1 month of discharge and 3 (12%) died within 1-3 months of discharge. Median OS from the date of first Ipi-Nivo dose was 14.6 months in the ECOG PS 0-1 and 6.5 months in the ECOG PS 2-3. ECOG PS of 0-1 was associated with a significantly decreased risk of mortality (HR [hazard ratio] 0.33, 95 % CI [confidence interval]: 0.15-0.70; p=0.0025) compared to ECOG PS of 2-3. **Conclusions:** This is the first analysis to evaluate the outcomes of Ipi-Nivo in patients ≥ 80 years. Approximately 60% of the patients required systemic steroids and a quarter were hospitalized with grade 3-4 irAEs. As expected, patients with ECOG PS 2-3 did significantly worse than ECOG PS 0-1. Ipi-Nivo should be used with caution in patients ≥ 80 years. Research Sponsor: None.

12052

Poster Session

Association of frailty and high-risk immuno-nutritional score with outcomes in patients with relapsed and refractory multiple myeloma treated with chimeric antigen receptor T-cells. *First Author: Karnav Modi, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL*

Background: Multiple myeloma is a disease of older adults with a median age at diagnosis of 68 years (y). Patients (pts) receiving chimeric antigen receptor T-cell (CAR-T) therapy for relapsed/refractory MM (RRMM) often experience detrimental effects due to frailty, comorbidity, and cumulative toxicities. In this study, we evaluated the prevalence and impact of frailty, defined by the simplified frailty score, (SFS; Facon et al, Leukemia 2020), and immuno-nutritional status, using Glasgow prognostic score (GPS; Proctor et al, Br J Cancer 2011) in a real-world cohort of pts receiving CAR-T therapy for RRMM. **Methods:** We included all pts treated with commercial CAR-T therapy for RRMM between 2021 - 2023 at Moffitt Cancer Center. The SFS and GPS (CRP > 10 mg/dL, 1 point; albumin < 3.5, 1 point) were calculated for all pts at lymphodepletion. Primary endpoints included overall survival (OS) and progression free survival (PFS). Pearson's chi-squared tests or Fisher's exact tests were used to compare association between categorical variables. OS and PFS were estimated using Kaplan-Meier methods; the log-rank test was used to compare OS and PFS, and a cox-proportional model was used for multivariable analysis (MVA). **Results:** A total of 139 pts were included, with a median follow up of 6.3 months (m; range, 0.2 to 20.3 m). Median age was 66 y (IQR, 58-72 y); 38% were ≥ 70 y. Pts were treated with either idecabtagene vicleucel (83%) or ciltaabtagene autoleucel (17%). Around 1/3rd of pts had features of high-risk disease [high disease burden, 30%; high-risk cytogenetics (HR-Cyto), 37%; extramedullary disease (EMD), 37%]. Overall, 30% of pts were categorized as frail and 14% were classified as high-risk GPS (score = 2). There were no significant differences in GPS between older (≥ 70 y) and younger pts (< 70 y; $p = 0.8$). Median OS in the cohort was not reached (NR) and median PFS was 11.7 m. Both frailty and high-risk GPS were associated with inferior PFS (frail vs non-frail, HR 2.0, $p = 0.03$, high GPS vs low/int, HR 1.7 $p = 0.009$) and OS (frail vs non-frail, HR 3.0, $p = 0.006$, high GPS vs low/intermediate, HR 2.1 $p = < 0.001$). The association of GPS with OS remained significant in a MVA, even after adjusting for high-risk disease factors (high disease burden, HR-Cyto and EMD) and frailty. Pts categorized as frail had a lower median PFS of 5.4 m (vs 12.7m non-frail group, $p = 0.025$), and inferior median OS of 9.7 m (vs NR in non-frail, $p = 0.0039$). **Conclusions:** In a real-world setting, frailty affects almost a third of pts with RRMM receiving CAR-T therapy and is associated with inferior PFS and OS. The GPS, a simple immuno-nutritional score, is highly predictive of survival even after adjusting for the presence of high-risk disease. Studies looking at role of pre-habilitation and other modalities to reduce inflammatory burden prior to CAR-T therapy are warranted. Research Sponsor: None.

12054

Poster Session

Understanding treatment toxicity patterns through remote symptom monitoring and examining the effect of frailty in older men with metastatic prostate cancer. *First Author: Mithy Parthipan, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada*

Background: Advancements in metastatic prostate cancer (mPC) treatments have increased survival, but using multiple lines of therapy has increased the prevalence and severity of toxicities. Older men and those living with frailty experience higher symptom burden associated with treatment. Although toxicities have been described in previous trials, much of the focus has been on pain and fatigue among fit and younger men, and only a few trials have examined the effects of frailty on toxicity. Thus, the aims of this study were to (1) understand the prevalence, duration, and changes in symptom severity among older men receiving mPC treatments; and (2) examine differences among frail and non-frail men. **Methods:** Men aged 65+ with mPC starting chemotherapy (chemo), androgen receptor-axis-targeted (ARAT) therapies, or radium-223 (Rad223) from two academic Canadian cancer centres were enrolled in a prospective cohort study. Participants self-reported symptoms daily using the Edmonton Symptom Assessment Scale (ESAS) for the first treatment cycle via internet or telephone. Frailty status was determined using the Vulnerable Elders Survey (VES-13). Study outcomes were the development of moderate-to-severe symptoms (ESAS ≥ 4), their duration, and the proportion of participants who had improvements in symptom severity (ESAS < 4) after reporting moderate-to-severe symptoms at baseline. Outcomes were determined using descriptive statistics. Associations between symptom prevalence, duration, and frailty were assessed using t-tests and chi-square tests. **Results:** 90 men (mean age = 77 $\pm$ 6.1 years, 58% frail (VES-13 ≥ 3)) starting chemo ($n = 34$), an ARAT ($n = 43$), or Rad223 ($n = 13$) were included. The most common moderate-to-severe symptoms across cohorts were fatigue (46.8%), insomnia (42.9%), poor wellbeing (41.2%), decreased appetite (37.1%), and pain (35.9%). These symptoms were numerically higher in frail men, but differences between frail and non-frail were only statistically significant for poor wellbeing (62.5% in frail vs. 31.4% in non-frail, $p = 0.039$). On average, poor wellbeing lasted 6.5 days (SD = 7.6) days, decreased appetite lasted 5.5 days (SD = 4.9), fatigue lasted 5.1 days (SD = 7.3), pain lasted 4.7 days (SD = 5.6), and insomnia lasted 4.6 days (SD = 6.2) across cohorts. Fatigue and pain lasted numerically longer in frail men whereas insomnia, poor wellbeing, and decreased appetite lasted numerically longer in non-frail men, but these differences were not statistically significant. Among participants who reported moderate-to-severe symptoms at baseline, 15.4%, 10.7%, 7.7%, 5.3% and 3.6% had improvements in pain, appetite, wellbeing, insomnia, and fatigue, respectively. **Conclusions:** Understanding temporal patterns of symptoms and the impact of frailty in older men receiving mPC treatments may help inform supportive care approaches. Clinical trial information: NCT04193657. Research Sponsor: Prostate Cancer Canada.

12053

Poster Session

The influence of sex on the impact of age and frailty on acute care use among older adults receiving immune checkpoint inhibitor (ICI) treatment: A population-based study. *First Author: Elizabeth Faour, Princess Margaret Cancer Centre, Toronto, ON, Canada*

Background: ICIs are commonly used across solid tumors and although better tolerated than chemotherapy, patients may develop immune related adverse events (irAEs) requiring hospitalization. Older adults were poorly represented in trials evaluating ICIs. We previously demonstrated that among older adults receiving ICIs, increasing age was associated with reduced risk of irAE hospitalizations, while frailty was associated with increased acute care use (ASCO 2022). However, sex may impact irAE rates. Here, we evaluated sex-specific differences based on age and frailty, on acute care use and irAEs among older adults receiving ICIs. **Methods:** We performed a retrospective, population-based study of a cohort of patients with cancer, age ≥ 65 , receiving ICIs between June 2012 and October 2018 in Ontario, Canada using administrative data. Databases were deterministically linked to obtain socio-demographic and clinical covariates, and acute care outcomes. Acute care use was defined as emergency department visits or hospitalizations from the start of ICIs to 120 days following last dose; irAE specific hospitalizations were identified using ICD-10 codes. Frailty was assessed using the McIsaac Frailty Index. Using death as the competing risk, multivariable competing risk analyses with Fine Gray sub-distribution hazards evaluated the effect of age and frailty on both acute care use and irAE hospitalizations, adjusted for body mass index (BMI), history of autoimmune condition, comorbidity score, rurality, and hospitalization within 60 days prior to starting ICI, stratified by sex. **Results:** 2737 patients were identified; 60% male. Median age 73 (IQR 69-78); 43% received Nivolumab, 41% Pembrolizumab and 13% Ipilimumab; 53% had lung cancer, 34% melanoma. 70% were robust (R), 26% pre-frail (PF) and 4% frail (F). 72% of patients had an acute care episode and 8% had an irAE hospitalization, which did not differ by sex (72%/8% male; 71%/8% female). Increasing frailty was associated with greater acute care use in males (PF vs R aHR 1.20 [95% CI 1.02-1.40] $p = 0.03$, F vs R aHR 1.42 [1.05-1.91] $p = 0.02$) and females (PF vs R aHR 1.24 [1.03-1.49] $p = 0.02$, F vs R aHR 1.55 [0.99-2.40] $p = 0.05$) but was not associated with irAE hospitalization in either sex. Using age as a continuous variable, increasing age was associated with reduced irAE hospitalizations in males (aHR 0.97 per year [0.94-0.99] $p = 0.04$), but not in females ($p = 0.18$); no significant associations were identified modelling age as a categorical variable. **Conclusions:** Among older adults receiving ICIs, increasing age was associated with reduced rates of irAE related hospitalization in males but not in females, while increasing frailty was associated with increased acute care use among both sexes. Sex should be taken into consideration when evaluating potential toxicity among older adults receiving ICIs. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology.

12055

Poster Session

Feasibility of daily physical activity monitoring and associations with treatment toxicity in older adults with metastatic prostate cancer. *First Author: Gregory Feng, University Health Network, Toronto, ON, Canada*

Background: Accelerometry research suggests physical activity may be associated with treatment toxicity, but generalizability to geriatric oncology is unclear. As many older adults have low levels of physical activity and technology use, further exploration is warranted. This study explores the feasibility of daily physical activity monitoring and the association between step counts and symptoms. **Methods:** Older adults aged 65+ starting treatment (chemotherapy, enzalutamide/abiraterone, or Radium-223) for metastatic prostate cancer were enrolled in a prospective cohort study. Participants reported step counts (measured via smartphone and a free commercial app) and symptoms (Edmonton Symptom Assessment Scale (ESAS)) daily for their first treatment cycle (~1 month). The feasibility of daily monitoring was assessed with descriptive statistics and thematic analysis. The association between a 15% decline in steps (compared to pre-treatment baseline) and the emergence of moderate-to-severe symptoms and pain (ESAS ≥ 4) in the next 24 hours was assessed using logistic regression. The utility of a 15% step count decline in predicting the development of moderate-to-severe symptoms and pain was evaluated using sensitivity and positive predictive value (PPV). **Results:** Of 90 participants, 47 engaged in step count monitoring (mean age 75y; 52.2% participation rate). Daily physical activity monitoring was found to be feasible (90.5% median response rate; 94% retention rate) with numerous patient-reported benefits including increased self-awareness and motivation to engage in physical activity. During the first treatment cycle, instances of a 15% decline in steps were common ($n = 37$, 78.7%), as was the emergence of moderate-to-severe symptoms overall ($n = 40$, 85.1%) and pain ($n = 26$, 55.3%). Overall, daily physical activity did not appear to be significantly predictive of symptoms (OR = 1.8, 95% CI = 0.42-7.74) overall or pain (OR = 0.95, 95% CI = 0.22-3.81). Predictive validity estimates revealed reasonable sensitivity for both moderate to severe symptoms overall (sensitivity = 88.8%, 95% CI = 68.7-95.0; PPV = 73.0%, 95% CI = 58.7-87.3) but poor PPV for pain (sensitivity = 77.8%, 95% CI = 58.6-97.0; PPV = 37.8%, 95% CI = 22.2-53.5). **Conclusions:** Despite recent studies framing physical activity changes as predictive of toxicity, PPV was only poor to fair. However, daily activity monitoring in older cancer patients appears feasible and may have other uses. Clinical trial information: NCT04193657. Research Sponsor: Prostate Cancer Canada.

12056

Poster Session

Associations between sarcopenia and clinical outcomes in men with metastatic castrate-resistant prostate cancer. *First Author: Efthymios Papadopoulos, University Health Network, Toronto, ON, Canada*

Background: Understanding the impact of sarcopenia on clinical outcomes in patients with metastatic cancer will assist clinicians with risk stratification, treatment decision-making, and inform the need for targeted supportive care strategies. Our objective was to comprehensively assess sarcopenia using measures of muscle mass (radiographically) and function (i.e., muscle strength and walking speed) and examine its impact on severe treatment toxicity, time to first emergency room (ER) visit, prostate-specific antigen (PSA) progression, radiographic progression, and overall mortality in men initiating androgen receptor-axis targeted therapy (ARAT) or chemotherapy for mCRPC. **Methods:** This was a secondary analysis of a prospective observational study of older men with mCRPC at the Princess Margaret Cancer Centre. Sarcopenia was defined as the combination of low muscle strength (grip strength < 35.5kg), slowness (walking speed < 0.8m/s), and low muscle quantity or quality prior to treatment initiation. The skeletal muscle index and skeletal muscle density were assessed through computed tomography scans prior to ARAT or chemotherapy initiation to determine muscle quantity and quality, respectively, using published cut-offs. Severe treatment toxicity, unplanned healthcare use, and disease progression were assessed from treatment initiation until treatment termination or loss to follow up. The associations between sarcopenia and severe treatment toxicity (i.e., grade 3+ toxicity) were assessed using multivariable logistic regression. Survival analyses were used to assess the impact of sarcopenia on the time to first ER visit, PSA progression, radiographic progression, and overall mortality. An interaction term for sarcopenia by treatment was introduced in all multivariable models and when necessary, an analysis by treatment was performed. **Results:** In total, 110 men participated, of whom 30 (27.3%) had sarcopenia prior to initiating treatment. Sarcopenia was associated with severe treatment toxicity (adjusted odds ratio (aOR) = 6.26, 95%CI = 1.17-33.58, P = 0.032) and time to first ER visit (adjusted hazard ratio (aHR) = 4.41, 95%CI = 1.26-15.43, p = 0.020) in the group that was initiating ARAT but not chemotherapy. Sarcopenia was a significant predictor of radiographic progression (aHR = 2.39, 95% CI = 1.06-5.36, p = 0.035) and overall mortality (aHR = 2.44, 95%CI = 1.17-5.08, p = 0.018) in the entire cohort. **Conclusions:** Sarcopenia may predict severe treatment toxicity and emergency room visits in men starting ARAT for mCRPC. Additionally, sarcopenia predicts radiographic progression and overall mortality regardless of treatment type in men with mCRPC. Confirmation is needed from large-scale studies. Assessment of sarcopenia can assist clinicians in treatment decision making while identifying high-risk patients that require targeted supportive care strategies. Research Sponsor: Ride for Dad/Prostate Cancer Fight Foundation.

12058

Poster Session

Sedentary lifestyle as a predictor of early death in older adults with cancer: A prospective cohort study with 2692 patients. *First Author: Jurema Telles O Lima, IMIP-Instituto de Medicina Integral Professor Fernando Figueira, Recife, PE, Brazil*

Background: Physical activity is an important aspect of the global health of older adults with cancer (OAC). The aim of this study was to determine sedentary lifestyle as a predictor of early death in OAC. **Methods:** Prospective cohort involving elderly (60+) with cancer, cared for in a public hospital in Pernambuco, from January 2015 to December 2021. Sociodemographic, clinical, and lifestyle variables were considered. The level of physical activity was assessed before cancer treatment by the International Physical Activity Questionnaire (IPAQ), short version, with classification into active (active/very active) and inactive (sedentary/inadequately active) and comprehensive geriatric assessment (CGA). The outcome was death within 180 days. Kaplan-Meier survival curves and Cox multivariate analysis were performed. **Results:** 2692 patients were included, most were men, with family income less than 01 minimum wage in almost 30%. The presence of two or more comorbidities was observed in 70.1% of patients. The main primary sites were prostate (30.8%), breast (17%) and digestive system (25.8%), gynecological system (10.6%), lung (5.9%), and the majority (67.6%) had no metastatic disease. There were 461 deaths (25.7% sedentary and 9.7% non-sedentary). Sedentary lifestyle was an independent risk factor for early death (HR=1.28, 95% CI=1.07-1.64 p< 0.036), controlled by tumor topography and presence or absence of metastasis, presence of polypharmacy and Karnofsky performance scale, recent hospitalization and nutritional status. At 180 days, survival among patients with some level of physical activity was higher (90% (0.88 - 0.92)) than among sedentary patients (74% (0.72 - 0.77, p < 0.01). **Conclusions:** Sedentary lifestyle at the time of cancer diagnosis was an independent risk factor for early death among Older adults with cancer. Encouraging physical activity is an important public health action to face aging-related health problems, such as cancer. Research Sponsor: facepe/CNPQ.

12057

Poster Session

A study of frontline therapy in adults >80 years with chronic lymphocytic leukemia (CLL). *First Author: Mazie Tsang, Mayo Clinic, Phoenix, AZ*

Background: Although CLL primarily affects older adults (median age 71 years), limited data exists about the outcomes of adults who are ≥80 years old because they are under-enrolled on clinical trials. **Methods:** The Mayo Clinic CLL Database was used to conduct a retrospective cohort study of adults ≥80 years at the time of frontline CLL treatment. Kaplan-Meier analysis was used to plot OS, and cumulative incidence was used to plot TTNT, accounting for competing risk of death. The Mayo Clinic IRB approved the study. **Results:** Our study included 216 patients with CLL who were age ≥80 years at the time of frontline CLL therapy between 1/1995 and 11/2022 (Table). The median time from CLL diagnosis to initiation of frontline therapy was 3.1 years. The median OS after start of frontline therapy was 3.9 years. The median OS was 3.3 years (95% CI 2.6-4.2) for patients who received alkylating agents (e.g., chlorambucil, n=96), 3.8 years (95% CI 2.8-not reached [NR]) for purine analogues (e.g., fludarabine, n=11), 3.9 years (95% CI 3.2-4.9) for anti-CD20 monoclonal antibody monotherapy (e.g., obinutuzumab, n=64), and not reached (95% CI 3.3-NR) for novel agents (n=43) (P=0.02). The types of novel agents included ibrutinib (n=19), acalabrutinib (n=16), venetoclax (n=7), and orelabrutinib (n=1). There was no difference in OS between 36 patients who received a BTKi compared to the 7 patients who received venetoclax-based therapy. At a median follow-up time of 6.7 years from the first visit, 143 patients died from the following: progressive CLL (n=63), infections (n=12), other cancer (n=11), non-CLL reasons (n=21). Cause of death was unavailable for 36 patients. On multivariable analyses, older age (i.e., any 5-year increase in age) was associated with a 50% increased risk of death (HR 1.5, 95% CI 1.2-1.9, p=0.001), and treatment with non-novel agents was associated with 3.2 times increased risk of death (HR 3.2, 95% CI 1.2-8.9, p=0.02). Of the 216 patients, 76 patients required second-line therapy; the median TTNT was 4.2 years (95% CI 2.9-NE). The most used second-line agents were monoclonal antibodies alone (20/76, 26%) and single-agent alkylators (18/76, 24%). **Conclusions:** When compared to all other CLL treatments, novel agents such as BTKi and venetoclax-based treatments are associated with significantly improved OS in patients with CLL ≥80 years old when used in the frontline setting. Research Sponsor: None.

Baseline patient characteristics (N=216).	
Pre-treatment	N (%) or Median (range)
Age	83 (80-95)
Sex	
Female	70 (32)
Male	146 (68)
Labs	
Absolute lymphocyte count (x10 ⁹ /L)	33.8 (0.4-360.5)
White blood cell count (x10 ⁹ /L)	42.8 (2.2-610)
Hemoglobin (g/dL)	11.4 (6.3-16.3)
Platelet count (x10 ⁹ /L)	144 (3-748)
FISH, pretreated	
Missing	90
Normal	28 (22.2)
13q-	38 (30.2)
Trisomy 12	29 (23.0)
11q-	20 (15.9)
17p-	11 (8.7)
IGHV mutation status	
Missing	115
Unmutated	59 (58.4)
CLL-IPI Risk Group	
Missing	142
Low	1 (1.4)
Intermediate	10 (13.5)
High	54 (73.0)
Very High	9 (12.2)

12059

Poster Session

Safety of checkpoint inhibitors in older patients with genitourinary cancers. *First Author: Brian Hemendra Ramnarain, University of Florida/UF Health Cancer Center, Gainesville, FL*

Background: Immune checkpoint inhibitors (ICIs) have revolutionized the care of patients with genitourinary (GU) cancers however many of the clinical trials that have led to the approval of ICIs in GU cancers often have low enrollments of older patients aged 65 and above for which safety data in this cohort is limited. **Methods:** A retrospective study was performed that included all patients aged 65 and older with kidney, bladder, and upper tract urothelial carcinoma (UTUC), who were treated at the University of Florida Health Cancer Center between January 2018 and September 2022, and received at least one dose of ICI (pembrolizumab, nivolumab, ipilimumab with nivolumab, avelumab, or atezolizumab). Data was collected on all documented immune related adverse events (irAEs) that were deemed attributable to the checkpoint inhibitor by the treating provider. The grading of toxicities was determined by the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. **Results:** We identified a total of 139 patients who met the inclusion criteria of our study. The ages of patients ranged from 65 to 93 and the median age was 74. Females accounted for 31 patients (22%) while 108 patients (78%) were male. There were 56 patients (40%) with bladder cancer, 58 patients (42%) with kidney cancer, and 25 patients (18%) with UTUC. An irAE was documented in 76 patients (55%) while 63 patients (45%) had no documented irAE. Patients were categorized by the highest grade of toxicity experienced. A Grade 1 toxicity was found in 15 patients (11%), while a grade 2 toxicity was found in 41 patients (29%), with 18 patients (13%) having a grade 3 toxicity, and 2 patients (1%) experiencing a grade 4 toxicity. There were no documented grade 5 toxicities, i.e. no deaths were directly attributed to treatment. We found that 27 patients (19%) required either oral or intravenous steroids to manage their irAE. Discontinuation of treatment due to an irAE was observed in 16 patients (12%). Inpatient hospitalization due to an irAE occurred in 12 patients (9%). **Conclusions:** Our study demonstrates that the majority of patients aged 65 and older either have no irAEs or developed mild irAEs when treated with ICIs. Severe and life-threatening adverse events are uncommon, rarely require hospital admission, and did not lead to any deaths. This study should help to provide valuable information on the safety of checkpoint inhibitors in older patients with GU cancers and assist in the shared decision-making process for cancer treatment. Research Sponsor: None.

Age Group	Patients	Patients with no reported irAE	Patients experiencing an irAE (G1-2)	Patients experiencing an irAE (G3+)	Need for Oral or IV steroids	Discontinuation due to irAE	Hospitalization due to irAE
65-74	72	35 (49%)	23 (32%)	14 (19%)	15 (21%)	10 (14%)	7 (10%)
75-84	49	19 (39%)	26 (53%)	4 (8%)	10 (20%)	3 (6%)	4 (8%)
85+	18	9 (50%)	7 (39%)	2 (11%)	2 (11%)	3 (17%)	1 (6%)
Total	139	63 (45%)	56 (40%)	20 (14%)	27 (19%)	16 (12%)	12 (9%)

12060

Poster Session

Demographic stratification, evaluation of symptoms burden on basis of gender, and implications of G8 questionnaires in elderly patients with cancer in Bangladesh. *First Author: Muhammad Rafiqul Islam, National Institute of Cancer Research and Hospital, Dhaka, Bangladesh*

Background: Geriatric oncology is a new concept worldwide, as well as in Bangladesh. Presently, there is a scarcity of data regarding the geriatric perspective of malignant patients in Bangladesh. Our study investigated the demographic differentiation, evaluation of symptoms burden on the basis of gender, and implications of the G8 questionnaires in elderly cancer patients from a tertiary cancer care center in Bangladesh. This will help physicians to understand cancer in the elderly better, integrate their biological and epidemiological characteristics, and promote a longer life expectancy without compromising their quality of life in resource-constrained regions. **Methods:** This study included all the newly diagnosed and histologically confirmed primary solid tumors among age ≥ 60 years at the National Institute of Cancer Research & Hospital (NICRH), a tertiary care center in Bangladesh, during the year 2019 and 2020. For all statistical analyses, $P < 0.05$ was considered significant. **Results:** Of 8057 solid tumor patients, 2823 were geriatric patients (35.04%). Male dominant patients' mean BMI was $20.23 \pm SD 4.26$ and 35.4% were malnourished. The low SES was 63.7% and 68.5% of patients were illiterate. Pain was the most common symptom (37.44%), followed by GI symptoms (31.77%), whereas 33.1% suffered from more than one symptom. In the disease distribution, lung cancer was 52.4% irrespective of sex, followed by GIT 17% and HBS cancer 10%. Breast 24.58% and GIT 17.77% were the second most common malignancy in females and males, respectively. Among them, 22.1% of patients were metastatic at presentation and 25% had a comorbid condition. About 17.4% of patients were completely disabled. Low BMI with high ECOG status had more symptoms ($p = .004$). Gender, nutrition and socioeconomic condition strongly correlated with the patient's functional status and symptomatic presentation. Females were more comorbid with symptomatic metastases at presentation ($p = 0.020$), and males presented with late-stage cancer ($p = 0.002$). Compared to male elderly patients, female elderly patients suffered more from malnutrition and obesity ($p < .000$). Polypharmacy rates for elderly males were lower than those for elderly females ($p = 0.000$). Food intake behavior, weight loss, mobility, and health-related perception did not differ based on gender during or after treatment. Based on G8 scoring, we found that 12.3% were in the worse group, 70.2% in the intermediate group and the good group contained 17.5%. According to the cut-off value (≤ 11), 71.9% of patients needed the CGA evaluation. **Conclusions:** A high number of elder patients with multiple symptoms makes comprehensive management more challenging. A frail elderly patient's gender, SES, education, disease type, and stage along with performance status at the time of presentation of their disease are important prognostic factors. Research Sponsor: None.

12062

Poster Session

Frailty IO: Frailty parameters and incidence of immune related adverse events in older patients treated with immune checkpoint blockers (ICB). *First Author: Capucine Baldini, Drug Development Department (DITEP), Gustave Roussy, Villejuif, France*

Background: Immune checkpoint blockers (ICB) are one of the cornerstone of cancer treatment. The favorable tolerance profile makes it an interesting option in older patients with cancer. However, few evidence is available in patients aged 70 years and older according to geriatric parameters. We aimed to determine the impact of frailties on immune related adverse events (irAEs) in a real-life population of older patients treated with ICB. **Methods:** This retrospective French multicentric cohort study enrolled all patients aged 70 years or over who underwent a geriatric assessment before the start of ICB in monotherapy or in combination between January 1st 2016 and December 31st 2021. Main endpoint was to assess frailty and incidence of irAEs. **Results:** In total, 224 patients were included. Median age was 82 years old (Q1:77-Q3:87). Patients were mostly men (66%), 40% were treated for a skin cancer (melanoma or squamous), 35% lung and 15% genitourinary. Median number of comedications was 5 (3-8) and median G8 was 12 (9-14). Median ADL (6) was 6 and IADL (4) was 3 (2-4). Most patients were treated with ICB in monotherapy (80%). Altogether, 49% of patients experienced all-grade toxicity and 25% had more than 1 adverse event during the treatment course. The incidence of high-grade toxicity (≥ 3) was 14%. The most frequent types of toxicity were gastro-intestinal (17%), skin (13%), thyroid (9%) and rheumatoid (7%). Male gender ($p < 0.02$), normal IADL ($p < 0.01$), normal Timed up and go test ($p < 0.02$), not having falls in the last 6 months ($p < 0.001$) and visual impairment ($p = 0.02$) were significantly associated with toxicity in univariate analysis. Multiple toxicities were associated with male gender ($p = 0.03$), vision impairment ($p < 0.001$), normal IADL ($p < 0.05$), normal Timed up and go test ($p < 0.02$) not having falls in the last 6 months ($p < 0.001$). There were no association with 4-month hospitalization ($p = 0.73$). Median overall survival (OS) was 16.33 months [95%CI 12.78 - 20.63] and the 3-month OS rate 84.83% [95%CI 79.26 - 89.11]. Median progression free survival (PFS) was 6.08 [95%CI 5.13 - 8.71] in the overall population. Toxicity was associated with better PFS compared to no toxicity (logrank test : $p < 0.01$) with a median PFS (toxicity group) of 6.14 months [95%CI 5.13 - 8.94] versus median PFS (no toxicity group) of 5.26 months [95%CI 3.25 - 8.41]. Median PFS for patients with multiple toxicity was longer 9.86 months [95%CI 5.13 - 23.92] ($p < 0.01$). **Conclusions:** Older patients without IADL or walk impairments but with visions problem had increased incidence of irAEs. The PFS analysis shows a positive association of toxicity confirming that longer exposure to ICB might result in higher risk of irAE. The absence of IADL or mobility impairment may be associated with longer benefit from ICB. Further analysis will be presented at the meeting. Research Sponsor: BMS.

12061

Poster Session

Impact of comorbidity burden on immune-related adverse events and survival among older adults with cancer on immunotherapy. *First Author: Andrew T. Fauchaux, Wake Forest Baptist Medical Center, Winston-Salem, NC*

Background: Comorbidities are more prevalent among older adults and predict worse outcomes for cytotoxic chemotherapy. Immunotherapies are increasingly used to treat various cancers and have a milder but less predictable toxicity profile. This study aimed to evaluate the association of comorbidity burden with immune-related adverse events (irAEs) and survival among older adults treated with these immunotherapies for any cancer type. **Methods:** We created a retrospective registry of consecutive patients ≥ 70 years old treated with one or more doses of an immune checkpoint inhibitor for any cancer indication between 2/1/2011- 4/7/2022 at our comprehensive cancer center. Treatment outcomes, including treatment-emergent adverse events, were captured via chart review. The comorbidity burden at the time of immunotherapy initiation was captured by chart abstraction and classified using the Charlson Comorbidity Index (CCI). We compared patients with high CCI scores (≥ 4) to patients with low CCI scores (CCI < 4) on the outcome of any irAE yes/no, using chi-square tests. We used the Kaplan-Meier method to compare progression-free survival (PFS) and overall survival (OS) between the two CCI groups. Survival analyses were calculated from the first dose of immunotherapy to death, last follow-up, or disease progression. A two-sided alpha of 0.05 was used for analyses. The study had institutional IRB approval. **Results:** Our cohort consisted of 1,216 patients (median age 76 years [interquartile range 73 to 80]), of which 217 (18%) had a high CCI score. The most common comorbidities were chronic obstructive lung disease (45%), coronary artery disease (29%), and diabetes (29%). The most common cancer type was lung cancer (46%), followed by melanoma (15%). Patients with a high CCI score had a shorter median overall survival than patients with a low CCI (11.2 vs. 13.8 months, respectively, $p = 0.049$). However, there was no significant difference in PFS between the high and low CCI groups (median PFS 27.1 vs. 25.0 months, $p = 0.32$). There was no association between the CCI group and the incidence of any-grade irAEs (39% vs. 40%, $p = 0.82$). There was also no association between CCI group and high-grade (grade ≥ 3) irAEs (17% vs. 15%, $p = 0.35$). We did not find any associations between any individual CCI comorbid condition and risk of irAE. **Conclusions:** A high comorbidity burden, as measured by the CCI, was not associated with increased immunotherapy toxicity or shorter PFS among older adults. The presence of comorbidities was associated with shorter OS. These data can support informed decision-making for older adults with comorbidity considering immunotherapy. Reference: 1. Charlson ME, Carrozzino D, Guidi J, Patierno C. Charlson Comorbidity Index: A Critical Review of Clinimetric Properties. *Psychother Psychosom.* 2022;91(1):8-35. doi: 10.1159/000521288. Epub 2022 Jan 6. PMID: 34991091. Research Sponsor: U.S. National Institutes of Health.

12063

Poster Session

Older patients with early-stage triple-negative breast cancer: The Memorial Sloan Kettering Cancer Center experience. *First Author: Iris Zhi, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Approximately 15% of cases of early-stage triple-negative breast cancer (TNBC) are diagnosed in individuals over the age of 70. Despite studies indicating that older patients derive similar benefits from polychemotherapy as younger patients, breast cancer specific mortality among older patients remains disproportionately high. Use of the comprehensive geriatric assessment (CGA) and individualized risk tools can help tailor treatment and minimize negative side effects while preserving quality of life. We performed a retrospective analysis of patients ≥ 70 years of age diagnosed with stage I-III TNBC at Memorial Sloan Kettering Cancer Center between 2015 and 2019 to describe clinical practices for managing this population. **Methods:** Demographics, CGA, systemic therapy data were collected from electronic medical records. A multivariable logistic regression model was used to identify factors that were independently associated with the probability of receiving chemotherapy. **Results:** We included 159 women, with a median age of 74.5 years (range 70-96). 67 (42%) had stage I disease, 71 (45%) had stage II, and 21 (13%) had stage III. 29 (18%) reported difficulty in Activities of Daily Living (ADL), 34 (21%) reported difficulties in Instrumental Activities of Daily Living (IADL), and 40 (26%) were identified as having a high risk for falls. 25 (17%) patients underwent CGA per physician's choice. The prevalence of cardiac risk factors was as follows: hypertension in 80 patients (50%), diabetes in 25 (16%), obesity in 7 (4.4%), heart failure in 1 (0.6%). 147 underwent breast surgery, with 106 (67%) receiving lumpectomy and 41 (26%) mastectomy. 97 (61%) patients received chemotherapy: 35 (22%) neoadjuvant and 62 (40%) adjuvant. Anthracycline, Cyclophosphamide, Paclitaxel (AC-T) and Cyclophosphamide, Methotrexate, Fluorouracil (CMF) were the most common regimens. In multivariable logistic regression analysis, use of chemotherapy was associated with younger age (odds ratio [OR] 0.84 for one year increase in age, 95% confidence interval [CI] 0.75-0.93, $p = 0.001$) and higher disease stage (stage II vs. I OR 4.97, 95% CI 1.66-16.4, $p = 0.006$; stage III vs. I OR 22.0, 95% CI 3.3-312, $p = 0.006$). No significant difference was found in geriatric referrals, cardiovascular risk factors, or difficulties with ADL or IADL between those receiving or not receiving chemotherapy. **Conclusions:** In our single center experience, 61% of older patients with early-stage TNBC received chemotherapy, with AC-T and CMF being the most common regimens. The referral rate for CGA was low. Age < 75 years and higher disease stage were significantly associated with receiving chemotherapy. Overcoming barriers to incorporating CGA and toxicity prediction into routine clinical practice is crucial for personalized treatment in this population. Research Sponsor: NIH/NCI Cancer Center grant (grant # P30 CA008748) to Memorial Sloan Kettering Cancer Center.

12064

Poster Session

Frailty and pre-frailty associated with physical functional performance and quality of life in breast cancer and bone marrow transplant survivors. *First Author: Shuo Wang, University of Minnesota, Minneapolis, MN*

Background: Frailty in cancer survivors poses a great challenge to health care providers. Frailty is associated with premature mortality, functional decline, and poor quality of life (QOL). We aimed to examine the associations of frailty and pre-frailty with physical functional performance and QOL in breast cancer survivors and bone marrow transplant (BMT) survivors. **Methods:** 43 breast cancer survivors and 55 BMT survivors who had received chemotherapy and did not have active cancer were recruited to the study. Based on Fried frailty phenotype, survivors were classified as frail if 3 or more criteria were present: unintentional weight loss, exhaustion, slow walking speed, low physical activity, and weakness. Pre-frail was classified if 1 or 2 criteria were present. Physical functional performance was assessed by Karnofsky performance scale (KPS) and continuous summary performance score (CSPS, comprises walking speed, standing balance, and repeated chair stands tests). $p16^{INK4a}$, a marker for cellular senescence, was measured from survivors' blood samples. QOL was measured using the 36-Item Short Form Survey. Groups were compared using chi-square test for categorical variables and rank-sum test for continuous variables. **Results:** Median age of survivors was 59 yrs (39% male). 13% of survivors (N = 13) were frail and 26% (N = 25) were pre-frail. Frail/pre-frail survivors tended to be older, male, and BMT survivors and had worse results for KPS, walking speed, repeated chair stands, and CSPS (p-values<0.03). Frail/pre-frail versus non-frail survivors had a higher $p16^{INK4a}$ expression (p-value<0.01). For QOL, frail/pre-frail survivors had lower median scores of physical functioning, role limitations due to physical health, role limitations due to emotional problems, energy/fatigue, social functioning, bodily pain, and general health (p-values<0.04), but the median scores of emotional well-being for frail/pre-frail and non-frail survivors were similar (p-value=0.06). **Conclusions:** Frailty and pre-frailty in a study of breast cancer and BMT survivors were associated with worse physical functional performance, higher $p16^{INK4a}$ expression, and lower quality of life. Research Sponsor: Division of Hematology/Oncology/Transplantation University of Minnesota.

Summary of characteristics among frail/pre-frail and non-frail survivors.

	Frail/Pre-frail (n=38) 62 (40-81)	Non-frail (n=60) 55 (27-79)	P-value <0.01
Age, median yrs (min-max)	47.6	25.0	0.02
Male, %			
Walking speed [1 - (9/speed in cm/s)], median (min-max)	0.91 (0.85-0.94)	0.93 (0.86-0.98)	<0.01
Standing balance [time in s/30], median (min-max)	1.00 (0.00-1.00)	1.00 (0.77-1.00)	0.02
Repeated chair stands [1 - time in s/32.1], median (min-max)	0.57 (-0.60-1.00)	0.67 (0.31-1.00)	<0.01
CSPS, median score (min-max)	2.48 (0.81-2.91)	2.60 (2.21-2.78)	<0.01
$p16^{INK4a}$ expression, median (min-max)	2.00 (0.11-9.84)	0.51 (0.02-5.72)	<0.01

12067

Poster Session

Dissecting the prognostic role of baseline body mass index (BMI) in early breast cancer (BC): Individual patient-level analysis from five mammella interGruppo (MIG) and gruppo italiano mammella (GIM) randomized clinical trials (RCTs). *First Author: Davide Soldato, IRCCS Ospedale Policlinico San Martino, Università degli Studi di Genova, Genova, Italy*

Background: Nearly half of patients (pts) are overweight or obese at BC diagnosis (dx). Higher BMI at dx has been associated with cardiometabolic comorbidities, higher risk of severe treatment-related sequelae, and worse quality of life. Previous studies showed inferior survival outcomes among patients with early BC and high BMI, although not consistently. The aim of this study was to explore the prognostic role of BMI at dx using data from five RCTs of adjuvant therapy for early stage BC with long-term follow-up. **Methods:** Pts with known BMI at dx, randomized in the MIG-1, MIG-5, GIM-2, GIM-3 and GIM-6 phase III RCTs were included. BMI was categorized as lean (< 25 kg/m²), overweight (25-30 kg/m²) or obese (≥ 30 kg/m²). Outcomes included disease-free survival (DFS), breast cancer free-interval (BCFI) and overall survival (OS). Survival estimates were compared using the Kaplan-Meier method and log-rank test. Multivariable Cox proportional hazard models stratified by trial and relevant prognostic factors assessed associations between BMI and outcomes. **Results:** Among 7334 pts in the overall population, mean age was 56.4 years (SD 11.2), 67.8% had node-positive disease, 76.9% received chemotherapy and 83.0% endocrine therapy. Most pts were overweight (33.1%) or obese (21.0%) and 45.9% were lean. Higher BMI was associated with older age, larger tumor size, higher nodal status, and HR+/HER2- subtype. At a median follow-up of 10.0 years (IQR 6.1-15.1) there were 2165 DFS, 1674 BCFI and 1354 OS events. Pts with higher BMI had worse DFS and OS (log-rank p = 0.007 and p < .0001, respectively), but similar BCFI (p = 0.48). BMI at dx was an independent risk factor for worse OS, but not for DFS and BCFI (Table). Results in the HR+/HER2- population (n = 4093) were consistent: pts with higher BMI had worse DFS, BCFI, and OS (log-rank p = 0.001, p < .006, and p < .0001, respectively) and BMI at dx was an independent risk factor only for worse OS (aHR [95%CI] 1.06 [0.84-1.32] and 1.31 [1.02-1.67] for overweight and obese vs lean pts, respectively). **Conclusions:** In this large study of pts with early BC treated in RCTs with long-term follow-up, higher BMI at dx was an independent risk factor for overall mortality but not for BC-specific outcomes. Weight loss interventions may mitigate the detrimental effect of excess body weight on outcomes of BC survivors, including by reducing the burden and risks of associated cardiometabolic comorbidities. Research Sponsor: "Associazione Italiana per la Ricerca sul Cancro", AIRC (MFA 2020 ID 24698).

	DFS, 10y rate	aHR	BCFI, 10y rate	aHR	OS, 10y rate	aHR
Lean	71.8 (70.1-73.4)	Ref	76.7 (75.1-78.2)	Ref	83.1 (81.6-84.4)	Ref
Overweight	69.3 (67.1-71.4)	1.01 (0.90-1.12)	75.7 (73.6-77.6)	0.96 (0.85-1.08)	80.0% (78.0-81.8)	1.06 (0.92-1.21)
Obese	67.7 (64.7-70.5)	1.08 (0.96-1.23)	74.3 (71.5-76.8)	1.04 (0.90-1.20)	79.7% (77.0-82.1)	1.22 (1.04-1.43)
Parenteses show 95% CIs						

12065

Poster Session

Geriatric-assessment-guided interventions for older adults with multiple myeloma: A feasibility study. *First Author: Christopher Edward Jensen, University of North Carolina School of Medicine, Chapel Hill, NC*

Background: Multiple myeloma (MM) is disproportionately a disease of older adults, and aging-related impairments are common in this population. Geriatric assessment (GA) guided supportive care programs have been linked to improved treatment outcomes among older adults with solid-organ cancers. We sought to evaluate the feasibility of a GA-guided supportive care program among older adults treated for MM. **Methods:** We leveraged an existing registry of adults with plasma cell disorders at the University of North Carolina. Registry participants meeting inclusion criteria were offered referrals to supportive care resources by their MM provider during routine visits in 2021-2022. Inclusion criteria were diagnosis of MM, age ≥60, and presence of ≥1 selected problem areas (physical function, polypharmacy, mental health) on the GA. Function deficits were defined as self-report of requiring assistance with ≥1 instrumental activities of daily living or recent fall(s), polypharmacy as ≥10 daily medications, and anxiety/depression on the Mental Health Index 13. Individuals with physical function deficits were offered referral to physical therapy (PT). Those with polypharmacy were offered referral to an oncology Clinical Pharmacist Practitioner (CPP) for comprehensive medication reconciliation and evaluation for de-prescribing. Patients with mental health symptoms were offered referral to our center's Comprehensive Cancer Support Program (CCSP). **Results:** 59 individuals were identified as having at least one deficit on the GA (Table). Of these, 14 were already utilizing all relevant resources, leaving 45 individuals eligible for a new resource. Among these, 16 accepted a referral to at least one resource. An additional 16 were approached and declined all offered referrals. For the remaining 13 screened individuals, providers were prompted regarding a referral recommendation prior to the patient's visit, but a referral was not offered during the visit. Physical therapy was the most commonly identified relevant resource (n = 46), followed by CPP visits (n = 33). Referral acceptance rates were highest among those recommended for a pharmacy visit (55% of those approached) and lowest for CCSP (0%). **Conclusions:** Given the prevalence of polypharmacy or physical function deficits and acceptance rates for related interventions, future interventions focusing on collaboration with CPPs or physical therapists appear feasible in this setting. Methods to direct patients to supportive care resources that do not rely on provider recommendations during the limited window of clinic visits may also be beneficial. Clinical trial information: NCT04999085. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology; AHRQ.

	Individuals Eligible for Each Type of Resource (can be multiple resources per patient)		
	PT	Pharmacist	CCSP
Problem Identified via GA	46	33	18
Already Utilizing Resource(s)	14	3	7
Eligible – No recommendation from provider	10	10	4
Eligible - Approached	22	20	7
Accepted Referral	8	11	0
Declined Referral	14	9	7

12068

Poster Session

A pilot study of intraneural facilitation versus standard physical therapy for prevention of chemotherapy-induced peripheral neuropathy. *First Author: Dan Ran Castillo, Division of Medical Oncology and Hematology, Loma Linda University of Medicine, Loma Linda, CA*

Background: Chemotherapy-induced peripheral neuropathy (CIPN) is a debilitating side effect necessitating chemotherapy (CT) dose adjustments or early termination. Intraneural Facilitation (INF) is a novel form of manual physical therapy (PT) developed to mitigate CIPN-related symptoms and improve patients' functional outcome. We conducted a randomized pilot study evaluating the efficacy of INF vs. standard PT in the prevention of CIPN (NCT 03272919). **Methods:** Eligible participants were patients with newly diagnosed breast cancer (stages I-III) and gynecologic cancer without preexisting peripheral neuropathy planning to receive platinum-based and/or taxane-based CT. Participants were randomly assigned to either INF or PT arm and received two 45-minute treatments twice a week for six weeks during their CT course. Outcomes reported here are a) assessment of pain between the 2 arms using the Pain Quality Assessment Scale (PQAS), and b) measurement of vascular patterns using ultrasound (US), evaluating pulsatility index, volume flow and peak systolic velocity between the 2 arms. Participants were evaluated at baseline, week 3 (W3), week 6 (W6), and month 3 (M3). PQAS scores ranged from 0 to 10 with subscale evaluations of paroxysmal, surface, and deep pain. Pain scores on a scale from 0 to 10 were grouped into none (0), mild (1-3), moderate (4-6) and severe (7-10). The use of neuropathy medications, CT dose reductions, premature CT discontinuation and participant satisfaction surveys between the two groups were previously reported at SABCS 2022. **Results:** Of 104 screened participants, 44 met the eligibility criteria, with 38 eligible for analysis (n=20 INF arm and n=18 PT arm). Participants reporting moderate or severe pain in either arm were combined (Table). Pain symptoms peaked at W6 coinciding with cumulative CT effects. At M3, none in the INF arm reported moderate or severe paroxysmal pain compared to two participants in the PT arm. One participant in each arm reported moderate or severe surface or deep pain at M3. The US results showed physiologic impact in both arms at W3 and W6, suggesting their role in preserving neural tissue blood flow and reducing vascular damage. **Conclusions:** Our study shows fewer number of participants on both intervention arms reporting pain, with numerically lower scores on PQAS in INF arm compared to PT arm, especially during ongoing CT. The US results suggest that INF has a unique pathophysiological impact on the microvasculature compared to standard PT; further studies are needed to validate these findings and potentially address their clinical significance as a combined modality. Clinical trial information: NCT03272919. Research Sponsor: GRASP grant.

Type of Pain	INF n =20(%)	PT n= 18(%)
Paroxysmal-W3	1(7.7)	2(13.3)
W6	1(7.7)	3(23.1)
M3	0(0)	2(16.7)
Surface - W3	0(0)	1(7.1)
W6	0(0)	3(23.1)
M3	1(11.1)	1(6.7)
Deep - W3	0(0)	2(14.3)
W6	1(6.3)	4(28.6)
M3	1(9.1)	1(6.3)

12069

Poster Session

The effect of exercise on physical function and medication adherence in women receiving endocrine therapy for breast cancer: The breast cancer endocrine therapy fitness (BE-FIT) randomized controlled trial. *First Author: Samantha Myers, University of British Columbia, Vancouver, BC, Canada*

Background: Approximately 20% of women receiving endocrine therapy (ET) for early-stage breast cancer (BrCa) discontinue their regimen due to side effects, including vasomotor symptoms and arthralgias, subjecting them to higher rates of disease recurrence. Exercise is one approach to mitigate ET-related toxicity and potentially improve medication adherence by mitigating ET-related symptoms. However, only 11% of women with BrCa adhere to recommended exercise guidelines. **Purpose:** To examine the effect of a virtual supervised exercise program for women receiving ET for early-stage BrCa on physical function (PF) (primary outcome) and adherence to ET (secondary outcome). **Methods:** Participants were recruited through referral by oncology care providers from multiple BC Cancer sites and self-referral. Eligible participants were: females with stage I-III BrCa being treated with curative intent, 19-75 years, taking ET for at least 3 months up to 3 years. Using a partial cross-over design (NCT04824339), participants were randomized to the immediate exercise group (INT) or the delayed exercise group (CON), which crossed over at 8 weeks. The 8-week intervention was comprised of a 50-minute resistance exercise circuit, delivered virtually by an exercise physiologist twice per week via Zoom, and self-directed aerobic exercise (progressing to 90 minutes or more per week of at least moderate intensity). PF was assessed using the 30-second chair stand test. ET adherence was measured by the Voils self-reported medication non-adherence questionnaire. Values reported as means and standard deviations. The difference at 8 weeks by intervention arm was examined using two sample t-test (continuous) or kappa measure of agreement (categorical). **Results:** A total of 132 women were randomized. On average, women were 54 years, White (European) (47%), married (64%), had at least a bachelor's degree or higher (51%), and had a body mass index of 27.7 kg/m². The most common type of ET women received was Letrozole (43%), followed by Tamoxifen (36%). At 8 weeks, there was a significant improvement in PF for INT versus CON (mean change +2.5±2.9 vs. +0.7±2.2 stands, $p < 0.001$). There was no difference between groups in change in medication adherence status ($k = 0.35$). **Conclusions:** An 8-week virtual supervised exercise program for women receiving ET for early-stage BrCa significantly improved PF but did not change medication adherence at 8 weeks. The potential impact of the intervention on long-term medication adherence will be explored up to one year and with covariates. Based on improvement in PF, future trials to establish effectiveness and inform implementation are warranted. Clinical trial information: NCT04824339. Research Sponsor: BC Cancer Foundation.

12071

Poster Session

Preliminary outcomes of a financial navigation program among lower socioeconomic patients with cancer. *First Author: Chiu Yi Joey Tan, School of Social Policy & Practice, University of Pennsylvania, Philadelphia, PA*

Background: Cancer patients receiving treatment are at risk of experiencing financial hardship, especially among those from lower socioeconomic status (SES) households. Patients experiencing financial toxicity are more likely to report poorer physical-wellbeing, higher anxiety, housing or food insecurity, and treatment non-adherence. While financial navigation programs are present, there is a lack of standardized practice to mitigate financial hardship among cancer patients. The purpose of this study is to evaluate the preliminary efficacy of Family Reach's oncology financial treatment program (FTP) on financial toxicity, quality of life, and anxiety in low SES patients. FTP consists of individualized resource navigation, financial education services, and a \$1000 patient assistance grant that was used towards non-treatment related expenses. **Methods:** 152 cancer patients undergoing active treatment, with household incomes under the 400% poverty line were recruited from two NCI-designated cancer centers. 99 participants completed the baseline and 2-month follow-up survey, consisting of these measures: COST: A FACIT Measure of Financial Toxicity (COST), Hospital Anxiety and Depression Scale (HADS), 36-Item Short Form Health Survey (SF-36), poverty exposure and treatment adherence items (secondary outcomes). **Results:** Participants were 69% female; roughly half (51%) were African American/Black, 34% were white, 4% were mixed, 3% were Asian and 8% reported 'other' or preferred not to answer. COST score at baseline (M=10.5, SD=6.4) significantly increased after 2 months (M=12.9, SD=7.9), $t(176.2) = -2.3$, $p < .05$. HADS-Anxiety score at baseline (M=11.1, SD=4.7) significantly decreased after 2 months (M=9.2, SD=4.4), $t(186.0) = 2.88$, $p < .01$. SF-36 Physical functioning score at baseline (M=34.0, SD=27.2) significantly increased after 2 months (M=43.9, SD=31.0), $t(170.3) = -2.26$, $p < .05$. See Table for secondary outcomes. **Conclusions:** Early evidence of FTP indicates promising results to increase financial and physical well-being, and in reducing anxiety among lower SES cancer patients. FTP showed improvements in COST scores and reduced non-medical cost concerns. However, COST scores reported in this study are still lower compared to other studies. A planned future study involving monthly guaranteed income payments will be carried out to examine if financial well-being and treatment adherence can be achieved. Supported by: One Family Foundation/Social Impact Fund Secondary outcomes. Research Sponsor: One Family Foundation/Social Impact Fund.

	Baseline	Follow-up	χ^2
Patient/Caregiver/family concerned about non-medical costs related to treatment	71.4%	45.3%	32.1*
1 or more utilities at risk of shutting off	34.7%	29.5%	45.1**
Missed/rescheduled a cancer related appointment in the past month	16.3%	19.8%	37.2*
Skipped/taken smaller doses of a prescribed medication to make it last longer in the last 3 months	4.1%	6.5%	49.3**

* $p < .05$, ** $p < .01$.

12070

Poster Session

Evaluation of a mobile behavior change program for weight loss in breast cancer survivors: A prospective single-arm pilot study. *First Author: Sherry Shen, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Post-diagnosis weight gain is common among women with early-stage breast cancer and is associated with increased risk of recurrence, breast cancer death, and all-cause mortality. Intentional weight loss following diagnosis is difficult to maintain. Targeted lifestyle interventions focusing on behavioral changes and education that can be implemented long-term are needed. **Methods:** This was a prospective single-arm pilot study in patients with history of early-stage breast cancer (NCT04753268). Key eligibility criteria included body mass index (BMI) ≥ 27.5 kg/m², stage I-III breast cancer, and completion of active cancer treatment ≥ 6 months prior to study enrollment. Patients were recruited at the Dempsey Center in Lewiston, ME and via social media. Participants were given access to the Noom mobile application, which utilizes cognitive behavioral therapy, motivational interviewing, and self-determination theory to induce behavior change using an educational curriculum of daily articles, virtual health coaching, social networking, food records, and physical activity logs. The primary endpoint was change in self-reported weight from baseline to 26 weeks. Secondary endpoints included change in physical activity measured using step count and the Global Physical Activity Questionnaire (GPAQ), change in diet patterns analyzed using the Nutrition Data System for Research, patient-reported outcome (PRO) measures, and metrics for engagement with the mobile application. **Results:** 31 patients were enrolled; 24 at the Dempsey Center and 7 via social media. Mean age was 56.8 and mean baseline BMI was 33.5 kg/m². Mean weight change was -4.8 kg (range +0.6 to -19.9 kg, $p < 0.001$) and mean percent weight change was -5.6%; 11/31 patients (35.5%) lost $\geq 5\%$ of their initial weight. Average daily step count increased by 54.7% ($p = 0.004$). Mean GPAQ score for physical activity increased from 990 to 1773 ($p = 0.01$), and the proportion of patients who met physical activity guidelines increased from 45.1% to 74.2%. Mean energy intake did not change significantly over 26 weeks ($p = 0.779$). Improvements were observed in PROMIS-Physical Functioning T-scores and Body Image Scale scores ($p = 0.04$, $p < 0.001$ respectively). Metrics of engagement with Noom that were predictive of weight loss $\geq 5\%$ included total articles read ($p = 0.012$), total weights logged ($p = 0.006$), total food records logged ($p = 0.001$), messages sent to coach ($p = 0.001$), and number of times the application was opened ($p = 0.014$). **Conclusions:** In this pilot study, breast cancer survivors lost weight and became more physically active using a commercially-available mobile application. This digital weight loss program is a scalable intervention, and these findings support future studies investigating impact on breast cancer outcomes. Clinical trial information: NCT04753268. Research Sponsor: Noom, Inc.

12072

Poster Session

Nutritional program among patients with prostate cancer receiving androgen deprivation therapy (ADT). *First Author: Dr. Paulo Sergio Lages, Oncoclinicas, Brasília, Brazil*

Background: Treatment with ADT can lead to changes in body composition, including an increase in body fat and a decrease in muscle mass. To minimize the nutritional risks associated with ADT, a nutritional program was developed. Thus, this study sought to determine the benefit of this program among patients with prostate cancer receiving ADT. **Methods:** Patients were recruited in a cancer center located in Brasília, Brazil. Patients were eligible if they were diagnosed with prostate cancer, and about to initiate treatment with ADT. They were assessed before starting ADT and at follow-up assessment (3 months). Based on their risk, patients were instructed to follow either a normocaloric (20-25 kcal/kg) or a hypocaloric (18-20 kcal/kg) diet, and both groups were required to consume a hyperprotein diet (1-1.2 g/kg), including the use of whey protein supplementation as needed. Outcomes measures included nutritional risk (Patient-Generated Subjective Global Assessment; PG-SGA), body composition (Medical software Lookin'Body120), and muscle strength (Jamar Hydraulic Hand Dynamometer). Descriptive statistics were generated, and paired T-test, Wilcoxon signed rank on paired samples and ANOVA-RM were used to evaluate changes in variables over time. **Results:** A total of 62 patients were included in this program. Participants had a median age of 75 years (range from 41-97) and were predominantly married (87%). A great proportion of patients (65%) were diagnosed with a stage IV disease. Notably, 23% were diagnosed with moderate to severe nutritional risk at baseline; 47% were overweight, 13% were obese and 14% were with sarcopenia. The nutritional program resulted in maintenance of total body weight (median 74.1 vs 75.6 kg, $P=0.12$), lean body weight (median 29.1 vs 29.4 kg, $P=0.11$), and muscle strength (median 30 vs 30 kg, $P=0.62$), while a statistically significant loss of body fat weight (median 22.0 vs 20 kg, $P=0.003$) was found over the 12-week period. Despite no change in the PG-SGA scores were noted overtime, the rate of sarcopenia has decreased (15% vs 13%, $P=0.03$) and the proportion of eutrophic patients has increased (18% vs 27%, $P=0.001$), as seen in the contingency table below. **Conclusions:** These findings suggest that this program may improve body composition and maintain muscle strength in men receiving treatment with ADT after only three months of intervention. Future studies should validate the benefit of this program in randomized trial with a longer follow-up assessment (6 and 12 months after treatment initiation). Research Sponsor: None.

	Myopenia	Sarcopenia	Eutrophic	Overweight	Obesity	Total baseline
Myopenia	5	0	0	0	0	5 (8%)
Sarcopenia	1	8	0	0	0	9 (15%)
Eutrophic	0	0	11	0	0	11 (18%)
Overweight	0	0	6	23	0	29 (47%)
Obesity	0	0	0	1	7	8 (13%)
Total at week 12	6 (10%)	8 (13%)	17 (27%)	24 (39%)	7 (11%)	

12073

Poster Session

Dietary and lifestyle profiles between patients with and without cancer in the national health interview survey. *First Author: Emma Gong, New York Medical College, Valhalla, NY*

Background: Although poor diet and lifestyle has been associated with cancer development and progression, it is unclear how the diagnosis of cancer impacts diet and lifestyle. We examined the dietary patterns and overall nutrition of adults diagnosed with cancer versus those never diagnosed with cancer in the 2015 National Health Interview Survey (NHIS). **Methods:** NHIS adults who reported having cancer (n=2,853) and not having cancer (n=27,002) were identified. A dietary/lifestyle score was developed based on World Cancer Research Fund and American Institute for Cancer Research Cancer Prevention Recommendations (Table). Participants were given a score for each recommendation which was then summed as an overall score, with seven meeting all requirements fully and zero meeting none of the requirements. **Results:** The mean composite score for the cancer population was 4.28 ± 0.88 and for the noncancer population was 4.30 ± 0.90 ($p = 0.18$). Compared to patients without cancer, those with a cancer diagnosis had higher rates of adherence to recommendations for fruit/vegetable consumption (0.08 vs. 0.07 , $p < 0.001$) and limitation of sugar-sweetened beverages (0.77 vs. 0.74 , $p < 0.001$), but had lower rates of the recommended physical activity (0.43 vs. 0.49 , $p < 0.001$). **Conclusions:** Patients with and without diagnosis of cancer had mediocre adherence (4.3 out of 7) to lifestyle recommendations, although those with diagnosis of cancer had a higher consumption of fruits/vegetables, lower consumption of sugary beverages, and lower level of physical activity than those without cancer. The data suggests a cancer diagnosis may prompt change in people's diet, but may limit their ability to exercise. The magnitude of lifestyle change that one can make after a cancer diagnosis may also be influenced by age or social connections. There is great opportunity for integrating healthy lifestyle interventions into routine cancer care. Research Sponsor: None.

	Patients with history of cancer (n = 2,853)						Patients without history of cancer (n = 27,002)						p-value
	Yes (score=1)	Mostly	Halfway	Minimally	No (score=0)	Mean $\pm$ Standard Deviation	Yes (score=1)	Mostly	Halfway	Minimally	No (score=0)	Mean $\pm$ Standard Deviation	
Was the below lifestyle recommendation met?													
1) Be at a healthy weight	30%	-	35%	-	34%	0.48 ± 0.40	33%	-	34%	-	33%	0.50 ± 0.40	.08
2) Be physically active	37%	-	12%	-	51%	0.43 ± 0.46	43%	-	13%	-	44%	0.49 ± 0.47	<0.001
3a) Eat a diet rich in fruits and vegetables	-	-	4%	25%	71%	0.08 ± 0.13	-	-	4%	22%	75%	0.072 ± 0.13	<0.001
3b) Eat enough fiber	-	-	0.3%	0.5%	99%	0.003 ± 0.03	-	-	0.2%	0.7%	99%	0.003 ± 0.03	.99
4) Limit consumption of fast foods	92%	-	7%	-	1%	0.95 ± 0.16	91%	-	8%	-	1%	0.95 ± 0.17	.44
5) Limit consumption of red meat and processed meat	27%	38%	20%	10%	5%	0.49 ± 0.28	27%	35%	21%	11%	6%	0.47 ± 0.29	.31
6) Limit consumption of sugar sweetened beverages	39%	36%	20%	5%	0.4%	0.77 ± 0.22	30%	40%	24%	5%	0.7%	0.74 ± 0.22	<0.001
7) Limit alcohol consumption	81%	-	14%	-	4%	0.89 ± 0.25	79%	-	15%	-	5%	0.87 ± 0.27	.09

12075

Poster Session

Survivorship care and breast and cervical cancer screening. *First Author: Marco Santos Teles, Rutgers New Jersey Medical School, Newark, NJ*

Background: Studies suggest that despite their history, cancer survivors may be equally or less likely to be screened for various cancers. The impact of the components of survivorship care on post-treatment screening is unknown. We aim to gauge the association of receipt of treatment summaries, follow-up care instructions (including where to obtain "routine cancer check-ups"), and type of doctor providing survivorship care on breast cancer screening (BCS) and cervical cancer screening (CCS) in female cancer survivors. **Methods:** A cross-sectional, retrospective analysis using Behavioral Risk Factor Surveillance System (BRFSS) survey data from 2016 and 2018 was conducted. BCS-eligible women were aged 40-74; CCS-eligible women were 30-64. BCS completion was defined as a mammogram within 2 years and CCS completion as a pap smear within 3 years or an HPV test within 5 years. Univariate analysis was conducted using chi-square. Multivariate logistic regression was used to determine which survivorship care factors were associated with BCS and CCS. **Results:** 4,533 BCS and 2,566 CCS-eligible survivors were identified. In the BCS-eligible group, 85.9% were aged ≥ 50 , 89.7% were white, 62.5% had a degree beyond high school, 48.7% earned $\leq \$50,000$, and 96.1% were insured. In the CCS-eligible group, 68.1% were aged ≥ 50 , 87.9% were white, 63.7% had a degree beyond high school, 45.0% earned $\leq \$50,000$, and 93.3% were insured. 82.0% were up-to-date (UTD) with BCS; 92.6% were UTD with CCS. BCS and CCS were higher for insured survivors (82.2% vs. 66.2%, $p = 0.009$; 93.8% vs. 83.3%, $p = 0.013$, respectively). 48.7% of BCS-eligible and 50.5% of CCS-eligible survivors received a treatment summary. 75% of BCS-eligible and 77% of CCS-eligible survivors received follow-up instructions. Among BCS-eligible survivors, recipients of treatment summaries and follow-up instructions were significantly more UTD with BCS than non-recipients (84.9% vs. 78.5% and 84.5% vs. 74.3%, respectively, $p < 0.001$). Among CCS-eligible survivors, recipients of follow-up instructions were significantly more UTD with CCS (94.5% vs. 88.9%, $p = .021$); there was no significant difference for recipients of treatment summaries ($p = .201$). In both groups, there was no significant difference in BCS or CCS based on the type of physician providing survivorship care ($p = .732$ and $p = .098$, respectively). On multivariate analysis, receipt of follow-up instructions was the only factor significantly associated with BCS (OR 1.46; 95% CI: 1.05-2.03) and CCS (OR 2.57; 95% CI: 1.19-5.55). **Conclusions:** Follow-up instructions, which are part of the survivorship plan, have the greatest association with BCS and CCS among cancer survivors. Despite this, about 25% of BCS and CCS-eligible cancer survivors did not receive them. Additional research should focus on improving the practice of survivorship care, particularly follow-up instructions, as a method to increase uptake of BCS and CCS among cancer survivors. Research Sponsor: None.

12074

Poster Session

Associations between body mass index with cancer recurrence and all-cause mortality among survivors of breast cancer. *First Author: Po-Hua Chen, Northwestern Medicine McHenry Hospital, McHenry, IL*

Background: It is widely recognized that obesity is associated with increased breast cancer incidence. While body mass index (BMI) does not capture measures of body composition, it is routinely collected during clinical care. However, we do not know whether BMI at breast cancer diagnosis affects cancer recurrence or all-cause mortality. This study aims to investigate the associations between clinical categories of BMI, cancer recurrence, and all-cause mortality in this population. **Methods:** All breast cancer survivors treated at Northwestern Medicine on or after 1/1/2005 were included. We applied the WHO classification of BMI (kg/m²): underweight (< 18.5), normal (18.5-24.9), overweight (25-29.9), class I obesity (30-34.9), class II obesity (35-39.9), and class III obesity (≥ 40). Cox proportional hazards models were used to determine the associations between BMI category at baseline and cancer recurrence plus all-cause mortality for breast cancer survivors. Models were adjusted for potential confounders including age, gender, race, ethnicity, histological grade, clinical stage, chemotherapy use, smoking, alcohol use, history of coronary artery disease, and history of Diabetes Mellitus. **Results:** Among all the 20,322 breast cancer survivors, 1,371 all-cause deaths and 1,183 cancer recurrences were observed. For patients aged 55 and above at diagnosis, there were 964 deaths and 632 cancer among 11,818 cases. When compared with a normal BMI (18.5-24.9), a BMI of 40 and above is associated with a higher risk of all-cause mortality among stage 1 breast cancer survivors (HR 1.90, 95% CI 1.17-3.09), whereas a BMI of lower than 18.5 is associated with a higher risk of all-cause mortality among stage 4 breast cancer patients (HR 3.21, 95% CI 1.24-8.30). For cancer recurrence, when compared with a normal BMI (18.5-24.9), a BMI of 40 and above is associated with a higher risk of cancer recurrence among stage 0 breast cancer survivors (HR 3.78, 95% CI 1.21-11.81) and a BMI of 35 to 39.9 is associated with a higher risk of cancer recurrence among stage 3 breast cancer patients (HR 1.91, 95% CI 1.01-3.61). We did not observe effect modification for either association by age at diagnosis using a cut-point of 55 years, which is considered as reaching postmenopausal status. **Conclusions:** Higher levels of obesity are associated with a higher mortality risk among early-stage breast cancer survivors whereas underweight is associated with a higher mortality risk for terminal-stage breast cancer. The associations between high-class obesity and increased risk of cancer recurrence were observed among stage 0 and stage 3 breast cancer survivors. These findings emphasize the importance of BMI as a tool for monitoring the health of breast cancer survivors. However, further study is needed to better understand the impact of BMI, and more importantly body composition, on the health and longevity of breast cancer survivors. Research Sponsor: U.S. National Institutes of Health.

12076

Poster Session

Phase 3 randomized placebo-controlled trial of donepezil for cancer-related cognitive impairment among breast cancer survivors: Results on patient-reported cognitive function from the wake forest nCI community oncology research program (NCORP) research base REMEMBER trial (WF97116). *First Author: Alayna E Ernster, Wake Forest University School of Medicine, Winston-Salem, NC*

Background: Cancer-related cognitive impairment (CRCI) is prevalent and persistent among breast cancer survivors (BCS). The REMEMBER prospective, randomized, double-blind, placebo-controlled trial compared the efficacy of donepezil, an acetylcholine esterase inhibitor, versus placebo to reduce late CRCI among BCS. (Clinical Trials #: NCT02822573). **Methods:** Women ≥ 18 years of age, with a history of breast cancer who completed ≥ 4 cycles of cytotoxic chemotherapy 1 to 5 years prior to enrollment, self-reported CRCI, with evidence of a memory deficit on the Hopkins Verbal Learning Test were eligible. Women were randomized to a 24-week course of daily donepezil (5mg) or placebo. If tolerated, the donepezil/placebo oral daily dose was increased to two tablets (donepezil 10mg) Weeks 7-24. The Functional Assessment of Cancer Therapy-Cognitive Function (FACT-Cog) Version 3 patient-reported outcomes (PRO) measure was administered at Baseline and weeks 12, 24, and 36. Mixed effects repeated measures analysis of covariance (RMANCOVA) models were used to assess treatment differences in FACT-Cog subscale scores with model covariates of treatment, time, time by treatment interaction, baseline outcome level, age stratification and an unstructured covariance matrix to account for within participant correlation over time. **Results:** A total of 276 patients from 87 NCORP sites (mean age = 57.1 yr., SD = 10.5) an average of 29.6 months post-chemotherapy completion were randomized to donepezil ($n = 140$) or placebo ($n = 136$). Participants in both arms experienced an improvement in all FACT-Cog subscale scores from baseline to week 12 (e.g., FACT-Cog Perceived Cognitive Impairment change: Donepezil = 14.8, SD = 14.6; Placebo = 13.9, SD = 15.7), with a slight improvement in week 24 (Donepezil = 3.6, SD = 11.4; Placebo = 3.1, SD = 11.4) and slight decrease in week 36 (Donepezil = -1.7, SD = 12.4; Placebo = -1.2, SD = 12.2). The magnitude of change was comparable across treatments at all timepoints (week 12 $p = 0.64$; week 24 $p = 0.75$; week 36 $p = 0.76$). There were no statistically significant differences across treatments at 12, 24 and 36 weeks on any FACT-Cog subscale. Exploratory analyses adjusting for education, baseline fatigue and depression as well as independent analyses considering treatment interaction with endocrine therapy and menopausal status also did not result in group differences for any outcome. **Conclusions:** There were no differences in PRO-assessed cognitive function domains between donepezil or placebo. The magnitude of improvement in patient-rated cognitive function was comparable across treatment arms. These results underscore the importance of placebo controls for CRCI intervention trials. Funding: NIH/NCI 2UG1CA189824. Clinical trial information: NCT02822573. Research Sponsor: U.S. National Institutes of Health.

12077

Poster Session

Impact of exercise on chemotherapy-induced peripheral neuropathy (CIPN) in survivors with post-treatment primary breast cancer. *First Author: Kirin Saint, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Chemotherapy-induced peripheral neuropathy (CIPN) is a common and debilitating side effect of neurotoxic chemotherapy with limited treatment options. We examined the association between exercise and CIPN symptoms in patients with post-treatment primary breast cancer.

Methods: Using a retrospective design, patients completing a standardized survey assessing exercise exposure, neuropathy symptoms, and pain in a tertiary cancer center survivorship clinic were included. Exercise was assessed using a standardized questionnaire quantified in standardized metabolic equivalent tasks (MET-h/wk). Chi-square tests, Mann-Whitney U-tests, Kendall's rank correlations, and multivariable logistic regressions adjusting for important clinical covariates examined the relationship between exercise and CIPN and whether this differed as a function of chemotherapy regimen (taxane vs. non-taxane based therapy). **Results:** A total of 5,444 patients with primary breast cancer previously treated with adjuvant chemotherapy (median age 62 years (IQR: 55, 71); median of 4.7 years post chemotherapy completion (IQR: 3.3, 7.6)) were identified. The overall prevalence of CIPN was 34% (95% CI: 33%, 36%); 33% (95% CI: 31%, 34%) for non-taxane and 37% (95% CI: 35%, 39%) for taxane based chemotherapy. The prevalence of CIPN was 28% (95% CI: 26%, 30%) among exercisers (≥ 5 days of moderate or ≥ 3 days of strenuous exercise per week) and 38% (95% CI: 37%, 40%) among non-exercisers (difference 11%; 95% CI: 8%, 13%; $p < 0.001$). Associations appeared dose-dependent. CIPN prevalence was 42% for < 6 MET-h/wk, 33% for 6-20.24 MET-h/wk and 29% for > 20.25 MET-h/wk (p -value < 0.001). Exercise was associated with reduced prevalence of all individual CIPN symptoms (numbness and tingling, pain, interference in daily living). Higher exercise was associated with lower CIPN regardless of chemotherapy regimen. **Conclusions:** CIPN is persistent several years following chemotherapy cessation in patients with breast cancer but significantly reduced by exercise in a dose-dependent manner. Research Sponsor: Memorial Sloan Kettering Cancer Center, Fund #: 50027/05160.

12079

Poster Session

Pharmacological cardioprotective strategy for non-metastatic patients affected by breast cancer receiving an anthracycline-based chemotherapy: Final results of the phase 3 SAFE trial. *First Author: Lorenzo Livi, Department of Experimental and Clinical Biomedical Sciences "M. Serio", University of Florence, Florence, Italy*

Background: Several studies have evaluated cardioprotective strategies to prevent myocardial dysfunction in patients receiving cardiotoxic therapies. However, the optimal approach still represents a controversial issue. We aim to determine whether pharmacological cardiac prevention could reduce subclinical heart damage in breast cancer (BC) patients treated with anthracycline-based chemotherapy. **Methods:** The SAFE trial is a four-arm, randomised, phase 3, double-blind, placebo-controlled study. Patients were eligible for trial inclusion if they had indication to primary or postoperative systemic therapy using an anthracycline-based regimen. Patients with prior diagnosis of cardiovascular disease were excluded. Cardioprotective therapy (bisoprolol (B), ramipril (R), or both drugs (B+R), as compared to placebo) was administered for 1 year from the initiation of chemotherapy or until the end of trastuzumab therapy in case of HER2 positive patients. Doses for all groups were systematically up-titrated, up to the daily target dose of B (5 mg, once daily), R (5 mg, once daily), and placebo, if tolerated. The primary endpoint was defined as detection of any subclinical impairment (worsening $\geq 10\%$) in myocardial function and deformation measured with standard and 3-dimensional (3D) echocardiography, left ventricular ejection fraction (LVEF) and global longitudinal strain (GLS). **Results:** 262 women (median 48 years; range 24-75 years) were enrolled and treated in the study. We analysed patients who had completed the pre-planned cardiologic assessment at 24 months. All patients received an anthracycline-based chemotherapy, 215 patients received at least 3 cycles of anthracyclines (range 1-6) and 128 patients had postoperative radiation therapy. At Univariate logistic analysis to evaluate the risk of GLS worsening $> 10\%$ at 24 months, Odds ratios (OR) for improvement were 0.055, 0.083 and 0.060 for B, R and B+R, respectively ($P < 0.0001$), if compared to placebo arm. At Univariate logistic analysis to evaluate the risk of 3DLVEF worsening $> 10\%$ at 24 months, OR for improvement were 0.019, 0.048 and 0.054 for B, R and B+R, respectively ($P < 0.0001$), if compared to placebo arm. Study drugs were well tolerated with no serious adverse events, the ramipril plus bisoprolol arm showed significantly more toxic effects and had a significantly higher rate of allocated treatment discontinuation as compared to the other arms. **Conclusions:** Cardioprotective pharmacological strategies in patients affected by BC receiving an anthracycline-based chemotherapy are well tolerated and seem to protect against cancer therapy-related LVEF decline and heart remodelling. Clinical trial information: NCT2236806. Research Sponsor: None.

12078

Poster Session

Cardiac dysfunction (CD) among breast cancer survivors (BCS): Role of cardiotoxic therapy and cardiovascular risk factors. *First Author: Geoffrey S. Bostany, University of Alabama at Birmingham School of Medicine, Birmingham, AL*

Background: CD is the leading cause of mortality in BCS. Limited information regarding the long-term risk of CD after exposure to cardiotoxic agents (anthracyclines, trastuzumab/pertuzumab and left breast/chest wall radiation) and additional factors that place BCS at highest risk has precluded development of surveillance guidelines for early detection of CD in BCS. **Methods:** Patients, who survived ≥ 1 y after BC and received potentially cardiotoxic therapy, underwent q2y echocardiographic (echo) screening at a single center. All echos from BC diagnosis to CD or last follow-up were processed in Python via automated text analysis. New-onset CD was defined as left ventricular ejection fraction (LVEF) $< 50\%$ or fractional shortening (FS) $< 28\%$. Treatment exposures, demographics and cardiovascular risk factors (CVRFs: diabetes, hypertension, dyslipidemia, obesity, smoking) were abstracted from medical records. Cumulative incidence of CD described the magnitude of risk in the entire cohort and among those who received anthracyclines ($\pm$ radiation), trastuzumab/pertuzumab ($\pm$ radiation), and radiation alone (without anthracyclines/trastuzumab/pertuzumab). Cox proportional hazards models estimated hazard ratios (HRs) and 95% CIs of associations between CD and treatment, adjusting for CVRFs (time varying) and demographics. Longitudinal echocardiographic analyses (adjusted for covariates) estimated trends in cardiac function prior to CD. **Results:** We evaluated 2,540 echos in 847 BCS exposed to potentially cardiotoxic therapy (median age at BC: 54.4y; median follow-up: 7.6y). Overall, 39% of BCS received anthracyclines, 17% received trastuzumab/pertuzumab, 5% received anthracyclines + trastuzumab/pertuzumab, and 39% received radiation alone. The cumulative incidence of CD in the entire cohort was 12.3% at 2y, increasing to 29.7% by 10y after BC. Multivariable analysis revealed the following to be independently associated with CD: treatment (anthracyclines: HR=2.72, 95% CI=1.9-3.9; trastuzumab/pertuzumab: HR=1.92, 95% CI=1.1-3.2; ref: radiation alone), presence of CVRFs before CD diagnosis (hypertension: HR=1.77, 95% CI=1.3-2.4; obesity: HR=1.82, 95% CI=1.4-2.4; and dyslipidemia: HR=1.63, 95% CI=1.3-2.1). Adjusted longitudinal echo analyses revealed a statistically significant decline in SF over 20y from BC diagnosis (but prior to CD onset) for the entire cohort ($p=0.0007$), trastuzumab/pertuzumab ($p=0.006$), anthracyclines ($p=0.037$), and radiation alone ($p=0.01$). **Conclusions:** In this large cohort of BCS followed longitudinally for an extended period, exposure to potentially cardiotoxic therapy results in a substantial burden of CD; the risk increases over time, and with CVRFs. These results provide evidence for close surveillance of BC survivors at increased risk of CD for extended periods, and aggressive management of CVRFs before, during and after BC. Research Sponsor: Breast Cancer Research Foundation of Alabama.

12080

Poster Session

Serum cytokines and autoantibodies to GM-CSF and immune-related colitis in ipilimumab-treated patients with cancer. *First Author: Edgar Gonzalez-Kozlova, Icahn School of Medicine at Mount Sinai, New York, NY*

Background: Despite the demonstrated efficacy of immune checkpoint inhibitors (ICI) including CTLA-4 and PD-(L)1 blockade, serious immune related adverse events including immune-related colitis (irColitis) often limit their use. Understanding the mechanisms that drive irColitis as well as predictive biomarkers is critical to informing the benefit-toxicity ratio of these medications. **Methods:** We tested serial blood specimens from 63 patients enrolled in six ipilimumab-containing clinical trials to evaluate changes in circulating cytokines and autoantibodies (auAb) to GM-CSF with irColitis occurrence. Retrospective blood specimens were analyzed from 31 patients who developed irColitis and 32 age and sex matched controls. irColitis was defined as either: 1) histologically confirmed colitis or 2) clinically significant diarrhea prompting initiation of corticosteroid therapy. Over a 24-week period, serum samples were collected at baseline, week 6, symptom onset, and post-symptom resolution. Serum proteins were assessed using the Immuno-Oncology and Inflammatory Olink panels. Anti-GM-CSF auAb were measured by enzyme-linked immunosorbent assay. Unsupervised clustering and mixed linear models were used to evaluate the changes associated with irColitis. Demographics, treatments, and technical variables were modeled for controlling artifacts. Significance was defined as $\text{Log2FC} > 0.5$, $P < 0.05$ and FDR < 0.05 (false discovery rate adjusted p-values) denoted with * and **, respectively. **Results:** While 69 proteins were significantly dysregulated with ICI treatment, patients who developed irColitis compared to those who did not showed higher levels of CD8A*, CXCL10* at baseline and prior to colitis onset at week 6, and then higher MMP10**, IL17A*-C*, CCL20**, OSM**, among others, at time of colitis and resolution. Further, patients who experienced irColitis showed an increase in anti-GM-CSF IgA** and IgG** Ab titers at Week 6 and at colitis onset compared with baseline, with higher IgA* after irColitis resolution compared to no colitis, while no significant differences were identified at baseline. **Conclusions:** Indicators of clinical outcomes can be obtained easily and minimally invasively by measuring circulating soluble proteins. Here, we identified differentially expressed cytokines associated with irColitis from retrospective cohorts. These potential biomarkers point to transient dysregulation of gut homeostasis that could help to stratify patients developing irColitis and to consider targeted mitigation strategies. These observations are currently being prospectively investigated. NCI support: Scientific and financial support for the IOTN Network is provided through the National Cancer Institute (NCI) U01DK124165. Institutional Review Board (IRB) STUDY #19-0246. This research was funded in part through the NIH/NCI P30 CA008748. Research Sponsor: U.S. National Institutes of Health.

12081

Poster Session

Long-term longitudinal patterns of patient-reported quality of life (QOL) after breast cancer (BC) to inform the implementation of personalized pathways of care. *First Author: Maria Alice B Franzi, Cancer Survivorship Group, INSERM Unit 981, Gustave Roussy, Villejuif, France*

Background: There is substantial inter individual variability in long-term trajectories of patient-reported quality of life (QOL) after early BC. Previous work focused on a selected group of patients (pts) treated with chemotherapy (CT) identified a cluster of pts with upfront poor QOL but also pts with severe, persistent post-chemotherapy QOL deterioration. We aimed to expand this work to a non-selected group of pts with early BC to identify latent clusters of pts at risk for QOL deterioration, and to assess the relationship of actionable host factors and health behaviors with trajectory group membership. **Methods:** We performed a detailed longitudinal analysis of QOL using a large ongoing national prospective clinical cohort (CANcer Toxicity, NCT01993498) of pts with stage I-III BC treated from 2012-2018. QOL (EORTC QLQ-C30 summary score) was assessed at diagnosis (dx, baseline) and year 1, 2, 4 and 6 post-dx. Baseline clinical, sociodemographic, behavioral, tumor-related, and treatment-related characteristics were available. Trajectories of QOL and group membership associations were identified by iterative estimations of group-based trajectory models and multi-variable multinomial logistic regression, respectively, among the whole cohort. **Results:** Among 10,792 pts, 5,695 received adjuvant CT and 8,805 received adjuvant endocrine therapy (ET). Four QOL trajectory groups were identified: excellent (N = 4,934, 45.8%), very good (N = 3,596, 33.3%), deteriorating (N = 1,745, 16.1%), and poor (N = 517, 4.8%). The deteriorating trajectory group reported fairly good baseline QOL (73.3 [95% CI], [72.4 to 74.2]), which significantly worsened at year-1 (63.0 [62.1 to 63.9]) and never recovered to pretreatment values through year-6 (64.7 [63.3 to 66.0]) post diagnosis. Factors associated with membership to the deteriorating group included younger age (aOR, 10-years decrement 1.10 [95% CI, 1.05 to 1.16]), overweight or obesity (aOR v lean, 1.90 [95% CI, 1.60 to 2.25]; 1.25 [95% CI, 1.07 to 1.46], respectively), physical inactivity (aOR v active, 1.13 [95% CI, 1.04 to 1.35]), former smoking behavior (aOR v never, 2.14 [95% CI, 1.80 to 2.54]), Charlson comorbidity score ≥ 1 (aOR v 0, 1.56 [95% CI, 1.33 to 1.83]), lower household income (< 3000 EU/month) (aOR v ≥ 3000 , 1.50 [95% CI, 1.30 to 1.72]), receipt of adjuvant CT (aOR v no, 1.35 [95% CI, 1.14 to 1.59]) and receipt of adjuvant ET (aOR v no, 1.46 [95% CI, 1.22 to 1.75]). **Conclusions:** This study will help identify latent clusters of pts who are at risk of persistent QOL deterioration after BC, independently of receipt of CT. Trajectory clustering can help facilitate the creation of personalized pathways that may include early addressal of actionable factors, including referral to social work and healthy lifestyle interventions. Clinical trial information: NCT01993498. Research Sponsor: ANR; Conquer Cancer Foundation of the American Society of Clinical Oncology; Breast Cancer Research Foundation (BCRF).

12083

Poster Session

Cardiac safety of reduced surveillance for cancer therapy related cardiac dysfunction in patients with breast cancer treated with HER2-targeted therapy. *First Author: Anthony Francis Yu, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Non-anthracycline-based therapy is a treatment option for patients (pts) with HER2-positive breast cancer (BC) and is associated with lower risk of cancer therapy related cardiac dysfunction (CTCRD) compared to anthracycline-based treatment. Given the reduced CTCRD risk with non-anthracycline HER2-targeted therapies, updates to practice guidelines that recommend surveillance echocardiograms (TTE) every 3 months are needed. We evaluated the cardiac safety of reduced CTCRD surveillance in pts receiving non-anthracycline HER2-targeted therapies. **Methods:** Pts with BC treated with non-anthracycline HER2-targeted therapy were enrolled in this single-arm prospective study. Pts with previous anthracycline exposure, uncontrolled hypertension (systolic blood pressure ≥ 160 mmHg), or significant cardiovascular disease were excluded. TTEs were performed at baseline, 6 months, and 12 months during HER2-targeted treatment. The primary endpoint was a cardiac event, defined by clinical heart failure (New York Heart Association Class III/IV) or cardiovascular death, with a prespecified non-inferiority margin of 2.9% relative to a cardiac event rate of 1.1% based upon prior studies. Secondary endpoints were CTCRD, defined by decline of left ventricular ejection fraction (LVEF) $\geq 10\%$ to $< 53\%$, and interruption of HER2-targeted treatment secondary to CTCRD. **Results:** Between May 2019 and January 2022, 190 pts (age 52 ± 11 y) with HER2-positive BC were enrolled: 143 (75%) had stage I disease, 8 (4%) had diabetes, 38 (20%) had hypertension, and baseline LVEF was $64 \pm 5\%$ (Table). Additional TTEs outside the prespecified 6- and 12-month timepoints were performed for 35 (18%) pts, of which 20 were to assess for possible cardiac symptoms. After 1-year follow-up, there were 0 (0%; 95% CI 0-1.9%) cardiac events. Two (1.1%) pts developed CTCRD and 1 (0.5%) pt had a temporary CTCRD-related treatment interruption. **Conclusions:** Reduced CTCRD surveillance every 6 months is feasible and safe for selected pts with HER2-positive BC receiving non-anthracycline HER2-targeted therapy. Our findings support the need to update cardiology practice guidelines and allow for less frequent surveillance TTEs among pts at low-risk for CTCRD. Clinical trial information: NCT03983382. Research Sponsor: U.S. National Institutes of Health.

	Total Cohort (N = 190)
Age, mean	52 $\pm$ 11
SD, years	10.1
Race	
Asian	24 (13%)
Black	14 (7%)
White	159 (83%)
Other/unknown	13 (7%)
EB-positive	159 (83%)
PR-positive	111 (58%)
Stage	
I	143 (75%)
II	29 (15%)
III	2 (1%)
IV	14 (8%)
Treatment regimen	
Trastuzumab	143 (75%)
Trastuzumab, pertuzumab	15 (8%)
Trastuzumab, pertuzumab, trastuzumab	2 (1%)
Docetaxel, carboplatin, trastuzumab	4 (2%)
Docetaxel, carboplatin, trastuzumab, pertuzumab	23 (12%)
Docetaxel, cyclophosphamide, trastuzumab	1 (1%)
Trastuzumab	2 (1%)
Baseline LVEF, %	64 $\pm$ 5
Hypertension	38 (20%)
Diabetes	8 (4%)
Smoking (current/former)	58 (31%)

Values are mean $\pm$ SD or (%).

12082

Poster Session

Estimating burden of cardiovascular disease among survivors of breast, colorectal, lung, and prostate cancer in the detroit research on cancer survivors (ROCS) cohort. *First Author: Vidhya Nair, Ascension Providence Hospital/Michigan State University, Southfield, MI*

Background: With new advances in cancer treatment, cancer-specific mortality has decreased by 31% over the past 3 decades. The growing number of cancer survivors has led to increased risk of other chronic conditions including cardiovascular disease (CVD), which has become an important competing cause of mortality. This study evaluates the incidence of CVD, including heart failure (HF), myocardial infarction (MI), coronary artery disease (CAD), atrial fibrillation (AF) and stroke after cancer in the Detroit ROCS cohort. **Methods:** ROCS is an African American cancer survivorship cohort that enrolled participants residing in the tri-county Detroit Metropolitan area. This study included survivors of breast, colorectal, lung, and prostate cancer who provided socio-demographic and clinic information on self-administered questionnaires. We calculated incidence as percentages and rates per 1,000 person-years of HF, MI, CAD, AF, and stroke after cancer. Multivariate logistic regression analysis was used to evaluate the relationship between socio-demographic and clinical predictors of CVD by using factors with p-value < 0.1 . **Results:** After excluding patients with pre-existing CVD or lack of data on comorbidities, the study cohort consisted of 2,865 participants. The mean (SD) age at cancer diagnosis was 60.3 (9.4) years with median follow up of 3.0 (1.0-9.3) years. The incidence rate for any CVD was 23.3 per 1,000 person-years. In the study sample, stroke was the leading CVD, followed by HF, AF, CAD and MI. Lung cancer survivors had the highest incidence of CVD followed by prostate, breast, and colorectal cancer. Age at cancer diagnosis, household income, insurance, aspirin, smoking, body mass index, hypertension, diabetes, and high cholesterol were included in the final model. In the multivariate analysis, decreased household income [OR 1.26 (95% CI 1.05-1.52)], prior aspirin use [OR 1.83 (95% CI 1.34-2.49)], and history of hypertension [OR 1.71 (95% CI 1.20-2.44)] were associated with higher odds of CVD. **Conclusions:** CVD is a relatively common outcome within years after cancer diagnosis in an African American survivorship cohort. Intervention should focus on the possible impact of socioeconomic variables and control of hypertension in reducing the risk of CVD after cancer. Research Sponsor: Epidemiology Research Core and Service Incentive Program by the Karmanos Cancer Institute.

	Total		Breast		Colorectal		Lung		Prostate	
	N	%	N	%	N	%	N	%	N	%
Total	2865		1160		309		290		1106	
Any CVD	230	8.0%	89	7.7%	23	7.4%	27	9.3%	91	8.2%
Atrial fibrillation	54	1.9%	17	1.5%	5	1.6%	6	2.1%	26	2.4%
Coronary heart failure	72	2.5%	35	3.0%	7	2.3%	3	1.0%	27	2.4%
Coronary artery disease	48	1.7%	13	1.1%	5	1.6%	5	1.7%	25	2.3%
Myocardial infarction	38	1.3%	18	1.6%	3	1.0%	2	0.7%	15	1.4%
Stroke	87	3.0%	31	2.7%	11	3.6%	17	5.9%	28	2.5%

12084

Poster Session

Social determinants of health and neurocognitive and psychosocial outcomes in adult childhood cancer survivors: A report from the childhood cancer survivor study (CCSS). *First Author: Jinbing Bai, Nell Hodgson Woodruff School of Nursing, Emory University, Atlanta, GA*

Background: Limited data exist on the impact of social determinants of health on neurocognitive, psychological, and quality of life (QOL) outcomes in adult childhood cancer survivors. **Methods:** We examined patient-reported outcomes (PROs) of neurocognitive function, psychological symptoms, and QOL in association with the Area Deprivation Index (ADI) and neighborhood ambient air quality in 5,131 survivors (52.1% female, mean [SD] age 29.9 [7.1], mean [SD] age at diagnosis 7.9 [6.2], 81.5% White, and 42.3% leukemia) from the Childhood Cancer Survivor Study. The ADI, which reflects neighborhood socioeconomic deprivation, was coded using survivors' residential 9-digit ZIP codes; neighborhood ambient air quality was coded by the NASA Satellite-based pollution measures PM_{2.5} and NO₂ by ZIP codes. Impairment on PROs was identified from scores on the Neurocognitive Questionnaire ($\leq 10^{\text{th}}$ %ile), the Brief Symptoms Inventory (BSI; $\geq 90^{\text{th}}$ %ile), the pain survey (yes vs. no), and the Medical Outcomes Study Short Form-36 ($< 16^{\text{th}}$ %ile). Multivariable logistic regression assessed associations between social determinants and PROs with odds ratios (OR) and 95% confidence intervals (CI), adjusting for demographic and treatment (chemotherapy and radiation) factors. **Results:** Among survivors, impaired neurocognitive function was reported in 26.5% for task efficiency, 25.4% memory, 15.4% emotional regulation, and 11.6% organization. For the BSI and pain survey, 56.7%, 11.3%, 8.3%, and 7.3% reported total pain, depression, somatization, and anxiety, respectively. Poor physical and mental domains of QOL were reported by 10.9% and 17.0% of survivors, respectively. Survivors with an ADI in the top deprived 20% neighborhoods (compared to the bottom 80% neighborhoods) reported worse neurocognitive function (task efficiency, OR 1.89, 95% CI 1.45-2.46; emotional regulation, OR 1.74, 95% CI 1.30-2.34; and memory, OR 1.67, 95% CI 1.29-2.17), more severe symptoms (pain, OR 1.34, 95% CI 1.05-1.70; somatization, OR 1.55, 95% CI 1.05-2.28; and depression, OR 1.70, 95% CI 1.19-2.44), and poorer QOL (physical, OR 1.75, 95% CI 1.28-2.38; mental, OR 1.79, 95% CI 1.35-2.36), controlling for treatment factors. Survivors from the 20% most deprived neighborhoods showed worse task efficiency (OR 1.50, 95% CI 1.03-2.17), adjusting for all confounders. PM_{2.5} and NO₂ levels were not associated with impairment on PROs, adjusting for all confounders. **Conclusions:** Social determinants, particularly living in the top deprived neighborhoods, are adversely associated with neurocognitive, psychological, and QOL outcomes in adult childhood cancer survivors. These findings indicate the critical need of evaluating childhood cancer survivors' area-level deprivation and tailoring support and interventions for survivors based on their social and structural contexts. Research Sponsor: U.S. National Institutes of Health.

12085

Poster Session

12087

Poster Session

A prospective study evaluating the association of patient-reported outcomes with activity level and sleep patterns in sarcoma survivors. *First Author: Elizabeth J. Davis, Vanderbilt University Medical Center, Nashville, TN*

Background: Sarcomas are a rare heterogeneous malignancy group affecting both sexes and all ages. Treatment is often intensive, resulting in long-term toxicities. Given the rarity of sarcoma, there is a paucity of data defining physical and emotional outcomes. The Cohort to Augment the Understanding of Sarcoma Survivorship Across the Lifespan (CAUSAL) was constructed at Vanderbilt University Medical Center (VUMC) to evaluate health-related outcomes. **Methods:** Sarcoma patients treated at VUMC from 2012 – present are enrolled into CAUSAL. Patient demographics, tumor and treatment data are abstracted from the electronic medical record. Participants complete surveys including PROMIS-57 consisting of seven domains including physical function, sleep disturbance, fatigue, and satisfaction with participation in social roles, which are reported here. Participants who have completed treatment are given a FitBit to track activity level and sleep over 12 weeks. Data are synced to an online platform, Fitabase. Body mass index (BMI) is assessed at study entry. For each participant, FitBit data were summarized using medians. To estimate the association between PROMIS-57 scores and activity and sleep data (FitBit), linear regression models were fit controlling for age, sex, and BMI of participants. **Results:** Of 306 CAUSAL participants who completed the PROMIS-57, 193 were post completion of sarcoma therapy. Of these, 76 also had FitBit data and are included in this analysis. Median step count was 5826 (quartiles: 3668, 7967), which was lower than average Fit Bit step count data for the US population (8170). Median daily active minutes was 252 minutes (quartiles: 174, 307). Median duration of sleep was 447 minutes (quartiles:381, 474) which was greater than the average reported by FitBit for the general US population (436 min). Step count was correlated with higher physical function score ($p < 0.001$). A 10-point increase in physical function led to an average increase of 1291 (95% CI: 609,1973) steps when adjusting for age and sex. Compared with participants receiving treatment within 30 days prior to CAUSAL enrollment, participants not receiving treatment had 4.50 (95% CI: 1.53, 7.47) higher physical function score and 6.26 (95% CI: 1.87, 10.65) higher satisfaction in their social roles. There was no correlation between minutes of sleep recorded by FitBit and PROMIS responses. **Conclusions:** Using PROMIS-57, and FitBits, we demonstrated an association between higher step counts and self-reported higher physical function but did not find a correlation between FitBit recorded activity level/sleep and self-reported sleep disturbance or fatigue scores. Further, our data suggests patients with sarcoma sleep more and walk less than the general US population. As enrollment continues in CAUSAL, we will focus on PROMIS scores over time and their association with activity level and sleep. Research Sponsor: U.S. National Institutes of Health.

12088

Poster Session

A genome-wide association study for doxorubicin-induced cardiomyopathy in childhood cancer survivors from the St. Jude lifetime cohort (SJLIFE) and the childhood cancer survivor (CCSS) studies. *First Author: Kateryna Petryk, St Jude Childrens Research Hospital, Memphis, TN*

Background: Treatment of childhood cancer using doxorubicin is associated with a well-established dose-related risk of cardiomyopathy, which can lead to heart failure and affects ~7-10% of exposed children and adolescents. Here, we identified a genetic variant associated with risk of doxorubicin-induced cardiomyopathy (diCM) in survivors of childhood cancer. **Methods:** A genome-wide association study using common variants ($MAF \geq 5\%$; whole-genome sequencing data) was performed among 993 SJLIFE survivors of European ancestry (median age, 36.6 years; range, 8.7-62.2 years) treated with doxorubicin only (210 with diCM; defined as CTCAE grade ≥ 2 clinically assessed cardiomyopathy). Replication analyses were performed separately among 1,430 CCSS survivors of European ancestry (median age, 35.4 years; range, 15.8-60.7 years) and 159 SJLIFE survivors of African ancestry (median age, 32.6 years; range, 8.9-61.1 years) exposed to doxorubicin only. Analyses were adjusted for age at primary cancer diagnosis, sex, doxorubicin dose, age at last contact and top five principal components. **Results:** We identified a genome-wide significant association between a novel locus near *HS3ST4* and diCM risk in SJLIFE survivors of European ancestry ($rs112474856$; $OR = 2.78$; $P = 3.3 \times 10^{-8}$). This association replicated in CCSS survivors of European ancestry ($OR = 1.74$, $P = 0.036$) but had an opposite effect among SJLIFE survivors of African ancestry ($OR = 0.34$, $P = 0.028$). SNP $rs112474856$ did not show significant association with diCM risk in two independent datasets including survivors of European ancestry in SJLIFE ($OR = 1.20$; $P = 0.71$) and CCSS ($OR = 1.02$; $P = 0.98$) who were not exposed to doxorubicin but were treated with daunorubicin or chest radiotherapy, suggesting doxorubicin specificity. No association was observed between $rs112474856$ and risks of cardiomyopathy ($OR = 1.00$; $P = 0.88$) or heart failure ($OR = 1.00$; $P = 0.59$) in 361,194 UK Biobank participants from the general population. *HS3ST4* was significantly upregulated ($P = 4.7 \times 10^{-6}$) in response to doxorubicin treatment in human induced pluripotent stem-cell-derived cardiomyocytes from patients with diCM. *HS3ST4* encodes heparan sulfate, the latter was recently linked to immune activation, cardiac fibrosis, and heart failure. **Conclusions:** Leveraging the two largest cohorts of childhood cancer survivors in North America, we identified and replicated a novel locus for diCM which was associated with increased risk in survivors of European ancestry but decreased in their African counterpart. Research Sponsor: U.S. National Institutes of Health; American Lebanese Syrian Associated Charities; Cancer Center Support [CORE].

Training and validation of a model predicting clusters of long-term cancer-related behavioral symptoms (CRBS) after breast cancer (BC). *First Author: Martina Pagliuca, INSERM Unit 981, Gustave Roussy, Villejuif, France*

Background: Fatigue, cognitive impairment, emotional distress, and sleep disturbance are prevalent and challenging symptoms among patients (pts) with BC. These symptoms often tend to cluster, they are usually responsive to similar behavioral interventions (e.g., exercise, psychosocial), and can be collectively defined as CRBS. We aimed to generate a model to predict clusters of long-term CRBS. **Methods:** CANcer Toxicity (CANTO; NCT01993498) is a prospective cohort of pts with stage I-III BC collecting longitudinal data at diagnosis (dx) and yearly post-dx. Our outcome was the proportion of pts reporting a cluster of ≥ 3 severe CRBS (EORTC QLQ-C30/HADS) 4 years post-dx. Clinical, behavioral, treatment (tx)-related predictors, and the baseline Behavioral Symptoms Score (BSS; based on the number of severe CRBS as proxy of symptom burden at dx) were tested in a training cohort (Mar 2012 - Feb 2015) with a multivariable logistic regression model implementing bootstrapped Augmented Backwards Elimination and 10-fold internal cross-validation. Performance was externally validated in pts from a subsequent enrolment period (Mar 2015 - Apr 2018). **Results:** In the training cohort (N=3555), 92.1% of pts had stage I-II BC, 52.6% received chemo, and 81.9% endocrine tx. At dx, 22.0% pts had severe fatigue (C30 $\geq 40/100$), 29.7% severe cognitive impairment (C30 $< 75/100$), 33.9% and 6.5% clinically suggestive anxiety and depression (HADS $\geq 11/21$), respectively, and 35.2% severe insomnia (C30 $> 50/100$). 19.0% of pts reported a severe CRBS cluster at dx, then 21.0% did so 4 years post-dx. Younger age, previous psychiatric disorders, and higher baseline BSS were predictors of CRBS clusters (Table:AUC 0.73 [95%CI 0.71-0.75]). Results were confirmed in the validation cohort (N=1533). **Conclusions:** 1 in 5 pts reports a cluster of severe CRBS 4 years post-dx of BC. Younger pts with previous psychiatric disturbance and a higher symptom burden at dx have greater risk of long-term CRBS. Systematic clinical implementation of predictive tools at dx of BC can aid a more thorough screening and referrals to targeted behavioral interventions. Clinical trial information: NCT01993498. Research Sponsor: National Research Agency (ANR), Grant No. ANR-10-COHO-0004; Conquer Cancer Foundation of the American Society of Clinical Oncology; Rising Tide Foundation for Clinical Cancer Research.

Adjusted* predictive model of CRBS clusters 4 years post-dx.		
Predictor	Prevalence at dx (%)	Odds Ratio (95% CI)
Age		for 5-years decrease
Mean (SD)	56.4 (10.9)	1.06 (1.02-1.11)
Previous psychiatric disorders		
No	84.4	Ref
Yes	15.6**	1.27 (1.01-1.60)
Baseline BSS		
0	39.6	Ref
1	23.5	2.17 (1.66-2.85)
2	17.8	3.96 (3.04-5.18)
3	10.7	5.96 (4.44-8.02)
4	6.3	10.11 (7.19-14.26)
5	2.1	12.30 (7.33-20.87)

*by all predictors + BMI, comorbidities, neurological disorders, socioeconomic, alcohol, tobacco, exercise, local and systemic tx.
**56.6% depression, 21.1% anxiety, 11.2% anxiety-depressive syndrome, 5.4% sleep problems, 1.5% manic-depressive disorder, 1.1% eating disorders, 0.8% drug or alcohol addiction, 0.7% burn-out, 0.6% self-harm, 0.4% post-traumatic stress disorder.

12089

Poster Session

Burden of chronic health conditions (CHCs) among people with HIV (PWH) and non-AIDS defining cancers (NADC): A report from the center for AIDS research (CFAR) network of integrated clinical systems (CNICS). *First Author: Gaurav Goyal, University of Alabama at Birmingham, Birmingham, AL*

Background: Advances in anti-retroviral therapy (ART) have led to improved life expectancy of PWH and a growing population of PWH who are at an increased risk of NADC. While the risk of CHCs in HIV uninfected cancer survivors is well known, the burden of morbidity (CHCs) borne by PWH-NADC remains understudied and can adversely influence long-term survival. **Methods:** We utilized CNICS data for PWH ≥ 18 y from 1995- 2018. CNICS data are harmonized across 8 academic sites, comprising patient-level clinical, morbidity, and outcomes data in the ART era. We included individuals with the five most common NADCs: anal squamous cell cancer, non-small cell lung cancer (NSCLC), prostate cancer, classic Hodgkin lymphoma (cHL), and hepatocellular cancer (HCC). For controls, we conducted a 1:2 matching (age at CNICS entry, year of CNICS entry, sex) for each NADC subgroup to select PWH and no NADC at last follow-up. Comorbidities diagnosed after cohort entry are validated in CNICS and were graded using the Common Terminology Criteria for Adverse Events into grade 1 (mild) through grade 4 (severe/life-threatening). **Results:** We included 693 PWH-NADC and 1,345 non-cancer PWH controls in this study. The NADC distribution was anal cancer (n = 195, 28%), NSCLC (n = 155, 22%), prostate cancer (n = 144, 21%), cHL (n = 124, 18%), and HCC (n = 75, 11%). Mean age at CNICS entry was 45y for cases and controls (SD: 10.4). At a median follow-up of 12.5y for cases and 9.5y for controls, the prevalence of all-grade and grade ≥ 3 CHCs was higher in PWH-NADC compared with controls (94% vs. 88%, and 25% vs. 14%, respectively [$p < 0.01$]). PWH-NADC had a higher prevalence of all-grade HTN (87% vs. 80%), CKD (49% vs. 46%), hyperlipidemia (56% vs. 50%), DM (26% vs. 18%), VTE (4% vs. 1%), MI (12% vs. 5%), and CHF (7% vs. 3%) compared with controls (p-value for all < 0.01). In Cox regression including type of NADC, age at CNICS cohort entry, ART use, race/ethnicity, NADCs were associated with increased risk of new-onset grade 3 or 4 CHCs (HR 2.94, $p < 0.01$). When examining specific CHCs, all NADCs were associated with increased risk of new-onset grade 3 DM (anal cancer HR 2.34, HCC HR 5.02, NSCLC HR 3.89, cHL HR 2.77, and prostate cancer HR 1.88), p-value for all < 0.01). Additionally, NSCLC was associated with increased risk of G3-4 MI (HR 2.79, $p = 0.04$), and prostate cancer with G3-4 CHF (HR 6.19, $p < 0.01$). **Conclusions:** In this large multi-institutional study, 25% of PWH-NADC had developed severe/life-threatening CHCs at last follow up. Occurrence of NADC among PWH was associated with increased hazards of developing grade ≥ 3 morbidities. The specific types of CHCs observed in PWH with NADC subtypes could be used to inform risk-based anticipatory surveillance and risk reduction strategies. Research Sponsor: U.S. National Institutes of Health; Walter B. Frommeyer Jr. Award, UAB.

12090

Poster Session

Polygenic risk of anthracycline-related cardiomyopathy in childhood cancer survivors: Report from children's oncology group and childhood cancer survivor study. *First Author: Noha Sharafeldin, Department of Hematology & Oncology, School of Medicine, University of Alabama at Birmingham, Birmingham, AL*

Background: Considerable inter-patient variability in anthracycline-related cardiomyopathy (aCM) risk exists among childhood cancer survivors (CCS). A polygenic risk score (PRS) that accounts for combined effects of multiple genetic variants is established in other clinical situations, but remains understudied in anthracycline-exposed CCS. **Methods:** For discovery, a case-control set of 278 anthracycline-exposed non-Hispanic White (NHW) CCS (129 aCM cases; 149 controls) matched on primary cancer diagnosis, year of diagnosis and duration of follow-up was included from a Children's Oncology Group study (COG-ALTEO3N1). Genomic DNA underwent whole exome sequencing (100X depth). We searched Medline and Embase databases between 2005 and 2022 to curate evidence for published single nucleotide polymorphisms (SNPs) associated with CM. We identified 1,156 SNPs on 343 genes with minor allele frequency [MAF] ≥ 0.05 in white populations. We constructed a weighted PRS using sequenced SNPs that were linkage disequilibrium pruned, yielding a final list of 279 independent SNPs. Conditional logistic regression models adjusted for anthracycline dose, age at diagnosis, sex, chest radiation and cardiovascular risk factors (CVRFs; diabetes, hypertension, dyslipidemia) were used to estimate PRS-aCM associations. An independent population of 475 anthracycline-exposed NHW CCS from the Childhood Cancer Survivor Study (CCSS: 96 cases; 379 matched controls) was used to replicate the PRS-aCM association. Area under the receiver operating characteristic curve (AUC) was used to evaluate the performance of a model including the PRS. **Results:** Median age at primary cancer diagnosis was 7y for cases and controls in the Discovery and 11y in the Replication set. Mean anthracycline dose was higher for cases (Discovery: 312 $\pm$ 186 mg/m²; Replication: 333 $\pm$ 289 mg/m²). Cases were more likely to have received chest radiation (Discovery: 35.7% ν 24.8%; Replication: 34.3% ν 23.2%); and were more likely to have a CVRF (Discovery: 37.2% ν 8.7%; Replication: 55.2% ν 31.9%). PRS_{continuous} was significantly associated with aCM (aOR = 2.09, 95%CI: 1.1-4.0, p = 0.024) in the Discovery set. Compared to a model with clinical variables only, a model including the PRS had significant predictive performance: AUC_{clin} = 0.72, 95% CI: 0.65-0.79. ν AUC_{clin+PRS} = 0.91, 95% CI: 0.87-0.95, p < 0.001. In the Replication set, the top PRS quartile (top 25%) was significantly associated with aCM (aOR = 2.14, 95%CI: 1.05-4.37, p = 0.036; reference: lowest PRS quartile). **Conclusions:** The significant association between this comprehensively curated PRS and aCM in CCS could serve as an important tool to identify survivors at increased risk for CM and inform targeted interventions. Research Sponsor: U.S. National Institutes of Health; Leukemia & Lymphoma Society and V Foundation.

12092

Poster Session

The impact of population pharmacogenomics and risk allele frequencies on cisplatin-induced peripheral sensory neuropathy (PSN). *First Author: Swetha Nakshatri, University of Chicago, Chicago, IL*

Background: Taxane-treated breast cancer patients with genetically African ancestry have worse PSN than other groups. However, no study has examined the association between ancestry and PSN after cisplatin-based chemotherapy. Increased risk could be partially explained by differing risk allele frequencies across populations for alleles increasing the general vulnerability to PSN or altering drug metabolism. **Methods:** The Platinum Study enrolled cisplatin-treated testicular cancer survivors (TCS) who completed clinical exams and surveys. A PSN score was derived from the mean of 8 sensory items (using EORTC-CIPN20), assigning severity on a 0-2 scale. Multidimensional scaling scores for each TCS were calculated, plotted and anchored by data from the 1000 Genomes Reference population to determine genetic ancestry. Multinomial logistic regression assessed the association between genetic ancestry and PSN. To determine risk alleles for PSN and allele frequencies across populations, risk allele panels were created, including ancestry-informative markers (AIMs) determined by the AncestrySNPMiner tool. Allele frequencies were calculated in each group; SNPs with frequency differences > 0.3 in the African (AFRAFR) population vs. others were included. For filtering the AIMs, GTEx data was used to identify expression quantitative trait loci (eQTL) or splicing quantitative trait loci (sQTL) in nerve/brain tissue. Multinomial logistic regression assessed associations between SNP genotype and PSN phenotype for SNPs with differing allele frequencies across populations. **Results:** Despite small numbers of non-Europeans, TCS with African ancestry had increased incidence and severity of PSN vs. TCS with European ancestry. In a subset analysis of EUR (n = 681) and AFRAFR (n = 13) patients who received 400-450 mg/m² of cisplatin, the relative risk ratio (RRR) in the AFRAFR vs. EUR TCS of severe neuropathy vs. none was 7.96 (P = 0.074) and the RRR for any neuropathy vs. none was 7.79 (P = 0.049). There were 394 independent AIMs with significant (> 0.3) allele frequency differences between the AFRAFR and other populations that were eQTLs and/or sQTLs in nerve/brain tissue. Using multinomial logistic regression between genotype and phenotype for all TCS (n = 1513) with covariates for age at survey and 10 genetic principal components: 16 SNPs had P-values < 0.05 for severe PSN vs. none and/or any PSN vs. none. Although not statistically significant with multiple testing corrections, these suggestively significant SNPs could be potentially validated in additional populations. **Conclusions:** These results are preliminary evidence for the potential importance of differing risk allele frequencies across populations in explaining some disparities in cisplatin-related PSN. If confirmed, genotyping for risk variants could impact treatment decisions and enable monitoring to mitigate PSN. Research Sponsor: U.S. National Institutes of Health.

12091

Poster Session

Long-term prospective data on correlation between overall mortality and HADS (Hospital Anxiety and Depression Scale) assessed psychological distress in prostate cancer patients (11 year follow-up data). *First Author: Santhanam Sundar, Nottingham University Hospitals NHS Trust, Nottingham, United Kingdom*

Background: We prospectively assessed whether Psychological factors such as anxiety and depression can have a detrimental effect on long term overall survival of prostate cancer patients (pts). **Methods:** Prostate cancer pts participating in an ethics Committee approved, Prospective study evaluating an Andropause rating scale. All pts had radical radiotherapy with androgen deprivation therapy. Pts completed a baseline HADS questionnaire before any treatment was initiated & at 3mths & after completion of hormone therapy. Patient characteristics: Median age: 69 yrs (50 to 78 yrs). Charlson Comorbidity Index (CCI) prevalence at baseline as follows CCI-I 6.1%; CCI-II: 33.8%; CCI-III: 37.2%; CCI-IV: 14.2%; CCI-V: 6.1% and CCI-VI: 2.7%; At the survival update in Feb 2023, 49.3% of patients have died [n = 148]; Gleason grade was Low risk in 7.2%; Intermediate in 53.4% and high risk in 39.2%; Baseline PSA was < 10 ug/L in 45.3%; 10-20 ug/L in 33.1% and > 20 ug/L in 21.6%; Tumour stage was T1 in 8.1%; T2 in 63.5% and T3 in 28.4%. Baseline Median serum testosterone was 11.9 nmol/l (min 2.6 and max 26.7). Hormone duration was < 3 mths in 22.3%; 3-6mths in 35.8%; 6 to < 36mths in 19.6% and > 36mths in 22.3%. Cox regression models estimated hazard ratios (HR) and 95% confidence intervals (CI) of overall mortality, while controlling for the following covariates (Age, T stage, Gleason risk category, PSA Category, Baseline Serum Testosterone, ADT duration category and Charlson Comorbidity index). **Results:** Higher anxiety at time of diagnosis had a statistically significant adverse effect on overall survival (table); Higher depression symptoms at baseline did not affect survival but depressive symptoms after completing cancer treatment did affect all-cause mortality in this mature dataset with a median follow up of more than 11 years. **Conclusions:** Higher anxiety and depression symptoms in prostate cancer patients are associated with significantly higher long-term all-cause mortality. Research Sponsor: None.

	Normal HADS SCORE (1-7) Median survival	Abnormal HADS SCORE (>=8) Median survival	Cox Regression Exp(B) with 95.0% CI for Exp(B)
Anxiety subscale (HADS-A): Baseline	15.32 yrs	12.29 yrs	P = 0.006 Exp(B) 2.38; (1.28 - 4.44)
HADS-A : At 3 months	15.32 yrs	13.11 yrs	P = 0.013 Exp(B) 2.10 (1.17, 3.78)
HADS-A : Post therapy	14.81 yrs	13.05 yrs	P = 0.043 Exp(B) 2.25 (1.02, 4.94)
Depression subscale (HADS-D):Baseline	14.81 yrs	12.29 yrs	P = 0.067 Exp(B) 2.41 (0.94 - 6.16)
HADS-D : At 3 months	15.32 yrs	13.20 yrs	P = 0.20 Exp(B) 1.59 (0.77 - 3.26)
HADS-D : Post therapy	15.02 yrs	11.79 yrs	P = 0.007 Exp(B) 3.18 (1.37 - 7.35)

12093

Poster Session

Racial and ethnic disparities in survival among persons with subsequent primary cancer. *First Author: Hyuna Sung, American Cancer Society, Atlanta, GA*

Background: Racial and ethnic disparities in survival after first primary cancer diagnoses have been well documented. Yet comprehensive data for disparities after subsequent primary cancer (SPC) are lacking despite the growing burden of SPCs. **Methods:** This study included 230,370 persons diagnosed with one of the 13 common SPCs at ages ≥ 20 years during 2000-2013 in 18 Surveillance, Epidemiology, and End Results registries. Cause-specific proportional hazards models were used to estimate HR (hazard ratio), overall and stratified by SPC types, comparing the risk of cancer or cardiovascular death in Hispanic, non-Hispanic Asian or Pacific Islander (API), or non-Hispanic Black (Black) persons to that in non-Hispanic White (White) persons. HRs were adjusted for sex, first primary cancer type and stage, age and year of SPC diagnosis (base model); and additionally household income, urbanicity, SPC stage, subtype, and treatment receipt (surgery, radiotherapy, chemotherapy) (final model). **Results:** During 54 months of median follow-up, 109,757 cancer deaths and 18,283 cardiovascular deaths occurred among persons with SPCs. Overall, HRs for cancer death were higher among Black (HR = 1.21, 95% CI = 1.18-1.23) and Hispanic (HR = 1.10, 95% CI = 1.07-1.13) persons compared with White persons, but lower among API persons (HR = 0.93, 95% CI = 0.90-0.96) in the base model. When stratified by SPC types, the increased HRs were evident for 10 of 13 cancers among Black persons with the greatest HR among those with uterine corpus cancer (HR = 1.87, 95% CI = 1.63-2.15) and for 7 of 13 cancers among Hispanic persons with the highest HR among those with melanoma (HR = 1.46, 95% CI = 1.21-1.76). For cardiovascular death, compared with White persons, the overall HR was higher among Black (HR = 1.42, 95% CI = 1.35-1.49) persons but lower among API (HR = 0.75, 95% CI = 0.69-0.81) and Hispanic (HR = 0.90, 95% CI = 0.84-0.96) persons. The risk of cardiovascular death was higher for 11 of 13 cancers among Black persons with the greatest HR among those with pancreatic (HR = 1.80, 95% CI = 1.17-2.75), thyroid (HR = 1.70, 95% CI = 1.12-2.57), and kidney (HR = 1.63, 95% CI = 1.38-1.93) cancers. Additional adjustments in the final model reduced the elevated HRs substantially especially for cancer death among Black or Hispanic persons, although the associations remained statistically significant for most cancers. **Conclusions:** Among persons with SPCs, Black persons had a higher risk of death from both cancer and cardiovascular disease, whereas Hispanic persons had a higher risk of death from cancer. Adjusting for differences in potentially modifiable factors attenuated the associations substantially, highlighting opportunities for interventions toward health equities among cancer survivors. Research Sponsor: None.

12094

Poster Session

Sexual dysfunction in patients with cancer: Results from the CLARIFY project. *First Author: Aylene Vanessa Ospina Serrano, Instituto de Investigación Sanitaria Puerta de Hierro - Segovia de Arana. Hospital Universitario Puerta de Hierro, Majadahonda, Madrid, Spain*

Background: Survivors patients with cancer may suffer long-term consequences related to antineoplastic treatments and tumor itself, leading to deterioration of quality of life and resulting in disturbances including sexual dysfunction (SD). We aimed to identify and characterize SD in a cohort of Spanish patients. **Methods:** Analytical observational study in patients included in the CLARIFY H2020 project at the Hospital Universitario Puerta de Hierro. From October 2020 to May 2022, clinical and demographic variables were collected as well as measures of sexual function using a validated Spanish-language, gender-targeted separately questionnaire. A descriptive domain on frequency of sexual activity during the last four weeks (DFS) and multiple domains assessing phases of sexual response (DESR), according to DSM IV and DSM V parameters including desire, arousal, lubrication, orgasm, satisfaction with sexual performance, global sexual satisfaction, anticipatory anxiety and sexual initiative were evaluated. Descriptive, trend associations and logistic regression analyses were performed. **Results:** 383 patients were included, cancer type distribution was breast cancer 68.14% (261), lung cancer 26.37% (101) and lymphomas 5.50% (21). The average age was 56.5 years (range 33-88). 19.58% (75) of patients were men and 80.42% (308) woman. 69% of men and 31% of women reported they were sexually active. The absolute frequency of Global sexual dissatisfaction (GSD) was 76% in women and 24% in men, according to neoplasia; GSD was 36% in patients with early breast cancer, 14% in men with lymphoma, and 9% in men with lung cancer. Women with metastatic breast cancer presented the highest tendency to have severe disorders of DESR. In multinomial logistic regression, significant associations were found in women with metastatic breast cancer and severe disorders of: arousal (p 0.000), lubrication (p 0.002) orgasm (p 0.000), as well as dissatisfaction with sexual performance (p 0.000) and global sexual dissatisfaction (p 0.000). On the other hand, in women with lung cancer, severe arousal disorder (p 0.016) and global sexual dissatisfaction (p 0.044) were observed. **Table. Conclusions:** In our study, cancer survivors have high prevalence of SD related with oncological treatment and clinical characteristics of malignancy, being women the most affected population. Efforts should be made to support SD during follow-up to improve the quality of life of this growing oncologic population. Research Sponsor: European Commission, H2020 programme.

Breast cancer (BC).

Sexual performance dissatisfaction	
Metastatic breast cancer	p 0.000 OR 5.14 IC 95% (2.19-12.06)
Early breast cancer	p 0.000 OR 2.61 IC 95% (1.37-4.98)
Long-term survivors BC	1 ref.
Global sexual dissatisfaction	
Metastatic breast cancer	p 0.000 OR 4.4 IC 95% (1.94-10.22)
Long-term survivors BC	1 ref.
LUNG CANCER	
Global sexual dissatisfaction	
Women with lung cancer	p 0.044 OR 3.12 IC 95% (1.02-9.51)
Men with lung cancer	1 ref.

12096

Poster Session

Propensity score matched analysis of major adverse cardiac events in patients with localized prostate cancer receiving short term vs long term ADT. *First Author: Ye Yuan, Atropos Health, Palo Alto, CA*

Background: ADT is often used with radiation for dose-intensification in intermediate-risk prostate cancer (PrCa). ADT includes gonadotropin-releasing hormone (GnRH) agonists, often started with antiandrogens to prevent the initial surge in serum testosterone as well as GnRH antagonists. Studies have reported associations of ADT with increased risks of cardiovascular events. This is thought to be related to atherosclerosis, dyslipidemia and insulin resistance. Therefore, there is an opportunity to individualize ADT use to balance risk of PrCa specific outcomes with risk of MACE. To address this, we assessed whether there is a difference in major adverse cardiac events (MACE) between ST-ADT (< 6 months) or LT-ADT (> 6 months) in patients with localized PrCa. **Methods:** A nationally representative EHR-derived dataset was queried for patients with at least 90 days of longitudinal records and 90 days of continuous follow up. The inclusion criteria was a diagnosis of PrCa based on standardized diagnoses codes (ICD9 and ICD10). Patients who had a history of MACE (defined as combination of diagnosis and procedure codes associated with CAD, MI, unstable angina, CABG, PCI, catheterization) metastases, PSA above 10ng/mL, imaging for metastatic PrCa, or having received abiraterone or docetaxel within 3 months of inclusion were excluded. Patients were defined as receiving ADT if they received leuprolide, goserelin, bicalutamide, triptorelin, degarelix, flutamide, or nilutamide. The primary outcome of risk of any new MACE was compared between arms with Cox proportional hazards regression. Secondary outcomes including 10 year rates of new diagnoses of CAD, metastases, and new heart procedures were compared between arms with the Chi-square test. Significance was set at a two sided p-value of 0.05. All analyses were performed without matching, with age and gender matching, and high dimensional propensity-score matching (hdPS) using R version 4.05. **Results:** We identified 1209 patients with local PrCa and no prior MACE or use of abiraterone or docetaxel within 3 months of diagnosis. 385 patients received ST-ADT and 824 received LT-ADT. Baseline characteristics were comparable between the two arms with similar ages, and comorbidity scores. There was no significant difference in metastatic recurrence between arms in hdPS-matched analysis HR 0.95 [0.64-1.38] p = 0.8. There was also no significant difference in the composite endpoint of MACE HR 1.42 [0.86-2.36] p = 0.173. More patients in the LT-ADT arm had new CAD, which was significant after hdPS-matched analysis OR 1.84 [1.07-3.14], p = 0.024. **Conclusions:** In a national dataset analysis of patients with local PrCa and no history of MACE or abiraterone or docetaxel within 3 months of diagnosis LT-ADT was associated with increased odds of CAD but there was no difference in the composite endpoint of MACE or metastatic recurrence. Research Sponsor: None.

12095

Poster Session

Associations among anesthesia-induced brain biomarkers during surgery, preoperative exposure to cancer therapeutics, and clinical outcomes. *First Author: Tom A.D. Stone, Massachusetts General Hospital, Boston, MA*

Background: Cognitive impairment represents a key concern in oncology, as issues with memory and concentration can be a debilitating side effect of cancer and its treatment. Prior work demonstrates that the power of the alpha wave, a pattern of electroencephalographic (EEG) signals in the brain in patients under general anesthesia, correlates with cognitive function. In this study, we sought to investigate the associations among anesthesia-induced alpha power, preoperative exposure to cancer therapeutics, and clinical outcomes in a large cohort of patients undergoing surgery. **Methods:** We analyzed intra-operative EEG recordings of a retrospective cohort of patients with and without cancer who underwent surgery with general anesthesia at a single institution between 4/2016 - 12/2019. We used multivariable regression models (adjusted for age, sex, history of dementia) to determine associations of cancer-related covariates with patients' alpha power (measured in decibels [dB]), and to determine associations of alpha power with clinical outcomes, such as hospital length of stay, discharge location, hospital readmission, and survival. **Results:** Among 1,084 total patients included in this study, 377 (35%) had a preoperative diagnosis of cancer. The most common cancer diagnoses were breast (87, 23% of those with cancer), gastrointestinal (85, 23%), genitourinary (73, 19%), and lung (47, 12%). We found that a cancer diagnosis alone was not associated with alpha power (-0.015 dB, p = 0.95). However, among patients with cancer, receiving chemotherapy within 3 months before surgery was associated with a 1.6dB drop in alpha power (p < 0.001). By comparison, having a preoperative diagnosis of dementia was associated with a drop of 2.86dB (p < 0.001). Decreased alpha power was associated with longer hospital stays (1.03 times longer per dB drop, p < 0.001), higher rates of discharge to a rehab facility (odds ratio [OR] = 1.22 per dB drop, p < 0.001), and higher mortality (hazard ratio = 1.085 per dB drop, p < 0.001). We found no association between alpha power and 30-day readmission (OR = 1.04, p = 0.24). **Conclusions:** In this large cohort of patients undergoing surgery, we found that alpha power correlated with several important clinical outcomes, and that recent receipt of chemotherapy was associated with a decrease in alpha power. Of note, the observed drop of 1.6 dB among those with recent chemotherapy is roughly equivalent to aging 10-15 years, while a diagnosis of dementia was associated with a nearly 3dB drop in alpha power. As evidence suggests that alpha power corresponds with patients' cognitive function, our findings highlight the need to prospectively monitor and track longitudinal alpha power in patients receiving cancer treatment to determine if early detection of changes in alpha power may predict for future treatment-related cognitive decline. Research Sponsor: U.S. National Institutes of Health.

12097

Poster Session

Associations of employment disruptions and financial hardship among individuals diagnosed with cancer in the US. *First Author: Michael T. Halpern, National Cancer Institute, Bethesda, MD*

Background: Financial hardship is experienced by approximately half of working-age individuals diagnosed with cancer. Many working individuals diagnosed with cancer also experience disruptions with their employment. This study examines whether employment disruptions are associated with financial hardship among individuals diagnosed with cancer in the US. **Methods:** We utilized data from the 2016/2017 Medical Expenditure Panel Survey (MEPS) Experiences with Cancer self-administered questionnaires and identified individuals diagnosed with cancer at age >18 who worked for pay at the time of or following their cancer diagnosis. Employment disruption was defined as taking extended paid time off work; switching to a part time or less demanding job or to a flexible work schedule; and/or retiring early due to cancer, cancer treatment, or late effects. Financial hardship was defined in 3 domains: material (borrowing money, financial sacrifices, or being unable to cover medical costs); psychological (worrying about medical bills, financial stability, keeping job/income, or future earnings); and behavioral (delaying/forgoing medical care because of cost). Multivariable logistic regression analyses adjusting for the MEPS survey design were used to determine associations of employment disruption due to cancer with any financial hardship and with financial hardship intensity while controlling for patient demographic, health insurance, and clinical characteristics. **Results:** Among 732 individuals with a cancer history, 47.4% experienced employment disruptions and 55.9% experienced any financial hardship. Financial hardship was significantly more common among cancer survivors with employment disruptions than without disruptions (68.7% vs. 44.5%; p-value of difference < 0.0001). Findings were consistent across multiple hardship measures/domains and across years since last cancer treatment. In multivariable logistic regression analyses, cancer survivors with employment disruptions were significantly more likely to have greater (OR = 2.8; 95% CI 2.0, 3.9) financial hardship intensity. Individuals of race/ethnicity other than non-Hispanic White; who had Medicare (vs. private) insurance and were age < 65 years old at diagnosis; or had breast, colon, or prostate cancer (vs. melanoma reference group) were also more likely to experience financial hardship. Older individuals and those who were married were less likely to experience financial hardship. **Conclusions:** Employment disruptions are common and significantly associated with multiple types of financial hardship among cancer survivors. Employer workplace accommodation and other policies to minimize disruptions among individuals diagnosed with cancer may reduce financial hardship in this vulnerable population. Research Sponsor: None.

LBA12098

Poster Session

Dexamethasone and exercise for cancer-related fatigue: A phase III randomized controlled trial. *First Author: Vanita Noronha, Tata Memorial Centre, Mumbai, India*

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2023, issue of the *Journal of Clinical Oncology*.

12099

Poster Session

Patient-reported symptom monitoring linked to an alert algorithm: Effects on progression-free and overall survival in the SYMPRO-Lung trial. *First Author: Nicole Erica Billings, Amsterdam UMC, Amsterdam, Netherlands*

Background: Physician-initiated (active) monitoring of patient-reported outcomes (PROs) improves health-related quality of life (HRQOL) and overall survival (OS) in comparison to care as usual. We recently reported data from the SYMPRO-Lung trial showing for the first time that patient-initiated (reactive) PRO monitoring is equally effective as physician-initiated (active) monitoring in improving HRQOL. Here we investigate whether online PRO symptom monitoring via the active and reactive approach is also associated with improvements in 1-year progression-free survival (PFS) and OS compared to care as usual in lung cancer patients. **Methods:** SYMPRO-Lung is a Dutch multicenter randomized trial using a stepped wedge design. Inclusion criteria were (non-)small cell lung cancer stage I-IV, starting treatment. Patients in the intervention groups reported PRO symptoms weekly up to 1 year follow-up using the PRO-CTCAE lung cancer subset. If symptoms exceeded a pre-determined threshold, an alert was sent to a physician/nurse (active intervention group) or to the patient themselves (reactive intervention group). Survival was defined as time from start of treatment until progression (PFS), death (OS) or loss to follow-up. Follow-up time of all groups was calculated using the reverse Kaplan-Meier method. Cox proportional hazard analyses were performed to estimate the effect of PRO symptom monitoring on PFS and OS, adjusting for potential confounding (i.e. clinical characteristics and baseline EORTC QLQ-C30 domain scores). **Results:** 515 patients were included in the study (266 control, 249 intervention). The most pronounced uneven distribution in baseline characteristics was that the active intervention group had significantly more stage IV patients compared to the control group and the reactive intervention group (63% vs. 44% vs. 44%, $p=0.001$). The median follow-up duration was 12 months for all groups. Age, sex, cancer staging, ECOG performance status and some baseline EORTC domain scores affected the association and were included as covariates in the analyses. Although not significant, we observed a tendency towards a PFS benefit for the active intervention group compared to care as usual (HR .78, 95%CI: .58 – 1.04) and an OS benefit for both of the intervention groups compared to care as usual (active: HR .80, 95% CI: .55 – 1.15; reactive: HR .69, 95% CI: .42 – 1.15). **Conclusions:** Although not significant, weekly PRO symptom monitoring linked to an alert algorithm showed a tendency towards a small 1-year survival benefit in lung cancer patients. Since we did not power the trial to demonstrate a survival benefit, the non-significant association might be due to a limited sample size. However, the positive results of symptom monitoring in improving HRQOL within our trial still provide sufficient evidence for implementation of PROMs in standard (lung) cancer care. Clinical trial information: NL7897. Research Sponsor: Roche; Zorg Innovatiefonds and Stichting Kwaliteitsgelden Medisch Specialisten.

12100

Poster Session

Patient- versus clinician-reported symptoms in the POLARIX study. *First Author: Carrie A. Thompson, Mayo Clinic College of Medicine, Rochester, MN*

Background: The safety profiles of novel agents are mainly based on clinician-reported adverse events (AEs) from clinical trials. Patient-reported outcomes (PROs) may better represent the treatment burden experienced by patients (pts) compared with clinician-reported AEs. Using data from POLARIX, a double-blind, placebo-controlled, randomized Phase 3 international study (NCT03274492), we previously presented PRO and clinician-reported data showing similar rates of neuropathy (Trnėný et al. 2022). Here, we evaluate the reporting of other common symptoms using PRO and clinician-reported data in POLARIX. **Methods:** POLARIX methods were previously described (Tilly et al. 2022); this analysis included all pts with PRO data. PRO and clinician-reported data described the incidence and severity of fatigue, constipation, diarrhea, nausea, and vomiting. Clinician-reported severity grading was based on the NCI Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.0. PROs were collected using the European Organisation Research and Treatment of Cancer Quality of Life-Core 30 questionnaire (EORTC QLQ-C30), which was administered to pts at clinic visits on Day 1 of Cycles 1 (baseline), 2, 3, and 5, and end of treatment (EOT). PRO severity scores included 'A little', 'Quite a bit', and 'Very much'. **Results:** Overall, 825 pts were evaluable. From baseline to EOT, PROs showed a higher incidence of symptoms compared with clinicians for fatigue (98% vs 27%), constipation (68% vs 29%), diarrhea (56% vs 26%), nausea (58% vs 40%), and vomiting (24% vs 15%). PRO severity scores of 'Quite a bit' or 'Very much' were reported in 33% of pts for fatigue, 29% for constipation, 17% for diarrhea, 19% for nausea, and 7% for vomiting. Clinicians reported Grade ≥ 2 symptoms in 11% of pts for fatigue, 11% for constipation, 11% for diarrhea, 14% for nausea, and 6% for vomiting. **Conclusions:** In POLARIX, pts reported a higher incidence and severity of symptoms compared with clinicians. Although distinct scales were used, the differences in symptom rates reported by pts and clinicians were clinically meaningful. These data may have implications for symptom management, including physician evaluation and communication of symptom expectations for pts. Reporting of symptoms by PROs should be incorporated into clinical trials as an adjunct to standard AE reporting to better characterize the patient experience. Clinical trial information: NCT03274492. Research Sponsor: The POLARIX study (NCT03274492) was sponsored by F. Hoffmann-La Roche Ltd and Genentech, Inc. Third-party editorial assistance was provided by Leen Al-Mohammad, BSc, of Ashfield MedComms, an Inizio company, and was funded by F. Hoffmann-La Roche Ltd.

Symptom,* n (%)	Clinician-reported severity, Grade ≥ 2	Patient-reported severity, 'A little'	Patient-reported severity, 'Quite a bit'	Patient-reported severity, 'Very much'
Fatigue	88 (10.7)	532 (64.6)	245 (29.7)	28 (3.4)
Constipation	93 (11.3)	330 (40.2)	143 (17.4)	91 (11.1)
Diarrhea	87 (10.5)	316 (38.4)	90 (10.9)	52 (6.3)
Nausea	119 (14.4)	317 (38.5)	112 (13.6)	46 (5.6)
Vomiting	46 (5.6)	143 (17.4)	33 (4.0)	25 (3.0)

PRO-evaluable population: n=825. *From baseline to EOT; [†]Based on NCI-CTCAE v4.0; [‡]Based on EORTC QLQ-C30.

12101

Poster Session

Acupuncture versus massage for pain in patients living with advanced cancer: The IMPACT randomized clinical trial. *First Author: Jun J. Mao, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Pain represents a challenging symptom for patients living with advanced cancer and is often associated with fatigue and insomnia. While American Society for Clinical Oncology clinical guidelines recommend acupuncture and massage for oncological pain management, the long-term comparative effectiveness between these two therapies is unknown, particularly among those living with advanced cancer. **Methods:** We conducted a pragmatic randomized clinical trial to compare acupuncture and massage for musculoskeletal pain among patients living with advanced cancer who experienced at least moderate pain and had a life expectancy of at least six months. Patients received weekly acupuncture or massage treatments for ten weeks, followed by monthly booster sessions up to 26 weeks. The primary endpoint was the change in worst pain intensity score measured by the Brief Pain Inventory (BPI) from baseline to 26 weeks. The secondary outcomes included pain-related interference (BPI), pain medication usage, patient-reported fatigue, insomnia, and quality of life. Analyses were performed using linear mixed models adhering to intent to treat. **Results:** Among 298 participants (mean age [SD] 58.7 [14.1] years, baseline worst pain 6.6 [1.5], 67.1% women, 25.9% non-white, 15.4% Hispanic, cancer types [21.5% hematologic, 19.8% breast, 14.4% gynecological, and 11.7% gastrointestinal, 9.7% lung, and 9.7% prostate]), 242 (81.2%) completed the primary endpoint. From baseline to week 26, acupuncture reduced worst pain by 2.53 points (95% CI 2.15-2.92) while massage reduced worst pain by 3.01 points (95% CI 2.63-3.38); the between-group difference was not significant (0.48, 95% CI -0.03-0.98, $p=0.066$). Both treatments reduced pain-related interference and pain medication usage and improved comorbid fatigue, insomnia, and quality of life to a similar degree without between-group differences. Adverse events were mild: bruising was reported by 9 (6.5%) acupuncture patients, and transient soreness was reported by 21 (15.1%) massage patients and 8 (5.8%) acupuncture patients. Despite receiving close in-person treatment, no known COVID-19 transmission was reported between patients and providers. **Conclusions:** Among patients living with advanced cancer, acupuncture and massage produced similar clinically meaningful improvements in pain and comorbid fatigue and insomnia, decreased use of pain medications, and improved quality of life. Integrating these non-pharmacological therapies into comprehensive cancer care can improve symptom management and quality of life for the ever-growing number of patients living with advanced cancer as a chronic illness. Clinical trial information: NCT04095234. Research Sponsor: Patient-Centered Outcomes Research Institute (PCORI); U.S. National Institutes of Health.

12102

Poster Session

12103

Poster Session

Early palliative care for patients with metastatic upper gastrointestinal cancers: A survival analysis of the EPIC randomized trial. *First Author: Antoine Adenis, Institut du Cancer de Montpellier, Montpellier, France*

Background: In 2010, Temel et al. reported that early palliative care (PC) (EPC) led to significant improvements in quality of life and, surprisingly, on overall survival (OS) over standard oncologic care (SOC) for patients (pts) with metastatic lung cancer. The American Society of Clinical Oncology then recommended “combined standard oncologic care and PC earlier in the course of the illness for any patient with metastatic cancer”. The median OS of unselected pts with metastatic upper gastrointestinal cancers (mUGIC) does not exceed 11 m. Whether EPC benefits also apply to pts with mUGIC was unknown. **Methods:** EPIC (NCT02853474) is a randomized 1:1, open-label, multicenter, phase 3 trial aiming to evaluate the OS benefit of EPC compared to SOC in pts with mUGIC (esophageal, HER2 negative esogastric junctional and gastric, pancreatic, and biliary tract cancers), with ECOG PS ≤ 2 , to be treated by first-line chemotherapy (CT). EPC included 5 PC visits scheduled every month, starting within 3 weeks of randomization. Pts allocated to SOC could access to PC visits upon request in case of worsening of health status. The primary endpoint was OS. Other endpoints included quality of life, and depression and anxiety assessment. A total of 381 deaths was required (1 year OS 40% vs. 50.3%, HR = 0.75, 2-sided alpha 5%, 80% power). Randomization was balanced on center, ECOG-PS and tumor site. **Results:** 473 pts were randomized from 10/2016 to 12/2021 in 19 French centers. Modified intention-to-treat population was 470. Median age = 67.5 (range, 24-90); 273 males; tumor site: esophagus 39, esogastric 48, pancreas 297, biliary tract 86; ECOG PS 0/1/2: 104/278/88. 74/233 pts (32%) in EPC arm had less than the planned EPC visits (major deviation): 3 related to treatment, 17 due to pt decision, 45 due to the clinical team decision, 2 other reasons, 7 unknown. 57/237 pts in the SOC arm got at least 1 PC visit, including 3 major deviation (performed < 6 months of treatment and set for a reason other than worsening of the health condition). Median follow-up was 46 m, and 35/470 pts were still alive. We did not observe any OS difference between arms (EPC, median OS: 7.0 m [95%CI: 6.1-8.8 m] and 1-year OS: 33%; SOC, median OS: 8.6 m [6.8-9.8 m] and 1-year OS: 32%; stratified HR = 1.04 [0.86-1.26], p = 0.68). Results were similar on the per-protocol dataset (excluding major violations). Results were homogeneous across the different tumor locations, and ECOG-PS groups. **Conclusions:** OS was lower than expected in both arms, which may reflect the difference between pharma-sponsored and academic trials with less stringent exclusion criteria. Also, only 68% of the pts got the planned number of PC visits in the experimental arm. EPC was not found to prolong OS over SOC in pts with mUGIC in this EPIC trial. Clinical trial information: NCT02853474. Research Sponsor: Ligue contre le cancer, France; National Cancer Institute, France; Région Nord-Pas de Calais, France.

12104

Poster Session

A risk prediction model for cisplatin-induced acute kidney injury in patients with head and neck cancer who receive chemoradiotherapy: A supplement analysis of a phase II/III trial of JCOG1008. *First Author: Yoshinori Imamura, Kobe University Hospital, Kobe, Hyogo, Japan*

Background: Cisplatin-induced acute kidney injury (C-AKI) is a common reason for treatment interruption in head and neck cancer patients who receive chemoradiotherapy (CRT). We developed a risk prediction model for C-AKI in patients from a randomized phase II/III trial of JCOG1008, which demonstrated that CRT with weekly cisplatin at 40 mg/m² (weekly arm) was noninferior to 3-weekly cisplatin at 100 mg/m² (3-weekly arm) in terms of overall survival for postoperative high-risk head and neck cancer (*J Clin Oncol* 2022; 40: 1980-90). **Methods:** Two hundred fifty-one patients received RT with a total of 66 Gy/33 fr concurrently with 3-weekly or weekly cisplatin. AKI was defined using the AKI Network classification/staging system as an increase in serum creatinine of ≥ 0.3 mg/dL or a 1.5-fold or greater increase from baseline ($\geq$ stage I) by 30 days after the completion of CRT. AKI risk prediction models were developed by combining explanatory variables which were expected to contribute, including age, sex, ECOG performance status, primary site, pathological stage, diabetes mellitus, hypertension, main nutritional method, treatment arm, serum albumin, serum magnesium, and creatinine clearance (CCr) at registration. A logistic regression model with the Akaike information criterion was used to explore the optimal model. **Results:** Ninety-four of 251 (37.5%) patients developed C-AKI in this study. The optimal C-AKI risk prediction model was composed of four factors, including a primary site (hypopharynx/larynx or oral cavity/oropharynx, odds ratio [OR] 1.92 [95% CI, 1.10 to 3.30]), treatment arm (3-weekly arm or weekly arm, OR 1.75 [95% CI, 1.02 to 3.00]), serum albumin (≤ 3.5 g/dL or > 3.5 g/dL, OR 2.06 [95% CI, 1.11 to 3.87]) and CCr (< 90 mL/min or ≥ 90 mL/min, OR 1.85 [95% CI, 1.05 to 3.26]). The incidence of C-AKI increased in accordance with a total count of the four factors (Table): with a total count of 0-1, 2 and 3-4, the incidence of clinically relevant stage II/III C-AKI was 2.9%, 11.5%, and 22.6%, respectively. When total count was ≤ 1 , the positive and negative predictive values for stage II/III C-AKI development were 16.1% and 97.0%, respectively. **Conclusions:** We developed a risk prediction model for C-AKI in head and neck cancer patients who receive CRT using primary site, cisplatin administration method, serum albumin, and CCr. The high negative predictive value of this prediction model may help rule out the development of moderate to severe C-AKI. Clinical trial information: JRCTs031180135. Research Sponsor: National Cancer Center Research and Development Funds (29-A-3, 25-B-2, and 2020-J-3); AMED under Grant Nos. JP16ck0106055, JP16ck0106093, and JP19ck0106321; and a Grant-in-Aid for Clinical Cancer Research (H23-009 and H26-052) from the Ministry of Health, Labor and Welfare of Japan.

Frequency of cisplatin-associated acute kidney injury across proposed factors.				
Acute Kidney Injury Network-defined AKI stage		A total count of the four factors		
0-1 (n = 102)		2 (n = 87)	3-4 (n = 62)	
I	16 (15.7%)		30 (34.5%)	21 (33.9%)
II	1 (1.0%)		5 (5.7%)	6 (9.7%)
III	2 (2.0%)	5 (5.7%)	5 (5.7%)	8 (12.9%)
Total	19 (18.6%)	40 (46.0%)	40 (46.0%)	35 (56.5%)

Prospective evaluation of factors associated with acceptance of feeding tube (FT) placement and clinical outcomes during radiation therapy (RT) or radiochemotherapy (RTCT) for head and neck squamous cell carcinoma (HNSCC). *First Author: Florian Clatot, Department of Medical Oncology, Centre Henri Becquerel, Rouen, France*

Background: RT/RTCT during HNSCC treatment is associated with a high rate of severe dysphagia requiring the use of a FT. Randomized trials have failed to show a benefit of a prophylactic enteral nutrition in case of RTCT. Even when indicated, numerous patients refuse the placement of a FT. We assessed the factors associated with FT acceptance and outcomes between patients that had a FT, or not. **Methods:** The monocentric NutriNeck study (NCT02900963) recruited all HNSCC patients between 2014 and 2018 treated by RT/RTCT for curative intent. Patients fed by enteral nutrition before RT initiation were excluded. A daily monitoring of the weight and a weekly clinical evaluation during RT/RTCT were performed, as well as a quality-of-life (QoL) assessment using QLQ-C30 and HN 35 at baseline, 3 and 9 months after the end of treatment. A nutritional intervention by FT was systematically proposed in case of 2 kg weight loss under treatment or severe dysphagia. Patients were considered into 3 groups: FT indication and acceptance, FT indication but refusal, no FT indication. A p value < 0.05 was considered significant. **Results:** Among the 250 HNSCC patients included, 119 (48%) were treated by RT and 131 (52%) by RTCT. Overall, 114 patients (46%) accepted FT, 48 (19%) refused an indicated FT and 88 (35%) had no FT indication. In multivariable analysis, the only factor associated with an indication of a FT tube was having a RTCT vs a RT (p < 0.0001). Among the 162 patients (65%) with FT indication, in multivariate analysis factors associated with FT placement acceptance were having a RTCT (p = 0.01), being treated by exclusive RT+/-CT instead of adjuvant RT/CT (p = 0.05), having a tumor of the oral cavity (p = 0.02), having at baseline a decreased role functioning score (p = 0.04). When using linear mixed models for QoL analyses, over time role functioning, social functioning and pain were the only categories significantly different between patients that accepted FT and patients that refused or had no FT indication. At the end of treatment, median weight loss was significantly more important among patients with FT indication, compared to patients without FT indication (-4% vs -1%, respectively, p < 0.0001). This difference remained significant 3 and 9 months after the end of treatment. Among patients with FT indication, there was no difference in case of FT placement acceptance or refusal regarding grade 3 toxicities during treatment or weight loss at the end of treatment, after 3 and 9 months of follow-up. **Conclusions:** One third of the patients with an indicated FT have refused the FT placement, and did as well as those that accepted. Using baseline QoL items such as decreased role or social functioning, or increased pain may help identifying a subgroup of patients for which an earlier FT placement should be considered. Research Sponsor: Academic support by Centre Henri Becquerel.

12105

Poster Session

Out-of-pocket costs burden for cancer treatment toxicities and symptoms management in Italy: A prospective, multicenter pilot study. *First Author: Giusti Raffaele, Medical Oncology, St. Andrea Hospital, Rome, Rome, Italy*

Background: Financial Toxicity (FT) refers to the financial burden and stress experienced by cancer patients as a result of the high costs associated with their treatment and care. This burden can significantly impact patients and families, affecting not only their financial well-being but also their physical and mental health. With the increasing cost of cancer care, FT has become a primary concern for those affected by the disease. Although there have been plenty of studies on the cost of cancer drugs and policy issues relating to curbing these increasing costs, studies on addressing FT in individual patients for drug-related toxicity and symptom management are still lacking. **Methods:** From January to October 2022, we conducted a cross-sectional, descriptive study to identify patient-administered drugs used to manage cancer treatment toxicities or cancer-associated symptoms. We recognize six common symptoms (anorexia/cachexia, fatigue, nausea and vomiting, pain, constipation, and diarrhea). All social and demographic data, including information on gender, age, performance status, education, and income, have been gathered and recorded. We collected information about the type of cancer disease and active treatment (on/off). Symptom assessment and financial distress were analyzed by administering the PERSONS and COST questionnaires, respectively, at the time of enrollment. **Results:** A total of 211 patients were enrolled and completed the questionnaires. 28/211 patients (13%) do not take any medications to control symptoms. Of the remaining 183 taking at least one prescription for managing these symptoms, 90% (165) pay for at least part of these drugs. Most frequently, patients assumed medicines for controlling pain (45%) and constipation (28%). Unlike all the other drug categories, these medicines correlate with financial distress (p > 0.0001 and p > 0.001). None of the following variables (age, type of tumor, and work situation) significantly interacted with COST and PERSONS at the univariate analyses. In contrast, a lower level of education significantly associates with the worst COST and PERSONS scores (p > 0.0001). As expected, patients in palliative home care have a higher mean score for symptom burden than those without home care and, surprisingly, a higher financial distress score. **Conclusions:** Our results identify cancer pain and constipation as the most incident and challenging problems associated with cancer diagnosis and treatment. Moreover, they ultimately lead to a higher financial hardship due to patient self-prescribing and out-of-pocket purchases of over-the-counter drugs to control them. In our population, a lower education level is an independent risk factor for developing financial distress. Research Sponsor: None.

12106

Poster Session

Quality of pain management in patients with cancer in the outpatient setting.

First Author: Biplov Adhikari, MedStar Union Memorial Hospital, Baltimore, MD

Background: Pain represents a common health issue among patients with cancer. Uncontrolled pain significantly impairs the quality of life, resulting in increased healthcare utilization and costs. We examined the patterns of pain medication prescriptions among patients with cancer pain in the outpatient setting. **Methods:** We used the National Ambulatory Medical Care Survey (NAMCS), an annually administered survey designed to collect data regarding the use of ambulatory medical services from office-based physicians in the United States. We analyzed NAMCS data from 2005 to 2019 for all types of cancer visits. The primary outcome was prescription of pain medications among patients with cancer pain. We performed multivariate logistic regression to identify factors associated with opioid and non-opioid prescription among patients with cancer pain. **Results:** We captured a total of 520.8 million outpatient visits from 2005-2019. Breast cancer (18.7%) followed by cancer of the male genital tract (11.0%) represented the highest proportion of patient visits. 4.8% of cancer patients reported pain. Majority (60%) complaining of pain did not receive any pain medications. 14.9% received opioids and 25.1% received nonsteroidal anti-inflammatory drugs, acetaminophen, or adjuvant pain medications. The odds of receiving opioids were 3.4 times higher among 45-65 years vs patients over 75 years. African-Americans had 84% higher odds of receiving opioid prescription compared to white patients. The odds of receiving opioids were 61% lower for privately insured vs patients on Medicare. Patients visiting oncologic care had 2.1 times higher odds of receiving opioids compared to primary care (Table). **Conclusions:** This is one of the largest drug utilization studies among patients with cancer in outpatient setting, covering half a billion patient visits. A significant proportion of outpatients with cancer who reported pain did not receive a prescription for analgesics suggesting a possibility of undertreatment of pain. Within the limitation of this dataset, undertreatment of pain in outpatients with cancer remains a major unmet patient need. Research Sponsor: None.

Factors associated with pain medication prescription among cancer patients with pain in settings.

Covariates	Opioid Odds Ratio (95% CI)	p-value	Non-opioid Odds Ratio (95% CI)	p-value
Age (vs 75+)				
45-64 years	3.43 (1.82, 6.45)	0.0007	1.89 (1.16, 3.08)	0.0035
65-74 years	1.58 (0.94, 2.68)	0.3796	1.32 (0.90, 1.95)	0.5603
Female (vs Male)	1.15 (0.77, 1.74)	0.4947	0.71 (0.50, 1.00)	0.0528
Race (vs White)Black				
	1.84 (1.027, 3.31)	0.0058	0.89 (0.50, 1.58)	0.3305
Payer (vs Medicare)Private insurance				
	0.39 (0.23, 0.68)	0.0002	0.85 (0.56, 1.30)	0.1465
Medicaid	1.45 (0.66, 3.19)	0.0228	1.12 (0.50, 2.49)	0.8636
Specialty (vs Primary care)Oncology				
	2.12 (1.08, 4.16)	<.0001	0.68 (0.36, 1.25)	0.4053
Surgical care	0.12 (0.06, 0.22)	<.0001	0.57 (0.37, 0.88)	<.0001

12108

Poster Session

Efficacy of paxman scalp cooling system at lower temperatures for prevention of anthracycline associated chemotherapy induced alopecia.

First Author: Shari Beth Goldfarb, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Chemotherapy induced alopecia (CIA) significantly impairs QoL. Scalp cooling devices typically used at -5°C decrease CIA. However, there is still room to improve efficacy with anthracycline therapy. This prospective study was performed to evaluate the safety, tolerability, and efficacy of the Paxman Scalp Cooling System (PSCS) when used at cooler temperatures of -7.5°C and -10°C. **Methods:** Patients with stage I-III breast cancer receiving anthracycline chemotherapy at Memorial Sloan Kettering Cancer Center from 12/23/2019 – 10/12/2022 were enrolled on this IRB-approved study. They were evaluated for hair loss at baseline, weeks 4, 8 (primary endpoint), end of treatment, and 24 weeks post treatment using clinical photography and trichoscopy, which measures hair width and count. Degree of hair loss was graded using the Common Terminology Criteria for Adverse Events (CTCAE) v4. Successful hair preservation is indicated by alopecia grades 0 and 1. **Results:** 34 patients (mean age 44) used the PSCS at cooler temperatures with no DLTs. 7 patients received scalp cooling at -7.5°C and 27 patients at -10°C. 19 women (55.9%) were included in the final analysis; 7 patients withdrew or were taken off study prior to the primary endpoint and 8 patients did not successfully complete photographic or trichoscopic follow-up assessments. At the baseline visit, 95% of patients had grade 0 alopecia (n = 18) and 5.3% had grade 1 alopecia (n = 1). At week 8 (primary endpoint) 53% of patients had grade 1 alopecia and 47% had grade 2 alopecia. At completion of therapy, 7% of patients had grade 0 alopecia, 36% had grade 1 alopecia, 7% are pending and 50% had grade 2 alopecia. At 24 weeks post treatment completion, 23% of patients had grade 0 alopecia (n = 3), 31% had grade 1 alopecia (n = 4), and 46% of patients are pending results (n = 6). At baseline, the average hair count was 149.0 per cm² (n = 19) and the average hair width was 68.9µm (n = 19). At week 4 and 8, there was a -27% and -8.9% change in hair count and -8.6% and -9.3 percent change in hair width (n = 18) respectively. By end of treatment, percent change was -37.8 and -11.6 for hair count and hair width, respectively (n = 14). At 24 weeks post treatment completion, both the average hair count and hair width for patients were higher compared to their baseline (hair count = 242 per cm² and hair width = 70.7µm (n = 13; 6 patients pending). **Conclusions:** Overall, use of the PSCS for successful hair preservation is effective, safe, and tolerable at lower temperatures for patients being treated with anthracycline chemotherapy. 43% of patients had hair preservation at the completion of the study. At 24 weeks post treatment, the average hair count and width was higher than the values at baseline indicating thicker, full hair regrowth. None of the patients displayed grade 2 alopecia at 24 weeks post treatment, allowing patients to avoid the use of a wig to hide resulting CIA. Clinical trial information: NCT04180579. Research Sponsor: Paxman Coolers LTD.

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Poster Session

The efficacy of hydrocolloid dressing as a prophylactic use for hand-foot skin reaction induced by multitargeted kinase inhibitors: A phase 3 randomized self-controlled study, J-SUPPORT 1701 APRON trial.

First Author: Atsuo Takashima, Gastrointestinal Medical Oncology Division, National Cancer Center Hospital, Tokyo, Japan

Background: Hand-foot skin reaction (HFS) is a well-known adverse event that affects the quality of life in patients (pts) who receive multitargeted kinase inhibitors (TKIs). To prevent HFS, prophylactic depressurization is considered to be one of the important strategies. However, the evidence of depressurization as a prophylactic use for HFS is limited. Therefore, we conducted a phase 3 trial to evaluate the efficacy of depressurization using hydrocolloid dressing, which was usually used for wounds such as decubitus ulcers. **Methods:** This is a phase 3 randomized self-controlled study to evaluate the efficacy of hydrocolloid dressing by comparing whether or not to add hydrocolloid dressing to prophylactic moisturizing for HFS. The eligible pts were to have unresectable colorectal cancer (CRC), gastrointestinal tumor (GIST), or hepatocellular carcinoma (HCC) and planned to receive either regorafenib or sorafenib. From the start of regorafenib or sorafenib, standard supportive care with moisturizing care alone was performed on one sole of the foot. Moisturizing care plus hydrocolloid dressing was applied to the other side soles of the foot. The primary endpoint was an incidence of grade 2 or more severe HFS (soles of the feet only) assessed by NCI CTCAE v.4.0. Grading of HFS was done according to pre-determined criteria, which consists of blinded central review of photographs of the foot, pain intensity (numerical rating scale) and interference score assessed by pts. The ethical approval was obtained from National Cancer Center Hospital. This study was registered with UMIN Clinical Trial Registry (UMIN000034853). **Results:** Between Jan 2019 and May 2021, 50 pts were enrolled. The median age was 62.5 years old, and cancer types were CRC in 78%, GIST in 12%, and HCC in 10% of the patients. 48 pts received regorafenib, and 2 pts received sorafenib. The table shows the summary of HFS in each arm. The primary endpoint of the incidence of grade 2 or more severe HFS was significantly lower in the hydrocolloid dressing arm than in the control arm (20% vs. 50%, p < 0.0001). Time to grade 2 or more severe HFS was significantly longer in the hydrocolloid dressing arm (hazard ratio 0.32, p = 0.0017). The incidence of moderate, severe, or very severe in patient-reported HFS using PRO-CTCAE was also lower in the hydrocolloid dressing arm (10% vs. 32%, p = 0.0002). **Conclusions:** Our study showed the efficacy of the prophylactic use of hydrocolloid dressing for HFS induced by multitargeted kinase inhibitors. Prophylactic moisturizing plus depressurization is the standard of care for this population. Multidisciplinary care plays an important role in the success of treatment with TKIs. Clinical trial information: UMIN000034853. Research Sponsor: Kimura foundation for nursing education.

HFS	Hydrocolloid dressing (n = 50)	Standard supportive care (n = 50)	
Grade1	29 (58%)	8 (16%)	
Grade2	10 (20%)	21 (42%)	
Grade3	0 (0%)	4 (8%)	
≥ Grade2	10 (20%)	25 (50%)	P < 0.0001

12109

Poster Session

Patient-reported hope, prognostic understanding, quality of life, symptom burden, coping mechanisms, and financial wellbeing in early phase clinical trial participants.

First Author: Debra Lundquist, Massachusetts General Hospital, Boston, MA

Background: Early phase clinical trials (EP-CTs) investigate novel treatment options in oncology, with recent advances in personalized therapy leading to improved outcomes and offering hope to patients with cancer. However, little research has sought to understand hope in EP-CT participants, thus we sought to study associations of patient-reported hope with prognostic understanding, quality of life (QOL), symptom burden, coping mechanisms, and financial wellbeing in EP-CT participants. **Methods:** We prospectively enrolled consecutive adults with cancer participating in EP-CTs at Massachusetts General Hospital from 04/2021-01/2023. Participants completed baseline surveys prior to treatment initiation that assessed hope (Herth Hope Index [HHI]), higher scores indicate greater hope), prognostic awareness (Prognosis and Treatment Perceptions Questionnaire [PTPQ]), QOL (Functional Assessment of Cancer Therapy-General), symptom burden (physical: Edmonton Symptom Assessment System [ESAS]; psychological: Patient Health Questionnaire-4 [PHQ4]), coping mechanisms (Brief COPE), and financial wellbeing (Comprehensive Score for Financial Toxicity [COST]). We used descriptive statistics and regression models to explore associations of hope with patient characteristics as well as patient-reported prognostic awareness, QOL, symptom burden, coping, and financial wellbeing. **Results:** Of 221 eligible patients, we enrolled 204 (enrollment rate 92.3%, median age = 63.4 years [range 54.8-70.5]; 56.9% female, and 94.0% metastatic cancer). Most common cancer types were gastrointestinal (34.8%), breast (19.6%), and head and neck (10.3%). Patients had a mean HHI score of 27.2 (range 12.0-36.0), with 27.1% reporting their cancer is curable (mean hope scores were higher for those reporting curable vs incurable on the PTPQ: 28.8 vs 26.7, p = 0.016). Higher hope scores were associated with better QOL (B = 0.21, p < 0.001), lower symptom burden (ESAS-physical: B = -0.10, p < 0.001; PHQ4-depression: B = -2.10 p = < 0.001; PHQ4-anxiety: B = -0.99, p < 0.001), more adaptive coping strategies (self-blame [B = -1.34, p < 0.001]; acceptance [B = 1.30, p < 0.001], denial [B = -1.31, p < 0.001], support [B = 1.03, p < 0.001], active [B = 0.97, p < 0.001], disengage [B = -2.69, p < 0.001], religion [B = 0.63, p < 0.001]), and greater financial wellbeing (B = 0.10, p = 0.013). **Conclusions:** In this prospective cohort study, we found novel associations of higher hope scores with prognostic understanding, better QOL, lower symptom burden, more adaptive coping mechanisms, and greater financial wellbeing. Future studies should measure patient-reported hope and explore its role as a potential moderator of other outcomes in EP-CT participants. Research Sponsor: MGH Connell Nursing Research Scholar Grant.

12110

Poster Session

12111

Poster Session

Self-reported overall wellbeing and physical function among chemotherapy and surgery patients completing symptom questionnaires across six health systems. *First Author: Michael J. Hassett, Dana-Farber Cancer Institute, Boston, MA*

Background: Health systems have begun using electronic patient reported outcomes (ePROs) to evaluate and ideally mitigate patients' symptom burden following treatment for cancer and other conditions. However, the optimal number of symptoms and approach to capturing this information is unknown. We hypothesized that self-reported overall wellbeing (OWB) and physical function (PFN) would provide distinctive information, beyond that described by a multi-item symptom questionnaire, and augment the clinical utility of an ePRO system. **Methods:** eSyM, an EHR-integrated symptom management program, was deployed across six health systems for patients receiving chemotherapy or surgery for a suspected or confirmed thoracic, gastrointestinal, or gynecologic malignancy. eSyM prompts patients to complete a 12-item symptom questionnaire 2-3 times per week. This questionnaire also includes two pictogram questions that assess OWB and PFN – each scored using a four-point scale from 0 (best) to 3 (worst). We sought to identify patient characteristics associated with the lowest OWB and PFN (i.e., score = 3), to describe Spearman correlations between OWB and PFN, and to elucidate the relationships between symptom scores and OWB/PFN. Ordinal logistic regression models were used to adjust for potential confounding. **Results:** From September 2019-December 2022, 9753 patients submitted 75,166 questionnaires. There were 3846 chemotherapy patients (median age 66, 58% female, 17% non-white) and 5907 surgery patients (median age 61, 73% female, 7% non-white). The plurality of responses indicated mild impairment for OWB and PFN (Table). OWB and PFN scores were moderately correlated with each other (chemotherapy 0.62; surgery 0.59); with the sum of all symptom scores for chemotherapy (OWB 0.48, PFN 0.45) and surgery (OWB 0.51, PFN 0.45) patients; and with pain, fatigue, and anorexia (correlation coefficients 0.40-0.61). No individual symptoms were strongly correlated (coefficient > 0.7) with OWB or PFN. After controlling for other factors, OWB and PFN scores varied significantly by health system. Patients with disability were more likely to report low OWB and PFN (ORs 1.99-3.26; $p < 0.05$) versus other employment statuses. **Conclusions:** In a large cohort of chemotherapy and surgery patients from six community-based cancer centers, self-reported OWB and PFN scores were moderately correlated with common symptoms. These items offer discriminant and face validity and provide distinctive information that supplements a multi-item symptom questionnaire. Routine use of OWB and PFN can guide management strategies for symptomatic cancer patients. Clinical trial information: NCT03850912. Research Sponsor: U.S. National Institutes of Health.

	Score (impairment)	Chemotherapy (% of 3846 pts)	Surgery (% of 5907 pts)
Overall Wellbeing	0 (none)	17	29
	1 (mild)	41	45
	2 (moderate)	34	20
	3 (severe)	8	6
Physical Function	0 (none)	24	32
	1 (mild)	44	39
	2 (moderate)	19	16
	3 (severe)	13	13

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Poster Session

Phase 3 RCT of dexamethasone versus placebo for chemotherapy induced fatigue in patients with advanced solid malignancies. *First Author: Venkattraman Radhakrishnan, Cancer Institute (WIA), Chennai, India*

Background: Short-term steroids (<2 weeks) have been used to alleviate fatigue in patients with advanced cancer. However, the efficacy and safety of long-term steroids (12 weeks) in patients with advanced cancer receiving palliative chemotherapy have not been studied. **Methods:** The study was an open-label, placebo-controlled, phase 3 RCT to evaluate the efficacy and safety of low dose dexamethasone (DEX) in reducing chemotherapy and cancer associated fatigue. Patients aged 18-60 years with performance status ≤ 2 , undergoing palliative chemotherapy for advanced solid malignancies were randomized 1:1 to receive either DEX (4mg/day) or a placebo for 12 weeks. Fatigue was measured using the Symbolic Assessment of Fatigue Extent (SAFE) scale and EORTC FA12 scale, and quality of life (QOL) was assessed using the EORTC QLQ c30 at baseline, 6 weeks, and 12 weeks. The primary endpoint was to compare fatigue between the study arms at 6 weeks. Secondary endpoints were to compare fatigue at 12 weeks, QOL and toxicities. With a power of 80%, α of 5% (2-sided), 126 patients (including 25% drop-outs) were required to show the superiority of DEX in reducing SAFE fatigue extent score by 50% at 6 weeks. **Results:** A total of 126 patients were randomized (64 in the placebo arm and 62 in the DEX arm) between Oct 2018-Sep 2022. The median age was 46.5 years and 67% were females. Metastatic breast (28%) and lung (16%) cancer were the common diagnosis. Twelve and 23 patients in the placebo arm and 13 and 22 patients in the DEX arm did not undergo week 6 and 12 assessment respectively due to disease progression. The results showed no significant differences in mean SAFE scores, FA12 scores, or QOL between the study arms at 6 and 12 weeks, except for higher FA12 social sequelae in the DEX arm at 12 weeks ($P=0.048$) (Table). There were no significant differences in toxicities between the arms. **Conclusions:** The results of this study suggest that low-dose DEX is not effective in reducing chemotherapy associated fatigue or improving QOL in patients with advanced cancer. Clinical trial information: CTRI/2018/08/015222. Research Sponsor: Cancer Institute (WIA).

Fatigue Scale	Baseline		Week 6		Week 12	
	Placebo (n=64) Mean (SD)	DEX (n=62) Mean (SD)	P*	Placebo (n=52) Mean (SD)	DEX (n=49) Mean (SD)	P*
SAFE						
Fatigue extent	5.8 (4.3)	5.9 (3.6)	0.88	4.5 (3.2)	5.3 (3.3)	0.21
Fatigue Impact	10.7 (9.5)	11.3 (7.8)	0.67	8.04 (6.5)	9.04 (6.8)	0.45
FA12						
Physical fatigue	31.7 (27.4)	32.2 (24.1)	0.91	24.1 (16.6)	24.5 (17.6)	0.89
Emotional fatigue	28.7 (29.9)	25.5 (25.2)	0.51	17.4 (22.3)	15.3 (18.9)	0.62
Cognitive fatigue	18.2 (26.1)	18.2 (24.6)	0.98	14.4 (8)	15.9 (24)	0.71
Interference with daily life	28 (36.7)	25.7 (30.4)	0.7	20.3 (22.9)	16.3 (28.1)	0.42
Social sequelae	11.9 (21.6)	20.3 (30.3)	0.07	17.8 (22.3)	16.9 (28.1)	0.85

*T-Test.

Effects of yoga vs placebo on inflammation among cancer survivors: A nationwide multicenter phase III randomized controlled trial (RCT). *First Author: Po-Ju Lin, Wilmot Cancer Institute, University of Rochester Medical Center, Rochester, NY*

Background: Inflammation, both acute and chronic, is universally associated with primary and secondary cancer development and progression, as well as a myriad of toxicities that negatively affect cancer treatment adherence and survival. The effectiveness of targeting inflammation with non-pharmaceutical therapies such as yoga is not known. As part of a nationwide, multicenter, phase III RCT with cancer survivors, we compared the effects of yoga (Yoga for Cancer Survivors; YOCAS) to a behavioral placebo (survivorship health education) on inflammation (i.e. pro-inflammatory, anti-inflammatory, and overall inflammatory status). **Methods:** Participants were recruited via the URCC NCORP Research Base in partnership with 23 community oncology practices across the United States. Eligible participants were cancer survivors with insomnia 2-60 months post-treatment. They were randomized to receive YOCAS (gentle Hatha and Restorative yoga, 75-min./session, 2x/week, 4 weeks) or placebo (ASCO survivorship recommendation-based health education, 75-min./session, 2x/week, 4 weeks). Serum samples were collected at baseline and post-intervention to assess inflammation (i.e., pro-inflammatory markers IL-1 β , IL-6, TNF- α , IFN- γ and anti-inflammatory markers IL-4, IL-8, IL-10, sTNFRI), via Luminex multiplex assays. Analysis of covariance (ANCOVA) and structural equation modeling (SEM) were used to access yoga's effects on inflammation. **Results:** 502 survivors (94% female, mean age 56 $\pm$ 11 years, 74% breast cancer) were enrolled. ANCOVAs revealed significantly lower levels of pro-inflammatory markers in YOCAS participants compared to placebo participants (IL-1 β : -0.07 $\pm$ 0.03, $p = 0.01$; TNF- α : -0.04 $\pm$ 0.02, $p = 0.08$; IFN- γ : -0.07 $\pm$ 0.03, $p = 0.02$) where YOCAS participants exhibited stable pro-inflammatory responses (all $p > 0.05$) and placebo participants exhibited significant increases in pro-inflammatory responses (all $p \leq 0.05$) from baseline to post-intervention. ANCOVAs also revealed a statistical trend toward lower levels of anti-inflammatory markers in YOCAS participants compared to placebo participants (IL-4: -0.06 $\pm$ 0.04, $p = 0.10$; IL-10: -0.06 $\pm$ 0.04, $p = 0.09$; sTNFRI: -0.06 $\pm$ 0.04, $p = 0.09$). SEM also demonstrated significantly lower pro-inflammatory status (-0.16 $\pm$ 0.03, $p < 0.01$), significantly lower anti-inflammatory status (-0.14 $\pm$ 0.03, $p = 0.03$), and significantly lower overall inflammatory status (-0.15 $\pm$ 0.03, $p = 0.01$) in YOCAS participants compared to placebo participants. **Conclusions:** Our data suggest that YOCAS yoga significantly reduces inflammation among cancer survivors. Clinicians should consider prescribing yoga for survivors experiencing inflammation, which may lead to a high chronic toxicity burden and increased risk of progression, recurrence, and second cancers. Funding: NCI UG1CA189961, R01CA181064, T32CA102618. Clinical trial information: NCT02613364. Research Sponsor: U.S. National Institutes of Health.

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Poster Session

Apixaban versus rivaroxaban for treatment of acute deep venous thrombosis in patients with cancer. *First Author: Brittany Miles, Department of Biochemistry and Molecular Biology, University of Texas Medical Branch, League City, TX*

Background: Direct oral anticoagulants (DOAC) such as Apixaban and Rivaroxaban are increasingly used for the treatment of acute venous thromboembolism (VTE) over traditional vitamin K antagonists. Malignant neoplasms predispose to acute VTE and clinical management necessitates anticoagulation to prevent further complications. We compare Apixaban to Rivaroxaban for the treatment of acute VTE in the setting of malignancy with the endpoint of chronic deep venous thrombosis (DVT) development after 2 years. **Methods:** The TriNetX Research network was used for this study. TriNetX provides access to anonymized medical record information on more than 107 million patients in 76 large healthcare organizations. Two cohorts were created for this study using the International Classification of Disease-10 (ICD-10) codes. All patients were required to have a diagnosis of breast (C50), lung (C34), colon (C18), or prostate cancer (C61). All were diagnosed with acute deep venous thrombosis (DVT) of the lower extremities (I82.409). One cohort was treated with rivaroxaban while the other was treated with apixaban within 3 days of DVT diagnosis. Each cohort was excluded from being treated with the other anticoagulant. The cohorts were balanced for age, race, gender, and ethnicity, then evaluated for the development of chronic DVT (I82.509) within the subsequent twelve months. **Results:** The development of chronic DVT was significantly more common in the apixaban cohort, with a risk ratio of 1.36 (95% CI (1.12,1.65), p -value 0.0015). See table. **Conclusions:** Patients with acute VTE in the setting of malignancy were at a significantly higher risk of developing chronic DVT following treatment with Apixaban compared to those who received Rivaroxaban at 2 years post-treatment. These results may contribute to increased discussion between physicians and patients when deciding between these two direct oral anticoagulants for the management of acute VTE. Diagnosis of chronic DVT in cancer patients treated with apixaban and rivaroxaban. Research Sponsor: None.

Cohort	Cohort Size	Events	Risk
Apixaban	4,971	237	4.77%
Rivaroxaban	4,971	174	3.50%

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Poster Session

Rose geranium in sesame oil nasal spray to improve symptoms of nasal vestibulitis: A phase III double blinded randomized controlled trial. *First Author: Elizabeth Jane Cathcart-Rake, Department of Medical Oncology, Mayo Clinic, Rochester, MN*

Background: A retrospective study suggested a potential benefit from rose geranium in sesame oil nasal spray for alleviating nasal vestibulitis symptoms in patients (pts) undergoing chemotherapy. **Methods:** Pts undergoing active chemotherapy who reported moderate or worse nasal symptoms were randomized 1:1 to receive a rose geranium in sesame oil nasal spray (RG) or an isotonic saline nasal spray (IS), administered twice daily for two weeks. Consenting pts completed nasal symptom questionnaires at baseline and then weekly while on treatment. The number and percentage of pts experiencing improvements in their nasal symptoms 2 weeks after initiating the nasal spray, defined as symptoms moderately (2) or very much (3) better on a 7-point global impression of change score (ranging from scores of -3: very much worse, to 3: very much better), was estimated within and then between each randomized arm, using Fisher's exact test (5% significance level). The estimated odds ratio was determined (95% confidence interval). After 2 weeks, pts initially randomized to IS were allowed to cross-over to RG and completed weekly surveys. **Results:** 106 pts consented to this study; 43 pts in the RG arm and 41 in the IS arm were evaluable for the primary endpoint. Pts had a mean age of 57.8 (SD 13.9). Demographic characteristics and baseline nasal symptoms were similar between arms. The most prominent baseline nasal symptoms were dryness (36%) and bleeding (35%). Of the 43 evaluable pts who received RG, 67.4% reported improved nasal symptoms, compared with 36.6% of the 41 pts who received IS ($p=0.009$; Table). On the global impression of change score, pts who received RG had a mean score of 1.93 (SD 1.16), compared to a mean score of 0.98 (SD 1.41) among pts who received IS. Adjusting for potential confounding factors, pts who received RG had a 4.56 odds of responding to the nasal spray, compared with those who received IS ($p=0.005$). There were no significant differences between pt responses based upon type of nasal symptoms, age, allergies, or gender. Adverse events were sparse and did not differ between arms. 34 pts crossed over to RG after week 2. Among the 29 pts who completed final surveys, 37% reported a response on IS, 79% reported a response on RG. **Conclusions:** Rose geranium in sesame oil nasal spray significantly improves nasal vestibulitis symptoms among patients undergoing chemotherapy. Clinical trial information: NCT04620369. Research Sponsor: Breast Cancer Research Foundation (BCRF) and the Minnesota Cancer Clinical Trials Network (MNCCTN).

		Rose Geranium in Sesame Oil (N=43) N (%)	Isotonic Saline (N=41) N (%)
Global Impression of Change Score	Scale Value		
Very Much Worse	-3	0	0
Moderately Worse	-2	1 (2.3%)	3 (7.3%)
A Little Worse	-1	1 (2.3%)	1 (2.4%)
About the Same	0	1 (2.3%)	12 (29.3%)
A Little Better	1	11 (25.6%)	10 (24.4%)
Moderately Better	2	12 (27.9%)	8 (19.5%)
Very Much Better	3	17 (39.5%)	7 (17.1%)

12116

Poster Session

Nationwide phase II randomized controlled trial of low-dose ibuprofen vs placebo for cancer-related cognitive impairment (CRCI). *First Author: Michelle Christine Janelins, University of Rochester Medical Center, Wilmot Cancer Institute, Rochester, NY*

Background: CRCI is an important clinical problem encompassing difficulties in attention, memory, and executive function. Interventions for CRCI during chemotherapy have not been established. Inflammation is associated with CRCI and thus targeting inflammation may alleviate CRCI. In a nationwide study, we investigated a low-dose of ibuprofen for alleviating CRCI in patients self-reporting cognitive problems during chemotherapy or after recent completion of chemotherapy. **Methods:** Participants with cancer currently on or recently completed chemotherapy and who self-reported cognitive problems were recruited via the NCI Community Oncology Research Program (URCC NCORP) and 11 affiliates. Participants completed pre-intervention assessments and were stratified by disease type (breast cancer; gastrointestinal cancer; other) and randomized to one of 2 groups for 6 weeks: ibuprofen (200 mg BID) or blinded placebo equivalent. At pre-intervention and post-intervention, participants completed a perceived cognitive function measure (FACT-Cog Perceived Cognitive Impairment (PCI)) and cognitive assessments including Rapid Visual Processing (RVP) latency, Delayed Match to Sample (DMS) visual memory, and Verbal Recognition Memory (VRM) word recall. ANCOVA was used to assess between group differences pre- to post-intervention adjusting for baseline cognitive test score. **Results:** In total, 87 participants were randomized; 45 were randomized to ibuprofen and 42 randomized to placebo (mean age = 55; 85% female; 47% breast cancer, 29% colon/colorectal cancer; 24% other diagnoses). Most participants were fully compliant and completed post-intervention assessments (86% in Ibuprofen arm, 87% in placebo arm). There were no gastrointestinal bleeding events of any grade in the ibuprofen arm and serious adverse events were rare in both arms occurring in only 4% and 7% of patients in the ibuprofen and placebo arms, respectively. For PCI, both groups significantly reported less impairment from pre- to post-intervention; there were no difference between groups. Patients randomized to ibuprofen had a significant improvement on RVP latency time compared to placebo (110.63 milliseconds; $p < 0.005$). On the DMS, patients receiving ibuprofen had a trend toward improved function compared to placebo (7.39%; $p = 0.08$). However, patients in placebo performed better in word recall compared to ibuprofen from pre- to post-intervention (1.64 words; $p < 0.05$). **Conclusions:** Low-dose, short duration ibuprofen was safe with minimal adverse events in patients with cancer receiving chemotherapy or recently completed chemotherapy. Ibuprofen showed improvements in processing speed time and visual memory in patients with cancer as hypothesized, but not verbal memory. These novel Phase II findings need to be replicated in a Phase III RCT. Funding: R21CA187500, UG1CA189961. Clinical trial information: NCT03186638. Research Sponsor: U.S. National Institutes of Health.

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Poster Session

Feasibility and acceptability of implementing electronic patient reported outcomes (ePRO) collection in Zambia: Findings from a patient needs assessment. *First Author: Susan K. Peterson, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Studies in high-income countries have shown that systematic, remote and electronic collection of patient-reported outcomes (ePROs) during chemotherapy, with provider intervention if symptoms worsen, is associated with fewer symptoms, better quality of life (QOL), and improved survival. It is unknown whether similar ePRO interventions, often using electronic medical record patient portals or mobile devices, can improve outcomes for cancer patients in low- and middle-income countries (LMICs). In sub-Saharan Africa (SSA), cervical cancer (CC) is the second most common cancer and most common cause of cancer deaths in women. As most patients are diagnosed with locally advanced disease, chemoradiotherapy is standard care; many have severe comorbidities such as HIV. Due to patients' increased risk for high symptom burden, remote monitoring of ePROs during CC treatment may improve outcomes. We evaluated the feasibility and acceptability of ePRO collection in CC patients from SSA. **Methods:** Patients were recruited from a prospective cohort study of women with newly diagnosed CC at the Cancer Diseases Hospital in Lusaka, Zambia from June 2022 through January 2023. Patients completed an in-person interview regarding mobile technology usage comprising questions adapted from the 2019 Pew Report on Mobile Connectivity in Emerging Economies and the 2019 Global System for Mobile Communication Association Mobile Gender Gap Report. Questions were translated into 4 primary Zambian languages (Tonga, Nyanga, Lozi and Bemba). **Results:** Respondents' (n = 100) mean age was 49.6 years (range, 29-75, SD 9.2), 55% were diagnosed with stage III-IV disease and 59% were HIV+. Most (70%) completed only primary school or no school, 29% reported not being able to read at all and 29% could read only parts of a sentence. Most personally owned a mobile phone (90%) and 8% reported using a phone that belonged to another person. Most used phones to make or receive calls (98%), for banking/mobile money (92%), and text messaging (67%). Of the 26% who owned a smartphone, only half connected to the internet by phone more than once weekly. Nearly all indicated willingness to use a phone to self-report CC-related symptoms if compensated for costs (98%), with 97% preferring to do so via a phone call and fewer via text message (43%) or mobile app (17%). Most (71%) were able to charge phones at home using electricity or solar power and 18% traveled more than 30 minutes to charge phones. **Conclusions:** Nearly all patients owned or had access to mobile phones and expressed willingness to self-report CC symptoms via phone. Findings support the feasibility and acceptability of ePRO collection and provide contextual data to guide implementation in LMICs, including consideration of telecommunications infrastructure and literacy, low internet use, and ePRO reporting preferences (i.e., calls vs text). Research Sponsor: None.

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Poster Session

Baseline symptom, health status, and health utilities in patients in early-phase clinical trials combining immune checkpoint blockade with other anticancer therapies. *First Author: Goldy C George, Department of Symptom Research, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: The overall goal of our prospective and longitudinal study (NCT01CA242565) is to examine the use of patient report to evaluate symptomatic adverse events associated with combination treatment including at least one immune checkpoint inhibitor in early-stage clinical trials. We present here the baseline symptom, health status and utilities in patients prior to trial start, and their association with clinical factors. **Methods:** Patients scheduled to start an early-phase trial of combination treatment with at least one immune checkpoint inhibitor and who had not received clinical trial-related treatment completed the validated MD Anderson Symptom Inventory - Immunotherapy (0-10, higher scores = worse severity) and the validated EuroQoL-5 dimensions questionnaire including a visual analog scale (EQ5D VAS) (0-100, higher scores = better health status) and health utility items (e.g., self-care, mobility). Clinical data were extracted from the EMR. Statistical tests included Spearman's correlation coefficients. **Results:** At baseline prior to start of trial-related treatment, 38% of patients (N = 164; median age = 60 y; 52% male; 85% White; 17% ECOG PS 0, 89% ECOG PS 1, 3% ECOG PS 2) experienced at least 1 severe symptom (≥ 7 on 0-10 scale). The most frequent severe baseline symptoms were pain (21% of patients), fatigue (17%), disturbed sleep (15%), drowsiness (12%), lack of appetite (10%), distress (10%), and pain in the abdomen (10%). Less than 2% of pts experienced severe immunotherapy-specific symptoms of rash, fever/chills and swelling of the hands and feet at baseline. Moderate-severe symptom-related interference (≥ 4 on 0-10 scale) was worst for activity (40% of patients), work (38%), and enjoyment of life (30%). For the EQ5D health utility dimensions, patients reported the most problems with pain or discomfort (75%) and fewest problems with self-care (10%). Worse composite symptom severity ($P = 0.013$) and worse problems with activity ($P = 0.001$) and pain ($P = 0.012$) were associated with worse and higher ECOG PS. Worse symptom severity (-0.54 , $P < 0.001$), symptom interference with activity (-0.57 , $P < 0.001$) and mood (-0.42 , $P < 0.001$) related functioning were associated inversely with superior health status. Worse symptom interference with activity-related functioning was linked with lower concurrent lymphocyte counts ($P = 0.01$), hemoglobin ($P = 0.01$) and serum albumin ($P = 0.004$) levels and higher platelet ($P = 0.02$) counts. **Conclusions:** Patients in early-phase trials that combine immunotherapy with other anti-cancer therapies may experience severe symptom burden and symptom interference with functioning, even at baseline prior to treatment start. Thus, it is important to baseline symptoms to fully understand the impact of combination treatments including checkpoint inhibitors in early-stage clinical trials. Research Sponsor: U.S. National Institutes of Health.

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Poster Session

12119

Poster Session

Experiences with pain management for survivors of complex cancers: Focus on opioids and cannabis. *First Author: Talya Salz, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Survivors of complex cancers often experience pain. Clinical practice guidelines for pain management in cancer survivors cautiously recommend opioids and cannabis for subgroups with certain pain phenotypes, despite limited evidence regarding benefits and harms in survivor populations. We aimed to better understand pain management for these survivors, focusing on attitudes toward, and experiences with, opioids and cannabis. **Methods:** We conducted 7 90-minute focus groups with 26 disease-free survivors of head and neck and lung cancer who still experience cancer-related pain. Multiple coders conducted thematic analyses to identify themes regarding 1) experiences with post-treatment pain and pain management and 2) utilization, benefits, and harms of post-treatment cannabis and opioids. **Results:** Survivors (7-35 months from treatment completion) experienced post-treatment physical and psychological pain that affected multiple aspects of their daily life. Since treatment completion, 69% used opioids previously and 8% currently using. Fifty-four percent had used any cannabis product since treatment completion, and 35% currently use cannabis. While some survivors experienced no pain management challenges, others enumerated various difficulties, including fears of addiction to opioids or cannabis, perceived stigma around both products, and access challenges around provider attitudes, cost and insurance coverage, and legality. Survivors reported that providers did not know how to advise about cannabis; for example: "When I talked [to providers] about marijuana they didn't want to talk about it. They couldn't recommend it because there's no clinical data." Opioids were often perceived as critical to pain management but came with unpleasant side effects. Cannabis was effective at reducing both pain and anxiety for many, but not all, survivors. For some, cannabis reduced anxiety, which in turn reduced pain: "It just keeps my mind occupied enough where I'm not thinking of pain." Reducing anxiety also helped some survivors eat: "I have a lot of anxiety around eating because I have a fear of choking, so sometimes it helps that." Survivors described a balance of benefits and harms of opioids and cannabis; for example: "Where [the doctor has] me now...if I go down any lower, it's not going to work. If I go up any higher, I'm going to be not able to function." **Conclusions:** Post-treatment survivors of complex cancers continue to experience cancer-related pain, both psychological and physical, for which both opioids and cannabis present a complex set of harms and benefits that vary across survivors. Providers who care for cancer survivors should be aware of the interplay between psychological and physical pain, patient concerns and stigma around opioids and cannabis, and nuances of the harms, benefits, and access issues regarding these treatments. Research Sponsor: U.S. National Institutes of Health.

12120

Poster Session

Unveiling inequities in palliative care and clinical trial participation among patients with metastatic breast cancer in the state of Florida. *First Author: Oluwadamilola Temilade Oladeru, Department of Radiation Oncology, University of Florida College of Medicine, Gainesville, FL*

Background: Persistent inequities in the care for patients with metastatic breast cancer (mBC) were recognized by ASCO and, in partnership with Pfizer, awarded our team a grant to understand and address them in people of color. Florida has a higher age-adjusted percentage of breast cancer in females and a higher mortality rate in those under the age of 65 compared to the United States. The racial disparity in mortality is further magnified among female patients with mBC. Therefore, we sought to characterize the prevalence and trends of palliative care utilization and clinical trial participation (CTP) among Floridians with mBC and quantify the associated factors. **Methods:** Using the OneFlorida+ Data Trust, a repository of patient-level electronic health records of ~17 million Floridians seen in public and private health care systems, including those enrolled in Medicaid, we obtained demographics of mBC patients, including sex, age, race, and ethnicity, insurance type, zip-code based socioeconomic status, Charlson comorbidity index (CCI) and rural/urban residence. CPT codes were obtained for palliative care services between the date of mBC diagnosis and death, including pain management, psychology, psychiatry, nutrition, and advanced care planning. Our analysis included the Cochran-Armitage trend test and bivariate analysis to correlate patient characteristics to palliative care receipt and CTP. **Results:** In Florida, 25,225 individuals (1.5% men and 98.5% women) were diagnosed with mBC between 2012 and 2021; 49.3% were under age 60. 19.5% of this cohort received palliative care at a median time of 10.1 months (IQR 2.1 – 27.1) from the initial diagnosis of mBC. The median survival was 13.6 months (IQR 3.4 – 31.6). On multivariable analysis, significant variables ($p < 0.001$) associated with increased palliative care utilization were Non-Hispanic Black, self-pay/uninsured and Medicaid insured, and a CCI of 5+. Only 3% of the study cohort had advanced care planning. There was a declining trend in CTP among patients with mBC, from 13.9% in 2012 to 7.9% in 2021. Among those participating in clinical trials, 80.2% did not receive palliative care. Variables associated with higher CTP ($p < 0.001$) were younger age (18-49), Asian and Hispanic race/ethnicity, the highest quartile of median household income and education level, private insurance, metropolitan residence, and CCI of 0. Further, there was a trend towards more prolonged survival among those enrolled in clinical trials. **Conclusions:** This robust statewide assessment highlights that less than 20% of patients with mBC receive palliative care, and its receipt is exclusive of CTP. We identified significant racial and socioeconomic disparities in CTP. Educational interventions with palliative care trained navigators, partnerships with providers on palliative care benefits, and state policy support are needed. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology.

Opioid use, gabapentinoid use, and pain-related emergency department visits for patients living with advanced cancer. *First Author: Vikram Jairam, Department of Therapeutic Radiology, Yale School of Medicine, New Haven, CT*

Background: Regulatory efforts in response to the United States opioid epidemic have resulted in a decrease in opioid prescribing among oncologists and non-oncologists. Understanding how decreased opioid prescribing affects cancer-related pain can provide key insights into the downstream effects of these efforts. In this study, we explored temporal trends in opioid use, gabapentinoid use, and pain-related emergency department (ED) visits in older adult patients with advanced cancer and those without cancer. **Methods:** We queried the Surveillance, Epidemiology, and End Results (SEER)-Medicare database from 1/1/2012 to 12/31/2017 to identify patients aged 66 years or older diagnosed with advanced solid tumor cancer (defined as stage IV and/or metastatic disease). A cohort of patients without a cancer diagnosis was identified using the Medicare 5% random sample. The three dependent outcomes assessed were opioid use, gabapentinoid use, and pain-related ED visits. Multivariable logistic regression was used to identify predictors of these outcomes and to calculate the predicted probability of each outcome for patients with and without cancer. We determined the absolute change in the predicted probability of each outcome from 2012 to 2017. **Results:** A total of 294,113 patients were included in the cohort: 45,899 (15.6%) with cancer and 248,214 (84.4%) without cancer. Between 2012 and 2017, the absolute change in predicted probability of opioid use declined less in the cancer [-6.1%; 68.6% to 62.5%] compared to the non-cancer cohort [-8.2%; 35.8% to 27.6%] ($p < .001$ for difference). Gabapentinoid use increased more in the cancer [3.9%; 10.8% to 14.7%] than non-cancer [1.8%; 10.5% to 12.3%] cohort ($p < .001$ for difference). There was no statistically significant change in pain-related ED visits in patients with cancer [0.6%; 12.4% to 13.0%] and a decrease in patients without cancer [-0.5%; 2.6% to 2.1%] ($p = 0.005$ for difference). **Conclusions:** Our findings showed that opioid use decreased to a lesser degree among older patients with advanced cancer compared to patients without cancer, whereas gabapentinoid use increased to a greater degree among patients with cancer. There was no corresponding rise in pain-related ED visits, suggesting that these shifts in medication use may not have adversely affected this important outcome. Research Sponsor: American Cancer Society.

Outcome	Cancer Status	Predicted Probability (95% CI) of outcome in:		Absolute Change (95% CI)
		2012	2017	
Receiving opioids	Non-cancer	35.8 (35.4, 36.3)	27.6 (27.3, 28.0)	-8.2 (-8.8, -7.6)*
	Cancer	68.6 (67.9, 69.3)	62.5 (61.8, 63.2)	-6.1 (-6.9, -5.3)*
Receiving gabapentinoids	Non-cancer	10.5 (10.2, 10.8)	12.3 (12.1, 12.6)	1.8 (1.4, 2.2)*
	Cancer	10.8 (10.4, 11.2)	14.7 (14.2, 15.1)	3.9 (3.3, 4.4)*
Pain-related ED visits	Non-cancer	2.6 (2.5, 2.8)	2.1 (2.0, 2.3)	-0.5 (-0.7, -0.3)*
	Cancer	12.4 (11.7, 13.1)	13.0 (12.3, 13.6)	0.6 (-0.3, 1.5)

*p-value < 0.001.

12121

Poster Session

End-of-life outcomes after implementation of an embedded, criteria-based palliative care consultation service in inpatient oncology. *First Author: Kathryn Norman, Beth Israel Deaconess Medical Center, Boston, MA*

Background: Specialty palliative care (PC) improves outcomes for patients with advanced cancer, including quality of life and end-of-life (EOL) care utilization. In 2017, the American Society of Clinical Oncology recommended that patients with advanced cancer see specialty PC within 8 weeks of diagnosis. Despite this, inpatient PC referrals exceed outpatient referrals nationwide. Recognizing the importance of earlier PC access, our cancer center implemented a criteria-based PC consultation service in the inpatient oncology setting. We now report pre/post EOL outcomes from this novel care model. Care model: Our center embedded a "Palliative Oncology" consult team on the oncology floor consisting of 1 physician, 1 nurse practitioner (NP), 2 social workers, and 2 spiritual care providers, all with PC specialization. Admitted patients were screened by a floor nurse or PC NP for 2 referral criteria: 1) advanced/metastatic solid cancer, or 2) moderate/severe symptoms. The inpatient oncology team was informed of patients meeting criteria through daily prompting supported by ongoing education. Referrals remained at discretion of the oncology team rather than triggering automatically. **Methods:** We identified all cancer center decedents with advanced solid cancers who experienced an admission to the oncology floor before (10/1/19-6/30/20) or after (7/1/20-9/30/21) the new model. Six trained abstractors performed chart review. We compared outcomes between patients who died pre- and post-implementation using a t-test (continuous variables) and χ^2 test (categorical variables). **Results:** Of 820 decedents, 186 died pre-intervention and 634 died post-intervention. During the post-intervention period, more decedents saw inpatient PC (72% vs. 59%, $p < .001$) and outpatient PC (34% vs. 23%, $p < .01$). Post-intervention decedents had more inpatient PC visits (mean: 11.1 vs. 8.9, $p < .05$) and had their first PC visit sooner before death (mean: 159 vs. 76 days, $p < .001$). During the post-intervention period, fewer decedents had ED (41% vs. 52%, $p < 0.05$), hospital (57% vs. 71%, $p < .001$), or ICU encounters (17% vs. 25%, $p < .01$) in the last 30 days of life. For post-intervention decedents, the proportion referred to hospice remained stable (67% vs. 60%, $p = .09$), but mean hospice length-of-stay increased (36 vs. 22 days, $p < .05$), as did the proportion who died at home (50% vs. 41%, $p < .05$). Fewer post-intervention decedents received systemic cancer therapy in the last 14 days of life (5% vs. 9%, $p < .05$). There were no between-group differences in age at cancer diagnosis, age at death, gender, race/ethnicity, insurance, or primary cancer. **Conclusions:** A criteria-based "Palliative Oncology" inpatient consult service was associated with earlier, more intense PC and improved EOL quality outcomes, representing a successful effort to enhance PC integration in the inpatient oncology setting. Research Sponsor: None.

12122

Poster Session

A supervised remote exercising program for patients receiving immunotherapy alone or in combination with chemotherapy in Brazil: ExIO. *First Author: Paulo Gustavo Bergerot, Centro de Cancer de Brasília, Instituto Unity de Ensino e Pesquisa, Grupo Oncoclinicas, Brasília, Brazil*

Background: Exercise has been shown to ameliorate the side effects of cancer therapy, improve quality of life, and may even enhance treatment response. Since immunotherapy is widely used and approved for over 18 indications, studies are needed to determine the effect of exercise on immunotherapy outcomes. Additionally, there is a crucial need for understanding how to make such interventions cost-effective and accessible in low- and middle-income countries. We aimed to explore the feasibility and efficacy of a remote exercise program for patients receiving immunotherapy alone or in combination with chemotherapy in Brazil. **Methods:** This is a 12-week prospective study of a supervised remote exercise program. Patients diagnosed with any solid cancer receiving immunotherapy alone or in combination are eligible. The program is supervised using the WhatsApp and Vedio platforms and consists of resistance and aerobic exercises for 3 to 5 hours per week (4 to 6 days a week). Outcome measures include treatment-related symptoms (FACT-IT, scale 0-100), fatigue (BFI, scale 0-90), and overall quality of life (FACT-G, scale 0-108). Descriptive statistics were generated, and RM-ANOVA were used to evaluate changes in outcome measures over time. **Results:** A total of 40 patients have been enrolled to date, with 87.8% of complete adherence. Participants had a mean age of 59 years (SD = 12.2) and were predominantly female (53.7%), white (68.3%), married (68.3%), and had a college degree or higher education (56.0%). Patients were mostly diagnosed with breast (24.4%) or kidney (22.0%) cancers; 63.4% of patients had stage IV disease. Notably, significant improvements in treatment-related symptoms ($M_1 = 86.5$, $M_2 = 96.0$, $p = 0.001$), fatigue ($M_1 = 21.4$, $M_2 = 9.6$, $p = 0.001$) and quality of life ($M_1 = 87.5$, $M_2 = 98.6$, $p = 0.001$) have been observed. **Conclusions:** To our knowledge, this is the first study to examine the feasibility and efficacy of a supervised remote exercise program among patients with cancer receiving immunotherapy in Latin America. Our findings suggest that this remote program has high adherence and may improve treatment-related symptoms, fatigue, and overall quality of life while providing a practical and easily accessible alternative to patients. This study will be validated in an upcoming randomized clinical trial. Research Sponsor: None.

12124

Poster Session

Patient-controlled subcutaneous analgesia with hydromorphone versus oral oxycodone for opioid titration of cancer pain: A prospective multicenter randomized trial. *First Author: Xiaoguang Xiao, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China*

Background: Studies have shown that oral oxycodone sustained-release (SR) tablets can be used for opioid titration. The European Society for Medical Oncology (ESMO) guidelines for adult cancer pain recommend opioid titration through the parenteral route, usually the intravenous or subcutaneous route. Patient-controlled subcutaneous analgesia (PCSA) with hydromorphone needs further evaluation for opioid titration. This prospective multicenter study was designed to compare the efficacy and safety of hydromorphone PCSA with oral oxycodone SR tablets for opioid titration of cancer pain. **Methods:** Eligible patients with cancer pain were randomly assigned in a 1:1 ratio to the PCSA group or the oxycodone group for dose titration. Different titration methods were given in both groups depending on whether the patient had an opioid tolerance. The primary endpoint of this study was time to successful titration (TST). **Results:** A total of 256 patients completed this study. The PCSA group had a significantly lower TST compared with the oxycodone group [median [95% confidence interval (CI)], 5.5 [95%CI: 2.5-11.5] hours vs. 16.0 [95%CI: 11.5-22.5] hours; $p < 0.001$]. PCSA reduced the frequency of breakthrough pain (Btp), especially in patients with opioid tolerance. The number of Btp was 121 ± 28 times and 186 ± 31 times in the PCSA and oxycodone groups, respectively ($p < 0.001$). The 12-hour numeric rating scale (NRS) score was significantly lower in the PCSA group than that in the oxycodone group [median [95%CI], 2.5 [95%CI: 1.4-2.9] vs. 4.4 [95%CI: 3.2-5.8] ($p < 0.001$)]. Similar equivalent morphine consumption and significantly improved quality of life were observed in the two groups. No between-group difference in the incidence of opioid-related adverse effects was observed. **Conclusions:** Compared with oral oxycodone SR tablet, the use of PCSA with hydromorphone achieved faster pain relief and a shorter titration duration for patients with cancer pain without increasing adverse events. Clinical trial information: ChiCTR2000037845. Research Sponsor: None.

12123

Poster Session

Risk of severe toxicity from topical fluoropyrimidine treatment in patients carrying DPYD variant alleles. *First Author: Javier Granados, University of Michigan, Ann Arbor, MI*

Background: Patients carrying variant alleles of *DPYD* that reduce activity of dihydropyrimidine dehydrogenase have unacceptably high risk of severe toxicity from systemic fluoropyrimidine chemotherapy. *DPYD* testing prior to systemic fluoropyrimidine treatment is standard of care across Europe and is increasingly used in USA. There is a published case report of fatal toxicity from topical fluoropyrimidine chemotherapy in a *DPYD* variant carrier, but the risk of severe toxicity in these patients is unknown. This information is critical to determine whether patients receiving topical fluoropyrimidine treatment should also undergo *DPYD* genetic testing. The objective of this retrospective cohort study was to determine whether patients carrying *DPYD* variant alleles have increased risk of severe toxicity from topical fluoropyrimidine treatment. **Methods:** Individuals who received topical fluoropyrimidine treatment at Michigan Medicine and had available *DPYD* genotype data, due to participation in the Michigan Genomics Initiative institutional genetic data repository, were eligible for this analysis. Clinical data for the first cycle of topical fluoropyrimidine treatment was abstracted from the electronic medical record by an investigator blinded to genetic data. Toxicities were graded based on the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The primary endpoint was grade 3+ toxicity. The secondary endpoint was grade 1+ toxicity. Genotypes for five validated decreased- or null-activity *DPYD* variant alleles were included: *DPYD**2A (rs3918290), *DPYD**13 (rs55886062), *DPYD* p.D949V (rs67376798) *DPYD* HapB3 (rs56038477) and *DPYD* p.Y186C (rs115232898). Toxicity rates in *DPYD* variant carriers vs. wild-type were compared using Fisher's Exact tests. **Results:** 201 patients receiving topical fluoropyrimidine therapy who had available *DPYD* genotype data were included in the analysis. Most patients were self-reported white (97%), male (71%), and received topical fluoropyrimidine for a diagnosis of actinic keratosis (79%). As expected in a US patient cohort, 7.0% (14/201) of patients carried a *DPYD* variant. No patients experienced grade 3+ toxicity. Patients carrying a *DPYD* variant allele had nominally higher risk of grade 1+ toxicity (21.4% vs. 10.2%, odds ratio = 2.40 [95% Confidence Interval: 0.10-2.53], $p = 0.19$). **Conclusions:** Patients carrying *DPYD* variant alleles may have increased risk of non-severe toxicity from topical fluoropyrimidines, but the risk of severe toxicity is minimal regardless of genotype. *DPYD* genetic testing to prevent severe and fatal fluoropyrimidine toxicity should be reserved for patients receiving systemic treatment and need not include patients receiving topical treatment, in whom risk of severe toxicity is minimal. Research Sponsor: None.

12125

Poster Session

Concurrent hospice healthcare utilization in the hematology/oncology patient population at veterans affairs. *First Author: Anshu Hemrajani, Loyola University Medical Center, Maywood, IL*

Background: The benefits of early hospice enrollment include improved quality of life and overall survival (Kumar, 2017). Yet, most oncology patients continue to receive aggressive treatments including chemotherapy, radiation therapy, and hospitalizations until close to death (Ersek, 2017). Veterans have the unique opportunity to receive concurrent hospice which allows patients enrolled in hospice to receive disease modifying treatments and other interventions not typically provided under the traditional Medicare hospice benefit. **Methods:** A single institution retrospective review of 72 hematology and oncology patients who enrolled in the concurrent care program at the Hines VA between 12/28/2018-4/3/2021 was conducted. Patients were eligible for the concurrent care program if they (1) had a life-limiting illness with a prognosis of less than six months (2) were willing to enroll in hospice (3) had an oncologist willing to administer cancer-directed therapy. Data were summarized with descriptive statistics including medians and percentages. **Results:** Patients in the concurrent care hospice program were predominantly White (69.4%) and older than 70 years of age (63.9%). Most patients were diagnosed with primary gastrointestinal (29.2%), thoracic (22.2%), or genitourinary (19.4%) malignancies. While enrolled in concurrent care hospice, 15.3% of patients visited the emergency department and 45.8% had at least one hospitalization. Few patients received cytotoxic chemotherapy (27.8%), immunotherapy (20.8%), palliative radiation (20.8%), or pain procedures (4.2%) while enrolled in concurrent care hospice. Of the 19 patients who received chemotherapy, only one patient received treatment within 7 days prior to death. The minority of patients (11.1%) received a blood product and of those patients that did, 8.3% required one to three transfusions and 2.8% required three or more transfusions. Most (91.7%) patients died while in concurrent care hospice; 21.2% died within 30 days of enrollment and 56.1% died within 31 to 180 days of enrollment. Patients were more likely to die at home (63.6%) or in inpatient hospice (13.6%) as opposed to the hospital (3%). **Conclusions:** Enrollment in concurrent hospice care prevents patients from having to choose between comfort care and cancer-directed treatments, which is often a barrier to early hospice enrollment (Salz, 2009). At Hines VA, most patients receiving concurrent hospice care rarely or never utilized cancer directed treatments, pain procedures, blood products, or emergency room visits/hospitalizations despite having access to these resources. Furthermore, the majority of patients died with hospice-style care at home or in inpatient hospice rather than in the hospital. This observational study demonstrates that when offered the choice to pursue cancer-directed treatments, most patients opt instead to focus on comfort care at end of life. Research Sponsor: None.

12126

Poster Session

Denosumab biosimilar (LY01011) in the treatment of bone metastases in patients with solid tumors: A multicenter, randomized, double-blind, active comparator-controlled phase 3 study. *First Author: Mingchuan Zhao, Fudan University Shanghai Cancer Center, Shanghai, China*

Background: The study was to evaluate the equivalence of LY01011 to the reference product denosumab in terms of reduction of bone metabolism markers. **Methods:** Eligible patients were randomized at 1:1 ratio to receive 120 mg LY01011 injection or 120 mg denosumab every four weeks subcutaneously. Following the completion of three doses of 120 mg LY01011 or denosumab in a 12-week double-blind treatment period (DBTP), all enrolled patients would continue to receive LY01011 administration until the week 53 of follow-up period. The primary end point was the natural logarithm change at week 13 from baseline in urinary cross-linked N terminal telopeptide of type I collagen, corrected for urine creatinine (uNTX/uCr). The equivalence between LY01011 and denosumab would be concluded if the 90% CI was completely inside the pre-defined equivalence boundary between -0.135 and 0.135. A formal blinded sample-size re-estimation (BSSR) was planned to take place once 60% of the planned participants had completed the Week 13 assessments. After BSSR, the sample size increased from 560 to 850 according to prespecified procedure based on pooled standard deviation from the blinded data, which was set as a cap to ensure a feasible sample size for the study and no need to do any multiplicity adjustment. **Results:** All eligible 850 patients, included in the full analysis set, were randomized into the LY01011 group (n = 424) and denosumab group (n = 426). The samples from the 12-week DBTP were collected for analysis in both groups. The least square mean (LSM) (SE) of the natural logarithm change of uNTX/uCr at week 13 from baseline was -1.740 (0.0420) in the LY01011 group and -1.745 (0.0421) in denosumab group. The LSM difference was 0.005 between LY01011 and denosumab groups with 90% CI of [-0.088, 0.097] (p > 0.05). Skeletal related events occurring in the LY01011 and denosumab groups were 3.5% and 2.8%, respectively. The mean (SD) percentage changes of serum bone-specific alkaline phosphatase (s-BALP) from baseline to week 13 were -31.154% (39.6790) and -33.021% (37.3826) in the LY01011 and denosumab groups, respectively. The median was -36.866% and -37.457% (p > 0.05). The incidence of treatment-emergent adverse events (TEAEs) of any grade was 91.7% and 90.8% in LY01011 and denosumab groups (p > 0.05). Both groups had 38.4% of Grade ≥3 TEAEs, of which 5.4% (LY01011) and 4.5% (denosumab) were judged to be related to the study drug. Immunogenicity analysis showed that no participant (0/399) had a positive ADA test in denosumab group and only one participant (0.2%, 1/401) was tested ADA positive in LY01011 group. **Conclusions:** The study demonstrated the equivalent efficacy of LY01011 in the reduction of bone metabolism biomarker NTX to reference product, denosumab, which met the primary endpoint. It had a good safety profile with no unexpected adverse reactions in the study. Clinical trial information: NCT04859569. Research Sponsor: Shandong Boan Biotechnology Co, LTD.

12128

Poster Session

Utilization of early integrated palliative medicine among patients with metastatic solid tumor cancers: Findings from a safety net medical center treating a majority African American population. *First Author: Aneasha Ananthula, Louisiana State University Health Sciences Center, New Orleans, LA*

Background: Early interdisciplinary Palliative Medicine (PM) involvement is known to provide significant benefits when added to usual oncology care, however a study by Ferrari et al looking at oncologic patients between 2001 to 2016 found that only 36% of patients with cancers with a very poor prognosis received Palliative Medicine services. In 2016 ASCO provided a practice guideline recommending specialty PM services to begin within 8 weeks of diagnosis. Our study aimed to assess the integration of the above recommendation in a newly built academic, safety net hospital serving as a regional tertiary healthcare facility with a newly built PM service that included a free-standing outpatient clinic. **Methods:** This is a retrospective cohort study of all patients on the tumor registry with de novo stage IV cancer diagnosed in a four-year period from 2018 to 2021. Patient data was collected from the electronic medical record (EMR) and included demographics, health history, PM utilization, and advance care planning documentation. Logistic regression was used to analyze key predictors of PM utilization and advance care planning. **Results:** The majority of patients (N = 510) were African American (race: Black [56.5%], White [35.7%], all other racial groups [7.8%]; mean age = 59.8 [range from 18 or over 90]; sex: 60.6% male). Diagnoses included gastrointestinal (38.2%), thoracic (27.8%), genitourinary (26.3%), and other (7.7%) cancers. Out of the group, 60.5% of the patients received PM services and 55% of those had a visit within the ASCO recommendations of 8 weeks. A surprising 32.7% of those referred to PM had a first visit within the first 2 weeks via an urgent referral system, most often for symptom management. About 40.0% of initial visits were outpatient rather than inpatient and there were no racial or other demographic differences in the setting of the first visit. Patients receiving cancer care in more recent years (P < .001), who were younger (P = .025), and with non-genitourinary cancers (P = .005) were more likely to receive PM services. Also, patients who received PM were more likely to have a medical power of attorney (P < .001) and living will (P < .001) documented in the EMR. **Conclusions:** This study demonstrates that in centers with a robust PM team including an outpatient clinic, patients with advanced cancer are receiving early Palliative Medicine evaluation in accordance with the 2016 ASCO guidelines. In contrast to a previous study by Johnson et al our study shows that African-Americans were also equally referred and established with PM services. Our study is limited by the presence of a free-standing PM clinic rather than embedding into a cancer center which may assist with even earlier integration. Research Sponsor: None.

12127

Poster Session

A phase III, double-blind, non-inferiority, randomized controlled trial of antiemetic prophylaxis for highly emetogenic chemotherapy without dexamethasone: CINV POD study. *First Author: Venkatraman Radhakrishnan, Cancer Institute (WIA), Chennai, India*

Background: Chemotherapy-induced nausea and vomiting (CINV) is a common side effect of highly emetogenic chemotherapy (HEC). Current guidelines recommend the use of dexamethasone (DEX) for prophylaxis, but the effectiveness and safety of a DEX-free regimen for CINV prophylaxis in HEC is not known. **Methods:** This was an investigator-initiated, double-blind, phase 3 RCT designed to show the non-inferiority of a DEX-free regimen (olanzapine, palonosetron, and fosaprepitant; OPF) compared to the NCCN recommended DEX-containing regimen (olanzapine, palonosetron, and dexamethasone; OPD). Chemotherapy-naïve patients aged 18-80 years receiving single-day HEC were randomized 1:1 to receive either the OPD regimen (olanzapine 5 mg once a day on days 1-4, palonosetron 0.25 mg on day 1, and DEX 12 mg on day 1) or the OPF regimen (olanzapine and palonosetron as above, and fosaprepitant 150 mg on day 1). The primary endpoint was to compare complete response (CR) rates for vomiting (no vomiting and no rescue medication) during the overall phase (start of chemotherapy to 120 h). The secondary endpoints were CR for nausea (ESAS), toxicities (CTCAE), and patient reported outcome measures (PROM) using MDASI. Assuming CR for vomiting for the overall phase of 77% (power = 90%, 2-sided alpha = 5%, and non-inferiority margin [NI] = 15%), 175 patients in each arm were required (including 5% dropout). **Results:** Between May 2022-Dec 2022, 350 patients were randomized and 346 received the study interventions (OPD arm n = 174 and OPF arm n = 172). The most common chemotherapy used was adriamycin/cyclophosphamide (66%) followed by cisplatin (27%). CR rates for vomiting for the overall phase were 48.8% in the OPD arm and 79.6% in the OPF arm (P < 0.001), with an absolute difference of -30.8% and 2-sided 95% CI = (-40.31, -21.24) which was within the pre-defined NI margin of 15% and also showed superiority. The DEX-free arm also had significantly higher CR rates for nausea and total control (vomiting and nausea combined) (Table). There were no significant differences in any grade CTCAE toxicities. PROM for fatigue (P = 0.009) and drowsiness (P = 0.002) were more in the OPF arm in the acute phase, and insomnia (P < 0.001) in the OPD arm in the delayed phase. **Conclusions:** This study shows that a DEX-free OPF regimen is superior to the DEX-based OPD regimen and should be considered a standard option for CINV prophylaxis for HEC. Clinical trial information: CTRI/2022/03/040906. Research Sponsor: Cancer Institute (WIA).

Phase		OPD (n = 174) % of patients	OPF (n = 172) % of patients	Absolute difference % (95% CI)	P (Chi-square)
CR for Vomiting	Acute (0-24 h)	85.6	94.7	-9.1 (-15.3, -2.9)	0.004
	Delayed (24-120 h)	50.5	81.9	-31.4 (-40.8, -22)	< 0.001
	Overall (0-120 h)	48.8	79.6	-30.8 (-40.3, -21.2)	< 0.001
CR for Nausea	Acute	81.6	77.9	3.7 (-4.7, 12.1)	0.39
	Delayed	39.6	53.4	-13.8 (-24.2, -3.3)	0.009
	Overall	39.1	50.5	-11.4 (-21.8, -0.9)	0.031
Total control	Overall	29.8	45.3	-15.5 (-25.5, -5.4)	0.002

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Poster Session

Palliative care in hematopoietic stem cell transplant recipients and impact on survival: A nationwide analysis. *First Author: Naveen Premnath, University of Texas Southwestern Medical Center, Dallas, TX*

Background: Palliative care benefits have been widely studied in solid tumors with early palliative care demonstrating prolonged survival in several malignancies including lung and esophageal cancer. There are limited data and guidelines for use of palliative care in hematopoietic stem cell transplants (HSCT). **Methods:** We used the National cancer database (NCDB) to identify HSCT recipients between 2004 to 2017 and retrospectively examined the outcomes based on receipt of palliative care. Chi-square and Wilcoxon tests were used to compare categorical and continuous variables respectively. Kaplan Meier analysis and a Cox multivariable proportional hazards model were used for survival analysis using R software. The NCDB is available as de-identified data. Hence, this study was exempt from a full IRB review. **Results:** We identified 17,464 eligible patients with hematologic malignancies who underwent HSCT during 2004-2017. The table below shows differences in baseline characteristics in patients who received palliative care vs no palliative care and shows an improved median survival in those receiving vs those not receiving (43.5 vs 31.6 months) (p = 0.0003). Patients with median household income in the lowest quartile as per 2016 survey data were taken as low-income group. A multivariable cox regression analysis that adjusted for age, sex, Charlson-Deyo Comorbidity Index, insurance status, income and Hispanic ethnicity found that integration of palliative care was associated with improved survival outcomes (HR 0.85, CI 0.77- 0.93, p = 0.0002). **Conclusions:** To our knowledge, this is the largest study demonstrating improved outcomes in HSCT recipients when palliative care was incorporated despite there being more economically challenged patients in the group that received palliative care. Although these data are retrospective and correlational, it underscores how palliative care should be incorporated as part of national society guidelines for HSCT recipients. Research Sponsor: None.

Characteristic	All transplanted patients N = 17464		P value
	Palliative care received	NO Palliative care received	
Cases(n)	636	16828	
Age(years)	58	57	< 0.001
Sex- Male (%)	60.5	58.8	0.40
Hispanics (%)	4.24	6.16	0.06
Uninsured (%)	2.9	3.36	0.69
Low income (lowest quartile) (%)	16.5	13.01	0.009
Charlson Deyo comorbidity index			0.38
0 (%)	81.6	83	
1 (%)	13.6	13.2	
2 (%)	3.8	2.7	
3 (%)	0.9	1.1	
Median survival (months)	43.5	31.6	< 0.001

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Poster Session

Key components of goals of care conversations on determining end-of-life care for advanced cancer patients. *First Author: Amy An, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Early goals of care (GOC) conversations appear to improve end of life (EOL) care in patients with advanced cancer. However, interventions to facilitate GOC conversations may be unsuccessful in changing EOL outcomes due to incomplete understanding of the components of such conversations essential to impacting EOL care. This study seeks to identify the specific components of GOC conversations between patients and oncologists that are associated with less aggressive EOL care. **Methods:** This was a secondary, sequential mixed-methods analysis of data collected as part of the Values and Options in Cancer Care (VOICE) study, an RCT to improve communication between patients and oncologists. We used qualitative methods to describe and quantify components of GOC conversations occurring in recorded oncology office visits. We then conducted logistic regression analyses to examine the associations between key components identified with less aggressive EOL care. **Results:** 107 patients who died within 1 year of the recorded visit were included for analysis. Content related to GOC conversations could be found in 80.4% of visits. Most commonly discussed content was related to treatment (72.9%), followed by prognosis (43.9%), EOL care (17.8%), and patient values and preferences (16.8%). In adjusted analyses, discussion of treatment expectation, offer of an alternative to cancer-directed treatment, and mention of hospice were significantly associated with less aggressive EOL care, OR 4.66 ($p = 0.047$), OR 6.09 ($p = 0.008$), and OR 7.60 ($p = 0.046$) respectively. We did not find significant association between discussion of life expectancy and EOL care. **Conclusions:** GOC conversations may be more effective at impacting EOL care when it includes discussion regarding treatment expectations and offer of an alternative option to cancer-directed therapy, such as hospice. Research Sponsor: None.

12132

Poster Session

Facilitating the transition to posttreatment survivorship for adolescent and young adults: A randomized waitlist control trial of a virtual mind-body intervention. *First Author: Giselle Katiria Perez, Massachusetts General Hospital, Boston, MA*

Background: Adolescent and young adults (AYAs) with cancer experience chronic stress and poor quality of life, particularly in early posttreatment as AYAs grapple with a "new normal." Mind-body programs introduced early posttreatment hold promise for providing AYAs with skills to mitigate the adverse psychosocial and physiological effects of stress. **Methods:** We adapted and piloted an 8-session virtual, mind-body stress management and resilience group program for AYAs (3RP-AYA) to support the posttreatment transition. AYAs were randomized to receive the 3RP-AYA immediately (intervention group; IG) or after 3 months (waitlist control; WC). Data were collected at baseline (T0), 3 (T1) and 6 months (T2). We assessed feasibility by examining 3RP-AYA participation and survey completion rates. Paired-samples t-tests evaluated within-group effects of the 3RP-AYA on coping, distress (worry, depression, uncertainty intolerance), and resilience from T0-T1 (intervention period for IG, waitlist period for WC). Independent-samples t-tests of T0-T1 change scores for each group tested between-group differences in strength of change. Cohen's d characterized strength of within- and between- group differences. Acceptability (i.e., content satisfaction and perceived helpfulness) was assessed at program end (T1 for IG, T2 for WC). **Results:** From 05/19-09/20, 72 AYAs (77% participation rate; $Mage = 23.8$; 73.6% female; mean 18-months posttreatment; 59.7% non-Hispanic white; 20.8% Hispanic; 25% international) were randomized to IG ($n = 35$) or WC ($n = 37$); 85.9% completed 6/8 sessions (median = 7), and 87.5% completed the T1 survey. At enrollment, AYAs presented with elevated worry ($M = 52.5$, $SD = 12.2$) and uncertainty intolerance ($M = 33.8$, $SD = 8.7$), resembling patients with generalized anxiety. From T0-T1, the IG demonstrated moderate-to-large improvements in coping ($d = 0.78$, $p < .001$), worry ($d = 0.45$, $p = .04$), depression ($d = .31$, $p = .11$), tolerance of uncertainty ($d = .37$, $p = .06$) and resilience ($d = .34$, $p = .09$). When examining between-group differences, the IG showed significantly greater improvement in coping ($d = 0.72$, $p = .01$), with non-significantly greater change in worry, depression, tolerance of uncertainty, and resilience ($ds = 0.27-0.49$, $ps > .09$) relative to WC. Notably, 96.6% of participants reported overall content satisfaction, and 91.7% reported the 3RP-AYA was helpful. **Conclusions:** A virtual mind-body program is feasible, acceptable and shows promising efficacy in improving coping and distress among posttreatment AYAs. Findings offer a paradigm shift in the way survivorship care is delivered, suggesting that integrating a mind-body program into early posttreatment survivorship care can facilitate adjustment to life after treatment. This can have downstream effects on the long-term emotional and physical health of AYAs. Clinical trial information: NCT03768336. Research Sponsor: U.S. National Institutes of Health.

12131

Poster Session

Adjuvant endocrine therapy adherence changes among patients after a virtual behavioral intervention. *First Author: Jamie M. Jacobs, Massachusetts General Hospital, Boston, MA*

Background: Adjuvant endocrine therapy (AET) reduces risk of breast cancer (BC) recurrence; however, adherence is suboptimal and interventions are needed. We conducted a randomized controlled trial of a novel telehealth intervention (STRIDE), which led to improvements in symptom distress, coping, quality of life, and mood. Here we examine which patients had improved adherence following STRIDE by exploring characteristics that may moderate intervention effects. **Methods:** Women ($n = 100$) with nonmetastatic BC who reported AET-related distress were randomized to receive STRIDE or a medication monitoring control (MM) between 10/2019-6/2021. STRIDE consisted of six weekly, small-group cognitive behavioral telehealth sessions to enhance symptom management and adherence. All patients stored their AET in electronic MEMS Caps bottles to measure objective adherence. We collected patient characteristics (i.e., months on AET, education) and self-report measures at baseline. Patients completed the Medication Adherence Report Scale (MARS-5) and Cancer Therapy Satisfaction Questionnaire to report adherence behaviors (e.g., "I alter the dose") and AET perceptions (e.g., convenience, expectations, satisfaction), respectively. We conducted hierarchical linear modeling to test moderators of intervention effects on adherence rates (MEMS Caps) across months 1-3, controlling for ovarian suppression receipt and baseline distress due to group differences/stratification. We report the 'time X group X moderator' effects here. **Results:** Among participants reporting greater difficulty (lower MARS-5) with their AET regimen at baseline, STRIDE participants had greater improvement in adherence over time compared to MM participants ($b = -13.80$, $SE = 4.56$, $p < .01$). Greater expectations of therapeutic benefit predicted improvements in adherence for STRIDE versus MM participants ($b = 0.25$ $SE = 0.10$, $p = .01$). Additionally, among participants who reported greater convenience of taking AET ($b = 0.33$ $SE = 0.17$, $p = .06$), had lower education levels ($b = -4.02$, $SE = 2.12$, $p = .06$), and had been taking AET for fewer months ($b = -0.43$ $SE = 0.25$, $p = .09$), STRIDE participants showed adherence increases that approached significance. Other moderators were not significant. **Conclusions:** STRIDE demonstrated effects of a behavioral intervention on AET adherence. Participants reporting greater difficulty adhering to their AET regimen and who expected more benefit showed improved adherence following STRIDE. Gains in adherence from STRIDE were also more pronounced among those who reported that AET was convenient, started the medication more recently, and had lower levels of education. Patient-level and socioeconomic factors influence response to AET adherence interventions. Clinicians may play a key role in addressing modifiable targets at AET initiation (e.g., logistical barriers, perceived benefit) to enhance adherence. Clinical trial information: NCT03837496. Research Sponsor: U.S. National Institutes of Health.

12133

Poster Session

Will we have a match? Observations from decision making conversations between hematologists and White and Black patients considering allogeneic stem cell transplant. *First Author: Thorunn Halldora Thordardottir, University of Wisconsin, Madison, WI*

Background: Allogeneic stem cell transplant (alloSCT) is the only treatment associated with cure for high-risk myelodysplastic syndrome (MDS), but carries substantial risks. One routinely mentioned concern is donor source. While white patients have an 80% chance of finding an unrelated fully matched donor, Black patients have among the lowest chance at 30%. The aim of this secondary analysis, from a telemedicine study assessing how hematologists engage in shared decision making with patients considering alloSCT, is to analyze how hematologists navigate discussions about donor concerns related to the apparent race of the patient. **Methods:** This is a qualitative analysis of transcribed video-recorded virtual encounters. We recruited US hematologists who perform alloSCT and randomized them to meet with a patient actor of Black or white race. The hematologists conducted a new patient encounter with the actors who were trained to portray the same 67 year old man with newly diagnosed high-risk MDS referred for specialty consultation to discuss treatment options. The patient character had multiple healthy siblings and children. **Results:** Transcripts from a total of 33 hematologists were available at the time of analysis (61% male, 30% non-white, mean age 46 +/- 11 years). Hematologists spent varying amounts of time discussing the concept of transplant donation. While some used complex language to describe matching and HLA tissue markers, others used simplified terms of finding a donor with "an immune system that's similar to your own," to eradicate foreign MDS cells and avoid attack on healthy cells. The majority emphasized searching for a donor among siblings, given the highest likelihood of matching. Conversations with the white actor included reassurance of finding a fully matched donor, whether through family or the international registry. Hematologists frequently disclosed the highest chance of success for people of European ancestry. While hematologists mentioned the registry in conversations with the Black actor, they rarely disclosed the lower chance of finding a fully matched unrelated donor. Instead they reassured that with better technology haploidentical match could be an option through donation from their child, "with as favorable outcomes." Some gave the Black actor an overestimation of finding a fully matched donor through the registry. Non-white hematologists more frequently acknowledged the concept of race in stem cell donation. **Conclusions:** Hematologists use multiple strategies to help patients understand the donor process. They reveal to white patients the high likelihood of finding a fully matched donor while appearing to avoid discussing the lower odds for a Black patient. Research Sponsor: University of Wisconsin's "Understanding and Reducing Inequality Initiative" grant.

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Poster Session

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Poster Session

Associations between psychosocial risk factors and immune checkpoint inhibitor outcomes. *First Author: Heather Derry-Vick, Center for Discovery and Innovation, Hackensack Meridian Health, Nutley, NJ*

Background: Psychosocial risk factors such as anxiety and depression can affect immune responses and cancer-related outcomes. Accordingly, we investigated whether an existing anxiety or depression diagnosis influenced immune checkpoint inhibitor (ICI) safety or efficacy. **Methods:** In our multicenter retrospective study across all cancers, we identified 913 patients who began anti-PD-1 or anti-PD-L1 monotherapy [PD(L)-1] between 2011-2018 with follow up until January 2021. Depression and anxiety disorder diagnosis at the time of treatment initiation were abstracted from medical charts. Immune-related adverse events (irAEs) were graded according to CTCAE v4.03. Overall survival (OS) and time to treatment failure (TTF) were recorded. Multivariable logistic regression models and proportional hazard models were used to test relationships between anxiety (or depression) diagnosis and irAEs (any grade vs. none), OS, and TTF, respectively, while adjusting for race, gender, age, and other relevant clinical variables associated with each outcome ($p < 0.1$) in the univariate analysis (e.g., performance status, autoimmune disease, and number of metastatic sites). **Results:** At the time of treatment initiation, 11% ($n = 102$), 12% ($n = 106$), and 4% ($n = 41$) of patients in the overall PD(L)-1 ICI cohort had an anxiety diagnosis, depression diagnosis, or both, respectively. The overall incidence of any grade irAEs was 32% ($n = 295$), including 44% ($n = 45$) and 37% ($n = 39$) among those with anxiety and depression history, respectively. Patients with an anxiety diagnosis had a greater likelihood of experiencing an irAE [Odds ratio (OR) = 1.80; 95% CI = 1.16 to 2.80, $p = 0.009$]. There was not a statistically-significant relationship between depression diagnosis and irAEs (univariable OR = 1.25; 95% CI = 0.82 to 1.91, $p = 0.295$). In the subset of patients with lung cancer ($n = 443$) receiving PD(L)-1 ICI, the rates of any grade irAEs, anxiety, and depression diagnosis were 32% ($n = 143$), 10% ($n = 44$), and 12% ($n = 52$), respectively. In multivariable analysis, anxiety diagnosis was associated with better OS (HR = 0.61; 95% CI = 0.39 to 0.97; $p = 0.038$) and TTF (HR = 0.68; 95% CI = 0.47 to 0.98; $p = 0.038$). The link between anxiety diagnosis and irAEs was weaker in this subsample (OR = 1.46; 95% CI = 0.74 to 2.87, $p = 0.274$). No significant associations between depression diagnosis and any grade irAEs (OR = 0.83; 95% CI = 0.44 to 1.57, $p = 0.573$), OS (HR = 1.06; 95% CI = 0.73 to 1.55, $p = 0.755$), or TTF (HR = 1.13; 95% CI = 0.83 to 1.54, $p = 0.433$) were observed. **Conclusions:** Our results suggest that baseline psychosocial risk factors, especially anxiety disorders, may influence ICI efficacy and safety. Prospective studies are warranted to better understand the relationship between psychosocial risk factors and ICI outcomes. The study also suggests a possible role for targeted supportive care in influencing cancer-related outcomes for those with psychosocial risk factors. Research Sponsor: U.S. National Institutes of Health.

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Poster Session

Analysis of delivery of cancer survivorship education to community health-care professionals. *First Author: Ashley Pariser, Division of Medical Oncology, The Ohio State University Comprehensive Cancer Center, Columbus, OH*

Background: There are currently 18.1 million cancer survivors in the United States; anticipated to reach 26.0 million survivors by 2040. Educational opportunities for healthcare providers in survivorship care is needed to insure capacity for this rapidly growing population particularly in the community setting. This pilot study implemented a cancer survivorship Project ECHO model in two community hospitals within a larger community health system. **Methods:** Providers affiliated with the Mercy Health System were enrolled in one of two cohorts. Eligible participants included physicians, advanced practice providers, nurses, social workers, and dietitians. Six one-hour sessions were developed from a needs assessment and delivered over a 12-week period. Participants were invited to complete pre and post session surveys to evaluate the following 3 domains: professional improvement (PI), self-efficacy (SE), and knowledge (KN). A Likert scale was used with each survey item rated 1-5, where 1 represents lowest and 5 highest (agreement/confidence/knowledge). The average score for survey items within each domain was utilized to compare pre- and post-survey results. **Results:** Fourteen multidisciplinary providers were enrolled in both Cohort 1 and Cohort 2. Twenty-six completed the baseline survey and 22 completed the post-study survey. The mean change of each domain (PI, SE, KN) and mean overall change are summarized in the table. For cohort 1, the overall score significantly increased 0.94 (0.45,1.42) ($P=0.0023$). While the SE and KN domain scores increased significantly (1.1 (0.5,1.7), 1.03 (0.45,1.62) and $p = 0.003$, 0.0036, respectively), the PI did not change -0.09($p=0.726$). For cohort 2, the overall score significantly increased 0.617 (0.042,1.193) ($P=0.0378$). While the SE and KN domain increased significantly (0.728(0.048,1.407), 0.665 (0.041,1.289) and $p = 0.0379$, 0.0387, respectively), the PI did not change ($p=> 0.999$). **Conclusions:** The Cancer Survivorship ECHO model may serve as a scalable strategy for building cancer survivorship care capacity in community-based oncology practices through equipping multidisciplinary teams to meet the needs of cancer survivors within their community. Further research is needed to assess implementation of this model into novel settings and evaluate its impact on patient outcomes. Research Sponsor: U.S. National Institutes of Health.

Summary for PI, SE, KN and overall.									
Domains	Cohort 1					Cohort 2			
	Pre_survey		Post_survey		P_values	Pre_survey		Post_survey	P_values
	N	N	mean (95% CI)	Changes*		N	N	mean (95% CI)	
PI	(2Qs)	12	10	-0.09 (-0.67,0.49) *	0.726	14	12	0.000 (-0.7904,0.7904)*	> 0.999
SE	(8 Qs)	12	10	1.1 (0.5,1.7)*	0.003	14	12	0.728(0.048,1.407)*	0.0379
KN	(8 Qs)	12	10	1.03 (0.45,1.62)	0.0036	14	12	0.665 (0.041,1.289)*	0.0387
Overall (18Qs)		12	10	0.94 (0.45,1.42)	0.0023	14	12	0.617 (0.042,1.193)*	0.0378

* based on linear mixed model for repeated data, SAS software (version 9.4, SAS Inst Inc, NC, USA).

Comparing the time toxicity of cancer treatments in the CCTG LY.12 trial. *First Author: Arjun Gupta, University of Minnesota Masonic Cancer Center, Minneapolis, MN*

Background: When different cancer treatments have similar oncologic outcomes, their respective time-related burdens can aid patient-oncologist decision-making regarding which treatment approach to pursue. We have previously developed a pragmatic and patient-centered metric of these time burdens— which we term “time toxicity”— as any day with physical healthcare system contact. This includes outpatient (e.g., bloodwork, scans, clinician, etc.) and emergency room visits, and overnight stays in a healthcare facility. Herein we sought to assess time toxicity in a completed RCT. **Methods:** We conducted a secondary analysis of the Canadian Cancer Trials Group LY.12 RCT that evaluated 2-3 outpatient cycles of gemcitabine, dexamethasone, and cisplatin (GDP) vs. dexamethasone, cytarabine, and cisplatin (DHAP) in 619 patients with relapsed/refractory lymphoma prior to stem cell transplant. Primary analyses reported similar response rates, transplantation rates, event-free-survival, and overall survival across arms. We calculated patient-level time toxicity by analyzing RCT forms. The study period was the date of assignment to the date of progression or the day before stem cell transplant. We considered days without healthcare contact as “home days”. We compared time measures across arms. **Results:** The median study duration was longer in the GDP arm (50, vs. 47 days in the DHAP arms, $p=0.007$). Median time toxic days were comparable in both arms (18 vs 19 days, $p=0.79$), but median home days were higher in the GDP arm (33 vs 28 days, $p<0.001$). The proportion of time toxic days (time toxic days divided by study duration) was lower in the GDP arm (34%, vs. 38%, $p=0.009$). The GDP arm experienced more time toxicity related to planned outpatient chemotherapy (median, 10 vs. 8 days), but the DHAP arm experienced many more hospitalization days (median, 11 vs. 0 days) (Table). **Conclusions:** This study demonstrates that measures of time toxicity can be extracted from RCTs. These measures can add clinical insight into patient burdens. In LY.12, despite broadly comparable short- and long-term oncologic outcomes, the GDP arm experienced less time toxicity. Such information can guide decision-making for patients with aggressive hematologic cancers, who already spend a significant portion of time with healthcare contact. Clinical trial information: NCT00078949. Research Sponsor: Canadian Cancer Society Research Institute; Roche Canada and Eli Lilly Canada.

Time toxicity measures in LY.12.			
Time toxicity measure, median (interquartile range)	GDP N=306	DHAP N=304	p-value
Study duration, days	50 (43, 64)	47 (42, 62)	0.007
Time toxic days	18 (15, 23)	19 (14, 26)	0.79
Home days	33 (25, 43)	28 (20, 39)	<0.001
Proportion of time toxic days (time toxic days /study duration), %	34 (29, 44)	38 (28, 50)	0.009
Sources of time toxicity (not mutually exclusive)			
Chemotherapy	10 (10, 14)	8 (8, 10)	<0.001
Bloodwork	6 (4, 8)	6 (4, 9)	0.981
Scans	1 (1, 2)	1 (1, 1)	0.01
Additional outpatient visits	0 (0, 0)	0 (0, 0)	0.665
Transfusions	0 (0, 1)	0 (0, 2)	<0.001
Hospitalized	0 (0, 5)	11 (8, 17)	<0.001

TPS12137

Poster Session

The FARGO study: Frailty assessment for risk prediction in gynecologic oncology. *First Author: Julie My Van Nguyen, Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, McMaster University, Hamilton, ON, Canada*

Background: Little is known about how to best predict postoperative outcomes and chemotherapy tolerance in an increasingly aging and complex gynecologic oncology (GO) population. Frailty is a multidimensional age-related and disease-related state of vulnerability to stressors due to reduced capacity of different physiological systems. Resource limitations are a barrier to routine adoption of frailty assessments through comprehensive clinical evaluations in daily practice. This highlights the relevance of studying potential biomarkers of frailty, which could complement or replace clinical assessments. Frailty has been associated with worse perioperative and oncologic outcomes in many subspecialties, however the literature in patients with gynecologic malignancies is very limited. **Methods:** The FARGO study is a multi-centre prospective cohort study of 280 patients aged ≥ 55 years-old undergoing surgery, with or without chemotherapy for a suspected or confirmed gynecologic malignancy. Patient recruitment will occur over 13 months. The over-arching goal is to evaluate the predictive value of frailty assessments in predicting surgical and chemotherapy outcomes. The two primary objectives are: 1) To evaluate the predictive value of preoperative frailty assessment based on the Frailty Phenotype (FP), compared to a perioperative cardiovascular risk assessment, in predicting the composite of all-cause death or new disability at 6 months after surgery 2) To create of a biobank to explore possible biomarkers of frailty, including mitochondrial DNA levels. Secondary objectives include to evaluate the predictive value of clinical and biomarker frailty assessment for 30-day postoperative complications, for chemotherapy tolerance and 1-year recurrence-free survival. Patients will undergo frailty and cardiovascular risk assessment prior to surgery and/or neoadjuvant chemotherapy. A trained clinical research assistant will measure frailty based on the clinical frailty scale (CFS) and the FP. The cardiovascular risk calculation will be based on the preoperative Revised Cardiac Risk Index, age, and occurrence of myocardial injury after non-cardiac surgery (MINS). Research personnel blinded to the frailty and cardiovascular risk assessment will evaluate study outcomes including death, disability, and clinical events at 30 days, 6 months, and 12 months after surgery. Disability will be measured with the WHODAS 2.0 (World Health Organization Disability Assessment Schedule), a validated patient-reported outcome measure. Pre-specified blood biomarkers will be measured. Our study emphasizes patient-centered outcomes (i.e. loss of independence, short and long-term disability) and system-level outcomes. Our findings may have important implications to assist in risk stratification and planning for oncologic treatments and perioperative care needs. Research Sponsor: Population Health Research Institute; Hamilton Health Sciences Foundation, Juravinski Hospital and Cancer Centre Foundation.

TPS12138

Poster Session

Comprehensive geriatric assessment based multidisciplinary team intervention for hospitalized frail patients in oncology: COMPASS-ONCO/KCSG AL21-13. *First Author: Yun-Gyoo Lee, Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, South Korea*

Background: Comprehensive geriatric assessment (CGA) is a multidimensional, interdisciplinary assessment for evaluating older patients' medical, psychological, physical functions and social status. CGA-based multidimensional intervention is the gold standard in geriatric oncology to identify patients at high risk of adverse outcomes and optimize cancer and overall management. Numerous studies have demonstrated that CGA could modify oncologic treatment decision. However, little is known about the treatment outcomes of a multidisciplinary team intervention based on CGA. **Methods:** The COMPASS study is the first pragmatic multicentre trial within a cohort comprising three randomized controlled trials focusing on focusing on CGA and multidisciplinary intervention for hospitalised elderly patients in various healthcare settings of Korea. COMPASS-ONCO compares the effect of an oncologist-led multidisciplinary team intervention based on the CGA to that of conventional treatment for older cancer patients without the involvement of geriatricians. The patients will be randomised into the intervention or control groups in a 1:1 ratio. The inclusion criteria are as follows: (1) 65 years of age or older, (2) prefrail or frail status assessed by Korean version of the Fatigue, Resistance, Ambulation, Illnesses and Loss of Weight scale questionnaire, (3) having two or more of the following diseases: hypertension, diabetes, ischaemic heart disease, chronic lung disease, arthritis, stroke, depression, chronic kidney disease and dementia. (4) living at home for more than 3 months before hospitalization, (5) subject to palliative chemotherapy and (6) histologically confirmed gastric, colorectal, lung, pancreatic or biliary tract carcinoma. The intervention includes CGA and CGA-based multidisciplinary interventions by oncologists, nurses, nutritionists and pharmacists. The multidisciplinary intervention includes nutritional support, medication review and adjustment, rehabilitation, early discharge planning and prevention of geriatric syndromes (falls, delirium, pressure sore and urinary retention). The analysis will be based on an intention-to-treat principle. The primary outcome is overall treatment utility which is a clinical outcome incorporating objective and subjective measures of anticancer efficacy, tolerability and acceptability. Additionally, recognition of advance directives, changes in body composition and validity of anticancer drug toxicity prediction model will also be assessed. Approximately 1040 patients will be required for COMPASS study, and 260 will be enrolled in the COMPASS-ONCO substudy at five hospitals in Korea. Participants have been recruited from 2 November 2021, and recruitment will continue until December 2024. Clinical trial information: KCT0006270. Research Sponsor: Patient-Centered Clinical Research Coordinating Center (PACEN) funded by the Ministry of Health & Welfare, Republic of Korea (Grant number: HC20C0086).

TPS12140

Poster Session

Evaluating the impact of exercise in women living with indolent metastatic breast cancer: The EMBODY trial. *First Author: Martha Cancilla, IU School of Medicine, Indianapolis, IN*

Background: Exercise is associated with improved survival, physical function, treatment tolerability, and quality of life in early-stage breast cancer. Prospective trials support the positive impact of exercise on cardiorespiratory fitness (CRF), physical function, and muscle mass. These same endpoints matter in metastatic breast cancer (MBC). CRF is a predictor of worse cancer-specific survival, and there is a high prevalence of physical impairment and sarcopenia in patients with MBC, both associated with worse quality of life and survival. Two previous exercise trials in those with MBC have found exercise to be not feasible or of limited benefit. These findings may be due to a heterogeneous participant population that is primarily receiving cytotoxic chemotherapy. Patients with MBC have variable disease trajectories and supportive care needs; those with indolent MBC have longer life expectancy, lower symptom burden and distinct priorities, and are well-positioned to participate in and benefit from an exercise program. The EMBODY trial is focused on enrolling a homogeneous patient population with indolent, stable MBC and improving endpoints known to correlate with survival outcomes in this population. Here, we evaluate the impact of a multimodal exercise intervention on CRF, physical function, body composition, and PROs. This study will be a step toward redefining "survivorship" to extend to those living with MBC. **Methods:** In this prospective phase II trial (NCT05468034), 100 patients with MBC are randomized 1:1 to exercise intervention or wait-list control, stratified by baseline function. Eligible patients have no evidence of disease progression in the prior 12 months and may be receiving endocrine, targeted, immuno-, or antibody drug conjugate therapy. Patients receiving cytotoxic chemotherapy are not eligible as this subgroup did not benefit in prior trials. Target enrollment is 3-4 participants per month over 2.5 years, beginning January 2023. The virtually-delivered exercise intervention arm achieves moderate intensity exercise with oncology-certified exercise physiologists 3 days/week for 16 weeks. The 60-minute sessions include aerobic, resistance, balance and stretching exercises. The exercise arm receives informational sessions on the role of exercise in cancer and principles of habit and self-efficacy. The primary endpoint is 16 week change in CRF on a ramp treadmill test between the exercise and control arms. Secondary endpoints include change in a physical function battery, muscle mass assessed by CT scans, and PROs of fatigue and quality of life. Exploratory analysis includes behavioral modifiers of exercise adherence and effectiveness and serologic measures of inflammatory, metabolic, and immune pathway biomarkers, as well as changes in circulating tumor cells. Patients will be followed post-intervention for sustained behavior change and survival trajectory. Clinical trial information: NCT05468034. Research Sponsor: Susan G Komen Career Catalyst Research Grant.

TPS12139

Poster Session

Digital voice analysis as a measure of frailty and distress: A feasibility study (DIVAN). *First Author: Marcus Vetter, Cancer Center Baselland, Liestal, Switzerland*

Background: Assessing of frailty is essential not only in older patients with cancer, because frailty changes management of cancer therapy. Same is true for the routine assessment of distress to identify patient suffering and initiate adequate symptom control or psychosocial interventions. Here we present new potential method of frailty and distress assessment with digital voice analysis as a proof of concept trial. (NCT requested pending, DIVAN-1). **Methods:** Adult patients with the diagnosis of active incurable cancer can be enrolled into this study. Every participant will describe two to four images presented to him or her on a tablet computer in up to four sessions, and the patient's voice will be recorded digitally. Baseline characteristics including cancer type, stage, therapy, G8 questionnaire and distress questionnaire (ESAS) will be collected at every session. Acoustic features like mean fundamental frequency (F0) and first few formants (F1, F2, etc.), jitter (variation in F0 from cycle to cycle), shimmer (variation in peak-to-peak amplitude), etc. will be explored digitally along with for example and voice strength (volume). Additionally, a vowel test will conducted and explored. Depending on the distribution of the data, the Pearson R correlation test or the Spearman's R correlation test will be applied for each variable. The primary research question of this feasibility study is to identify quantitative parameters out of the audio signal to describe the changes in patient's state in relation to frailty and distress. Trial enrolment has begun in December 2022 and 11 out of 100 patients have been included. Clinical trial information: NCT05783401. Research Sponsor: Research Funding by FHNW, PZH, KSBL, Switzerland.

TPS12141

Poster Session

Comprehensive Outcomes for After Cancer Health: COACH. *First Author: Robin Mary Lally, University of Nebraska Medical Center, Omaha, NE*

Background: The landscape for cancer survivors continues to evolve as individuals live longer following primary therapy. For some, treatment is complete; for others, active surveillance or maintenance therapy may be indicated. Individual survivorship needs are diverse, influenced by tumor and treatment type, as well as social determinants of health. Digital interventions may support survivors in achieving personalized health goals throughout survivorship. The Comprehensive Outcomes for After Cancer Health (COACH) Study (NCT05349227) explores the feasibility of a digital health coaching (DHC) program for individuals enrolled with diverse tumor types and geographic regions. **Methods:** COACH is a multi-center, randomized, wait-list control trial enrolling 550 individuals ≥ 18 years old who are within 1-year of completion of primary cancer therapy at enrollment. Up to 100 participants, will be recruited at each of 6 study sites, of which 3 are currently enrolling. Consented individuals are randomized to 6 months of DHC or 6 months of data collection only, then cross-over for follow-up to 12-months. Both groups wear an activity tracker; complete patient reported outcome measures; and provide fecal specimens. The DHC program includes weekly Health Advisor calls and supplemental delivery of evidenced-based content via text, email or mobile platform. Topics fall in health domains of physical, mental/emotional, financial, social, and sexual, and emphasize nutrition, physical activity, sleep, and screening for recurrent or de novo cancer. Feasibility for this study is defined as a retention rate greater than or equal to 70%, and acceptability will be defined as less than or equal to 20% scoring "not at all helpful." Trends over time will be assessed using linear mixed models using time as a fixed effect, as well as any covariates and interactions of interest. Descriptive statistics will be used to evaluate exploratory endpoints. A cross-cohort end-point related to physical function as measured by the PROMIS Physical Function 10a, will also be evaluated. To date, 72 individuals have enrolled, with Nebraska as the lead site, including 71 women, with a mean age of 61.78 (Range 33-74), from the U.S. Midwest (n = 57) and Northeast (n = 15). 4 identify as African American/Black, 68 as White. 50 have a breast, 13 ovarian, 8 endometrial, 1 gastric diagnosis. Nine have completed the first 6 months of the study. The study is novel in the breadth of data collected and potential to understand variability in patient experiences and provide insights into the feasibility, acceptability, and efficacy of a DHC intervention supporting individuals after primary cancer treatment. Clinical trial information: NCT05349227. Research Sponsor: Daiichi-Sankyo; Gilead Sciences; GSK; Ohio State University; University of Florida.

TPS12142

Poster Session

The CROWN study (CaRdiac outcomes with near complete estrogen deprivation): A multicenter, prospective cohort study of cardiovascular outcomes in premenopausal women with hormone receptor positive breast cancer treated with ovarian suppression and an aromatase inhibitor. *First Author: Emily H. Douglas, Wake Forest University School of Medicine, Winston-Salem, NC*

Background: Treatment for premenopausal women with high or intermediate risk hormone receptor (HR)+ breast cancer (BC) now includes the concurrent use of ovarian function suppression (OFS) and an aromatase inhibitor (AI) to induce near complete estrogen deprivation (NCED). The long-term cardiovascular (CV) sequela for women treated with NCED is unknown. Premature menopause in non-cancer populations is associated with CV disease. Taken together with the CV morbidity associated with other aspects of BC treatment and the future life-years of these women, the CV impact of NCED warrants further study. The CROWN study will use sophisticated imaging assessments of cardiac dysfunction to understand the evolution of CV injury, as well as biomarker and demographic correlates, with the goal of developing tools to assess and mitigate CV risk. **Methods:** This is a NIH funded prospective cohort study conducted at 3 regional NCI-supported Cancer Centers (Atrium Health Wake Forest Baptist, Virginia Commonwealth and Duke) that will include premenopausal women, age $\leq$ 55, with Stage I-III BC following completion of planned chemotherapy, surgery and radiation with an ECOG 0-1. HR+ BC patients will receive an AI and OFS. Women with HR- BC are included as comparators. CV imaging and biomarkers will be obtained at baseline, 1 year and 2 years (Table 1). These assessments will include serial cardiac magnetic resonance (CMR) and coronary computed tomography angiography (CCTA) imaging as well as laboratory measurements, including exploratory biomarkers. The primary objective is to determine the 24-month difference in stress myocardial blood flow as measured by adenosine CMR imaging in both groups. We will correlate CMR imaging with CCTA to provide complementary detail of coronary plaque changes. The study will also assess the relevance of pre-existing risk factors on study outcomes, including an emphasis on racial disparities, and dynamic change in modifiable and treatment related risk factors. We plan to enroll 90 women, 67 in the NCED group and 23 in the HR-group, allowing for a 10% drop out rate. There are two primary types of statistical analyses. The first includes testing hypotheses between group (NCED vs HR-) and within group (longitudinal changes within the NCED group). The second analyses, involve developing predictive equations utilizing a stepwise linear regression approach to determine if patient demographics, clinical parameters and serum biomarkers are associated with cardiovascular changes over time. Present accrual is 4. Clinical trial information: NCT05309655. Research Sponsor: U.S. National Institutes of Health; Williams Family Chair in Breast Oncology.

Study procedures.			
Evaluation/Procedure	Baseline	Year 1	Year 2
Vitals	X	X	X
Body measurements: (Height, Weight, BMI, Waist circumference)	X	X	X
Labs/Biomarkers	X		X
CMR	X	X	X
CCTA	X		X
EKG	X		X
Patient questionnaires	X	X	X

TPS12144

Poster Session

A randomized phase III clinical trial of acupuncture for chemotherapy-induced peripheral neuropathy in survivors of cancer. *First Author: Ivana Lopez-Nieves, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Chemotherapy-induced peripheral neuropathy (CIPN) is a common and debilitating side effect in cancer survivors that can last long after completion of neurotoxic chemotherapy. Patients with CIPN often experience neuropathy symptoms such as pain, tingling, numbness, paresthesia, and dysesthesia, which can lead to significant functional decline and diminished quality of life. This outcome highlights the importance of developing effective CIPN treatments to improve quality of life for this population. Identifying nonpharmacological approaches to reduce CIPN symptoms and improve cancer survivors' outcomes is urgently needed. Acupuncture is a widely used, minimally invasive Traditional Chinese Medicine technique that has shown promising evidence as an effective and safe treatment for CIPN. We hypothesize that acupuncture may reduce CIPN pain and improve overall CIPN symptoms in cancer survivors. **Methods:** We are conducting a two-arm, parallel randomized clinical trial comparing electro-acupuncture (EA) versus sham acupuncture (SA) in cancer survivors. The EA arm includes ten sessions of EA over eight weeks using a standardized, semi-fixed protocol developed by our group. The SA arm includes a sham technique that uses a combination of non-acupuncture points and a non-insertion procedure in ten sessions over eight weeks. The primary outcome of this study is the Brief Pain Inventory-Short Form average pain item. The secondary outcomes are quantitative sensory testing measures and patient-reported outcomes that include the Neuropathic Pain Scale, Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity, CIPN-20, PROMIS Global Health Scale, and Patients' Global Impression of Change. The primary end point is week 12 and the secondary end point is week 24; treatment effects are assessed at baseline and at weeks 4, 8, 12, 18, and 24. The eligibility criteria includes: 1) Patients must be have no evidence of disease or have stable disease; 2) CIPN diagnosis with moderate-to-severe CIPN pain, defined by a score of 4 or greater on a scale 0-10 numerical scale rating; 3) completed neurotoxic chemotherapy at least three months prior; and 4) no changes in anti-neuropathy medications within three months of enrollment. As of February 2023, we have accrued 89 participants, with a total accrual target of 250 participants. Accrual completion is anticipated by December 2024. The demographic breakdown of our participants is as following: 71% white, 15% black or African American, 10% Asian, 3% more than one race, and 1% Native Hawaiian or Pacific Islander. 89% of the participants are non-Hispanic or Latino, 10% are Hispanic or Latino, and 1% are unknown. 71% of the participants are female and 29% are male. Clinical trial information: NCT04917796. Research Sponsor: U.S. National Institutes of Health.

TPS12143

Poster Session

A randomized phase III clinical trial of yoga for chemotherapy-induced peripheral neuropathy treatment. *First Author: Kirin Saint, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Chemotherapy-induced peripheral neuropathy (CIPN) is a common, painful, and debilitating side effect of many standard chemotherapy regimens. CIPN symptoms include pain, paresthesia, and muscle weakness, and patients may exhibit functional decline and lower quality of life. Our prior study showed more than half of breast cancer survivors experience persistent CIPN up to a mean duration of 5.6 years, which is associated with a doubled fall risk. Identifying non-pharmacological approaches to reduce CIPN symptoms and improve cancer survivors' outcomes is urgently needed. Yoga is a meditative movement therapy that includes stretching, and flexibility and balance training. Our pilot study (NCT03292328) demonstrated that yoga reduced CIPN-related symptoms, and improved quality of life and functional reach scores compared to waitlist control. We hypothesize that yoga can reduce CIPN symptoms, improve function, and reduce the risk of falls. **Methods:** We are conducting a three-arm randomized education and usual care-controlled trial in cancer survivors with chronic CIPN pain at Memorial Sloan Kettering Cancer Center (MSK), New York, NY. Participants in the intervention arm will receive twice-weekly one-hour Hatha yoga classes taught virtually by MSK instructors and practice yoga at home daily for eight weeks. Participants in the education control arm will receive one-hour virtual education classes twice per week taught by an MSK instructor for eight weeks. Participants in the usual care arm will continue their usual care for CIPN for eight weeks. The primary endpoint is the Brief Pain Inventory-Short Form average pain item at weeks 8 and 24. Secondary outcomes include the Neuropathic Pain Scale, Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity, Patient-Reported Outcomes Measurement Information System Global Health, Brief Fatigue Inventory, Insomnia Severity Index, Hospital Anxiety and Depression Scale, Quality of Life Questionnaire of CIPN twenty-item scale, functional assessments, and quantitative sensory testing at weeks 0, 4, 8, 12, 18, and 24. Eligibility criteria include: 1) Moderate-to-severe CIPN pain, defined by a score of 4 or greater on a 0-10 numerical rating scale; 2) completion of neurotoxic chemotherapy at least three months prior; 3) no changes in anti-neuropathy medications within three months of enrollment; and 4) changes in balance and functionality. As of February 2023, we have accrued 64 of our total target of 268 participants. We anticipate completing accrual in March 2025. We have 35 participants in the yoga intervention, 15 participants in education control, and 14 participants in usual care control. The majority (89%) of participants are female and 11% are male. 78% of our participants are white, 16% are black or African American, 1% are Asian, and 5% identify as more than one race. Clinical trial information: NCT05121558. Research Sponsor: U.S. National Institutes of Health.

TPS12145

Poster Session

Objective assessment of fatigue, sleep and insomnia in breast cancer survivors on estrogen deprivation therapy. *First Author: Lauren A. Fowler, University of South Carolina School of Medicine, Greenville, Greenville, SC*

Background: Fatigue, insomnia and sleep problems are common among breast cancer survivors (BCS). These symptoms remain underassessed, underreported and undertreated. Validated and objective measures of sleep metrics have yet to be widely incorporated into BCS studies to help examine the role that these play on patient patient reported fatigue and insomnia. While more than 50% of BCS experience fatigue and insomnia, most research on BCS fatigue is limited to short-term, self-report data that does not objectively assess sleep metrics. Estrogen Deprivation Therapy (EDT) has been shown to exacerbate sleep problems and contribute to perceptions of fatigue and insomnia, yet there is a paucity of research examining the specific effects of EDT on sleep metrics over time, especially objective measures. Wrist actigraphy is a non-invasive, objective measure of rest/activity cycles and sleep via a wrist-worn device. This study utilizes a novel instrument, called Readwatch (Fatigue Sciences). It is widely validated in the military and in industry but has not been used in patient studies. The Readwatch assesses fatigue and estimates cognitive performance, based on the Sleep Activity and Task Effectiveness (SAFTE) model developed in conjunction with the Department of Defense in 2004. The Readwatch syncs with the Fatigue Avoidance Scheduling Tool (FAST) app on the participant's smartphone to provide a score, called Readscore, based on previous sleep and activity. It has been shown to have greater than 92% accuracy with lab polysomnography results. The Readscore also serves as a "cognition" measure that represents the person's cognitive capacity based on sleep metrics. This novel, objective feedback to the BCS could be very accessible and useful in community medical practice. **Methods:** This single-center, pilot study of BCS, receiving endocrine therapy, possessing a smartphone and Scoring >8 on the Insomnia Severity Index (ISI), has enrolled 25 of 50 planned participants. Participants wear the Readwatch for two months to objectively assess their sleep metrics. Patient reported levels of fatigue and insomnia will be assessed prior to, midway, and following the two-month period. Participants document their self-reported experiences through surveys and track their own sleep and fatigue metrics using their smartphone app. At the conclusion of the study participants are provided with personalized feedback about their sleep metrics, along with detailed information related to sleep hygiene. Data analysis will model the effect of actigraphy fatigue measures on reported pain, anxiety, depression, and cognitive impairment and will also examine sleep metrics, perceptions of fatigue and insomnia scores in relation to type of EDT the patient is currently undergoing to determine if there are specific types of adjuvant therapy that are associated with fewer fatigue and insomnia problems. Research Sponsor: University of South Carolina School of Medicine Greenville seed grant.

TPS12146

Poster Session

Phase III, international, multicentre, double-blind, dose increment, parallel-arm, randomised controlled trial of duloxetine versus pregabalin for opioid-unresponsive neuropathic cancer pain. *First Author: Hiromichi Matsuoka, National Cancer Center Japan, Tokyo, Japan*

Background: Management of neuropathic cancer pain (NCP) refractory to regular opioids remains an important challenge. The efficacy of pregabalin for NCP except chemotherapy-induced peripheral neuropathy has already been confirmed in two randomised controlled trials (RCTs) compared with placebo. Duloxetine offers the potential of analgesia in opioid refractory NCP. However, there are no RCT of duloxetine for the management of opioid-refractory NCP as a first line treatment. Both classes of drugs have the potential to reduce NCP, but there has been no head-to-head comparison for the efficacy and safety, especially given differing side effect profiles.

Methods: An international, multicentre, double-blind, dose increment, parallel-arm, RCT. Eligibility criteria include: adult cancer patients experiencing NCP refractory to opioids; Brief Pain Inventory (BPI)-item 3 (worst pain) ≥ 4 ; Neuropathic Pain on the Leeds Assessment of Neuropathic Symptoms and Signs Pain Scale ≥ 12 despite of an adequate trial of regular opioid medication (≥ 60 mg/day oral morphine equivalent dose). The study will recruit inpatients and outpatients in Japan and Australia. Participants will be randomised (1:1 allocation ratio) to duloxetine or pregabalin. Dose escalation is to day 14 and from day 14 to 21 is a dose de-escalation period to avoid withdrawal effects. Dose escalation schedule in each-arm is shown in Table 1. The primary endpoint is the mean difference in BPI item 3 over the previous 24 hours on day 14 between groups. Null hypothesis is there is no difference in BPI item 3 in the previous 24 hours on day 14 between both groups for patients with opioid refractory NCP. Comparison of the BPI item 3 on day 14 between duloxetine groups and pregabalin groups will be conducted using a two-sided Student's t-test at a significance level of 5% according to the intention-to-treat principle. Point estimates and 95% CIs for the difference between two groups will be calculated. A sample size of 160 participants is required with 67 subjects enrolled to date. The DSMC last reviewed the trial in December 2022 and case accumulation expected to be completed by the end of 2024. Table 1 : Dose escalation schedule in each-arm. Duloxetine Arm Stage 1 (Day 1-3): Duloxetine (30 mg) 1 capsule (morning) and Placebo 1 capsule (bedtime) Stage 2 (Day 4-7): Same as Stage 1 Stage 3 (Day 8-14): Duloxetine (30 mg) 1 capsule twice a day (morning and bedtime). Pregabalin Arm Stage 1 (Day 1-3): Pregabalin (25 mg) 1 capsule twice a day (morning and bedtime). Stage 2 (Day 4-7): Pregabalin (75 mg) 1 capsule twice a day (morning and bedtime). Stage 3 (Day 8-14): Pregabalin (75 mg) 2 capsules (150 mg) twice a day (morning and bedtime). Clinical trial information: ACTRN12620000656932, jRCTs051190087. Research Sponsor: The Australian Government National Health and Medical Research Council; Japan Agency for Medical Research and Development (AMED), Grant-in-Aid for Scientific Research.

TPS12148

Poster Session

Prospective observational study to evaluate lemborexant utility in insomnia among women with breast cancer (WJOG14921B, LUNAR study). *First Author: Yukinori Ozaki, Breast Medical Oncology Department, The Cancer Institute Hospital of JFCR, Tokyo, Japan*

Background: Insomnia occurs in approximately 60% of cancer patients. The importance of early intervention to treat insomnia has been advocated because insomnia may be associated with poor prognosis, early discontinuation of treatment and decreased quality of life. It has been reported that breast cancer patients receiving endocrine therapy have the highest rate of insomnia among all cancer patients due to vasomotor symptoms (ie, hot flashes) and comorbid symptoms associated with fatigue and depression. Insomnia has also been found to occur in patients with metastatic/recurrent breast cancer. Lemborexant (LEM) is a dual orexin receptor antagonist, which has been shown to be effective for insomnia patients without malignancies. In clinical practice, while LEM has been administered to cancer patients with insomnia, there are no prospective data. The aim of this study is to evaluate prospectively whether LEM improves insomnia in patients with breast cancer receiving endocrine therapy.

Methods: This is an open-label, prospective, multicenter, observational study to evaluate efficacy and safety of LEM to treat insomnia in patients with breast cancer receiving endocrine therapy [UMIN000047718]. The primary endpoint is change from baseline of total Insomnia Severity Index (ISI) score at 1 month. Secondary endpoints include change from baseline of cancer fatigue scale scores, EORTC QLQ C-30 and BR23 score, and Patient Health Questionnaire-9 score after 1 month and 3 months, change from baseline in total sleep time and sleep efficiency using an electronic sleep diary after 2 weeks, 1 month and 3 months, and safety profile. Exploratory endpoints include biomarker analysis including evaluation of cytokines and orexin A levels, and evaluation of sleep parameters using Oura ring, which is a ring-type wearable device. The primary endpoint will be assessed by the Wilcoxon signed-rank test. Total sample size will be 70 patients (adjuvant cohort: 50 patients, recurrent and/or metastatic cohort: 20 patients). Patients ≥ 20 , meeting Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition for Insomnia Disorder and ISI score ≥ 10 will be eligible. LEM 5mg will be administered orally every night. Dosage of LEM will follow clinical practice and the Japanese LEM label. Enrollment began in September 2022; 14 patients have been recruited in adjuvant cohort as of January 2023. Clinical trial information: UMIN000047718. Research Sponsor: Eisai.

TPS12147

Poster Session

Phase 2 study to assess the efficacy, safety, and tolerability of the GDF-15 inhibitor ponesegromab in patients with cancer cachexia. *First Author: Jeffrey Crawford, Duke Cancer Institute, Durham, NC*

Background: Cancer cachexia is a multifactorial metabolic syndrome of wasting characterized by anorexia, unintended weight loss, and decreased skeletal muscle mass, leading to progressive functional impairment, fatigue, diminished quality of life, poor response to anticancer therapy, and reduced survival. One of the biomarkers associated with cancer cachexia is cytokine growth differentiation factor 15 (GDF-15), which is secreted by tumor cells. Preliminary phase 1 data suggest that suppression of GDF-15 may lead to improvement in cachexia-related symptom burden. Ponesegromab is a potent and selective humanized monoclonal antibody that inhibits GDF-15-mediated signaling. The primary objective of this study (NCT05546476) is to assess the effect of ponesegromab on body weight in patients with cancer, cachexia, and elevated circulating GDF-15 concentrations. Secondary objectives include assessing physical activity, gait, anorexia/appetite, nausea and vomiting, fatigue, and safety. Exploratory objectives include evaluating pharmacokinetics, pharmacodynamics, and immunogenicity. **Methods:** This phase 2 study will enroll approximately 168 adults with non-small cell lung, pancreatic, or colorectal cancers who have cachexia and elevated GDF-15 concentrations. The study will be conducted in 2 parts. The initial 12-week treatment period will be a randomized, double-blind, placebo-controlled study wherein participants who meet eligibility criteria will be randomized 1:1:1 to one of 3 dose groups of ponesegromab (administered subcutaneously [SC] every 4 weeks [Q4W]) or placebo. The double-blind period will be followed by optional open-label treatment (OLT) with ponesegromab Q4W SC for up to 1 year. Upon completion of the optional OLT period, there will be a follow-up visit at Week 72. Participants who do not proceed with the optional OLT period will complete the Week 12 visit and a follow-up visit at Week 16. The primary endpoint is the mean change from baseline in body weight at Week 12. A mixed model for repeated measures followed by a Bayesian E_{max} model will be used for the primary analysis. Secondary endpoints include physical activity and gait measured by remote digital sensors; patient-reported appetite-related symptoms assessed by Functional Assessment of Anorexia-Cachexia Therapy scores; anorexia/appetite, nausea, vomiting, and fatigue evaluated according to questions from the Cancer-related Cachexia Symptom Diary; and incidence of adverse events, safety laboratory tests, vital signs, and electrocardiogram abnormalities. © 2023 American Association for Cancer Research®. Reused with permission. Clinical trial information: NCT05546476. Research Sponsor: Pfizer.

TPS12149

Poster Session

Study for the prevention of oral mucositis. *First Author: Artem Oganessian, Hematology Center after R. Yeolyan, Yerevan, Armenia*

Background: Oral mucositis (OM) is a serious complication of cancer treatments characterized by erythema and ulcerations of the mouth. Consequences of OM include pain, diminished functionality, and infections leading to decreased quality of life and discontinuity in therapy. About 20-40% of patients receiving chemotherapy develop OM within 7 days of treatment initiation. Current clinical guidelines recommend prophylactic oral care, cryotherapy, KGF-1, palifermin, and photobiomodulation to prevent OM in specific patient groups. Benzydamine is approved for the prevention of OM in head and neck cancer patients receiving radiotherapy or radio-chemotherapy but has not been well studied for chemotherapy alone. The effectiveness of oral topical treatments is limited by dilution in the saliva and swallowing shortening the duration of their action. Bocaliner is a novel medical device that is hypothesized to enhance the effects of treatments by prolonging the oral retention of topical therapies within the oral cavity.

Methods: The Study for the Prevention of Oral Mucositis (SPOM) is a randomized controlled Phase I/II trial that aims to evaluate the efficacy of two different tools (benzydamine mouthwash and Bocaliner) in reducing the incidence and severity of OM in patients undergoing systemic chemotherapy (NCT05338398). A total of 100 adult patients with hematologic malignancies undergoing chemotherapy in a centralized hematology center in Armenia will be randomized into two different treatment groups: saline mouthwash and benzydamine mouthwash (0.15%, 120mL) 3-5 times a day for a total of two weeks. Half of the patients within each group will also randomly receive Bocaliner, which will be placed inside of their mouth immediately after the application of the mouthwash for 20 minutes. Block randomization will be applied with 4 patients per block with 1:1 randomization based on gender, Bocaliner use, and mouthwash type. The primary endpoint is the difference in OM incidence measured by the WHO Oral Toxicity Scale. The secondary endpoints are differences in OM symptoms evaluated using a modified version of the PROMS questionnaire. Safety and tolerability of the medical device will be determined for the Phase I component of the study based on responses to standardized tryout (Day 0) and follow-up questionnaires (Day 14). Other outcomes include the duration and severity of OM. Statistical analysis will explore further clinically meaningful associations between patient data, received therapies, and outcomes. Forty-two patients have already completed the study, while the enrollment of other participants continues and is planned to be completed by the end of 2023. Clinical trial information: NCT05338398. Research Sponsor: E2Bio Life Sciences.

TPS12150

Poster Session

Effects of virtual reality on pain and anxiety in patients with cancer undergoing bone marrow biopsy. *First Author: Jacek K. Pinski, USC/Norris Comprehensive Cancer Center, Los Angeles, CA*

Background: Patients with cancer endure numerous procedures over their diagnosis and treatment course, many of which are invasive, causing significant distress beyond the emotional hardship of living with cancer. The utility of virtual reality (VR) as a companion to bone marrow biopsy will be evaluated in terms of its psychological and biological impacts, through patient reported pain scores, anxiety surveys and through assessment of serum biomarkers correlated with pain and anxiety. VR is the immersive simulation of a realistic, three-dimensional environment, generated via interactive software and hardware. The objectives of this study are to determine the feasibility of VR in patients undergoing a bone marrow biopsy and to estimate differences between the two arms in terms of pain and anxiety. In addition, we plan to explore the use of biomarkers associated with stress as a tool to reflect the impact of this intervention. We hypothesize a decrease in pain, anxiety and stress levels peri- and post-procedure in the VR arm compared to the non-VR arm (standard of care).

Methods: Patients with hematologic malignancies at USC/Norris Cancer Hospital or Keck Medical Center of USC are being randomized 1:1 to either arm 1 (experimental: VR) or arm 2 (control: no VR). Eight out of 30 planned patients have been enrolled. The VR content is standardized for every subject. It consists of relaxing techniques through visual and auditory input which can last up to one hour. We are using visual analogue scale for both pain (VAS-P) and anxiety (VAS-A) that utilizes numbers and graphic representations between 0 and 10, 0 representing no pain/anxiety at all, to 10 being the worst possible pain/anxiety. Both scales are being measured at 3 defined time points before, during and after the procedure. Usage of pain medications and anesthetics are being recorded for both arms. In addition, we are obtaining baseline levels of the following biomarkers: serum cortisol, highly sensitive C-reactive protein, and fibrinogen. Repeat levels are being collected at specified time intervals to determine if there is a correlation between biomarker levels and perceived pain or anxiety using patient assessed scales. This is a descriptive, feasibility trial that will determine the impact of VR on pain, anxiety, and stress biomarkers during a bone marrow biopsy. Feasibility (i.e. proportion of patients with a successful procedure) will be estimated for each arm separately. The standard error associated difference in success proportions will have a standard error that is less than 0.18. With 30 patients (15 assigned to VR and 15 to standard of care), we will be able to estimate the mean levels of pain and anxiety and biomarkers, as well as changes and differences between the arms with reasonable precision. The implementation of VR in the healthcare setting may serve as a cost-effective, non-pharmacological agent to alleviate pain, anxiety, and stress. Clinical trial information: NCT03568292. Research Sponsor: Tower Foundation.

TPS12151

Poster Session

Exploratory study investigating the efficacy and safety of olanzapine prophylaxis for opioid-induced nausea and vomiting (JORTC-PAL20). *First Author: Eriko Satomi, Department of Palliative medicine, National Cancer Center Hospital/Department of Palliative medicine, Juntendo University Graduate school of Medicine, Tokyo, Japan*

Background: In opioid therapy for cancer pain, it is essential to manage opioid-related adverse effects. Opioid-induced nausea and vomiting (OINV) is common, occurring in 20–40% of patients during initial opioid treatment or after opioid doses are increased. Tolerance to OINV develops within a few days to a week. In patients with cancer, OINV results in decreased quality of life as well as failure to relieve pain due to poor opioid adherence, thus increasing the psychological barriers to opioid use. Therefore, antiemetics are used for OINV prophylaxis, but their efficacy and safety in this context have not yet been fully elucidated. Olanzapine is a promising antiemetic for prophylaxis against nausea and vomiting induced by highly emetogenic chemotherapy, and it is less likely to cause extrapyramidal symptoms than haloperidol and prochlorperazine. We are conducting this exploratory study to evaluate the efficacy and safety of olanzapine prophylaxis against OINV. **Methods:** This single-arm, single-center exploratory study will evaluate the prophylactic antiemetic efficacy and safety of olanzapine (5 mg PO once a day for 5 days) in patients with cancer pain reserving initial regular opioid therapy. Thirty-five patients will be enrolled. This study was designed to provide preliminary efficacy data, with a primary objective of assessing the proportion of patients who achieved complete control (CC) of OINV during 120 hours of opioid treatment. CC was defined as the absence of emetic episodes, the lack of a need for rescue medication to treat nausea, and minimal or no nausea (3 or less on an 11-point categorical scale). Secondary endpoints include the following: the complete response (CR) rate, defined as the percentage of patients with no emetic episodes and no rescue medication use; the total control (TC) rate, defined as the percentage of patients with no emetic episodes, no rescue medication use, and no nausea during the 120 hours of opioid treatment; the time from opioid initiation to the first emetic episode; the time from opioid initiation to the first administration of a rescue antiemetic; the time to treatment failure, defined as the time from opioid initiation to the first emetic episode or to the administration of a rescue antiemetic; the number of emetic episodes; the levels of nausea, anorexia, sleepiness, pain, and fatigue, all determined using a numerical rating scale (0–10); the impact of antiemetic therapy on daily life severity and patient satisfaction, determined using a 7-grade categorical scale; and adverse events graded by PRO-CTCAE ver.1.0 and CTCAE ver. 5.0. The study is currently open, and 25 patients have been enrolled at time of abstract submission. Clinical trial information: jRCTs031220008. Research Sponsor: Japanese Society of Palliative Medicine.

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Poster Session

Empathic communication skills training: Randomized controlled trial to reduce lung cancer stigma in lung cancer care. *First Author: Jamie S. Ostroff, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Stigma is commonly experienced by people diagnosed with lung cancer and is often triggered during clinical encounters with their oncology care provider (OCP), particularly associated with routine assessment of smoking history. Lung cancer stigma is associated with gaps in quality of care as well as poorer psychological and physical health-related outcomes for patients. The overall objective of this multi-site national clinical trial is to test whether an OCP-facing training intervention in empathic communication skills (ECS) reduces stigma and distress and promotes patient engagement. Our prior pilot work has demonstrated that the ECS intervention is both feasible and efficacious to reduce stigma during clinical encounters. **Methods:** This NCI-funded multi-site national trial employs a cluster randomized design comparing usual care (waitlist control) with ECS training (intervention). With outreach and site recruitment support provided by G02 for Lung Cancer and the American Cancer Society, community oncology sites (n = 16) nationwide will be randomized 1:1 to each arm. 9-11 OCPs will be recruited per site with 6 unique patients per OCP enrolled (total 54-66 patients/site). Statistical analysis will evaluate the effect of ECS training on primary OCP outcomes (e.g., empathic skill uptake) and secondary patient-reported outcomes (e.g., psychological distress). The 2.5 hour ECS training is delivered live using a videoconference platform. The didactic content covers knowledge and consequences of stigma on patients with lung cancer and in-depth review of specific ECS strategies. Participants then engage in experiential small-group role-play sessions with trained patient actors, where they are given tailored feedback by trained facilitators and their peers. Eligible sites must have at least 15 OCPs and clinic volume of at least 20 new patients with lung cancer per month. Eligible OCPs (physicians, NPs and PAs) must currently be treating and conducting outpatient clinic consultations with at least 1 patient with lung cancer per week. Eligible patients must be receiving treatment for lung cancer, English and/or Spanish speaking, currently or formerly smoking, and have had no more than 5 prior visits with the participating OCP. Currently, this trial is open to accrual and has 5 sites across the nation completing paperwork for activation. Clinical trial information: NCT05456841. Research Sponsor: U.S. National Institutes of Health.

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